

Brain network communication models

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Abstract

Communication between neural elements underpins all aspects of brain functioning. Large-scale neural signalling unfolds atop the human connectome, the complex network that describes how gray matter regions are interconnected by white matter projections. The mechanisms governing the propagation and communication of signals across the connectome remain unknown. The main focus of this thesis is the investigation of network communication models aimed at elucidating how the anatomical substrate of nervous systems facilitates and constrains functional interactions between gray matter regions.

To date, the vast majority of network neuroscience studies have assumed neural signalling occurs via topological shortest paths. This is reflected by the widespread use of graph measures such as global efficiency, betweenness centrality and the small world coefficient. In recent years, researchers have begun to question this assumption on the basis that communication via shortest paths is contingent on centralized knowledge of connectome topology, and thus may not be a biologically realistic signalling model. This has led to the exploration of decentralized strategies of network propagation. Most efforts in this direction are focused on diffusive communication, which typically models neural signalling from the perspective of random walk processes. While these approaches do not mandate knowledge assumptions about network organization, they fail to promote efficient and energetically frugal neural information transfer. Therefore, the literature on brain network communication models is currently concentrated on the opposing strategies of shortest path routing and diffusive communication. This thesis aims to reconsider this dichotomous state by investigating alternative brain network communication models.

In Chapter 3, we explore the concept of navigation in mammalian connectomes. Navigation is a greedy routing strategy in which information is propagated based on the spatial positioning of brain regions. Using human, macaque and mouse brain networks, we provide evidence that connectome organization is conducive to decentralized efficient communication under navigation. Specifically, the combination of empirical connectome topology and geometry was necessary for successful network navigation, with disruptions to either attribute resulting in marked decreases of navigation efficiency. These findings suggest that brain network architecture may have evolved to facilitate efficient decentralized information transfer, and indicate a three-way relationship between topology, geometry and communication in nervous systems.

Decentralized network communication models can be asymmetric. This means that the efficiency of signalling paths may vary depending on the direction of information flow. Importantly, this behaviour occurs even in undirected networks. This unexplored facet of network communication provides the opportunity to study directional patterns of signalling in the human structural connectome, in which all connections are considered bidirectional due to the inability of diffusion imaging to resolve axonal directionality. In Chapter 4, we develop the statistical framework of send-receive asymmetry and demonstrate that it contributes novel insight into large-scale neural signalling directionality. Crucially, this chapter provides cross-modal evidence for the utility of decentralized communication models by demonstrating a statistical association between send-receive asymmetry and the directionality of effective connectivity.

Lastly, in Chapter 5 we perform a systematic evaluation of the main neural signalling models proposed in the network neuroscience literature. We evaluate several network communication models in terms of their (i) predictive utility of interindividual variation in human behaviour and (ii) structure-function coupling strength. We hypothesize that communication models performing better in these criteria may provide more parsimonious characterizations of information transfer mechanisms in the human brain. Importantly, we benchmark communication models against structural connectivity, and provide evidence that accounting for polysynaptic communication improve the behavioural and functional predictions derived from direct anatomical connections alone. Combining

behavioral and functional results into a single ranking of communication models positioned navigation as the top model, suggesting that it may more faithfully recapitulate biological neural signalling patterns. The results in this chapter contribute to elucidating the relationship between human behaviour, functional connectivity and connectome communication.

Collectively, the findings reported in this thesis further our knowledge of large-scale neural signalling, promoting a unified understanding of brain structure, function and communication.

Declaration

This is to certify that

1. the thesis comprises only my original work towards the PhD,
2. due acknowledgement has been made in the text to all other material used,
3. the thesis is less than 100,000 words in length, exclusive of tables, maps, bibliographies and appendices.

Caio Pimentel Seguin, July 2020

Preface

This thesis presents the scientific research developed during the approximately three and a half years of my PhD candidature. The major contributions of my work are presented in Chapters 3, 4 and 5. Chapters 3 and 4 have been published in international peer-reviewed research journals. Chapter 5 is currently in under peer review. Additional details on these chapters are provided below.

Chapter 3 was published in the *Proceedings of the National Academy of Sciences of the United State of America* on June 12 2018 (doi.org/10.1073/pnas.1801351115) and Chapter 4 was published in *Nature Communications* on September 19 2019 (doi.org/10.1038/s41467-019-12201-w). These chapters comprise the final published versions of these works, including both main text and supplementary information. Chapter 5 is presented as the manuscript submitted to peer review.

In accordance to the University of Melbourne's doctoral thesis guidelines, I was responsible for all analyses conducted in this thesis, as well as for the interpreting of results, and writing of original and revised manuscripts for publication. My supervisor Associate Professor Andrew Zalesky provided crucial guidance to the planning, analysis, interpretation, writing and revision stages of Chapters 3, 4 and 5. In Chapter 3, author Associated Professor Martijn van den Heuvel assisted with the writing of the manuscript. In Chapter 4, author Dr Adeel Razi provided important data analytical tools and assisted with the writing of the manuscript. In Chapter 5, author Dr Ye Tian performed preprocessing analyses of human behavioural data. All investigators who contributed to the work in this thesis have been included as co-authors in relevant chapters.

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I would like to thank my supervisor Andrew for his knowledge, guidance and mentorship. Thanks to my friends and colleagues from the Melbourne Neuropsychiatry Centre. In particular, I would like to thank Kate Bray for always being there through the ups and downs of the PhD journey. Finally, I thank my family in Brazil for their unconditional support.

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List of publications

First author refereed articles

- **C Seguin**, A Razi, A Zalesky. Inferring neural signalling directionality from undirected structural connectomes. *Nature Communications* (2019).
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Co-author refereed articles

- T Sarwar, **C Seguin**, K Ramamohanarao, A Zalesky. Towards deep learning for connectome mapping: A block decomposition framework. *NeuroImage* (2020).
- X Wang, **C Seguin**, A Zalesky, W Wong, W Chiu-wing Chu, R Kai-yu Tong. Synchronization lag in poststroke: relation to motor function and structural connectivity. *Network Neuroscience* (2019).
- EP Ganella, **C Seguin**, C Pantelis, S Whittle, BT Baune, J Olver, GP Amminger, PD McGorry, V Croy, A Zalesky, CF Bartholomeusz. Resting-state functional brain networks in first-episode psychosis: A 12-month follow-up study. *Australian & New Zealand Journal of Psychiatry* (2018).
- EP Ganella, **C Seguin**, CF Bartholomeusz, S Whittle, C Bousman, CMJ Wannan, MA Di Biase, C Phassouliotis, I Everall, C Pantelis, A Zalesky. Risk and resilience brain networks in treatment-resistant schizophrenia. *Schizophrenia research* (2018).

- EP Ganella, CF Bartholomeusz, **C Seguin**, S Whittle, C Bousman, C Phassouliotis, I Overall, C Pantelis, A Zalesky. Functional brain networks in treatment-resistant schizophrenia. *Schizophrenia research* (2017).
- MP van den Heuvel, SC de Lange, A Zalesky, **C Seguin**, BTT Yeo, R Schmidt. Proportional thresholding in resting-state fMRI functional connectivity networks and consequences for patient-control connectome studies: Issues and recommendations. *NeuroImage* (2017).

A minha casa pobre é rica de quimera.

Chapter 1

Introduction

1.1 Network neuroscience: a brief introduction

Nervous systems are networks of interconnected neural elements. In the past decade, network neuroscience has emerged as a field dedicated to mapping, analysing and stimulating brain networks (Bassett and Sporns, 2017; Fornito et al., 2016). Capitalizing on parallel advances in neuroimaging techniques and the mathematics of complex networks, network neuroscience has led to significant progress in our understanding of brain structure and function. The concept of the connectome plays a central role in network neuroscience. At the microscopic resolution of cellular interactions, the connectome describes how neurons are linked by synapses. To date, the nematode worm *C. elegans* is the only organism to have its complete connectome mapped at the cellular scale (Cook et al., 2019; White et al., 1986). The human nervous system is typically characterized by meso- and macro-scale connectomes comprising between 100 to 10^4 gray matter regions, with interregional connections representing either structural or functional interactions. Human structural connectomes describe how gray matter regions are interlinked by white matter projections, providing an anatomical map of brain connectivity (Hagmann et al., 2008; Sporns et al., 2005), while human functional connectomes capture statistical patterns of neural co-activation or synchrony, describing the extent to which pairs of gray matter regions are functionally coupled (Achard and Bullmore, 2007; Achard et al., 2006).

Network science and graph theory provide a quantitative framework to understand the properties of complex networks (Barrat et al., 2004; Newman, E J; Strogatz, 2001). Analytical methods from these fields have revealed that human structural and functional

connectomes are characterized by a small-world and modular architecture featuring a heterogeneous degree distribution and a core of densely connected hubs (Bullmore and Sporns, 2009; van den Heuvel and Sporns, 2011; Watts and Strogatz, 1998). Interestingly, these properties are ubiquitous to connectomes of a wide range of species, from relatively simple organisms such as *C. Elegans* and the *Drosophila* fruit fly to mammals such as the mouse and macaque (Markov et al., 2014; Oh et al., 2014; Shih et al., 2015; van den Heuvel et al., 2016; Varshney et al., 2011). This universality suggests that nervous systems are organized according to fundamental principles of network architecture. Disruptions to these principles have been associated with numerous psychiatric and degenerative brain disorders (Crossley et al., 2014; Fornito et al., 2015, 2012b; Griffa et al., 2013; van den Heuvel and Sporns, 2019), highlighting that mental illness and neuropathology are often characterized by network-level dysfunctions in neural circuitry rather than focal abnormalities.

Hallmark principles of connectome organization are thought to be instrumental in facilitating information transfer between brain regions (Avena-Koenigsberger et al., 2017; Bullmore and Sporns, 2012; Mišić et al., 2015). In its first decade of existence, network neuroscience has led to significant advances in our understanding of structural and functional connectomes as separate systems. However, the question of how signals are propagated through the structural connectome in order to facilitate functional interactions between gray matter regions remains poorly understood. Addressing this question is the central topic of this thesis.

In the remainder of this section, we will provide a primer on graph theory and network science, and a brief introduction to basic concepts regarding structural and functional connectomes. The rest of the Introduction chapter will review the literature on brain network communication models and delineate the rationale and aims of this thesis.

1.1.1 A primer on graph theory and network science

This section aims to provide an intuitive introduction to concepts in graph theory and network science that are central to the work developed in this thesis.

1.1.1.1 Nodes, connections and networks

A network (or graph) is a collection of interconnected nodes. Nodes (or vertices) represent discrete individual elements of a system. Examples include people, websites, airports, train stations, power plants, proteins, genes, neurons, brain regions, amongst many others. Connections (or edges) denote relationships between nodes, characterising social ties, hyperlinks, direct flights, railway links, power cables, metabolic interactions, regulatory links, synapses, white matter projections, amongst other relationships. Hence, networks can be used as mathematical abstractions of social, virtual, flight, transportation, infrastructure, metabolic, regulatory, nervous and countless other types of systems.

Connections can be of different types: directed or undirected and weighted or unweighted. A directed connection between nodes i and j implies a unilateral relationship $i \rightarrow j$, e.g., website i links to website j , but i has no link to j . An undirected connection implies a bilateral relationship, e.g., if user i is friends with user j on social media, then i is also friends with j . The weight of a connection measures the strength of the relationship between a pair of nodes. A weighted connection between airports i and j in a flight network could indicate the number of daily flights leaving from i to j . Similarly, a flight network could have unweighted connections, describing only the presence or absence of a direct flight between pairs of airports. Unweighted networks are often referred to as binary networks.

Mathematically, a network comprising N nodes can be described as an adjacency matrix $W \in \mathbb{R}^{N \times N}$, where W_{ij} is the connection weight from node i to node j . The adjacency matrix of a directed network is asymmetric about its main diagonal with $W \neq W^T$. Meanwhile, undirected networks are symmetric about their main diagonal with $W = W^T$. For unweighted networks, $W_{ij} \in [0, 1]$.

Connected nodes are said to be neighbours. In a undirected network, the degree of a node is its number of neighbours. In a directed network, a node's in- and out-degree refer to its number of incoming and outgoing connections, respectively. In a weighted network, the strength of a node is the sum of its connection weights. Analogous definitions for in-strength and out-strength apply.

1.1.1.2 Walks, trails and paths

Walks, trails and paths are concepts from graph theory that are central to the study of network communication, for they describe how an entity can travel along the nodes and connections of a network. A walk is an ordered sequence of connections in which any pair of successive connections share a common node, allowing an entity to “walk” through the network with no restrictions on the number of times a given node or connection is visited. A trail is a walk in which all connections are unique. A path is a walk in which all connections and nodes are unique. Fig. 1.1 shows examples of a walk, trail and path.

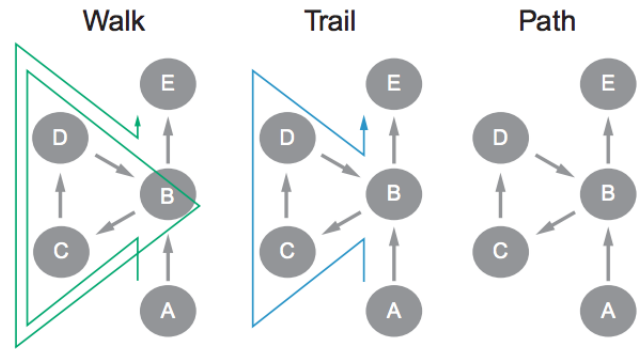


Figure 1.1: Examples of a walk (green), trail (blue) and path (red) between nodes *A* and *E* in a directed network. Source: (Fornito et al., 2016).

The cost associated with the traversal of a given path is called path length. It can be defined by the hop count (number of connections traversed in the path) or in terms of the weights of the connections traversed. The shortest path between two nodes is the optimal (least costly) way to travel from one node to the other, while the shortest path length is the cost of the optimal path.

As an illustrative example, consider the toy network in Fig. 1.2. Let us image that this network describes a railway system. Nodes represent train stations, connections denote the existence of a direct service between stations, and connection weights are length of services in number of hours. What is the most efficient way to travel from station *A* to station *F*? Note that there is no direct train between them so a traveller must take a sequence of services. There are six possible train sequences (i.e., paths) from *A* to *F*. A traveller might be interested in the path that minimizes the number of service changes. This corre-

sponds to computing the shortest path from A to F in an unweighted or binary manner, also known as the hop count between two nodes. The paths $\{A, B, D, F\}$, $\{A, B, E, F\}$, and $\{A, C, E, F\}$ all have the lowest hop count of 3, characterizing three options to travel along the binary shortest path from A to F . However, in order to minimize the amount of time necessary to travel from A to F , one needs to compute the weighted shortest path. This reveals that $\{A, B, E, F\}$ is the best option, leading to the minimal total travel time of 7 hours. Note that although equivalent in number of service changes, $\{A, B, D, F\}$ and $\{A, C, E, F\}$ paths are much longer in terms of travel time.

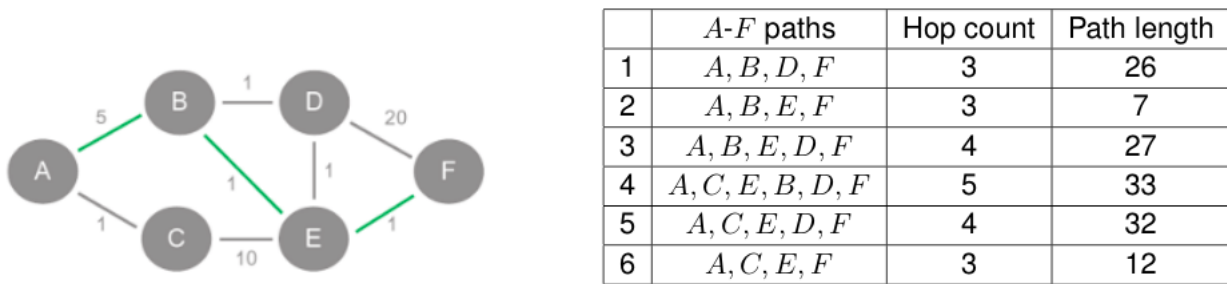


Figure 1.2: Illustrative example of shortest paths. **Left:** Toy network in which connection weights denote the travel cost between nodes. Connections highlighted in green are part of the weighted shortest path from node A to node F . Figure adopted from (Fornito et al., 2016). **Right:** Table listing all paths from A to F . The hop count and path length columns show the binary and weighted path lengths from A to F , respectively.

A crucial point illustrated in this example is that the computation of shortest paths requires knowledge about all nodes and connections in the network. In order to identify $\{A, B, E, F\}$ as their preferred option, a traveller planning their journey needs a complete description of the railway network. Lack of information about a single service means they are not guaranteed to be able to identify the A to F shortest path. This requirement is known as centralized knowledge of network topology. We will revisit it in Section 1.3. It is also worth noting that a greedy approach that chooses the train with the shortest travelling time at each station fails to identify the shortest path.

1.1.1.3 Characteristic path length, clustering coefficient and small worlds

The characteristic path length (CPL) of a network is computed by averaging the shortest path length of all its node pairs. A short CPL means that, on average, information can be efficiently routed between network nodes. The clustering coefficient is a measure related to the number of closed triangles found in a network. In an undirected network, a closed triangle is a three-node motif in which node i is connected to j , j is connected to k and i is connected to k . The clustering coefficient of a node i quantifies the proportion of i 's neighbours that share a connection between themselves. In a social network, computing the clustering coefficient of person i would be equivalent to asking: what's the probability that if two people are friends with i they will also be friends themselves? The clustering coefficient of all nodes can be averaged to compute the clustering coefficient of the whole network. CPL and clustering coefficient are two of the most important graph measures in the study of complex networks, constituting the cornerstones of the famous small-world network architecture (Watts and Strogatz, 1998).

To understand the importance of these concepts, let's begin by considering a regular network (Fig. 1.3, left). Its lattice-like structure is characterized by nodes being densely connected to nearby nodes, resulting in a high clustering coefficient. However, the lack of long-range connections means that many hops are necessary to transmit information between distant nodes, leading to a high CPL. Random networks reside at the opposite end of the spectrum to regular networks (Fig. 1.3, right). Their architecture is characterized by randomly formed connections, in which all node pairs have the same probability of being connected. This contributes to a low clustering coefficient, since closed triangles are unlikely to be formed by chance. However, paths being nodes tend to be short, yielding a low CPL.

Imagine these systems represent the social network of residents of a city. In a regular architecture, people would have social ties with others living in the same neighbourhood, but would not know those inhabiting different parts of the city. On the one hand, this would lead to a strong and resilient community life, in which people would cluster in tight-knit local groups. On the other hand, news and trends originating in one part of the city would spread slowly to other locations, perhaps contributing to insular social

dynamics. Meanwhile, in a random architecture, people would have social ties randomly distributed across the entire city. As a result, local communities would be unlikely to form. However, information would be quickly propagated across distant parts of the city.

Ideally, a city would combine both strong local communities (high clustering coefficient) and the ability to quickly disseminate information across people in different neighbourhoods (short CPL). This is precisely what a small-world architecture achieves (Fig. 1.3, centre). It has been found that the introduction of a few long-range connections to a regular network is sufficient to drastically decrease its CPL while maintaining its high clustering coefficient (Watts and Strogatz, 1998). The simultaneous presence of these two attributes allows small-world networks to foster both locally segregated units of specialized information processing and efficient global communication between distant network elements (Latora and Marchiori, 2001). This balance between segregation and integration is desirable beyond social systems, and is conjectured to be the reason why small-world architectures are universally found across scientific domains. Social, biological, financial, technological, infrastructural, and indeed neural networks are reported to be small-world (Barrat et al., 2004; Bassett and Bullmore, 2006; Latora and Marchiori, 2003; Newman, E J; Strogatz, 2001; Watts and Strogatz, 1998).

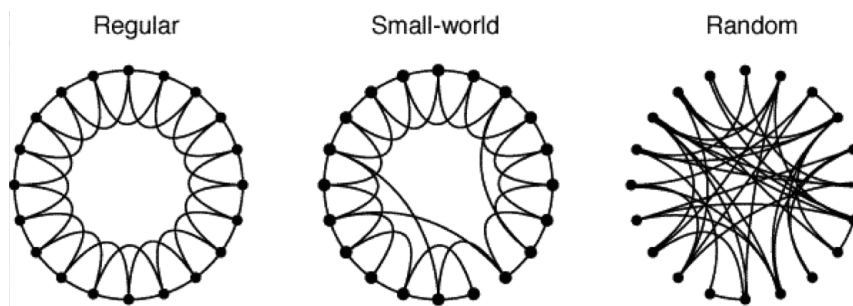


Figure 1.3: Three network architectures. **Left:** regular topology with high clustering coefficient and large CPL. **Centre:** small-world topology with high clustering coefficient and short CPL. **Right:** random topology with low clustering coefficient and short CPL. Figure adapted from (Watts and Strogatz, 1998).

1.1.2 Structural connectivity

The structural connectome describes how brain regions are anatomically interconnected. Here, we will focus on how human structural connectivity is non-invasively mapped from diffusion magnetic resonance imaging (MRI) data (Fig. 1.4a). White matter fibres restrict the movement of water molecules to be aligned with the orientation of axonal projections (Le Bihan, 2003). Diffusion data can be used to estimate the extent to which the water molecule flow is constrained, a measure called fractional anisotropy (FA), as well as the orientation of the constraint at each voxel (Basser and Pierpaoli, 1996, 2011). Low FA indicates an unrestricted and disorderly water flow, suggesting the absence of axonal projections. Conversely, high FA indicates the presence of white matter fibres that limit the movement of water molecules along a given orientation.

Once axonal fibre orientations have been estimated for all white matter voxels, whole-brain tractography is applied to delineate fibre bundles. This is achieved by the propagation of so-called “streamlines” along the estimated fibre orientations (Fig. 1.4b). A streamline behaves as a random walker whose stepwise propagation is guided by the fibre orientations of each new visited voxel. Typically, 10^6 to 10^8 streamlines are propagated to generate a tractogram—a model of the large-scale white matter structure of the brain (Fig. 1.4c).

The nodes of the connectome are defined by a parcellation segmenting cortical and subcortical structures into separate gray matter regions (Fig. 1.4d). Following co-registration, the parcellation is superimposed onto the tractogram in order to define connections between nodes (Fig. 1.4e). A region pair ij shares a connection in the resulting connectome if there exists at least one streamline with one endpoint in i and the other in j . Thresholding and filtering techniques can be applied to cull potentially spurious connections due to tractography biases and artefacts (Betz et al., 2019a; Smith et al., 2013a). Connections are bilateral (i.e., undirected) due to the inability of diffusion imaging to resolve axonal fibre directionality. Connection weights are defined as a function of the total number of streamlines identified between two regions. Streamline counts are conjectured to reflect the integrity, density and calibre of white matter fibre bundles (Zalesky and Fornito, 2009). While their precise biological meaning remains unclear, it is generally ac-

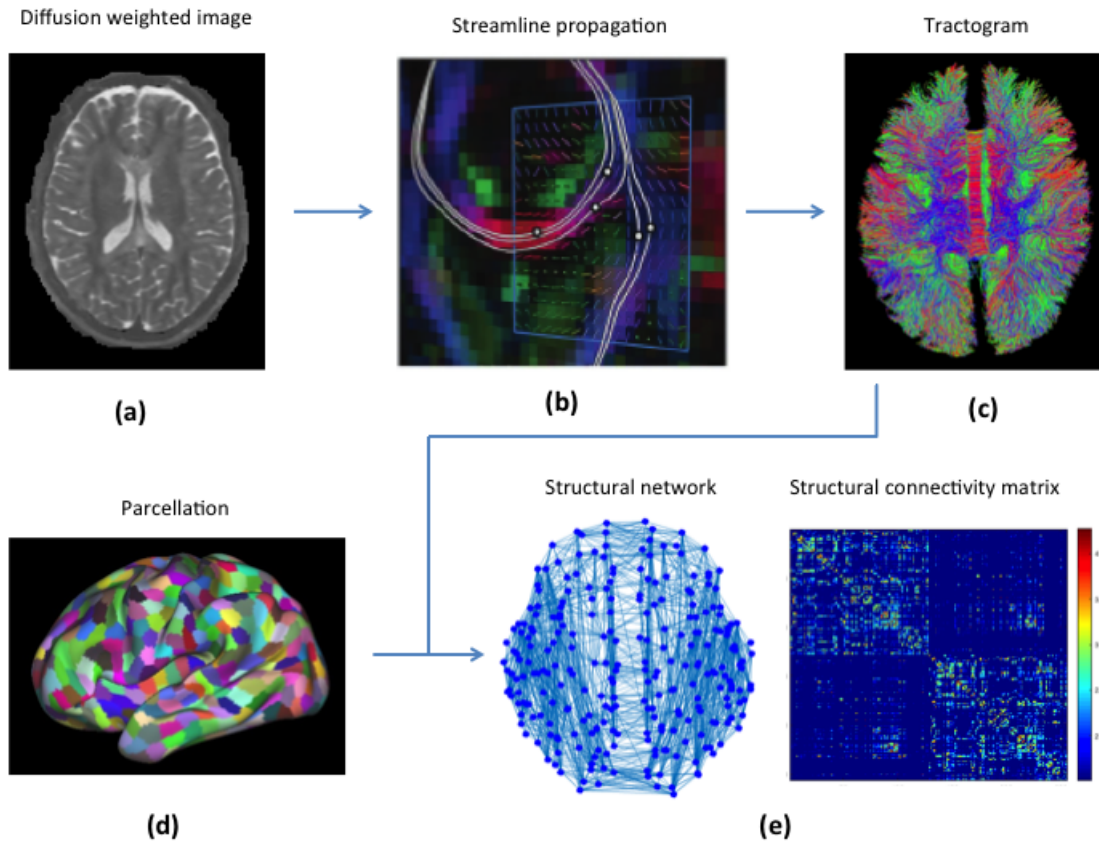


Figure 1.4: Structural connectome mapping pipeline. **(a)** Axial slice of a diffusion weighted image. Data from this image is used to estimate fibre orientation directions in each voxel. **(b)** Streamlines are propagated according to the estimated fibre orientations. Figure adapted from (Fornito et al., 2016). **(c)** Axial view of a whole-brain tractogram produced by the initiation and propagation of 10^6 streamlines. **(d)** A gray matter parcellation of the cortical surface is used to define the nodes in the connectome. **(e)** Network and matrix presentations of the human structural connectome. After co-registration, the parcellation is superimposed onto the tractogram. Streamlines with endpoints in gray matter region pairs are enumerated to generate a weighted connectivity matrix. Circles and connections depict gray matter regions and white matter projections, respectively.

cepted that larger streamline counts indicate stronger anatomical connections (Fornito et al., 2016).

In summary, the pipeline for the construction of the human structural connectome implements (i) voxel-wise estimation of fibre orientations from diffusion imaging, (ii) whole-brain white-matter tractography and (iii) assignment of connections based on the location of streamline extremities with respect to a gray matter parcellation (Hagmann

et al., 2008; Sporns et al., 2005). Each of these steps entails numerous methodological challenges and can be performed using different techniques and algorithms (Maier-Hein et al., 2017; Sotiropoulos and Zalesky, 2019). These issues are revisited in Section 2.1.3, where we detail aspects of the structural connectome mapping pipelines adopted in the empirical chapters of this thesis.

1.1.3 Functional connectivity

The functional connectome describes patterns of co-activation between brain regions. Functional connections are more abstract than anatomical ones. They rely on statistical or information-theoretical dependencies to characterize the extent to which region pairs have their neural activities coupled (Fornito et al., 2013). Functional connectomes can be constructed from several data modalities, including functional MRI, electroencephalogram (EEG) and magnetoencephalography (MEG). In this thesis, we will focus on functional connectivity (FC) derived from blood-oxygenation level dependent (BOLD) times series recorded during rest (Biswal et al., 1995; Fox and Raichle, 2007). Despite the slow frequency of haemodynamics (< 1 Hz) and the existence of several physiological confounding factors (Murphy et al., 2013), a wealth of evidence supports that BOLD fMRI is related to underlying neural activity (Britz et al., 2010; Brookes et al., 2011; Buckner et al., 2013; Logothetis et al., 2001).

Fig. 1.5 illustrates the functional connectome mapping pipeline. As with structural connectivity, FC is computed with respect to a gray matter parcellation. For each gray matter region, a single BOLD time series is calculated by averaging signals across all of its voxels. Measures employed to quantify FC include partial correlation, mutual information, phase coherence and several others (see (Smith et al., 2011) for a review). The most ubiquitous technique to estimate FC is the Pearson correlation coefficient between regional activity time series (Bullmore and Sporns, 2009; Fornito et al., 2016). In this thesis, functional connectomes are defined as the pairwise Pearson correlation matrix of BOLD regional signals.

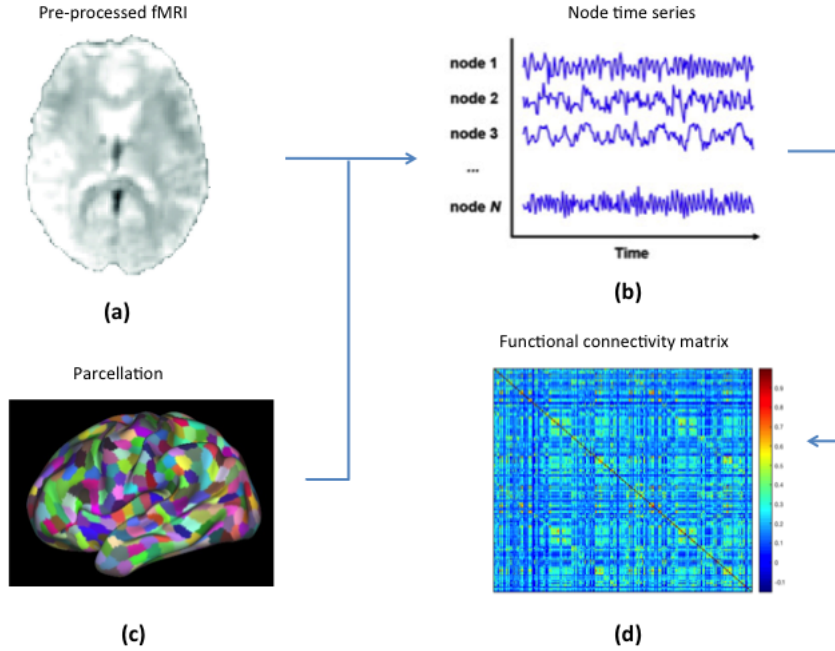


Figure 1.5: Functional connectome mapping pipeline. **(a)** Axial view of a preprocessed functional MRI volume. **(b)** Time series computed for each node defined in the parcellation. For a given region, the BOLD fMRI signals comprised in each of its voxels are averaged into a single time series. **(c)** A gray matter parcellation of the cortical surface is used to define the nodes in the connectome. **(d)** Matrix representation of the functional connectome derived by calculating the pairwise Pearson correlations between all regional time series.

1.2 Intercellular neural signalling

Communication in the brain can be studied at multiple spatial scales. The focus of this thesis is on large-scale neural signalling, that is, information transfer taking place between gray matter regions encompassing an astonishing number of neurons. Adopting this perspective allow us to explore how macroscopic properties of connectome organization may contribute to the coordination of brain-wide patterns of neural activity. However, before considering neural signalling at the spatial resolution of the human connectome, it is important to review aspects of communication unfolding at the cellular scale of individual neurons. This section provides a brief introduction to structural and biophysical aspects of neuron-to-neuron communication.

Most neurons are composed of four main parts (Fig. 1.6a). The *soma*, or cell body, houses the nucleus and is responsible for the regulation of the neuron's metabolism and synthesis of necessary proteins. *Dendrites* are extensions responsible for receiving most of incoming signals arriving at the neuron. Outgoing signals are transmitted along the *axon*, a typically long projection extending from the soma and branching into various *axon terminals* at its distal extremity. Neurons are connected by structures called synapses, which are responsible for the transmission of information from the axon terminals of presynaptic neurons to the dendrites of postsynaptic neurons.

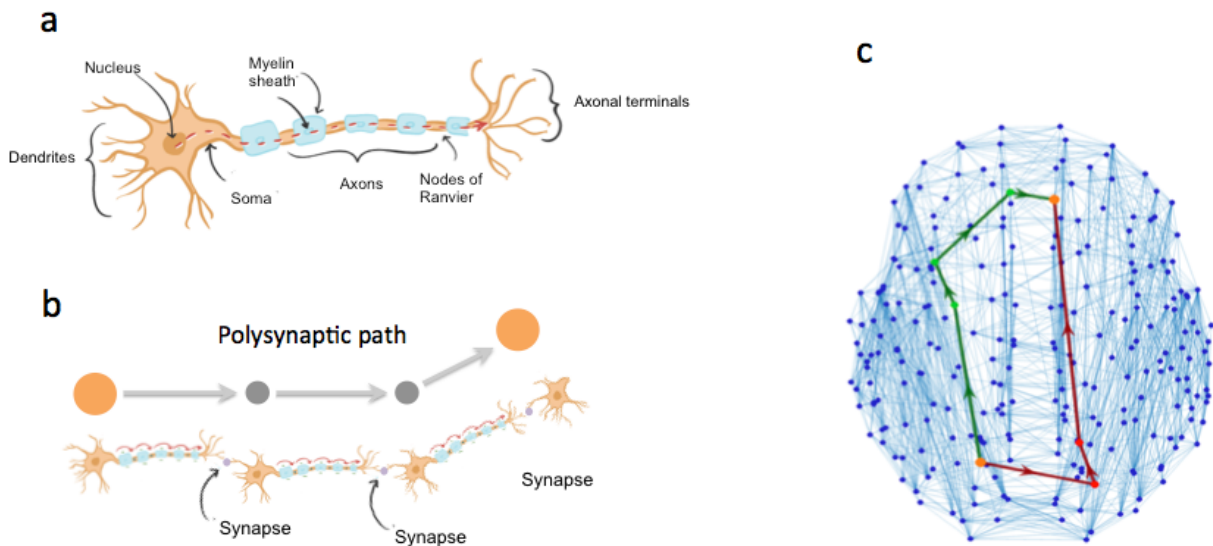


Figure 1.6: Different scales of neural signalling. **(a)** Schematic of the anatomy of a typical neuron. **(b)** Polysynaptic intercellular signalling pathway at the microscopic scale. **(c)** Polysynaptic interregional signalling pathway at the macroscopic scale of the human connectome.

Neuron-to-neuron communication can be broadly decomposed into the stages of intra- and intercellular signalling. Intracellular communication consists of the propagation of electrical signals—known as action potentials—along axons. Action potentials are sharp and discrete depolarizations of the axonal membrane. Incoming electrical signals cause a rapid influx and outflux of ions in the neuron's membrane, contributing to its depolarization. Suprathreshold levels of depolarization elicit the flow of action potentials along the axon from the soma to the axon terminals, a process known as conduction. Conduc-

tion is typically faster and more reliable for thick and well-insulated (myelinated) axons. Once electrical signals reach axon terminals, intercellular communication takes place via synaptic transmission. This process can be electrical or chemical in nature. Electrical transmission takes place when two neurons are physically connected by synaptic gap junctions, enabling electrical activity in one neuron to directly effect the other. Alternatively, pre- and postsynaptic neurons can be separated by a synaptic cleft. In these cases, intercellular communication requires a neurotransmitter to convert action potentials into analog chemical information capable of bridging the cleft to elicit a postsynaptic electric response (Debanne et al., 2013).

Communication between two neurons requires them to be connected by a synapse. However, information can be propagated between unconnected neurons via a chain of intermediate cells. This constitutes a polysynaptic path (Fig. 1.6b). Ultimately, polysynaptic chains of neurons shape the network architecture of the macroscale human connectome (Fig. 1.6c). Models of large-scale brain network communication deliberately abstract away biophysical details on the mechanisms of neuron-to-neuron signalling. This enables the study of emergent brain-wide patterns of interregional information transfer that may provide more direct relations to cognition and behaviour, as well as to macroscale manifestations of pathology and functional connectivity measured using MRI (Mišić et al. (2015)). Despite a resolution difference spanning several orders of magnitude, intercellular and interregional connectivity and signalling are thought to be shaped by similar principles of conservation of energy, time and space (Bullmore and Sporns, 2012; Laughlin and Sejnowski, 2003; Misic et al., 2018). Therefore, progress in understanding the mechanisms of large-scale connectome communication may provide insight into the signalling of microscopic neuronal networks.

1.3 Brain network communication models

Understanding the mechanisms governing large-scale neural signalling is an important open question for neuroscience. Communication between gray matter regions underpins multiple facets of brain functioning and is crucial for memory, cognition and be-

haviour (Friston, 2002; Laughlin and Sejnowski, 2003; McIntosh, 2000). The structural connectome provides the anatomical scaffolding on top of which neural communication unfolds. In turn, information transfer between neural elements gives rise to patterns of activity synchronization which ultimately shape functional connectivity (Deco and Kringelbach, 2016; Hahn et al., 2018). Knowledge of how signals are propagated through the connectome is therefore crucial to our understanding of neural information processing and computation, as well as to illuminating the relationship between brain structure and function (Avena-Koenigsberger et al., 2017; Goñi et al., 2014; Mišić et al., 2015; Vázquez-Rodríguez et al., 2019).

Brain network communication models aim to describe how signals are propagated through the connectome. Communication between anatomically connected regions can trivially take place via direct structural connections. However, signalling among region pairs that do not share an anatomical connection must occur through polysynaptic paths embedded in the connectome topology. A network communication model proposes a propagation strategy to delineate signalling paths between pairs of regions. In turn, a network communication measure quantifies the communication efficiency of paths identified by a given model. Efficient communication paths typically promote fast and reliable signalling by prioritizing the traversal of few synaptic crossing and utilising high calibre, high integrity white matter connections (Fornito et al., 2016).

1.3.1 Shortest path routing

In 1998, Watts and Strogatz published their seminal work introducing the concept of small-world networks (Watts and Strogatz, 1998). They showed that three unrelated complex networks (including the *C. Elegans* connectome (White et al., 1986)) shared the topological traits of a small-world architecture. As discussed in Section 1.1.1, small-world networks combine short CPL and high clustering coefficient. A large body of work quickly formed around reporting on the “small-worldness” of various social, infrastructure and biological networks (see (Albert and Barabási, 2002) for a review). Not long after, neuroscience studies provided evidence for the small-world topology of large-scale brain networks of several mammals, including the macaque monkey, cat and human (Achard

et al., 2006; Bassett and Bullmore, 2006).

The discovery of the small-world architecture of nervous systems deeply influenced how the field of network neuroscience came to characterise the properties of connectomes. In particular, an influential research direction focused on the selective pressures and adaptive advantages leading to the emergence of small-worldness in the brain. The prevailing notion is that nervous systems evolved to balance a trade-off between cost and efficiency, aiming to minimise wiring metabolic costs and maximise the capacity for efficient information transfer (Achard and Bullmore, 2007; Bullmore and Sporns, 2009, 2012). Importantly, due to its dependence on CPL, the small-world concept makes the tacit assumption that neural signalling takes place along shortest path routes. Similarly, other graph theoretical measures based on shortest paths have been widely used in system neuroscience, such as global efficiency (Latora and Marchiori, 2001) and betweenness centrality (Barthelemy, 2004). Therefore, the notion that neural communication is optimally efficient has been ubiquitous to graph-theoretical studies of the connectome since the inception of network neuroscience.

Shortest path routing is an attractive model of connectome communication. As discussed in the railway network analogy in Section 1.1.1.2, shortest paths could be computed from binary (e.g., unweighted) or weighted perspectives. For a binary connectome, optimal communication would entail minimizing the number of synaptic junctions required to be bridged by travelling action potentials. For a weighted connectome, it would prioritize propagation through high calibre, high integrity white matter projections. In either scenario, shortest path communication would promote fast, energetically frugal and reliable routing of action potentials across the brain (Bullmore and Sporns, 2012; Fornito et al., 2016).

However, as also exemplified in Section 1.1.1.2, the computation of shortest path routes demands knowledge of all connections comprised in the network. This is referred to as centralized or global knowledge of network topology. This means that individual connectome nodes (e.g., gray matter regions or single neurons, depending on the scale) necessitate a bird's eye view of the whole connectome architecture in order to compute and propagate signals along optimally efficient paths. As most biological systems,

the brain is a decentralized network, for which individual nodes are unlikely to possess knowledge about network elements outside their vicinity. Therefore, the centralized knowledge requirement mandated by shortest path routing are unlikely to be met by the connectome and its individual components (Avena-Koenigsberger et al., 2016; Goñi et al., 2014; Mišić et al., 2015; Papo et al., 2016).

1.3.2 Network navigation

Nodes of complex networks representing real-world systems often do not possess global knowledge of network topology. This is the case for social and neural networks alike, for which individual persons or brain regions have no or limited knowledge of the connectivity between elements beyond their own locality. As discussed in the previous section, this renders shortest path routing an unlikely candidate to explain how information is propagated in decentralized systems.

Nevertheless, certain real-world complex networks do manage to integrate information with surprising efficiency. The 1969 work of sociologists Jeffrey Travers and Stanley Milgram on small-world networks is perhaps the most famous example of decentralized efficient network communication (Milgram, 1967; Travers and Milgram, 1969). In this seminal experiment, a group of participants in one city of the United States were asked to route a letter to residents of another city who they did not personally know. The participants were given the address and professional occupation of their target recipients. Crucially, the participants were not allowed to post the letters directly to the recipients. They were restricted to forwarding the letter to someone they knew on, at least, a first name basis. Each new participant was to follow the same rules and forward the letter along to another acquaintance, with the goal of eventually reaching the original target recipient. Travers and Milgram reported that letters reached their targets after passing by, on average, 5.2 intermediary recipients. Naturally, each person involved in the path from the initial participant to the target recipient did not have global knowledge of the social network through which the letters were routed. Remarkably, not only the letters reached their targets, but they did so with a surprisingly small number of hops along the network.

The letters were routed using what is now known as network navigation (Kleinberg, 2000). Navigation is a communication scheme that does not rely on the assumption of centralized knowledge of network topology. Instead, navigation proposes a routing strategy based on local knowledge of node similarity (Serrano et al., 2008). The routing from source to target nodes is done by following a simple rule: starting from the source, each node along the way forwards the signal (e.g., letters) to its neighbour (e.g., first-name-basis acquaintance) that is most similar to the target.

The concept of node similarity is key for navigation. Inherent features of nodes define a measure of similarity (or distance) between them. Computed for all pairs of nodes, this similarity measure defines a nodal metric space, which can be used to greedily route information via the network topology. For instance, in a social network, possible metric spaces can be based on the professional occupation or geographic location of nodes. This way, computing distances between nodes in the occupational metric space provides a measure of the similarity between the jobs of two individuals. Indeed, participants in Milgram's experiment reported that they forwarded letters to acquaintances who had the most similar job or lived the closest to the target recipient. The authors concluded that the topology of the first-name-basis social network is conducive to efficient navigation, providing the earliest evidence for the navigability of complex networks.

Forty years after Milgram's original work, Boguña and colleagues leveraged advancements in network science to investigate the navigability of several complex networks spanning multiple scientific domains (Boguña et al., 2009). They showed that successful navigation routing depends on particular traits of network topology. Specifically, navigable networks were characterized by high clustering coefficient and a scale-free degree distribution contributing to a core of densely connected high-degree nodes. The authors demonstrated that network navigation takes advantage of these topological features by following a "fine-, coarse-, fine-grained" signalling strategy (Fig. 1.7a). Signal propagation from a source to a target node typically proceeds as follows. First, signals travel locally via peripheral connections close to the source node. Once a high-degree node is reached, signals are forwarded towards the target via long-range connections, allowing them to traverse large distances in the metric space in a small number of hops. Finally,

once at the vicinity of the target node, signals take advantage of the high clustering to home in on the destination.

Boguña and colleagues propose that the small-world architecture of complex networks may have evolved to facilitate signalling through this mechanism, by balancing integration—high-degree nodes with long-range connections for quick coarse-grained propagation across distant parts of the network—and segregation—locally clustered vicinities that allow for fine-grained information processing and addressing. The authors charted a Cartesian space of clustering coefficient $\times$ scale-free distribution exponent, which was divided into navigable and non-navigable zones (Fig. 1.7b). Several real-world networks such as the internet, airports and metabolic reactions of *E. coli* were found to populate the navigable region.

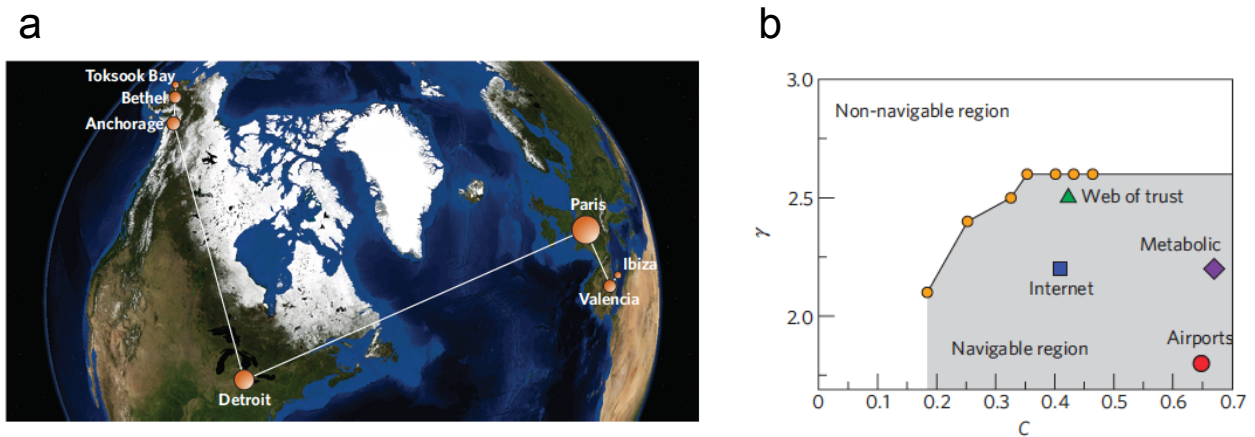


Figure 1.7: Navigation of real-world complex networks. **(a)** “Fine-, coarse- fine-grained” navigation exemplified in an airport network. Two airports are connected if there exists a direct flight between them. The figure shows the navigation path between two low-degree airports: Toksook Bay in Alaska, USA and Ibiza, Spain. The path begins by exploring the vicinity of the source airport until Anchorage—a local hub—is reached. From there, the path quickly covers long distances by hopping across the high-degree of airports of Detroit and Paris. From there, Valencia—another local hub—is selected, which then facilitates homing into the final target node. This “zoom-in/zoom-out” mechanisms is supported by the presence of hubs and high clustering. Example sourced from (Boguna et al., 2009). **(b)** Navigability space of complex networks. Horizontal and vertical axis denote, respectively, clustering coefficient and the exponent of degree distribution. Real-world complex networks sit in different positions of the navigability space. The position of brain networks remains uncharted.

In 2015, Gulyas and colleagues proposed a game-theory algorithm to build synthetic

networks that maximize navigability while minimizing wiring costs (Gulyás et al., 2015). They showed that synthetic fully navigable networks share important structural properties with a variety of real-world complex networks, including the human structural connectome. The authors emphasize that the synthetic networks were designed to optimise information routing by navigation, without seeking to reproduce topological features of empirical networks. Hence, the agreement found between the structural properties of synthetic and empirical networks is as a by-product of maximising navigability, supporting the notion that navigation might be the strategy used for the routing of information in real-world networks.

Navigation remains largely unexplored in brain networks. Although there is evidence that the structural connectomes of several mammals have the necessary topological traits to support efficient navigation (Goñi et al., 2014; Harriger et al., 2012; van den Heuvel et al., 2012), a detailed assessment of navigation as a model for neural communication is lacking.

1.3.3 Diffusion processes

Shortest path routing and navigation assume that signals travel through a single deterministic path between two nodes. In contrast, diffusion processes and spreading dynamics propose communication schemes based on dispersive flows of information. Rather than a unique signal being routed from source to target regions, information is propagated simultaneously along multiple fronts in the network. Diffusion processes require the least amount of knowledge about network topology, and thus possibly constitute the most biologically realistic class of network communication models in nervous systems (Fornito et al., 2016; Mišić et al., 2015). Many different diffusion and spreading strategies have been proposed to model information propagation in complex networks from various scientific fields, such as epidemiology (Pastor-Satorras and Vespignani, 2001), social sciences (Tang et al., 2013) and neuroscience (Mišić et al., 2015; Raj et al., 2012).

Diffusion processes are often modelled in terms of random walks. A “random walker” can be thought of as a entity travelling through the network. At each node, the random walker determines which connection to traverse at random. A connectome adjacency

matrix can be adapted into a transition probability matrix, allowing for the propagation of a random walker to be mathematically described in terms of a Markov chain process (Zhou, 2003).

Using this mathematical framework, Goñi and colleagues (2013) explored diffusion processes in a range of complex network topologies (Goñi et al., 2013). The authors proposed several communication measures to characterize different facets of information transfer via random walks. In particular, they proposed the measure of diffusion efficiency to capture how quickly, on average, a random walker travels between a pair of nodes. They benchmarked diffusive communication against shortest path routing to quantify how efficient random walkers are compared to shortest paths for a particular network topology. Based on these results, they created a topology morphospace charting which network architectures favour diffusive versus optimal communication. The structural network of the human brain was reported to strike a balance between topological features favouring random walks and shortest path routing.

In a subsequent 2014 study, Goñi and colleagues further explored the interplay between shortest paths and diffusion (Goñi et al., 2014) in the first investigation of search information in brain networks. Search information is related to the probability that a random walker will serendipitously travel between two nodes via their shortest path. It quantifies the amount of information required to identify optimal communication routes, providing a measure of how hidden efficient signalling pathways are in the connectome topology. Interestingly, the authors show that search information and other related network communication measures are able to predict interregional resting-state functional connectivity, providing evidence that neural communication does not take place exclusively along optimal routes.

In 2008, Estrada and Hatano proposed the concept of network communicability (Estrada and Hatano, 2008). Consistent with the notion of diffusive signal propagation, communicability measures the ease of information flow between two nodes by accounting for all possible walks linking them. Walks are weighted proportionally to the inverse of their length, so that short and long walks provide big and small contributions to communication. This way, communicability reflects the network's capacity for parallel infor-

mation transfer, in which signals are simultaneously broadcast along multiple network fronts. The original version of communicability was designed for binary networks. Aiming to apply the same concept to weighted connectomes, Crofts and colleagues proposed a weighted communicability measure that normalized the influence of disproportionately large connection weights (Crofts and Higham, 2009). Several studies have demonstrated the utility of communicability for network neuroscience. It was been applied to separate stroke patients from healthy controls (Crofts et al., 2011), study the effect of *in silico* connectome lesions (Andreotti et al., 2014), and model the impact of pharmacogenetic inactivation of brain regions to the topology of monkey functional connectomes (Grayson et al., 2016).

1.3.4 Asymmetric network communication models

Decentralized network communication models iteratively identify paths based on local topological features. For example, a naive random walker travelling through a network decides which connection to traverse solely based on the connectivity profile of its current node. Similarly, under network navigation, routes are delineated by considering the spatial positioning of nodes directly connected to each new node visited along the navigation path. An interesting consequence of decentralized propagation is that it can lead to asymmetric communication. Asymmetric in this context means that communication may take place via different paths depending on the direction of information flow. In other words, it is possible for a decentralized strategy to identify a certain communication path from node i to node j and a different path from node j to node i .

Importantly, this behaviour is not contingent on the presence of directed connections. Since communication paths are identified based on local knowledge, and node pairs involved in signalling process occupy potentially different vicinities of the network, swapping source and target nodes may lead to communication asymmetry even in undirected networks. Indeed, several studies of the human connectome—for which connection directions are missing due to limitations of diffusion MRI in resolving axonal fibre directionality—have reported on the asymmetric character of communication measures such as diffusion efficiency and search information (Goñi et al., 2013, 2014).

Currently, the asymmetric property of decentralized communication models is treated as a nuisance. Typically, studies compute asymmetric communication measures as the average across both propagation directions, in order to avoid dealing with asymmetric interregional communication matrices. However, doing so does not consider the inherently directional and hierarchical character of neural communication (Laughlin and Sejnowski, 2003; Mišić et al., 2014b). It is possible that different brain regions and systems are more prone to signalling in a particular direction of information transfer. To date, large-scale communication asymmetry in the human structural connectome remains unexplored.

1.3.5 Validation of brain network communication models

A major challenge for studies in connectome communication is the difficulty of model validation. Empirical evidence of large-scale neural signalling patterns requires technologies capable of recording whole-brain activity at high spatiotemporal resolution (Avena-Koenigsberger et al., 2017). Current neuroimaging techniques generally fail to meet this requirement. Functional MRI provides a proxy measure for neural activity with high spatial resolution that can reach sub-millimetre scales. However, it is limited to characterizing slow fluctuations at the temporal scale of BOLD haemodynamics. Electroencephalography (EEG) suffers from the opposite shortcomings. While capable of recordings at the millisecond resolution of neural signalling, its spatial granularity is impaired by source reconstruction issues due to electrical interference from the skull, scalp and cerebrospinal fluid (Grech et al., 2008; Huster et al., 2012). Finally, invasive methods such as electrocorticography (ECoG) and stereoelectroencephalography (SEEG) allow for high quality recordings combining high spatiotemporal resolution (Buzsáki et al., 2012; Parvizi and Kastner, 2018). However, data from these methods is usually restricted to activity from small cortical patches or a limited number of gray matter regions. In addition, invasive techniques are only justified in clinical cases, for which the positioning of recordings devices is clinically determined (Zijlmans et al., 2019). These limitations have precluded the use of invasive methods to investigate connectome-wide signalling pathways.

The current barriers to direct validation of brain network communication models have led researchers to adopt alternative criteria to assess the plausibility and fea-

sibility of propagation strategies as models of neural signalling. Three main criteria have been investigated: (i) communication efficiency, (ii) knowledge assumptions and (iii) associations with functional connectivity. The first criterion stems from the notion that neural signalling should be fast, reliable and energetically frugal (Bullmore and Sporns, 2012). From a graph-theoretical standpoint, this means that communication models should identify signalling paths that traverse few synapses and comprise strong connections (Fornito et al., 2016). Knowledge assumptions relate to the feasibility of implementing a communication strategy under the constraints inherent to biological systems such as the brain. For instance, individual neural elements (e.g., brain regions) are unlikely to possess centralized knowledge about the entire topology of the connectome (Avena-Koenigsberger et al., 2016, 2019). Lastly, multiple studies have reported that network communication measures computed on the structural connectome can explain significant variance in interregional resting-state functional connectivity (Abdelnour et al., 2014; Goñi et al., 2014; Mišić et al., 2015). This provided cross-modal evidence that many of the recently proposed brain network communication models significantly capture aspects of the brain functioning.

1.3.5.1 A spectrum of brain network communication models

In two influential papers, Avena-Koenigsberger and colleagues have proposed that brain network communication models can be organized along an information spectrum (Avena-Koenigsberger et al., 2017, 2019). Here, the term information is related to the amount of knowledge required to propagate signals under a certain communication strategy (criterion (ii)). For instance, as previously discussed, shortest path routing mandates global knowledge of network topology, and therefore resides at the end of the spectrum in which communication requires the greatest amount of information. At the opposite end are naive random walk processes which do not rely on any topological information to propagate signals. While diffusive processes may be more biologically plausible than shortest path routing from the standpoint of knowledge requirements, they generally fail to implement efficient communication (criterion (i)). Random relaying of action potentials would result in slow and metabolically expensive signalling. Indeed, evidence sug-

gests that the topology of the human structural connectome is not conducive to efficient signalling via random walks (Avena-Koenigsberger et al., 2014). Therefore, shortest path routing and diffusion process suggest that connectome topology may promote a trade-off between communication efficiency and knowledge assumptions (criteria (i) and (ii)).

As discussed in Section 1.3.1, the ubiquity of graph-theoretical measures based on shortest path routing means that a large proportion of network neuroscience studies have tacitly assumed that neural communication takes place along optimal routes (Bullmore and Sporns, 2009, 2012; Rubinov and Sporns, 2010). Efforts to deviate from this assumption have largely resorted to modelling neural signalling based on different flavours of random walk processes (Abdelnour et al., 2014; Betzel et al., 2013; Raj et al., 2012) and the interplay between optimal and diffusive communication (Goñi et al., 2013, 2014). Certain studies have moved away from this dichotomy by exploring connectome communication via path ensembles (Avena-Koenigsberger et al., 2014), package switching simulations (Mišić et al., 2014b), Markov queueing network models (Mišić et al., 2014a), linear transmission spreading dynamics (Mišić et al., 2015) and ant colony propagation strategies (Tipnis et al., 2018). While these studies have furthered our knowledge of how connectome topology may support signalling, the space between opposite ends of the information spectrum remains mostly uncharted.

Are there network communication models capable of striking a balance between efficiency and knowledge assumptions? Of particular unexplored promise are propagation strategies related to network navigation. In the wider context of complex networks, navigation is conjectured to explain the empirically observed communication efficiency of decentralized networked systems (Allard et al., 2017; Boguna et al., 2009; Travers and Milgram, 1969). Additionally, the human structural connectome possess the topological traits reported to facilitate efficient navigation in other real world networks (Gulyás et al., 2015; van den Heuvel et al., 2012). Nevertheless, the feasibility of navigation as model for connectome communication has not yet been investigated.

1.3.5.2 Neural communication as bridge between brain structure and function

An alternative validation avenue proposes that brain network communication models should be evaluated with respect to their ability to explain variance in empirically measured patterns of interregional functional interactions (criteria (iii)). Understanding the relationship between brain structure and function is a longstanding goal of neuroscience (Amico and Goñi, 2018; Mišić et al., 2016; Park and Friston, 2013). Early multimodal studies of the human connectome reported significant correlations between the connection weights of structural and functional brain networks mapped from diffusion and functional MRI, respectively (Hagmann et al., 2008; Honey et al., 2009). This cross-modality agreement provided the first pieces of evidence that non-invasively derived structural connectivity is indeed relate to aspects of neural activity and computation.

The relationship between structural and functional connectivities stems from the notion that interregional functional coupling is associated to how easily region pairs can communicate via the structural connectome. Consider two gray matter regions linked by a high-calibre, dense and well-myelinated white matter projection. One would expect this connection to establish a fast and reliable communication channel between these regions. The presence of such efficient means of signalling would facilitate the propagation of information between them, in turn promoting synchrony in their activation profiles. Ultimately, this synchrony is measured as FC.

Crucially, several structurally unconnected brain region pairs show strong FC, providing empirical support to the notion that functional interactions between anatomically unconnected regions are facilitated by multi-hop communication paths (Hagmann et al., 2008; Honey et al., 2009). Following these initial observations, Goñi and colleagues (2014) demonstrated that network communication measures computed on the structural connectome were capable of explaining significant variance in interregional FC computed from functional MRI (Goñi et al., 2014). Interestingly, the authors reported that network communication schemes based on deviations from shortest path routing, such as search information, resulted in stronger associations with FC than shortest path lengths themselves, supporting the notion that neural communication does not strictly follow optimal routes.

The rationale for the relationship between communication and function is the polysynaptic extension of association between structural and functional connection weights (Fig. 1.8). First, network communication models are used to identify signalling paths between regions pairs. Based on these paths, the efficiency of information transfer between every region pair is computed. This results in an interregional pairwise communication matrix that can be correlated to the FC matrix. Evidence of a strong association between entries of the communication and functional matrices indicates that the adopted network communication model captured underlying patterns of neural information flow shaping interregional FC. Therefore, neural communication models can bridge the gap between structural and functional descriptions of nervous systems (Avena-Koenigsberger et al., 2017; Mišić et al., 2014a).

Shortly after Goñi's initial report that network communication measures such as search information can accurately model FC, similar studies have demonstrated that diffusion processes (Abdelnour et al., 2014), linear transmission models of spreading dynamics (Mišić et al., 2015) and communicability (Grayson et al., 2016) also led to significant associations with FC. These studies indicate that different conceptualizations of neural communication are able to model neural functional interactions.

One might conclude that the communication strategy leading to the strongest associations with FC may be the current best descriptor of underlying neural signalling processes. However, to date, reports on these associations have been scattered across multiple studies, with researchers employing different pipelines for the reconstruction of structural and functional connectivity. As a result, communication measures have been computed and evaluated on connectomes varying in diffusion and functional MRI acquisition and preprocessing, tractography algorithms, gray matter parcellations and many other parameters. This heterogeneity impedes cross-study conclusions of which communication measures best model FC. A systematic and internally consistent evaluation of the association between network communication measures and FC is lacking.

It is important to note that network communication is not the first framework to be employed to characterize the relationship between structural and functional connectivities. Traditionally, computational neuroscientists have used biophysical models to de-

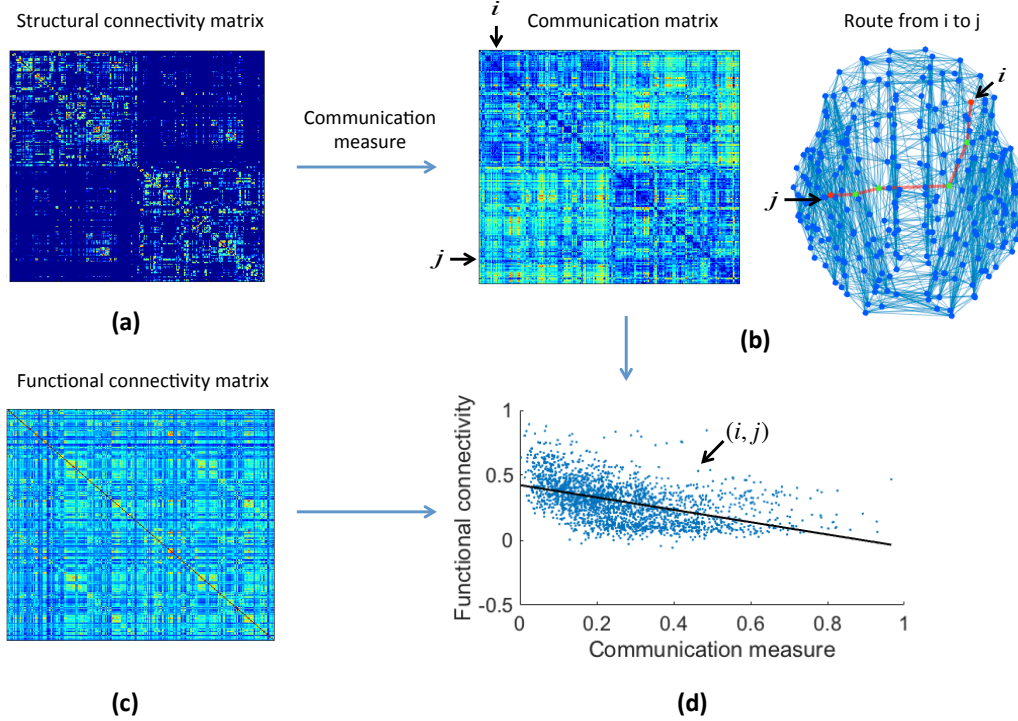


Figure 1.8: Association between functional connectivity and measures of network communication computed over the structural connectome. **(a)** Matrix representation of a structural connectome **(b)** Left: Communication matrix computed by applying a network communication measure to the structural connectome. The communication between all (i, j) node pairs is computed and stored in the communication matrix. Right: Schematic of the (i, j) communication path. **(c)** Matrix representation of a functional connectome. **(d)** Correlation between the FC and network communication measure computed across node pairs.

scribe patterns of cortical oscillations (Breakspear et al., 2010, 2003). These approaches combine nonlinear dynamical systems theory and physiological details on the functioning of single neurons to simulate neural activity at multiple spatiotemporal scales, ranging from microscopic models of single neuron spikes to large-scale characterizations of whole-brain dynamics (Breakspear, 2017; Cocchi et al., 2017a; Deco et al., 2008). With the advance of network neuroscience, these methods began to couple individual neural mass models according to empirically derived structural connectivity, thus simulating the functional interactions amongst the gray matter regions comprising the connectome (Honey et al., 2007, 2009). Through careful tuning of model parameters governing the

behaviour of individual neural oscillators and the coupling strength between oscillators, these approaches were capable of explaining significant variance in empirically derived FC. A important advantage of biophysical modelling is that it allows for the study of FC dynamics (Deco et al., 2017; Wang et al., 2019a), rather than the static perspective currently afforded by network communication measures. On the other hand, network communication are parameter-free and can in most cases be derived analytically, while computational models are prone to the pitfalls of high-dimensional parameter tuning such as overfitting and potential lack of computational tractability. Therefore, the two approaches offer complementary avenues to study the relationship between brain structure and function.

1.3.5.3 Associations between neural communication and behaviour

An important goal of network neuroscience is to understand how the organizational principles of brain networks relate to behaviour and cognition (Bassett and Mattar, 2017; Medaglia et al., 2015; Mišić and Sporns, 2016; Sporns, 2014). Several studies have reported on associations between varied behavioural phenotypes and topological properties of the human functional connectome mapped from fMRI. When computed across a sample of participants, a host of architectural traits were shown to be associated to or predictive of individual variance in behavioural, cognitive and mental health variables. Prominent topological features of the functional connectome included its heterogeneous degree distribution (Bertolero et al., 2018; Ito et al., 2017), modular structure (Bassett et al., 2011; Crossley et al., 2013; Fornito et al., 2012a; Pedersen et al., 2018) and low CPL (Cocchi et al., 2017b; van den Heuvel et al., 2009). In addition, recent work has brought attention to how fluctuations in dynamical properties of FC topology are also related to dynamic changes in cognitive demands (Shine et al., 2016).

In contrast to the rapidly growing body of knowledge concerning functional connectomes, less attention has been given to relating structural brain network properties and behaviour. Most efforts in this direction have focused on connectome topology disruptions due to lesion or disease, with the aim of relating clinical assessments of behaviour and cognition to graph-theoretical measures of brain organization. Examples including

research on stroke (Kuceyeski et al., 2016; Wang et al., 2019b), traumatic brain injury (Caeyenberghs et al., 2014; Imms et al., 2019), psychiatric disorders (Crossley et al., 2014; Griffa et al., 2013) and neurodegenerative conditions (Fornito et al., 2015). Investigations of the relationship between behavioural traits and network communication measures computed on healthy structural connectomes are currently lacking.

A wealth of evidence suggests that behaviour, perception and cognition emerge from the concerted activity of distributed large-scale brain regions and systems (Friston, 2002; Ito et al., 2017; McIntosh, 2000; Sepulcre et al., 2012). This coordination must be implemented via information transfer facilitated by the structural connectome. Accordingly, putative signalling strategies that closely model underlying patterns of neural communication may be useful in explaining interindividual variance in behaviour. Therefore, evaluating signalling strategies on the basis of their associations with behavioural traits is an unexplored validation scheme for brain network communication models.

1.4 Rationale and aims

The overarching goal of this thesis is to expand the current knowledge on large-scale neural signalling. As the surveyed literature demonstrates, while significant advances in mapping structural and functional connectomes have been made, several lacunas remain in our understanding of neural communication. The question of how signals are propagated through the complex architecture of structural connectomes in order to support functional interactions amongst gray matter regions remains a crucial challenge for network neuroscience. This thesis contributes to the tackling of this challenge by seeking to address three important knowledge gaps in the current literature.

As reviewed in Section 1.3.2, navigation routing has been used to describe information transfer in a wide range of complex networks. Initial evidence suggests that the human connectome possess the topological traits necessary for efficient navigation. In Chapter 3, we aim to comprehensively investigate the feasibility of network navigation as a large-scale neural communication model. In particular, an important objective of this project is to determine whether connectome topology is conducive to efficient decentral-

ized communication via navigation. This way, we seek to escape from the dichotomy between optimal and diffusive communication by exploring a model conjectured to promote efficient information transfer without the requirements of global knowledge of network architecture. To further interrogate connectome navigation, we aim to (i) analyse how navigation paths are mediated by different brain regions, providing insight into global patterns of signalling traffic burden related to communication bottlenecks and congestions; and (ii) determine whether navigation path lengths can explain significant variation in interregional functional connectivity. Finally, with the goal of characterizing fundamental properties of mammalian nervous systems, we seek to perform our analyses on mouse, macaque and human structural connectomes.

Chapter 4 aims to explore the communication asymmetry inherent to many putative models of neural signalling. As discussed in Section 1.3.4, the asymmetric character of network propagation strategies has largely been ignored in previous network neuroscience studies. In Chapter 4, we seek to formalize a statistical framework to measure communication asymmetry. The primary goal of this project is to apply this framework to determine whether communication asymmetry in structural connectomes results in meaningful patterns of neural signalling directionality. Crucially, non-invasively directed human structural connectomes do not contain information on connection directionality. Therefore, this project intends to examine the extent to which the undirected topology of the human brain contributes to shaping neural signalling directionality. To answer this question, we aim to assess the relationship between communication asymmetry and empirical measures of signalling directionality derived from human functional imaging data. Additionally, we seek to further our understanding of communication asymmetry by considering the directed connectomes derived from fruit fly, mouse and macaque nervous systems.

In Chapter 5, we aim to perform a systematic comparison of previously proposed candidate models of brain network communication. The main goal of this chapter is to contribute to the assessment of which communication strategies more accurately model underlying principles of neural signalling. To this end, we seek to evaluate putative network communication models based on the strength of their associations with (i) interregional

functional connectivity and (ii) behavioural phenotypes. As discussed in Sections 1.3.5.2 and 1.3.5.3, coordination between distributed gray matter regions and cortical systems is crucial for the emergence of behaviour and cognition, as well as for functional connectivity. Therefore, we conjecture that models capable of explaining the largest amounts of variance in interindividual behavioural and functional measures may be more accurate descriptors of neural signalling processes. As an outcome of this project, we aim to generate insight on which communication models researches should adopt to characterize information processing in structural connectomes.

In summary, this thesis aims to address the three open questions listed below, with the broader goal of furthering our understanding of large-scale neural signalling.

1. Is network navigation a feasible model of connectome communication? Specifically, can network navigation, applied to the topology and geometry of brain networks, lead to simultaneously efficient and decentralized communication?
2. Does the asymmetric character of decentralized network communication lead to meaningful insight into the directionality of neural signalling processes? In particular, are communication asymmetry measures computed on human structural connectomes (for which knowledge on connection directionality is missing) associated to functionally-derived measures of neural signalling directionality?
3. Which brain network communication models lead to the strongest associations to behavioural phenotypes and functional connectivity?

Chapter 2

General Methodology

In this section, we provide an overview of the general materials and methods adopted throughout the projects of the thesis. We focus on describing datasets, connectome mapping pipelines, statistical models and network communication measures that featured prominently in all three empirical chapters. Data and techniques specific to single projects are detailed in the material and methods sections of their corresponding chapters.

2.1 Human connectivity data

2.1.1 The Human Connectome Project

Human connectivity data used in this thesis was sourced from the Human Connectome Project (HCP). The HCP is a consortium aimed at providing publicly available data on human brain structure and function, as well as behaviour (<https://www.humanconnectome.org/>) (Van Essen et al., 2013). The consortium is led by the Washington University in Saint Louis and the University of Minnesota, and also includes the University of Oxford, Saint Louis University, Indiana University, D’Annunzio University, Ernst Strungmann Institute, Warwick University, Radboud University Nijmegen, University of California at Berkeley.

As part of the Young Adult project, the HCP has released 3T MRI, 7T MRI and MEG data for a total of 1200 subjects aged between 22 and 35 years old. MRI data included structural, diffusion and functional imaging modalities. Functional MRI data was acquired during resting-state as well as for a range of tasks conditions. The consortium has

developed an array of methods for neuroimaging data acquisition, preprocessing and analysis (Glasser et al., 2013; Smith et al., 2013b; Sotiropoulos et al., 2013). To date, the Young Adult HCP database is one of the highest-quality publicly available resources for neuroimaging and behavioural data of a large sample of healthy adults. In this thesis, we utilized mainly diffusion and resting-state MRI data. The following paragraphs provide a brief description of the HCP acquisition protocols and preprocessing pipelines for these imaging modalities.

Spin-echo planar diffusion weighted images were acquired for each participant on a customized Siemens Skyra 3T scanner. The following parameters were used: 5520 ms repetition time, 89.5 ms echo time, 78 degree flip angle, 160 degree refocusing flip angle, 210×180 mm field of view, 168×144 matrix, 1.25 mm isotropic voxels, 3 shells of $b=1000$, 2000 and 3000 s/mm² and approximately 90 diffusion weighted directions per gradient table. Images were preprocessed according to the following sequence of steps: 1) b_0 intensity normalization, 2) top-up EPI distortion correction, 3) Eddy current distortions and subject motion correction, 4) gradient distortion correction and 5) resampling to 1.25mm native structural space. Further details are described in (Glasser et al., 2013; Sotiropoulos et al., 2013).

Four resting-state functional MRI volumes were acquired for each participant on a customized Siemens Skyra 3T scanner. Sessions were 14m33s each, divided across two separate days, and acquired for right-to-left and left-to-right phase encodings. The following acquisition parameters were used: gradient-echo EPI sequence, 720 ms TR, 33.1 ms TE, 52 degree flip angle, 208×180 mm FOV, 104×90 matrix, 2.0 mm slice thickness, 72 slices, 2.0 mm isotropic voxels, 8 multiband factor and 0.58 ms echo spacing. Images were preprocessed according to the following sequence of steps: 1) spatial and gradient distortion corrections, 2) correction of head movement, 3) intensity normalization 4) single spline re-sampling of EPI frames into 2mm isotropic MNI space and 5) HCP's FIX+ICA pipeline for the removal of temporal artefacts. Further details are provided in (Glasser et al., 2013; Smith et al., 2013b).

2.1.2 Gray matter parcellations

Nodes in the human connectome are defined by parcellations that segment gray matter into N contiguous regions. In this thesis, discovery analyses were predominantly performed on connectomes comprising the $N = 360$ cortical regions present in the HCP multimodal atlas 1.0 (Glasser et al., 2016). Regions in this parcellation were delineated based on sharp changes in cortical gradients of structural and functional MRI data from 210 healthy adults participating in the HCP. It is well known that graph-theoretical analyses of connectomes can be sensitive to the number of regions used to construct brain networks. For this reason, whenever feasible, we aimed to replicate our findings for a range of parcellation granularities.

In order to consider a wide range of connectome resolutions, we developed an algorithm to generate cortical parcellations comprising a user-defined number of regions. The method achieves this by splitting the regions of a coarse-grained input parcellation into smaller sub-regions. The Desikan-Killiany (DK) atlas is a widely used gray matter parcellation containing 68 cortical and 14 subcortical structures defined based on anatomical landmarks (Desikan et al., 2006). We used the $N = 68$ DK cortical regions as the coarse-grained input parcellation to our algorithm. Briefly, regions were split based on three criteria: (i) the resulting number of regions is specified by the user as a power of 2; (ii) subdivisions must respect original anatomical boundaries of the DK atlas, so that all resulting parcels can be attributed to a single anatomical structure; and (iii) each resulting sub-region has approximately the same surface area. Criterion (i) allows for a systematic investigation of the robustness of graph theory measures to variations in parcellation resolution. Criterion (ii) ensures that the resulting parcellation comprises biologically meaningful regions that can be assigned to a single anatomical input region. Finally, criterion (iii) minimizes tractography biases related to the surface area and volume of regions (Li et al., 2012). Further details on this procedure are provided in Chapter 3, Supplementary Information. Using this method, we generated cortical parcellations with $N = 256, 512, 1024$ regions (Fig. 2.1).

The parcellations described so far ($N = 256, 360, 512, 1024$) contained only cortical regions. The inclusion of subcortical structures in high-resolution connectomes is diffi-

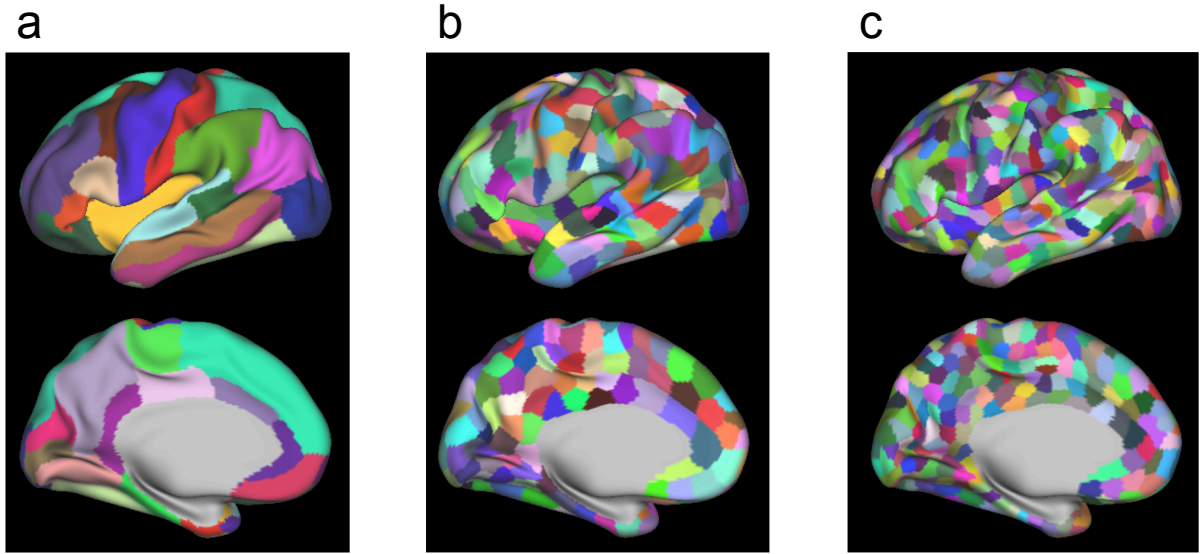


Figure 2.1: Cortical gray matter parcellations with different number of regions. **(a)** Original 68 cortical regions of the DK atlas. Parcellations comprising **(b)** 512 and **(c)** 1024 cortical regions obtained by subdividing the 68 areas in the DK atlas using our algorithm. Divisions were designed to yield evenly-sized tile-shaped regions which can be uniquely assigned to an original parcel of the DK atlas.

cult for two reasons. First, fine-grained parcellations are usually defined based on surface files that describe the cortical mantle as a mesh data structure. Surface files have gained popularity in neuroimaging since they afford higher precision in the mapping of anatomical and functional features than voxel-based volumetric representations of the cortex (Coalson et al., 2018; Eickhoff et al., 2018). However, subcortical nuclei are still defined in terms of voxels. Therefore, the methods used to produce fine cortical parcellations are not translatable to the subcortex. Second, certain subcortical regions such as the thalamus are composed of both grey matter nuclei and white matter fibres, performing the dual role of computational units and signal relays (Guillery and Sherman, 2002). It is currently unclear how to handle this behaviour during the tractography process. However, it is well known that the subcortex plays a key role in neural signalling. Therefore, despite these barriers, we sought to replicate findings in connectomes with both cortical and subcortical regions. To this end, we constructed a custom gray matter parcellations containing the 360 cortical regions of the HCP multimodal atlas in addition to the 14 subcortical structures defined in the DK atlas, resulting in a $N = 374$ parcellation (see

Chapter 4, Supplementary Note 6 for more details).

2.1.3 Mapping structural connectomes

Structural connectomes were mapped using whole-brain white matter tractography applied to diffusion MRI. As described in Section 1.1.2, this process generally involves three stages: (i) estimation of fibre orientations at the voxel level, (ii) reconstruction of white matter projections by means of the propagation of streamlines along the estimated fibre orientations and (iii) computation of interregional connectivity strength based on the location of streamline endpoints. Each of these steps requires a choice of at least one algorithm or method, as well as the tuning of their corresponding parameters (Tournier et al., 2012). To date, there is little agreement on what are the best practices to accurately construct structural connectomes from diffusion data (Maier-Hein et al., 2017; Petrov et al., 2017).

One of the broadest categorizations of connectome mapping pipelines is the division between deterministic and probabilistic approaches. The key difference between them is the strategy used to sample fibre directions for streamline propagation. In deterministic algorithms, a fixed propagation direction is computed for each voxel, based on single or multiple fibre orientation estimates (Jeurissen et al., 2019). In this case, streamlines entering a given voxel will always be deterministically propagated along the same direction. In contrast, probabilistic methods estimate a distribution of fibre orientations for each voxel (Tournier et al., 2010). Every time a streamline enters a voxel, a random propagation direction is sampled from the distribution. Deterministic methods are considered more susceptible to noise and uncertainties inherent to diffusion data, as well as less accurate in modelling crossing fibres. Meanwhile, probabilistic algorithms are computationally expensive and prone to false positives. Therefore, both approaches have strengths and weaknesses, and which should be adopted remains an active topic of debate in the network neuroscience community (Sarwar et al., 2019; Smith et al., 2020; Zalesky et al., 2019).

From a whole-brain connectivity perspective, a practical distinction between deterministic and probabilistic methods lies in the connection density of the resulting connec-

tomes. Deterministic connectomes are typically sparse and thus suffer from the presence of many false negatives; while probabilistic connectomes are typically dense, being impaired by the opposite problem, i.e., the presence of many false positives. Recent evidence indicates that false negatives are more detrimental to graph-theoretical measures and network analyses of brain networks than false positives (Zalesky et al., 2016). Therefore, in this thesis, we adopted a deterministic algorithm in our primary connectome reconstruction pipeline, which we describe below. Importantly, we also replicated our key findings on probabilistic connectomes (see Chapter 4, Supplementary Note 5) and invasively-derived tract-tracing connectomes from a host of non-human species.

Whole-brain deterministic tractography was performed using MRtrix3 software (<http://www.mrtrix.org/>) (Tournier et al., 2012). Preprocessed diffusion images were used to compute voxel-level tensors using an iteratively reweighted linear least squares estimator. White matter masks were extracted from structural segmentation files provided by the HCP and dilated by 1 voxel in all directions to fill potential gray–white matter gaps resulting from slight registration imperfections. Streamlines were uniformly seeded across white matter mask voxels and propagated along diffusion tensor directions until they exited the white matter mask or reached a low fractional anisotropy (FA) voxel (FACT tracking algorithm, 5×10^6 streamlines, 0.5 mm tracking step-size, 400 mm maximum streamline length and 0.1 FA cutoff for termination of tracks). Unless stated otherwise, connection strength between two regions was determined as the number of streamlines with extremities located within the regions.

2.2 Non-human connectivity data

Non-human connectomes are invasively derived using tract tracing techniques that can overcome certain shortcomings of MRI-based connectivity estimates. Most notably, invasive methods can resolve axonal fibre directionality, allowing for the construction of directed connectomes. These brain networks are useful to understanding the impact of connection directionality in neural communication. More generally, considering non-human connectomes in our analyses aids us in uncovering fundamental principles of

nervous system organization and computation that may be phylogenetically conserved across species (van den Heuvel et al., 2016).

2.2.1 Fruit fly connectome

Single neurons in the female *Drosophila* brain were genetically labelled using a green fluorescent protein (Chiang et al., 2011). Three-dimensional images of 12,995 projection neurons from the FlyCircuit 1.1 database were used to outline labelled neurons and register them to a fruit fly template brain. Identified neurons were grouped into 49 local processing units based on their morphology and function. Adopting local processing units as nodes and the delineated axonal projections as connections, researchers constructed a 49-region fruit fly connectome. The resulting network was directed, 83% dense and characterized by a heterogeneous connection weight distribution spanning several orders of magnitude (Shih et al., 2015).

2.2.2 Mouse connectome

Oh and colleagues used anterograde axonal injections of a viral tracer to map a mesoscale connectome describing the mouse nervous system (Oh et al., 2014). Two-photon tomography was used to identify axonal projections originating from the 469 injection sites and terminating at total of 295 target regions. Expanding on these efforts, Rubinov and colleagues used the publicly available connectivity data from Oh's study to construct a whole-brain mouse connectome comprising 112 regions spanning cortical and subcortical structures (Rubinov et al., 2015). The resulting connectome was directed, bilaterally symmetric, 53% dense and reported to display similar topological properties to the human connectome. Connections were weighted by the ratio of tracer density injected at the source to the tracer density measured at the target. The resulting weights were reported to follow a log-normal distribution.

2.2.3 Macaque connectome

Markov and colleagues constructed a sub-network of the macaque connectome by injecting 29 regions of the macaque cerebral cortex with a total of 1,615 retrograde tracers (Markov et al., 2013, 2014). The 29 areas are a subset of a 91-region parcellation, defined based on histological data and anatomical landmarks, that covered occipital, temporal, parietal, frontal, prefrontal and limbic systems. The resultant 29-region connectome was directed, 66% dense and comprised of cortico-cortical connections with log-normally distributed weights. Connection weights were defined as the number of neurons labelled by the tracer found in source and target regions divided by the amount found in whole brain.

2.3 Brain network communication measures

In Section 1.3, we discussed brain network communication models from a primarily conceptual perspective. Here, we focus on the mathematical definitions of the network communication measures used in our empirical analyses. Measures covered below are further described, interpreted and analysed in the context of neural communication throughout the empirical chapters of this thesis. We point interested readers towards the chapters containing further information on each measure. Importantly, MATLAB code used to implement the computation of all communication measures used in this thesis is publicly available as part of the Brain Connectivity Toolbox (sites.google.com/site/bctnet/) (Rubinov and Sporns, 2010).

At this point, it is helpful to reiterate the distinction between brain network communication models and measures, first mentioned in Section 1.3. A communication model describes a strategy used to delineated paths between pairs of nodes in a network. Hence, communication models identify sequences of connections that putatively facilitate information transfer between nodes. In turn, a communication measure aims to quantify the efficiency of the paths identified by a given model. As we shall see, certain communication models can have their efficiencies quantified by means of different communication measures, while other model–measure pairs are exclusively related.

2.3.1 Weight-to-length remapping

A structural connectome comprising N regions can be mathematically expressed as a weighted connectivity matrix $W \in \mathbb{R}^{N \times N}$. Here, entry $W(i, j)$ denotes the strength of the anatomical connection from region i to region j . For instance, $W(i, j)$ can be the number of streamline with endpoints in regions i and j identified by white matter tractography. However, the computation of certain network communication measures requires a matrix of connection lengths $L \in \mathbb{R}^{N \times N}$. In this case, $L(i, j)$ is a measure of the distance or travel cost from i to j . Connection length matrices are computed using weight-to-length transformations that monotonically remap large connection weights into short connection lengths. The assumption here is that high-integrity high-throughput white matter projections are fast and reliable communication channels.

The two most popular weight-to-length transformations are the inverse ($L = 1/W$) and logarithmic ($L = -\log(W)$) remappings (Avena-Koenigsberger et al., 2016; Rubinov et al., 2015). The inverse approach results in skewed length distributions that highlight the importance of large weight connections, while the logarithmic method yields approximately normally distributed lengths that attenuate the impact of large weight connections. Both transformations are adopted in the literature and it remains unclear which approach is preferable from a biological standpoint (Fornito et al., 2016; Goñi et al., 2014). An in-depth description and evaluation of weight-to-length remappings is provided in Chapter 5.

2.3.2 Shortest path efficiency

The shortest path routing network communication model proposes that signalling takes place along optimally efficient paths that minimize the sum of connection lengths traversed between nodes. Let $\{u, \dots, v\}$ be the sequence of nodes visited along the shortest path from node i to node j . The shortest path length from i to j is computed as $\Lambda^*(i, j) = L(i, u) + \dots + L(v, j)$ (Watts and Strogatz, 1998). Alternatively, the ease of communication from i to j can be quantified as the shortest path efficiency $E_{sp}(i, j) = 1/\Lambda^*(i, j)$ (Latora and Marchiori, 2001, 2003) (Chapters 3 and 5).

The shortest path length (Λ^*) and efficiency (E_{sp}) measures exemplify that network communication can be quantified from the point of view of signalling cost (path length) or easiness of signalling (efficiency). Intuitively, these measures are inversely proportional and describe complementary conceptualizations of the same communication process. In this thesis, we focus on network communication measures that quantify signalling efficiency rather than length. We investigate shortest path efficiency in the context of neural communication in Chapters 3, 4 and 5.

2.3.3 Navigation efficiency

We explore the concept of network navigation in Chapter 3. Briefly, the navigation path from node i to node j is identified as follows. First, progress to i 's directly connected node that is closest in distance to j . Then, for each new visited node, repeat this process until j is reached (successful navigation) or a node is revisited (failed navigation) (Boguna et al., 2009). In the case of successful communication, the navigation path length from i to j is defined as $\Lambda(i, j) = L(i, u) + \dots + L(v, j)$, where $\{u, \dots, v\}$ is the sequence of nodes traversed during navigation. Failed navigation is characterized by $\Lambda(i, j) = \infty$. Analogous to shortest path routing, we define navigation efficiency $E_{nav}(i, j) = \Lambda(i, j)$. Connectome navigation is examined in Chapters 3, 4 and 5.

2.3.4 Diffusion efficiency

Diffusion efficiency models network communication as a random walk process. Let T denote the transition probability matrix of a Markov chain process with states corresponding to nodes in the adjacency matrix W . The probability of a random walker at node i stepping to node j is given by $T_{ij} = W_{ij} / \sum_{n=1}^N W_{in}$. The expected number of hops $\langle H_{ij} \rangle$ a random walker takes to travel from node i to node j is given by (Fornito et al., 2016; Zhou, 2003):

$$\langle H_{ij} \rangle = \sum_{h=0}^{\infty} h P(H_{ij} = h) = \sum_{h=0}^{\infty} P(H_{ij} > h).$$

The probability of a walker requiring more than h hops to reach node j is equal to

the sum of the probabilities of the walker being at any node other than j after exactly h hops. To compute this, we define T_j as the matrix T with all elements in the j th column set to zero, so that it is impossible for a walker to arrive at node j . This way, we have $P(H_{ij} > h) = \sum_{n=1}^N [T_j^n]_{in}$, where $[T_j^n]_{in}$ expresses the probabilities of walkers departing from i and reaching any other node except j in exactly n hops. It follows that

$$\langle H_{ij} \rangle = \sum_{h=0}^{\infty} \sum_{n=1}^N [T_j^n]_{in} = \sum_{n=1}^N \left[(\mathbb{1} - T_j)^{-1} \right]_{in}.$$

Diffusion efficiency is defined as $E_{dif}(i, j) = 1/H_{ij}$, quantifying the expected communication efficiency of a random walker aiming to travel from nodes i to j (Goñi et al., 2013). Diffusion efficiency is explored in Chapters 4 and 5.

2.3.5 Search information

Search information is related to the probability of a random walker serendipitously travelling between two nodes via their shortest path (Rosvall et al., 2005). Hence, search information is a communication measure that combines the diffusion and shortest path routing models. Let $\{u, \dots, v\}$ be the sequence of nodes along the shortest path from node i to node j . The probability of a random walker travelling from i to j via this node sequence is given $P(i, j) = T(i, u) \times \dots \times T(v, j)$, where T is the previously defined transition probability matrix computed from W . Search information is typically defined as $SI(i, j) = -\log_2(P(i, j))$ (Goñi et al., 2014), providing a measure of the amount of information a biased random walker is required to follow the shortest path from i to j . The original formulation of search information provides a measure of the difficulty or cost of efficient diffusive communication. In keeping with the adoption of measures that quantify ease of signalling, we defined search information efficiency as $E_{si}(i, j) = -SI(i, j)$. We investigate search information in Chapters 4 and 5.

2.3.6 Communicability

Communicability proposes that neural information is broadcast along all possible walks in the network simultaneously (Estrada and Hatano, 2008). Communicability between

nodes i and j is defined as the weighted sum of the total number of walks between them, with each walk weighted by its length (i.e., number of connections traversed). This yields the sum $CMY(i, j) = \sum_{n=0}^{\infty} W(i, j)^n / n!$, which converges to $CMY(i, j) = e^{W(i, j)}$ as $n \rightarrow \infty$. A normalization process has been proposed to attenuate the influence of large connection weights prior to the computation of weighted communicability (Crofts and Higham, 2009). The normalized connectivity matrix W' is computed as $W'(i, j) = W(i, j) / (\sqrt{s(i)} \sqrt{s(j)})$, where $s(i) = \sum_{u=1}^N W(i, u)$ is the strength of node i . Connectome communicability is investigated in Chapter 5.

2.4 Statistical inference methods

The analyses carried out in this thesis rely on a host of statistical inference methods. Most tests and methods were implemented using standard parametric and non-parametric techniques. These included one- and two-sample t-tests and Wilcoxon rank sum tests, Pearson and Spearman correlation coefficients, Bonferroni correction for multiple comparisons, amongst others. An important inference technique for this thesis that deviates from classic statistical approaches is the non-parametric permutation test. In this section, we briefly describe the basic concept of permutation tests and highlight their role in statistical inferences based on null network models, a method central to the analyses of Chapters 3 and 4.

2.4.1 Non-parametric permutation testing

Permutations tests construct a distribution of test statistics under a null hypothesis by considering all (exact test) or several permutations of the empirically observed data. Permutations are implemented in different ways depending on the nature of the data at hand and the null hypothesis being evaluated. For instance, differences between the means of two groups of random variables can be determined by permuting data points' group labels. For each random permutation of group labels, the difference between the means of randomly permuted groups is computed. Repeating this procedure several times results in a null distribution of differences, characterizing the probability of observing a certain

value of mean differences when group labels are randomly permuted across observations. The null hypothesis of lack of statistical difference between the groups' means can be assessed by a p-value computed as the proportion of permutations resulting in larger group differences than the one observed for the empirical groups. Importantly, this approach is non-parametric and does not entail the common assumptions of parametric statistical tests, such as normality requirements.

2.4.2 Null connectome models

Null connectomes (also referred to as randomized network models) are commonly used to determine if a property of interest can be explained by certain organizational traits of the connectome (Fornito et al., 2016; Rubinov, 2016; Rubinov et al., 2015). A typical null model analysis is carried out as follows. First, a property of interest is computed based on the empirical connectome. This could be a property of the connectome itself (e.g., communication efficiency under a given signalling strategy) or a relationship between the connectome and another variable (e.g., the correlation between communication efficiency and a measure of cognition). Next, the connectome topology is disrupted by randomly swapping connections between nodes. Importantly, partial randomizations can rewire the network while leaving certain topological properties intact. For instance, the Maslov-Sneppen algorithm (Maslov and Sneppen, 2002) randomizes the topology of a network while preserving its original degree distribution. This procedure can be repeated multiple times to generate an ensemble of random networks with the same original degree distribution. We can compute the variable of interest for each random network in the ensemble, obtaining a null distribution. Comparing the values of the null distribution with the empirical variable measurement determines whether the randomized networks are capable of replicating the results observed for the original connectome. This comparison is implemented as a non-parametric permutation test. A significant difference between the null distribution and the empirical measurement is evidence that the topological property preserved in the random network ensemble is not explanatory of the observed property of interest.

Three main types of null connectome models were used in this thesis: (i) topologi-

cally randomized (rewired) networks, (ii) spatially randomized networks with preserved topology, and (iii) topologically randomized networks with preserved network cost. All three randomization procedures preserved the degree distribution and network connection density of the original connectomes. Rewired null networks (i) were built using the Brain Connectivity Toolbox implementation of the Maslov-Sneppen routine (Rubinov and Sporns, 2010). Spatially randomized networks (ii) were constructed by randomly permuting the spatial positioning of brain region centroids while leaving connectome topology unaltered. Network cost was operationalized as the sum of the Euclidean distances between anatomically connected nodes, providing a proxy for the metabolic cost associated with building and maintaining white matter connections (Betz et al., 2016; Bullmore and Sporns, 2012). Cost-preserving rewired networks (iii) were obtained by modifying the topological randomization of routine (i). Connection swaps continued to be selected at random, but were only carried out if they did not alter the total network cost by more than a user defined threshold (set to 1mm). Further details on null network model implementations and analyses are found in Chapters 3 and 4.

Chapter 3

Navigation of brain networks



Navigation of brain networks

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Understanding the mechanisms of neural communication in large-scale brain networks remains a major goal in neuroscience. We investigated whether navigation is a parsimonious routing model for connectomics. Navigating a network involves progressing to the next node that is closest in distance to a desired destination. We developed a measure to quantify navigation efficiency and found that connectomes in a range of mammalian species (human, mouse, and macaque) can be successfully navigated with near-optimal efficiency (>80% of optimal efficiency for typical connection densities). Rewiring network topology or repositioning network nodes resulted in 45–60% reductions in navigation performance. We found that the human connectome cannot be progressively randomized or clustered to result in topologies with substantially improved navigation performance (>5%), suggesting a topological balance between regularity and randomness that is conducive to efficient navigation. Navigation was also found to (i) promote a resource-efficient distribution of the information traffic load, potentially relieving communication bottlenecks, and (ii) explain significant variation in functional connectivity. Unlike commonly studied communication strategies in connectomics, navigation does not mandate assumptions about global knowledge of network topology. We conclude that the topology and geometry of brain networks are conducive to efficient decentralized communication.

connectome | neural communication | network navigation | complex networks

Nervous systems are networks and one of the key functions of a network is to facilitate communication. Complex topological properties such as small worldness (1, 2), modularity (3), and a core of highly interconnected hubs (4) are universally found across the brain networks of advanced and simple species, including mouse (5, 6), macaque (7, 8), and human connectomes (9). Support for efficient communication between neuronal populations is conjectured to be one of the main adaptive advantages behind the emergence of these complex organizational properties (10, 11).

Understanding how neural information is routed and communicated through complex networks of white matter pathways remains an open challenge for systems neuroscience (12, 13). To date, connectomics has largely focused on network communication based on optimal routing (14, 15), which proposes that information traverses the shortest path between two nodes. However, identifying shortest paths requires individual elements of nervous systems to possess global knowledge of network topology. This requirement for centralized knowledge has been challenged on the basis that nervous systems are decentralized, motivating alternative models of large-scale neural communication, such as spreading dynamics (11), path ensembles (16), communicability (17, 18), and diffusion models (19–21). These studies indicate that brain networks may support efficient communication without the need for centralized knowledge. For instance, random walkers can be biased to travel via efficient routes (22) and shortest paths help facilitate fast spreading of local stimuli (11).

Navigation is a network communication strategy that routes information based on the distance between network nodes (23). Navigating a network is as simple as progressing to the next node that is closest in distance to a desired target. Navigation is not guaranteed to successfully reach a target destination. Moreover, targets might be reached using long, inefficient paths. However, several real-world networks are known to be efficiently navigable, including biological, social, transportation, and technological systems (24–26). Successful navigation depends on certain topological properties such as small worldness (23) and a combination of high clustering and heterogeneous degree distribution (24), all of which are found in the brain networks of several species (9).

Here, we comprehensively investigate the feasibility of navigation routing as a model for large-scale neural communication. We develop a measure of navigation efficiency and apply it to publicly available connectomics data acquired from the macaque, mouse, and human brain. We find that brain networks are highly navigable, with connectome topology well poised between regularity and randomness to facilitate efficient navigation. In addition, we characterize the centrality of nodes and connections under navigability and investigate the relation

Significance

We show that the combination of topology and geometry in mammalian cortical networks allows for near-optimal decentralized communication under navigation routing. Following a simple propagation rule based on local knowledge of the distance between cortical regions, we demonstrate that brain networks can be successfully navigated with efficiency that is comparable to shortest paths routing. This finding helps to conciliate the major progress achieved over more than a decade of connectomics research, under the assumption of communication via shortest paths, with recent questions raised by the biologically unrealistic requirements involved in the computation of optimal routes. Our results reiterate the importance of the brain's spatial embedding, suggesting a three-way relationship between connectome geometry, topology, and communication.

Author contributions: C.S. and A.Z. designed the research; C.S. and A.Z. performed research; C.S. and A.Z. contributed new reagents/analytic tools; C.S. and A.Z. analyzed data; and C.S., M.P.v.d.H., and A.Z. wrote the paper.

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Data deposition: All data analyzed in this work are publicly available. Human data are from the Human Connectome Project (<https://db.humanconnectome.org/>); macaque data can be found at core-nets.org/; and mouse data were gathered from the following publicly available resources: connectivity.brain-map.org/; developingmouse.brain-map.org/; and mouse.brain-map.org/.

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between navigation path lengths and functional connectivity (FC) inferred from resting-state functional magnetic resonance imaging (MRI). Compared with shortest path routing, we find that navigation uses the brain's resources more uniformly and yields stronger correlations with FC.

Results

Navigation Performance Measures. We consider neural communication from the graph-theoretic standpoint of delineating paths (routes) in the connectome between pairs of nodes (gray matter regions). A routing strategy defines a set of rules for identifying a path from a source node to a target node. Path length refers to the number of connections that compose a path (hops) or the sum across the lengths of these connections. To minimize conduction latency, noise introduced by synaptic retransmission, and metabolic costs, neural communication should take place along paths with short path lengths (12, 13).

Navigation is a decentralized communication strategy that is particularly suited to spatially embedded networks (24, 25). Navigating a network involves following a simple rule: Progress to the next directly connected node that is closest in distance to the target node and stop if the target is reached (Fig. 1). To implement navigation, we defined the distance between pairs of nodes as the Euclidean distance between node centroids (27, 28). Importantly, navigation can fail to identify a path. This occurs when a navigation path becomes trapped between nodes without neighbors closer to the destination than themselves (Fig. 1B). The success ratio (S_R) measures the proportion of node pairs in a network that can be successfully reached via navigation.

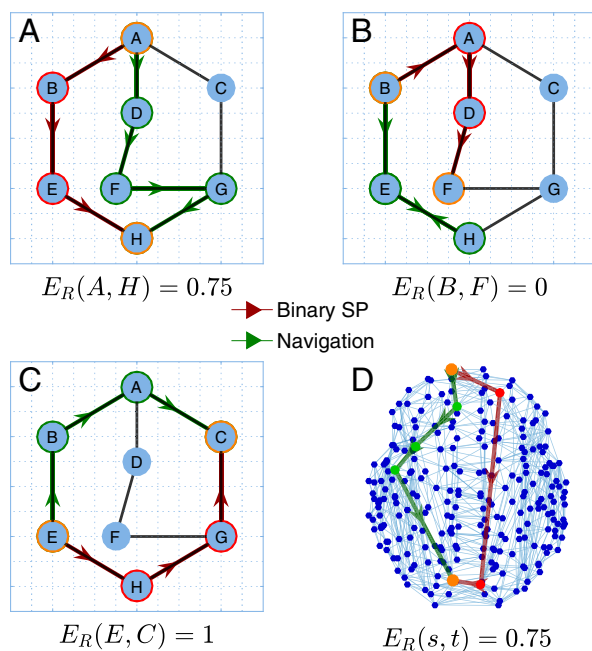


Fig. 1. Illustrative examples of navigation (green) and shortest (red) paths from a source to the target node (circled in orange) in a binary network. Grid indicates spatial embedding of the networks. Efficiency ratios ($E_R(i, j)$) are the ratio of the number of hops in the navigation path to the number of hops in the shortest path. (A) The shortest path between A and H has three hops (A-B-E-H) while navigation leads to a four-hop path (A-D-F-G-H). Navigation routes information from A to H at 75% of optimal efficiency. (B) Navigation fails to find a path from B to F, becoming trapped between E and H. (C) Both strategies lead to three-hop paths, and navigation routes information from G to B at 100% of optimal efficiency. (D) Example of a successful navigation path in the human connectome that achieves 75% efficiency.

Let $L \in \mathbb{R}^{N \times N}$ denote a matrix of connection lengths for a network comprising N nodes, where L_{ij} measures the length of the connection from node i to j , and let Λ denote the matrix of navigation path lengths. If node i cannot navigate to node j , $\Lambda_{ij} = \infty$. Otherwise, $\Lambda_{ij} = L_{iu} + \dots + L_{vj}$, where $\{u, \dots, v\}$ is the sequence of nodes visited during navigation. We define navigation efficiency as $E = 1/(N^2 - N) \sum_{i \neq j} 1/\Lambda_{ij}$. Analogous to global efficiency (29) [$E^* = 1/(N^2 - N) \sum_{i \neq j} 1/\Lambda_{ij}^*$, where Λ_{ij}^* is the shortest path length from node i to j], both measures characterize the efficiency of information exchange in a parallel system in which all nodes are capable of concurrently exchanging information. In the same way that global efficiency can incorporate network disconnectedness, navigation efficiency incorporates unsuccessful navigation paths ($E_{ij} = 0$ if i cannot reach j under navigation). Therefore, E quantifies both the number of failed paths and the efficiency of successful paths. We defined the efficiency ratio

$$E_R = \frac{1}{N^2 - N} \sum_{i \neq j} \frac{\Lambda_{ij}^*}{\Lambda_{ij}} \quad [1]$$

to compare navigation with shortest path routing. For any network, $E^* \geq E$ and thus $0 \leq E_R \leq 1$. The closer E_R is to 1, the better navigation is at finding paths that are as efficient as shortest paths (Fig. 1).

We focus on binary (E_R^{bin}) and weighted (E_R^{wei}) navigation efficiency ratios, quantifying how efficient navigation paths are compared with shortest paths computed on binarized and weighted connectomes, respectively. In addition, we compute E_R^{dis} to determine how close navigation paths are to routes that minimize the sum of physical (Euclidean) connection distances traversed between nodes.

Navigability of the Human Connectome. High-resolution diffusion MRI data from 75 healthy participants of the Human Connectome Project (HCP) (30) were used to map structural brain networks at several spatial resolutions ($N = 256, 360, 512, 1,024$). Whole-brain tractography was performed for each individual and the number of streamlines interconnecting each pair of nodes was enumerated to provide a measure of structural connectivity (SI Appendix, Connectivity Data). A group-level connectome was computed as the average of all individual connectivity matrices (22). Connection weights were remapped into binary, weighted, and distance-based connection lengths to allow for the computation of communication path lengths (SI Appendix, Network Analysis).

Consistent with previous reports (24, 25), we found that navigation can successfully identify paths for the majority of nodes pairs composing the human connectome ($S_R = 89\%$, 94% , and 96% for 10% , 15% , and 20% connection density, respectively, $N = 360$; Fig. 2A). Remarkably, navigation was only marginally less efficient than shortest paths (e.g., $E_R^{\text{wei}} = 72\%$, $E_R^{\text{bin}} = 83\%$, and $E_R^{\text{dis}} = 83\%$, for $N = 360$ at 15% connection density; Fig. 2B–D), with navigation performance improving as connection density increased. Note that navigation does not use connection weights, and thus E_R^{wei} quantifies the extent to which navigation can blindly identify weighted shortest paths. Navigation remained efficient and successfully identified paths for the majority of node pairs across various parcellation resolutions (SI Appendix, Fig. S1), with moderate decreases in success and efficiency ratios as the number of nodes increased ($S_R = 95\%$, 91% , and 90% and $E_R^{\text{bin}} = 84\%$, 80% , and 81% for $N = 256, 512$, and $1,024$, respectively, at 15% connection density; Fig. 2E). When stratified by hop count, navigation performance remained high for long, multihop paths (61% median E_R^{wei} and 79% median E_R^{dis} benchmarked against five-hop shortest paths; Fig. 2F and

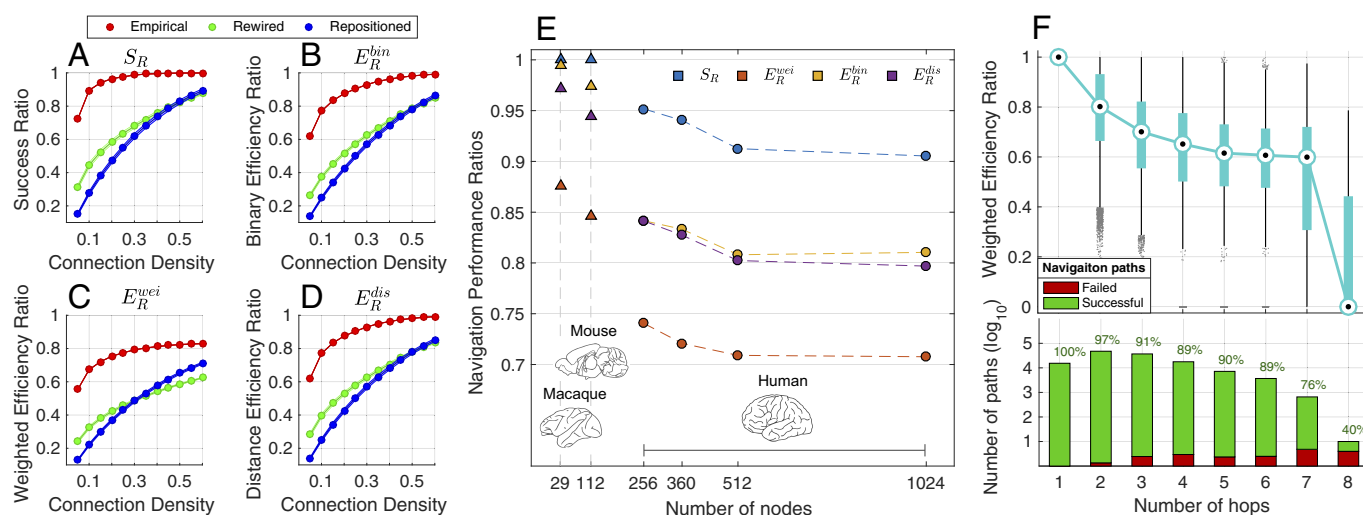


Fig. 2. Navigability of mammalian connectomes. (A–D) Success ratio (S_R), binary efficiency ratio (E_R^{bin}), weighted efficiency ratio (E_R^{wei}), and distance efficiency ratio (E_R^{dis}) for human connectomes ($N=360$) at several connection density thresholds. Empirical measures (red) for group-averaged connectomes were compared with 1,000 rewired (green) and spatially repositioned (blue) null networks. Shading indicates 95% confidence intervals. (E) The same performance metrics shown across different parcellation resolutions of mammalian structural networks (S_R shown in blue, E_R^{wei} in orange, E_R^{bin} in yellow, and E_R^{dis} in purple). Triangles denote nonhuman species while circles denote human data. Dashed lines denote the same connection density (15%) across all human networks. (F) Navigability stratified by hop count ($N=360$ at 15% connection density). Blue box plots indicate the quartiles of E_R^{wei} navigation paths benchmarked against shortest paths with matching hop count. Bar plots show the number of shortest paths for a given hop count, with colors indicating the proportion of successful (green) and failed (red) navigation paths. Brain diagrams reproduced from ref. 9, with permission from Elsevier.

(SI Appendix, Fig. S2), suggesting that navigation efficiency is not due to directly connected node pairs or node pairs that can be navigated in only a few hops.

Having established that the human connectome can be successfully and efficiently navigated, we next sought to determine whether efficient navigation is facilitated by the connectome's topology or its spatial embedding. Navigation performance was benchmarked against ensembles of random null networks in which (i) the spatial position of nodes was shuffled; (ii) connectome topology was randomized (31); or (iii) connectome topology was randomized while preserving total network cost, defined as the sum of Euclidean distances between structurally connected nodes (10, 28) (SI Appendix, Network Analysis). Navigability of both the spatial and topological null networks was markedly reduced in comparison with the empirical networks (46% and 60% decrease in E_R^{bin} and 48% and 60% decrease in E_R^{wei} , for topological and spatial randomization, respectively, at 15% connection density; Fig. 2A–D, blue and green curves). In contrast, cost-preserving topological randomization resulted in null networks that, although significantly less navigable than the human connectome ($P < 10^{-4}$; 13% and 11% decrease in E_R^{bin} and E_R^{wei} , respectively, at 15% connection density; SI Appendix, Fig. S3), showed greater navigation performance than the less constrained null models. Taken together, these results suggest that navigation is jointly facilitated by both the connectome's topology and its geometry. Randomization of either of these attributes markedly impeded navigation, while restricting topological randomization to realistic spatial embeddings accounted for a large extent of empirical navigation performance.

These findings were robust to variations in node distance measures and streamline count normalizations (SI Appendix, Supplementary Analyses and Figs. S4 and S5). Navigation performance of individual connectomes was comparable to the performance determined for the group-averaged connectome (SI Appendix, Fig. S6). Furthermore, navigation performance significantly deteriorated with age (SI Appendix, Fig. S7 and Table S1), but did not differ between males and females (SI Appendix, Fig. S8).

Navigability of Nonhuman Mammalian Connectomes. Invasive tract-tracing studies provide high-quality connectomes for a number of nonhuman species (9). We aimed to determine whether a 112-region mouse connectome (52% connection density) (5, 6) and a 29-region macaque connectome (66% connection density) (8) were navigable. Navigation performed with $S_R = 100\%$ and near-optimal communication efficiency for both species ($E_R^{bin} = 99\%, 97\%$; $E_R^{dis} = 97\%, 94\%$; and $E_R^{wei} = 87\%, 84\%$, for the macaque and mouse, respectively; Fig. 2E). As with the human connectome, navigation performance was significantly increased compared with the topologically rewired and spatial null networks (all $P < 10^{-4}$, with the exception of $P=0.012$ and $P=0.002$ for the macaque S_R of topological and spatial null networks, respectively). However, the null hypothesis of equality in navigation performance between the connectomes of both species and the cost-preserving null networks could not be rejected (SI Appendix, Fig. S9).

The efficient navigation of connectomes across a variety of species, scales, and mapping modalities suggests that the topology and spatial embedding of nervous systems is conducive to efficient decentralized communication.

Connectome Topology and Navigation Performance. We sought to explore the impact of progressive topological alterations on the navigability of the human connectome. First, we tested whether navigation efficiency can be improved by progressively altering the topology of the human connectome to either increase its regularity (clusterize) or increase its randomness and wiring cost. Randomization was performed by progressively swapping connections between randomly chosen node pairs, while preserving connection density and degree distribution (31). With sufficient iterations, this yielded the topologically randomized null networks shown in Fig. 2A–D (green curves). To clusterize topology, the same procedure was used with the additional constraint that each connection swap must lead to an increase in the overall clustering coefficient. Applying these procedures generated two sets of networks that progressively tended toward different ends of an order spectrum, ranging from orderly and

regular networks with a high clustering coefficient to disordered and costly random networks (*SI Appendix, Network Analysis*). Clusterization was found to progressively decrease navigation efficiency, whereas slight randomization of connectome topology yielded networks with marginal increases in navigation performance (Fig. 3A). Specifically, peak E_R^{wei} was, on average, 0.8%, 1.4%, and 4.7% more efficient than the connectome after 4.0%, 3.3%, and 4.8% of connections were randomly swapped, for $N = 256, 360, 512$, respectively. Further randomization beyond these peaks resulted in deterioration of navigation efficiency. Similar results were found for E_R^{bin} (*SI Appendix, Fig. S10*).

Next, we investigated the effects of connectome rewiring aimed to explicitly increase navigability. To this end, we progressively performed connection swaps between randomly chosen node pairs that (i) preserved connection density and degree distribution, (ii) led to an increase of a measure of navigation performance, and (iii) preserved total network cost. We performed a total of 2×10^6 connection swap attempts, with rejection of swaps that did not simultaneously meet all three conditions. Direct optimization of network navigability led to an 18–20% increase in E_R^{wei} , with 16–18% of the improvement taking place in the first 10^6 swap attempts. Therefore, increasing connectome navigability rapidly became more difficult as a function of swap attempts, suggesting that the observed improvements converge to an asymptote. Comparable improvements between 5% and 22% were found for other measures of navigation performance (*SI Appendix, Fig. S11*). Collectively, these results indicate that the human connectome is well poised between randomness and regularity to facilitate efficient navigation, while explicit optimization by connectome rewiring converges to 5–22% improvements in navigability.

Navigation Centrality. The number of shortest paths that traverse a node defines its betweenness centrality (BC), a measure that finds utility in identifying connectome hub nodes (12) and nodes mediating the bulk of neural communication (7). We defined a new path-based centrality measure called navigation centrality (NC), which quantifies the number of successful navigation paths that traverse each node (*SI Appendix, Network Analysis*).

We computed NC and BC for the human connectome (group average, $N = 360$, at 15% connection density), with BC based on weighted shortest paths. We found that both NC and BC spanned four orders of magnitude and were positively corre-

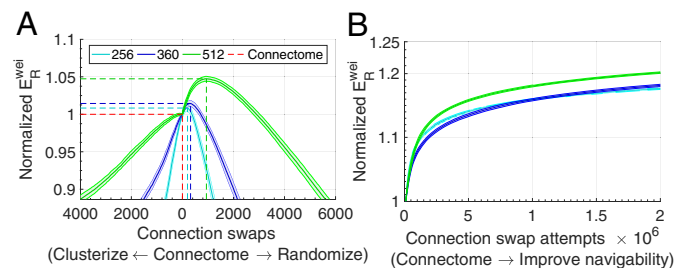


Fig. 3. Navigation performance (E_R^{wei}) of progressively rewired connectome topologies (at 15% connection density). The E_R^{wei} of rewired topologies was normalized by the empirical value found for the human connectome. Curves indicate the mean values (inner line) and 95% confidence intervals (outer shadow) obtained from several runs of the rewiring routines. (A) Normalized E_R^{wei} of clusterized and randomized networks for 100 runs of the randomization–clusterizing procedure and different parcellation resolutions. Dashed lines show performance peaks (vertical axis) and number of connection swaps (horizontal axis), with red indicating the values obtained for the empirical brain. (B) Normalized E_R^{wei} obtained from direct optimization of the connectome’s empirical E_R^{wei} , as a function of connection swap attempts, for 50 ($N = 256$), 50 ($N = 360$), and 30 ($N = 512$) independent rewiring runs.

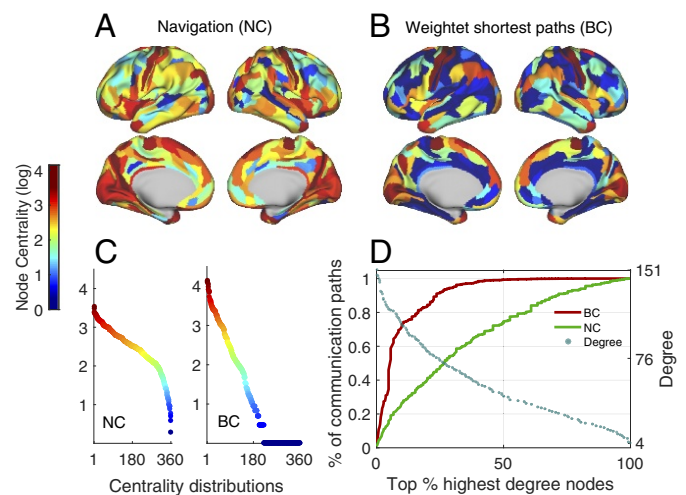


Fig. 4. Comparison between navigation (NC) and weighted betweenness (BC) node centralities for $N = 360$ at 15% connection density. Centrality values are logarithmically scaled. (A and B) NC (A) and BC (B) projected onto the cortical surface. (C) NC (Left) and BC (Right) sorted from highest to lowest values. (D) Relationship between the cumulative sum of centrality measures and degree. The horizontal axis is a percentage ranking of nodes from highest to lowest degree (e.g., for $N = 360$, the 10% most connected nodes are the 36 nodes with highest degree). Solid curves (left-hand vertical axis) represent the cumulative sum of BC (red) and NC (green) over all nodes ordered from most to least connected, divided by the total number of communication paths in the network, indicating the fraction of communication paths mediated by nodes. Blue dots (right-hand vertical axis) show the original degree associated with each percentage of most-connected nodes.

lated (Pearson correlation coefficient $r = 0.54$). Several regions were central to both shortest paths (BC) and navigation (NC), including portions of the left and right superior frontal gyrus, insula, central gyri, and precuneus (Fig. 4A and B). However, NC was more uniformly distributed across nodes compared with BC, suggesting that navigation uses network resources more homogeneously (Fig. 4C). High values of BC were found only in a small group of high-degree nodes ($r = 0.86$ between logarithm of BC and degree), which mediated most of the network’s communication routes. For instance, 99.3% of all shortest paths traveled exclusively through the top 50% most connected nodes (Fig. 4D). In contrast, although high-degree nodes showed high NC ($r = 0.61$ between logarithm of NC and degree), medium- and low-degree regions were responsible for mediating a share of navigation paths, with the 50% least-connected nodes responsible for 26% of navigation paths. Greater diversity in paths may lead to fewer communication bottlenecks and less signal congestion (32), as well as stronger resilience against failure of network elements (16, 33). Similar results were obtained for BC computed in binarized connectomes (*SI Appendix, Fig. S12*) and for edge-centric definitions of BCs and NCs (*SI Appendix, Fig. S13*). All correlation coefficients (r) were significant ($P < 10^{-8}$).

Navigation and Functional Connectivity. Finally, we tested whether navigation path lengths can explain variation in functional connectivity across nodes pairs of the human connectome. The strength of functional connectivity between node pairs that are not directly connected can be attributed to signal propagation along multisynaptic (multihop) paths (22, 34). Therefore, if multihop neural communication is indeed facilitated by navigation, we hypothesized that navigation path lengths should be inversely correlated with functional connectivity strength. Resting-state functional MRI data from the same 75 participants of the HCP were used to map functional brain networks. A group-averaged

functional network was obtained by averaging FC across all participants (*SI Appendix, Connectivity Data*).

Given the geometric nature of navigation, an intuitive definition of navigation path length is the total distance traveled from one node to another along the navigation path (*SI Appendix, Network Analysis*). Navigation path lengths and FC were significantly associated across node pairs (*SI Appendix, Fig. S14*), with Pearson correlation coefficient $r = -0.32$ and $r = -0.43$, for the whole brain and right hemisphere, respectively, for $N = 360$ at 15% connection density. This relationship was consistent across density thresholds, with navigation path lengths yielding stronger correlations with FC than shortest path lengths ($r = -0.35$, right hemisphere) and the direct Euclidean distance between node pairs ($r = -0.40$, right hemisphere). Correlations with navigation path lengths remained significant when stratified by structurally connected ($r = -0.51$, right hemisphere) and unconnected ($r = -0.28$, right hemisphere) node pairs. All correlations remained significant when interregional Euclidean distances were regressed from navigation path lengths and the resulting residuals correlated with FC ($P < 10^{-5}$).

Discussion

This study investigated navigation as a model for large-scale neural communication. Using a measure of navigation efficiency, we evaluated the navigability of a range of mammalian connectomes. We found multiple lines of evidence suggesting that the topology (wiring) and spatial embedding (geometry) of nervous systems is conducive to efficient navigation. Our measure of navigation centrality indicated that navigation uses network resources more uniformly compared with shortest paths. We conclude that navigation is a viable neural communication strategy that does not mandate the centralized knowledge assumptions inherent to shortest paths, nevertheless achieving near-optimal routing efficiency.

Navigation performance was assessed for binary, weighted, and distance-based connectomes, each emphasizing a distinct attribute of network communication. While binary and weighted brain networks are commonly used in connectomics (12), distance-based connectomes were introduced to provide a geometric benchmark for navigation efficiency. Interestingly, navigation paths were simultaneously efficient in all three regimes, suggesting that neural signaling may favor communication routes that combine few synaptic crossings (binary), high axonal strength and reliability (weighted), and short propagation distances (distance based).

The topology of the human connectome was found to be well poised between regularity and randomness to promote efficient decentralized communication. While our focus on this order spectrum was motivated by canonical work on brain and real-world networks (1, 10), other dimensions of connectome topology such as degree diversity or hierarchical structure could be investigated (35). In fact, progressive rewiring explicitly seeking to optimize navigation indicates that connectome topology has a 5–22% margin for improvement in navigability. These findings support the notion that communication efficiency was likely only one of several evolutionary pressures that shaped connectome architecture (10, 13) (*SI Appendix, Supplementary Analyses*).

The significant association between navigation and FC is further evidence that neural communication is not necessarily constrained to optimal routes (22). This association could not be entirely attributed to navigation path lengths approximating interregional distances. Therefore, our findings build on previous work on the relationship between Euclidean distance and FC (27, 36), indicating that the combination of topological and geometric distances may contribute to the relationship between brain structure and function. Alternative formulations of interregional distances taking into account fiber-tract length or tract myelination could improve the biological relevancy of node

distances, potentially improving the association between navigation path lengths and FC.

Connectome Geometry, Topology, and Communication. Several recent studies have drawn attention to the link between geometry and topology in neural and other real-world networks (24, 27, 28). Our findings indicate that the interplay between connectome geometry and topology may be relevant for neural communication: The association between network geometry and topology (28, 37) contributes to the appearance of topological attributes conducive to navigation (24, 26), while the spatial positioning of nodes guides navigation of the topology, facilitating efficient decentralized communication. This notion is supported by our analyses of the navigation performance of different null models. Randomization of either connectome topology or geometry was sufficient to render connectomes less navigable, while topological randomizations that preserved characteristics of connectome geometry led to marked improvements in the navigability of null networks (see *SI Appendix, Supplementary Analyses* for further discussion).

Successful navigation has been linked to small-world topologies that combine spatially separated hubs and high-clustering coefficients (23, 24). Hub-to-hub long-range connections facilitate rapid information transfer across distant regions of the brain (although see ref. 38 for a counterpoint), while high clustering enables navigation to home in on specific destinations (4, 24) (*SI Appendix, Fig. S15*). This mechanism for information transfer is consistent with observations suggesting that nervous systems are small-world networks, balancing integration supported by long-range connections and segregation due to locally clustered modules (10).

Biological Plausibility and Communication Efficiency. To date, the study of brain network organization has been anchored to the assumption of communication under shortest path routing (12, 15). Two examples are the characterization of the brain as a small-world network (1, 2) and the use of global efficiency as a measure of network integration (10, 14). These topological properties are derived from the shortest paths between all pairs of nodes. Building on previous work suggesting that efficient neural communication may take place in a decentralized manner (11, 22), we found that navigation can approximate the overall efficiency of shortest paths without requiring centralized knowledge of global network topology. Thus, we provide reassurance that previous findings obtained under the shortest paths assumption remain pertinent, despite the biologically implausible requirements for the computation of optimal routes, and reaffirm the importance of the brain's small-world architecture in the light of decentralized routing schemes.

Navigation depends on network nodes possessing information about the relative spatial positioning between their direct neighbors and a target node. While the biological mechanisms that might endow nodes with this spatial information remain unclear, it is important to remark that navigation demands less information about network topology than shortest path routing and thus requires fewer assumptions to support its biological plausibility. Hence, in terms of biological plausibility, navigation occupies a middle ground between shortest paths and other decentralized models such as communicability (17, 18) and diffusion processes (19–21), which mandate fewer assumptions. However, navigation is near-optimally efficient and metabolically parsimonious (information is routed through a single path), thus overcoming important shortcomings of diffusion (39) and communicability (13) models, respectively.

Future research on large-scale neural communication models is necessary to explore alternative decentralized, efficient, and parsimonious network communication strategies. Exploring alternative spatial embeddings of brain networks (e.g., in

hyperbolic space) may provide further insight into the navigability of nervous systems across species (40). In parallel, brain stimulation techniques could be used to evaluate evidence for competing communication strategies by means of electrophysiological tracking of local perturbations (41, 42).

Materials and Methods

Details on the acquisition and preprocessing of network datasets are described in *SI Appendix, Connectivity Data*. *SI Appendix, Network Analysis* provides details on network modeling. Supporting and replication analyses are presented in *SI Appendix, Supplementary Analyses*.

Navigation Implementation. For a network with N nodes, navigation routing from node i to j was implemented as follows. Determine which of i 's neighbors is closest (shortest Euclidean distance) to j and progress to it. Repeat this process for each new node until j is reached—constituting a successful navigation path—or a node is revisited—constituting a failed navigation path.

Navigation paths are identified based on network topology and the spatial positioning of nodes and thus independent from how connection lengths are defined. Navigation path lengths, however, are the sum of connection lengths composed in navigation paths and will vary depending on

the definition of L . The matrix of navigation path lengths Λ was computed by navigating every node pair. Note that Λ is asymmetric, requiring $N^2 - N$ navigation path computations. Using different connection length measures (L^{bin} , L^{wei} , L^{dis}), we computed binary (Λ^{bin}), weighted (Λ^{wei}), and distance-based (Λ^{dis}) navigation path lengths. Navigation efficiency ratios (E_R^{bin} , E_R^{wei} , E_R^{dis}) were computed by comparing navigation path lengths to shortest path lengths (Λ^{bin*} , Λ^{wei*} , Λ^{dis*}) using Eq. 1.

Data Sharing. Human, macaque, and mouse datasets are publicly available. Our implementation of navigation routing is available at <https://github.com/caioseguin/connectomics/>.

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Supporting Information: Navigation of brain networks

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Overview

This supporting document provides details on the acquisition and preprocessing of the analyzed connectivity data. We also provide descriptions of the network measures and methods applied throughout this work. Finally, we include supplementary and replication analyses that indicate the robustness and universality of the results reported in the main manuscript. Figure numbering is with respect to the ordering of references in the main manuscript.

Materials and Methods

Connectivity data

Mouse. The Allen Institute for Brain Science mapped the mesoscale topology of the mouse nervous system by means of anterograde axonal injections of a viral tracer [1]. Using two-photon tomography, they identified axonal projections from the 469 injections sites to 295 target regions. Building on these efforts, Rubinov and colleagues constructed a bilaterally symmetric whole-brain network for the mouse, comprising $N = 112$ cortical and subcortical regions with 53% connection density [2]. Connections represent interregional axonal projections and their weights were determined as the proportion of tracer density found in target and injected regions. Connection weights followed a log-normal distribution and graph-theoretical analyses of the constructed topology revealed many organisational similarities to the human connectome.

Macaque. Markov and colleagues applied 1615 retrograde tracer injections to 29 of the 91 areas of the macaque cerebral cortex, spanning occipital, temporal, parietal, frontal, prefrontal and limbic regions [3, 4]. This resulted in a 29×29 directed interregional sub-network of the macaque cortico-cortical connections. Connection weights were estimated based on the number of neurons labelled by the tracer found in source and target regions, relative to the amount found in whole brain. In line with other tract-tracing studies, the network showed high connection density (66%) and weights were distributed log-normally.

Human data acquisition and preprocessing. Minimally preprocessed diffusion weighted MRI data from 75 unrelated healthy participants (age 22–35, 40 females) was obtained from the Human Connectome Project (HCP) ¹ [5]. Spin-echo planar diffusion weighted imaging was performed in a customized Siemens Skyra 3T scanner according to the following parameters: 5520 ms repetition time, 89.5 ms echo time, 78 degree flip angle, 160 degree refocusing flip angle, 210×180 mm field of view, 168×144 matrix, 1.25 mm isotropic voxels, 3 shells of $b=1000, 2000$ and 3000 s/mm² and approximately 90 diffusion weighted directions per

¹HCP participants ID: 100206, 100307, 100408, 101006, 101107, 101309, 101915, 102109, 102513, 102614, 102715, 102816, 103111, 103212, 103414, 103515, 103818, 104012, 105014, 105115, 105216, 105620, 106016, 106319, 106521, 106824, 107018, 107321, 107422, 107725, 108020, 108121, 108222, 108323, 108525, 108828, 109123, 109830, 110007, 110411, 110613, 111009, 111211, 111312, 111413, 111716, 112112, 112314, 112516, 112920, 113215, 113316, 113619, 113922, 114217, 100610, 102311, 104416, 118225, 105923, 111514, 114823, 115017, 125525, 128935, 131722, 140117, 146129, 146432, 155938, 156334, 157336, 158035, 158136, 162935.

gradient table. The obtained diffusion images were submitted to the HCP diffusion pre-processing pipeline [6] consisting of: 1) b_0 intensity normalization, 2) top-up EPI distortion correction, 3) Eddy current distortions and subject motion correction, 4) gradient distortion correction and 5) resampling to 1.25mm native structural space. Refer to [6, 7] for further details on HCP diffusion MRI acquisition and preprocessing.

Minimally preprocessed resting-state functional MRI data from the same 75 participants was also obtained from the HCP. Data acquisition consisted of four 14m33s runs, two runs (right-to-left and left-to-right phase encodings) in one session and two in another session, with eyes open with relaxed fixation on a projected bright cross-hair on a dark background (and presented in a darkened room). Data collection was performed in a customized Siemens Skyra 3T scanner according to the following parameters: gradient-echo EPI sequence, 720 ms TR, 33.1 ms TE, 52 degree flip angle, 208×180 mm FOV, 104×90 matrix, 2.0 mm slice thickness, 72 slices, 2.0 mm isotropic voxels, 8 multiband factor and 0.58 ms echo spacing. Acquired images were preprocessing according to the HCP functional preprocessing pipeline [6], which involves: 1) spatial and gradient distortion corrections, 2) correction of head movement, 3) intensity normalization 4) single spline re-sampling of EPI frames into 2mm isotropic MNI space and 5) HCP’s FIX+ICA pipeline for the removal of temporal artefacts. Refer to [6, 8] for further details on HCP resting-state functional MRI acquisition and preprocessing.

Human cortical parcellation. Connectome analyses are sensitive to the number of nodes used to reconstruct brain networks [9]. In order to assess the validity of our results across connectomes defined over different granularities of cortical segmentations, we generated parcellations of the human cerebral cortex containing $N = 256, 512, 1024$ regions. In addition, we also mapped connectomes using the Glasser Atlas [10], a multi-modal cortical parcellation built from the combination of structural, diffusion and functional imaging data from HCP participants.

We developed an algorithm to generate high-resolution cortical parcellations by means of sub-dividing an input low-resolution parcellation. Starting from a well established anatomical atlas ($N = 68$) [11] defined on FreeSurfer’s (<https://surfer.nmr.mgh.harvard.edu/>) *fsaverage* cortical sheet, each surface region was subdivided according to three criteria: (i) the resulting number of regions is specified by the user as a power of 2; (ii) subdivisions must respect the original anatomical boundaries, so that all resulting parcels can be attributed to a single anatomical structure; and (iii) each resulting sub-region has approximately the same surface area. Criterion (i) allows for a systematic investigation of the robustness of graph theory measures to variations in parcellation resolution. Criterion (ii) ensures that the resulting parcellation comprises biologically meaningful regions that can be assigned to a single anatomical input region. Finally, criterion (iii) minimizes tractography biases related to the surface area and volume of regions. Importantly, defining the parcellations over the cortical surface ensures that every grey matter region has an interface with white matter, making it accessible to tractography streamlines.

Input low-resolution regions were divided based on their size (number of vertices in the cortical sheet mesh) and the desired number of high-resolution output regions. Large input regions originated many output regions, while small input regions gave rise to few output regions. K-means++ [12] applied to the spatial coordinates of vertices was used to perform region division, leading to evenly sized, spatially contiguous, tile-shaped output regions (Fig. S16). The resulting cortical surface parcellations were registered to native

subject space and projected into parcellation volumes using Connectome Workbench (<https://www.humanconnectome.org/software/connectome-workbench>, [13]).

While cortical regions are commonly defined in terms of a surface mesh, representations of subcortical structures remain voxel-based [6]. Parcellating subcortical regions is therefore more challenging and requires different methodologies to those that we have applied to the cortex. For this reason, subcortical regions were not included in the connectomes reconstructed in this study.

Human network mapping. Structural networks (connectomes) were mapped for each individual using a deterministic tractography [14] pipeline from the MRtrix3 software (<http://www.mrtrix.org/>, [15]). Diffusion tensors were estimated from the preprocessed diffusion weighted images using an iteratively reweighted linear least squares estimator. White matter masks were extracted from structural segmentation files provided by the HCP. White matter boundaries were dilated by 1 voxel to fill potential gaps between grey and white matter caused by slight imperfections in subject registration. Streamlines were uniformly seeded from the white matter mask and tracked along diffusion tensor directions (eigenvectors) until they exited the mask into grey matter or reached a voxel with low fractional anisotropy (FA) (FACT tracking algorithm, 5×10^6 streamlines, 0.5 mm tracking step-size, 400 mm maximum streamline length and 0.1 FA cutoff for termination of tracks). Connection strength between any pair of regions was determined as the number of streamlines with extremities located in the regions, resulting in $N \times N$ weighted connectivity matrices. In order to capture general patterns of brain organization and filter out idiosyncratic variation, a group average connectome was computed by averaging the individual connectomes of all 75 participants. Subsequent network analyses were carried out on the group-averaged connectome.

Functional networks were mapped using command line tools from Connectome Workbench. For each subject, four runs of preprocessed resting-state fMRI volumes were averaged together and projected onto the subject’s cortical surface. The functional activation profile of each region was described as a single time series by averaging the signal of all the vertices comprised in the region. Pairwise functional connectivity was computed by means of the Pearson correlation coefficient between regional time series, resulting in $N \times N$ weighted connectivity matrices. A group-averaged functional network comprising the 75 individual connectivity matrices was computed and used in subsequent analyses.

Network analysis

Connection weights and lengths A weighted connectome can be expressed as a matrix $W \in \mathbb{R}^{N \times N}$, where W_{ij} is the connection weight between nodes i and j . Connection weights are a measure of similarity or affinity, denoting the strength of the relationship between two nodes (e.g., streamline counts in tractography or fraction of labelled neurons in tract tracing). Typically, the matrix of connection lengths L is computed from W by means of a weight-to-length transformation that monotonically remaps strong weights into short lengths and weak weights into long lengths. This way, connection lengths denote the dissimilarity, distance or travel cost between nodes. Defining nodal relationships in terms of lengths allows for the computation of short communication paths.

Connection length matrices were computed as follows. In the binary case, $L^{bin} \in [0, 1]$ denoting only the presence or absence of a connection in W . In the weighted case, $L^{wei} = -\log_{10}(W/\max(W))$ ensuring a monotonic weight-to-length transformation that produces

log-normally distributed connection lengths and attenuates extreme connection weights [16, 17] (for human connectomes weighted by streamline counts, $L^{wei} = -\log_{10}(W/\max(W)+1)$ to avoid remapping the largest weight to a length of zero.) In the distance-based case, connections lengths denote the physical distance between directly connected nodes, with $L^{dis} = D \odot L^{bin}$, where D is the Euclidean distance matrix between node pairs. Hence, shortest paths computed on L^{bin} , L^{wei} and L^{dis} minimize the number of traversed connections (hops), maximize the strength and reliability of traversed connections and minimize the physical distance traversed between nodes, respectively.

Connectome thresholding. Density-based thresholding of connection weights was applied to the group-averaged connectome in order to filter out potentially noisy and spurious connections [18]. A density threshold of 15% consists of keeping the top 15% highest weighted connections and deleting the remaining ones. Since the true connection density of the brain remains unknown [19], we sought to replicate our key analyses for a range of 5% to 60% connection density thresholds, at 5% intervals.

Null network models. Six null network models were used in this work: (M1) topologically randomized (rewired) networks, (M2) spatially randomized (repositioned) networks, (M3) topologically randomized cost-preserving networks, (M4) progressively randomized networks, (M5) progressively clusterized networks and (M6) progressively randomized, navigability-improving networks.

Null models (M1), (M2) and (M3) were employed in the sections *Navigability of the human connectome* and *Navigability of non-human mammalian connectomes*, while (M4), (M5) and (M6) were used in section *Connectome topology and navigation performance*.

Topological randomized networks (M1) were computed by rewiring the connectome using the Brain Connectivity Toolbox (<https://sites.google.com/site/bctnet/>, [20]) implementation of the Maslov-Sneppen algorithm [21]. Rewiring was carried out by swapping each connection once (on average) while preserving the network original degree distribution and connectedness. Spatially randomized networks (M2) had the spatial coordinates of their nodes randomly swapped with each other, while maintaining the topology unaltered.

For reasons of computational tractability, navigation performance in the human connectome (*Navigability of the human connectome*) was benchmarked against ensembles of 1000 ($N = 256$), 1000 ($N = 360$), 500 ($N = 512$) and 100 ($N = 1024$) topologically randomized networks (M1), per connection density threshold. Ensembles of the same size were generated for spatially randomized networks (M2). The benchmarking of non-human connectomes (*Navigability of non-human mammalian connectomes*) was done by constructing ensembles of 10^4 topologically randomized networks (M1) and 10^4 spatially randomized networks (M2). Non-parametric P-values for S_R , E_R^{bin} , E_R^{wei} and E_R^{dis} were computed as the proportion of times null networks outperformed the empirical connectomes. Cost-preserving randomized networks (M3) showed markedly improved navigability when compared to models (M1) and (M2). Therefore, to ensure an accurate characterization of the statistical differences between the navigability of cost-preserving null networks and empirical connectomes, we generated larger ensembles of 10^4 ($N = 256$), 10^4 ($N = 360$), 10^4 ($N = 512$) and 500 ($N = 1024$) cost-preserving networks for the human connectomes; and 5000 cost-preserving networks per non-human species (see *Cost-preserving topological randomization* for further details).

Progressively randomized networks (M4) were obtained by the same rewiring process as topologically randomized networks (M1), consisting simply of partially rewired networks for

which only a fraction of connections have been swapped. Progressively clusterized networks (M5) were produced by an adaptation of the (M4) procedure that only considers connection swaps that lead to an increase in the overall clustering coefficient of the network. The randomizing-clusterizing routine (*Connectome topology and navigation performance*) was repeated 100 times for $N = 256, 360, 512$, with E_R^{bin} and E_R^{wei} re-computed once every 5 connection swaps. The construction of progressively randomized, navigability-improving networks (M6) is detailed at *Optimizing connectome navigability with topological rewiring*.

Navigation centrality. The node navigation centrality of node i defined as $c(i) = \sum_{s \neq i \neq t} \pi_{st}(i)$, where $\pi_{st} = 1$ if the successful navigation path from s to t passes through i and $\pi_{st} = 0$ otherwise. In order to define a measure of edge navigation centrality (ENC), we first defined $c(i, j) = \sum_{s \neq t, i \neq j} \pi_{st}(i, j)$, where $\pi_{st}(i, j) = 1$ if the successful navigation path from s to t traverses the connection from node i to node j , and $\pi_{st}(i, j) = 0$ otherwise. Due to the asymmetric character of navigation, $c(i, j) \neq c(j, i)$. For simplicity, we adopted a symmetric definition of edge navigation centrality given by $c_{sym}(i, j) = (c(i, j) + c(j, i))/2$.

Node (edge) betweenness centralities were computed using the Brain Connectivity Toolbox (<https://sites.google.com/site/bctnet/>, [20]), representing the absolute number of shortest paths that pass through each node (edge) of the network.

Navigation and functional connectivity. Our implementation of navigation identifies paths based on the Euclidean distance between network nodes. Thus, a natural definition of navigation path length is to consider the physical distance traversed from one node to another. For our FC analysis, we defined navigation path length from i to j as $\Lambda_{ij}^{nav} = \log_{10}(D_{i_u} + \dots + D_{v_j})$, where $\{u, \dots, v\}$ is the sequence of nodes visited during navigation from i to j and D is the Euclidean distance matrix between node pairs.

The logarithmic transformation leads to a better differentiation of the distance covered by short navigation paths (Fig. S17), leading to an expansion of the left tail (short navigation distances) of the navigation path length distribution and a compression of the right tail (long navigation distances). The transformation leads to stronger correlations with FC, suggesting that a nuanced characterization of short communication paths might play an important role in understanding the relationship between structural and functional brain networks.

Supplementary analyses

Navigability of individual human connectomes. In order to confirm the results obtained for the group-averaged human connectome, we evaluated the navigability of each individual's connectome separately for several connection densities and parcellation resolutions. The navigability of individual connectomes was consistent with group-averaged performance ($S_R = 95\%$, $E_R^{bin} = 84\%$, $E_R^{wei} = 63\%$ and $E_R^{dis} = 83\%$, averaged over all individuals, for $N = 360$ at 15% connection density).

We tested the null hypothesis of equality in navigation performance between males and females, as well as between three age brackets. Our sample consisted of 35 males and 40 females; and 11, 33 and 31 individuals aged between 22 to 25, 26 to 30 and 31 to 35 years, respectively. Statistical testing was performed on the area under the curve (AUC) of the navigation performance measures shown in Figures S8 and S7. In particular, a three-way analysis of variance (F-test) was used to test the null hypothesis of equality in the AUC between the three age brackets, while a two-sample t-test was used to test for differences in

the AUC between males and females. We found significant differences in the navigability of age groups across all parcellation resolutions (Table S1), with navigation performance decreasing with age. This result is in line with previous analyses suggesting a decrease in measures of network efficiency with age [22]. No significant difference in navigation performance between genders was found. Individual connectomes mapped for representative males and females from each of the three age brackets ($N = 360$, 15% connection density) were significantly more navigable than rewired, repositioned and cost-preserving rewired null networks (Fig. S6).

Navigation with scaling of streamline counts. A common practice in connectomics studies based on white matter tractography is to scale streamline counts by average fiber lengths [23]. This is motivated by the notion that certain tractography algorithms are biased towards overestimating the streamline count of long fiber bundles, although it is important to remark that this effect varies substantially between algorithms and streamline seed strategies, with grey-matter seeding strategies often *underestimating* the streamline count of long fibers [24]. We chose not to perform distance-based scaling, since this would impart information about the distance between nodes in each connection weight, potentially leading to an artificial improvement in navigation performance. However, it is then possible that the observed values of E_R^{wei} are a result of the uncorrected tractography bias towards long fiber bundles, since long range connections would be more efficient for both streamline count and distance-based path length regimes. In order to test for this issue, we recomputed navigation performance after dividing streamline counts by the Euclidean distance between nodes. As initially hypothesized, this transformation led to slight improvements in navigation performance across parcellation resolutions and connection density thresholds (orange curve, Fig. S5).

Similarly, streamline count are often normalized by the volume of brain regions [23]. This is motivated by the notion that the number of streamlines terminating in a certain region is influenced by the volume (or surface area) of that region, leading to an artificial increase (decrease) in the strength of network nodes corresponding to large (small) cortical regions. In order to address this potential issue, we computed the navigability of the human connectome constructed after normalizing connection weights W_{ij} by $W_{ij} = (NOS_{ij})/(V_i V_j)$, where NOS_{ij} is number of streamlines between regions i and j and V_i is the volume of region i . This transformation lead to visible improvements in navigation performance, especially for E_R^{wei} , across several connection density thresholds and parcellation resolutions (yellow curve, Fig. S5).

Alternative distance measures for navigation. Navigation was performed using the Euclidean distance between region centroids as the distance measure between network nodes. While this approach has been extensively used as an approximation of the distance between neuronal populations [25, 26, 27], it has potential shortcomings.

First, brain regions such as the motor, pre- and post-central cortices are long and narrow, rendering a centroid-based distance measure not representative of distances between voxels. In order to address this potential issue, we defined the distance between nodes as $D_{max}(i, j) = \max(d_{\alpha\beta})$ and $D_{min}(i, j) = \min(d_{\alpha\beta})$, where $d_{\alpha\beta}$ is the set of pairwise Euclidean distances between all voxels comprising regions i and j , $\alpha \in i$ and $\beta \in i$. The purple and green curves in Fig. S5 show the navigation performance obtained for D_{max} and D_{min} , respectively, for several connection densities and parcellation resolutions. The ob-

tained results are consistent with previously presented analyses (Fig. S5, blue curve), with the marked exception of E_R^{dis} when navigation is computed over D_{min} . This discrepancy is caused by the skewed distribution of connection lengths for D_{min} (Fig. S18A). For any pair of adjacent regions i, j , $D_{min}(i, j) \propto 1$. Distance-based shortest paths are heavily mediated by these short connection lengths, which leads to unrealistic shortest paths composed of many hops but very small path lengths (Fig. S18B-D). For this reason, D_{min} is most likely an unsuitable distance measure for shortest paths.

Second, we assessed the navigability of the human connectome when introducing increasing amounts of noise to centroid coordinates. We added noise sampled from a Gaussian $(0, \sigma)$ to the spatial coordinates of each region centroid. We assessed the navigability of the human connectome (group-averaged, $N = 360$ at 15% connection density) using an Euclidean distance matrix computed on the noisy coordinates, for increasing values of σ (Fig. S4). We found that all measures of navigation performance (averaged over 100 simulations) were robust to small amounts of noise and gradually deteriorated as the centroid coordinates became noisier. Robustness to small amounts of noise is important when considering potential errors in node spatial coordinates due to, for instance, slight imperfections in image registration; whereas marked navigability reductions for large amounts of noise serves as an alternative null model that reiterates the importance of the spatial embedding of brain networks.

Finally, quantifying inter-regional distances with measures other than the Euclidean distance between regional centroids (e.g. fiber-tract length or tract myelination) may provide more realistic distance estimates and thereby improve connectome navigability. Fiber-tract length may represent a more realistic measure of the distance travelled between two nodes. However, in addition to the distance between structurally connected nodes, navigation also depends on the distance between structurally unconnected nodes, for which fiber-tract lengths cannot be computed. Techniques of fiber interpolation [27] or heavily seeded probabilistic tractograms leading to near-complete connectivity matrices [28] could guide future work on navigation based on fiber lengths.

Cost-preserving topological randomization. Longer connections are typically assumed to demand greater metabolic resources, and thus connection length is often used as a proxy measure of metabolic cost [19, 29]. In this study, we defined network cost as the sum of the Euclidean distances between connected nodes [27, 30, 31].

We implemented a rewiring routine that generates null networks that preserve the original network’s degree distribution and number of connected components, while approximately preserving its cost. The routine is an adaptation of the Maslov-Sneppen algorithm [21] that only considers connection swaps that do not alter the resulting network’s cost by more than a user defined threshold (set to 1mm). We assessed how closely null networks matched original costs by means of a relative cost measure $cost_{rel} = cost_{null}/cost_{emp}$. Ideally, this ratio should be exactly 1, but because cost was matched up to a prescribed tolerance for each connection swap ($\pm 1\text{mm}$), the a small difference in the cost of the empirical and null networks can accumulate with a growing number of swaps. Fixing the tolerance at 0 is not practical, since the vast majority of candidate swaps cannot lead to an exact preservation of cost. As shown in the results below, this strategy was able to match the total cost of connectomes within a 0.1% error margin.

Starting from the human connectome ($N = 360$), we generated 1000 cost-preserving rewired networks for each of several connection density thresholds. In addition, we gener-

ated 10^4 cost-preserving networks for the human connectome at parcellation resolutions of $N = 256, 512, 1024$ and 15% connection density threshold. Preserving network cost greatly improved the navigability of the null networks, as seen by the reduced gap between navigation performance measures computed on rewired and empirical networks (Fig. S3A-D). Despite this improvement, the human connectome remained significantly more navigable than the cost-preserving surrogate networks ($P < 10^{-4}$), across all navigation performance measures, parcellation resolutions (Fig. S3E) and connection density thresholds (with the exception of 5% connection density). Significance was assessed using a non-parametric P -value computed as the proportion of times null networks outperformed empirical connectomes.

Next, we next generated 5000 cost-preserving rewired networks for the macaque ($N = 29$) and mouse ($N = 112$) connectomes. For both species, the null hypothesis of equality in navigation performance between the empirical and cost-preserving null networks could not be rejected for any connection density (Fig. S9). Thus, preservation of network cost is sufficient to account for the efficiency of navigation in the non-human connectomes. The considered macaque connectome comprises a single hemisphere [4], and thus lacks long-range inter-hemispherical connections, which could potentially explain the non-significant results obtained for this species. However, this is not the case for the investigated mouse connectome [2]. In following, we provide several explanations of the importance of network cost to navigation performance, particularly for the non-human connectomes.

Network cost, being defined in terms of connection lengths, has a direct relationship with the distance between network nodes. A number of studies have documented the important influence of the spatial positioning of nodes in brain network topology [25, 27, 28], indicating that preserving network cost not only leads to null networks with more realistic spatial embedding, but also topological organization that more closely resembles that of empirical connectomes. Thus, the cost-preserving null model results in networks that (i) are less topologically random than the ones produced by simple rewiring routines, (ii) respect the original distance relationships between connectome nodes and (iii) match the original degree distribution of the connectome. In non-human species, preserving these three traits was sufficient to fully account for the extent to which brain networks are navigable. In contrast, the human connectome remained significantly more navigable than cost-preserving null networks. The human cortex exhibits more gyrification than those of the macaque and mouse [32, 33], resulting in a more complex anatomical configuration of cortical folding, and, consequentially, a more intricate spatial embedding. We hypothesized that, in order to facilitate navigation given this higher spatial complexity, the topology and geometry of the human connectome may have additional organizational factors not present in the mouse and macaque brains, and not captured by the cost-preserving null model.

Ultimately, the findings from the cost-preserving null model analysis reiterate the importance of connectome geometry for efficient communication under navigation routing, indicating that the relative spatial positioning of network nodes explains, to a large extent, the navigation performance of brain networks.

Optimizing connectome navigability with topological rewiring. We sought to test whether human connectome navigability could be improved (optimized) by topological rewiring explicitly seeking to improve navigation performance. More specifically, we implemented an adaptation of the Maslov-Sneppen rewiring routine [21] that only accepts connection swaps resulting in an increase of a given measure of navigation performance. In addition, we aimed preserved the total cost of connectomes during the connection swap

routine, where network cost was defined as the sum of the Euclidean distance between structurally connected node pairs [27, 29, 34]. Thus, topological rewiring was constrained to connection swaps between randomly chosen node pairs that (i) preserved connection density and degree-distribution; (ii) improved a measure of navigation performance; and (iii) did not result in a cost offset larger than a predefined threshold (set to 1mm). Connection swaps that did not simultaneously meet all three conditions were rejected.

Optimization was performed with respect to several different navigation performance measures. In the previous randomize/clusterize analysis we focused on E_R^{bin} and E_R^{wei} , quantifying how efficient navigation paths are in relation to shortest paths. However, seeking to optimize ratio measures by progressive alterations in topology could theoretically result in networks that are not efficient for navigation nor optimal routing, but show high efficiency ratios. For instance, in a regular lattice, both navigation and shortest paths have low absolute efficiencies but $E_R^{bin} = 1$. Thus, another possibility is to optimize “raw” measures of navigation performance (e.g., E^{bin} or E^{wei}) that capture the absolute efficiency of navigation paths.

Progressively altering network topology to optimize navigation is a time-intensive task, requiring the computation of navigation for each connection swap attempt. In contrast to the randomize/clusterize routine, the navigability of the networks generated in this analysis monotonically increases by design. As a result, in order to assess the room for improvement in navigation, it is necessary to perform enough connection swaps to adequately converge to an asymptote in the measures of navigation performance of the generated networks. We found that in the order of 10^6 connection swap attempts lead to a reasonable characterization of the margin to increase navigability.

We applied this swap routine to the human connectome (group-averaged, $N = 256, 360, 512$ at 15% connection density) aiming to optimize, in turn, E_R^{bin} , E_R^{wei} , E^{bin} and E^{wei} . We found that when explicitly optimizing these navigation measures, the margin for improvement in navigability is larger inferred from the randomize/clusterize analysis (Fig. S11). On average, the generated networks showed a 13%–17% increase in E_R^{bin} , while E_R^{wei} had a 18%–20% margin of improvement. Similarly, the swap routine lead to a 17%–20% improvement in E^{bin} and E^{wei} was increased by around 5% for $N = 256, 360$ and 13% for $N = 512$. In all cases, the majority of observed improvement took place in the first 10^6 swap attempts (87.5%, 88.1%, 88.6% and 88.0% of the average total improvement in E_R^{bin} , E_R^{wei} , E^{bin} and E^{wei} , respectively, for $N = 360$). Therefore, increasing connectome navigability quickly became more difficult as a function of swap attempts, suggesting that the observed improvements converge to an asymptote.

Importantly, the 5%–22% margin for navigability improvement identified by our connection swap analyses is not definitive. We attempted to optimize network navigability by means of a greedy connection swap strategy that is not guaranteed to converge to global maxima of navigation performance. Performing a higher number of navigation optimization connection swaps, or employing more sophisticated methodologies to alter connectome topology, could potentially result in more pronounced improvements to navigation.

There are many possible explanations for the fact that connectome navigability can be marginally improved with explicit optimization. First, evolutionary pressures for the development of desirable characteristics other than efficient communication are likely to have been influential in shaping connectome architecture. For instance, network robustness is conjectured to confer the brain resilience against lesions in cortical regions and white matter projections [30, 35, 36]. Second, the need to accommodate higher-order geometric constraints not captured by our length-based definition of network cost, such as the volumetric profile

Parcellation resolution	S_R		E_R^{bin}		E_R^{wei}		E_R^{dis}	
	P -value	F -stat	P -value	F -stat	P -value	F -stat	P -value	F -stat
256	0.02	4.05	0.75×10^{-4}	10.86	0.17	1.81	0.1×10^{-4}	10.40
360	0.02	4.03	0.001	6.87	0.02	4.05	0.003	6.07
512	0.26	1.36	0.03	3.75	0.06	2.95	0.05	3.14
1024	0.10	2.37	0.02	3.89	0.01	4.46	0.03	3.61

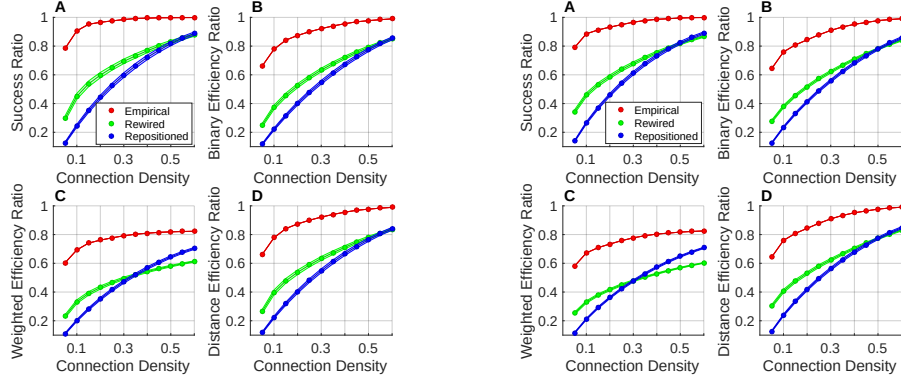
Table S1: Influence of age on connectome navigability. The table shows the P -values and F -statistics for a three-way analysis of variance of the AUC between three age brackets, computed for different navigation performance measures. Age significantly influenced connectome navigability, with navigation performance decreasing with age.

of axonal projections of different shapes and diameters [28], might result in sub-optimal arrangements of white matter fiber bundles within the brain. Third, it is plausible that certain patterns of connectivity between cortical regions, although sub-optimal from a communication efficiency standpoint, are necessary for the performance of high-order cognitive and perceptual functions. Conversely, it is possible that certain pairs of cortical regions do not exchange information under normal brain function, and thus communication channels between them would not have evolved to be efficient [37]. Therefore, while our analyses indicate that the navigability of brain networks can be improved with explicit optimization, this improvement would potentially be at the cost of other important aspects of brain network organization.

Edge navigation centrality. We computed edge navigation centrality (ENC), weighted edge betweenness centrality (EBC) and binary EBC for the human connectome (group-averaged, $N = 360$ at 15% connection density, Fig. S13). All three edge centralities spanned several orders of magnitude. ENC and weighted EBC were significantly but not strongly correlated (Pearson correlation coefficient $r = 0.03$), while a strong correlation was found between ENC and binary EBC ($r = 0.67$).

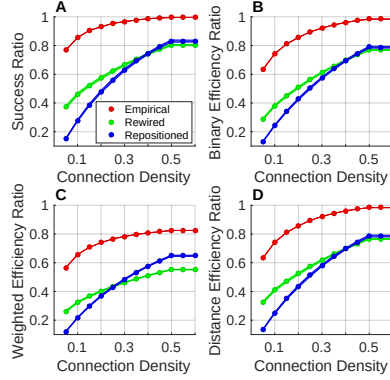
We found ENC to be more uniformly distributed across connections compared to both types of EBC (Fig. S13D). For instance, the top 15% most used connections were responsible for 59%, 76% and 83% of communication routes in navigation, binary shortest paths and weighted shortest paths, respectively (Fig. S13E). When ranking connections based on weight, we found the top 1% highest weighted connections to mediate 24% of weighted shortest paths; with the top 18% highest weighted connections responsible for 60% of weighted shortest paths (Fig. S13F). In contrast, the distribution of communication routes in binary shortest paths and navigation is, unsurprisingly, independent from connection weights.

The edge-based analysis of navigation centrality reiterates that navigation routing promotes a more resource-efficient distribution of the information traffic load than shortest paths, at the level of both nodes and connections.



(a) $N = 256$

(b) $N = 512$



(c) $N = 1024$

Figure S1: Navigation performance of human connectomes with different parcellation resolutions. (A-D) Success ratio (S_R), binary efficiency ratio (E_R^{bin}), weighted efficiency ratio (E_R^{wei}) and distance efficiency ratio (E_R^{dis}) at different connection density thresholds. Empirical measures (red) for group-averaged connectomes were compared to 1000 ($N = 256$), 500 ($N = 512$) and 100 ($N = 1024$) rewired (green) and spatially repositioned (blue) null networks. Shading indicates 95% confidence intervals.

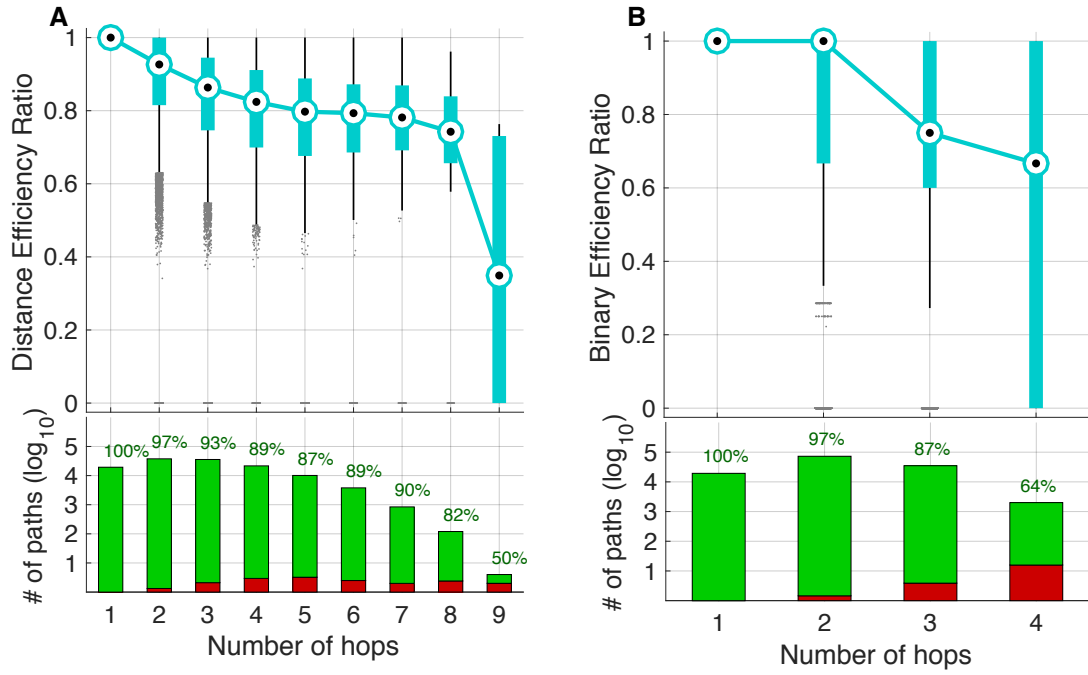


Figure S2: The performance of navigation routing in human SC stratified by shortest paths hop counts ($N = 360$ at 15% connection density). Blue boxplots indicate the quartiles of efficiency ratios of navigation paths benchmarked against shortest paths with matching hop count. Barplots show the number of shortest paths for a given hop count, with colors indicating the proportion of successful (green) and failed (red) navigation paths. Shortest paths computed over L^{dis} (A) and L^{bin} (B).

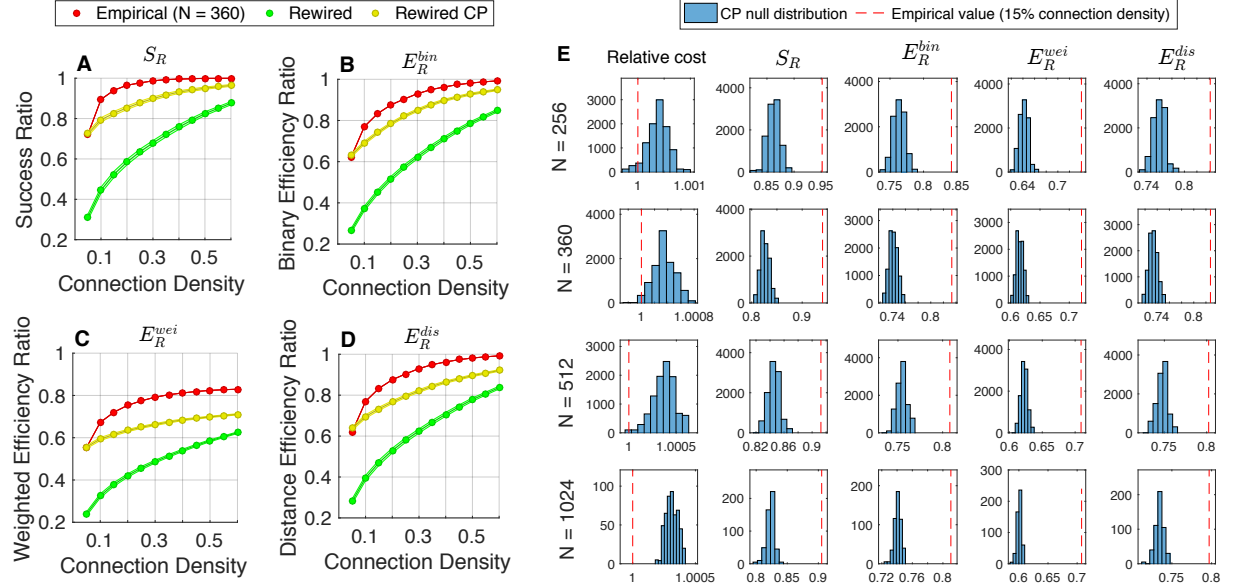


Figure S3: Navigation performance of the human connectome compared to cost-preserving null networks (group-averaged, $N = 360$, at 15% connection density). **(A-D)** Success ratio (S_R), binary efficiency ratio (E_R^{bin}), weighted efficiency ratio (E_R^{wei}) and distance efficiency ratio (E_R^{dis}) at several connection density thresholds. Curves show measures obtained for the human connectome (red), 10^4 rewired (green) and cost-preserving rewired (yellow) null networks. Shading indicates 95% confidence intervals. **(E)** Distributions of relative network cost ($cost_{null}/cost_{emp}$) and different navigation performance measures (columns) of ensembles of cost-preserving null networks, for several parcellation resolutions (rows). Cost-preserving ensembles consisted of 10^4 null networks for $N = 256, 360, 512$ and 500 null networks for $N = 1024$. Dashed red lines indicate empirical network cost and navigation performance measures. Cost-preserving null networks approximate connectome cost to an error margin of 0.1%. The human connectome remained significantly more navigable than cost-preserving rewired null networks across all parcellation resolutions and navigability measures.

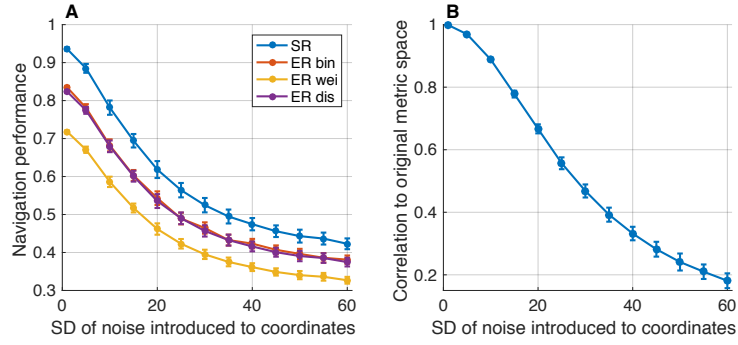


Figure S4: Navigation performance as a function of noise added to node centroid coordinates. Each node's three spatial coordinates were independently corrupted with additive Gaussian noise with zero mean and standard deviation (SD) that ranged between 0 and 60 (horizontal axis). **(A)** Navigation performance obtained by guiding navigation routing based on distances computed on the noisy coordinates. **(B)** Correlation between node distances computed on the original and noisy coordinates, as a function of standard deviation.

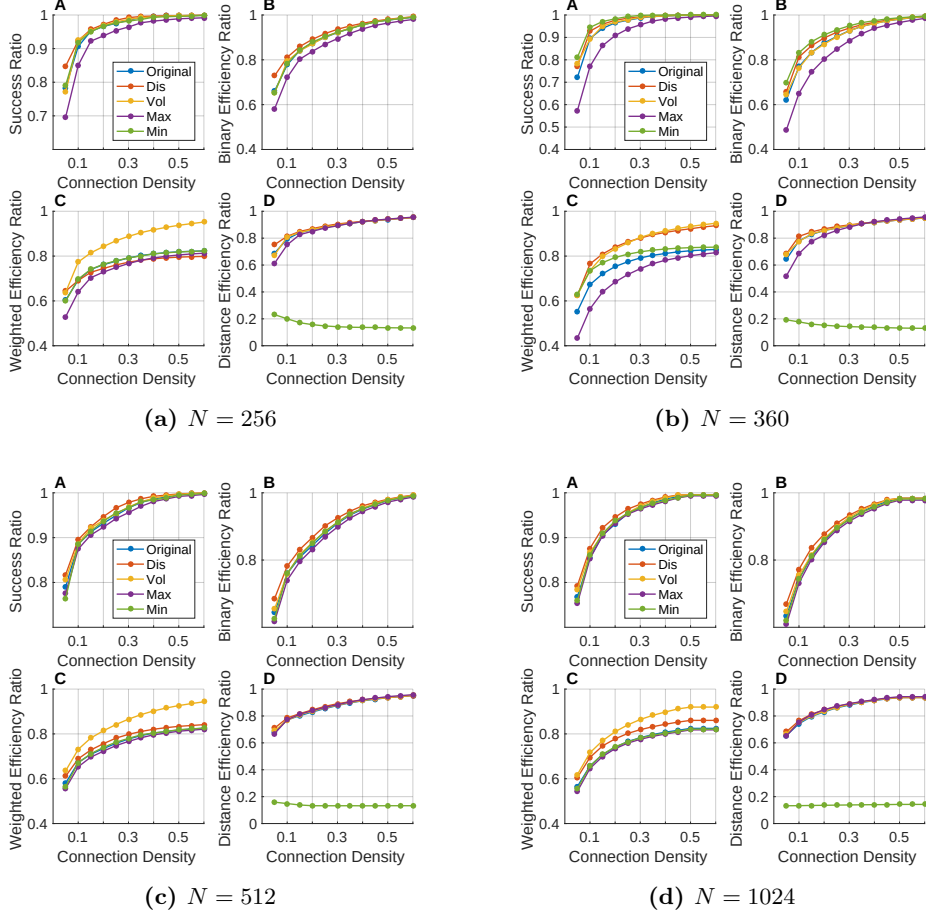


Figure S5: Human connectome navigation performance computed for different distance measures and streamline count normalizations, for several parcellation resolutions (a-d). Results in the main text (blue curves) were computed using the Euclidean distance between node centroids and connectomes without normalization of streamline counts. **(A-D)** Curves show the Success ratio (S_R), binary efficiency ratio (E_R^{bin}), weighted efficiency ratio (E_R^{wei}) and distance efficiency ratio (E_R^{dis}) obtained from variations of the original configuration, for several connection density thresholds. The variations are: distance scaling of streamline counts (“Dis”, orange curves); volume scaling of streamline counts (“Vol”, yellow curves); maximum voxel distance as the distance measure between nodes (“Max”, purple curves); and minimum voxel distance as the distance measure between nodes (“Min”, green curves).

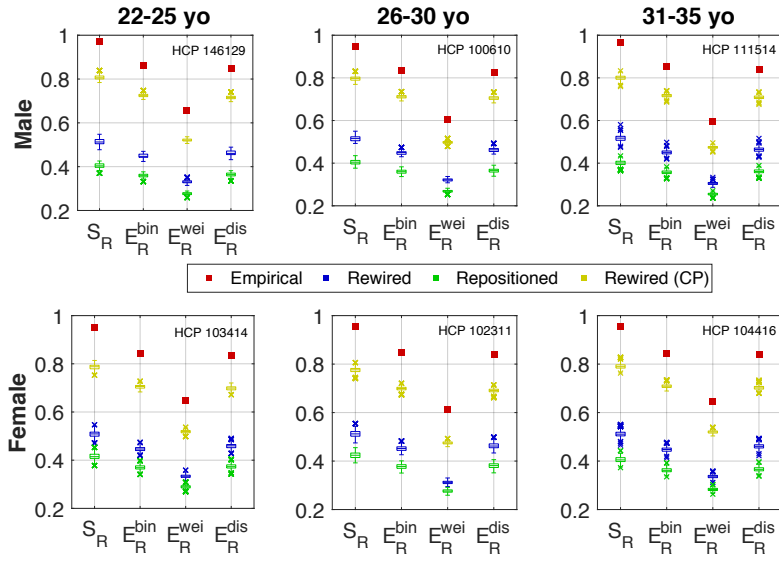


Figure S6: Connectome navigability of representative male and female individuals from each of the three age brackets investigated. Navigation performance was benchmarked against three null network models. Navigation performance was evaluated with respect to the success ratio (S_R), binary efficiency ratio (E_R^{bin}), weighted efficiency ratio (E_R^{wei}) and distance efficiency ratio (E_R^{dis}) (horizontal axis). The vertical axis shows the navigation performance of empirical (red), cost-preserving topologically randomized (yellow), topologically randomized (blue) and spatially randomized (green) null networks. Boxplots indicate the quartiles of performance measures obtained for null networks, with crosses denoting outliers.

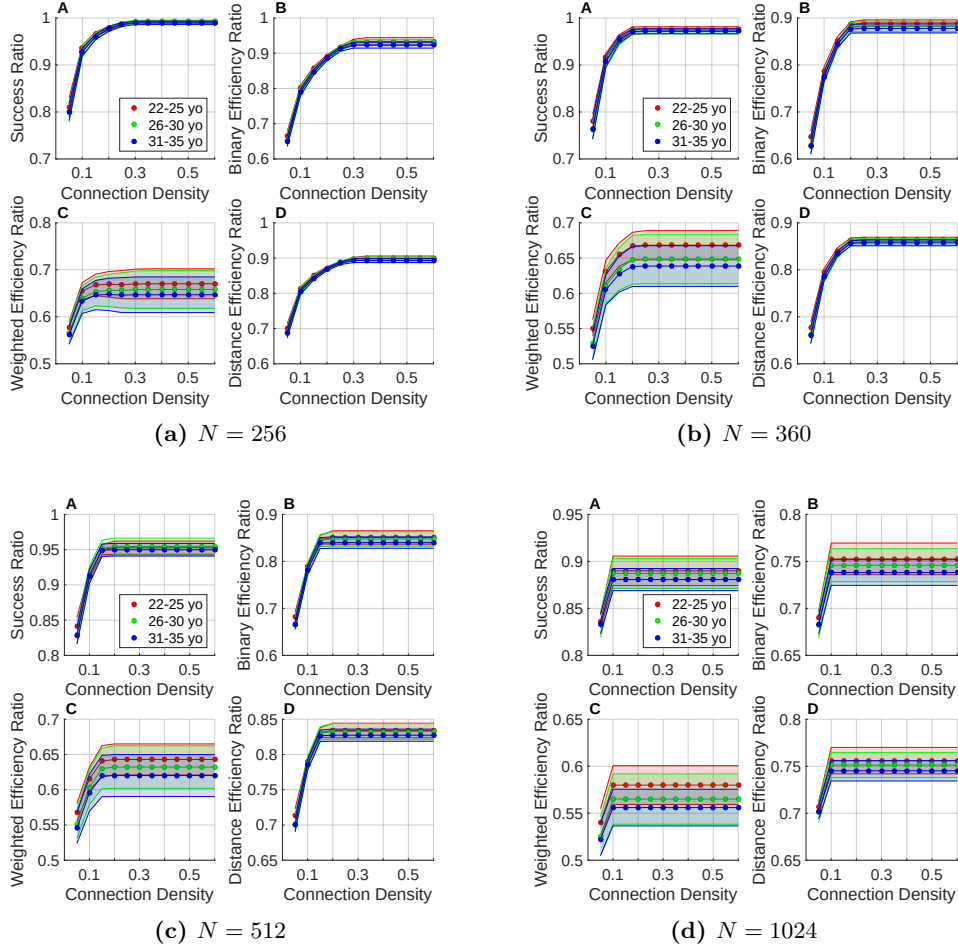
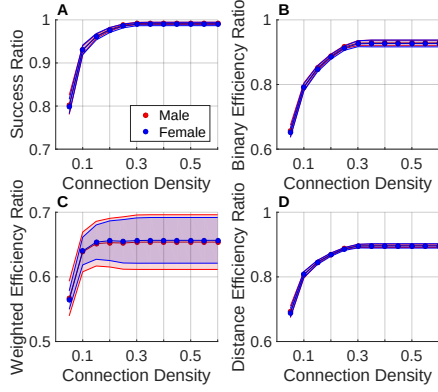
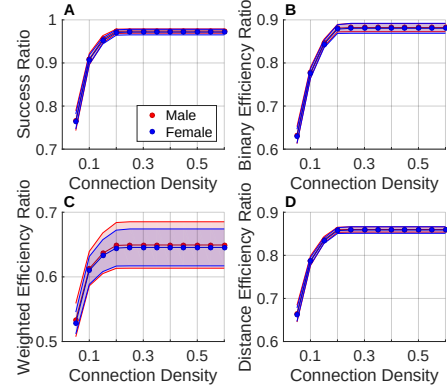


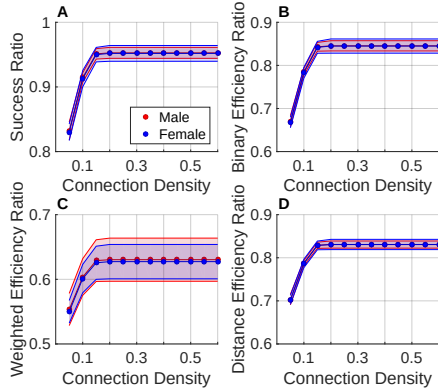
Figure S7: Influence of age on connectome navigability for several parcellation resolutions (a-d). Navigation performance was evaluated for each individual and the average performance within each of three age brackets was computed as a function of connection density. **(A-D)** Success ratio (S_R), binary efficiency ratio (E_R^{bin}), weighted efficiency ratio (E_R^{wei}) and distance efficiency ratio (E_R^{dis}) averaged across individual age: 22–25 (red), 26–30 (green) and 31–35 (blue) years, at different connection density thresholds. Shading indicates 95% confidence intervals.



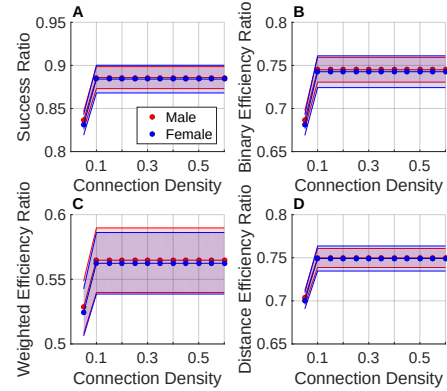
(a) $N = 256$



(b) $N = 360$



(c) $N = 512$



(d) $N = 1024$

Figure S8: Influence of sex on connectome navigability for several parcellation resolutions (a-d). Navigation performance was evaluated for each individual and the average of male and female navigability was assessed as a function of connection density. **(A-D)** Success ratio (S_R), binary efficiency ratio (E_R^{bin}), weighted efficiency ratio (E_R^{wei}) and distance efficiency ratio (E_R^{dis}) averaged across female (blue) and male (red) participants, at different connection density thresholds. Shading indicates 95% confidence intervals.

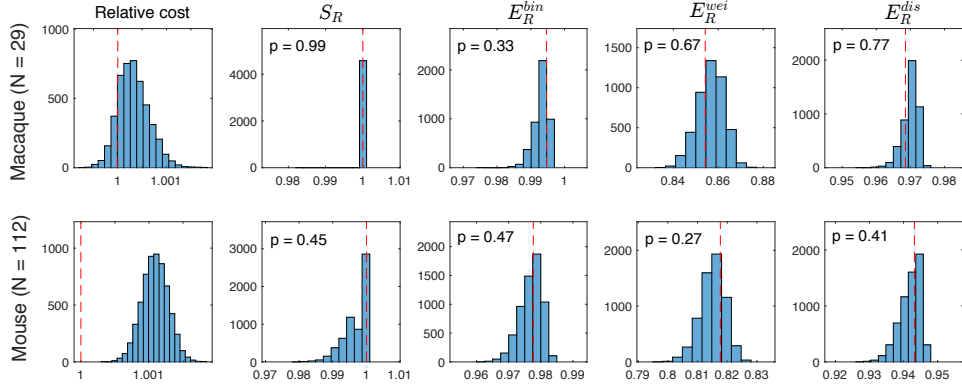


Figure S9: Navigation performance of non-human connectomes compared to cost-preserving rewired null networks. Distributions of relative network cost ($cost_{null}/cost_{emp}$) and different navigation performance measures (columns) of 5000 cost-preserving null networks, for the macaque (top row) and mouse (bottom row connectomes). Dashed red lines indicate empirical network cost and navigation performance measures. Cost-preserving null networks approximate connectome cost to an error margin of 0.1%. The null hypothesis of equality in navigation performance between the cost-preserving null networks and the empirical connectomes could not be rejected for the mouse and macaque ($P > 0.05$).

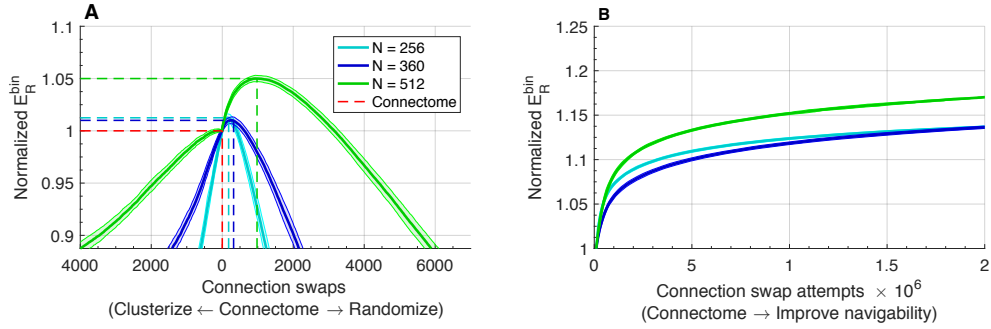


Figure S10: Navigation performance (E_R^{bin}) of progressively rewired connectome topologies (at 15% connection density). The E_R^{bin} of rewired topologies was normalized by the empirical value found for the human connectome. Curves indicate the mean values (inner line) and 95% confidence intervals (outer shadow) obtained from several runs of the rewiring routines. **(A)** Normalized E_R^{bin} of clusterized and randomized networks for 100 runs of the randomization-clusterizing procedure and different parcellation resolutions. Dashed lines show performance peaks (vertical axis) and number of connection swaps (horizontal axis), with red indicating the values obtained for the empirical brain. **(B)** Normalized E_R^{bin} obtained from direct optimization of the connectome's empirical E_R^{bin} , as a function of connection swap attempts, for 50 ($N = 2560$), 50 ($N = 360$) and 30 ($N = 512$) independent runs of the rewiring routine.

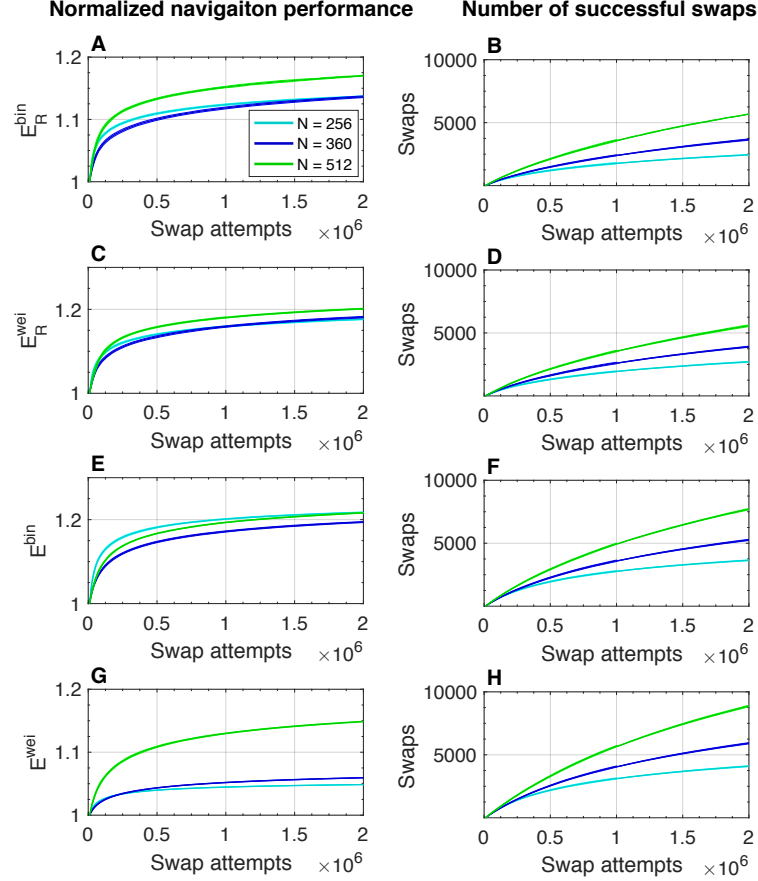


Figure S11: Optimization of the navigability of the human connectome (at 15% connection density) via progressive rewiring of empirical topology. Perturbations of connectome topology were carried out by random connection swaps that (i) preserved original network cost; (ii) resulted in an increase of given navigation performance measure; and (iii) preserved the original node degree distribution. Navigation measures obtained by topology rewiring were normalized by empirical values found for the human connectome. Curves indicate the mean values (inner line) and 95% confidence intervals (outer shadow) of 50 ($N = 256$, light blue), 50 ($N = 360$, dark blue) and 30 ($N = 512$, green) independent optimization runs. **(A,C,E,G)** Normalized navigation performances for 2×10^6 connection swap attempts. **(B,D,F,H)** Number of successful connection swaps as a function of the number of swap attempts. Successful swaps simultaneously satisfied conditions (i), (ii) and (iii).

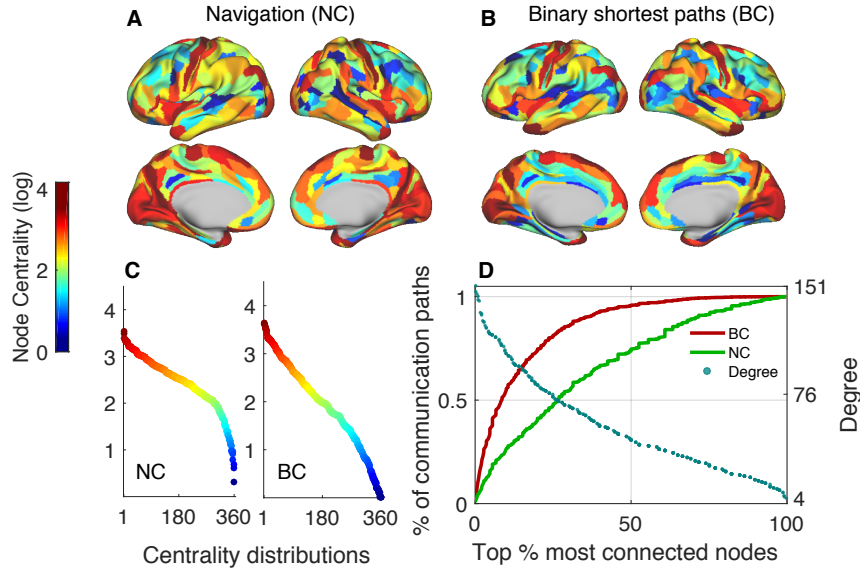


Figure S12: Comparison between navigation (NC) and binary betweenness (BC) node centralities for $N = 360$ at 15% connection density. Centrality values are logarithmically scaled. NC (A) and BC (B) projected onto the cortical surface. (C) NC (right) and BC (left) sorted from highest to lowest values (D) Relationship between the cumulative sum of centrality measures and degree. The horizontal axis is a percentage ranking of nodes from highest to lowest degree (e.g., for $N = 360$, the 10% most connected nodes are the 36 nodes with highest degree). Solid curves (left-hand vertical axis) represent the cumulative sum of BC (red) and NC (green) over all nodes ordered from most to least connected, divided by the total number of communication paths in the network, indicating the fraction of communication paths mediated by nodes. Blue dots (right-hand vertical axis) show the original degree associated with each percentage of most connected nodes.

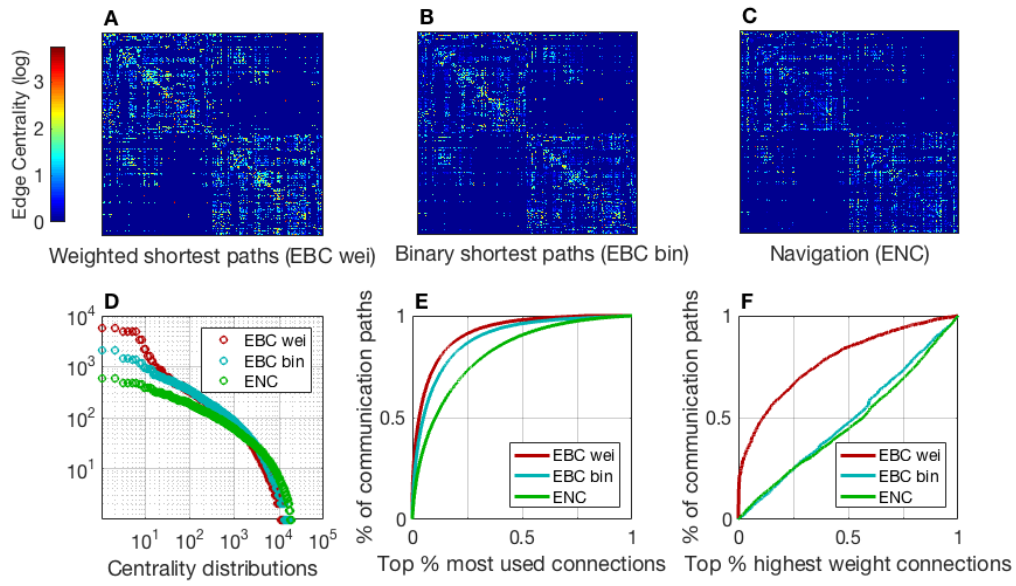


Figure S13: Comparison between edge navigation centrality (ENC), weighted edge betweenness centrality (EBC) and binary EBC (group-averaged connectome, $N = 360$, at 15% connection density). **(A-C)** Matrix representation of logarithmically scaled edge centrality values. **(D)** Edge centrality distributions for navigation (green), binary shortest paths (blue) and weighted shortest paths (red), sorted from highest to lowest values. **(E)** Fraction of communication paths mediated by connections. Connections were sorted according to their centrality values. The vertical axis shows the cumulative sum of centrality measures divided by the total number of communication paths in the network. **(F)** Fraction of communication paths mediated by connections, with connections sorted by weight. The vertical axis shows the cumulative sum of centrality measures divided by the total number of communication paths in the network.

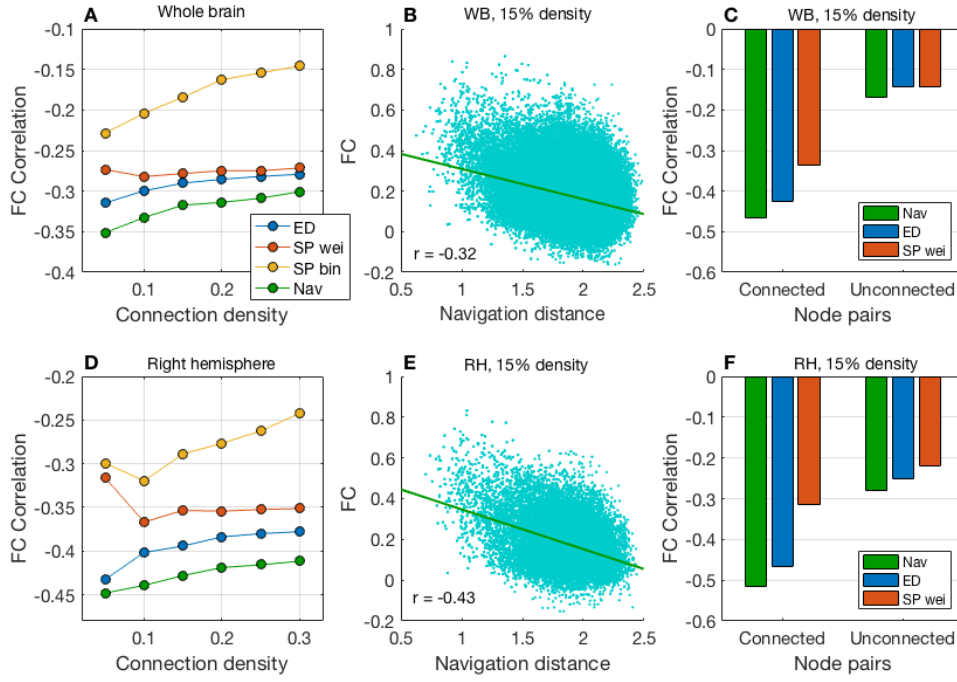


Figure S14: Correlation between FC and network communication measures (group-averaged connectome, $N = 360$, at 15% connection density). Correlations were computed for successful navigation paths. The navigation distance of nodes i, j was defined as the log of the sum of connection distances along the navigation path from i to j . **(A)** Whole brain correlations between FC and Euclidean distance (blue), weighted shortest paths (orange), binary shortest paths (yellow) and navigation distance (green). **(B)** Scatter plot between navigation distances and FC for all brain regions. Green line indicate the linear fit between the two measures. **(C)** FC correlations stratified for structurally connected and unconnected node pairs. **(D-F)** Right hemisphere equivalent of panels A-C.

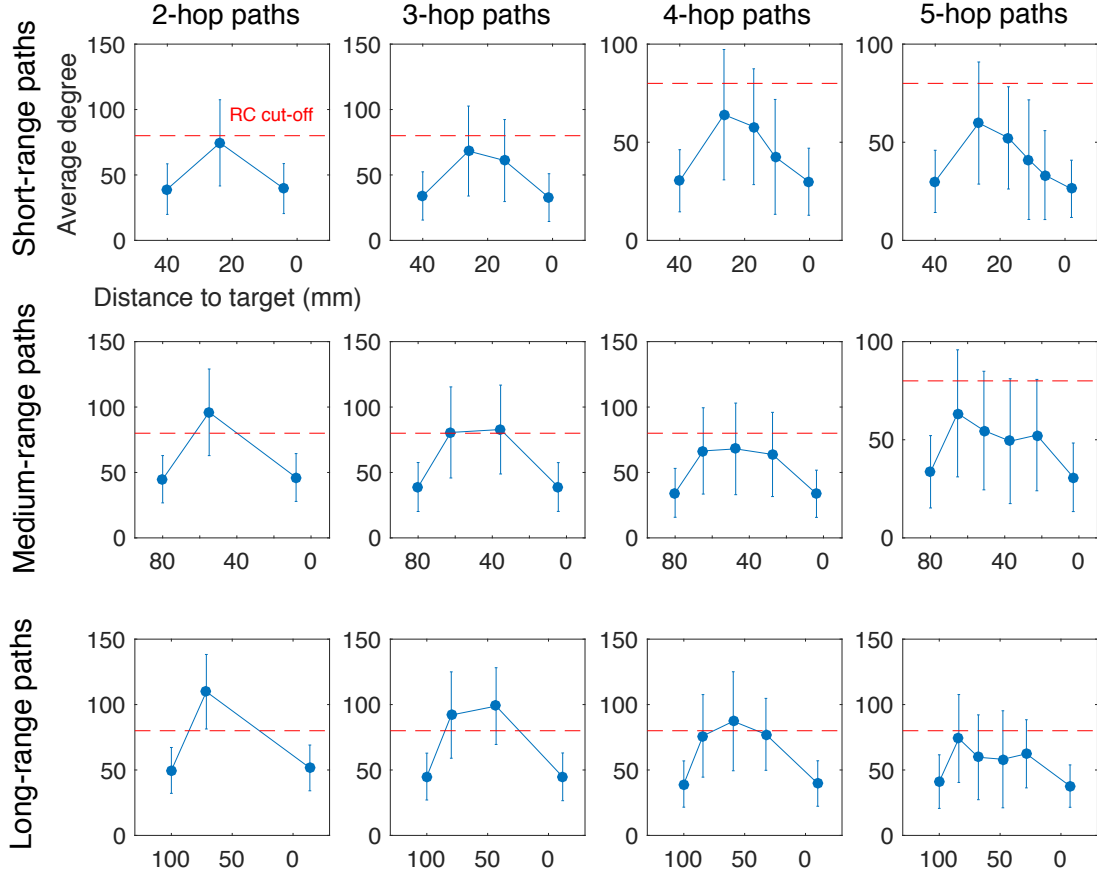


Figure S15: Structure of navigation paths between non rich club nodes ($N = 360$ at 15% connection density). Top, middle and bottom rows depict, respectively, short- (Euclidean distance from source to target nodes $d_{st} \leq 50$ mm), medium- ($50 \text{ mm} < d_{st} \leq 100$ mm) and long-range paths ($d_{st} > 100$ mm). Columns show paths 2 to 5 hops long. For each panel, the horizontal axis shows the average distance to the target, while the vertical axis shows the average degree (and standard deviation) of nodes along the path. The red dashed line marks the cut-off degree $k = 80$ for the binary rich club (computed as in [38]). Navigation paths follow a “zoom-out/zoom-in” structure, proceeding allowing sequences of low-, high- and low-degree nodes. This path structure is facilitated by a heterogeneous degree distribution and high clustering coefficient. First, information travels via peripheral connections around the locally clustered vicinity of the source. Once it reaches a high-degree node, it is forwarded towards the target via long-range connections, quickly traversing large distances in a small number of hops. Finally, once at the destination’s vicinity, the information again makes use of local clustering to home in on the target. This mechanism for information transfer is in line with the notion of the brain as a small world network that balances integration—high-degree nodes forming long-range connections that provide quick access to different parts of the brain—and segregation—specialized, locally clustered, information processing modules responsible for specific tasks. The rich club of highly interconnected hubs is predominantly used for long-range paths, while short- and medium-range communication takes place mostly via peripheral routes.

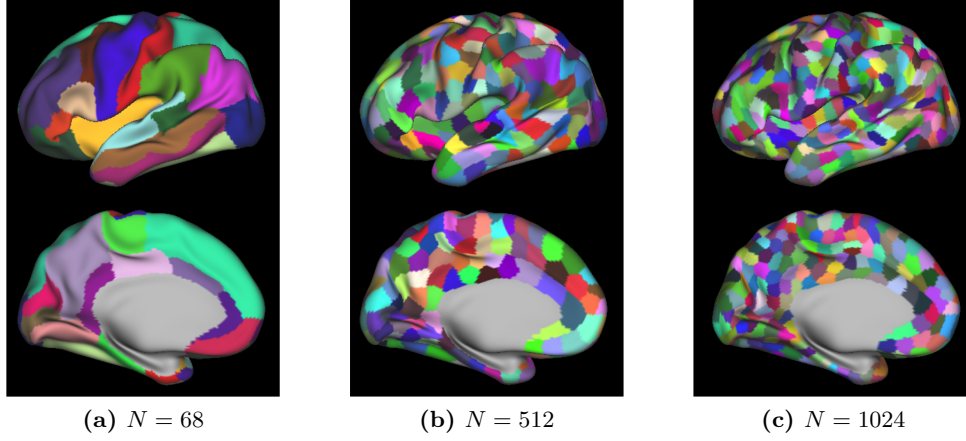


Figure S16: Cortical surface parcellation (left hemisphere). (A) Input low-resolution parcellation delineating 68 cortical regions. Output high-resolution parcellations with 512 (B) and 1024 (C) regions. All output sub-regions are contiguous, tile-shaped and have approximately the same surface area, while respecting the anatomical boundaries defined by the original 68 region atlas.

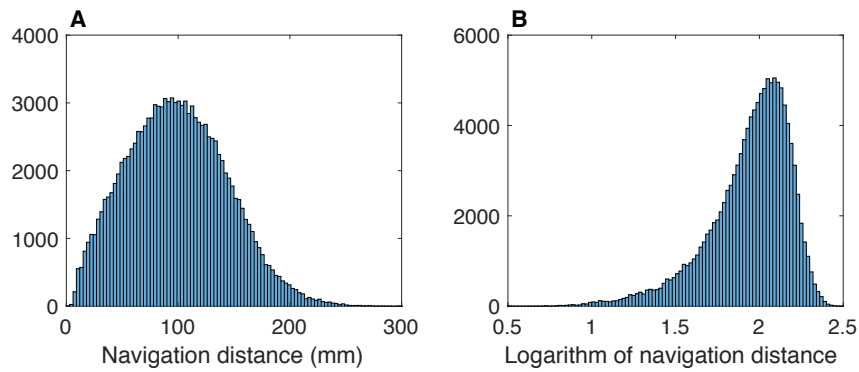


Figure S17: Distribution of raw (A) and log-transformed (B) navigation path lengths between all pairs of nodes ($N = 360$ at 15% connection density threshold).

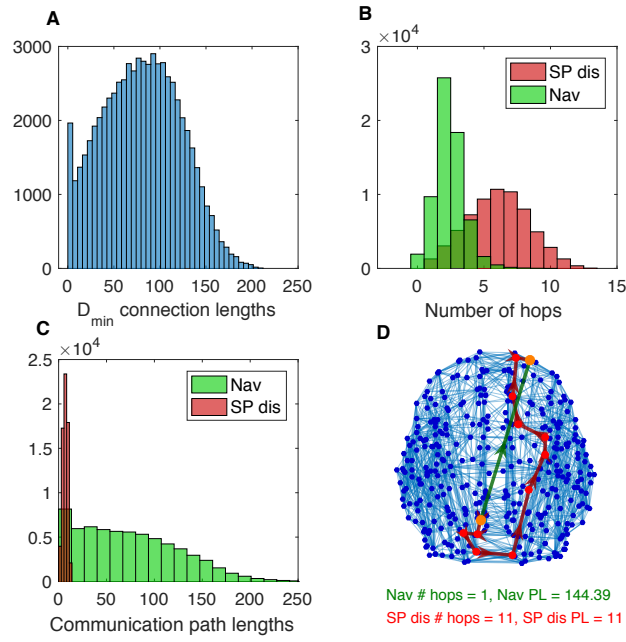


Figure S18: Exploration of navigation and distance-based shortest paths using minimum voxel distance (group-averaged connectome, $N = 360$ at 15% connection density). **(A)** Distribution of minimum voxel distances between node pairs. **(B)** Distribution of hop counts in navigation and distance-based shortest paths. **(C)** Distribution of path lengths in navigation and distance-based shortest paths. **(D)** Example of a distance-based shortest path and navigation path between structurally connected nodes.

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Chapter 4

Inferring neural signalling directionality from undirected structural connectomes

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Inferring neural signalling directionality from undirected structural connectomes

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Neural information flow is inherently directional. To date, investigation of directional communication in the human structural connectome has been precluded by the inability of non-invasive neuroimaging methods to resolve axonal directionality. Here, we demonstrate that decentralized measures of network communication, applied to the undirected topology and geometry of brain networks, can infer putative directions of large-scale neural signalling. We propose the concept of send-receive communication asymmetry to characterize cortical regions as senders, receivers or neutral, based on differences between their incoming and outgoing communication efficiencies. Our results reveal a send-receive cortical hierarchy that recapitulates established organizational gradients differentiating sensory-motor and multi-modal areas. We find that send-receive asymmetries are significantly associated with the directionality of effective connectivity derived from spectral dynamic causal modeling. Finally, using fruit fly, mouse and macaque connectomes, we provide further evidence suggesting that directionality of neural signalling is significantly encoded in the undirected architecture of nervous systems.

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Understanding how the structural substrate of connectomes^{1,2} gives rise to the rich functional dynamics observed in nervous systems is a major goal in neuroscience^{3–6}. Anatomical connectivity constrains and facilitates neural information transfer, which in turn gives rise to synchronization (i.e., functional connectivity) between neural elements. Therefore, knowledge of how neural signals are communicated in nervous systems can establish a bridge between structural and functional descriptions of brain networks^{7–10}.

While information can be directly communicated between anatomically connected neural elements, polysynaptic communication is needed for structurally unconnected elements. Network communication models describe a propagation strategy that delineates the signaling pathways utilized to transfer information between network nodes. In turn, a network communication measure quantifies the *communication efficiency* along the identified pathways from a graph-theoretic standpoint. Efficient communication pathways are generally short, traverse few synapses and comprise strong and reliable connections¹¹.

Several network models of polysynaptic communication have been proposed⁹. Shortest paths routing is the most ubiquitous model^{12–14}, which proposes that communication occurs via optimally efficient routes. However, the identification of shortest paths mandates global knowledge of network topology^{8,9,15,16}. This requirement is unlikely to be met in biological systems, in which individual elements (e.g., neurons or brain regions) do not possess information on all connections comprising the network. This has motivated research on decentralized models that capitalize on local knowledge of network properties to facilitate signaling. Examples include navigation^{15,17,18}, spreading dynamics^{19,20}, and diffusion processes^{21–24}.

Many decentralized communication models are asymmetric^{8,15,16,19}, meaning that sending information from region i to region j can be performed more efficiently than sending information from region j to region i . We coin the term *send-receive communication asymmetry*, or simply *send-receive*

asymmetry to describe this property. Importantly, the interplay between decentralized communication, network topology and possibly geometry can result in communication asymmetry in undirected networks (Fig. 1). This provides an opportunity to infer putative directions of information flow from current descriptions of the human structural connectome, for which knowledge about the directionality of individual connections is unknown due to inherent limitations of in vivo diffusion imaging. Therefore, decentralized network communication measures may help bridge the gap between our symmetric understanding of human connectome structure and the ample evidence for its asymmetric functional dynamics^{25–27}.

We provide multiple lines of evidence suggesting that decentralized communication measures, applied to undirected brain networks, can provide new insight into the directionality of neural information flow. We begin by classifying individual cortical regions and subsystems as senders (biased towards the efficiency of outgoing paths), neutral (symmetric communication efficiency) and receivers (biased towards the efficiency of incoming paths). We demonstrate that regional variation in send-receive asymmetry recapitulates established hierarchies of cortical organization. Next, we analyze pairwise send-receive asymmetries between cortical subsystems, providing multi-scale maps of communication directionality in the human cortex. Crucially, we validate these maps by showing a significant association between send-receive asymmetry and directionality of effective connectivity derived from dynamic causal modeling (DCM) applied to resting-state functional magnetic resonance imaging (fMRI). These results suggest that the undirected topology of the human connectome imposes constraints on neural signaling directionality. We further investigate this notion by examining fly, mouse and macaque connectomes. We leverage the presence of directed connections in these brain networks to provide additional evidence that neural signaling directionality is not exclusively contingent on directed axonal projections, being partially shaped by the undirected organization of nervous systems.

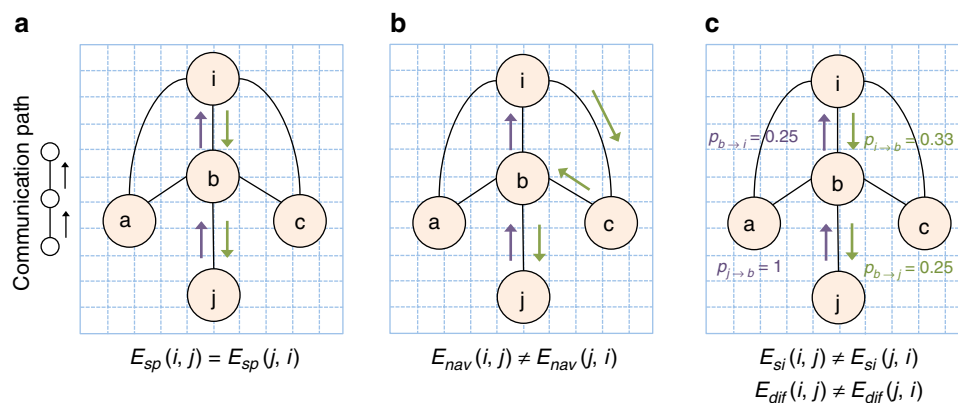


Fig. 1 Illustrative examples of send-receive communication asymmetry. The toy network is spatially embedded, unweighted and undirected. Communication efficiency from node i to j under measure $x \in \{sp, nav, si, dif\}$ is denoted $E_x(i, j)$. Shortest path and navigation efficiencies are computed as the inverse of the number of connections comprising shortest and navigation paths, respectively. Diffusion efficiency relates to how quickly, on average, a random walker can travel between two nodes, while search information relates to the probability that a random walker will travel between two nodes via the shortest path linking them. The path identified under each communication model is designated with green ($i \rightarrow j$) and mauve ($j \rightarrow i$) arrows. Send-receive communication asymmetry refers to $E_x(i, j) \neq E_x(j, i)$. **a** Shortest path efficiency is always symmetric in undirected networks, and thus $E_{sp}(i, j) = E_{sp}(j, i)$. **b** Navigation routes information by progressing to the next directly connected node that is closest in distance to the target node. This results in the $i \rightarrow c \rightarrow b \rightarrow j$ and $j \rightarrow b \rightarrow i$ navigation paths, with respective efficiency $E_{nav}(i, j) = 0.33$ and $E_{nav}(j, i) = 0.5$. Hence, navigation is more efficient from node j to node i . **c** Arrows denote the symmetric shortest paths between i and j . Arrows are annotated with the probabilities that a random walker will traverse their respective connections based on node degree (e.g., each of the 3 connections of node i has approximately 0.33 probability to be traversed by a random walker leaving i). We have $E_{si}(i, j) \propto 0.33 \times 0.25 = 0.0825$ and $E_{si}(j, i) \propto 1 \times 0.25 = 0.25$. Hence, a random walker has higher probability of traveling via the shortest path in the $j \rightarrow i$ direction, characterizing search information asymmetry between i and j . Similarly, on average, a random walker is expected to visit fewer nodes traveling from i to j than from j to i . Hence, $E_{dif}(j, i) > E_{dif}(i, j)$, characterizing diffusion efficiency asymmetry

Results

Measures of send-receive communication asymmetry. We investigated three asymmetric network communication measures: (i) navigation efficiency, (ii) diffusion efficiency, and (iii) search information (Methods section, and Network communication measures). Briefly, navigation efficiency¹⁵ relates to the length of paths identified by navigation or greedy routing^{17,28}, with higher values of efficiency indicating faster and more reliable communication between nodes. Diffusion efficiency²³ quantifies how many intermediate regions (synapses), on average, a naive random walker needs to traverse to reach a desired destination region. Finally, search information is related to the probability that a random walker will travel from one region to another via the shortest path between them^{8,29}, quantifying the extent to which efficient routes are hidden in the network topology. Together, these measures are representative of different conceptualizations of decentralized network communication^{9,16}, from single-path routing via geometric navigation to diffusive signaling unfolding along multiple network fronts.

Communication asymmetry is introduced by the decentralized character of certain network communication models (Fig. 1). Consider the flow of information from one region, termed the *source node*, to another region, termed the *target node*. If this source-target pair is not directly connected, information must flow via a polysynaptic path that traverses one or more intermediate nodes. Decisions on how signals are propagated through the connectome depend on the local topology around each node. Since source and target nodes occupy potentially different vicinities, communication may happen through distinct paths, and thus with different efficiency, depending on the direction of information flow. In contrast, centralized communication models such as shortest path routing always yield symmetric paths in undirected networks.

We use $C \in \mathbb{R}^{N \times N \times K}$ to denote a set of communication matrices for K individuals, where $C(i, j, k)$ denotes the communication efficiency from node i to node j for individual k , under an arbitrary communication measure (Fig. 2a). The difference in communication efficiency for opposing directions of information flow between i and j is given by $\Delta(i, j, k) = C(i, j, k) - C(j, i, k)$. We perform a one-sample t -test to determine whether the mean of the distribution $\Delta(i, j, k = 1 \dots K)$ is significantly different to 0 (Fig. 2c). This yields a t -statistic, termed $A(i, j)$, which quantifies the extent of communication asymmetry between i and j . In particular, if $A(i, j)$ is significant and greater than zero, we conclude that communication can occur more efficiently from node i to node j , rather than from node j to node i . Note that $A(i, j) = -A(j, i)$, and thus if $A(j, i)$ is significantly less than zero, we reach the same conclusion. Repeating this test independently for all pairs of nodes yields the communication asymmetry matrix A , for which values are symmetric about the main diagonal, but with opposite signs.

The above measure is specific to pairs of nodes. We use a variation of this test to compute regional send-receive communication asymmetry by taking into account all outgoing and incoming communication paths of a given node (Methods section, Communication asymmetry test, and Supplementary Fig. 1). Regions that show a significantly higher efficiency of outgoing (incoming) communication are classified as putative senders (receivers), while nodes that do not favor a direction of information flow are classified as neutral.

Senders and receivers of the human connectome. Whole-brain white matter tractography was applied to high-resolution diffusion MRI data acquired for $K = 200$ healthy adults (age 21–36, 48.5% female) participating in the Human Connectome Project³⁰. Structural brain networks were mapped at several spatial

resolutions ($N = 256, 360, 512$ regions; Methods section, Connectivity data. For each individual, the resulting weighted adjacency matrix was thresholded at 10%, 15%, and 20% connection density to eliminate potentially spurious connections³¹, and subsequent analyses were carried out on the obtained weighted connectomes. Communication matrices quantifying the communication efficiency between every pair of regions were computed (Fig. 2a, Methods section, Network communication models) and used to derive measures of send-receive communication asymmetry (Methods section, Communication asymmetry test). We focus on describing the results for $N = 360$, corresponding to a state-of-the-art cortical atlas derived from high-quality multi-modal data from the HCP³², and 15% connection density. Results for other connection densities and parcellation resolutions can be found in the Supplementary Information.

Significant asymmetries in the efficiency of sending versus receiving information were evident for most cortical regions (Fig. 3a, d, g). Regional values of send-receive asymmetry were significantly correlated across regions among the communication measures investigated (navigation and diffusion: $r = 0.29$, navigation and search information: $r = 0.31$, diffusion and search information: $r = 0.85$; all $P < 10^{-7}$). Based on these send-receive asymmetries, we classified all regions as senders, receivers or neutral. As expected from the strong correlation between them, diffusion and search information asymmetries led to similar classifications, likely due to their mutual dependence on random walk processes. While communication under navigation is guided by different mechanisms, classification consistency across measures was greater than expected by chance (Supplementary Note 1).

Primary sensory and motor regions were identified as senders (A1, S1, and M1 across all communication measures and V1 for navigation and diffusion). This is consistent with the notion that early auditory, visual and sensory-motor areas constitute the three main input streams to the cortex, being the first cortical regions to process sensory stimuli transmitted from subcortical structures^{32,33}. In contrast, expanses of the orbital and polar frontal cortices, the medial and dorsolateral prefrontal cortices, and the precuneus were classified as receivers. These regions have been proposed as putative functional hubs, supporting abstract and high-order cognitive processes by integrating multiple modalities of information^{34–36}. Other regions consistently identified as senders included portions of the superior temporal, medial temporal and posterior cingulate cortices, while parts of intraparietal sulcus cortex, dorsal, and ventral streams consistently ranked amongst receivers. The MT+ complex was also a prominent receiver, potentially reflecting the role of higher order sensory regions as integrators of signals transmitted from primary/earlier cortices. Certain regions were classified as senders under one communication measure but receivers under another measure, possibly reflecting how the three communication measures uniquely interact with connectome topology. Inconsistently classified regions included portions of the paracentral, cingulate, middle temporal, and inferior temporal cortices. Details on how to access complete send-receive asymmetry tables and cortical maps are provided in Methods section and Data availability.

Despite significant asymmetries in the efficiency of sending versus receiving information *within* individual regions, these send-receive asymmetries were superposed atop a strong correlation *across* regions between send and receive efficiency (navigation: $r = 0.95$, search information: $r = 0.79$; both $P < 10^{-15}$; Fig. 3b, e). In other words, efficient senders were also typically efficient receivers, and vice versa. Therefore, while all senders were by definition significantly more efficient at sending than receiving, some

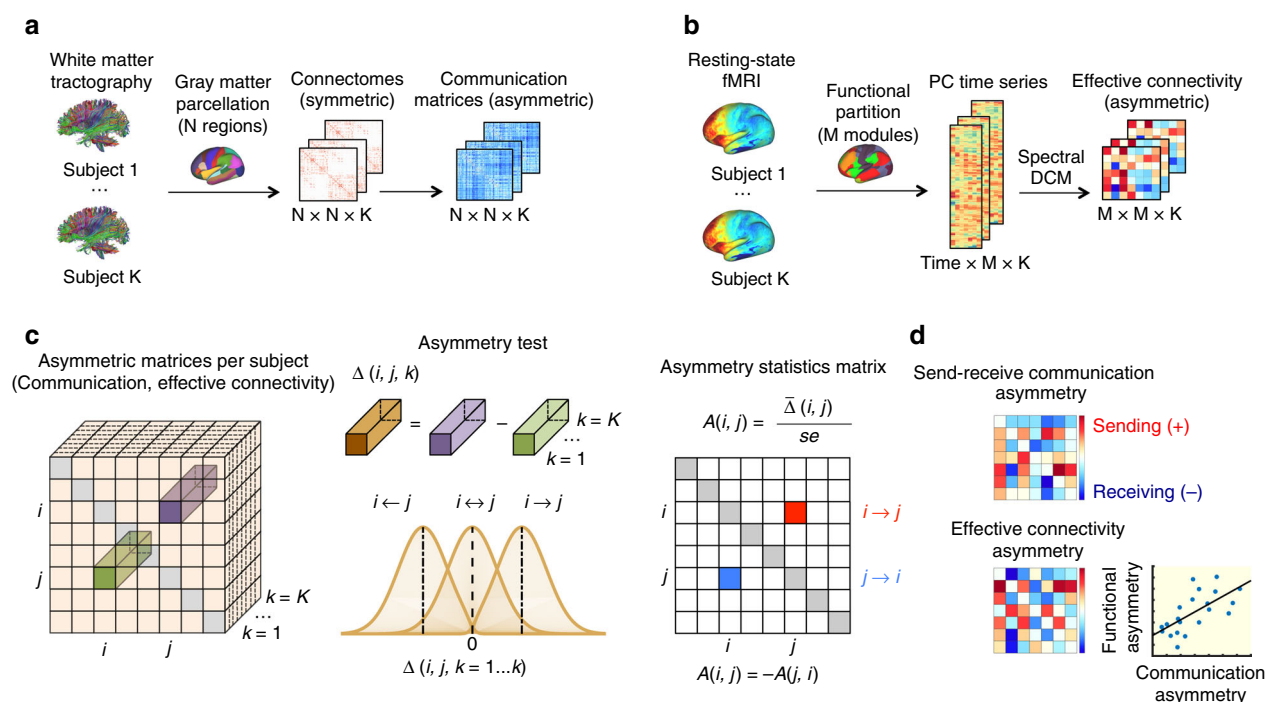


Fig. 2 Methodology overview. **a** White matter tractography applied to diffusion MRI data for $K = 200$ adults participating in the HCP was used to map undirected (i.e., symmetric) weighted adjacency matrices representing the structural connectivity between $N = 256,350,512$ cortical regions. Navigation efficiency, diffusion efficiency and search information were computed between every pair of regions to generate asymmetric communication matrices. **b** Resting-state fMRI data for the same HCP participants was used to compute principal component (PC) time series summarizing the functional activity of $M = 7,17,22$ cortical subsystems. For each individual, effective connectivity between cortical subsystems was computed using spectral DCM. **c** Schematic of the communication asymmetry test. First, for a pair of nodes i and j , the difference in communication efficiency between the $i \rightarrow j$ and $j \leftarrow i$ directions was computed. Performing this for K individuals yielded the distribution $\Delta(i, j, k = 1 \dots K)$. Communication asymmetry was assessed by performing a one-sample t -test to determine whether the mean of this distribution is significantly different to 0, with $A(i, j)$ defined as the resulting matrix of t -statistics. **d** The asymmetry test was applied to compute $M \times M$ matrices of communication and effective connectivity send-receive asymmetries between modules. We sought to test for correlations across the corresponding elements of these two matrices

senders were in fact *less* efficient at sending than some receivers. In contrast, send and receive efficiencies were not correlated under diffusion ($r = -0.1$, $P = 0.1$). In addition, send efficiency was relatively uniform across regions under diffusion, while receive efficiency showed markedly higher regional diversity.

Node degree and participation (Supplementary Note 2) were associated with send-receive asymmetries under diffusion and search information (degree: $r = -0.54$, -0.70 , participation: $r = -0.29$, -0.32 , respectively. All $P < 10^{-7}$), with senders and receivers characterized by low and high degree/participation, respectively. We regressed out the influence of degree on send-receive asymmetry and found that primary cortices remained senders while frontal and prefrontal regions remained receivers. We also noticed that sensory-motor and auditory cortices displayed a significantly higher propensity towards outgoing communication than expected based on their degree alone (Supplementary Fig. 2). Send-receive asymmetry under navigation was not correlated with degree or participation (both $P > 0.05$), with senders and receivers uniformly distributed across the degree distribution.

Senders and receivers situated within cortical gradients. Next, we aimed to test whether regional variation in send-receive asymmetry would accord with established hierarchies of cortical organization³⁷. To this end, we investigated whether senders and receivers would reside at opposing ends of a previously delineated unimodal to multimodal gradient of functional connectivity^{35,89}

Under all three communication measures, senders were more likely to be located at the unimodal end of the gradient, whereas the multimodal end was occupied by receivers. More specifically, send-receive asymmetry and the cortical gradient were significantly correlated across regions ($r = -0.20$, -0.30 , -0.29 , for navigation, diffusion and search information, respectively. All $P < 10^{-4}$). These associations remained significant after accounting for the influence of degree on send-receive asymmetries (all $P < 2 \times 10^{-4}$).

In further analyses, regions were classified as unimodal (U), transitional (T), or multimodal (M) based only on the cortical gradient (Methods section, Cortical gradient of functional heterogeneity). We compared the send-receive asymmetry of these groups and found that unimodal and transitional areas were significantly more efficient at outgoing communication compared to multimodal areas (Fig. 3c, f, i; $P_{T>M} = 0.01$, 2×10^{-4} , 2×10^{-4} and $P_{U>M} = 4 \times 10^{-4}$, 3×10^{-6} , 8×10^{-7} , for navigation, search information and diffusion, respectively). Send-receive asymmetry did not differ between unimodal and transitional regions.

These results were generally robust to variations in cortical parcellation and connection density thresholds (Supplementary Figs. 3 and 4). Taken together, our findings demonstrate that decentralized communication measures applied to the undirected human connectome unveil regional distinctions between putative senders and receivers. Furthermore, we show that knowledge about the direction of information flow can elucidate novel organizational structure within established cortical hierarchies,

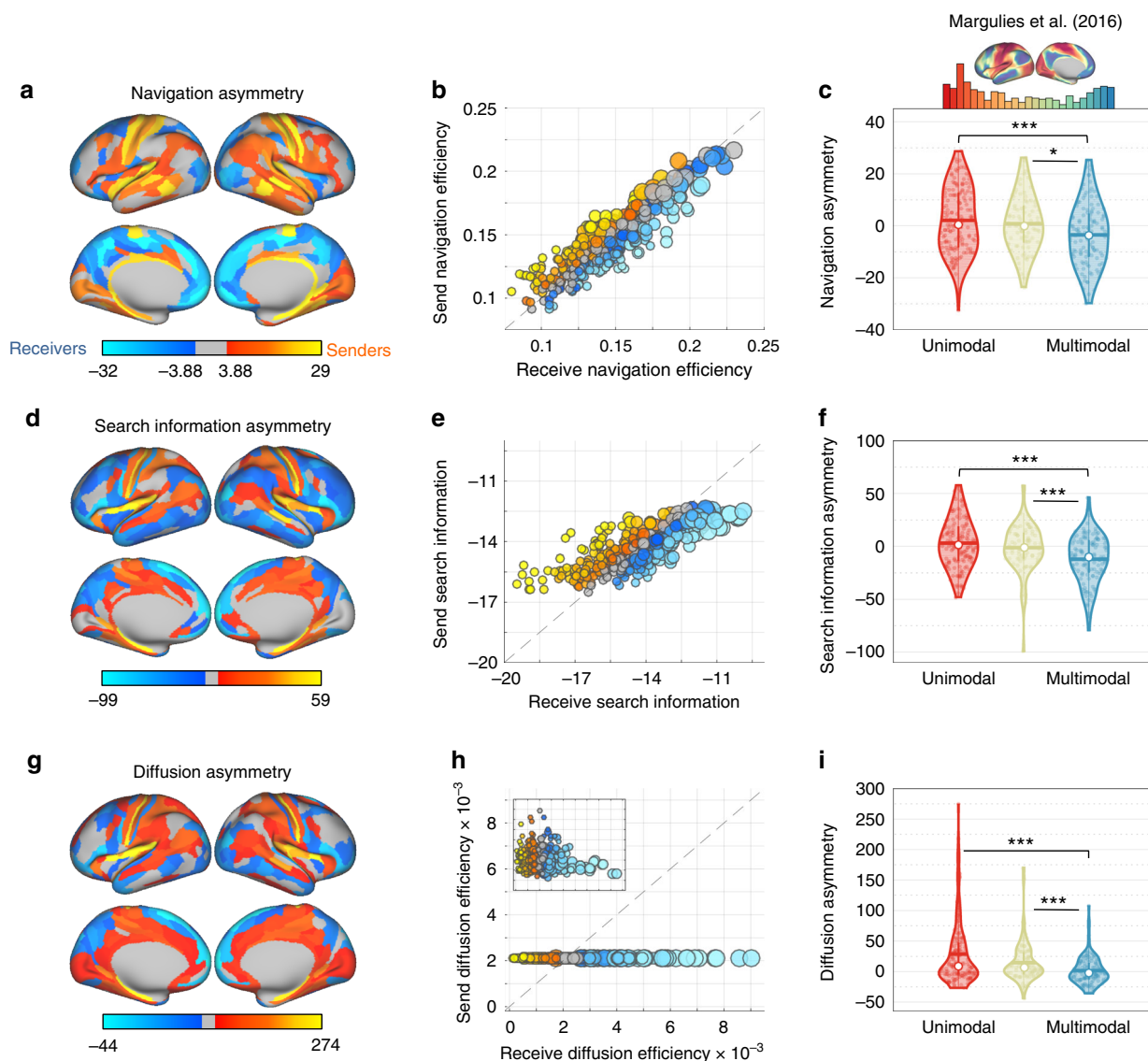


Fig. 3 Send-receive communication asymmetry in the human connectome ($N = 360$ at 15% connection density). **a** Cortical projection of send-receive asymmetry values under navigation. Regions associated with significant send-receive asymmetry are classified as putative senders (orange) and receivers (blue). Regions colored gray are neutral and do not show significant send-receive asymmetry. **b** Scatter plot showing correlation between send (vertical axis) and receive (horizontal axis) efficiency across regions under navigation. Send and receive efficiency values were aggregated across all individuals for each region. Markers are colored according to send-receive asymmetry values (colors approximately match that of panel **a**). Small, medium and large markers represent nodes with low ($\kappa < 50$), medium ($50 \leq \kappa \leq 100$) and high ($\kappa > 100$) degree, respectively. The dashed line marks the $x = y$ identity line. The distance between markers and the identity line provides a geometric interpretation of regional bias towards sending ($x < y$) or receiving ($x > y$) efficiencies. **c** Top: Distribution of the cortical gradient eigenvectors used as a measure of functional heterogeneity³⁵. Bottom: Violin plots showing distribution of send-receive asymmetries for regions classified as unimodal (red), transitional, (beige) and multimodal (blue) regions. Horizontal bars and white circles denote, respectively, the mean and median of the distributions. Stars denote significant differences in between-group medians given by a two-sided Wilcoxon rank sum test (one, two and three stars denote $P < 0.05$, 0.005 , 0.0005 , respectively). **d**, **e** Search information equivalent of **a**–**c**. **(g–i)** Diffusion efficiency equivalent of **a**–**c**

such as the biases towards outgoing and incoming communication efficiency of unimodal and multimodal regions, respectively.

Senders and receivers of cortical subsystems. Next, we sought to investigate pairwise send-receive asymmetries between large-scale cortical subsystems (Supplementary Fig. 5). We assigned cortical regions to distributed cognitive systems according to established resting-state networks comprising $M = 7$ and 17 subsystems³⁸. In addition, we employed a multimodal partition of the cortex into $M = 22$ spatially contiguous subsystems³². Regional communication matrices were downsampled to subsystem resolution and

send-receive asymmetries were computed at individual and pairwise subsystem levels (Methods section, Cortical subsystems).

In keeping with the regional findings, pairwise send-receive asymmetry values were significantly correlated across the communication measures investigated (e.g., navigation and diffusion: $r = 0.60$, navigation and search information: $r = 0.66$, diffusion and search information: $r = 0.96$; all $P < 10^{-15}$, $M = 17$). Given the consistency of findings across communication measures, we focus on navigation in this section (Fig. 4). Complete results for navigation, diffusion and search information are shown, respectively, in Supplementary Figs. 6–8).

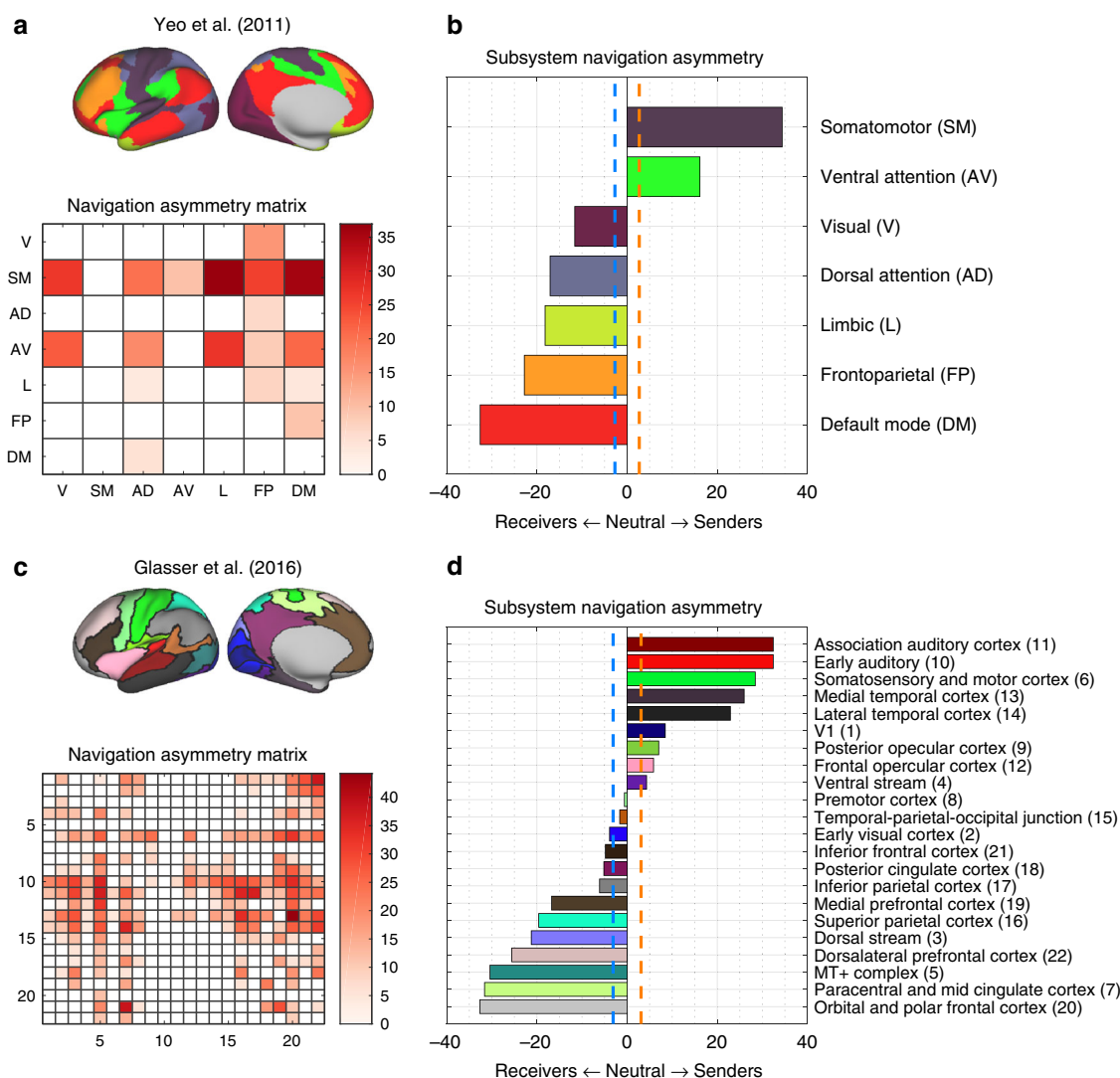


Fig. 4 Send-receive asymmetry of cortical subsystems under navigation ($N = 360$ at 15% connection density). **a** Projection of $M = 7$ distributed resting-state networks onto the cortical surface (top) and send-receive asymmetry matrix under navigation (bottom). A matrix element $A(i, j) > 0$ denotes that communication occurs more efficiently from i to j than from j to i . Send-receive asymmetry values that did not survive multiple comparison correction were suppressed and appear as white cells. For ease of visualization and without loss of information (since $A(i, j) = -A(j, i)$), negative values were omitted. **b** Resting-state networks ranked by propensity to send (top) or receive (bottom) information. Dashed vertical lines indicate a significant bias towards outgoing (orange) and incoming (blue) communication efficiency. **c, d** Same as **a, b**, but for $M = 22$ spatially contiguous cortical subsystems. Numbers listed next to module names identify corresponding rows and columns in the asymmetry matrix

As shown in Fig. 4a, b, the somatomotor and ventral attention networks were the most prominent senders for the $M = 7$ partition. Prominent receivers included the default mode, frontoparietal and limbic networks, which were more efficiently navigated from a number of cognitive systems than vice versa. Interestingly, adopting a higher resolution functional partition ($M = 17$) suggested that sub-components of coarse ($M = 7$) resting-state networks can assume different roles as senders and receivers. For instance, the visual network was segregated into early (e.g., V1 and V2) and late areas of the visual cortex (e.g., MT + complex and dorsal and ventral streams), with the first being a sender and the latter a receiver (Supplementary Fig. 6). Other systems that exhibited this behavior included the ventral attention, limbic, somatomotor and default mode networks. These findings reiterate that, despite the presence of asymmetries in send-receive efficiency, cognitive systems are not exclusively capable of sending or receiving, suggesting connectome topology

may allow for context-dependent directionality of neural information flow between functional networks.

We also identified senders and receivers for a high-resolution cortical partition comprising $M = 22$ subsystems³². This enabled a fine-grained, yet visually interpretable, characterization of send-receive asymmetries (Fig. 4c). Cortical domains associated with auditory, somatosensory and motor processes ranked amongst the strongest senders, while frontal and prefrontal areas consistently featured amongst the most prominent receivers (Supplementary Figs. 6–9). Together, these results provide putative multi-scale maps of how the structural substrate of the human connectome may facilitate directional information flow between cognitive subsystems.

Senders, receivers, and effective connectivity. We sought to validate our characterization of subsystems as senders or receivers using an independent data modality. To this end, time series

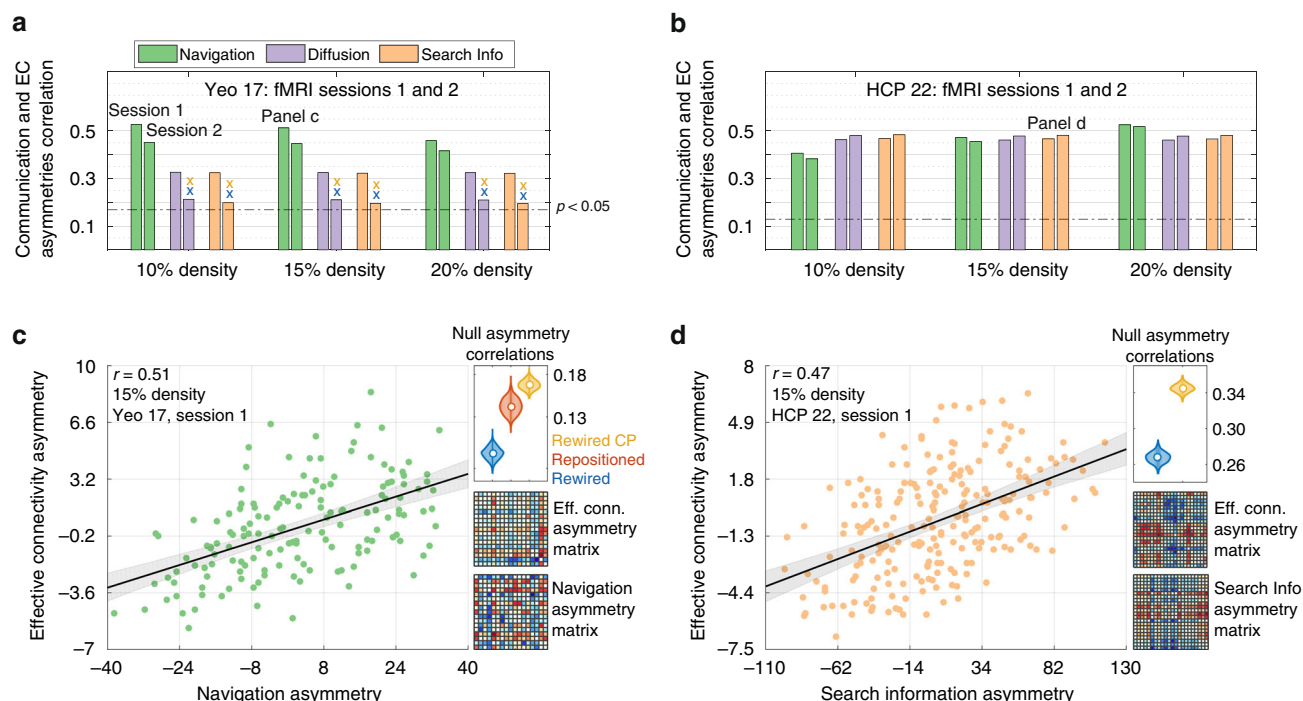


Fig. 5 Relationship between send-receive asymmetry and directionality of effective connectivity ($N = 360$). **a** Bars denote the Pearson correlation coefficients between send-receive and effective connectivity asymmetries for $M = 17$ cortical subsystems. Bars are colored according to the three communication measures: (i) navigation (green), (ii) diffusion (violet), and (iii) search information (beige). Correlations were computed for two independent resting-state fMRI sessions (Sessions 1 and 2) and multiple structural connection density thresholds (10, 15, and 20%). Significance threshold of $P < 0.05$ is indicated with a dotted line. Crosses mark associations that were not statistically stronger than those found in families of 1000 rewired (blue) and 1000 cost-preserving rewired (yellow) connectomes, respectively (repositioned connectomes, relevant for navigation, led to statistically weaker associations in all scenarios). **b** Replication of Panel **a** for a cortical partition comprising $M = 22$ subsystems. **c** Left: scatter plot illustrating the correlation between navigation and effective connectivity asymmetries for $M = 17$, 15% connection density and fMRI session 1. Shadows denote the 95% bootstrapped confidence interval. Top-right: Distribution of correlations obtained for families of 1000 rewired (blue), repositioned (red) and cost-preserving rewired (yellow) connectomes. Bottom-right: Send-receive asymmetry matrices for effective connectivity (resting-state functional MRI) and navigation (diffusion MRI). The upper-triangular elements of these two matrices were correlated to test whether senders and receivers were consistently identified across independent modalities. **d** Replication of Panel **c** for search information, $M = 22$, 10% connection density and fMRI session 2. EC effective connectivity, r Pearson correlation coefficient

summarizing the functional dynamics of cortical subsystems were extracted from resting-state functional MRI data for the same $K = 200$ HCP participants. For each individual, we used spectral DCM^{39,40} to compute effective connectivity between cortical subsystems ($M = 7, 17, 22$, see Methods section, Effective connectivity). Pairwise effective connectivity asymmetry was computed at the scale of subsystems by applying the previously described asymmetry test to the estimated effective connectivity matrices (Fig. 2c). Importantly, effective connectivity is an inherently directed (asymmetric) measure of connectivity. This allowed us to test whether send-receive asymmetries in communication efficiency (derived from diffusion MRI) and effective connectivity (derived from resting-state fMRI) are correlated (Fig. 2d).

Communication and effective connectivity send-receive asymmetries were significantly correlated across pairs of subsystems (Fig. 5). These associations were significant for all three communication measures and were replicated across two independent resting-state functional MRI sessions and multiple structural connection densities. For instance, for $M = 17$, fMRI session 1 and 15% connection density, we found $r = 0.51, 0.32, 0.32$ for navigation, diffusion and search information, respectively (all $P < 10^{-4}$). Similarly, for $M = 22$, fMRI session 2 and 15% connection density, we obtained $r = 0.45, 0.48, 0.48$ for navigation, diffusion and search information, respectively (all $P < 10^{-12}$). No significant correlations were found for $M = 7$, possibly

due to the lack of statistical power afforded by only 21 data points comprising the upper triangle of asymmetry matrices. These results suggest that biases in the directionality of neural signaling inferred from the structural connectome are related to the directions of causal functional modulation during rest. Therefore, they establish a correspondence between structural (connectome topology and network communication measures) and functional (effective) directions of neural information flow.

We sought to determine whether the above association between communication and effective connectivity could be explained by certain properties of connectome organization. We generated ensembles of randomized connectomes in which (i) connectome topology was rewired while preserving degree distribution⁴¹; (ii) connectome topology was rewired while preserving degree distribution and total network cost (defined as the sum of Euclidean distances between structurally connected nodes¹⁴); and (iii) nodes were spatially repositioned while preserving topology (relevant only for navigation; see Supplementary Note 3). For all families of randomized connectomes, correlations between asymmetries in effective connectivity and communication efficiency were significantly decreased compared to empirical results (e.g., Fig. 5c, d top-right corner, all $P < 10^{-3}$; with the exception of diffusion and search information for the $M = 17$ partition in fMRI session 2, Fig. 5a). These results indicate that the relationship between send-receive asymmetry and directionality of effective connectivity cannot be explained by

the combination of connectome degree distribution and network cost, since these properties were preserved in random ensembles (i) and (ii). For navigation, random ensemble (iii) highlights the importance of connectome geometry in addition to topology.

Control analyses. Having established several properties of the senders and receivers of the human connectome, we aimed to determine whether our results were robust to alternative definitions of send-receive communication asymmetry and changes in our connectome mapping pipeline. First, we redefined our communication asymmetry measure using non-parametric Wilcoxon rank sum tests instead of *t*-tests (Supplementary Note 4). This approach ensures that send-receive asymmetries are robust to deviations from normality and outliers. Second, we computed the send-receive asymmetries of connectomes derived with probabilistic tractography (Supplementary Note 5). Third, we investigated send-receive asymmetries in connectomes including subcortical structures (Supplementary Note 6). Send-receive asymmetries were compatible across all three scenarios and remained consistently associated with the directionality of effective connectivity (Supplementary Fig. 10). Interestingly, while the classification of nodes into senders and receivers in connectomes containing subcortical structures remained largely unaltered, biases towards incoming or outgoing communication were less pronounced (Supplementary Figs. 12 and 13), suggesting a role of subcortical structures as mediators of neural signaling directionality.

Senders and receivers of non-human connectomes. The association between effective connectivity directionality and the send-receive asymmetry of undirected connectomes indicates that signaling directions in the human brain are not exclusively determined by axonal directions. To further quantify this observation, we next sought to establish the extent to which signaling directionality is determined by axonal directions per se, compared to other potential determining factors such as network topology and geometry.

Invasive connectome reconstruction techniques allow for the resolution of axonal directionality, producing directed connectomes for a host of non-human species⁴². Here, we consider the connectomes of the fruit fly (*Drosophila*)^{43,44}, mouse^{45,46} and macaque⁴⁷ (Methods section, Non-human connectomes). We began by computing the send-receive asymmetries of these directed connectomes. In this case, communication asymmetry is introduced both by the asymmetric character of the network communication measures and by the presence of directed connections. Next, we symmetrized the connectomes by removing connection directionality, so that all connections could be traversed bidirectionally (Methods section, Symmetrized non-human connectomes), and recomputed send-receive asymmetries for the resulting undirected networks. In this scenario, as with human undirected connectomes, asymmetries are introduced solely by the asymmetry inherent to the network communication measures. We tested whether send-receive asymmetry values computed in the directed (original) and undirected (symmetrized) non-human connectomes were correlated across regions. Evidence of a correlation would suggest that the undirected topology and geometry of connectomes are influential in determining the directionality of neural signaling in the absence of directed connections.

We found that undirected and directed send-receive asymmetries were correlated for binarized (fly: $r = 0.95, 0.96$, mouse: $r = 0.58, 0.50$, macaque: $r = 0.87, 0.75$, for diffusion and search information asymmetries, respectively; Fig. 6a, c, d) and weighted (fly: $r = 0.58, 0.84, 0.41$, mouse: $r = 0.34, 0.32, 0.38$, macaque: $r = 0.67, 0.80, -0.26$, for navigation, diffusion and search information asymmetries, respectively; Fig. 6b, e, f) non-human connectomes. All reported r had $P < 10^{-10}$ and thus survived Bonferroni correction for multiple comparisons. The exception was the association for the macaque weighted search information ($P = 0.01$), potentially indicating the spurious nature of this negative correlation. It is worth noting that binary navigation paths are seldom asymmetric for densely connected networks such as non-human connectomes, resulting in weak/undefined correlations between directed and undirected send-receive asymmetries. In addition, due to the presence of connection weight asymmetries between bidirectionally connected node pairs, original and symmetrized connectomes are more similar for unweighted than weighted networks, explaining the stronger associations observed for binarized connectomes.

Finally, we observed that regional senders and receivers of undirected (symmetrized) non-human connectomes also recapitulated putative hierarchies of functional specialization (Supplementary Note 7). For instance, macaque sensory, visual and motor areas were senders, while portions of the frontal and prefrontal cortices were receivers (Supplementary Figs. 14g, h, i and 15). Collectively, these findings provide further evidence that the directionality of neural signaling is partially determined by the undirected architecture of nervous systems across species.

Discussion

The present study focused on characterizing the directionality of neural information flow arising from the application of decentralized network communication measures to connectomes. In a recent study, Avena-Koenigsberger and colleagues presented a first account of differences between send and receive communication in brain networks¹⁶. Here, we build on these efforts by contributing a statistical framework to compute send-receive communication asymmetry. We apply this framework to identify putative sender and receiver brain regions, as well as pairwise maps of neural signaling directionality for the nervous systems of several species.

Send-receive asymmetry recapitulated hierarchical patterns of cortical organization from a structural connectivity standpoint. Several studies of axonal tract-tracing and non-human connectomes^{34,48,49}, macroscale gradients of cortical organization^{35,37,50}, and computational models of neuronal dynamics^{27,51–54} converge to a common conceptualization of a cortical hierarchy of functional specialization. The bottom of the hierarchy tends to comprise high-frequency, low-degree, unimodal, sensory and motor areas that constitute the main inputs of perceptual information to the brain. At the top, low-frequency, high-degree, multimodal regions are conjectured to integrate multiple streams of information in order to support higher cognitive functions. Our observations of a send-receive spectrum of cortical regions and subsystems complements this description of neural organization, placing senders and receivers, respectively, at the unimodal and multimodal ends of the hierarchy.

Previous studies have demonstrated that navigation efficiency, search information and diffusion computed on structural connectomes are capable of inferring resting-state functional connectivity^{8,15,24}. Here, we provided further evidence for the utility of decentralized communication models by showing an association between send-receive asymmetry—inferred from connectomes mapped with tractography and diffusion MRI—and directionality of effective connectivity—computed from spectral DCM applied to resting-state fMRI. This relationship was robust to variations in tractography algorithms, cortical subsystem parcellations, treatment of subcortical structures, send-receive asymmetry statistical tests, structural connection density

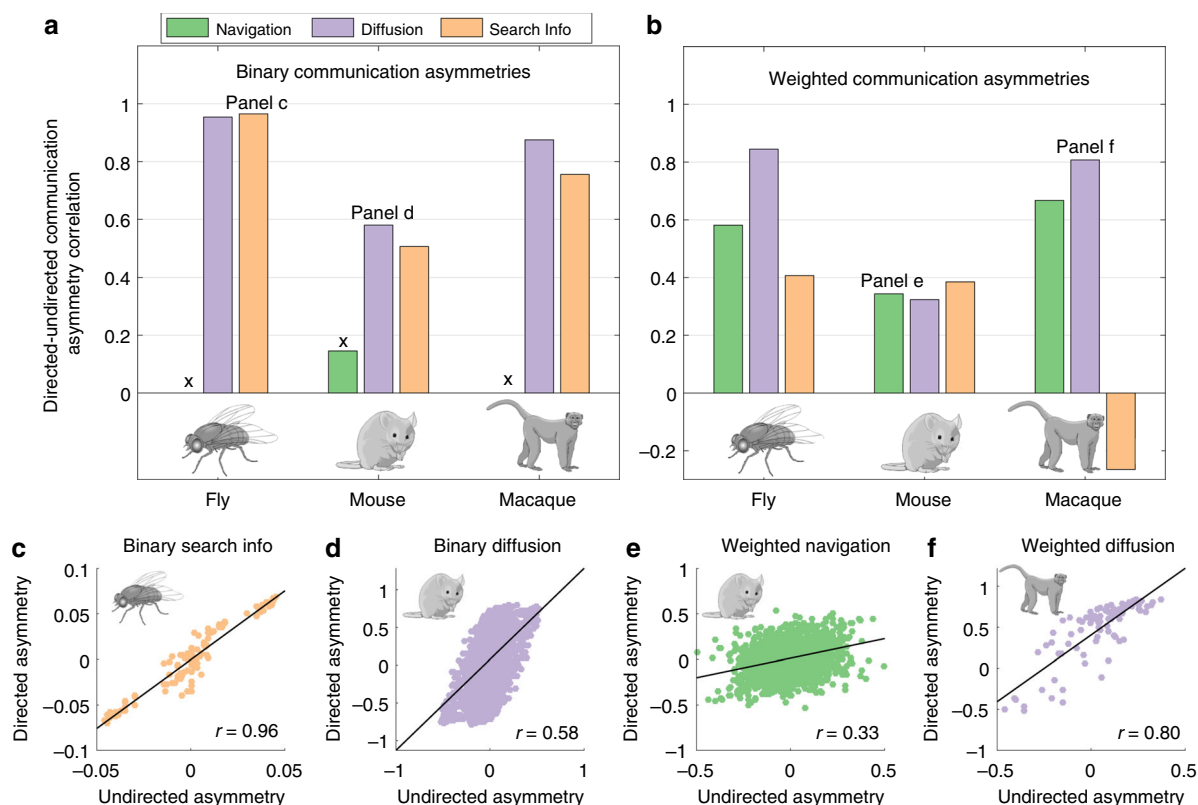


Fig. 6 Directed and undirected (symmetrized) send-receive asymmetries in non-human connectomes. **a** Pearson correlation coefficient across regions in send-receive asymmetry values between directed and undirected navigation (green), diffusion (violet) and search information (beige) asymmetries for binarized (unweighted) connectomes. Black crosses indicate *non-significant* ($P > 0.05$) or undefined (in the case of lack of communication asymmetry) correlations. **b** Same as panel **a**, but for weighted connectomes. **c–f** Scatter plots illustrating the association between directed and undirected communication asymmetries (r : Pearson correlation coefficient, P : associated P -value)

thresholds and two independent resting-state fMRI sessions. Compared to the first fMRI session, the strength of this relationship was weaker in the second session for the case of the $M = 17$ cortical subsystems. This may be due to the effect of MRI phase-encoding differences between the two sessions (Methods section, Send-receive effective connectivity asymmetry) on particular subsystem parcellations, although this requires further investigation.

Recent work has demonstrated the validity of spectral DCM in multi-site longitudinal settings⁵⁵ and using optogenetics combined with functional MRI in mice⁵⁶. The use of spectral DCM instead of the traditional task-based DCM was motivated by two important factors. First, spectral DCM infers effective connectivity from resting-state fMRI data, allowing validation of our findings independent of hypotheses about the directionality of causal connectivity specific to certain task scenarios. In addition, recent evidence indicates that functional connectivity topology at rest shapes task-evoked fluctuations, highlighting the cognitive relevance of resting-state neural dynamics^{57,58}. Second, spectral DCM is capable of handling relatively large networks comprising many regions⁵⁹. This enabled a direct comparison between asymmetries in send-receive efficiency and effective connectivity at the level of subsystems spanning the whole cerebral cortex. Our results provide cross-modal evidence that network communication measures accurately capture aspects of directional causal influences between neural systems. Structurally derived communication asymmetry may help formulate hypotheses for DCM studies, potentially reducing the search space of candidate network models⁶⁰. In addition, send-receive asymmetry may be

useful in understanding asymmetric responses in functional dynamics following exogenous stimulation of brain regions^{27,52}.

The analyses of human undirected connectomes indicate that meaningful patterns of neural signaling directionality can be inferred without knowledge of the directions of axonal projections. We provided further evidence for this notion by examining non-human connectomes, for which information on axonal directionality is invasively derived. Send-receive asymmetries computed for directed connectomes were significantly associated to those derived from networks for which the directionality of connections was suppressed. Moreover, senders and receivers computed from undirected version of non-human connectomes also recapitulated putative functional roles of brain regions. These results indicate that despite the documented importance of directed connections^{47,61}, the undirected architecture of nervous systems also imposes constraints on signaling directionality. This may suggest the presence of fundamental, cross-species organization properties of brain networks that facilitate decentralized communication between neural elements. It is worth noting that send-receive asymmetry is more pronounced between pairs of regions that are not directly connected, for which communication takes place along multi-hop paths. Consequently, as formulated here, send-receive asymmetry is not well suited to perform inference for structurally connected nodes, and thus should not be conceptualized as a methodology to transform an undirected structural connectome into a directed graph. Future work exploring alternative formulations of communication asymmetry could attempt to infer directed structural traits from undirected connectomes.

Send-receive asymmetry is a result of the interaction between asymmetric network communication models and the topology and geometry of brain networks. Navigation depends on local knowledge of the network's spatial embedding to identify communication paths, while diffusive processes rely solely on local connectivity knowledge to propagate signals. Despite these conceptual differences, navigation efficiency, search information and diffusion efficiency led to similar patterns of send-receive asymmetry. The classification of cortical regions into senders and receivers, as well as the association with effective connectivity directionality was generally consistent across measures. This indicates that our results may be primarily driven by how the architecture of brain networks gives rise to general patterns of communication asymmetry, rather than by specific strategies of neural signaling. An interesting deviation from these consistencies was observed in the relationship between regional send and receive efficiencies. While navigation and search information showed a positive correlation between send and receive efficiencies, this was not the case for diffusion. Moreover, as previously reported¹⁶, diffusion receive efficiency showed markedly greater regional variation compared to diffusion send efficiency. This is a consequence of high degree nodes being more accessible to incoming random walkers than low degree ones.

We reiterate that a significant send-receive asymmetry does not preclude information transfer in a particular direction, in the same way that regions classified as senders (receivers) are capable of receiving (sending) information. Interestingly, we also found that coarse functional networks with significant biases towards incoming or outgoing communication are typically comprised of subcomponents placed along different positions of the sender-receive spectrum. This may facilitate feedback loops in which high-order regions send information to sensory cortices, allowing for flexible and context-dependent transfer of neural information. These results support the notion that cortical computations do not follow a strictly serial paradigm, but rather involve distributed hierarchies of parallel information processing^{38,48}.

Several limitations of the present study should be considered. Send-receive asymmetry was defined statistically across subjects. Future developments are necessary to conceptualize robust measures of subject-level send-receive asymmetry. In addition, alternative asymmetric network communication measures such as Markovian queuing networks⁶², linear transmission models of spreading dynamics^{19,20} and cooperative learning⁶³ can lead to further insight into the large-scale directionality of neural signaling. Additional measures of directed functional connectivity such as transfer entropy and Granger causality may offer supplementary cross-modal validation of send-receive asymmetry. Importantly, tractography algorithms are prone to known biases, potentially influencing results regarding human structural connectomes^{31,64,65}. Lastly, navigation was computed based on the Euclidean distance between brain regions. Alternative distance measures taking it account axonal fiber length may provide more biologically realistic guidance for connectome navigation.

In conclusion, we showed that the large-scale directionality of neural signaling can be inferred, to a significant extent, from the interaction between decentralized network communication measures and the undirected topology and geometry of brain networks. These results challenge the belief that connectomes mapped from in vivo diffusion data are unable to characterize asymmetric interactions between cortical elements. Our findings introduce decentralized network communication models as a new avenue to explore directional functional dynamics in human and non-human connectomes.

Methods

Connectivity data. Minimally preprocessed diffusion-weighted MRI data from 200 healthy adults (age 21–36, 48.5% female) was obtained from the Human Connectome Project (HCP)³⁰. Details about the diffusion MRI acquisition and pre-processing are described in^{66,67}.

Connectome analyses are sensitive to the number of nodes used to reconstruct brain networks⁶⁸. We aimed to reproduce our key findings for human connectomes constructed with different granularities of cortical segmentation comprising $N = 256,360,512$ regions/nodes. The parcellations for $N = 256,512$ segment the cortex into approximately evenly sized regions that respect predefined anatomical boundaries. Details on the construction of these parcellations are described in¹⁵. In addition, we mapped connectomes using the HCP MMP1.0 atlas ($N = 360$), a cortical parcellation based on multi-modal data from the HCP³².

Diffusion tensor imaging combined with a deterministic tractography pipeline was used to map connectomes for each individual. Deterministic tractography leads to less false positive connections than other reconstruction methods, and thus may better suit connectome mapping compared to alternative tractography methods^{31,64,65}. Computations were carried out using MRtrix3⁶⁹ with the following parameters: FACT tracking algorithm, 5×10^6 streamlines, 0.5 mm tracking step-size, 400 mm maximum streamline length and 0.1 FA cutoff for termination of tracks. Connection strength between a pair of regions was determined as the number of streamlines with extremities located in the regions divided by the product of the surface area of the region pair, resulting in a $N \times N$ weighted connectivity matrix per subject. For each individual, the resulting weighted adjacency matrix was thresholded at 10, 15, and 20% connection density to eliminate potentially spurious connections³¹, and subsequent analyses were carried out on the obtained weighted connectomes.

The fruit fly connectome was mapped using images of 12,995 projection neurons in the female *Drosophila* brain available in the FlyCircuit database^{43,44}. Single neurons were labeled with green fluorescent protein and traced from whole brain three-dimensional images. Individual neurons were grouped into 49 local processing units with specific morphology and function. The resulting connectome is a 49×49 weighted, directed, whole-brain network for the fruit fly, with 83% connection density.

The Allen Institute for Brain Science mapped the mesoscale topology of the mouse nervous system by means of anterograde axonal injections of a viral tracer⁴⁵. Using two-photon tomography, they identified axonal projections from the 469 injections sites to 295 target regions. Building on these efforts, Rubinov and colleagues constructed a directed, bilaterally symmetric, whole-brain network for the mouse, comprising $N = 112$ cortical and subcortical regions with 53% connection density⁴⁶. Connections represent interregional axonal projections and their weights were determined as the proportion of tracer density found in target and injected regions.

Markov and colleagues applied 1615 retrograde tracer injections to 29 of the 91 areas of the macaque cerebral cortex, spanning occipital, temporal, parietal, frontal, prefrontal and limbic regions^{47,70}. This resulted in a 29×29 weighted, directed, interregional sub-network of the macaque cortico-cortical connections with 66% connection density. Connection weights were estimated based on the number of neurons labeled by the tracer found in source and target regions, relative to the amount found in whole brain.

Network communication measures. A weighted connectome can be expressed as a matrix $W \in \mathbb{R}^{N \times N}$, where W_{ij} is the connection weight between nodes i and j . Connection weights are a measure of similarity or affinity, denoting the strength of the relationship between two nodes (e.g., streamline counts in tractography or fraction of labeled neurons in tract tracing). The computation of communication path lengths mandates a remapping of connection weights into lengths, where connection lengths are a measure of the signaling cost between two nodes¹¹. The transformation $L = -\log_{10}(W/(\max(W) + \min(W_{>0})))$ ensures a monotonic weight-to-length remapping that attenuates extreme weights^{8,71}, where $\min(W_{>0})$ denotes the smallest positive value in W , preventing the remapping of the maximum value of W to 0.

Navigation (also referred to as greedy routing) is a decentralized network communication model that utilizes information about the network's spatial embedding to route signals without global knowledge of network topology²⁸. Navigation is reported to achieve near-optimal communication efficiency in a range of real-world complex networks, including the connectomes of several species^{15,17,18}.

Navigation from node i to j was implemented as follows. Progress to i 's neighbor that is closest in distance to j . Repeat this process for each new node until j is reached—constituting a successful navigation path—or a node is revisited—constituting a failed navigation path. The distance between two nodes was computed as the Euclidean distance between the centroids of their respective gray matter regions. For each parcellation resolution, a single Euclidean distance matrix was computed in standard space and utilized to guide the navigation of each individual's connectome.

Let Λ denote the matrix of navigation path lengths. If node i cannot navigate to node j , $\Lambda_{ij} = \infty$. Otherwise, $\Lambda_{ij} = L_{i,u} + \dots + L_{v,j}$, where $\{u, \dots, v\}$ is the sequence of nodes visited during navigation. Note that while navigation paths are identified

based on the Euclidean distance between nodes, navigation path lengths are computed in terms of connection lengths derived from the structural connectivity matrix W . Navigation efficiency is given by $E_{\text{nav}}(i, j) = 1/\Lambda_{ij}$, where $E_{\text{nav}}(i, j)$ is the efficiency of the navigation path from node i to j ¹⁵.

A diffusion process is a network communication model whereby information is broadcast along multiple paths simultaneously²². Diffusion can be understood in terms of agents, often termed random walkers, which are initiated from a given region and traverse the network independently of each other by randomly selecting a connection to follow out from each successive region that is visited. Diffusive communication does not mandate assumptions on global knowledge of network topology, constituting, from this perspective, a biologically plausible model for neural communication⁹. Diffusion efficiency²³ is related to how many intermediate regions (synapses), on average, a naive random walker needs to traverse to reach a desired destination region.

Let T denote the transition probability matrix of a Markov chain process with states corresponding to nodes in the adjacency matrix W . The probability of a random walker at node i stepping to node j is given by $T_{ij} = W_{ij} / \sum_{n=1}^N W_{in}$. The expected number of hops $\langle H_{ij} \rangle$ a random walker takes to travel from node i to node j is given by⁷²:

$$\langle H_{ij} \rangle = \sum_{h=0}^{\infty} h P(H_{ij} = h) = \sum_{h=0}^{\infty} P(H_{ij} > h). \quad (1)$$

This result is given by the fact that the expected value of a random variable is given by the sum of its complementary cumulative distribution. The probability of a walker requiring more than h hops to reach node j is equal to the sum of the probabilities of the walker being at any node other than j after exactly h hops. To compute this, we define T_j as the matrix T with all elements in the j th column set to zero, so that it is impossible for a walker to arrive at node j . This way, we have $P(H_{ij} > h) = \sum_{n=1}^N [T_j^h]_{in}$, where $[T_j^h]_{in}$ expresses the probabilities of walkers departing from i and reaching any other node except j in exactly h hops. It follows that

$$\langle H_{ij} \rangle = \sum_{h=0}^{\infty} \sum_{n=1}^N [T_j^h]_{in} = \sum_{n=1}^N \left[(1 - T_j)^{-1} \right]_{in}, \quad (2)$$

with the last derivation step following from the summation of an infinite geometric sequence. Further details on this derivation can be found in refs. 11, 23, 72. The diffusion efficiency communication matrix is given by $E_{\text{diff}}(i, j) = 1/H_{ij}$, where $E_{\text{diff}}(i, j)$ quantifies the efficiency of information flow from node i to node j under a diffusive process²³.

Search information relates to the probability that a random walker will serendipitously travel between two nodes via their shortest path²⁹, quantifying the extent to which efficient routes are hidden in the network topology. Previous studies suggest node pairs with an accessible shortest path—characterized by low search information—tend to show stronger resting-state functional connectivity⁸.

The connection length matrix L can be used to compute Ω , where $\Omega_{ij} = \{u, \dots, v\}$ denotes the sequence of nodes traversed along the shortest path from node i to node j . The search information from i to j is given by $SI_{ij} = -\log_2(P(\Omega_{ij}))$, where $P(\Omega_{ij}) = T_{iu} + \dots + T_{vj}$ and T is the transition probability matrix. We define communication efficiency under search information as $E_{\text{si}}(i, j) = -SI_{ij}$. This way, $E_{\text{si}}(i, j)$ quantifies the accessibility of the Ω_{ij} shortest path under diffusive communication.

Send-receive communication asymmetry measures. Send-receive communication asymmetry matrices $A \in \mathbb{R}^{N \times N}$ were computed as detailed in the Results. Measures of send-receive communication asymmetry section. For each pair of regions or subsystems, a one-sample t -test was used to assess whether the mean of the send-receive asymmetry values across all individuals was significantly different from 0 (see Supplementary Note 3 for an investigation of normality assumptions involved in t -tests and send-receive asymmetries based on non-parametric statistics). Bonferroni correction was then performed to control for the $N(N-1)/2$ multiple comparisons corresponding to distinct pairs of regions. This was repeated for each of the three communication measures.

The communication asymmetry matrix A refers to pairwise asymmetric interactions between regions. We performed a similar test to derive a regional (i.e., node-wise) measure of send-receive asymmetry. Let $\{S, R\} \in \mathbb{R}^{N \times K}$ denote, respectively, the average send and receive efficiencies of nodes in the network such that $S(i, k) = 1/N \sum_{j=1}^N C(i, j, k)$ and $R(j, k) = 1/N \sum_{i=1}^N C(i, j, k)$. The difference between outgoing and incoming communication efficiencies of node i is given by $\delta(i, k) = S(i, k) - R(i, k)$. Analogous to the pairwise asymmetry test, we performed a one-sample t -test to determine whether the mean of the distribution $\delta(i, k = 1 \dots K)$ is significantly different to 0. The resultant t -statistic, termed $a(i)$, quantifies the communication asymmetry of node i by taking into account all of its incoming and outgoing communication efficiencies. Nodes with significant and positive (negative) a were classified as senders (receivers), while non-significant values of a were characterized neutral nodes. For each network communication measure, Bonferroni correction was performed to control for multiple comparisons across the N regions.

Regionally aggregated send and receive efficiencies depicted in the scatter plots of Fig. 3e, h were computed as $s(i) = 1/K \sum_{k=1}^K S(i, k)$ and $r(j) = 1/K \sum_{k=1}^K R(j, k)$, respectively. For navigation (Fig. 3b), we display the median send and receive efficiencies in order to attenuate outlier efficiency values and aid visualization.

Non-human directed connectomes were constructed from the results of numerous invasive experiments, often combining experiments across multiple animals of a given species to yield a single, representative connectome. As a result, non-human brain networks were not available for multiple individuals, precluding use of the communication asymmetry test defined for human connectomes. As an alternative, for non-human brain networks, we computed the communication asymmetry between nodes i and j as $A(i, j) = (E(i, j) - E(j, i)) / (E(i, j) + E(j, i))$, where E is a communication efficiency matrix. While this measure does not constitute a statistical test of communication asymmetry, it allows us to evaluate differences in the directionality of information flow of non-human nervous systems.

Cortical gradient of functional heterogeneity. Margulies and colleagues applied a diffusion embedding algorithm to resting-state fMRI data to identify latent components describing maximum variance in cortical functional connectivity³⁵. The obtained components, termed “gradients”, are conjectured to describe macroscale principles of cortical organization³⁷. In particular, the resultant principal gradient (G_1) separated unimodal from multimodal regions, spanning a spectrum from primary sensory-motor areas on one end, to the regions comprising the default-mode network on the other. We used this gradient as a quantitative measure of cortical functional heterogeneity and compared it to regional send-receive communication asymmetries. To this end, we downsampled the gradient from vertex to regional resolution by averaging the values comprising each of the $N = 256,360,512$ cortical areas defined by the parcellations that we used. Regions were grouped into the unimodal ($G_1 \leq -2$), transitional ($-2 < G_1 < 2$) and multimodal ($G_1 \geq 2$) groups shown in Fig. 3.

Cortical subsystems. Yeo and colleagues proposed a widely used partition of the cortical surface into 7 and 17 resting-state functional networks³⁸. These networks constitute distributed (i.e., non-contiguous) functional communities that have been implicated in a wide range of cognitive demands, as well as in rest. Glasser and colleagues used multimodal HCP data to identify 360 cortical regions. Subsequently, they grouped these regions into 22 contiguous subsystems based on geographic proximity and functional similarities³². We use these definitions of cortical partitions to investigate send-receive communication asymmetry at the level of subsystems.

First, we transformed the Yeo partitions ($M = 7, 17$) from vertex to regional resolution. This was achieved by assigning each of $N = 360$ cortical regions to the resting-state network with the largest vertex count within the vertices comprising the region. The HCP partition ($M = 22$) does not necessitate this step, since it is already defined in terms of the $N = 360$ of the Glasser atlas.

Second, we downsampled individual communication efficiency matrices from regional ($N = 360$) to subsystem resolution ($M = 7, 17, 22$) by averaging the pairwise efficiency of nodes assigned to the same subsystem. For two subsystems u and v , we have

$$E'_{uv} = \frac{1}{|M_u||M_v|} \sum_{i \in M_u} \sum_{j \in M_v} E_{ij}, \quad (3)$$

where M_u and $|M_u|$ denote, respectively, the set and number of regions belonging to subsystem u , $E \in \mathbb{R}^{N \times N}$, and $E' \in \mathbb{R}^{M \times M}$. Across K subjects, this results in a set of communication matrices $C \in \mathbb{R}^{M \times M \times K}$ that is used to compute between-subsystems send-receive communication asymmetries as described in Fig. 2 and in the Results section, Measures of send-receive communication asymmetry.

The send-receive communication asymmetry for individual cortical subsystems was computed analogous to regional communication asymmetries as described in the Methods section, Send-receive communication asymmetry measures. For each network communication measure, Bonferroni correction for M and $M(M-1)/2$ multiple comparisons was applied to individual and pairwise subsystems asymmetries, respectively.

Send-receive effective connectivity asymmetry. Spectral DCM estimates effective connectivity from resting-state fMRI data. It receives as input time series characterizing the functional dynamics of neural activity and a network model describing how these elements are coupled. As opposed to the more common task-based DCM, spectral DCM estimates effective connectivity in the absence of experimental or exogenous inputs, characterizing functional modulations between neural elements based on intrinsic neural fluctuations at rest. Details on the generative models inherent to spectral DCM, as well as the frequency-domain model inversion are described in^{39,59}.

Minimally preprocessed resting-state fMRI data for the same $K = 200$ subjects was acquired from the HCP. Functional volumes were acquired during 14m33s at 96720 TR, resulting in 1200 time points. Data from two separate sessions (rfMRI

REST1 LR and *rfMRI REST2 RL*, i.e., right-to-left and left-to-right encoding, performed on different days) was used to compute two estimates of effective connectivity for each subject. HCP acquisition and preprocessing of resting-state fMRI are detailed in^{66,67}.

We computed the blood-oxygenation-level-dependent (BOLD) signal of $N = 360$ regions by averaging the time series of all cortical surface vertices belonging to a region. Next, the N regions were partitioned into M cortical subsystems as described in the Methods section, Cortical subsystems. For each subsystem, we performed a principal component analysis on all the time series belonging to it. The resultant first principal component was used to summarize the functional activity of a subsystem in a single time series. The $M \times 1200$ time series of principal components were used as input to spectral DCM, together with a fully connected model of coupling strengths ($1_M \times M$), enabling estimation of effective connectivity between subsystems covering the whole cortex⁵⁹. Spectral DCM estimations were carried out using SPM12.

Spectral DCM estimates signed effective connectivity, with positive and negative values indicating excitatory and inhibitory influences, respectively. Under the assumption that both excitatory and inhibitory processes are facilitated by communication between neural elements, we considered the absolute value of the estimated coupling strengths.

The obtained coupling strengths of each subject were concatenated. For each resting-state session, this yielded a $M \times M \times K$ effective connectivity matrix, which were used to compute effective connectivity asymmetry between cortical subsystems, as described in Fig. 2 and the Results, Measures of send-receive communication asymmetry section.

Symmetrized non-human connectomes. Directed non-human connectomes (W_d) were symmetrized in order to omit information on axonal directionality. Undirected (symmetric) networks (W_u) were computed as $W_u = (W_d + W_d^T)/2$, ensuring that all original connections in W_d can be traversed bidirectionally in W_u . Directly connected node pairs do not show send-receive asymmetry under navigation, since both directions of routing will necessarily occur via the single connection linking the two nodes. For this reason, we restricted the analyses in ‘Senders and receivers in non-human connectomes’ to node pairs that did not share a direct structural connection in W_u . Non-human binary connectomes were constructed by discarding information on connectivity weight and considering only the presence or absence of directed connections. Formally, $B(i, j) = 1$ if $W(i, j) \neq 0$ and $B(i, j) = 0$ otherwise.

Reporting summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

All analyses in this study were carried out on publicly available datasets. Structural and effective human brain networks were mapped from Human Connectome Project data³⁰ (<https://db.humanconnectome.org/>). The fruit fly connectome was collated from data available in <http://www.flycircuit.tw> and can be found in the Supplementary Information of ref. 44. The macaque connectome was derived from data available at <http://core-nets.org/>⁴⁷. The mouse connectome was constructed from resources provided by the Allen Institute for Brain Science (<https://mouse.brain-map.org/>)⁴⁵ and is available in the Supplementary Information of ref. 46. The cortical gradient of functional connectivity from ref. 35 is available at <https://www.neuroconlab.org/data/index.html>. Send-receive communication asymmetry measures, custom MATLAB code, and other data necessary to generate key figures in this work are available at https://github.com/caioseguin/sen_rev.

Code availability

Functions to compute navigation efficiency, diffusion efficiency and search information are available as part of the Brain Connectivity Toolbox (<https://sites.google.com/site/bctnet/>). Further analyses and computations were performed using MRtrix3 (www.mrtrix.org/), SPM12 (<https://www.fil.ion.ucl.ac.uk/spm/software/spm12/>) or custom MATLAB code available at https://github.com/caioseguin/sen_rev.

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Inferring neural signalling directionality from undirected structural connectomes

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SUPPLEMENTARY INFORMATION

Note 1: Consistency of send-neutral-receiver classification of cortical regions across communication measures

Extending our analyses of correlations between send-receive asymmetries across communication measures, we compared the sender-neutral-receiver classifications of cortical regions obtained from navigation efficiency, diffusion efficiency and search information (Supplementary Table I). As expected by their mutual dependency on random walk processes, classifications for send-receive asymmetries under diffusion efficiency and search information were tightly related (76% accuracy, Supplementary Table Ic). While classification under navigation showed less agreement with the other measures (46% and 44% accuracy for diffusion and search information, respectively; Supplementary Table Ia,b), the obtained three-way classification accuracy remained larger than the 33% baseline expected by chance.

We further explored this relationship by considering two-way classifications of regions into sender or not sender, and receiver or not receiver. This allowed us to assess the statistical significance of the association between the classifications from two communication measures by using Fisher’s exact test. The significance of the obtained P-values further supports the classification consistency across communication measures (Supplementary Table Id-i).

Note 2: Human connectome modularity and node participation

Modular decompositions were estimated for group-level connectomes computed as the average of all individual connectivity matrices for $N = 256, 360, 512$. The resulting group-level connectomes were thresholded at 10%, 15% and 20% connection density and analysed as weighted networks. Nodes were assigned to modules by means of the Louvain algorithm with iterative fine-tuning

[1], as implemented in the Brain Connectivity Toolbox [2]. Briefly, the algorithm aims to identify partitions of the network that maximize within-module connection weights. This notion is formalized by the optimization of the modularity statistic

$$Q = \frac{1}{2m} \sum_{ij} \left[W_{ij} - \gamma \frac{s_i s_j}{2m} \right] \delta_{ij}, \quad (1)$$

where W_{ij} is the connection weight between nodes i and j , γ is the resolution parameter (set to default value of 1), s_i is the strength of node i , $2m$ is a normalization constant equal to the sum of all connection weights in the network, and $\delta_{ij} = 1$ if i and j are assigned to the same module and 0 otherwise. For each group-level connectome, the Louvain algorithm was applied 100 times and the partition that maximized Q was selected. For each individual run of the algorithm, partitions were fine-tuned for k iterations until $Q_k - Q_{k-1} < 10^{-5}$ or $k = 100$. This procedure resulted in the identification of 7 modules for $N = 256$ (all connection densities); 6 modules for $N = 360$ (all connection densities); and 6, 7, 7 modules for $N = 512$, for 10%, 15%, 20% connection density, respectively.

The participant coefficient measures the diversity of inter-modular connections of individual nodes, and is defined as [3]

$$P_i = 1 - \sum_{g \in G} \left(\frac{s_i(g)}{s_i} \right)^2. \quad (2)$$

Here, G denotes the set of all modules, s_i the strength of node i and $s_i(g)$ the strength of i within module g . High and low P_i indicate that i has connections to nodes assigned to many and few distinct modules, respectively.

Note 3: Randomized connectomes

We used three families of randomized connectomes: i) topologically randomized (rewired) networks, ii) topologically randomized cost-preserving networks and iii) spatially randomized (repositioned) networks. For K subjects, each individual connectome was used to generate

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ensembles of 1,000 surrogate networks for each family. Computing communication measures for these networks resulted in 1,000 sets of $C_{N \times N \times K}$ null communication efficiency matrices, per family, per communication measure. These sets were downsampled to subsystem resolution and used to compute the correlation between effective connectivity and null network send-receive communication asymmetries. Non-parametric P-values testing the hypothesis of a lack of difference between empirical and null correlations were computed as the proportion of times the communication asymmetry of null networks yielded stronger correlations than the one obtained for the empirical connectome.

Topologically randomized networks were computed using the Maslov-Sneppen rewiring routine [4] implemented in the Brain Connectivity Toolbox [2]. In this procedure, each connection was swapped between nodes once (on average), while maintaining the network's original degree distribution and ensuring it remained connected.

One disadvantage of topologically randomized networks is the introduction of a disproportionate number of long-range connections, resulting in null networks with markedly increased wiring cost compared to the empirical network. To address this issue, we first computed the empirical wiring cost of a network as the sum of Euclidean distances between its connected nodes [5]. We then generated cost-preserving topologically randomized networks by adding a constraint to the Maslov-Sneppen routine, namely that connection swaps must not alter the original network's cost by more than 1mm. Previous studies report that this leads to surrogate networks that match empirical wiring cost within a 0.1% error margin [6].

Spatially randomized networks are relevant for navigation, which routes information based on local knowledge of network geometry. They are constructed by randomly swapping the spatial positioning of nodes, while maintaining network topology unaltered.

Note 4: Send-receive asymmetries and normality assumptions

Send-receive asymmetry between nodes/subsystems i, j is computed using a one-sample t-test on the distribution $\Delta(i, j, k = 1 \dots K) = C(i, j, k = 1 \dots K) - C(j, i, k = 1 \dots K)$, where C denotes an asymmetric communication matrix and K is the number of subjects. A similar approach is used to compute regional asymmetries based on the node-level distributions $\delta(i, k = 1 \dots K)$ (see *Materials and Methods, Send-receive communication asymmetry measures* for details). However, t-tests mandate an assumption of data normality. We tested the normality of δ for $i = 1 \dots 360$ and Δ for $i, j = 1 \dots M$, where $M = 7, 17, 22$ indicate the pairwise asymmetries at different cortical subsystems resolutions. Normality was assessed using a one-sample Kolmogorov-Smirnov test and we considered asymmetries computed for $N = 360$ at

15% connection density. At the regional level, the null hypothesis of normality for 87%, 47% and 85% of the δ distributions could not be rejected at the 5% significance level, for navigation, diffusion and search information, respectively. When accounting for the 360 multiple comparisons using Bonferroni correction, the respective percentages increased to 100%, 91% and 100%. For pairwise asymmetries between subsystems, the null hypothesis of normality could not be rejected at the 5% significance level for 100% of Δ distributions for $M = 7, 17, 22$.

These results suggest that the majority of regional and pairwise communication asymmetries are normally distributed. However, to address possible deviations from normality, we recomputed send-receive asymmetries using a one-sample Wilcoxon rank-sum tests instead of the t-tests. Importantly, the Wilcoxon test is non-parametric and does not require variables to be normally distributed. The resulting w-statistic can be interpreted as an assessment of whether the median of a distribution is significantly smaller or greater than 0. We found that t- and w-statistic based send-receive asymmetries were highly correlated, at both regional and subsystem pairwise levels and for all connection density thresholds. Regional send-receive asymmetries (for $N = 360$) under navigation: Pearson correlation coefficient $r = 0.96, 0.97, 0.97$ for 10%, 15% and 20% connection density thresholds, respectively; under diffusion: $r = 0.68$ for all connection densities; and under search information: $r = 0.89$ for all connection densities. Pairwise subsystem send-receive asymmetries (for $N = 360$ and 15% connection density) under navigation: $r = 0.96, 0.95$ for $M = 17, 22$, respectively; under diffusion: $r = 0.87, 0.89$ for $M = 17, 22$, respectively; and under search information: $r = 0.87, 0.88$ for $M = 17, 22$, respectively. Accordingly, we found that t- and w-statistic send-receive communication asymmetries were consistently correlated with the directionality of effective connectivity (Supplementary Fig. 10a,b).

Note 5: Send-receive asymmetries for connectomes mapped with probabilistic tractography

We sought to determine whether the send-receive asymmetry of the human connectome is robust to alternative connectome reconstruction techniques. To this end, we recomputed the connectomes of the same $K = 200$ subjects using a probabilistic tractography pipeline. Using MRtrix3 [7], we applied multi-shell, multi-tissue constrained spherical deconvolution to estimate the fibre orientation distribution of each white matter voxel [8]. Probabilistic tractography was carried out with the following parameters: iFOD2 algorithm [9], 5×10^6 streamlines, 0.5 mm tracking step-size, 400 mm maximum streamline length and 0.1 fractional anisotropy cut-off for streamline termination. The resulting tractograms were used to construct human connectomes comprising $N = 256, 360, 512$ cortical regions. The obtained connectivity matrices were thresholded at 10%, 15% and 20%

connection density and analysed as weighted networks. Regional and subsystem level send-receive communication asymmetries were computed as for the deterministic connectomes (*Materials and Methods, Send-receive communication asymmetry measures*).

We found that deterministic and probabilistic send-receive asymmetries were strongly correlated for all communication measures, connection density thresholds, parcellation resolutions and cortical subsystem partitions (Supplementary Table II and Supplementary Fig. 11). For instance, deterministic and probabilistic regional asymmetries showed a Pearson correlation coefficient of $r = 0.75, 0.74, 0.77$ under navigation, diffusion and search information, respectively ($N = 360$ at 15% connection density). Similarly, pairwise asymmetries between the two tractography approaches for $M = 22$ subsystems showed $r = 0.70, 0.76, 0.76$ under navigation, diffusion and search information, respectively ($N = 360$ at 15% connection density). All $P < 10^{-30}$.

Communication asymmetries derived from probabilistic connectomes were also correlated with effective connectivity directionality (Supplementary Fig. 10c,d; e.g., $r = 0.64, 0.48, 0.45$ for $M = 17$ under navigation, diffusion and search information, respectively). Interestingly, in most cases, probabilistic asymmetries yielded stronger correlations to effective connectivity directionality than the original deterministic ones. In addition, probabilistic asymmetries did not lead to the drop in association strength for $M = 17$ in fMRI session 2 present in deterministic-based results. However, regional probabilistic-based asymmetries were not associated to the cortical gradient of functional heterogeneity ($P > 0.05$ across all communication measures and parcellation resolutions).

Taken together, these results indicate that send-receive communication asymmetry measures are robust to different tractography pipelines. Regional and pairwise send-receive asymmetries were strongly correlated across deterministic and probabilistic connectome reconstructions and both approaches yielded strong correlations with neural signalling directionality estimated with spectral DCM. Differences in the association strength with effective connectivity directionality and local functional heterogeneity suggest the possibility that deterministic and probabilistic connectomes are better able to capture, respectively, regional and pairwise resting-state functional activity.

Note 6: Senders, receivers and the subcortex

In the main manuscript, we analysed brain networks comprising exclusively of cortico-cortical connections due to challenges in mapping connectomes containing subcortical structures. However, subcortical regions are important mediators of signalling between cortical areas. To investigate the potential impact of subcortical structures to our results, we aimed to reproduce our send-receive

asymmetry findings in connectomes including the subcortex. To this end, we mapped the connectomes of the same $K = 200$ subjects using a gray matter parcellation comprising 360 cortical and 14 subcortical regions (left and right thalamus, caudate, putamen, pallidum, hippocampus, amygdala and accumbens-area). The 360 cortical areas were defined according to the HCP MMP1.0 atlas [10], while subcortical structures were derived from the Freesurfer parcellation provided by the HCP (*aparc+aseg* file).

An important challenge in mapping whole-brain connectomes including the subcortex is that certain subcortical structures, in particular the thalamus, are composed of both gray and white matter, functioning both as signal relays and information processing units [11]. However, current parcellations of the subcortex do not provide sufficient detail to differentiate between gray matter nuclei and white matter fibers within subcortical structures. In order to address this issue, we employed a data-driven tractography pipeline with respect to subcortical structures. Subcortical regions were included in both white and gray matter masks. During tractography, subcortical voxels with sub-threshold fractional anisotropy (FA) were interpreted as gray matter, while supra-threshold voxels were considered white matter. Hence, if a streamline tracking through a subcortical region encounters a voxel with low FA (< 0.1), this is interpreted as a portion of gray matter within the subcortical structure, and the streamline's endpoint is assigned to the current subcortical region. However, if a streamline enters and exits a subcortical structure without passing through low FA voxels, this is interpreted as a white matter tract connecting two other (cortical or subcortical) regions. In this case, the streamline endpoint is not assigned to the current subcortical region, providing a data-driven model of subcortical structures as signal relays.

Using this approach, we applied the deterministic tractography algorithm described in *Materials and Methods, Human Connectomes* to map connectivity matrices comprising $N = 360 + 14 = 374$ nodes. Previously, in order to account for biases towards higher connectivity strength in larger regions, streamline counts between pair of regions were normalized by the product of their surface areas. In this case, since subcortical regions were defined only in volume space, we instead used the pairwise product of regional volumes as a normalization factor. Cortical surface-based parcellations were registered to subject-specific T1-weighted images and the number of voxels comprising gray matter regions was used as an approximation of their volume. This resulted in $K = 200$ subject-level 374×374 weighted connectivity matrices, which were thresholded at 10%, 15% and 20% connection density and analysed as weighted networks. It is noteworthy that subcortical regions ranked amongst the highest-degree nodes in the obtained connectomes (for the average degree across subjects, the thalamus, putamen, hippocampus, pallidum, amygdala, accumbens-area and caudate, ranked, respectively, amongst the top 0.83%,

1.9%, 3.6%, 4.4%, 6.7%, 8.6% and 11.4% most connected nodes).

We began by investigating whether cortical send-receive asymmetries computed on cortico-cortical connectomes were comparable to those derived from connectomes including the subcortex. At the regional level, we found that send-receive asymmetries of cortical regions were consistent across the two sets of connectomes (Supplementary Fig. 12). Pearson correlation coefficients between cortical send-receive asymmetries for connectomes with and without the subcortex: $r = 0.86, 0.84, 0.85$ under navigation; $r = 0.92, 0.93, 0.93$ under diffusion; and $r = 0.90, 0.90, 0.90$ under search information, for 10%, 15% and 20% connection density, respectively (all $P < 10^{-96}$; see Supplementary Fig. 12a,e,i for scatter plots of these associations at 15% connection density). Accordingly, the classification of cortical regions into senders, neutral and receivers was robust to the inclusion of the subcortex: three-way classification accuracy of 69%, 74% and 72% for asymmetries under navigation, diffusion and search information, respectively, at 15% connection density. After the inclusion of subcortical regions, primary sensory regions remained senders (with the exception of V1 for navigation and the right hemisphere M1 for search information), while portions of the precuneus, frontal and prefrontal cortices remained as receivers (Supplementary Fig. 12b,f,j).

Despite these consistencies, the inclusion of subcortical structures did influence the send-receive asymmetry of cortical regions. Supplementary Fig. 12c,g,k shows the difference in regional asymmetries for connectomes with and without the subcortex. Positive differences (shown in red) indicate shifts towards outgoing communication efficiency (increase in send-receive asymmetry), while negative differences (shown in blue) indicate shifts towards incoming communication efficiency (decrease in send-receive asymmetry). In other words, following the inclusion of the subcortex, regions shown in red and blue became relatively more biased towards sending and receiving information, respectively. For navigation (Supplementary Fig. 12c), considering subcortical communication pathways reduced the propensity of visual, somatosensory and auditory cortices towards outgoing communication efficiency. Accordingly, portions of the temporal-parietal-occipital junction, MT+ complex, and medial and dorsolateral cortices had their propensity towards incoming communication efficiency attenuated. Similar patterns of asymmetry differences were observed under diffusion and search information (Supplementary Fig. 12g,k), with the marked distinction that early visual areas (V1 and V2) increased their propensity towards outgoing communication. Importantly, as described above, the majority of cortical regions were consistently classified as senders, neutral or receivers, regardless of whether subcortical structures were present. Hence, these results indicate that subcortical nodes, by mediating communication between cortical areas, influence the intensity (rather than the sign) of cortical send-

receive communication asymmetries.

Next, we turned our attention to the send-receive asymmetry of individual subcortical regions. Across all communication measures, all subcortical structures showed a marked bias towards outgoing communication efficiency (Supplementary Fig. 12d,h,l). This is an interesting result, particularly because it opposes the propensity of high-degree regions towards incoming communication reported for diffusion and search information (see *Results, Senders and receivers of the human connectome*). The consistent classification of subcortical regions as senders (with exception of the accumbens-area) potentially reflects their role as inputs of sensory signals to primary cortices.

We also sought to investigate pairwise asymmetries between the subcortex and cortical subsystems. To this end, subcortical regions were grouped into a single subsystem. In keeping with regional results, pairwise asymmetry matrices between cortical subsystems were robust to the inclusion of the subcortex (Supplementary Fig. 13; navigation: $r = 0.89, 0.88$, diffusion: $r = 0.69, 0.76$, search information: $r = 0.71, 0.80$, for $M = 7, 22$, respectively. All $P < 10^{-3}$). Accordingly, individual cortical subsystems showed similar classification as senders and receivers following the addition of subcortical regions (Supplementary Fig. 13b,e,h,l,o,r). Interestingly, a comparison of the send-receive asymmetry of cortical subsystems with (colored horizontal bars) and without the subcortex (colored circles) corroborates the notion that subcortical pathways generally attenuate the communication asymmetry between cortical systems, but do not interfere with their directionality. Once more in agreement with regional results, the subcortex subsystem was consistently classified as a prominent sender.

Finally, we found that send-receive asymmetries between cortical subsystems remained correlated to effective connectivity following the inclusion of the subcortex (Supplementary Fig. 10e,f). Interestingly, associations for $M = 17$ subsystems (Yeo resting-state functional modules [12]) were weakened, while associations for $M = 22$ (HCP contiguous modules [10]) were strengthened, with search information asymmetry leading to correlations as high as $r = 0.68$ (resting-state session 2, 15% connection density).

Note 7: Senders and receivers of non-human connectomes

In this section, we explore send-receive asymmetries computed on symmetrized (undirected) non-human connectomes (*Materials and methods, Symmetrized non-human connectomes*). For sake of conciseness, we refer to those as simply send-receive asymmetries.

We begin by noting that for all non-human connectomes considered, send-receive asymmetries under navigation were not correlated to send-receive asymmetries under diffusion or search information (all $P > 0.05$). As

with the human results, diffusion and search information asymmetries were strongly correlated across species ($r = 0.96, 0.75, 0.75$ for fly, mouse and macaque regional send-receive asymmetries, respectively). Hence, the obtained classification of regions as senders and receivers was different between navigation and random walk based measures. A possible explanation for this disparity lies in the high connection density of the non-human connectomes (fly: 83%, 89%, mouse: 53%, 70%, macaque: 66%, 79%, directed (original) and undirected (symmetrized) connection densities, respectively). In undirected networks (as obtained after connectome symmetrization), there is no navigation asymmetry between directly connected node pairs (if $W(i, j) = W(j, i) \neq 0$ it follows that $E_{nav}(i, j) = E_{nav}(j, i)$. See *Materials and Methods, Navigation efficiency*). This may lead to a decrease in the biological relevance of navigation asymmetries in connectomes for which most regions are directly connected. Meanwhile, the stochastic nature of communication measures based on random walks gives rise to send-receive asymmetries even in densely connected networks. In support of this notion, we found that senders and receivers identified under diffusion and search information were consistent with the putative functional roles of different brain regions in the fly, mouse and macaque. Moreover, send-receive asymmetries computed on binary connectomes yield the most biologically relevant classification of senders and receivers. Given the agreement between diffusion and search information, we focus on describing the results obtained for binary diffusion send-receive asymmetry in the following paragraphs.

A limitation of non-human connectome analyses is the lack of subject-level data. Importantly, this shortcoming precludes the use of the same send-receive asymmetry framework developed for humans. As a result, send-receive asymmetry for these species are not defined statistically at the level of individual regions or pairs of regions. To address this limitation, we partitioned the nodes comprising non-human connectomes into M previously defined subsystems of the fly, mouse and macaque nervous systems. We downsampled the node-level $N \times N$ send-receive asymmetry matrices into subsystem-level $M \times M$ matrices. As a result, each subsystem pair is associated to a distribution of node-level pairwise asymmetries. For each subsystem pair i, j , we computed whether the mean of their distribution of node-level pairwise asymmetries was significantly larger than 0 by means of a one-sample t-test. Send-receive asymmetry between subsystems was defined as the resulting t-statistic. Note that while human asymmetries were statistically defined based on cross-subject distributions, here we define non-human subsystem asymmetries across node pairs. This allowed us to statistically test hypotheses on the agreement between communication asymmetry and the putative functional roles of subsystems of non-human connectomes.

Supplementary Fig. 14a shows the regional send-receive diffusion asymmetry of the 49 neuronal populations comprising the fly connectome. Following previ-

ous work on decentralized communication in the fly connectome, we classified neuronal populations into three groups: (i) sensors (ii) effectors and (iii) others [13]. Sensor nodes are involved in the processing and transducing of sensory information, and are thus hypothesised to be senders. Effectors are conjectured to integrate signals from different neuronal populations in order to coordinate motor execution, and are thus hypothesised to be receivers. In line with these hypotheses, 4 out of 6 sensor nodes were classified as senders (positive send-receive asymmetry) while all effector nodes were classified as receivers (negative send-receive asymmetry). Additionally, we found that the mean sensor $\rightarrow$ effector and other $\rightarrow$ effector asymmetries were significantly larger than 0 ($P = 1 \times 10^{-9}, 5 \times 10^{-24}$, respectively. Supplementary Fig. 14b). The average sensor $\rightarrow$ other asymmetry was positive, but not significantly larger than 0 ($P = 0.11$). Asymmetries between sensor $\rightarrow$ effector and other $\rightarrow$ effector nodes were not statistically different (two-sample t-test $P = 0.46$). Together, these findings indicate that diffusion send-receive asymmetry recapitulates the putative functional roles of neural populations in the fly connectome by characterizing sensor nodes as senders and effector nodes as receivers (Supplementary Fig. 14c).

Supplementary Fig. 14d shows the regional send-receive diffusion asymmetry of regions comprising the mouse connectome (values were averaged across homotopic regions). Consistent with the human results, we found that primary auditory (AUDp) and visual (VISp) areas were senders (positive send-receive asymmetry). However, primary motor (MOs) and sensory (SSp) were classified as receivers. We partitioned brain regions into 8 modules according to a previously established modular decomposition of the mouse connectome [14]. The 8 modules are: somatosensory-motor (SS-M), brainstem-cerebellum (BS-CE), auditory (AU), visual (VI), olfactory (OL), hippocampal (HI), hypothalamic (HY), and high-participation (Hi-Par, i.e., regions characterized by a large proportion of intermodule connections that could not be consistently assigned to a single module). Generally, subsystem associated with the processing of sensory information were senders (olfactory, visual and auditory), with the exception of somatosensory-motor (Supplementary Fig. 14e,f). The brainstem-cerebellum subsystem was the most prominent sender, potentially reflecting the role of subcortical structures in relaying sensory signals to primary cortices. In agreement with the human findings, regions with diverse intermodule connectivity (high participation) were prominent receivers. Together, these results indicate that the undirected topology of the mouse connectome leads to biases in outgoing information for auditory, visual and olfactory regions. Meanwhile, sensory and motor areas may be more dependent on axonal directionality to propagate information to higher-order areas of the mouse cortex.

Finally, Supplementary Fig. 14g shows the regional send-receive diffusion asymmetry of the 29 regions comprised in the macaque connectome. In agreement with

results reported for the human connectome, areas of the sensory (area 2), visual (V1 and V2) and motor (F1 and ProM) cortices were classified as senders (positive send-receive asymmetry), while portions of the frontal (8m and 8l) and prefrontal cortices (46d, 9/46v, 9/46d) were classified as receivers (negative send-receive asymmetry). Supplementary Fig. 15 compares the cortical projections of human and macaque send-receive asymmetries and provides further evidence for consistencies between the results of the two species: expanses of the occipital cortex and sensory-motor strip are classified as senders, while portions of the prefrontal cortex are classified as receivers. Certain differences between the two species were observed: higher-order visual areas such as V4 were receivers in humans but senders in the macaque, while expanses of the temporal lobe appear as senders in humans and receivers in the macaque. Cortical regions were assigned to 6 modules according to a previously established partition of the macaque connectome

[15]. Occipital and prefrontal modules were the most prominent senders and receivers, respectively (Supplementary Fig. 14h,i). Taken together, these findings indicate that the interaction between decentralized network communication measures and connectome topology leads to send-receive asymmetries that recapitulate uni-to heteromodal cortical hierarchies in both human and macaque connectomes. These results suggest that topological properties of undirected connectomes contributing to neural signalling directionality are phylogenetically conserved across higher primates.

It is important to notice that these analyses constitute a first account of send-receive asymmetry in non-human connectomes. Further work is necessary to consolidate the results presented here. Potential future steps in this direction include (i) a conceptualization of statistically defined send-receive asymmetry inferred from single-subject networks and (ii) a better understanding motivating the observed biological relevance of binary diffusion-based communication asymmetries.

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	S	N	R
S	86	15	24
N	35	20	36
R	61	22	61

(a) Navigation (rows) and diffusion (columns): $Acc = 0.46$.

	S	N	R
S	70	15	40
N	27	13	51
R	43	22	79

(b) Navigation and SI: $Acc = 0.44$.

	S	N	R
S	140	37	5
N	0	13	44
R	0	0	121

(c) Diffusion and SI: $Acc = 0.76$.

	S	$\neg S$
S	129	101
$\neg S$	49	81

(d) Nav & diff:
 $Acc = 0.58$,
 $P = 0.001$.

	R	$\neg R$
R	157	56
$\neg R$	82	65

(e) Nav & diff:
 $Acc = 0.67$,
 $P = 6 \times 10^{-4}$.

	S	$\neg S$
S	155	75
$\neg S$	65	65

(f) Nav & SI:
 $Acc = 0.61$,
 $P = 0.002$.

	R	$\neg R$
R	124	89
$\neg R$	66	81

(g) Nav & SI:
 $Acc = 0.57$,
 $P = 0.014$.

	S	$\neg S$
S	178	0
$\neg S$	42	140

(h) Diff & SI:
 $Acc = 0.88$,
 $P = 3 \times 10^{-62}$.

	R	$\neg R$
R	190	49
$\neg R$	0	121

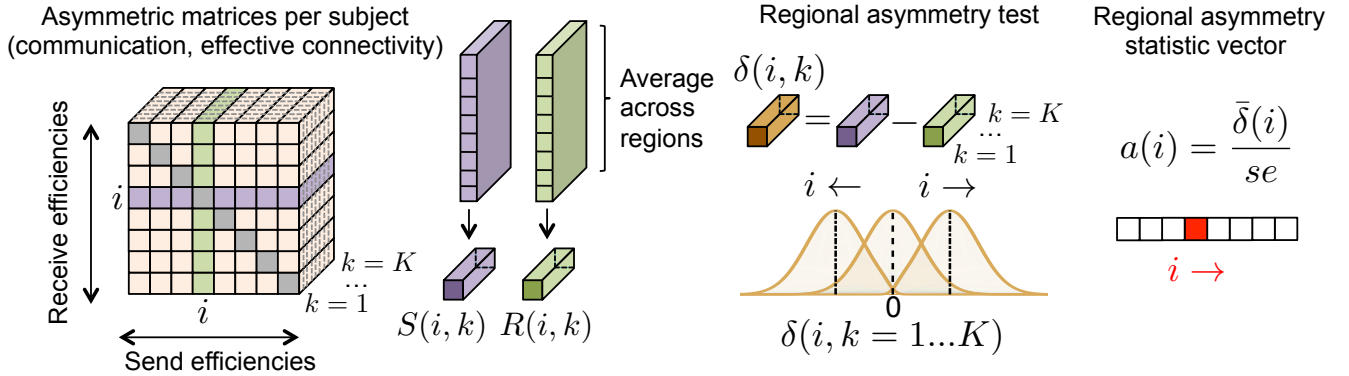
(i) Diff & SI:
 $Acc = 0.86$,
 $P = 5 \times 10^{-56}$.

TABLE I. Comparison of the classification of cortical regions as senders (S), neutral (N) and receivers (R) across network communication measures. The classification accuracy (Acc) is computed as the sum of values in the main diagonal (number of consistently classified regions) divided by the sum of values in the table (total number of regions). (a-c) Three-way contingency tables of the classification obtained from the send-receive asymmetries of two communication measures. Measures listed first and second in the captions have their classes displayed in the rows and columns of the tables, respectively. (d-i) Two-way contingency tables of the classification obtained from the send-receive asymmetries of two communication measures. In this case, for each pair of measures, regions are classified as sender (S) or not sender ($\neg S$), and receiver (R) or not receiver ($\neg R$). P-values obtained from Fisher's exact test were used to examine the significance of the association between the classifications of two measures.

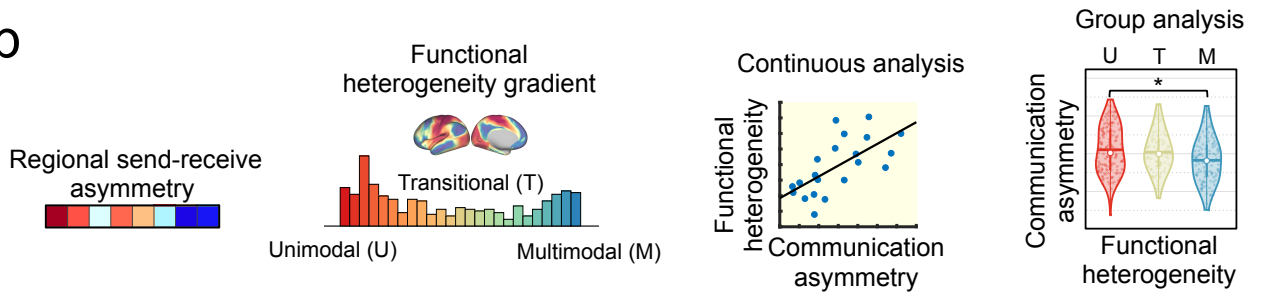
Parcellation resolution	Navigation			Diffusion			Search Info		
	10% CD	15% CD	20% CD	10%	15%	20%	10%	15%	20%
256	0.75	0.71	0.68	0.71	0.72	0.71	0.74	0.74	0.75
360	0.77	0.75	0.73	0.75	0.74	0.74	0.77	0.77	0.77
512	0.74	0.72	0.70	0.67	0.66	0.65	0.65	0.76	0.76

TABLE II. Pearson correlation coefficients between deterministic and probabilistic send-receive asymmetries for different communication measures, connection density (CD) thresholds and parcellation resolutions. All associated $P < 10^{-30}$.

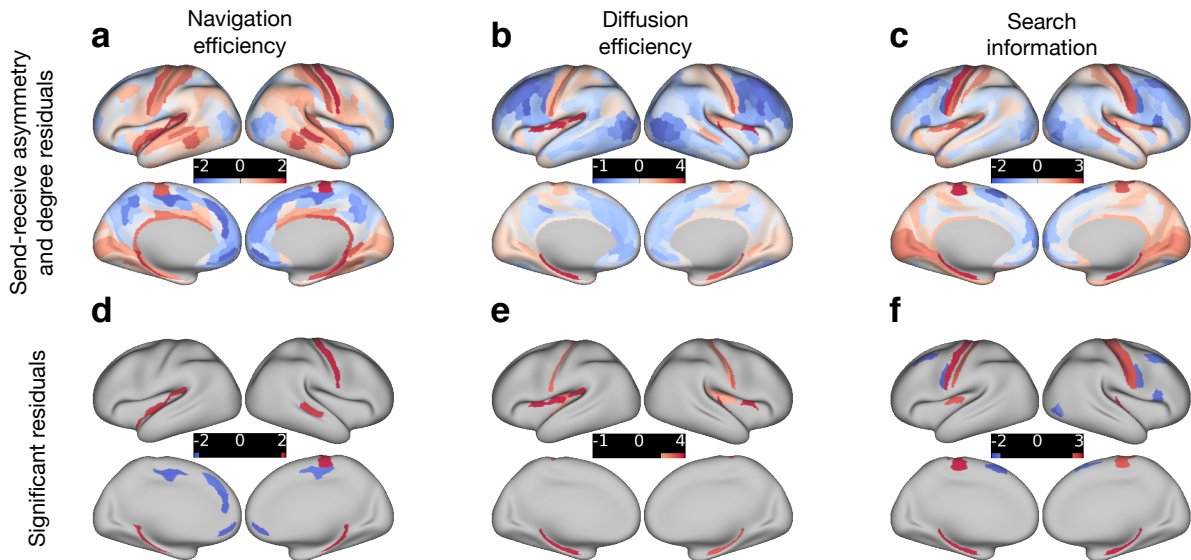
a



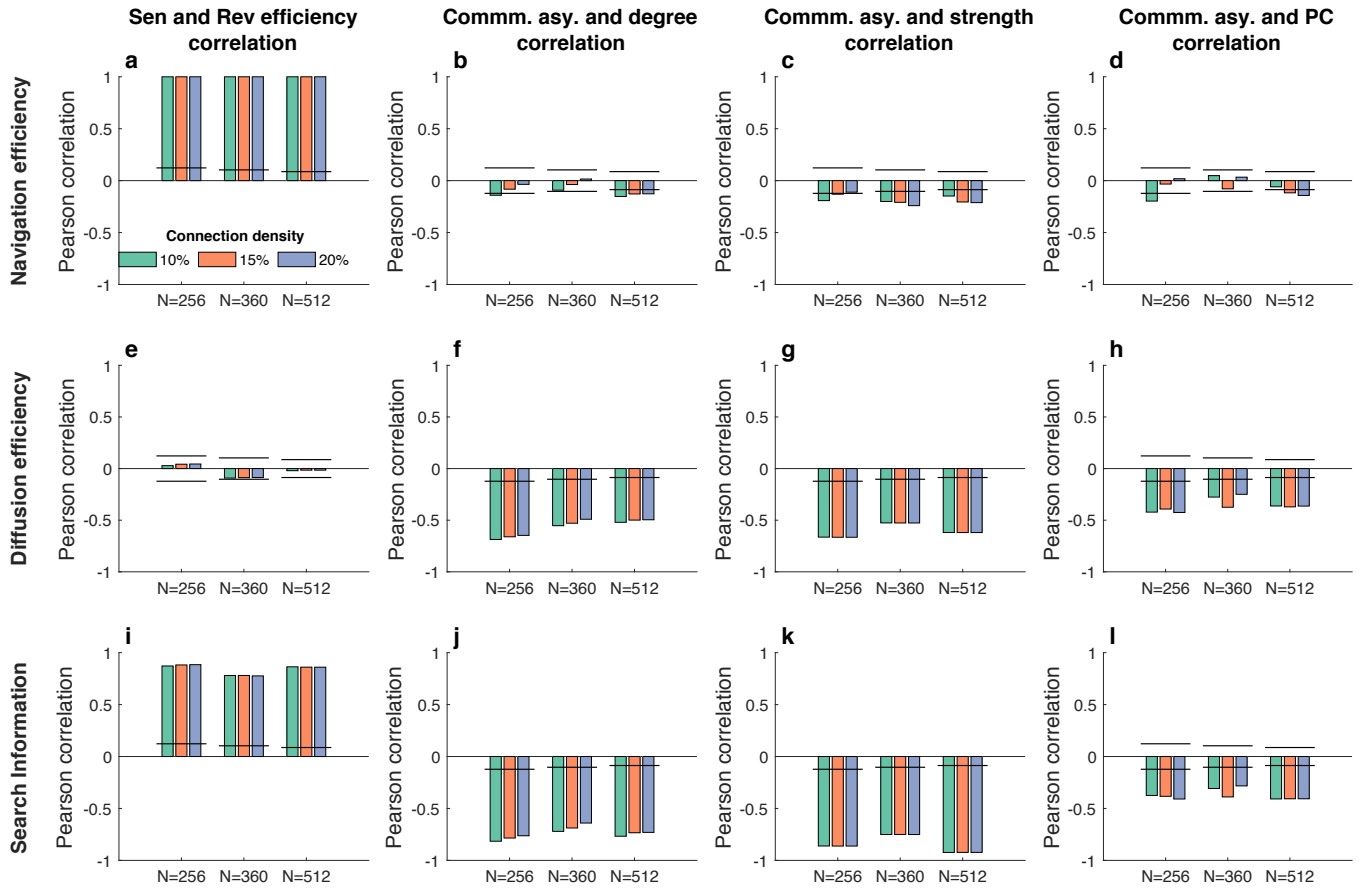
b



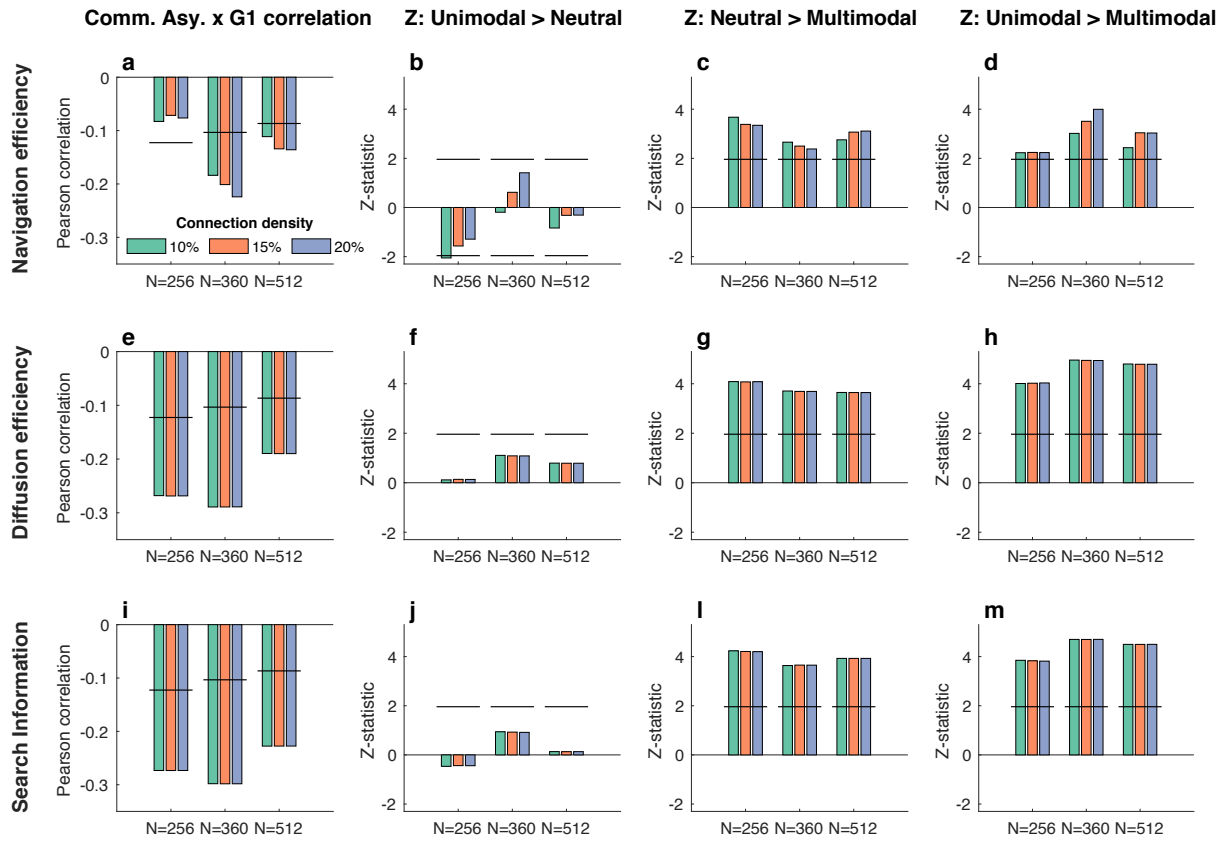
Supplementary Fig. 1. Methodology overview of regional send-receive asymmetry analyses. **(a)** Schematic of the regional communication asymmetry test as described in *Materials and Methods, Send-receive communication asymmetry measures*. **(b)** Schematic of the comparison between regional send-receive asymmetry and the Margulies' gradient of functional heterogeneity [16]. Cortical regions are divided into unimodal, transitional and multimodal based on their placement along the functional gradient, as per described in *Materials and Methods, Cortical gradient of functional heterogeneity*. Comparisons between send-receive asymmetry and functional heterogeneity are performed by means of continuous (i.e., linear correlation) and group-wise (i.e., between group differences) analyses.



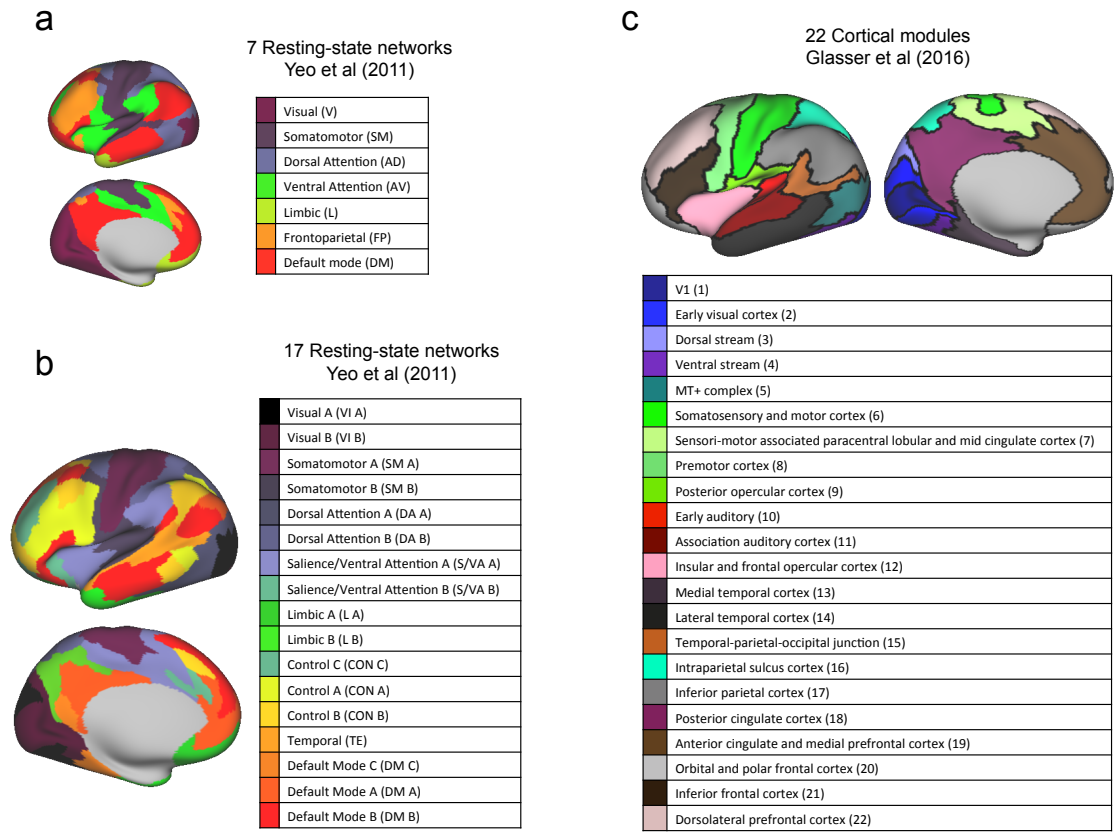
Supplementary Fig. 2. Standardized residuals ($\hat{\epsilon}$) obtained from regressing out node degree from send-receive asymmetry ($N = 360$ at 15% connection density) under **(a,d)** navigation, **(b,e)** diffusion, and **(c,f)** search information. Regions shown in red ($\hat{\epsilon} > 0$) and blue ($\hat{\epsilon} < 0$) are, respectively, stronger senders and receivers than expected based on their degree alone. Regions with statistically significant residuals ($|\hat{\epsilon}| > 1.96$) are highlighted in the bottom row.



Supplementary Fig. 3. Replication analyses regarding sending efficiency, receiving efficiency and send-receive communication asymmetry for $N = 256, 360, 512$ parcellation resolutions and 10%, 15% and 20% connection density thresholds. Vertical axes indicate the Pearson correlation's r , while black horizontal lines mark the effect size correspondent to a correlation with $P = 0.05$ for each N . **(a)** Correlation between sending and receiving navigation efficiencies. **(b)** Correlation between regional navigation asymmetry and node degree (averaged across the connectomes of all participants). **(c)** Same as b, but for node strength. **(d)** Same as a, but for node participation coefficient. **(e-h)** Same as a-d, but for diffusion efficiency. **(i-l)** Same as a-d, but for search information.

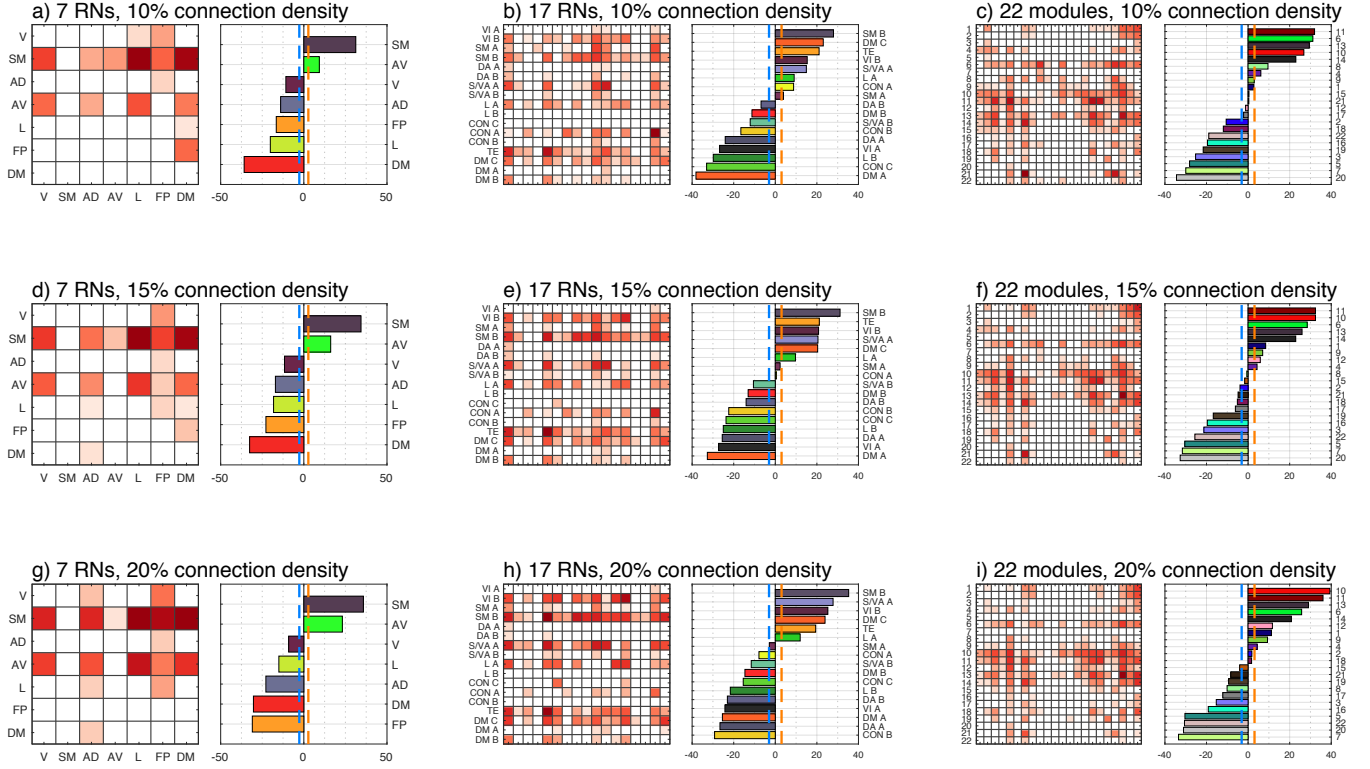


Supplementary Fig. 4. Replication analyses regarding the relationship between communication asymmetry and functional heterogeneity for $N = 256, 360, 512$ parcellation resolutions and 10%, 15% and 20% connection density thresholds. The obtained results are consistent across parcellations and connection densities, with the exception of the lack of correlation between send-receive asymmetry and the gradient of functional heterogeneity for $N = 256$. **(a)** Pearson correlation between regional navigation asymmetry and functional heterogeneity. Black horizontal lines mark the effect size correspondent to a correlation with $P = 0.05$ for each N . **(b)** Z-statistic from a two-sided Wilcoxon test evaluating the hypothesis that the median navigation asymmetry of unimodal regions is larger than that of neutral regions. Black horizontal lines mark the value of a Z-statistic correspondent to $P = 0.05$. **(c)** Same as b, but for neutral and multimodal regions. **(d)** Same as b, but for unimodal and multimodal regions. **(e-h)** Same as a-d, but for diffusion efficiency. **(i-m)** Same as a-d, but for search information.



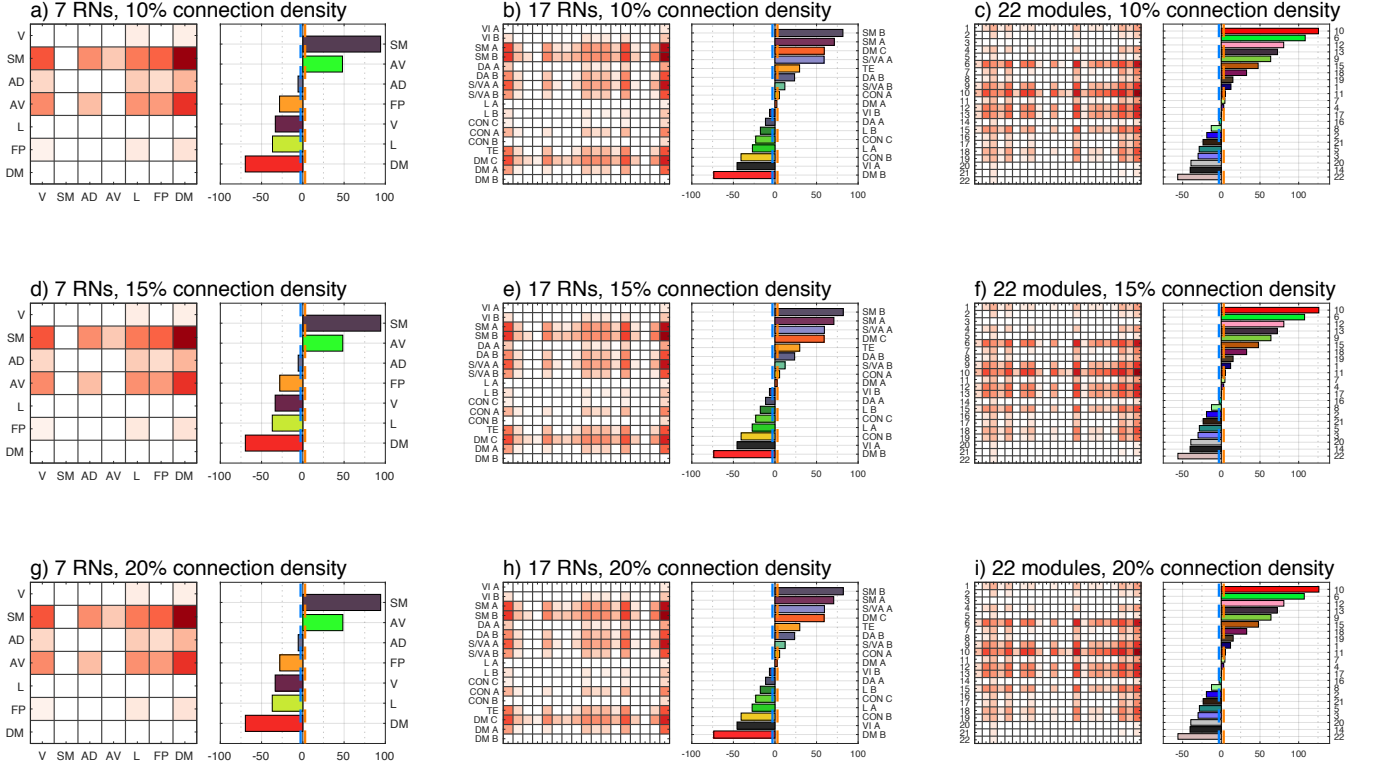
Supplementary Fig. 5. Definition of the $M = 7, 17, 22$ cortical subsystems utilized in sections *Send-receive communication asymmetries of cortical subsystems* *Send-receive communication asymmetry* and *effective connectivity*.

Navigation efficiency



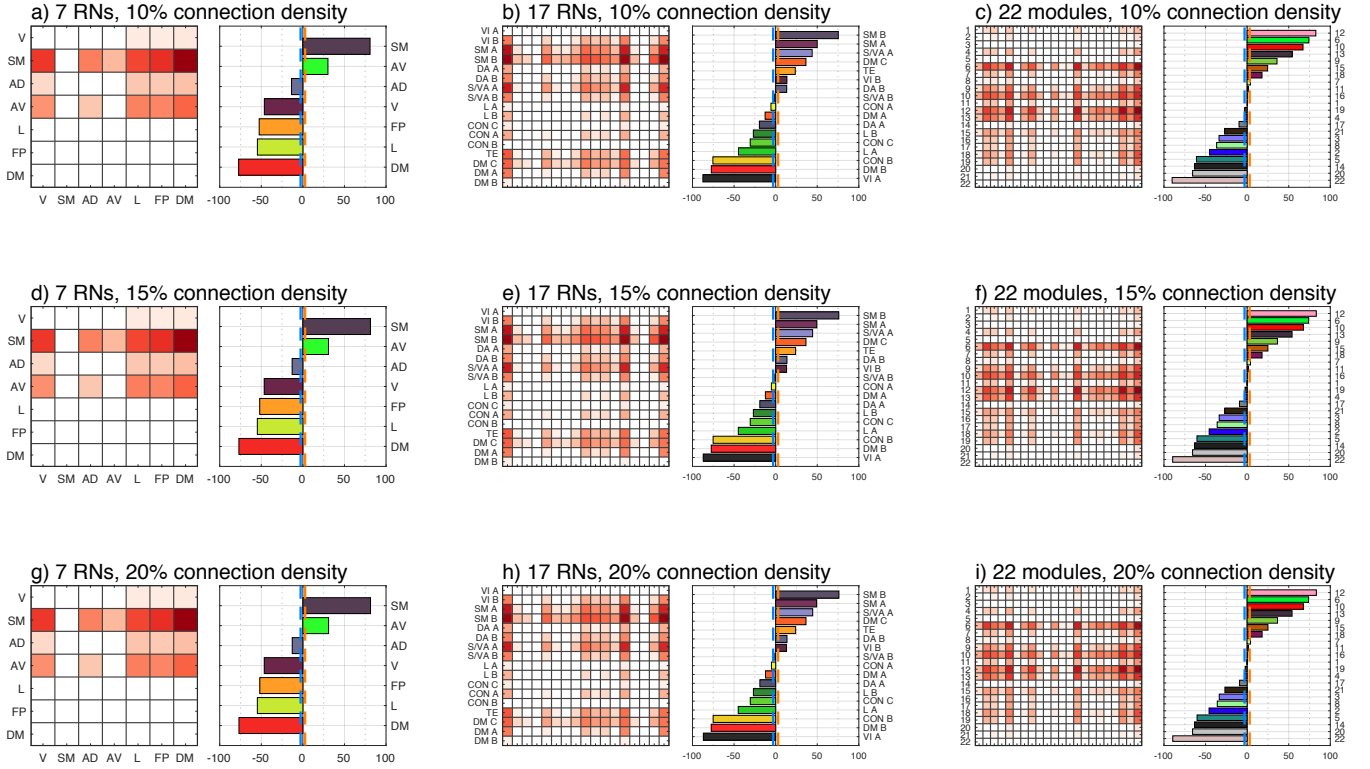
Supplementary Fig. 6. Send-receive navigation asymmetry of cortical subsystems for $M = 7, 17, 22$ and 10%, 15% and 20% connection density thresholds. Send-receive asymmetry matrices were thresholded to display only statistically significant values, while accounting for multiple comparisons. For ease of visualization and without loss of information (since $A(i, j) = -A(j, i)$), negative values were omitted. Thus, $A(i, j) > 0$ denotes that communication takes place more efficiently from i to j than from j to i .

Diffusion efficiency

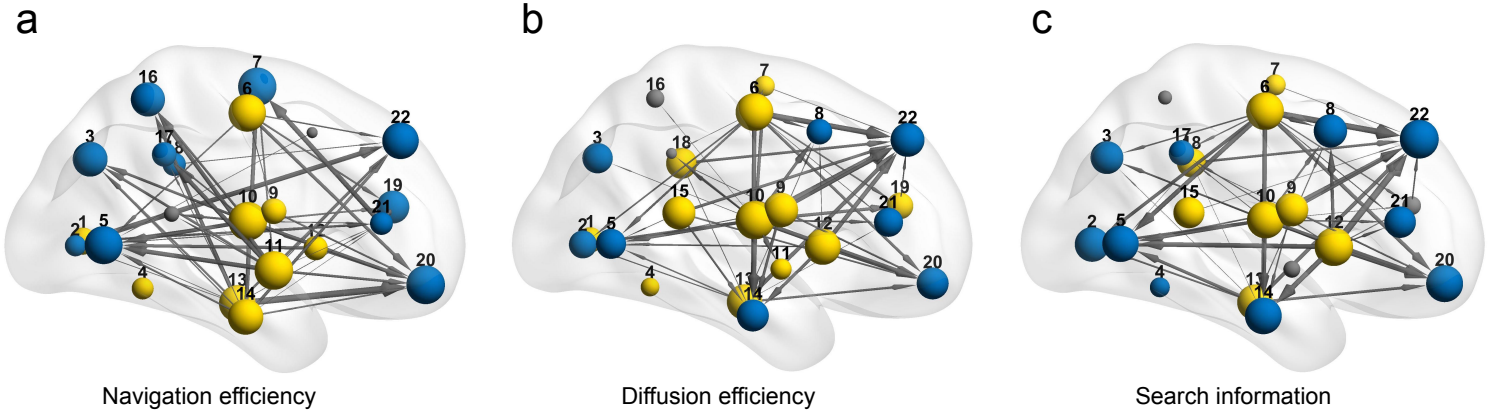


Supplementary Fig. 7. Send-receive diffusion asymmetry of cortical subsystems for $M = 7, 17, 22$ and 10%, 15% and 20% connection density thresholds. Send-receive asymmetry matrices were thresholded to display only statistically significant values, while accounting for multiple comparisons. For ease of visualization and without loss of information (since $A(i, j) = -A(j, i)$), negative values were omitted. Thus, $A(i, j) > 0$ denotes that communication takes place more efficiently from i to j than from j to i .

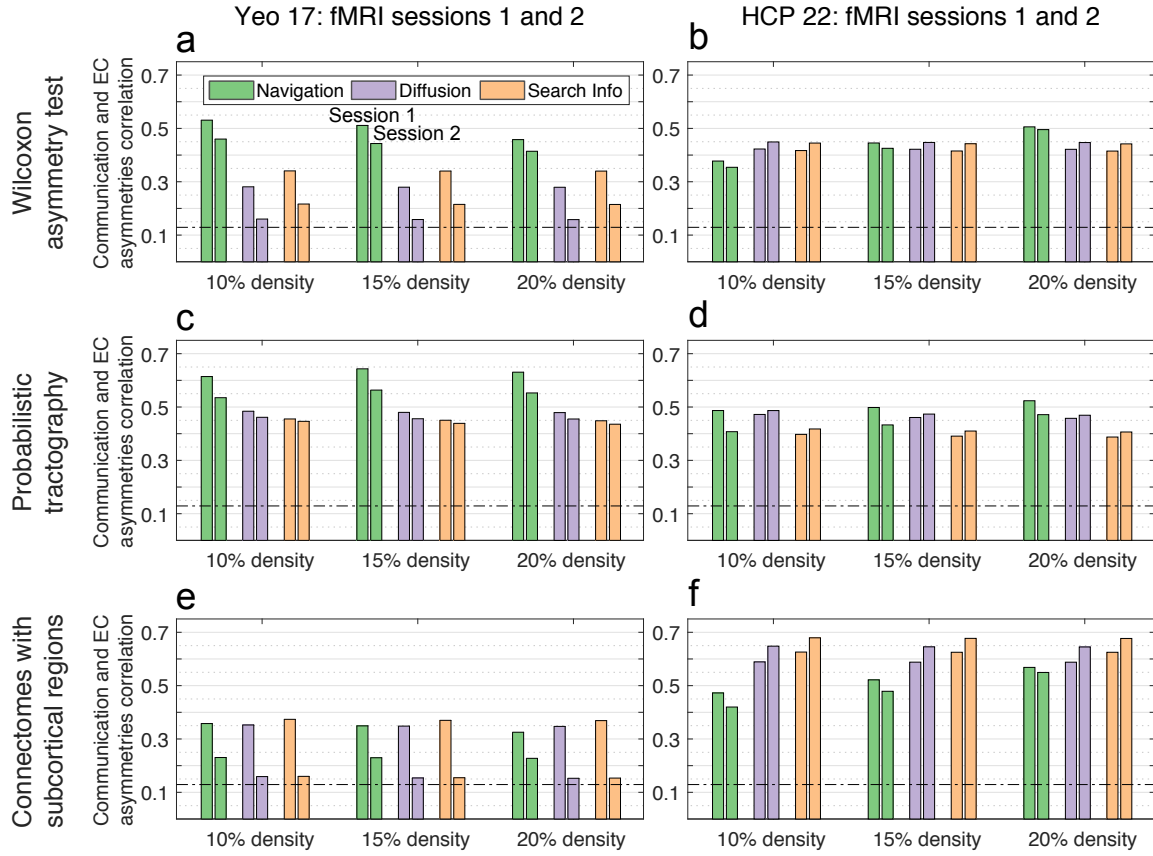
Search information



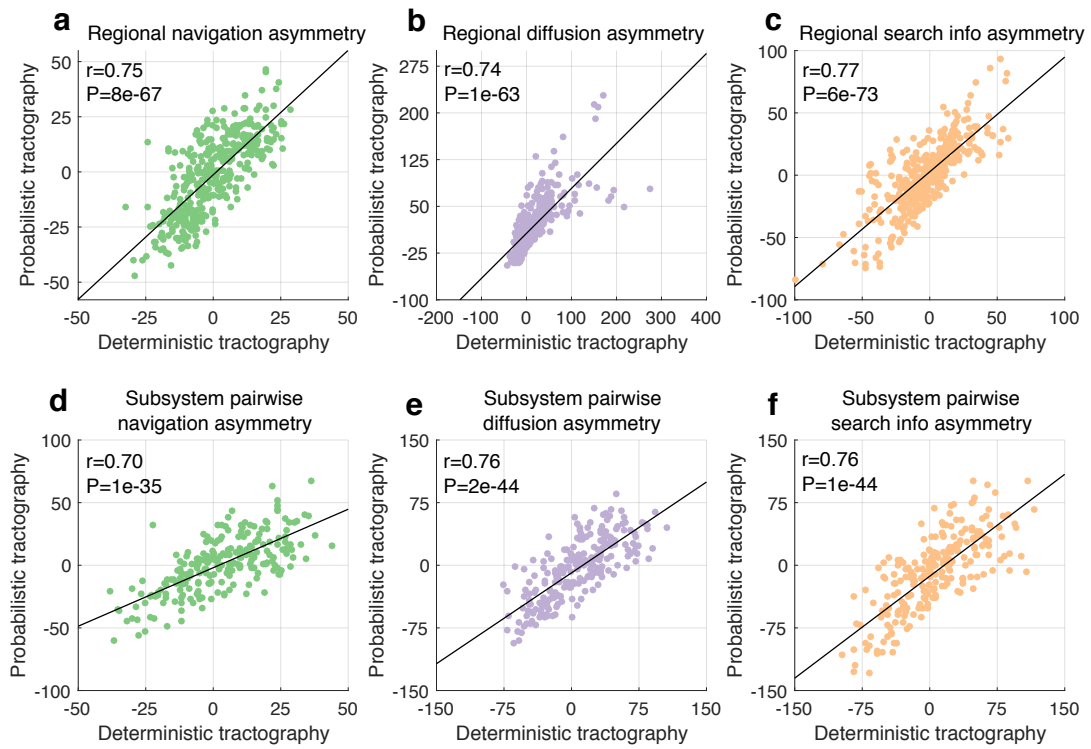
Supplementary Fig. 8. Send-receive search information asymmetry of cortical subsystems for $M = 7, 17, 22$ and 10%, 15% and 20% connection density thresholds. Send-receive asymmetry matrices were thresholded to display only statistically significant values, while accounting for multiple comparisons. For ease of visualization and without loss of information (since $A(i, j) = -A(j, i)$), negative values were omitted. Thus, $A(i, j) > 0$ denotes that communication takes place more efficiently from i to j than from j to i .



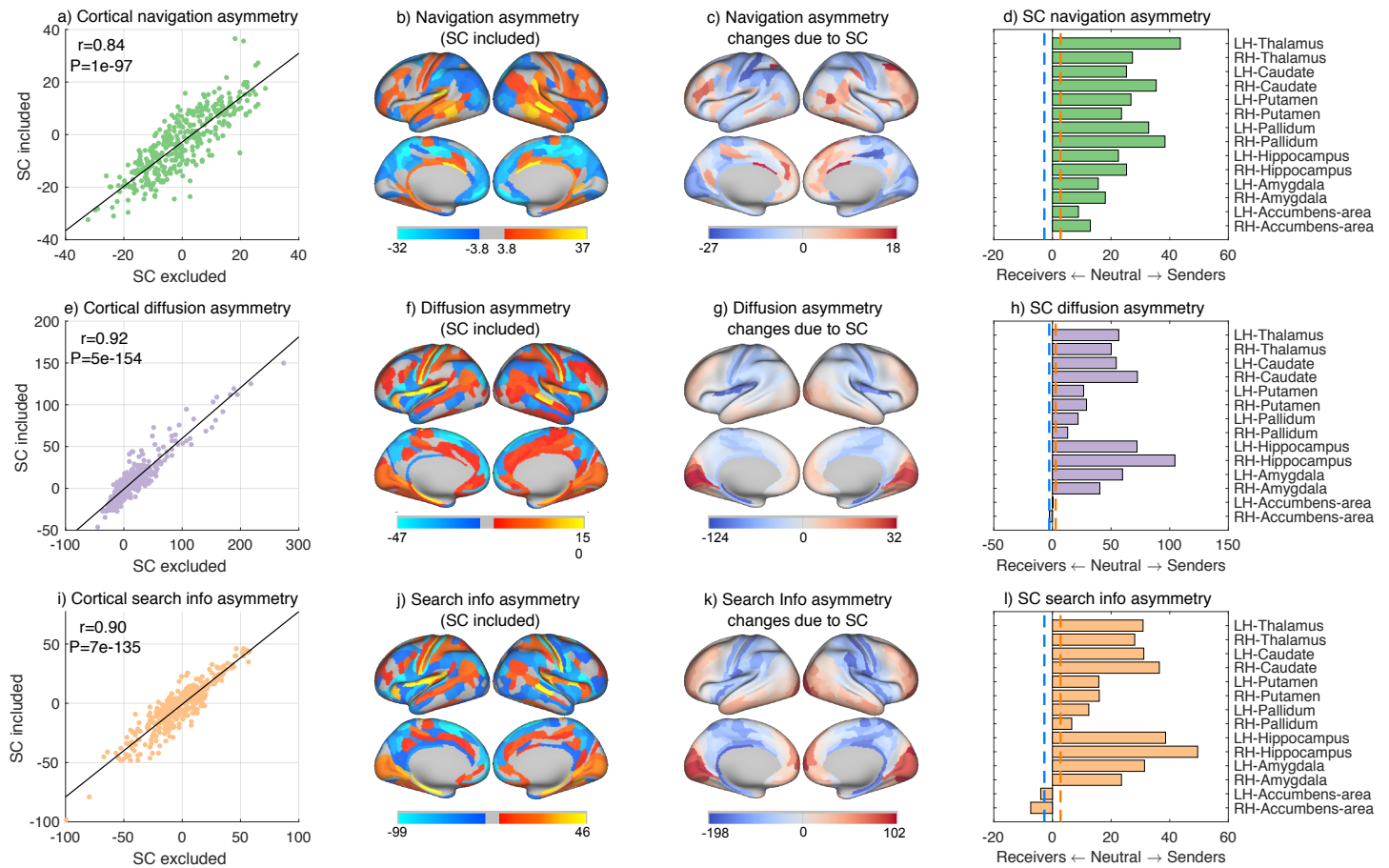
Supplementary Fig. 9. Network visualization of the 10% strongest pairwise send-receive asymmetries between $M = 22$ cortical subsystems ($N = 360$ at 15% structural connection density threshold) under (a) navigation, (b) diffusion and (c) search information. A directed connection between from subsystem i to subsystem j indicates that the communication efficiency from i to j is significantly higher than the communication efficiency from j to i . Connection width is proportional to the strength of the send-receive asymmetry. Subsystems classified as senders, neutral and receivers are shown in yellow, gray and blue, respectively. Visualization developed with BrainNet Viewer [17].



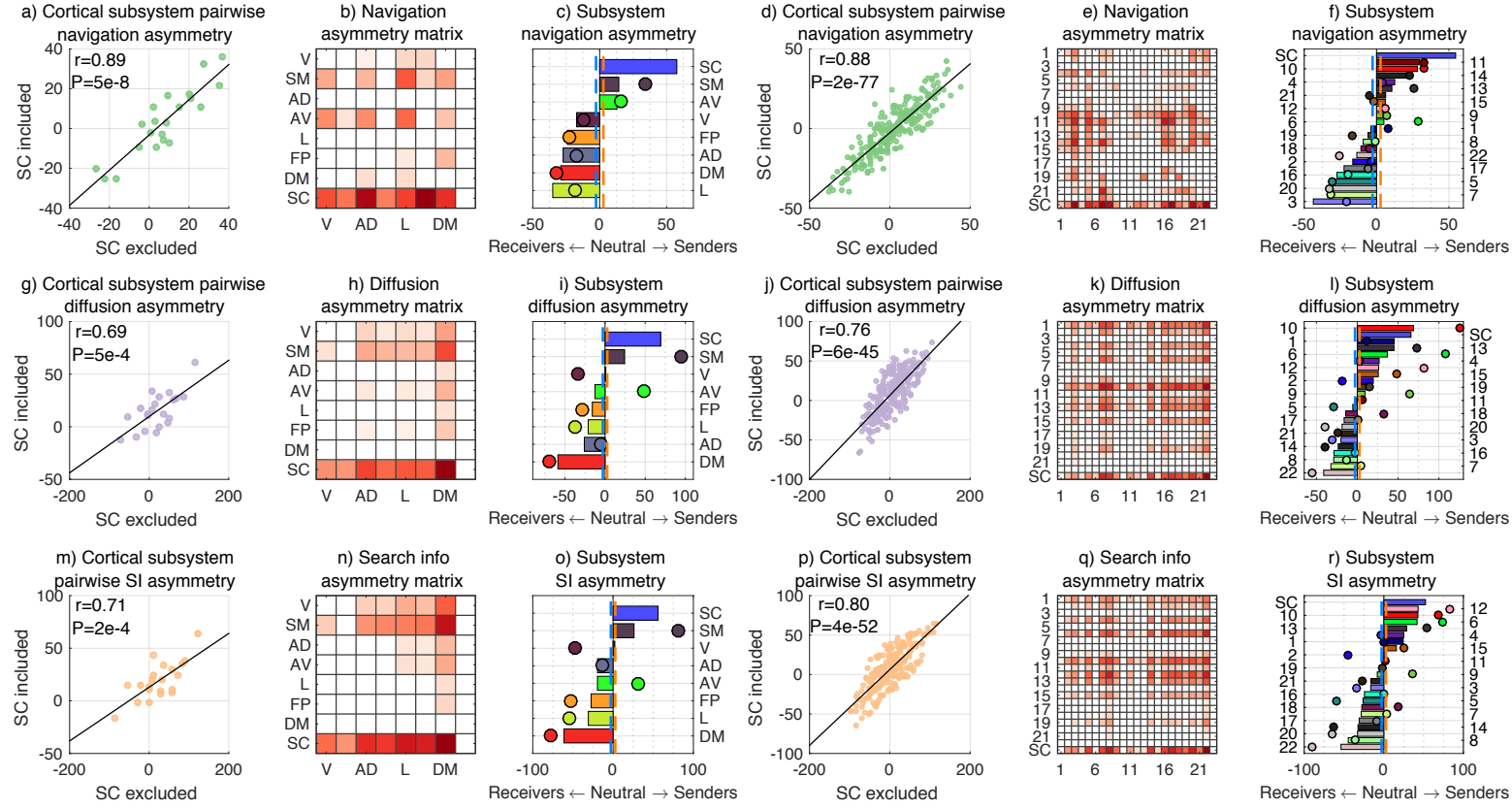
Supplementary Fig. 10. Relationship between send-receive asymmetry and directionality of effective connectivity across a range of methodological settings ($N = 360$). Bars denote the Pearson correlation coefficients between send-receive and effective connectivity asymmetries for $M = 17$ cortical subsystems. Bars are colored according to the three communication measures: i) navigation (green), ii) diffusion (violet), and iii) search information (beige). Correlations were computed for two independent resting-state fMRI sessions (Sessions 1 and 2) and multiple structural connection density thresholds (10, 15 and 20%). Significance threshold of $P < 0.05$ is indicated with a dotted line. **(a,b)** Non-parametric definition of send-receive asymmetry for $M = 17, 22$ cortical subsystems. **(c,d)** Send-receive asymmetry computed on connectomes derived using probabilistic tractography for $M = 17, 22$ cortical subsystems. **(e,f)** Send-receive asymmetry computed on connectomes including subcortical regions for $M = 17, 22$ cortical subsystems.



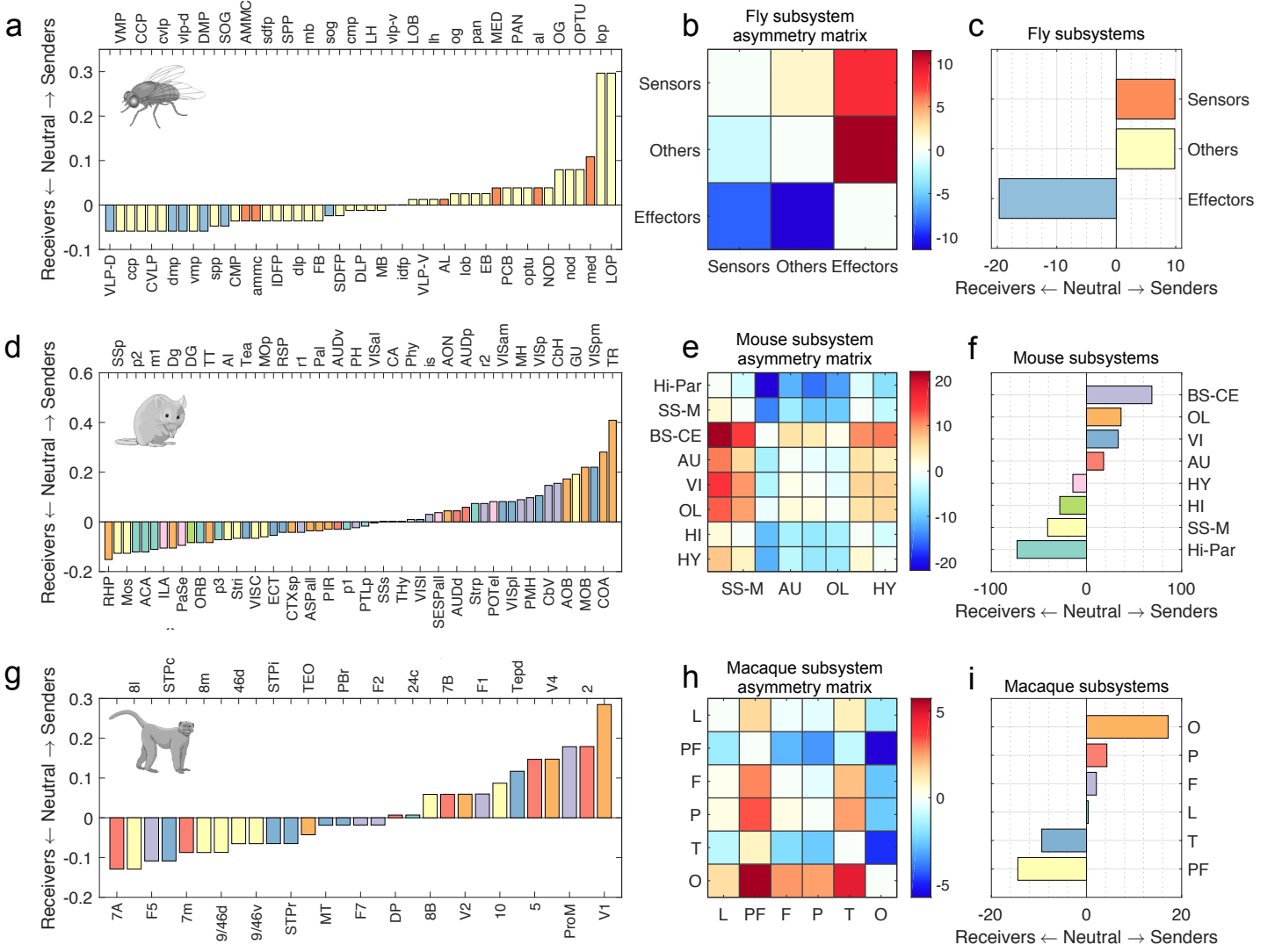
Supplementary Fig. 11. Scatter plots showing the relationship between send-receive asymmetries derived from deterministic and probabilistic connectomes ($N = 360$). **(a,b,c)** Deterministic and probabilistic regional send-receive asymmetries for navigation, diffusion and search information, respectively. **(d,e,f)** Subsystem pairwise send-receive asymmetry ($M = 22$) for navigation, diffusion and search information, respectively. r : Pearson correlation coefficient, P : associated P-value.



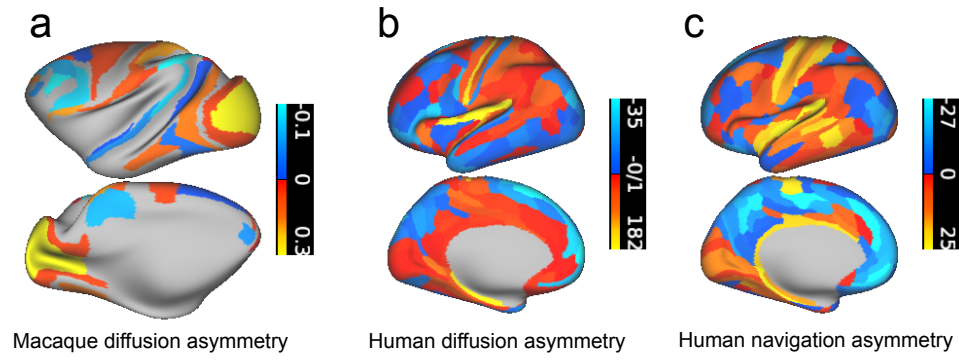
Supplementary Fig. 12. Regional send-receive asymmetry of human connectomes including subcortical regions. **(a)** Scatter plot of cortical navigation asymmetries computed from connectomes excluding subcortical structures (horizontal axis) and including subcortical structures (vertical axis). r : Pearson correlation coefficient, P : associated P-value. **(b)** Cortical navigation asymmetry computed from connectome including subcortical structures. Regions associated with significant send-receive asymmetry are classified as putative senders (orange) and receivers (blue). Regions colored gray are neutral and do not show significant send-receive asymmetry. **(c)** Differences in cortical navigation asymmetry following the inclusion of subcortical structures to the connectome. Positive differences (shown in red) indicate shifts towards outgoing communication efficiency, while negative differences (shown in blue) indicate shifts towards incoming communication efficiency. **(d)** Navigation asymmetry of subcortical regions. Dashed vertical lines indicate a significant bias towards outgoing (orange) and incoming (blue) communication efficiency. **(e–h)** Same as (a–d) for diffusion efficiency. **(i–l)** Same as (a–d) for search information.



Supplementary Fig. 13. Pairwise subsystem send-receive asymmetry of human connectomes including subcortical regions. **(a)** Scatter plot of pairwise cortical subsystem ($M = 7$) navigation asymmetries computed from connectomes excluding subcortical structures (horizontal axis) and including subcortical structures (vertical axis). r : Pearson correlation coefficient, P : associated P-value. **(b)** Navigation asymmetry matrix from connectomes including the subcortex. Subcortical regions were grouped to form a single subsystem (SC), resulting in $M = 7 + 1$ subsystems. A matrix element $A(i, j) > 0$ denotes that communication occurs more efficiently from i to j than from j to i . Send-receive asymmetry values that did not survive multiple comparison correction were suppressed and appear as white cells. For ease of visualization and without loss of information (since $A(i, j) = -A(j, i)$), negative values were omitted. **(c)** Subsystems ($M = 7 + 1$) ranked by propensity to send (top) or receive (bottom) information under navigation. Send-receive asymmetries computed for connectomes including and excluding the subcortex are shown as bars and circles, respectively. Dashed vertical lines indicate a significant bias towards outgoing (orange) and incoming (blue) communication efficiency. **(d–f)** Same as (a–c) but for $M = 22 + 1$ subsystems. **(g–i)** Same as (a–f) for diffusion. **(j–l)** Same as (m–r) for search information.



Supplementary Fig. 14. Send-receive asymmetry of undirected (symmetrized) non-human connectomes under binary diffusion efficiency. **(a)** Regions of the fly connectome sorted from receivers (negative send-receive asymmetry) to senders (positive send-receive asymmetry). Regions were divided into three subsystems [13], with sensor, effector and other nodes marked by orange, blue and beige bars, respectively. **(b)** Send-receive asymmetry matrix between subsystems of the fly connectome. For each subsystem pair i, j , we computed whether the mean of their distribution of node-level pairwise asymmetries was significantly larger than 0 by means of a one-sample t-test. Send-receive asymmetry between subsystems was defined as the resulting t-statistic. Red (positive t-statistic) and blue (negative t-statistic) indicate a bias towards communication efficiency in the $i \rightarrow j$ and $j \rightarrow i$ directions, respectively. **(c)** Fly subsystems sorted according to their send-receive asymmetry. Positive and negative values denote biases towards outgoing and incoming communication, respectively. **(d–f)** Same as (a–c) for the mouse connectome. Bar colors denote the affiliation of regions to previously identified subsystems [14]. **(g–i)** Same as (a–c) for the macaque connectome. Bar colors denote the affiliation of regions to previously identified subsystems [15].



Supplementary Fig. 15. Comparison between the regional send-receive asymmetries for human and macaque. Orange and blue colors denote senders and receivers, respectively. **(a)** Binary diffusion asymmetry for the macaque. Gray regions are missing from the macaque connectome. **(b,c)** Weighted diffusion and navigation asymmetries for the human connectome.

Chapter 5

Network communication models
improve the behavioral and functional
predictive utility of the human
structural connectome

Network communication models improve the behavioral and functional predictive utility of the human structural connectome

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The connectome provides a structural substrate facilitating communication between brain regions. We aimed to establish whether accounting for polysynaptic communication paths in structural connectomes would improve prediction of interindividual variation in behavior as well as increase structure-function coupling strength. Connectomes were mapped for 889 healthy adults participating in the Human Connectome Project. To account for polysynaptic signaling, connectomes were transformed into communication matrices for each of 15 different network communication models. Communication matrices were (i) used to perform predictions of five data-driven behavioral dimensions and (ii) correlated to resting-state functional connectivity (FC). While FC was the most accurate predictor of behavior, communication models, in particular communicability and navigation, improved the performance of structural connectomes. Communication models also strengthened structure-function coupling, with the navigation and shortest paths leading to 35-65% increases in association strength with FC. We combined behavioral and functional results into a single ranking that provides insight into which communication models may more faithfully recapitulate underlying neural signaling patterns. Comparing results across multiple connectome mapping pipelines suggested that modeling polysynaptic communication is particularly beneficial in sparse high-resolution connectomes. We conclude that network communication models can augment the functional and behavioral predictive utility of the human structural connectome.

INTRODUCTION

The structural connectome is a complex network that describes anatomical connections between neural elements [1, 2]. At the macroscale of magnetic resonance imaging (MRI), the human connectome delineates how gray matter regions are interlinked by white matter projections [3, 4]. Numerous studies have demonstrated that the macroscale human connectome is characterized by several nonrandom topological properties, including a small-world and modular architecture [5, 6], heterogeneous degree distribution [7] and a core of densely connected hubs [8]. This complex anatomical scaffold both facilitates and constrains neural signaling between brain regions. While region pairs that share a connection in the structural connectome may communicate directly, polysynaptic paths comprising two or more connections are required to establish communication between anatomically unconnected regions. Understanding the dynamics of polysynaptic communication in large-scale brain networks is a key open challenge in neuroscience [9].

Several network communication models have been proposed to describe large-scale neural signaling, ranging from naive random walk processes to optimal routing via shortest paths [10]. By considering polysynaptic paths, these models quantify the putative efficiency of communication between both connected and unconnected nodes, thus enabling a high-order structural description of inter-

actions among every pair of regions in the connectome [11]. Recent studies report that network communication models can improve the strength of coupling between structural and functional connectivity in the human connectome [12], explain established patterns of cortical lateralization [13], and infer the directionality of effective connectivity from structural connectomes [14]. These efforts provide evidence that network communication models capture meaningful aspects of brain functioning and dynamics. However, the extent to which different models contribute to our understanding of neural signaling remains unknown.

Here, we aimed to systematically investigate the utility of a range of candidate models of network communication. First, we sought to determine whether accounting for polysynaptic (multi-hop) paths in structural brain networks using models of network communication would: i) improve the prediction of interindividual variation in behavior, compared to predictions based on direct structural connections alone; and, ii) improve the strength of structure-function coupling. Second, we aimed to establish a ranking of communication models with respect to their predictive utility, with the goal of determining which models may more faithfully capture biological signaling patterns related to behavior and FC.

We considered five previously proposed communication measures: (i) shortest paths [15, 16], (ii) navigation [17, 18], (iii) diffusion [19], (iv) search information [12, 20], and (v) communicability [21–23]. Collectively, these models cover a wide-range of neural signaling conceptualizations. Shortest paths and navigation deterministically route information using centralized and decen-

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tralized strategies, respectively. In contrast, diffusion and search information model communication from the stochastic perspective of random walk processes. Finally, communicability implements a broadcasting model of signaling, in which signals are simultaneously propagated along multiple network fronts. While all these candidate models have been investigated in the human connectome, which particular models provide the most parsimonious representation of large-scale neural signaling remains unclear.

Using diffusion-weighted MRI and tractography, we mapped structural connectivity (SC) matrices for 889 healthy adults participating in the Human Connectome Project (HCP) [24]. Each individual's SC matrix was then transformed into a communication matrix, which represented the efficiency of communication between each pair of regions under a particular candidate model of network communication. For each model, communication matrices were fed to statistical techniques to perform out-of-sample prediction of individual variation in five behavioral dimensions [25], and also correlated with FC matrices mapped using resting-state functional MRI. This enabled a systematic ranking of network communication models in terms of behavior prediction and structure-function coupling. While these criteria do not constitute direct biological validation of signaling strategies, we hypothesize that the higher the predictive utility of a communication model, the more likely it is to parsimoniously recapitulate the signaling mechanisms of the human brain.

RESULTS

Brain network communication matrices

Structural connectomes were mapped using white matter tractography applied to diffusion MRI data acquired for 889 healthy adults participating in the Human Connectome Project [24] (*Materials and Methods*). We focus on reporting results for connectomes comprising $N = 360$ cortical regions [26] that were thresholded to eliminate potentially spurious connections [27]. Results for alternative cortical parcellations and connection density thresholds are reported in the *Supplementary Information*.

Connectome mapping yielded a structural connectivity (SC) matrix for each individual. These matrices represented connectivity between directly connected regions and were generally sparse due to an absence of white matter tracts between a majority of region pairs. To model the impact of polysynaptic neural signaling, each individual's connectivity matrix was transformed into a communication matrix (Fig. 1a). Communication matrices were of the same dimension as the SC matrices, but fully connected in most cases, and they quantified the efficiency of communication between indirectly (polysynaptic) as well as directly connected pairs of regions under a given network communication model. In contrast, the

SC matrices only characterized directly connected pairs of regions.

We considered three connectivity weight definitions: (i) *Weighted*: connection weights defined as the number of tractography streamline counts between regions; (ii) *Binary*: non-zero connection weights set to one; and (iii) *Distance*: non-zero connection weights set to the Euclidean distance between regions. Network communication models computed on these connectomes operationalize metabolic factors conjectured to shape large-scale signaling: (i) adoption of high-volume white matter projections that putatively enable fast and reliable signal propagation (weighted); (ii) reduction of the number of synaptic crossings (binary); and (iii) reduction of the physical length traversed by signals (distance) [1, 28, 29].

Predicting behavior with models of connectome communication

Statistical models were trained to independently predict five dimensions of behavior (cognition, illicit substance use, tobacco use, personality-emotional traits, mental health) based on features comprising an individual's communication matrix (Fig. 1b,c). Training and prediction were performed separately for a total of 15 communication matrices representing different connection weight definitions (binary, weighted, distance) and network communication models (shortest paths, navigation, diffusion, search information, communicability). Additionally, predictions based on an individual's SC and FC were computed to provide a benchmark. The five behavioral components represent orthogonal dimensions that were parsed from a comprehensive set of behavioral measures using independent component analysis (*Materials and Methods*).

Out-of-sample prediction accuracy was evaluated for 10 repetitions of a 10-fold cross-validation scheme. The Pearson correlation coefficient between the actual and out-of-sample predicted behavior was used to quantify prediction accuracy for each behavioral dimension. To ensure that our results were not contingent on the adoption of a particular statistical model, predictions were independently performed using lasso regression [30] and a regression model based on features identified by the network-based statistic (NBS) [31] (*Materials and Methods*). Prediction accuracies were averaged across cross-validation folds and repetitions, and visualized in the form of a matrix comprising behavioral dimensions (rows) and communication models (columns) (Fig. 2a,c).

We found that individual variation in some behavioral dimensions could be predicted with greater accuracy than others (lasso: $F_{(4,80)} = 10.67$, $p = 5 \times 10^{-7}$; NBS: $F_{(4,80)} = 47.18$, $p = 2 \times 10^{-20}$). Dimensions characterizing cognition (respective lasso and NBS accuracies averaged across all predictors: 0.068, 0.101) and tobacco use (0.061, 0.089) could be predicted more accurately on average, whereas comparably weaker predictions of il-

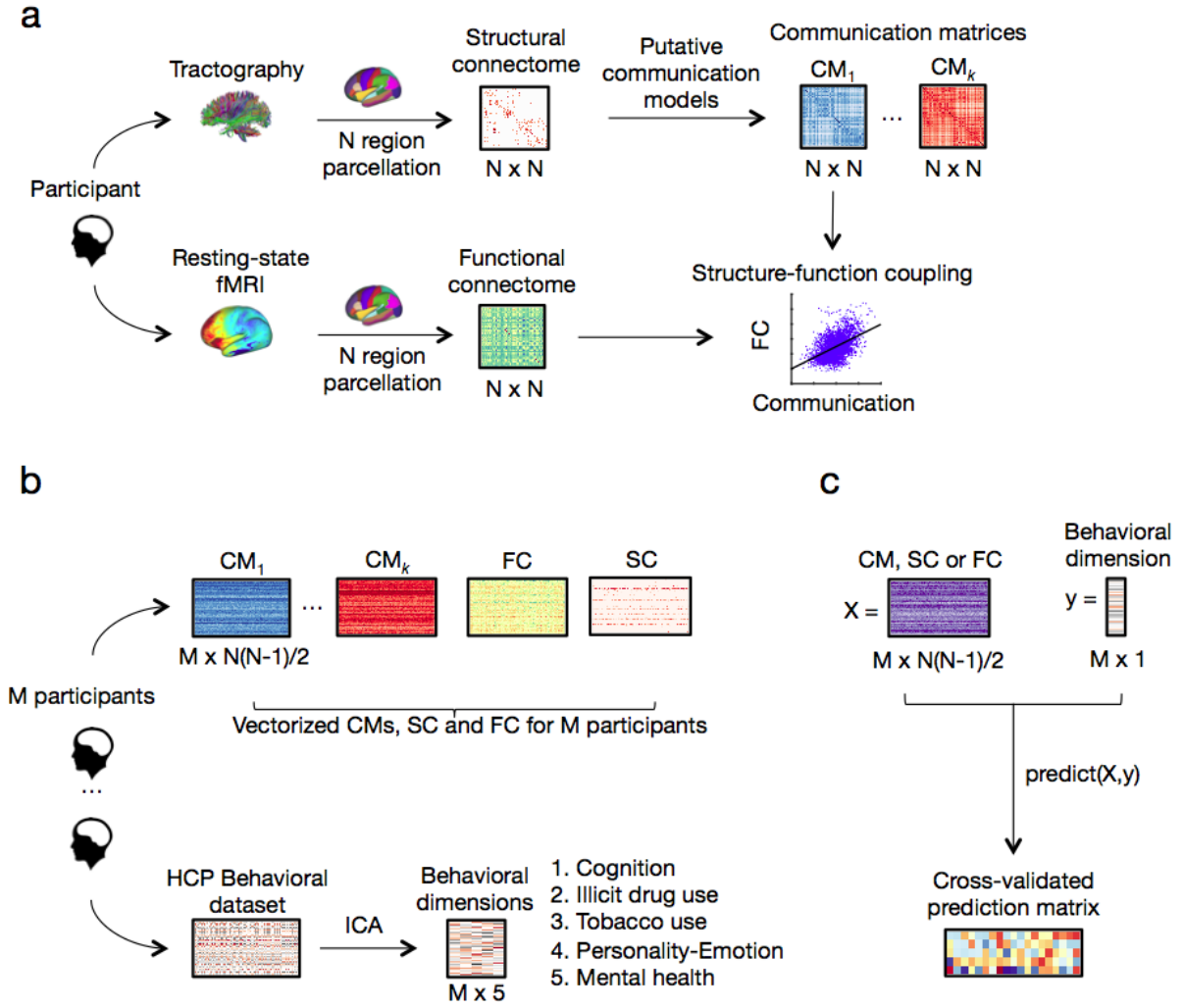


FIG. 1. Methodology overview. **(a)** For each participant in our sample, structural connectomes comprising N cortical regions were mapped using white matter tractography applied to diffusion MRI. Structural connectivity matrices were transformed into communication matrices $C \in \mathbb{R}^{N \times N}$, where $C(i, j)$ denotes the communication efficiency from region i to region j . For each participant, a total of 15 communication matrices were derived representing different combinations of network communication models (shortest paths, navigation, diffusion, search information, communicability) and connection weight definitions (binary, weighted, distance). To assess structure-function coupling, communication matrices were correlated with FC matrices computed from resting-state functional MRI data. **(b)** Communication, FC and SC matrices were vectorized and aggregated across $M = 889$ participants, resulting in 17 $M \times N(N - 1)/2$ matrices of explanatory variables. A set of five behavioral dimensions was computed by applying independent component analysis (ICA) to the HCP dataset of behavioral phenotypes. **(c)** Communication, SC and FC matrices were used to predict behavior. An entry in the resulting 5×17 prediction matrix corresponds to the mean cross-validated association between a communication or connectivity matrix and a behavioral dimension.

licit substance use (-0.003, -0.002), personality-emotion (-0.008, -0.003) and mental health (-0.014, -0.0003) were evident (Fig. 2b,d).

Prediction accuracies were consistent between the two statistical models (NBS, lasso), both when pooling the five behavioral dimensions (Spearman rank correlation coefficient $r_{(83)} = 0.60$, $p = 2 \times 10^{-9}$; Fig. 2e), as well as separately for cognition ($r_{(16)} = 0.56$, $p = 0.022$; Fig. 2f) and tobacco use ($r_{(16)} = 0.67$, $p = 0.004$; Fig. 2h). Lasso and NBS diverged for the dimensions that were less

accurately predicted (e.g., $p = 0.313$ for illicit substance use; Fig. 2g).

Focusing on lasso regression, we sought to determine whether behavioral predictions were robust to variations in our methodological settings. First, we found that adopting the mean square error to quantify predictive utility led to accuracies significantly associated to the ones computed based on Pearson correlation (Fig. S1). Second, we tested whether prediction accuracies were sensitive to changes in our connectome mapping pipeline.

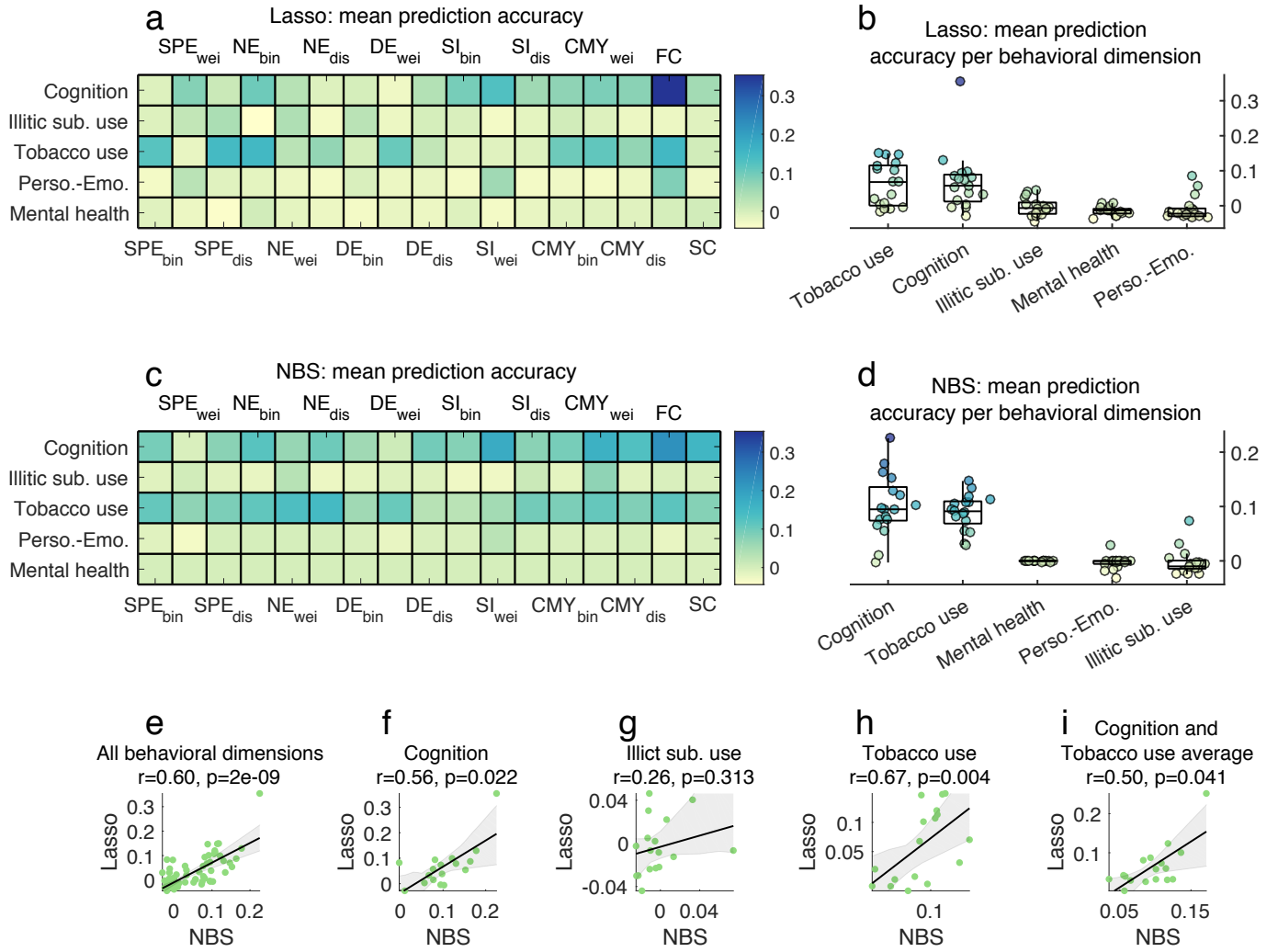


FIG. 2. Predicting individual variation in human behavioral dimensions using models of connectome communication, as well as structural and functional connectivity ($N = 360$ thresholded connectomes). **(a)** Matrix of Pearson correlation coefficients between actual and out-of-sample predicted behavior using lasso regression for five orthogonal behavioral dimensions (rows) and 15 connectome communication models as well as SC and FC (columns, predictors). **(b)** Lasso regression prediction accuracies stratified by behavioral dimensions. Each boxplot summarizes a row of the prediction accuracy matrix and the superimposed data points are colored accordingly. Top and bottom edges boxplots indicate, respectively, the 25th and 75th percentiles, while the central mark shows the distribution median. Mean prediction accuracies significantly differed between the five behavioral dimensions ($F_{(4,80)} = 10.67, p = 5 \times 10^{-7}$). **(c-d)** Same as (a-b), but for predictions carried out using a regression model based on features identified by the NBS. Again, mean prediction accuracies were significantly different between behavioral dimensions ($F_{(4,80)} = 47.18, p = 2 \times 10^{-20}$). Scatter plots showing the correspondence (Spearman rank correlation coefficient and p -value) between lasso and NBS prediction accuracies for **(e)** all behavioral dimensions, **(f)** cognition, **(g)** illicit substance use, **(h)** tobacco use, and **(i)** the average between cognition and tobacco use prediction accuracies. SPE: shortest path efficiency, NE: navigation efficiency, DE: diffusion efficiency, SI: search information, CMY: communicability, bin: binary, wei: weighted, dis: distance.

To this end, we recomputed behavioral predictions for three additional sets of connectomes: (i) $N = 360$ regions without connection thresholding, (ii) $N = 68$ regions with connection thresholding, and (iii) $N = 68$ regions without connection thresholding (*Materials and Methods*). Prediction accuracies were typically significantly correlated across low- and high-resolution, as well as

thresholded and unthresholded, connectomes (Fig. S2). More specifically, consistency across connectome mapping pipelines was strong when considering predictions pooled across all five behavioral dimensions and relatively modest when focusing on cognition and tobacco use, indicating a potential effect of parcellation and connection thresholding to the predictive utility of different commu-

nication models.

Together, these findings suggest that network communication models (as well as SC and FC) can explain out-of-sample inter-individual variance in behavior. More specifically, cognition and tobacco use were the most accurately predicted behavioral dimensions. For this reason, we henceforth focus subsequent analyses on the averaged prediction accuracy obtained for the cognition and tobacco use dimensions. This provides us with a single measure of how connectome communication relates to behavior by considering only the behavioral traits that can be predicted with relevant accuracy. The obtained prediction accuracy average was also consistent across the lasso and NBS methods ($r_{(16)} = 0.50$, $p = 0.041$; Fig. 2i).

Communication models improve the behavioral predictive utility of the human connectome

We sought to compare communication models, as well as SC and FC, in terms of their behavioral prediction accuracy. Figure 3a shows the distributions of out-of-sample accuracies (10 repetitions of 10-fold cross validation, averaged for the cognition and tobacco use dimensions) obtained for the each predictor using lasso regression. Accuracy distributions were ranked based on their medians. FC (median accuracy: 0.24) provided markedly greater accuracy than all communication models and SC. Binary navigation (median accuracy: 0.12) and weighted communicability (median accuracy: 0.10) followed as the second and third most predictive communication models. Crucially, we observed that the majority of communication models yielded greater prediction accuracy than SC (median accuracy: 0.03). This indicates that modeling polysynaptic signaling through the transformation of SC into communication matrices improved the behavioral predictive utility of structural connectomes.

We performed repeated measures t-tests to assess pairwise statistical differences in the predictive utility of communication models and connectivity measures. Figure 3b shows the effect size matrix (Cohen's d ; Bonferroni-corrected for 136 multiple comparisons with significance threshold $\alpha = 3.67 \times 10^{-4}$) of differences between mean prediction accuracies, with warm- and cool-colored cells indicating model pairs for which a significant difference was observed. As expected, FC outperformed all other predictors (e.g., $p = 1 \times 10^{-26}$ between FC and binary navigation). The lack of colored cells along the main diagonal of the effective size matrix indicates that predictors of similar ranking seldom yielded significantly different accuracy. Importantly, seven communication models (out of 15) significantly outperformed SC, including binary navigation; binary, weighted and distance communicability; binary and distance shortest paths; and weighted search information (all $p < 10^{-4}$). This underscores the improvement in behavioral predictive utility gained from accounting for polysynaptic communication

in structural connectomes, compared to predictions that only account for direct structural connections. The magnitude of statistical differences between communication models was better visualized when plotting effect size matrices excluding comparisons to FC (Fig. S3).

Importantly, the behavioral prediction accuracies reported in Fig. 3a were significantly larger than those obtained by computing network communication models on null sets of topologically randomized connectomes (*Supplementary Note 1*; Fig. S4). This corroborates the notion that network communication models are capable of predicting interindividual variation in human behavior, and that observed differences in prediction accuracies reflect meaningful distinctions in the predictive utility of different models. Additionally, we found that the pairwise comparisons between models shown in Fig. 3b were stable across each of the 10 repetitions of the performed 10-fold cross validation (*Supplementary Note 2*; Table S1).

Next, we aimed to separate the effects of communication model choice and connection weight definition on prediction accuracy. To this end, accuracies were averaged over the three weight definitions for each communication model (Fig. 3c,d), or averaged over the 15 models for each weight definition (Fig. 3e,f). Prediction accuracies for FC and SC, which were not computed for multiple weight definitions, remained the same as shown in Figure 3a. With respect to the effect of communication model, we found that communicability significantly outperformed other models and SC (e.g., $p = 3 \times 10^{-5}$, 2×10^{-11} for comparisons of communicability to navigation and SC, respectively), although FC remained the leading predictor. Navigation and shortest paths featured in second and third positions, both performing better than SC ($p = 3 \times 10^{-7}$, 3×10^{-5} , respectively) and with no statistical difference between them ($p = 0.26$). With respect to connection weight definition, binary connectomes yielded significantly higher prediction accuracies, on average, compared to weighted and distance connectomes ($p = 0.009$, 2×10^{-5} , respectively), albeit with a weaker effect size than differences between communication models. This suggests that the choice of communication model may be more important to behavior predictions than the definition of connection weights.

To gain further insight into these results, we executed additional analyses in which we considered predictions for the cognition and tobacco use dimensions separately (*Supplementary Note 3*; Figs. S5, S6). While these investigations reiterated the overall good performance of navigation and communicability, they also revealed the presence of certain dimension-specific relationships between communication and behavior. For instance, search information yielded top- and bottom-ranking predictions for cognition and tobacco use, respectively.

Finally, aiming to assess the robustness of our findings to the choice of prediction method, we analyzed behavioral predictions derived using a regression model applied

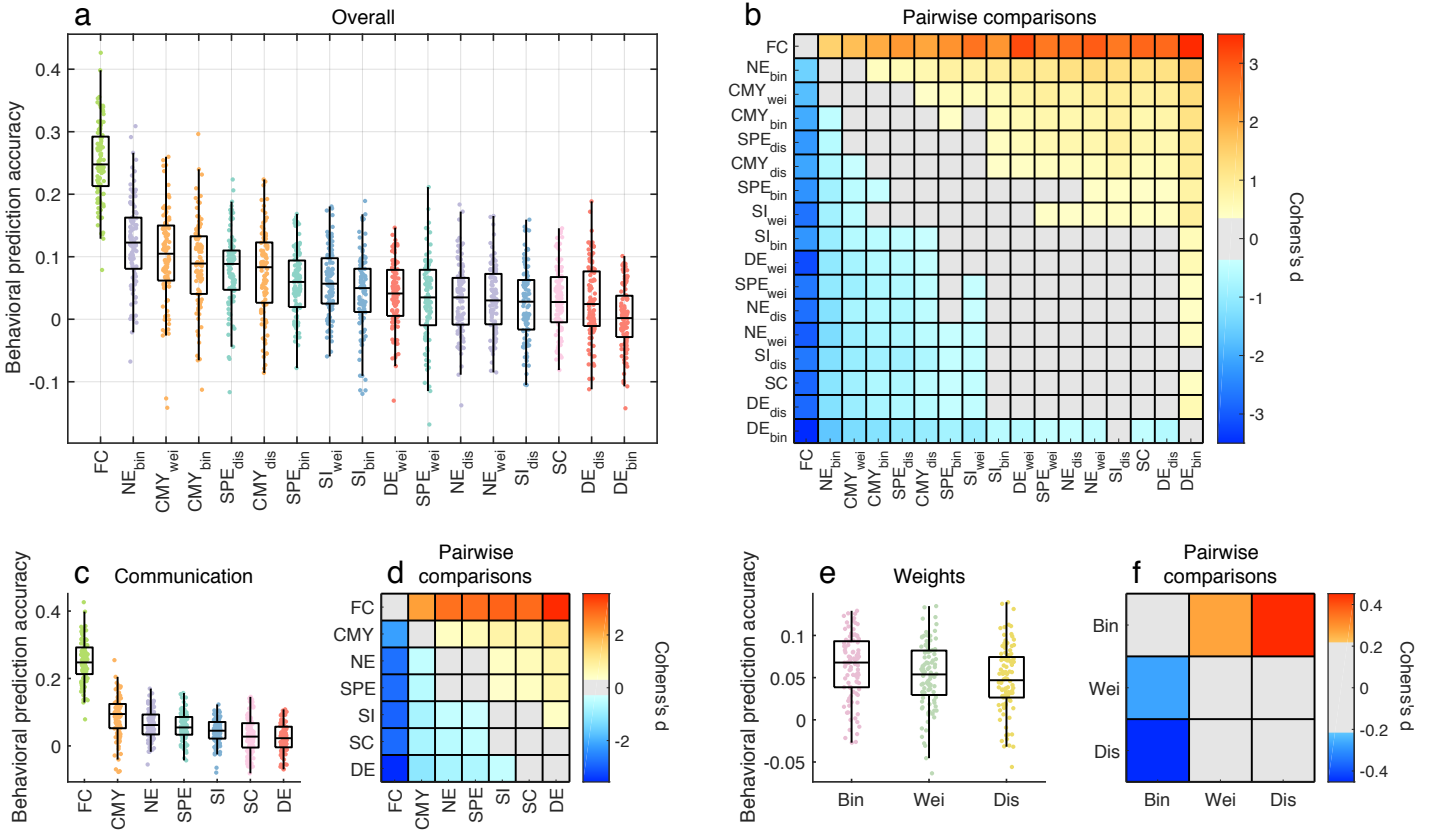


FIG. 3. Comparison of the behavioral predictive utility of connectome communication models (Lasso regression, $N = 360$ thresholded connectomes, average cognition and tobacco use prediction accuracies). Across panels, top and bottom edges boxplots indicate, respectively, the 25th and 75th percentiles, while the central mark shows the distribution median. **(a)** Prediction accuracy distributions for 10 repetitions of 10-fold cross-validation. Communication models, SC and FC were sorted based on their median prediction accuracy. **(b)** Effect size matrix of pairwise statistical comparisons between predictors. Warm- and cool-colored cells indicate predictor pairs with significantly different means, as assessed by a repeated-measures t-test (Bonferroni-corrected for 136 multiple comparisons with significance threshold $\alpha = 3.67 \times 10^{-4}$). A warm-colored i, j matrix entry indicates that predictor i yields significantly more accurate predictions than predictor j . **(c)** Prediction accuracy distributions of communication models averaged across connection weight definitions. SC and FC were not subjected to any averaging and accuracies remain the same as in panel (a). **(d)** Effect size matrix of pairwise repeated-measures t-tests between distributions in panel (c), with colored cells indicating significant differences in mean prediction accuracies (Bonferroni-corrected with significance threshold $\alpha = 0.0024$). **(e)** Prediction accuracy distributions of connectomes with different connection weight definitions averaged across communication models. **(f)** Same as panel (d), but Bonferroni-corrected with significance threshold $\alpha = 0.0167$.

to features identified by the NBS. As with the lasso, we examined NBS predictions combined across the cognition and tobacco use (Fig. S7), as well as for each of these dimension separately (Figs. S8, S9). As previously reported in Fig. 2, NBS and lasso prediction accuracies were significantly correlated. FC remained the strongest predictor of behavior, although with a smaller margin of difference to navigation and communicability. Despite this overall agreement, we observed that SC yielded higher ranking predictions under the NBS method (5th highest ranking predictor) than the lasso (15th predictor). Interestingly, SC's performance under the NBS diverged widely between the cognition (4th predictor) and

tobacco use components (16th predictor), reiterating the dimension-specific character of brain-behavior relations observed in the lasso results. It is worth noting that the NBS feature selection process is better suited to sparse graphs [31], which could confer a predictive advantage to sparse SC matrices over fully-connected communication and FC matrices.

Taken together, the behavioral prediction analyses led to three key findings. First, behavioral predictions were more accurate when performed based on functional rather than structural attributes. Second, while navigation and communicability typically showed high predictive utility, our results did not point towards a single com-

munication model as the best predictor of human behavior. This indicates that different communication models may be better suited to predict different behavioral dimensions, possibly suggesting the presence of behavior-specific signaling mechanisms in the human brain. Third, the transformation of SC (only direct connections) into communication matrices (models of polysynaptic interactions) typically led to an improvement of structural-based predictions, bringing them closer to the predictive utility of FC. Importantly, the magnitude of this improvement, as well as which and how many communication models conferred predictive benefits, varied depending on behavioral dimensions and prediction methods. Collectively, these findings indicate that connectome communication models capture higher-order structural relations among brain regions that can better account for interindividual variation in behavior than SC alone.

Communication models improve structure-function coupling

We next investigated whether accounting for network communication in the structural connectome can improve the strength of the relation between SC and FC, known as structure-function coupling. Classically, associations have been directly tested between structural and functional connections [32]. A growing body of work indicates that accounting for higher-order regional interactions through models of polysynaptic signaling (i.e., transforming structural connectomes into communication matrices) can improve structure-function coupling [11, 12, 14, 33, 34]. For two regions that are not directly connected with an anatomical fiber, strong FC is conjectured to indicate the presence of an efficient signaling path that facilitates communication through the underlying anatomical connections [9].

To test this hypothesis, we computed the association between FC and communication matrices for each individual in our sample. Additionally, as a benchmark, we also considered the association of FC to SC and to interregional Euclidean distance. Associations were computed as the Spearman correlation between upper triangular matrix entries. In addition to individual-level associations, we also analyzed structure-function coupling derived from group-level SC and FC. Finally, associations were derived for coarse- ($N = 68$ regions) and fine-grained ($N = 360$ regions) connectomes, which were thresholded prior to the computation of communication models. FC matrices were not thresholded. Further details on the computation of structure-function coupling are provided in the *Materials and Methods*.

As previously reported [12], communication matrices were correlated with FC, irrespective of the particular communication model (Fig. 4). In other words, FC was generally stronger between regional pairs interconnected by more efficient communication pathways. Group-level correlations (r_G ; black crosses) were universally stronger

than those obtained for the median individual (r_I ; box-plots), supporting the notion that predicting population-level FC traits is less challenging than modeling idiosyncratic relationships between brain structure and function.

We found that parcellation resolution had a strong influence on the strength of structure-function coupling. The link between structure and function weakened for high resolution connectomes, irrespective of the communication model (Fig. 4a). Moreover, the ranking of communication models in terms of structure-function coupling differed between connectome resolutions (Spearman rank correlation between low- and high-resolution FC predictions $p = 0.65$). For $N = 68$ regions, weighted and distance diffusion yielded the strongest structure-function couplings ($r_I = 0.46$ and $r_G = 0.53$ for weighted diffusion; Fig. 4b,c). This recapitulates previous work indicating the functional predictive utility of random walk models applied to connectomes comprising less than one hundred regions [33]. However, in sharp contrast, diffusion performed poorly for $N = 360$ regions, going from yielding the most accurate estimates of FC in low-resolution but ranking as the worst overall predictor in high-resolution. Conversely, the coupling between Euclidean distance and FC showed the opposite relationship to connectome resolution, with interregional distances leading to weak and strong associations for coarse- and fine-grained parcellations, respectively.

Navigation and shortest paths resulted in consistently high-ranked FC predictions regardless of connectome resolution. For $N = 68$ regions, weighted navigation and shortest paths showed comparable associations to the top-ranking diffusion models (e.g., $r_I = 0.42$ for weighted shortest paths). For $N = 360$ regions, distance navigation was the top-ranking model ($r_I = 0.18$ and $r_G = 0.22$; Fig. 4d,e), followed by distance shortest paths in second place, both outperforming the Euclidean distance benchmark in the third position.

Crucially, despite the effects of connectome resolution, modeling polysynaptic communication on top of structural connectomes tightened structure-function coupling. This was the case for 8 and 9 out of the 15 communication models considered, for low- and high-resolution connectomes, respectively. For instance, for the median individual, weighted diffusion in 68-region connectomes strengthened coupling by 46% compared to SC, while computing distance navigation in 360-region connectomes boosted FC predictions by 66% compared to SC.

Grouping couplings by communication models reiterated functional predictive utility differences between low- and high-resolution connectomes (Fig. 4f). Grouping couplings by connection weight definitions showed that, on average, communication models computed on weighted and distance connectomes led to stronger couplings for coarse- and fine-grained parcellations, respectively (Fig. 4g), suggesting that the established influence of interregional distance in SC and FC [35, 36] may be stronger for connectomes derived at finer levels of areal

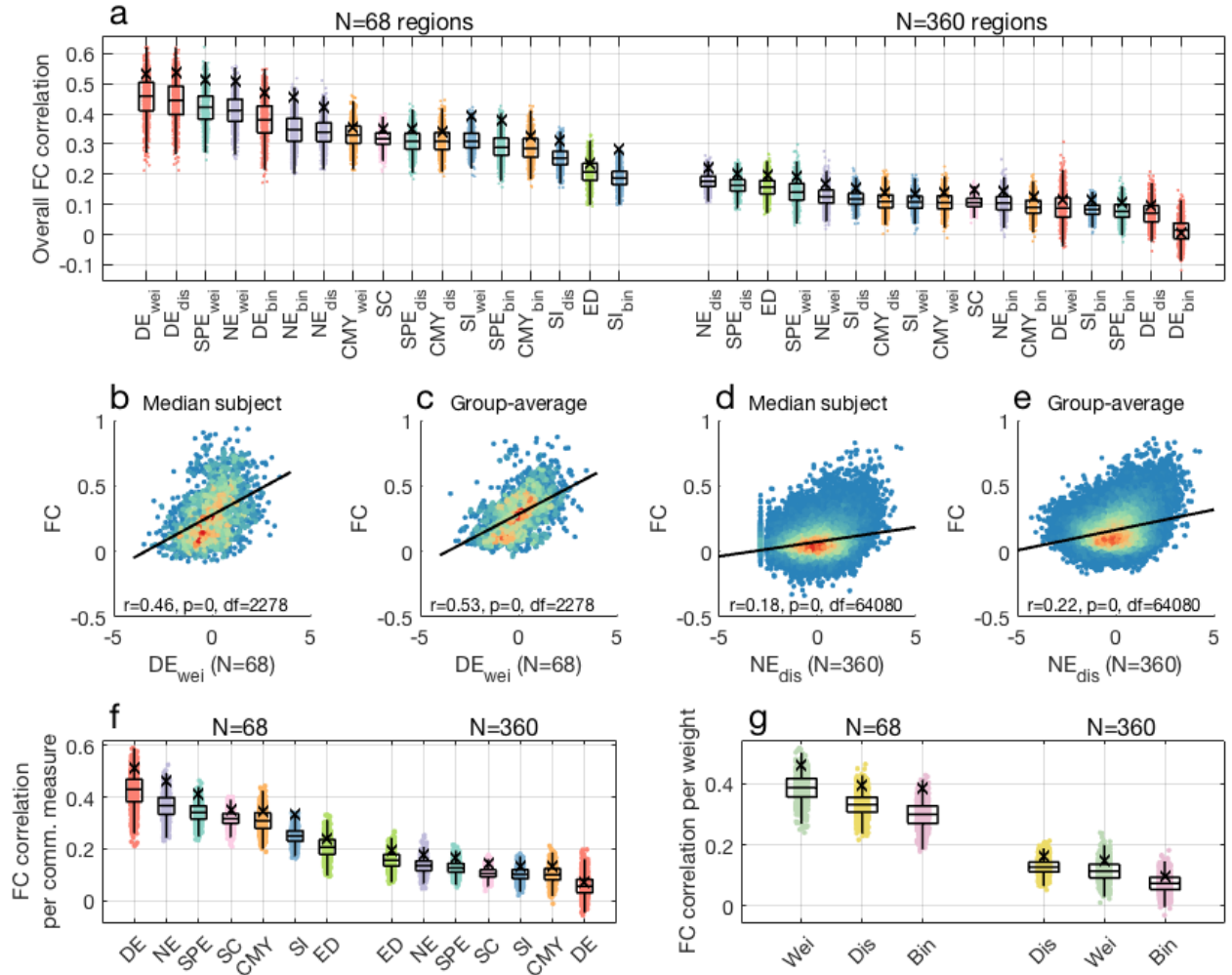


FIG. 4. Structure-function coupling across connectome communication models ($N = 68, 360$ thresholded connectomes). **(a)** Data points show individual-level correlation of FC to communication, SC and Euclidean distance matrices. Black crosses indicate correlations obtained for group-averaged matrices. Top and bottom edges boxplots indicate, respectively, the 25th and 75th percentiles, while the central mark shows the distribution median. Communication models, SC and Euclidean distance were ranked according to the median structure-function coupling strength across individuals. **(b)** Scatter plot depicting the relationship between FC and the top-ranked communication model for connectomes comprising $N = 68$ regions, for the median individual. For ease of visualization, communication matrix entries were resampled to normal distributions. Warm and cool colors indicate high and low data point density, respectively. **(c)** Same as (b), but for group-average matrices. **(d-e)** Same as (b-c), but for connectomes comprising $N = 360$ regions. **(f)** Structure-function coupling for communication models, SC and Euclidean distance, averaged across connection weight definitions. **(g)** Structure-function coupling obtained for binary, weighted and distance connectomes, averaged across communication models.

granularity.

In summary, we observed that structure-function coupling is affected by connectome resolution and by whether associations are computed on individual or population levels. Regardless of parcellation granularity, most connectome communication models contributed to strengthening structure-function coupling. Moreover, navigation and shortest paths yielded the most accurate and reliable predictions of FC. While here we focused on thresholded connectomes, similar results were observed for unthresholded networks (Fig. S10). Rankings of func-

tional predictive utility also remained consistent when stratifying analyses between structurally connected and unconnected region pairs, as well as for intrahemispheric structure-function associations (*Supplementary Note 4*; Fig. S11). Together, these observations build on the behavioral prediction findings, further supporting the notion that connectome communication models contribute to bridging the gap between brain structure and function.

Ranking communication models

Finally, we derived a combined ranking of predictive utility, as the average of behavioral and functional prediction rankings, for the 15 communication models explored and SC (Fig. 5). This was performed for the four connectome mapping pipelines explored in our analyses. Behavioral and functional results were given equal weight in the combined rankings. For $N = 360$ thresholded connectomes, the only case in which behavioral analyses were carried out using both lasso and NBS prediction methods, a weighted average assigning 0.25 weight to lasso behavioral rankings, 0.25 weight to NBS behavioral rankings and 0.5 weight to structure-function coupling rankings was applied.

For $N = 360$ thresholded connectomes, we found that distance navigation showed the highest combined predictive utility (average ranking $\tau = 3.7$; Fig. 5a), followed by a tie between distance shortest paths and weighted communicability ($\tau = 4.7$). SC featured in the 11th position ($\tau = 8.7$) and was outranked by most navigation, communicability, shortest paths and search information models.

Contrasting combined rankings across connectome mapping pipelines led to several interesting observations. First, $N = 360$ thresholded and unthresholded connectomes led to the only pair of significantly correlated overall rankings (Spearman rank correlation $r_{(15)} = 0.65$, $p = 0.007$). This corroborates our previous findings that parcellation choice and connection density influence the predictive utility of network communication models. Second, network communication models were more beneficial when computed on high-resolution and thresholded connectomes. Intuitively, a densely connected network requires few polysynaptic signaling paths, since most regions can communicate via direct connections. This renders the transformation of SC into communication matrices less relevant, and therefore less advantageous for predictions. Third, combined rankings did not provide a clear picture on what connection weight definition may be more relevant for behavioral and functional predictions (Fig. 5c,f,i,l). Fourth, for all connectome mapping pipelines, we found certain communication models that improved the predictive utility of the human connectome. In the case of unthresholded $N = 68$ connectomes, the scenario in which communication models provide the least benefits, we still observed that weighted navigation, shortest paths and communicability outranked SC. Fifth, navigation was the top-ranking model across all connectome mapping pipelines. This was the case when considering overall rankings (Fig. 5a,d,g,j) as well as rankings grouped by communication models (Fig. 5b,e,h,k). Weighted navigation outranked SC in all explored scenarios, and excluding unthresholded $N = 68$ connectomes, navigation outranked SC regardless of connection weight definitions.

Collectively, these results indicate that despite differences across connectome mapping pipelines, certain net-

work communication models improved the combined behavioral and functional predictive utility of the human connectome. In particular, navigation was consistently positioned as the highest ranking model, indicating that the transforming of SC into navigation communication matrices is reliably advantageous for predictions of human behavior and FC.

DISCUSSION

Human cognition and behavior arise from the orchestrated activity of multiple brain regions [37, 38]. Resting-state FC is currently one of the most widely used neuroimaging measures to quantify this concerted activity [39–41]. It is thus unsurprising that statistical methods trained on functional brain networks led to the most accurate predictions of human behavior. Importantly, the signaling processes that facilitate synchronous interregional activity must unfold along structural connections forming direct or indirect (polysynaptic) communication paths. Therefore, brain structure, brain function, neural communication, and human behavior are tightly intertwined. This is corroborated by the key conclusion of the present study: accounting for polysynaptic communication in SC matrices can substantially improve structure-function coupling and the predictive utility of SC. While accounting for communication did not lead to SC outperforming FC with respect to behavior prediction, it narrowed the gap between the predictive utility of SC and FC.

As investigators tackle the longstanding challenge of elucidating the relationship between brain structure and function [42–44], it has become increasingly clear that FC arises from high-order regional interactions that cannot be explained by direct anatomical connections [11]. In line with this notion, we found that taking polysynaptic signaling into account through network communication models strengthened structure-function coupling. This observation recapitulates earlier reports on the functional predictive utility of connectome communication models [12] and provides support to the notion that FC is facilitated by communication pathways in the underlying structural connectome. Taken together, the behavioral and functional prediction analyses contribute empirical evidence that connectome communication models act as a bridge between structural and functional conceptualizations of brain networks [9, 45].

Importantly, brain structure-function relationships encompass a rich and diverse field of research, with several alternative classes of higher-order models showing promise in modeling function from structure. Examples include biophysical models of neural activity [46–48], statistical methods [49, 50], and other approaches centered around network communication that we did not explore in the present work [34, 51–54]. Likewise, relating neuroimaging data to behavior is a central goal of neuroscience [55, 56]. Recent studies have explored

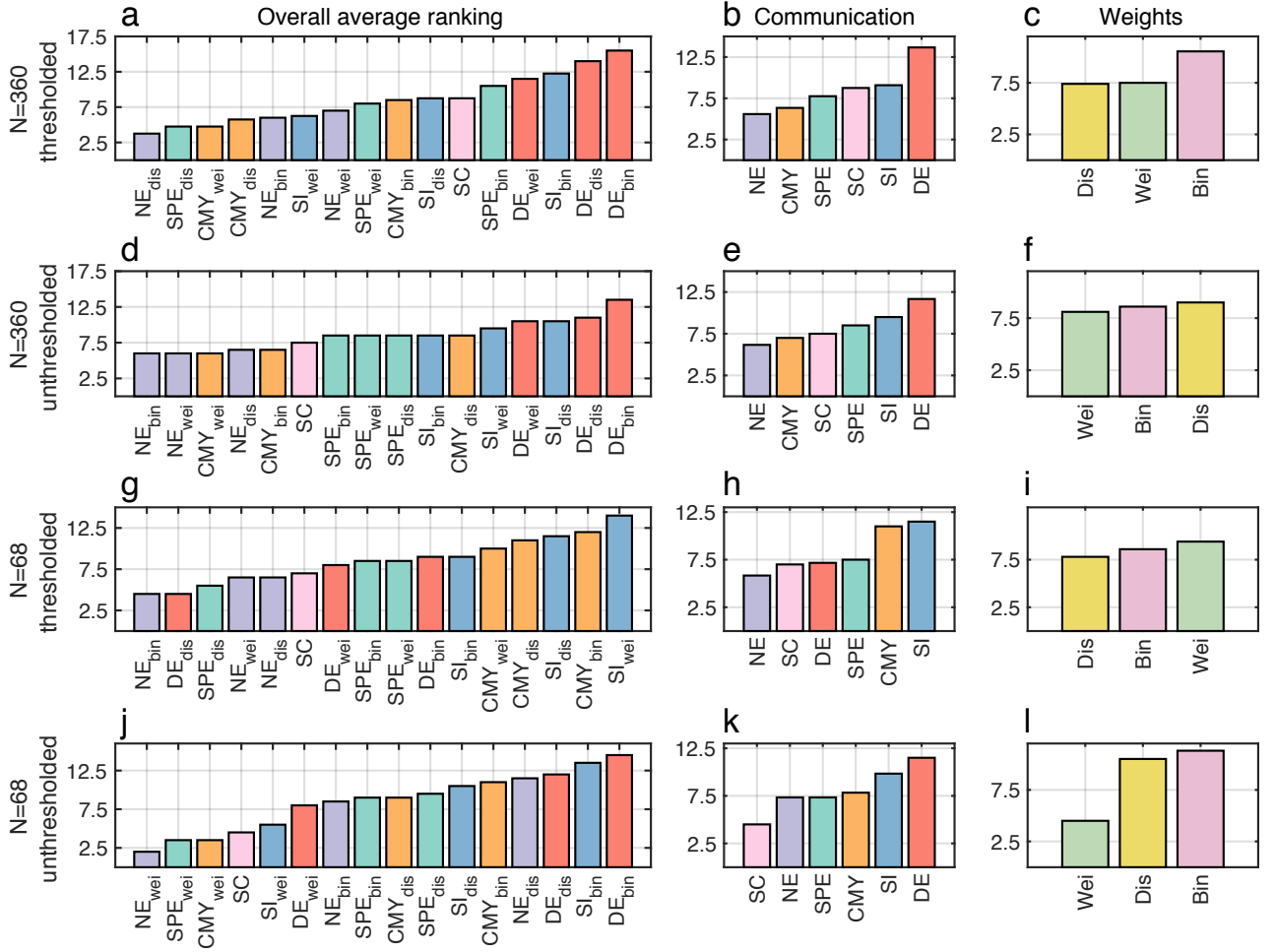


FIG. 5. Rankings of communication models combining behavioral and functional predictions. Overall, communication and weight definition rankings for (a-c) $N = 360$ thresholded, (d-f) $N = 360$ unthresholded, (g-i) $N = 68$ thresholded, and (j-l) $N = 68$ unthresholded connectomes.

neural correlates of behavior and cognition by leveraging graph measures of brain organization [57, 58], dynamic patterns of FC fluctuations [59, 60], multivariate correlation methods [61, 62] and machine learning techniques [63, 64]. Our analyses sought to complement these efforts from the perspective of connectome communication.

We reiterate that the goal of this paper was not to show that network communication models lead to more accurate predictions than alternative approaches, nor that our prediction scheme and statistical methods are superior to previously adopted techniques. Rather, we were interested in comparing the predictive utility of candidate models of connectome communication, as well as connectivity and distance benchmarks, in a controlled and internally consistent manner. Similarly, although we explored multiple brain network reconstruction pipelines, we were not primarily concerned with which mapping techniques produced connectomes with the highest predictive utility.

The choice of parcellation schemes [65] and whether or not to threshold structural connectomes [66, 67] are both challenging open questions that fall outside the scope of this work.

Comparisons between connectome communication models

Communication matrices computed with the navigation and communicability models typically led to the highest-ranking behavioral predictions amongst the candidate signaling strategies explored. It is important to notice, however, that search information, shortest paths and SC also performed well in certain scenarios. Therefore, while our behavioral results suggested the benefits of modeling polysynaptic signaling, they did not provide a clear answer to the question of which communication

models are most associated to human behavioral dimensions. Alternatively, our findings may indicate the interesting possibility that large-scale information integration in the brain is not facilitated by a unique signaling mechanism, and that different communication models may find more utility in describing varied behavioral and cognitive processes.

Navigation and shortest paths led to the most reliable FC predictions, featuring as the best models for high-resolution connectomes and closely following behind by diffusion for low-resolution connectomes. Navigation and shortest paths computed on distance connectomes led to FC predictions that surpassed those obtained from Euclidean distance, which exerts a well-documented influence on both SC and FC [35, 36, 68]. Furthermore, given the high efficiency of communication along navigation and shortest paths, these findings suggest that FC is facilitated primarily by highly efficient signaling pathways. This observation stands in contrast with previous work on the strong functional relevance of models that incorporate deviations from optimal routes, such as search information [12, 69] and communicability [53], underscoring the importance of further research on the validation of network communication models.

We evaluated network communication models across a wide range of methodological scenarios, including different gray matter parcellations, connection density thresholds, statistical learning methods and behavioral dimensions. While our results were stable for certain combinations of these factors, we found that the predictive utility of communication models substantially varied between some scenarios. This variability makes it difficult to draw strong conclusions about the extent to which different models are useful to understanding biological neural signaling patterns. Nonetheless, combining behavioral and functional prediction rankings consistently positioned navigation as the top-ranking model across connectome mapping pipelines. These findings contribute to the growing body of work supporting the neuroscientific utility of network navigation [18, 70–72] and highlights the potential of this signaling strategy as a model of information transfer in nervous systems.

In addition to investigating putative neural signaling strategies, we also considered different connection weight definitions. Polysynaptic transmission of neural signals entails metabolic expenditures related to the propagation of action potential along axonal projections and the crossing of synaptic junctions. Communication in the brain is thought to be metabolically frugal [29, 38], but what aspects of structural connectivity are relevant to energy consumption in large-scale signaling remain unclear. We found that weighted and distance connectomes typically led to communication matrices with higher predictive utility. This is initial evidence that neural signaling may favor communication paths prioritizing the adoption of physically short and high volume connections, instead of paths that reduce the number of synaptic crossings between regions. Additionally, these observations warrant

further investigation of the relatively unexplored distance connectome [73].

Previous evidence that connection thresholding is an unnecessary step in brain network analyses is primarily based on studies considering weighted connectomes [66], for which interregional connectivity strength is determined as a function of streamline counts or fractional anisotropy [74]. Along with these lines, we found that connectomes weighted by streamline counts led to the best performing predictors when considering unthresholded brain networks. However, we note that two thirds of the communication models explored in our analyses were based on binary and distance connectomes, which do not contain information on streamline counts. Therefore, it is expected that connection thresholding would impact the overall rankings of communication models.

In accordance to previous reports [75, 76], we observed that FC predictions were more accurate for low- rather than high-resolution connectomes, as well as for group- rather than individual-level analyses. This is not surprising since the number of functional connections grows quadratically with the number of regions and capturing idiosyncrasies in FC is more challenging than modeling general principles of connectivity. Despite their simplicity, these observations are important to the validation of FC prediction methods, suggesting that models constructed and evaluated on coarse and population-level networks may not generalize to more challenging settings.

Limitations and future directions

Several methodological limitations of the present work should be discussed. First, given the sensitivity of model rankings to some aspects of connectome mapping pipelines, further work exploring alternative brain network reconstruction methods is necessary. For instance, validation of our results for connectomes mapped using probabilistic tractography and/or larger numbers of streamline seeds would be valuable. We also note that white matter tractography algorithms are susceptible to a number of known biases that could potentially impact our findings [77].

A conceptual limitation of our behavioral analyses was that model selection was performed on the same data used to evaluate the accuracy of single models (out-of-sample test set). In addition, we note that behavioral prediction accuracy estimates from different cross validation folds are not independent from each other. This is a limitation of the statistical tests performed to compare the utility of communication models. Once again, these observations underscore the need for additional efforts to evaluate network communication models using alternative datasets and machine learning methods.

Another interesting future research direction is to investigate the contributions of specific brain regions to the predictive utility of different communication models. This could be achieved by examining lasso regression

weights and NBS connected components. Alternatively, behavior and functional predictions could be performed based on region-wise communication efficiencies, rather than complete communication matrices [78]. Efforts in these directions could help elucidate how different communication models utilize features of connectome topology to facilitate information transfer.

While we sought to evaluate a wide range of communication models, alternative network propagation strategies could provide valuable insight into mechanisms of neural signaling and warrant further research. These include linear transmission models [34], biased random walks [10], cooperative learning [79], dynamic communication models [80], and information-theoretic approaches [81].

In conclusion, we demonstrated that taking into account polysynaptic signaling via models of network communication can improve the behavioral and functional predictive utility of the human structural connectome. This work contributes to our understanding of which network communication strategies may be more useful as large-scale neural signaling models, providing novel insights to researchers interested in characterizing information processing in nervous systems.

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MATERIALS AND METHODS

Structural connectivity data

Minimally preprocessed high-resolution diffusion weighted magnetic resonance imaging (MRI) data was obtained from the Human Connectome Project (HCP) [24]. Details about the acquisition and preprocessing of diffusion MRI data are found in [82, 83]. Analyses were restricted to participants with complete HCP 3T imaging protocol, yielding a total sample of 889 healthy adults (age 22–35, 52.8% females). Whole-brain structural connectomes were mapped using diffusion tensor imaging and deterministic white matter tractography pipeline implemented using MRtrix3 [84] (FACT tracking algorithm, 5×10^6 streamlines, 0.5 mm tracking step-size, 400 mm maximum streamline length and 0.1 fractional anisotropy cutoff for termination of tracks). Deterministic tractography is less prone to false positive than alternative reconstruction approaches [77, 85],

which leads to connectomes that may be better suited for network and graph-theoretical analyses [27]. The connection weight between a pair of regions was defined as the total number of streamlines connecting them, resulting in a $N \times N$ weighted connectivity matrix for each participant. Group-level structural connectomes were computed by averaging the connectivity matrices of all subjects.

We used cortical parcellations containing $N = 68, 360$ regions. The 68-region parcellation consists of the anatomically delineated cortical areas of the Desikan-Killiany atlas [86]. The 360-region parcellation is a multimodal atlas constructed from high-resolution structural and functional data from HCP [26]. We also considered thresholded and unthresholded connectomes. Following connection density thresholding, only the top 15% and 20% strongest connections (in terms of streamline counts) were kept in connectomes comprising 360 and 68 regions, respectively. Connection density thresholds were chosen as the (approximate) lowest values that resulted in non-fragmented brain networks for all subjects in our sample. Unthresholded connectomes maintained all connections identified in the structural connectivity reconstruction process.

Connection weight and length definitions

Structural connectomes can be defined in terms of $N \times N$ adjacency matrices of connectivity weights (W) or lengths (L). Connection weights provide a measure of the strength and reliability of anatomical connections between regions pairs, while connection lengths quantify the distance or travel cost between regions pairs. Different network communication measures are computed based on W (e.g., diffusion efficiency and communicability), L (e.g., shortest path efficiency and navigation efficiency) or a combination of both (e.g., search information).

We considered three definitions of W : weighted, binary and distance. In the weighted case, $W_{wei}(i, j)$ was defined as the total number of streamlines with one endpoint in region i and the other in region j . The binary adjacency matrix was defined as $W_{bin}(i, j) = 1$ if $W_{wei}(i, j) > 0$ and $W_{bin}(i, j) = 0$ otherwise. Distance-based connectivity was defined as $W_{dis}(i, j) = 1/D(i, j)$ if $W_{wei}(i, j) > 0$ and $W_{dis}(i, j) = 0$ otherwise, where D is the Euclidean distance matrix between region centroids.

Similarly, L was also defined in terms of binary, weighted and distance connection traversal costs. In all three cases, $L(i, j) = \infty$ for ij region pairs that do not share a direct anatomical connection, ensuring that communication is restricted to unfold through the connectome. Binary (L_{bin}) and distance-based (L_{dis}) connection lengths are straightforwardly defined from their weighted counterparts as $L_{bin}(i, j) = 1$ if $W_{bin}(i, j) = 1$ and $L_{bin}(i, j) = \infty$ otherwise, and $L_{dis}(i, j) = D(i, j)$ if $W_{dis}(i, j) > 0$ and $L_{dis}(i, j) = \infty$ otherwise. Lengths

based on the streamline count between regions pairs are defined by monotonic weight-to-length transformations that remap large connection weights into short connection lengths. This way, white matter tracts conjectured to have high caliber and integrity are considered faster channels of communication than weak and unreliable ones. We considered a logarithmic weight-to-length remapping such that $L_{wei} = -\log_{10}(W_{wei}/\max(W_{wei}) + 1)$ (the unity addition to the denominator avoids the remapping of the maximum weight into zero length) [18], producing normally distributed lengths that attenuate the importance of extreme weights [87, 88].

Network communication models

In this section, we provide details regarding the definition of the five network communication models evaluated in this study. All computations were carried out using freely available code provided in the Brain Connectivity Toolbox (<https://sites.google.com/site/bctnet/>) [28].

First, we note a subtle but important distinction between network communication models and measures. A Network communication model (e.g., shortest path routing) delineates a strategy or algorithm to transfer information between node pairs. In turn, a network communication measure (e.g., shortest path efficiency) quantify, from a graph-theoretical standpoint, the efficiency of information transfer achieved by a given communication model. For simplicity, we used “model” throughout this paper to refer to both network communication models and measures.

We also note that certain communication measures are inherently asymmetric, in that $C_{asy}(i, j) \neq C_{asy}(j, i)$. While this asymmetry contains meaningful information on signaling properties of nervous systems [14], in the present study we consider symmetric communication matrices given by $C(i, j) = (C_{asy}(i, j) + C_{asy}(j, i))/2$. This simplification allows us to take into account only the upper triangle of C , substantially reducing the dimensionality of our predictive models and contributing to the computational tractability of our analyses.

Shortest path efficiency

Shortest path routing proposes that neural signaling takes place along optimally efficient paths that minimize the sum of connection lengths traversed between nodes. Let $\Lambda^* \in \mathbb{R}^{N \times N}$ denote the matrix of shortest path lengths, where $\Lambda^*(i, j) = L(i, u) + \dots + L(v, j)$ and $\{u, \dots, v\}$ is the sequence of nodes visited along the shortest path between nodes i and j . Shortest path efficiency was defined as $SPE = 1/\Lambda^*$ [15]. We computed binary (SPE_{bin}), weighted (SPE_{wei}), and distance (SPE_{dis}) shortest path efficiency matrices based on the L_{bin} , L_{wei} , L_{dis} connection length matrices, respectively.

Navigation efficiency

Navigation routing identifies communication paths by greedily propagating information based on a measure of node (dis)similarity [17]. Following previous studies on brain network communication, we used the Euclidean distance between region centroids to guide navigation [14, 18]. Navigating from node i to node j involves progressing to i ’s neighbor that is closest in distance to j . This process is repeated until j is reached (successful navigation) or a node is revisited (failed navigation). Successful navigation path lengths are defined as $\Lambda(i, j) = L(i, u) + \dots + L(v, j)$, where $\{u, \dots, v\}$ is the sequence of nodes visited during the navigation from i to j . Failure to navigate from i to j yields $\Lambda(i, j) = \infty$. Navigation efficiency was defined as $NE = 1/\Lambda$. Binary (NE_{bin}), weighted (NE_{wei}), and distance (NE_{dis}) navigation efficiency matrices were computed based on the L_{bin} , L_{wei} , L_{dis} , respectively.

Diffusion efficiency

Diffusion efficiency models neural signaling in terms of random walks. Let $T \in \mathbb{R}^{N \times N}$ denote the transition matrix of a Markov chain process unfolding on the connection weight matrix W . The probability that a naive random walker at node i will progress to node j is given by $T(i, j) = W(i, j) / \sum_{u=1}^N W(i, u)$. The mean first passage time $H(i, j)$ quantifies the expected number of intermediate regions visited in a random walk from i to j (details on the mathematical derivation of H from T are given in [1, 19, 89]). Diffusion efficiency is defined as $DE = 1/H$, thus capturing the efficiency of neural communication under a diffusive propagation strategy [19]. Binary (DE_{bin}), weighted (DE_{wei}), and distance (DE_{dis}) diffusion efficiency matrices were computed based on the W_{bin} , W_{wei} , W_{dis} , respectively.

Search Information

Search information is derived from the probability of random walkers serendipitously traveling along the shortest paths between node pairs [20]. Let $\Omega(i, j) = \{u, \dots, v\}$ be the sequence of nodes along the shortest path from node i to node j computed from the connection length matrix L . The probability of a random walker starting at i reaches j via $\Omega(i, j)$ is given by $P(\Omega(i, j)) = T(i, u) \times \dots \times T(v, j)$, where T is the previously defined transition probability matrix computed from W . We defined search information as $SI(i, j) = \log_2(P(\Omega(i, j)))$ [12, 14]. This definition quantifies how accessible shortest paths are to naive random walkers, capturing the degree to which efficient routes are hidden in network topology. Note that the computation of search information depends both on L —for the identification of shortest

paths—and W —for the simulation of random walk processes. We used W_{wei} combined with L_{bin} , L_{wei} , and L_{dis} to compute, respectively, binary, weighted, and distance versions of search information.

Communicability

Communicability models neural signaling as a diffusive process unfolding simultaneously along all possible walks in a network [21]. Communicability between nodes i and j is defined as the weighted sum of the total number of walks between them, with each walk weighted by its length (i.e., number of connections traversed). In the binary case, this yields $CMY(i, j) = \sum_{n=0}^{\infty} W_{bin}(i, j)^n / n!$. In the limit $n \rightarrow \infty$, this sum converges to $CMY(i, j) = e^{W_{bin}(i, j)}$. Non-binary connection weight matrices are typically normalized as $W'_{wei}(i, j) = W_{wei}(i, j) / (\sqrt{s(i)}\sqrt{s(j)})$ prior to the computation of communicability to attenuate the influence of high strength nodes [22], where $s(i) = \sum_{u=1}^N W_{wei}(i, u)$ is the total strength of node i . We used W_{bin} , W'_{wei} and W'_{dis} to compute, respectively, binary, weighted and distance-based versions of communicability.

Functional connectivity data

Minimally preprocessed resting-state functional MRI data from the same 889 individuals was also obtained from the HCP. Participants were scanned twice (right-to-left and left-to-right phase encodings) on two separate days, resulting in a total of four sessions per individual. In each session, functional MRI data was acquired for a period of 14m33s with 720ms TR. Further details on resting-state functional MRI data collection and preprocessing as described in [82, 90]. Functional activity in each of $N = 68,360$ regions was computed by averaging the signal of all vertices comprised in the region. Pair-wise Pearson correlation matrices were computed from the regional time series of each session, resulting in four matrices per participant. For each participant, the four matrices were averaged to yield a final $N \times N$ FC matrix. Group-level functional connectomes were computed by averaging the FC matrices of all subjects.

Behavioral dimensions

Information on HCP behavioral protocols and procedures is described elsewhere [91]. A total of 109 variables measuring alertness, cognition, emotion, sensory-motor function, personality, psychiatric symptoms, substance use and life function were selected from the HCP behavioral dataset [25]. Selected items consisted of raw (age- and gender-unadjusted), total or subtotal assessment scores. The set of 109 measures was submitted to

an independent component analysis (ICA) pipeline in order to derive latent dimensions summarizing orthogonal dimensions of behavioral information. This procedure contributed to the computational tractability of our analyses by enabling behavioral inferences to be performed on a small set of data-driven components, rather than restricted to arbitrarily selected measures.

Behavioral dimensions were computed as follows. A rank-based inverse Gaussian transformation [92] was used to normalize continuous behavioral variables (87 of 109). Age and gender were regressed out from all behavioral items. ICA was performed on the resulting residuals using the FastICA algorithm [93] implemented in the *icasso* MATLAB package [94]. Participants were sampled with replacement to generate a total of 500 bootstrap samples. ICA was independently performed on each sample with randomly selected initial conditions. Agglomerative clustering with average linkage was used to derive consensus clusters of independent components across different bootstrap samples and initial conditions. This procedure, including bootstrapping and randomization of initial conditions, was repeated for 10 trials of a set of candidate ICA models ranging from 3 to 30 independent components. The best number of components was estimated based on the reproducibility across the 10 trials by means of a cluster quality index. Clearly separated clusters indicate independent components were consistently and reliably estimated, despite being computed based on different bootstrap samples and initial conditions. This criterion identified the five component model as the most robust and parsimonious set of latent dimensions. This enabled the characterization of the five dimensions as cognitive performance, illicit substance use, tobacco use, personality and emotion traits, and mental health. Further details on the computation of the behavioral dimensions are provided in [25].

Behavioral prediction framework

Let $y \in \mathbb{R}^{n \times 1}$ be a vector of response variables corresponding to a given behavioral dimension, where $n = 899$ is the number of individuals in our sample. Let $X \in \mathbb{R}^{n \times p}$ be a matrix of p explanatory variables corresponding to the upper triangle of vectorized communication matrices $C \in \mathbb{R}^{N \times N}$, so that $p = N(N - 1)/2$. We applied two independent statistical models to predict y from X : lasso regression and a regression model based on network features identified by the NBS. These models implement different strategies of feature selection aimed at identifying a parsimonious set of variables in X to predict y .

The data was split into train and test sets to perform 10-fold cross-validation. The family structure in the HCP dataset was taken into account by ensuring that individuals of the same family were not separated between train and test sets [63]. Sensitivity to particular train-test data splits was addressed by repeating the 10-fold cross-validation 10 times. The same train and test sets

were used for lasso and NBS regressions. Model parameter estimation was performed exclusively on train sets while model performance was assessed exclusively on test sets.

Lasso regression

Let $\{X_a, y_a\}$ and $\{X_e, y_e\}$ denote a split of $\{X, y\}$ into train and test sets, respectively. We used lasso regression [30] to compute β as

$$\min_{\beta \in \mathbb{R}^p} \left\{ \frac{1}{n} \|y_a - X_a \beta\|_2^2 + \lambda \|\beta\|_1 \right\},$$

where $0 \leq \lambda \leq 1$ is a feature selection hyperparameter controlling model complexity. For each outer training set X_a , a nested 10-fold cross validation was carried out to tune λ . This was performed using the MATLAB function *cvglmnet* [95]. For each inner training fold, solutions were computed for a decreasing sequence of K logarithmically spaced hyperparameters from λ_{max} to λ_{min} , where λ_{max} was the smallest λ such that $\|\beta_{inner}\|_1 = 0$ and $\lambda_{min} = \epsilon \lambda_{max}$. Values of K and ϵ were separately determined for each inner fold by the algorithm, with typical values around $K = 100$ and $\epsilon = 0.01$ (further details are described in [96]). The obtained K models were then evaluated on the inner test folds. The λ resulting in the highest accuracy averaged across inner test folds was selected and used to compute β for the outer training set X_a . Model fit for each outer fold was evaluated as the Pearson correlation coefficient between $\hat{y}_e$ and y_e , where $\hat{y}_e = X_e \beta$. This procedure was repeated for 100 pairs of outer train and test tests (10 repetitions of 10-fold splits).

Network-based statistics regression

The NBS identifies sets of connected components that explain significant interindividual variation in a response variable [31]. We used the NBS as a feature selection technique to identify behaviorally relevant groups of connections. We then fit a regression model to the average connection weight of the selected connections in order to predict behavior. Importantly, connected components were identified exclusively in training sets, while prediction accuracy were computed based on held-out test sets.

Let $\{X_a, y_a\}$ and $\{X_e, y_e\}$ denote a split of $\{X, y\}$ into train and test sets, respectively. The cross-validated predictive utility of NBS connected components was computed as follows. For each column of X_a (corresponding to the value of a connection in the upper triangle of a communication matrix $C(i, j)$ across subjects in the train set), the inter-individual Pearson correlation between $C(i, j)$ and y_a was computed. Connections for which statistical association strength exceeded a t-statistic threshold $t > |3|$ were grouped into sets of positive ($t > 3$)

and negative ($t < -3$) connected components. This procedure was repeated for 1000 random permutations of y_a , and the likelihood of observing positive and negative connected components as large as empirical ones was assessed using a non-parametric test. Further details on the NBS are found in [31].

Let Γ^+ and Γ^- be, respectively, the largest positive and negative connected components identified by the NBS based on the train data $\{X_a, y_a\}$. We computed $g_a^{+,-} \in \mathbb{R}^{|y_a| \times 1}$ as the average weight of connections belonging to the connected component $\Gamma^{+,-}$:

$$g_a^{+,-} = \frac{1}{|\Gamma^{+,-}|} \sum_{u \in \Gamma^{+,-}} X_a(., u),$$

where $|\Gamma^{+,-}|$ indicates the number of connections comprising the connected component. We defined the matrix $G_a = [g_a^+ | g_a^-]$. Therefore, $G_a \in \mathbb{R}^{|y_a| \times 2}$ contains the average weight of connections identified as positively and negatively associated with the behavioral dimension y for subjects in the train set $\{X_a, y_a\}$. Using a bivariate linear regression model, we computed the coefficients β such that

$$\min_{\beta \in \mathbb{R}^2} \left\{ \frac{1}{n} \|y_a - G_a \beta\|_2^2 \right\}.$$

Analogously, we computed the average weight of connected components in the test set

$$g_e^{+,-} = \frac{1}{|\Gamma^{+,-}|} \sum_{u \in \Gamma^{+,-}} X_e(., u)$$

and $G_e = [g_e^+ | g_e^-]$. Finally, behavioral predictions were computed as $\hat{y}_e = G_e \beta$ and out-of-sample prediction accuracy was evaluated as the Pearson correlation coefficient between $\hat{y}_e$ and y_e . This procedure was repeated for 100 pairs of train and test sets (10 repetitions of 10-fold splits). In cases where no significant component was identified by the NBS ($|\Gamma^{+,-}| = 0$), model performance was set to 0.

Functional connectivity prediction framework

FC prediction utility was determined via Spearman correlation between empirical FC and analytically derived communication matrices. Therefore, none of the models and measures used to infer FC required training, statistical estimation of weights or parameter tuning (an advantage over other classes of high-order models). Hence, we oftentimes adopted the term FC “prediction” even though predictive utility was not assessed out-of-sample [12].

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SUPPLEMENTARY INFORMATION

Note 1: Null models of behavioral predictions

We sought to compare the behavioral predictions reported in Fig. 3 (Lasso regression, $N = 360$ thresholded connectomes) to predictions obtained for communication models computed on top of randomized structural connectomes. Structural connectomes were rewired using the Maslov Sneppen routine [97], which randomizes network topology while preserving connection density and degree distribution. Null estimates of behavioral prediction accuracy were computed as follows. The structural connectome of each subject was independently rewired resulting on one null dataset containing 889 randomized SC matrices. We then followed the same procedure used to predict behavior from empirical SC (Fig. 1). Null communication matrices were computed from randomized connectomes for all 15 network communication models, amounting to a total of 16 null datasets (FC was not considered in this analysis). Using lasso regression, the null datasets were used to derive out-of-sample predictions of the behavioral dimensions for 10 repetitions of 10-fold cross validation. This resulted in 100 null prediction accuracy estimates for each of the 16 predictors. Lastly, to account for within subject variations in the rewiring routine, the entire null behavioral prediction process was repeated 5 times (i.e., for 5 different initial sets of randomized SC matrices.) Final null prediction accuracies were averaged across the 5 repetitions. As with empirical results, we considered the average null prediction accuracy obtained for cognition and tobacco use components.

Figure S4a shows the empirical prediction accuracy distributions paired with their null counterparts. All communication models showed significantly greater average prediction accuracy when computed on empirical connectomes rather than randomized ones (Fig. S4b). The sole exception was the binary diffusion model, which was the worst-ranking model when computed on empirical connectomes. In fact, we observed that models with higher empirical predictive utility tended to outperform their null counterparts by larger margins (Spearman rank correlation $r_{(15)} = 0.89$, $p = 0$ between empirical accuracy and the t-statistics of pairwise comparisons of models to their null counterparts). In addition, when comparing accuracies across all possible pairs of empirical and null predictors, we found that most empirical models significantly outperformed most null models. This is evidenced by the predominantly warm- and cool-colored off-diagonal blocks in the effect size matrix shown in Figure S4c.

Together, these findings provide further evidence that network communication models are capable of predicting interindividual variation in human behavior, and that observed differences in empirical accuracies reflect meaningful distinctions in the predictive utility of different models. Disruptions to SC topology, even when preserving

degree distribution, led to significant reductions in the predictive utility of communication models. This suggests that the relationship between network communication models and behavior is contingent on high-order organizational features of the human structural connectome.

Note 2: Impact of cross validation repetitions on behavioral predictive utility comparisons

The behavioral predictive utility analyses performed in this paper were based on distributions comprising 100 estimates of prediction accuracy, computed by performing 10 repetitions of 10-fold cross validation. In this section, we evaluate whether our results are stable when considering single repetitions of the 10-fold cross validation. In other words, we aimed to compare communication models based on distributions comprising 10 estimates of prediction accuracy, one from each cross validation fold. Our goal was to determine whether statistical differences between predictors (or the lack thereof) reported when considering 100 accuracy estimates would be observed when only taking into account the accuracies from each individual cross validation repetition.

To this end, we separately recomputed the results shown in Fig. 3 for each of the 10 repetitions of the cross validation process. We derived 10 rankings of predictors (as in Fig. 3a) and 10 17×17 effect size matrices of pairwise statistical comparisons (as in Fig. 3b). We also computed a ranking of predictors and effect size matrix for the accuracy distributions obtained when averaging results across the cross validation repetitions. This resulted in a set of 11 predictor rankings and effect size matrices.

To facilitate comparisons, effect size matrices were binarized. Entries equal to 1 and 0 denoted, respectively, evidence for significant and non-significant differences between accuracy distributions (Bonferroni-corrected threshold for multiple comparisons $\alpha = 0.05/(17 \times 16/2) = 3.67 \times 10^{-4}$). This categorization of pairwise statistical test outcomes allowed us to compare our original results to the ones from individual cross validation repetitions by means of Fisher’s exact tests. Rejection of the null hypothesis provides evidence of nonrandom associations between significance outcomes computed on 100 accuracy estimates to those based on 10 accuracy estimates.

Results are shown in Table S1. We found that the average prediction accuracies shown in Fig. 3a were strongly correlated to those obtained for individual repetitions of the cross validation process. In addition, for each individual repetition, the outcome of pairwise statistical comparisons between predictors was significantly associated to the original outcomes shown in Fig. 3b.

Note 3: Behavioral predictive utility for the cognition and tobacco use dimensions

We have characterized the predictive utility of connectivity measures and communication models by considering a pooled prediction accuracy between the cognition and tobacco use dimensions. As we have seen, these behavioral dimensions led to the most accurate and consistent predictions in our sample. Considering the average prediction accuracy across the two traits facilitated the comparison of communication models by providing us with a single score on which to evaluate prediction accuracy. However, this approach may potentially obscure nuanced phenotype-specific relationships between brain and behavior. Indeed, we observed no correlation between the prediction accuracies obtained for cognition and tobacco use (Spearman rank correlation $p = 0.49, 0.69$ for lasso and NBS, respectively). Therefore, in this section, we sought to separately examine behavioral predictions for the cognition and tobacco use dimensions.

We observed that the outstanding performance of FC was mostly due to the cognition dimension (Fig. S5 and S8; this can also be observed in Fig. 2c,d). This is in line with several findings on the relationship between cognitive processes and the architecture of functional networks [55]. Interestingly, while FC still yielded top-ranking predictions of tobacco use, several communication models showed comparable predictive utility in this dimension (Fig. S6 and S9; again evident in Fig. 2c,d). For instance, navigation was the best predictor of tobacco use, with binary and distance navigation occupying the first positions under lasso and NBS, respectively. Although none of the communication models statistically outperform FC, this points towards a tighter margin of difference between the utility of structural and functional measures in predicting behavioral phenotypes not directly related to cognition.

Another interesting observation was that weighted search information was the best communication model in predicting cognition, but showed near bottom-ranking predictive utility of tobacco use, which resulted in a moderate performance when combining predictions from both behavioral dimensions. Along similar lines, we observed that rankings of connection weight definitions were sensitive different behavioral dimensions and prediction methods, painting an unclear picture of what weighting schemes best contribute to predict human behavior from structural connectomes.

Therefore, collectively, our results did not point towards a single communication model as the best predictor of human behavior. Despite the overall good performance of communicability and navigation, our observations indicate that different communication models may be better suited to predict different behavioral dimensions, possibly suggesting the presence of behavior-specific signaling mechanisms in the human brain. Importantly, across the multiple analyses performed, our results consistently

suggested that network communication models, in particular communicability and navigation, improve the behavioral predictive utility of the human connectome.

Note 4: Additional analyses of structure-function coupling

We further examined structure-function relationships by stratifying FC predictions across anatomically connected and unconnected regions pairs (Fig. S11a). In accordance to previous work [12, 18], associations to FC were stronger for connected regions. Despite these changes in association strength, rankings of communication models in terms FC predictions were consistent across the scenarios explored (Spearman rank correlation $r = 0.90, 0.68, 0.85$ and $p = 8 \times 10^{-7}, 3 \times 10^{-3}, 0$ between connected and all, all and unconnected, and connected and unconnected region pairs, respectively). Interestingly, certain communication models outperformed SC

for connected regions, suggesting that indirected polysynaptic signaling maybe relevant for communication even in the presence of direct anatomical links.

Estimates of structure-function coupling depend on accurate reconstruction of structural connectomes. However, white matter tractography is prone to a number of known biases, of which the underestimation of inter-hemispheric connections is an important concern [77]. To attenuate this issue, past studies have focused on intra-hemispheric characterization of structure-function coupling [49, 68]. Focusing on the right hemisphere, we found that, for all communication models, FC associations were stronger compared to whole-brain estimates (Fig. S11b). Importantly, the functional predictive utility ranking of communication models remained consistent (Spearman rank correlation $r = 0.93$ and $p = 0$ between whole-brain and right hemisphere rankings). This suggests that our analyses may provide a meaningful ranking of signaling strategies despite shortcomings in connectome mapping techniques.

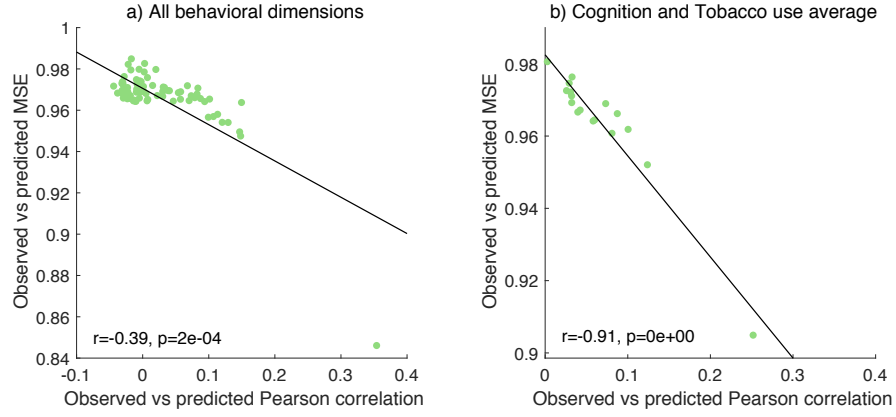


FIG. S1. Comparison between behavioral prediction accuracies computed using Pearson correlation and mean square error evaluated using Spearman rank correlation (Lasso regression, $N = 360$ thresholded connectomes). The least squares line is shown in black.

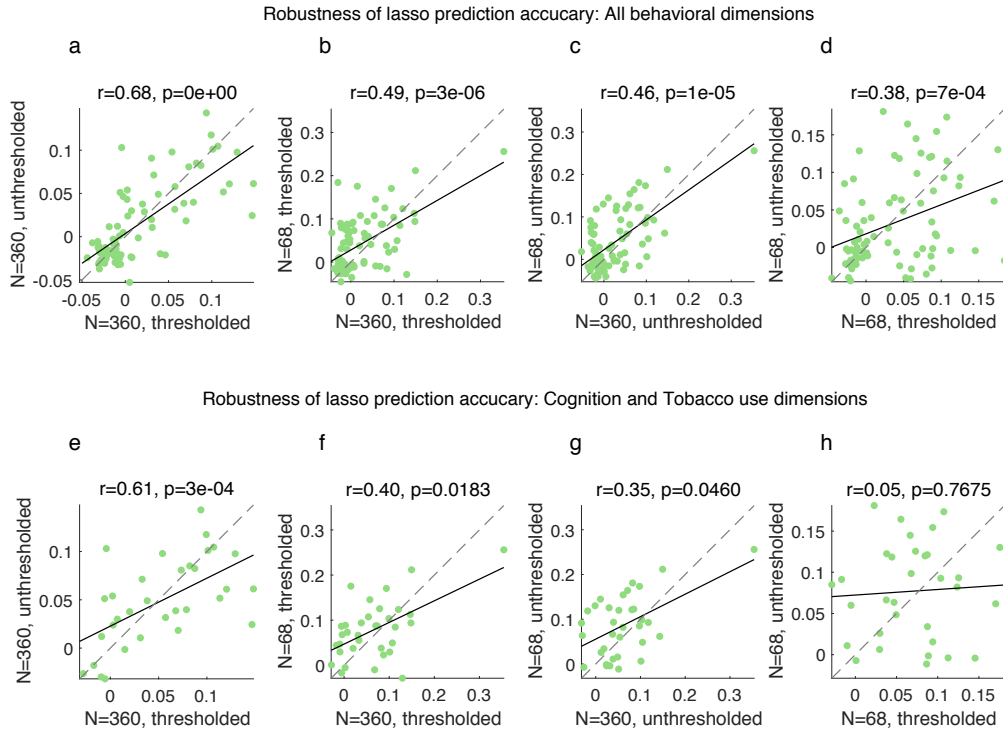


FIG. S2. Comparison between behavioral prediction accuracies across multiple connectome mapping pipelines (Lasso regression). Scatter plots show the least squares and $x = y$ lines are shown in solid black and gray dashed traces, as well as the Spearman rank correlation coefficient and p -value. Comparisons between results obtained for thresholded and unthresholded structural connectomes (panels a, d, e, h) do not include prediction accuracies obtained from FC, since functional matrices did not undergo connection thresholding. Comparisons between results obtained for structural connectomes comprising 68 and 360 regions (panels b, c, f, g) include prediction accuracies obtained from FC, since functional matrices are influenced by parcellation choice. Removing data points pertaining to FC prediction accuracies from panels b, c, f, g led to Spearman rank correlation $r = 0.49, 0.46, 0.29, 0.21$ and $p = 6 \times 10^{-6}, 2 \times 10^{-5}, 0.11, 0.24$, respectively.

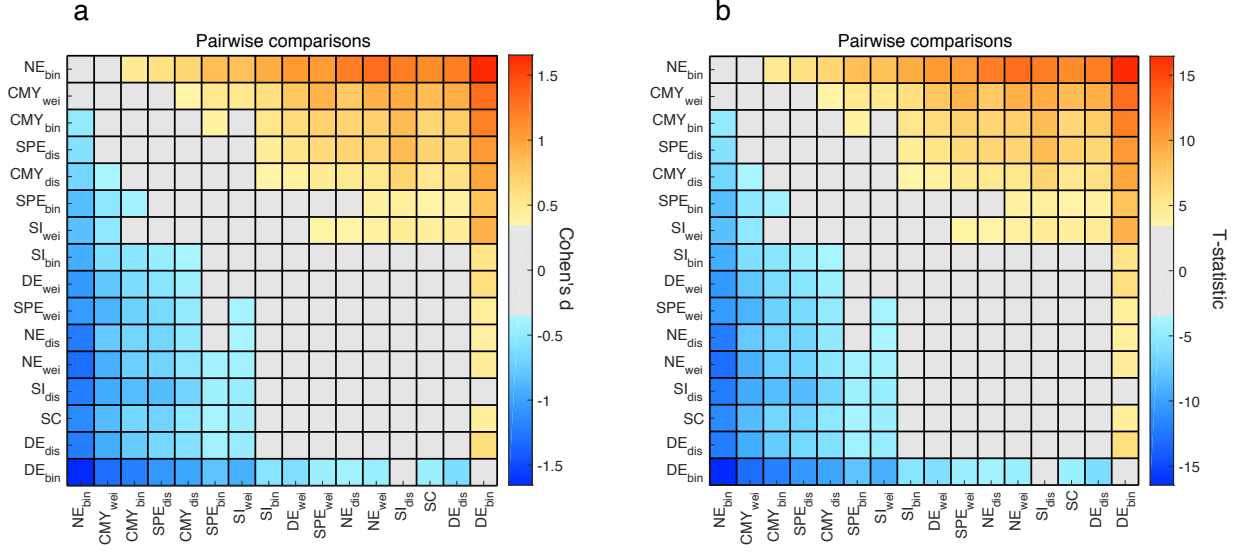


FIG. S3. Effect size matrices showing (a) Cohen's d and (b) t -statistics from pairwise statistical comparisons between network communication models and SC (same as Fig. 3b but excluding comparisons to FC for better contrast in effect size values; Lasso regression, $N = 360$ thresholded connectomes, average cognition and tobacco use prediction accuracies).

10-fold repetition	Comparison to results obtained for 10 repetitions of 10-fold cross validation	
	Average prediction accuracy correlation (Spearman rank coefficient $r_{(15)}$)	Outcomes from pairwise comparisons between predictors (Fisher's exact test p -value)
#1	0.91	0.0002
#2	0.96	5×10^{-7}
#3	0.96	2×10^{-5}
#4	0.97	0.0023
#5	0.92	2×10^{-5}
#6	0.98	0.0021
#7	0.91	0.0006
#8	0.92	0.0002
#9	0.98	0.0002
#10	0.91	0.0003
Average across repetitions	0.98	5×10^{-19}

TABLE S1. Comparison of results for individual repetitions of 10-fold cross validation (Lasso regression, $N = 360$ thresholded connectomes, average cognition and tobacco use prediction accuracies). For each cross validation repetition, the average prediction accuracy of 17 predictors as well as the outcomes of pairwise statistical tests between predictors are compared to those obtained when pooling prediction accuracies across the 10 repetitions of the cross validation process.

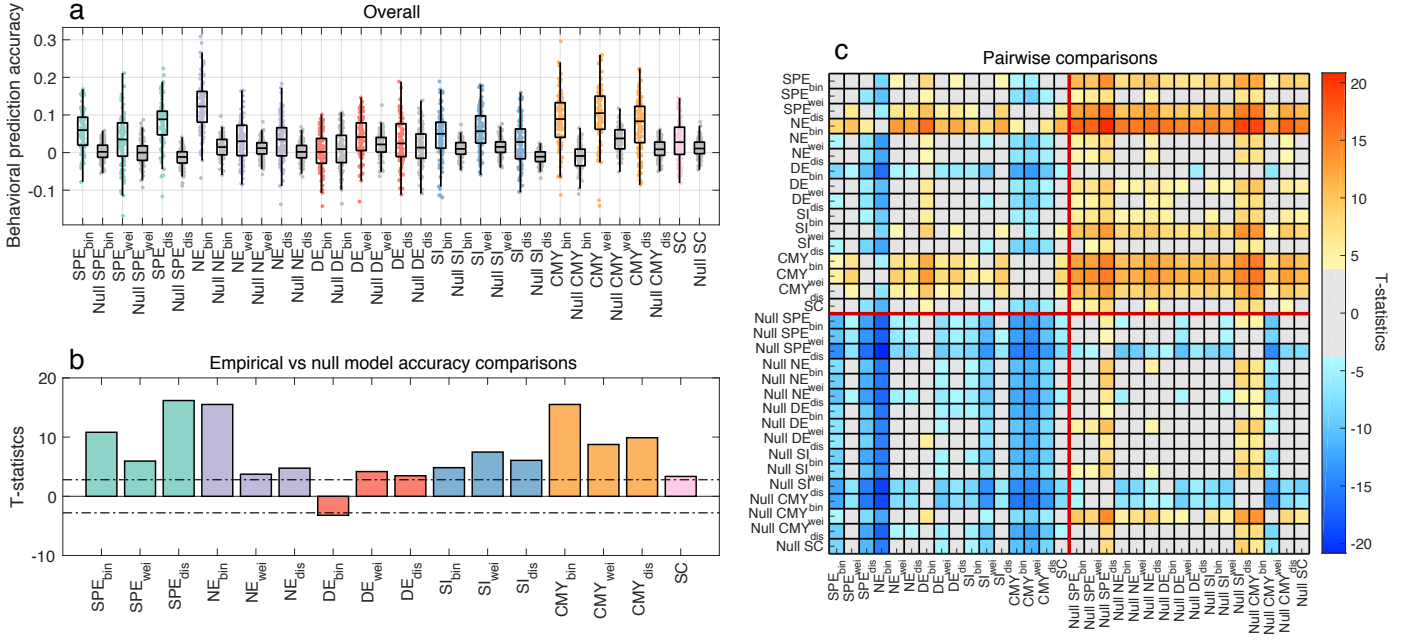


FIG. S4. Comparison of the behavioral predictive utility of network communication models computed on empirical and randomized connectomes (NBS, $N = 360$ thresholded connectomes, average cognition and tobacco use prediction accuracies). (a) Boxplots indicate the prediction accuracy distributions for 10 repetitions of 10-fold cross-validation. Boxplots are ordered to contrast empirical accuracy distributions (colored) with their null counterparts (grey). (b) T-statistics obtained from pairwise repeated-measure t-tests between empirical prediction accuracies and their null counterparts. Positive statistics indicate that models computed on empirical connectomes outperformed those computed on randomized connectomes. The dotted line denotes the Bonferroni-corrected significance threshold for 16 multiple comparisons ($\alpha = 0.0031$). (c) Effect size matrix of pairwise repeated-measures t-tests between distributions in panel (a), with colored cells indicating significant differences in mean prediction accuracies (Bonferroni-corrected for $32 \times 31/2$ multiple comparisons with significance threshold $\alpha = 1 \times 10^{-4}$).

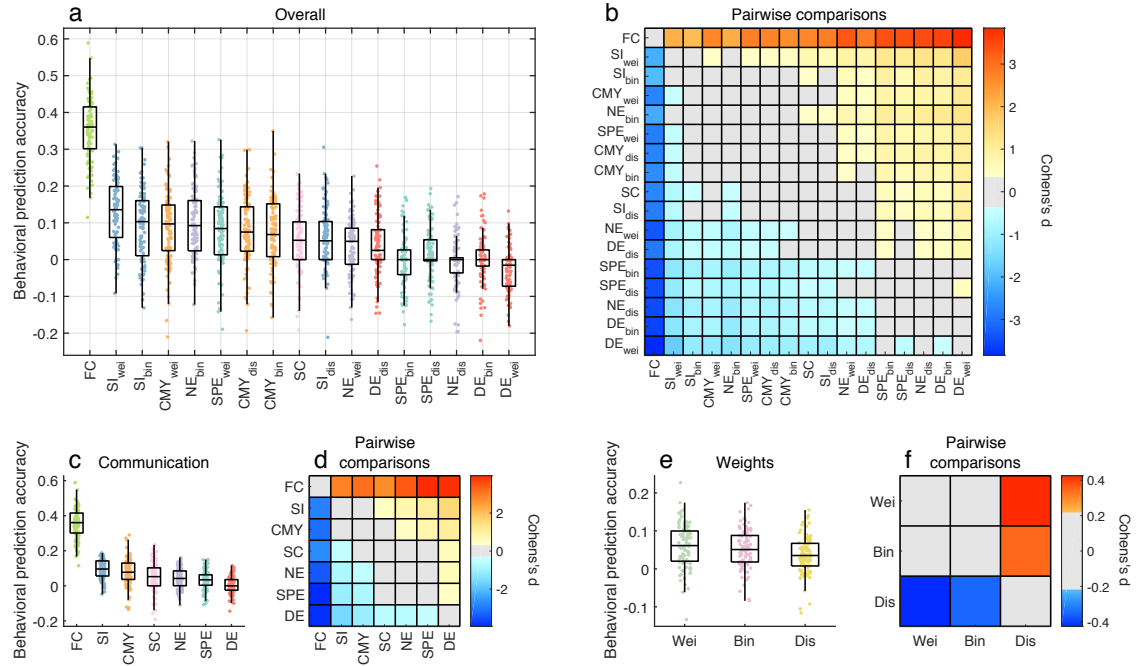


FIG. S5. Comparison of the behavioral predictive utility of connectome communication models (Lasso regression, $N = 360$ thresholded connectomes, cognition prediction accuracy).

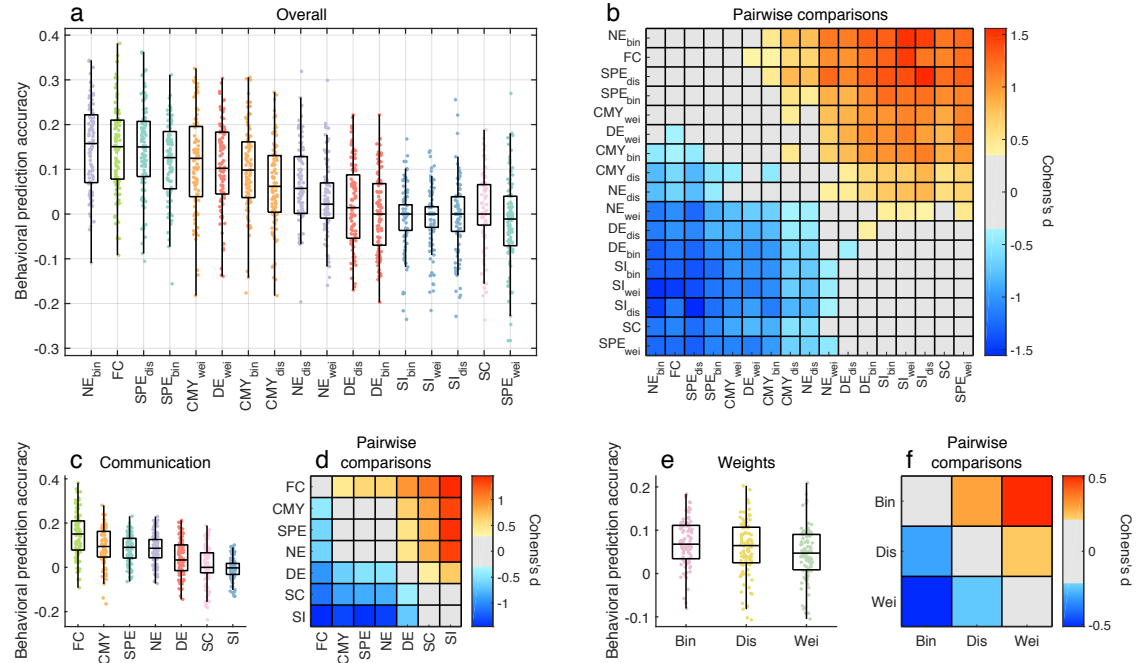


FIG. S6. Comparison of the behavioral predictive utility of connectome communication models (Lasso regression, $N = 360$ thresholded connectomes, tobacco use prediction accuracy).

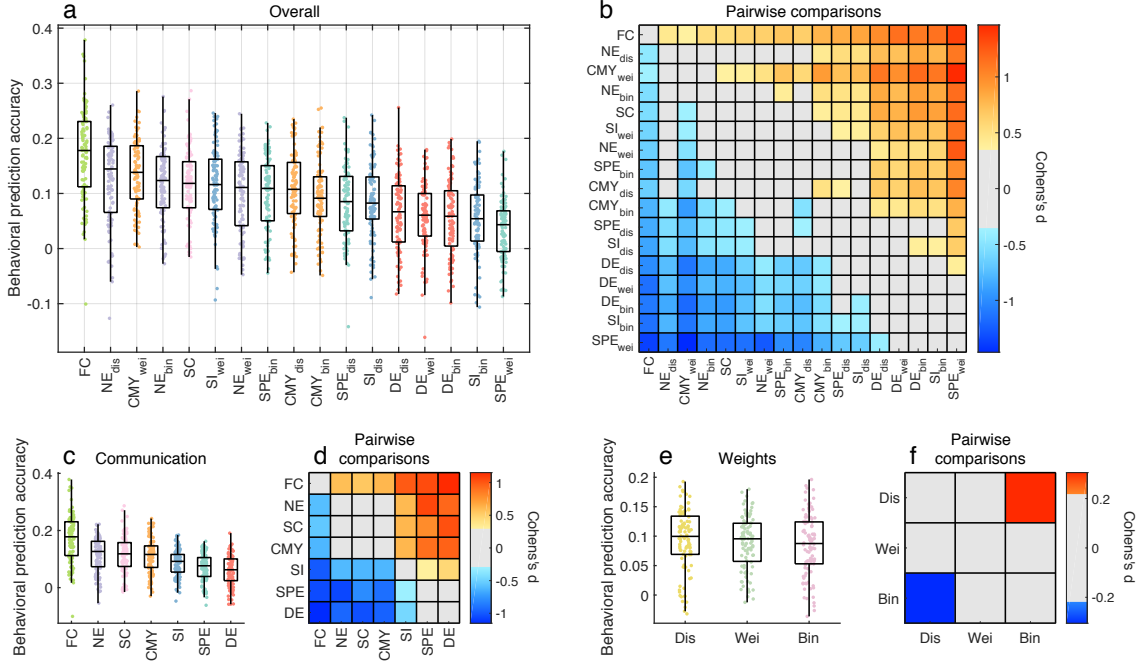


FIG. S7. Comparison of the behavioral predictive utility of connectome communication models (NBS, $N = 360$ thresholded connectomes, average cognition and tobacco use prediction accuracies). It is worth noting that the NBS feature selection process is better suited to sparse graphs [31], which could confer an advantage to sparse SC matrices over fully-connected communication and FC matrices.

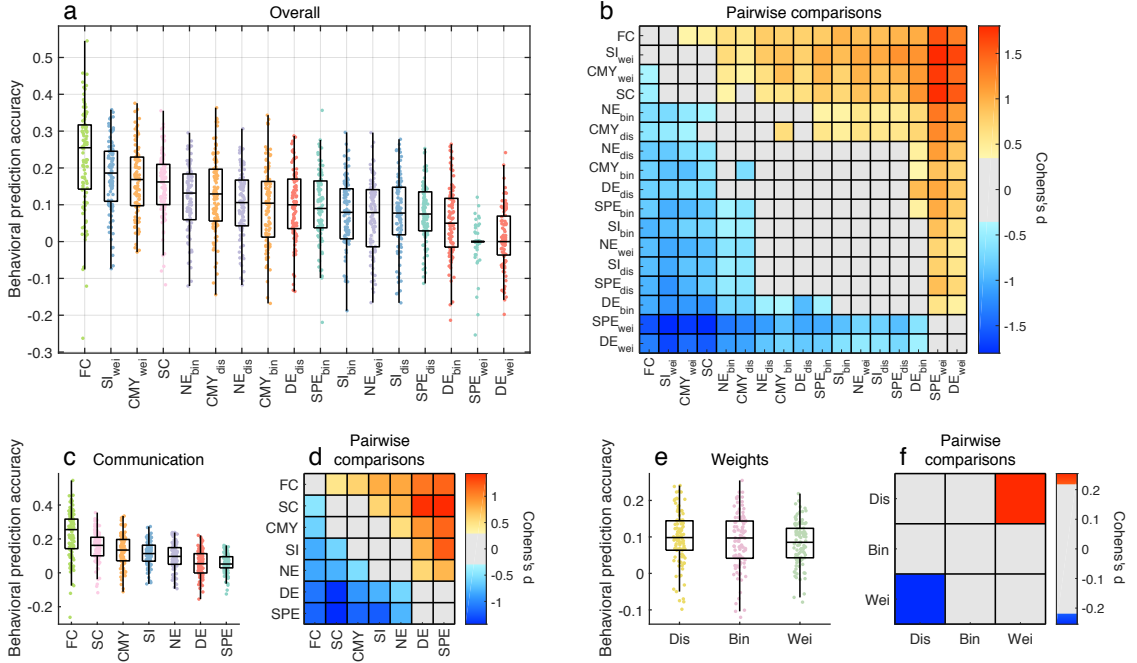


FIG. S8. Comparison of the behavioral predictive utility of connectome communication models (NBS, $N = 360$ thresholded connectomes, cognition prediction accuracy).

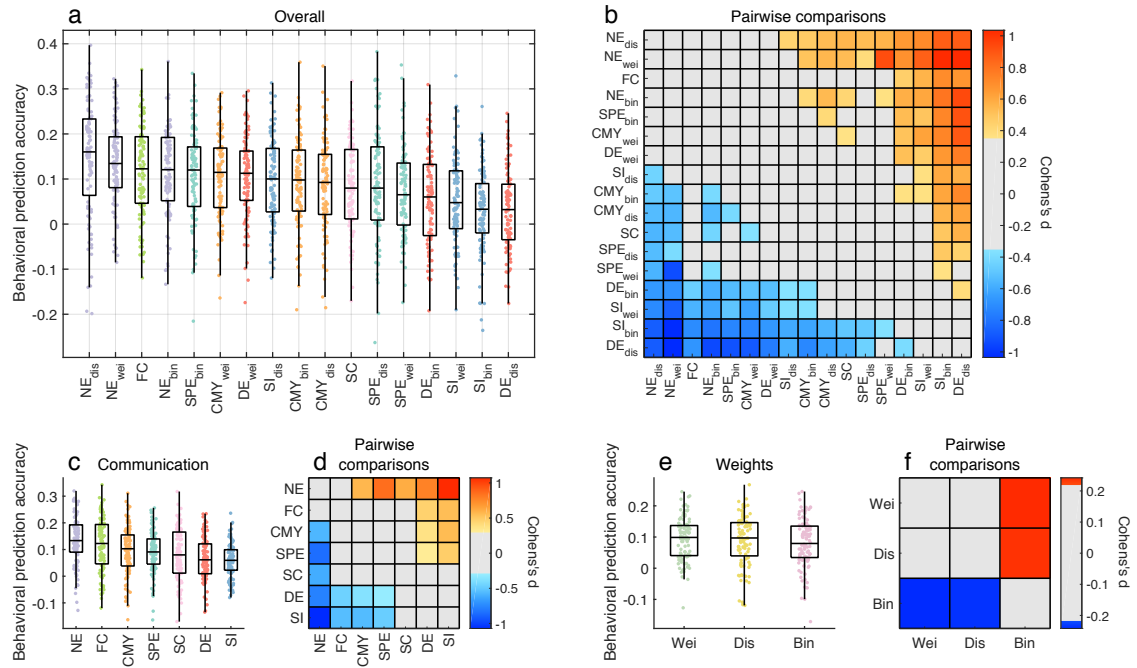


FIG. S9. Comparison of the behavioral predictive utility of connectome communication models (NBS, $N = 360$ thresholded connectomes, tobacco use prediction accuracy).

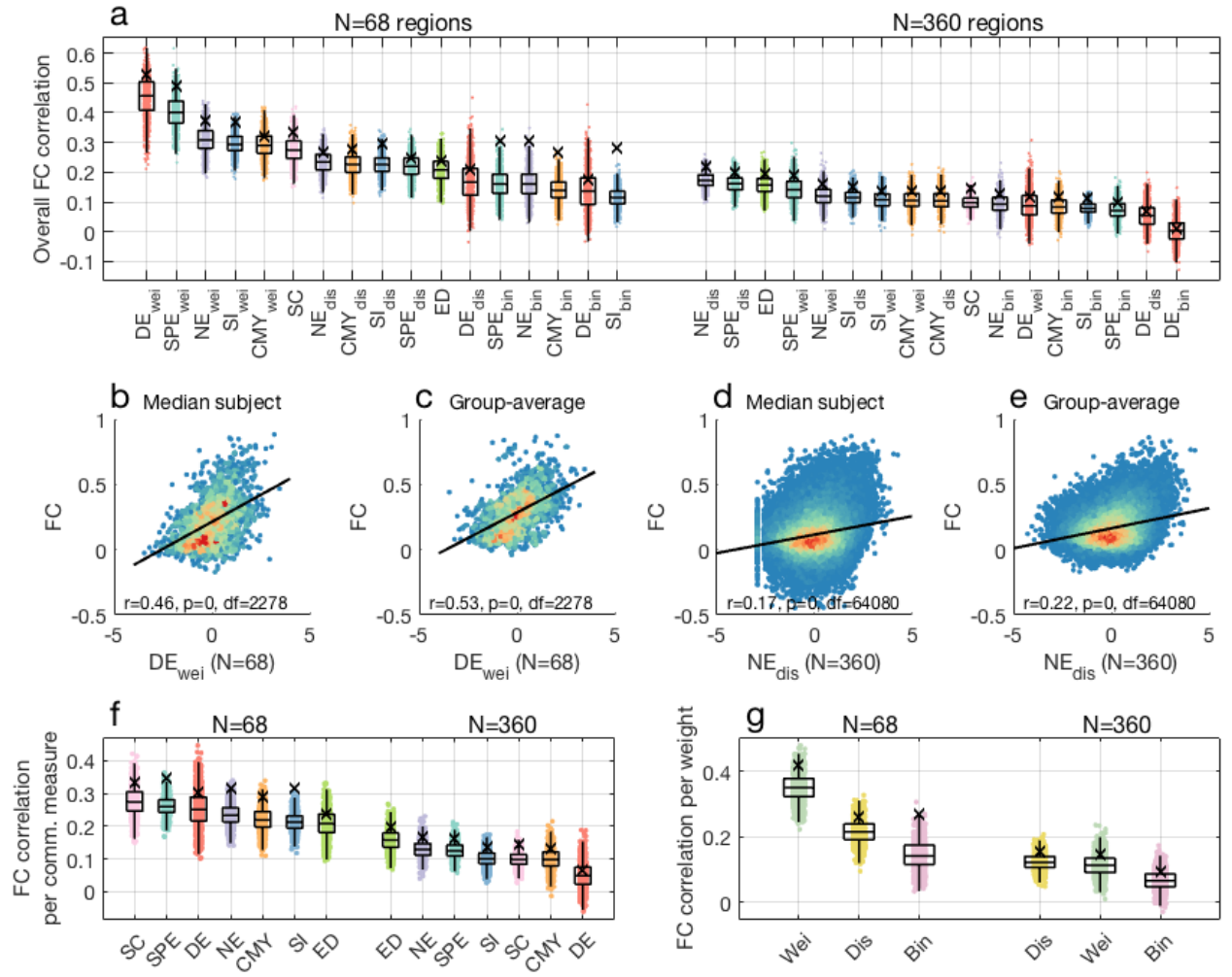


FIG. S10. Structure-function coupling across connectome communication models ($N = 68, 360$ unthresholded connectomes).

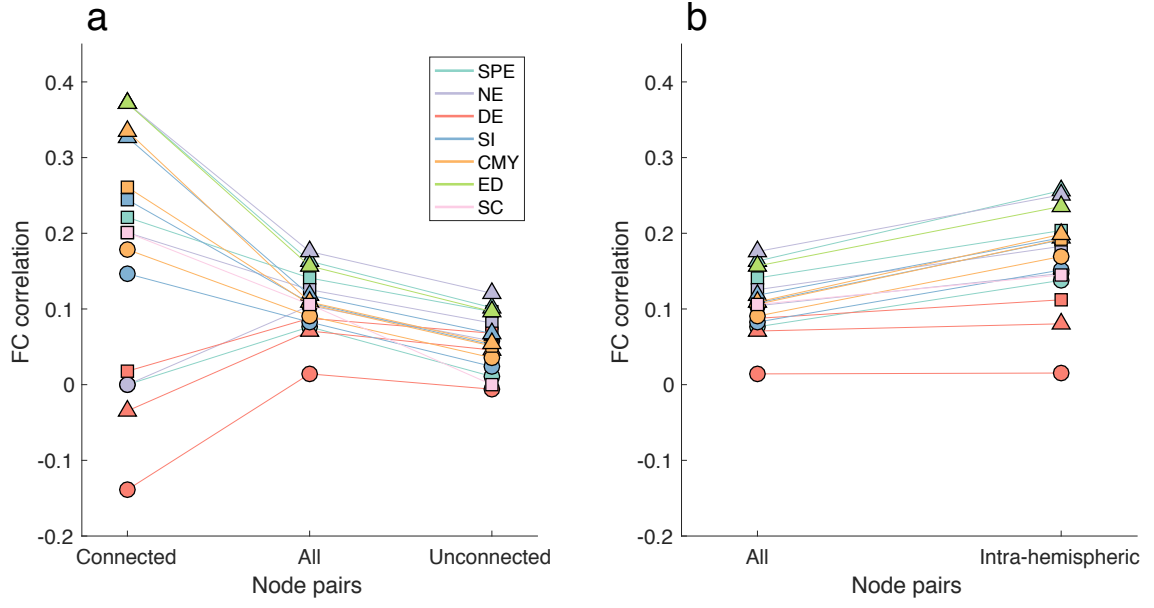


FIG. S11. Stratification of structure-function coupling across connectome communication models ($N = 360$ thresholded connectomes). Markers indicate median (across subjects) Spearman correlation between FC and communication models. Squared, circular and triangular markers denote models computed on weighted, binary and distance connectomes, respectively. Marker colors denote different FC predictors. Teal: shortest paths, violet: navigation, red: diffusion, blue: search information, orange: communicability, pink: SC, and green: Euclidean distance. **(a)** Structure-function coupling anatomically connected (left), all (center) and anatomically unconnected (right) region pairs. **(b)** Structure-function coupling for whole-brain (left) and right-hemisphere (right) connectomes.

Chapter 6

General discussion

6.1 Thesis overview and summary of results

In this thesis, we explored multiple facets of large-scale neural communication models with the goal of elucidating how the anatomical substrate of the human connectome supports functional interactions between gray matter regions. Firstly, in Chapter 3 we introduced the concept of network navigation to the field of neuroscience. We observed that mammalian connectomes are conducive to near-optimal communication under navigation. Importantly, we demonstrated that the high navigability of brain networks is contingent on both their topology and geometry, with disruptions to either of these traits resulting in marked decreases in navigation efficiency. In fact, we provided evidence that the human connectome strikes a delicate balance between random and regular topologies that facilitates navigation performance. In addition, we proposed the measures of node and edge navigation centrality. Based on these measures, we found navigation paths promote a more egalitarian distribution of signalling traffic amongst regions and connections than shortest paths, potentially improving the resilience and alleviating congestions of neural signalling processes. Finally, we found that navigation paths explained significant variance in interregional FC, supporting the notion that navigation captures, to a certain extent, patterns of functional interactions between gray matter regions.

Secondly, in Chapter 4, we demonstrated that the communication asymmetry inherent to decentralized network communication models provides meaningful insight on the directional character of neural signalling. We proposed the concept of send-receive asymmetry through the development of a statistical framework to measure significant differ-

ences between incoming and outgoing communication processes, both at regional and interregional levels. We applied this methodology to undirected structural human connectomes derived from diffusion MRI data. We found that several cortical regions are biased towards sending/receiving information and that pairwise interactions between cortical subsystems are also often biased towards particular directions of communication. Crucially, we validated these findings using resting-state functional MRI data. At the regional level, send-receive asymmetry explained significant variance in a functional cortical gradient differentiating unimodal (typically senders) and multimodal (typically receivers) areas. At the pairwise cortical systems level, communication asymmetry was significantly associated to the directionality of effective connectivity derived from spectral dynamic causal modelling. These results suggest that neural signalling directionality is partially shaped by the undirected topology of brain networks. To further investigate this notion, we analysed fly, mouse and macaque connectomes, for which fibre directionality is invasively resolved. Using these connectomes, we showed that decentralized communication promotes meaningful send-receive asymmetry above and beyond the influence of directed connections. Collectively, these results indicated that neural signalling directionality can be inferred from the undirected architecture of nervous systems.

Lastly, in Chapter 5 we performed a systematic evaluation of candidate neural communication models based on their associations with behavioural traits and resting-state functional connectivity in a large sample of individuals. To this end, we transformed structural connectomes into communication matrices capturing a total of 15 conceptualizations of network communication that covered a wide range of signaling strategies and connection weight definitions. Communication matrices were (i) used to perform predictions of five data-driven behavioral dimensions and (ii) correlated to resting-state functional connectivity. Based on the results obtained from these analyses, we derived behavioral, functional and combined predictive utility rankings of communication models. Rankings were computed for a number of methodological settings that included multiple connectome mapping pipelines and statistical learning techniques. While the utility of communication models varied according to these factors, certain key findings were consistently observed across all scenarios explored. While functional connectivity was

the most accurate predictor of behaviour, communication models, in particular communicability and navigation, improved the behavioural predictive performance of structural connectomes. In addition, communication models strengthened structure-function coupling of the connectome, with the navigation and shortest paths leading to the strongest correlations to functional connectivity. Combining behavioral and functional results into a single ranking consistently positioned navigation as the top model, suggesting that it may more faithfully recapitulate underlying neural signaling patterns. Together, these findings indicate that network communication models can augment the predictive utility of the human structural connectome; and highlight navigation as a promising model to understand the mechanisms of large-scale neural signaling.

6.2 General discussion

6.2.1 Are shortest paths relevant to network neuroscience?

Anatomical shortest paths are central to network neuroscience. They are the cornerstone of several influential discoveries and practices in the field, such as the view of nervous systems as small-world networks (Bassett and Bullmore, 2006; Watts and Strogatz, 1998) and the use of betweenness centrality to identify connectome hubs (Sporns et al., 2007; van den Heuvel and Sporns, 2013). Perhaps most notably, the conceptualization of the brain as an economic network that balances wiring costs and adaptive topological features—such as low characteristic path length or high global efficiency—is a prominent example of how graph-theoretical measures based around shortest paths are pervasive in the field (Bullmore and Sporns, 2012; Kaiser and Hilgetag, 2006). One of the main themes of this thesis is the notion that shortest path routing is not a realistic model for brain network communication, due to its dependence on centralized knowledge of network topology. If this is true, where does that leave the progress achieved by over a decade of connectomics research under the (often tacit) assumption of communication via shortest paths?

To answer this question, it is important to first note that most shortest-path-based measures are defined quantitatively in terms of path lengths or efficiency. That is, mea-

asures such as characteristic path length, global efficiency and small-worldness are characterized by sums of connection lengths traversed along shortest paths, rather than by the qualitative sequences of connections comprised along the shortest paths. Hence, these measures boil down to describing the efficiency with which communication takes place, rather than listing the connections supporting communication. In Chapter 3, we demonstrate that navigation paths are almost as efficient as shortest paths. From a quantitative point of view, navigation routing can be seen as a strategy to realize communication via (approximately) shortest paths in a decentralized fashion, thus providing evidence that shortest-path-based findings remain pertinent. Importantly, as previously discussed, the biological mechanisms supporting our geometry-guided conceptualization of connectome navigation remain unknown. Therefore, we reiterate that rather than a definitive model of brain network communication, navigation constitutes a step towards biologically plausible models that conciliate communication efficiency and the operational constraints inherent to decentralized systems.

A second point related to the relevance of shortest paths concerns a subtle distinction between two possible interpretations of network communication measures. Certain graph measures can be viewed as descriptors of both network structure and communication properties. For instance, the characteristic path length of a network may provide useful information on its topology, even if communication between nodes does not occur via shortest paths. In fact, topological features salient to the small-world architecture have been found to facilitate the navigation of many types of complex networks (Boguna et al., 2009; Travers and Milgram, 1969). This demonstrates that although we have come to describe topological properties in terms of shortest paths, these traits are not necessarily design to support optimal communication. Similarly, shortest-path-based measures that have been reported as disease biomarkers (Fornito et al., 2013; van den Heuvel et al., 2009) may still be relevant in light of decentralized communication schemes. However, we conjecture that they primarily index organization and structural changes, rather than capturing abnormalities in neural information processing and communication. Importantly, the same dual interpretation problem is applicable not only to shortest paths, but to other network communication measures. This issue highlights the importance of de-

veloping validation techniques to assess whether network communication measures are indeed related to underlying signalling phenomena.

6.2.2 Connectome organization and neural communication

Connectome organization is remarkably consistent across multiple scales (Betz et al., 2017) and species (van den Heuvel et al., 2016). Hallmark features of brain network topology include a heterogeneous degree distribution with a core of densely interconnected high-degree regions (Sporns et al., 2007; van den Heuvel and Sporns, 2011), simultaneous low characteristic path length and high clustering (Achard et al., 2006; Bassett and Bullmore, 2006; Watts and Strogatz, 1998), and a hierarchical modular structure (Betz et al., 2013; Sporns and Betz et al., 2016). These features are metabolically expensive. The connectome's low characteristic path length is afforded by the presence of long-range white matter connections that require resources to create and maintain (Kaiser and Hilgetag, 2006), while hubs are characterized by elevated energy consumption and disproportionately high wiring costs (Collin et al., 2014; van den Heuvel and Sporns, 2013). Given the metabolic burden entailed by these features, their universality amongst nervous systems must afford equally universal adaptive advantages (Bullmore and Sporns, 2012). Signalling is a fundamental process crucial to the functioning of all nervous systems (Laughlin and Sejnowski, 2003). Therefore, the need for efficient communication between neural elements is conjectured to be one of the key evolutionary drives leading to the emergence of hallmark properties of connectome organization (Avena-Koenigsberger et al., 2017; Mišić et al., 2015). Consequentially, we should observe a close relationship between brain network communication models and connectome organization. In this thesis, we performed several analyses that support this notion.

In Chapter 3, we demonstrate that disruptions to connectome topology or geometry lead to marked reductions in navigability. Navigation is the first communication model to take into account the brain's spatial embedding as an important facet of neural signalling. This proposes the existence of a three-way relationship between connectome topology, geometry and communication. Beyond complete wiring randomization, we also provide evidence that connectome topology strikes a fine balance between random

and regular architectures that is conducive to efficient navigation. Further to this, compared to shortest paths routing, navigation enlisted a much larger number of regions and connections as mediators of signalling traffic, indicating that decentralized propagation schemes may promote a more distributed use of the brain's expensive resources.

Along similar lines, in Chapter 4 we found that the relationship between the send-receive asymmetry of decentralized network communication measures and the directionality of effective connectivity is contingent on the topology and geometry (in the case of navigation) of empirical connectomes. Navigation efficiency, diffusion efficiency and search information computed on null networks, including the stringent random ensemble of cost-preserving random networks, resulted in significantly weaker associations to signalling directionality. Importantly, this is the first evidence that connectomes mapped from diffusion MRI can be used to infer information on the directions of neural signalling. Together with our analyses of directed non-human connectomes, this demonstrates that the undirected topology (as well as possibly geometry) of brain network contributes to shaping neural information flow directionality. While the exact topological features involved in this process remain unclear, these findings provide a new perspective of how nervous system architecture influences functional interactions between brain regions. Collectively, these results suggest that the utility of decentralized network communication measures is tightly coupled to hallmark principles of connectome organization.

6.2.3 Function and neural communication

We provide several lines of evidence for the utility of brain network communication models in inferring patterns of functional interactions between neural elements. Traditionally, regional functional profiles have been investigated using invasive tract-tracing techniques (DeYoe and Van Essen, 1988; Markov et al., 2013, 2014; Maunsell and van Essen, 1983). These studies aimed to elucidate the information processing roles of gray matter regions by mapping their incoming and outgoing axonal projections. These efforts culminated in the conceptualization of a hierarchy of distributed cortical computation (Felleman and Van Essen, 1991; Van Essen et al., 1992). With the advance of functional imaging and computational modelling methods, this notion was consolidated by numer-

ous studies reporting on hierarchical gradients of functional organization in the human cortex (Burt et al., 2018; Deco and Kringelbach, 2017; Demirtaş et al., 2019; Huntenburg et al., 2018; Margulies et al., 2016). Chapter 4 demonstrates that diffusion MRI data, in combination with decentralized network communication measures, can also be used to infer similar properties of cortical organization. This finding contributes to narrowing the gap between models of neural functional specialization afforded by different techniques and data modalities.

Moving from regional functional profiles to pairwise functional interactions, Chapter 5 coalesced evidence from multiple studies to show that network communication measures are capable of explaining significant variance in resting-state functional connectivity. Modelling how function emerges from structure is an active topic of research, with a large proportion of its efforts focused on biophysical models of neural activity (Breakspear, 2017; Deco et al., 2008; Honey et al., 2009; Wang et al., 2019a). These computational approaches incorporate physiological information on the functioning of single neurons in order to model the oscillatory behaviour of networked neural populations. While biophysical methods have been successful in describing static and dynamic patterns of functional connectivity (Cabral et al., 2012; Deco et al., 2017; Messé et al., 2015), they rely on parameter tuning and can be computationally intractable for subject-level analyses of high resolution connectomes. Crucially, our findings suggest that the evaluation of functional connectivity predictions should carefully consider individual variability and the impact of parcellation resolution. Despite the lack of consensus on which signalling strategies should be adopted to model functional connectivity, our results show that certain communication measures can provide parameter-free and computationally inexpensive models of functional connectomes with accuracy comparable to those of highly parametrized methods. Recent efforts to combine communication measures and biophysical models are a promising avenue to capitalize on the strengths and overcome the weaknesses of both approaches (Finger et al., 2019; Gilson et al., 2019).

Lastly, in Chapter 4 we demonstrate that our framework of send-receive asymmetry can exploit features of decentralized connectome communication to infer the directionality of effective connections. Importantly, effective connectivity goes beyond the sta-

tistical associations that characterize functional connectivity, being conjectured to reflect causal interactions between regions (Friston, 2011; Friston et al., 2003). Our analyses suggest that structural connectome organization may favour certain directions of functional modulation at rest, potentially facilitating intrinsic communication process that take place in the absence of external stimuli (Razi et al., 2017). Given the importance of resting-state networks as predictors of behaviour and biomarkers of disease (Liégeois et al., 2019; van den Heuvel and Hulshoff Pol, 2010; Woodward et al., 2011), a better understanding of causal structure–function relationships at rest may lead to new insights into intrinsic patterns of neural information processing.

6.2.4 Human behaviour and neural communication

Recordings of neural activity during specific behavioural contexts have started to elucidate how cognition, perception and learning are dependent on the organization and dynamics of functional brain networks (Bassett and Mattar, 2017; Medaglia et al., 2015; Mišić and Sporns, 2016; Sporns, 2014). In particular, a number of studies employing time-resolved network analyses indicate that the functional connectome alternates between integration and segregation states, with the first thought to support periods of high cognitive demand (Shine et al., 2018, 2016; Sporns and Betzel, 2016; Zalesky et al., 2014). This dynamic reorganization of functional topology must be orchestrated through signalling via the underlying structural connectome, but the role of anatomical connectivity in this process remains unexplored. The analyses in Chapter 5 constitute a first attempt to determine how structurally constrained signalling may support the concerted action between cortical systems necessary for cognition and behaviour (Friston, 2002; McIntosh, 2000). Combining results obtained for several behavioural dimensions, connectome mapping pipelines and statistical learning methods, we found that, on average, navigation most accurately and robustly predicted interindividual variance in human behaviour. Importantly, however, when considering behavioural dimensions separately, we observed that different communication models were better suited to predict different behavioural traits. This suggests the possibility of context-dependent and behavior-specific signaling mechanisms in the human brain. These findings should foment further re-

search on understanding how network communication models may bring together brain structure, function and human behaviour.

6.3 Limitations and future directions

Several limitations of the studies included in this thesis should be discussed. The validation of network communication measures by means of correlations with interregional resting-state functional connectivity has shortcomings. It is well known that functional interactions between certain gray matter regions are context-dependent, taking place to meet the needs of a particular task or cognitive demand. In the case of a particularly important task, these interactions may be facilitated by highly efficient communication paths in the underlying structural connectome. When considering only resting-state data, the presence of such an efficient communication channel would seem unwarranted, resulting in the weakening of the association between communication and function. This may lead to spurious conclusions on which communication measures most accurately model functional interactions between neural elements. The incorporation of task-based functional MRI is therefore an important step in improving the validation of communication measures (Tipnis et al., 2018).

Another limitation of our analyses is that we considered static descriptions of functional connectivity. A growing number of studies are focused on characterizing the rich information contained in temporally resolved features of BOLD signals, i.e., dynamic functional connectivity (Hutchison et al., 2013). Time-resolved analyses of functional interactions between gray matter regions have revealed non-random fluctuations in the topological properties of functional brain networks (Cocchi et al., 2017b; Zalesky et al., 2014). These fluctuations have been reported to explain significant variance in human behavioural traits (Liégeois et al., 2019; Pedersen et al., 2018). The models explored in this thesis are static characteristics of network communication, and thus provide limited insight into dynamic patterns of signalling. Dynamic models of network communication have been utilized in the context of neuroscience primarily to predict the spread of pathology in neurodegenerative diseases (Fornito et al., 2015; Raj et al., 2012; Zheng et al.,

2019). Future work applying these models to describe time-resolved functional connectivity could provide new insight into dynamic patterns of neural signalling.

As previously emphasized, we hope that our navigation model will pave the way for the conceptualization of connectome communication strategies conciliating signalling efficiency, biological plausibility and metabolic frugality. However, as highlighted in Chapter 5, the creation of new brain network communication models has to be accompanied by the development and refinement of empirical validation methods. We highlight two promising validation avenues. First, the increasing availability of ECoG and sEEG recordings has started to allow cross-subject compilations of whole-brain neural activity unfolding at high spatiotemporal resolution (Betz et al., 2019b; Cardinale et al., 2019). In combination with diffusion-derived connectomes, these datasets could enable the tracking of neural signalling through white matter connections, providing direct empirical evidence on how communication unfolds atop the connectome. Second, techniques such as transcranial magnetic stimulation (TMS) allow non-invasive delivery of localized stimuli to the activity of cortical regions (Chail et al., 2018; Fisher et al., 2002). Neuroimaging data collected before and after the systematic stimulation of multiple cortical sites could provide a map of how focal perturbations impact the activity of distant brain areas (Gollo et al., 2017). Such maps could help validate signal propagation predictions made by network communication measures.

Techniques of brain stimulation can provide an avenue for the validation of connectome communication strategies. In turn, network models of neural information transfer can also inform efforts to non-invasively modulate brain dynamics. A potential example of this mutually beneficial relationship is the clinical use of TMS to treat mental health conditions such as depression and obsessive-compulsive disorder (Cash et al., 2019a; Cocchi and Zalesky, 2018; Cocchi et al., 2018). While accumulating evidence supports the clinical efficacy of TMS, many open questions remain with relation to optimal stimulation sites, rates of treatment response across patients, and the mechanisms responsible for the amelioration of symptoms. Central to these issues is the realization that the impact of TMS on neural dynamics is not localized to stimulation sites, with stimuli spreading through anatomical connections to other brain regions (Fox et al., 2012; Hawco

et al., 2018). While this indicates that understanding the effects of brain stimulation is a complex task, it also provides an opportunity to non-invasively modulate the activity of deep brain structures. Importantly, the functional connectivity of regions inaccessible to direct TMS have been implicated in mental disorders, such as the subgenual cingulate in medication-refractory depression (Cash et al., 2019b; Fox et al., 2012; Weigand et al., 2018). Attempts to indirectly modulate neural activity in these areas would benefit from accurate models of how stimuli are propagated through the structural connectome.

Brain network communication models may also find clinical utility in indexing neural signalling abnormalities following brain lesions or in people suffering from mental disorders (Fornito et al., 2015). For instance, our navigation model has recently been applied to understand changes in communication efficiency in a cohort of stroke patients (Wang et al., 2019b). Results indicate that post-stroke functional connectivity synchronization lags are associated to the efficiency of structural navigation paths. Similarly, diffusion-based communication models have been reported to explain significant variance in structure–function decoupling following traumatic brain injury (Kuceyeski et al., 2019).

The influential dysconnectivity hypothesis proposes that schizophrenia results from abnormal functional integration of brain processes (Friston et al., 2016; Stephan et al., 2009). Naturally, these functional interactions are facilitated by signalling occurring atop the structural connectome. While several studies have attempt to model aberrant neural information processing in schizophrenia using shortest-path-based graph measures (Fornito et al., 2012b; Griffa et al., 2013), the potential for decentralized network communication measures as disease biomarkers remains relatively unexplored. Biologically plausible signalling strategies are expected to provide higher sensitivity and specificity biomarkers of aberrant neural information processing, potentially aiding in the early screening and diagnosis of psychosis and other mental disorders. Additionally, clinical studies could provide further validation of brain network communication models by assessing the utility of candidate measures in tracking disease progression and symptoms.

Finally, despite the wide range of signalling conceptualizations proposed by different communication models, from single-path optimal routing to all-paths diffusive broad-

casting, there are assumptions and limitations common to all graph-based measures of neural communication. First, network communication measures are computed for connectome node pairs, and thus assume that signalling processes have specific sources and targets. Contrary to this view is the notion that neural information transfer consists of ebbs and flows of activity originating in certain parts of the brain, in which signals do not possess predefined destinations. Similarly, pairwise communication matrices and connectome-wide measures of signalling efficiency assume that information transfer between all node pairs is equally important (Fornito et al., 2016). However, it is possible that communication between certain regions is rare and not relevant for brain functioning. The refinement of communication models capable of exploring signalling dynamics may help attenuate these issues (Finger et al., 2019; Gilson et al., 2019).

6.4 General conclusion

This thesis contributes novel insights to the understanding of how brain structure constraints and facilitates communication between gray matter regions. Our work establishes multiple lines of evidence in support of the utility of decentralized network propagation strategies in modelling large-scale neural signalling. We provide cross-species evidence that connectome organization is conducive to efficient decentralized communication via navigation, thus establishing a middle ground alternative to the prevailing dichotomy between optimal and diffusion signalling. The interaction between structural connectome topology and decentralized communication resulted in send-receive asymmetries significantly associated with measures of neural signalling directionality derived from fMRI. This finding challenges the belief that non-invasive connectomes constructed with diffusion MRI cannot be used to study asymmetric patterns of functional dynamics in nervous systems. Finally, we contribute evidence that certain decentralized communication measures and structural connectome mapping pipelines result in more accurate predictions of human behaviour and functional connectivity. These results start to etch new guidelines for researchers interested in applying graph-theoretical measures to model the information processing capacity of structural brain networks. Collectively, this

thesis contributes to bridging the gap between brain structure, communication, function and human behaviour.

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