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Author

Sipes, Benjamin Snow

Publication Date

2026-09-03

Peer reviewed|Thesis/dissertation

Understanding Brain Structure as a Scaffold for Brain Function

by

Benjamin S Sipes

DISSERTATION

Submitted in partial satisfaction of the requirements for degree of

DOCTOR OF PHILOSOPHY

in

Bioengineering

in the

GRADUATE DIVISION

of the

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

AND

UNIVERSITY OF CALIFORNIA, BERKELEY

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Acknowledgments

I am eternally grateful for the freedom Dr. Ashish Raj gave me to indulge my curiosity, pursue unconventional ideas, and ultimately design my own research program that has become this dissertation. Your guidance transformed my thinking from being philosophically abstract to scientifically precise. My doctoral achievements are all thanks to your mentorship. Sincerely, thank you.

Many others also contributed to my academic transformation. Thank you to Dr. Sri Nagarajan for always insisting on the most rigorous and visually persuasive presentation of my results. The thorough, and occasionally dissentious, discourse between Sri, Ashish, and I made us a great scientific team. Thank you to Dr. Jack Gallant for your work on my dissertation committee and for your incisive questions during my QE. Thank you also to the rest of my QE committee, Drs. Janine Lupo, Duygu Tosun, Lorenzo Pasquini, and Michael Silver for your support and the engaging discussions we had and continue to enjoy. Thank you to Drs. Olga Tymofiyeva and Tony Yang for taking me into your lab after my Master's, for encouraging my interests, and for guiding me through my first published articles. Thank you to Drs. Karen Bale, Brenda McCowan, Stefano Kaburu, and David Orzechowicz for being supportive mentors in my earliest academic years.

To my many friends old and new—all my interlocutors in scientific and philosophical discussions—you, too, shaped me. I am forever thankful to have such an intellectually curious and supportive network of people in my life.

Thank you to my parents for your dedication making sure I was the strongest student possible. You are the reason I could attend college with confidence and focus, and all of my success is also yours to share. Thank you to my grandparents, who took me to museums and always told me to become a scientist. Though I'm sorry that I will not be curing cancer like you hoped. I suppose you'll have to settle for my goal of unraveling the mysteries of the brain instead.

Finally, to Wilson—the most important person in my life, and the reason I stay sane across all moments—my deepest love and thanks are for you.

Contributions

Chapter 2 of this dissertation is a reprint of the material as it appears in:

Sipes, B.S., Nagarajan, S.S. & Raj, A. Integrative, segregative, and degenerate harmonics of the structural connectome. *Communications Biology* **7**, 986. (2024).

The article was published under the Creative Commons Attribution 4.0 International License, which permits reuse, distribution, and adaptation with appropriate attribution. The Version of Record is available at <https://doi.org/10.1038/s42003-024-06669-6>.

Chapters 3 & 4 of this dissertation are submitted and/or under review at time of writing, and they are posted as pre-prints on bioRxiv.

Chapter 3:

Sipes, B. S., Arab, F., Nagarajan, S. S., & Raj, A. HONeD-in on Brain Activity: Deconvolving Passive Diffusion on the Structural Network from Functional Brain Signals. *bioRxiv*, 2026-01. (2026).

Chapter 4:

Sipes, B. S., Arab, F., Nagarajan, S. S., & Raj, A. Gene Gradients Reveal Directed Structural Connectivity Across Species. *bioRxiv*, 2026-05. (2026).

The co-authors listed in these three publications/manuscripts directed and supervised the research that forms the basis for this dissertation.

“At each level of complexity entirely new properties appear.”

— P. W. Anderson, *More Is Different* (1972)

Understanding Brain Structure as a Scaffold for Brain Function

Benjamin Snow Sipes

ABSTRACT

Understanding how white matter pathways in the brain, or the structural connectome (SC), shape and constrain functional dynamics is a central problem in neuroscience known as the structure-function problem. Using diffusion MRI and functional MRI from large publicly available datasets, including the Human Connectome Project, I developed a framework for studying the graph Laplacian of the SC and its relationship to brain function. First, I investigated the group-level properties of graph Laplacian harmonics, including which are shared across subjects versus unique to individuals, and their relationships to resting-state brain organization. I found that these harmonics form an integration-to-segregation spectrum, in which the ends of the spectrum are shared across subjects and localize to sensory regions, whereas the center is more individualized and relates to multimodal brain regions. Second, to better understand how observed brain function embeds an underlying notion of SC, I developed a graph deconvolution method that models and removes the effect of passive signal diffusion through the SC. I found that the deconvolved signals exhibit remodeled functional connectivity, decoupled resting-state networks, and a disruption of the typical unimodal-multimodal functional divide. Finally, to investigate whether passive diffusion can be used to recover information about the SC itself, I developed a model that parsimoniously parameterizes directed SC using gene gradients and fits this model to brain function. I found that this directed SC model can estimate ground-truth directed SC across three non-human species—*C. elegans*, mouse, and macaque—and that the resulting human directed SC estimates are biologically plausible and predict a directed net flow that reproduces the original unimodal-multimodal functional divide. Together, these findings position the graph Laplacian of the SC as a scaffold for brain function and offer a principled framework for studying brain function through the lens of biological structure.

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Chapter 1

General Introduction

The brain is a complex dynamical system where cells, known as neurons, connect to each other and propagate signals between one another. The aggregate firing of these neuronal networks gives rise to the staggeringly intricate cognitive and behavioral features in animals. Understanding how a network of neurons emerges into these rich cognitive and behavioral consequences is at the heart of neuroscience research. Moreover, in principle, this understanding should illuminate how and why the brain malfunctions in various pathological and psychiatric conditions with the hope to reveal potential ways to address these health issues.

To guide our investigation into such complex phenomena, it is valuable to leverage two different but complementary perspectives. The first approach describes the brain from a strictly biological perspective, which builds new understanding of the brain from foundational principles in biology. For example, it is important to recognize that neurons have a receiving end (the dendrites) and a transmission end (the axon), and that generally signals travel from dendrites, to cell-body, to axon in a directional flow of signal through the brain. Another important principle in biology is recognizing that genes code for many guiding principles of biological organization, and therefore are likely to be an important part of any description for that organization. The biological perspective has the advantage of centering aspects of the brain that we have good reasons to believe are true, but it is significantly limited when it tries to answer the complex questions about the brain.

The second perspective aims to describe the brain in the language of mathematics and theory. For example, there is a mathematical object to describe things that are connected to each other—a *graph*. Graphs can describe nearly anything, from networks of people interacting to networks of neurons. When signals move through a graph, this opens yet another theoretical toolbox known as Graph Signal Processing, which describes a graph based from the properties of its *adjacency matrix* (see section below). Another critical mathematical framework involves understanding the nature of signals and the system that instantiates them. After all, the brain is such a system full of signals, but the mathematics is the language we must use to formalize our discussion of signals and systems. Therefore, the computational perspective has an advantage in its ability to formally address complex questions about what the brain does and how it works, but it becomes easy to get “lost” in the mathematical theory when it is untethered to the underlying biology.

Thus, the field of computational neuroscience balances between these approaches: explaining complex biology with elegant mathematical theory, yet not losing sight of simple biological mechanisms that constrain how elaborate the mathematics should be. Computational neuroscience aims to merge these mathematical and biological perspectives to better describe how the brain as a network transmits and transforms signals, and in turn leverage these principles to better understand the biology that underlies them.

1.1 Motivation and Central Problem

While there are many ways to leverage principles in computational neuroscience to describe the brain, among the most central and fundamental revolves around the *structure-function problem*. Recall the basic foundation of neuroscience, that neurons transmit signals downstream to neurons with which they connect. Given this simple rule, it would be intuitive that neurons, or parts of the brain, that are connected should have similar activity. However, research has shown that this relationship between the structural wiring and functional activation, even between neurons, is unclear and much more complicated than such a simple rule may imply [164]. This one example

is demonstrative of the deeper issue: the anatomy must constrain the dynamics we observe, but the mapping between anatomy and functional dynamics is indirect, multiscale, and likely context-dependent [92, 212, 63, 125]. Therefore, this structure-function problem in neuroscience seeks to resolve this apparent biological contradiction using mathematics to describe how the observed functional activity could emerge from a structural scaffolding.

Seeking answers to this central problem in neuroscience may further tell us about how the brain malfunctions in disease. Specifically, the relationship between brain structure and function are described in mathematical equations with free parameters that may have subject- and disease-specific consequences. For example, recent work in Alzheimer’s Disease (AD) has shown that a structure function model predicts the global time-scale of the brain (i.e., how long it takes for signals to move through the network) to *decrease* in AD with a relationship to cognitive decline [223]. Once we understand the structure-function relationship, we can try leveraging mathematical formulations in Network Control Theory to help treat these medical conditions [82]. Therefore, the structure-function problem in neuroscience is not only interesting from a theoretical view, but could have consequences in the medical treatment of brain disorders.

1.1.1 Introduction overview

In the following, I describe the relevant and essential background necessary to understand the advances in computational neuroscience that I articulate in later chapters. First, I review the fundamental principles of neuroimaging, particularly magnetic resonance imaging (MRI), and how we obtain measures of brain connectivity from MRI. Second, I review how we represent the brain as a graph and some of the major advances this perspective has delivered. Third, I transition to describing one particular approach to resolving the structure-function problem, which centers on a mathematical object known as the graph Laplacian matrix. Finally, I give a brief overview of the three open challenges and my work to resolve them, which together constitute the three main chapters of this dissertation.

1.2 Neuroimaging and the Study of Brain Connectivity

To study the brain, especially the human brain, *in vivo*, we leverage Magnetic Resonance Imaging (MRI) as a non-invasive imaging technique. MRI is powerful because it uses the magnetic properties of atoms and molecules, specifically hydrogen nuclei, to reconstruct images of soft tissues in the body without the need for any ionizing radiation. Moreover, MRI does not merely represent a single type of brain image, but in fact can be used to create many different kinds of brain images, each sensitive to different properties or features in biological tissues.

A thorough treatment of MRI physics is out of scope for this General Introduction, but I will give a brief description for completeness. Hydrogen is an atom within molecules, most notably water and various lipids. An MRI is a very strong magnet, with a magnetic field over 60,000 times stronger than the Earth's natural magnetic field. When hydrogen atoms throughout the body enter the bore of an MRI, a small but significant fraction align with this powerful magnetic field along a magnetic dipole moment associated with nuclear spin. Powerful secondary magnets, known as gradients, allow us to define a type of coordinate grid within the larger magnetic field which we can use to capture spatial information inside the magnet. A radiofrequency pulse then perturbs this magnetization away from equilibrium, and as the spins relax back toward equilibrium, they generate an *echo* that can be detected by receiver coils placed around the body. This echo is the data from which we can reconstruct the soft tissue images within the body and brain. By varying the pulse sequence and acquisition parameters, MRI can generate many different forms of contrast, each sensitive to different tissue properties. For more thorough treatments on MRI physics, see [199].

To obtain data related to brain networks, we use two main forms of MRI techniques: diffusion MRI for structural networks and functional MRI for functional networks.

1.2.1 Structural connectivity from diffusion MRI

Diffusion MRI (dMRI) is a type of MRI acquisition method that is sensitive to the diffusion of water. The important aspect is that the strength of the MRI signal is sensitive to the molecular diffusion within voxels. In essence, dMRI is acquired by using MRI gradients to define different spatial directions and then observe how much of the signal from water molecules decays along each of these directions. Within cells and biological tissues, water movement is constrained to specific directions, and dMRI can discern which directions allow for more water diffusion than others, known as *anisotropy*. This is highly relevant to the brain's anatomy, since neurons are encased in a fatty lipid layer known as a myelin sheath created by oligodendrocytes. These myelinated neurons form macroscopic white matter axonal bundles that exhibit anisotropic diffusion due to their tissue microstructure. Therefore, dMRI can be used to reconstruct a map of where water is diffusing in the brain, and since that diffusion is constrained by the anatomy, that map becomes a coarse-grained estimate of the white matter tracts between brain regions.

There are many data processing steps that take raw dMRI images and convert them into measures of structural connectivity between brain regions, but they can be conceptualized into three main steps. The first step is denoising, where we aim to eliminate all potential artefacts that may be present in dMRI images, such as motion and distortion from echo-planar imaging and air-tissue interfaces. The second step is tractography, which estimates an Orientation Distribution Function (ODF) reflecting which directions water is most likely to be moving, then probabilistically generates a *tractogram*, a collection of streamlines that follow these ODFs. The third main step takes the tractogram, transforms it to become a biologically interpretable measure of fiber bundle capacity [194], then consolidates all of the streamlines together based on a predefined set of N brain regions. The end product is a matrix $C \in \mathbb{R}^{N \times N}$ where the element $C_{i,j}$ denotes the estimated structural connectivity strength between brain region i and region j .

1.2.2 Functional connectivity from functional MRI

Functional MRI (fMRI) is a type of MRI acquisition method that is sensitive to hemoglobin in blood. Specifically, fMRI measures the Blood Oxygenation Level Dependent (BOLD) signal which senses the transition of hemoglobin from oxygenated to deoxygenated states because deoxyhemoglobin is paramagnetic and alters the local magnetic environment. Therefore, fMRI can be interpreted as a measure of *hemodynamics*, which is a proxy measure for cellular metabolism, since cells require oxygen from hemoglobin to stay alive and functioning. This proxy for cellular metabolism is in turn a proxy for neural activation, since neurons that are actively firing action potentials have increased metabolic load. Thus, the signal obtained with fMRI is a proxy of a proxy of a measure for neuronal activity in the brain. Given its tangential and approximate relationship to neural activity, it is striking that a significant amount of information about what the brain is doing can be obtained from fMRI. I cover some of these headline results below.

There are also many processing steps involved in denoising fMRI, most of which are similar to those described for dMRI above. The initial processing objectives are to remove artefacts due to motion and distortion from the air-tissue interfaces, but since fMRI is such a proxy measure of brain activity, there are other physiological concerns at hand. For instance, there are fMRI signals within the brain's cerebrospinal fluid (CSF), which is the watery fluid that encases and protects the brain. Since this fluid is not innervated with arteries or capillaries, presence of an fMRI signal in CSF is spurious and needs to be regressed out from the data. Since fMRI measures blood oxygenation, there is also a concern about signal change that occurs from the heartbeat, which at low sampling rates can fold itself (i.e., alias) into the data. Therefore, faster sampling and low-pass frequency filtering on fMRI data is necessary to eliminate cardiovascular as well as respiratory confounds. After averaging signals across a predefined set of brain regions, the end product is a matrix $X \in \mathbb{R}^{T \times N}$ where the element $X_{t,i}$ indicates a brain region i at time t . Commonly, the cross-correlation (or zero-lag covariance) of this matrix is taken as a measure of functional connectivity between brain regions. That is, brain regions that are synchronizing their activity across time are said to be functionally connected.

There are two main types of fMRI analysis: resting-state and task-based. In resting-state analyses, the research subject is asked to lie inside the MRI and do “nothing,” which means they are really just thinking about anything. This paradigm is useful because it allows for some simplifying assumptions during computational modeling, in particular that the brain is operating in some resting steady-state, but it has also come under significant critique since it is completely unconstrained [13, 59, 1]. Conversely, task-based fMRI asks for research subjects to complete a specific task during the scan such that we can observe changes in the brain related to the task being performed. This paradigm is useful insofar as the task itself has interesting features relevant to different forms of brain processing, but it prevents making simplifying assumptions during computational modeling. In general, it is useful to use both forms of fMRI, for each has strengths that complement the other’s weakness.

1.3 Network Neuroscience

Once we have acquired and processed dMRI for structural connectivity and fMRI for a brain signal or functional connectivity, the full suite of network science and graph theory become available.

1.3.1 Graph-theoretic representations of brain networks

Formally, a *graph* G is an ordered pair $(N(G), E(G))$ consisting of a set $N(G)$ of nodes and a set $E(G)$, disjoint from $N(G)$, of edges, together with an *incidence function* ψ_G that defines how nodes are connected by edges. Commonly, a graph is represented by a mathematical object known as an *adjacency matrix*. Let $A \in \mathbb{R}^{N \times N}$ (where $N = |N(G)|$) be such an adjacency matrix where the elements $A_{ij} \in E(G)$ correspond to an edge from the edge set, possibly with a real valued weight.

There are two main graph objects under investigation from a network neuroscience perspective. First is the structural connectivity (SC), which as described above is a matrix where C_{ij} is the adjacency matrix measuring the strength of white matter connectivity between regions i and j .

Second is the functional connectivity (FC) calculated as $FC = \frac{1}{T}X^T X$, which is the covariance of the fMRI brain signals X .

1.3.2 Resting-state networks

Among the most paradigm-defining results in network neuroscience was the discovery of resting-state networks (RSNs). The earliest work on RSNs were in part described by Calhoun et al. [35], who introduced group independent component analysis (ICA) to robustly identify spatially coherent network patterns. The same year, the so-called “Default Mode Network” (DMN) was formally characterized for the first time [161, 86]. The DMN and the more general idea of spatially distributed network patterns quickly took hold in network neuroscience. Ten years later, Yeo et al. [236] used von Mises-Fisher clustering to show that 7 RSNs, including the DMN and others from ICA, all lived coincident within resting-state FC. These RSNs show remarkable stability across varying analytical techniques [181, 180]. Significant efforts have been made to standardize and unify the nomenclature and analysis of these networks across studies and brain atlases [213, 113]. More recent work has emphasized that RSNs also show a subject-dependent organization across the cortex and even fracture into parallel interdigitated networks [25, 26]. While most work on RSNs has been in fMRI, they have also been shown in other non-invasive neuroimaging techniques, including magnetoencephalography (MEG), electroencephalography (EEG), and functional near-infrared spectroscopy (fNIRS) [36, 29, 241]. Some recent work suggests that these RSNs may emerge from the underlying SC [6, 233], but no one framework has taken hold as a clean explanation for how they arise. Their robust patterns across diverse imaging modalities have instantiated RSNs as a pillar of network neuroscience analyses.

1.3.3 Cortical hierarchy

Another key idea in network neuroscience analysis is the idea that the brain has a hierarchical organization. Classic works in the primate visual cortex were among the most prominent to articulate this view, showing feedforward and feedback connections through the visual system [56].

The concept of cortical hierarchy broadened to a more general conceptualization of a sensory-to-fugal organizational axis [142]. However, it was not until nearly two decades later that a landmark result from Margulies et al. [134] showed that the first principal gradient of FC in fact revealed this sensory-to-fugal or unimodal-to-multimodal axis in the human brain. This principal gradient spanned from the DMN to both visual and motor areas, clearly revealing a macroscale cortical organization that crystallized the modern view of a unimodal-to-multimodal hierarchy in the brain. Since then, many other works try to situate different features of brain networks in terms of these principal functional gradients [128, 158, 88]. The notion of hierarchy in the brain is now viewed as fundamental to its organization, yet it remains unclear how hierarchy in the structural organization produces hierarchy in functional organization.

1.3.4 Integration and segregation

A third area of network neuroscience investigates how the brain balances integrating information with segregated processing. Unifying integration and segregation in the brain has been a fundamental puzzle in neuroscience ever since the conception of the “binding problem,” which asks how an *integrated* experience arises from *segregated* sensory information [167]. This philosophical question has been investigated in terms of brain function, where integration and segregation are ends of a continuum from synchrony to asynchrony, respectively [208, 67, 198]. Yet, purely functional accounts cannot explain how this integration-segregation balance emerges from the underlying biological structure. It has been proposed that SC network topology subserves the integration-segregation balance, with integration originating from signal convergence via the rich-club and segregation originating from modularity [217, 197, 45]. However, graph metrics to measure these network properties in SC are incommensurable to a single integration-segregation continuum. Some recent work has noticed that *graph harmonics* (see section below) may also describe integration and segregation in the brain [177, 121, 93, 154, 158], yet so far these descriptions have been largely qualitative and separate from the larger integration-segregation discourse.

1.4 Addressing the structure-function problem

The structure-function problem in computational neuroscience is to determine how structural connectivity C constrains or generates an observed functional organization FC. Often the problem is approached through a mathematical model that expresses the observed brain activity as a function of the SC with some set of k model parameters ($\Theta = \{\theta_1, \theta_2, \dots, \theta_k\}$).

In general, there are two dominant approaches to formulating a structure-function model. One is to build a neural mass model (NMM), which has some equation for local neuronal biophysics within each node of a graph [179, 103]. Since these biophysical equations are aiming to model neurons, they are typically nonlinear, and therefore the model cannot generally be solved directly, instead requiring simulations to identify optimal model parameters.

My work uses a second approach, which builds a linear time invariant (LTI) model from classical dynamical linear systems theory, typically an equation of the form:

$$\frac{d\mathbf{x}(t)}{dt} = A\mathbf{x}(t) + B\mathbf{u}(t) \quad (1.1)$$

Here, $\mathbf{x}(t) \in \mathbb{R}^N$ is a vector specifying the state of the system's signal across N nodes, $A \in \mathbb{R}^{N \times N}$ is a state transition matrix (i.e., the system's internal dynamics), $\mathbf{u}(t) \in \mathbb{R}^M$ is a vector specifying the exogenous input into the system at M inputs, and $B \in \mathbb{R}^{N \times M}$ is an actuation matrix that specifies how the input distributes through the system. In neuroscience, this equation is commonly invoked when studying network control theory [109]. The internal system dynamics can be written as $A = f(C, \Theta)$ which includes the SC directly, and then certain aggregate properties of B and/or $\mathbf{u}(t)$ are either assumed or estimated from the data [1, 73, 82, 109]. Since this class of model is linear, they can often be solved in closed form, eliminating the need for simulating a large parameter space as NMMs must do. Although the underlying behavior of neurons are highly nonlinear, the success of these simple linear models has led some to argue that the brain may in fact be macroscopically linear [151].

Therefore, LTI models represent a parsimonious and practical way to approach the structure-

function problem in neuroscience. Yet, it remains unclear exactly what the function $f(C, \Theta)$ should look like. One common way to construct such a function of SC is to leverage the *graph Laplacian*.

1.4.1 The graph Laplacian and network diffusion

Passive diffusion is possibly the simplest way to describe something moving through a system. Moreover, nature often uses passive diffusion along concentration gradients to do work for minimal cost. Therefore, it is a reasonable starting assumption that some amount of the brain's functional connectivity may result from simple diffusion over the SC. When aiming to describe how a signal propagates through a network by passive diffusion, the graph Laplacian naturally falls out [154].

To see how, recall the brain's structural connectivity matrix ($C \in \mathbb{R}^{N \times N}$), where each row/column represents a single brain region of interest (ROI) and the matrix entry (C_{ij}) corresponds to the connectivity strength between regions i and j . Then the way in which a signal can be expected to change under passive diffusion is

$$\frac{dx_i(t)}{dt} = -\beta(x_i(t) - \frac{1}{\sqrt{D_{ii}}} \sum_j \frac{1}{\sqrt{D_{jj}}} C_{ij} x_j(t)) + \sum_j B_{ij} u_j(t) \quad (1.2)$$

Where $D_{ii} = \sum_j C_{ij}$ corresponds to the amount of connectivity (degree) at a given region i . Vectorizing this equation reveals the degree normalized graph Laplacian:

$$\frac{d\mathbf{x}(t)}{dt} = -\beta(I - D^{-1/2} C D^{-1/2}) \mathbf{x}(t) + B \mathbf{u}(t) = -\beta \mathcal{L} \mathbf{x}(t) + B \mathbf{u}(t) \quad (1.3)$$

The graph Laplacian ($\mathcal{L} \in \mathbb{R}^{N \times N}$) is a graph analogue to the Laplace-Beltrami operator for manifolds [104].

However, note that the above case is in fact a specific linearized truncation of a more general way to specify diffusion through a network. Instead of considering merely $-\beta \mathcal{L}$ as the operator

for diffusion, we can generalize this operator to be of the form

$$f(\mathcal{L}; \theta) = \sum_{p=0}^P \theta_p \mathcal{L}^p \quad (1.4)$$

Here, P is the order of the Taylor series approximation for a generalized *higher-order network diffusion* (HONeD) operator, and $\theta \in \mathbb{R}^{P+1}$ is the vector of HONeD parameters. The notion of a higher-order process based on SC is not entirely new, it has been explored in recent works as a way to model polysynaptic signal pathways in the brain ¹ [16, 39, 195].

1.4.2 Connectome harmonics

When one studies the properties of a network using the graph Laplacian, they are leveraging the rich field of Graph Signal Processing (GSP) [121, 1]. At GSP’s heart lies the graph Laplacian matrix and its decomposition into graph *harmonics* (eigenvectors or gradients [134]), reflecting orthogonal spatial patterns (wave functions) of a signal in the network, with each harmonic associated with an eigenvalue reflecting its graph frequency [37, 47]. The harmonic decomposition of the graph Laplacian is tantamount to a Fourier Transform; Laplacian harmonics form the Fourier basis that describes how hypothetical brain signals would “resonate” in the structural network, thereby linking structural graph topology to functional synchrony [121, 147]. Each harmonic is associated with an eigenvalue, and conventionally harmonics are sorted by their ascending eigenvalues. Commonly these eigenvalues are associated with graph frequencies, and the eigenvectors are treated analogously to a principal component analysis, where only the lowest graph frequencies are relevant [6, 155]. However, my work here will seek to investigate this relationship to graph frequencies more carefully.

¹The matrix power of a graph’s adjacency matrix, $G^p \forall p \in \mathbb{N}$, encodes walks of length n on the graph.

1.5 Open Challenges and Specific Contributions

1.5.1 Connectome harmonics as the basis of integration and segregation

Integration and segregation in neuroscience is most commonly described in terms of graph metrics such as measures for centrality, node hubness, or modularity [197, 45]. However, integration and segregation are commonly discussed as two ends of a spectrum between which the brain is dynamically balanced. Therefore, a limitation of conceptualizing and quantifying these different graph metrics as measures of integration and segregation is that they are mutually incommensurable to a single integration-segregation continuum. Moreover, lacking such a continuum inherently neglects what features lie at the center of this continuum.

In *Chapter 2: Integrative, Segregative, and Degenerate Harmonics of the Structural Connectome*, I argue that the graph Laplacian harmonics can be understood as describing such an integration-to-segregation continuum. A central concept that unifies this framework is the notion of the *gap-spectrum*, which is the spacing between graph Laplacian eigenvalues. The gap-spectrum allows for a principled way to divide harmonics into integrative, degenerate, and segregative regimes that I show each have distinct relationships to subject variability and functional participation. Notably, reconstructing a low-rank SC limited to each of these regimes reveals that the traditional graph theory metrics used to describe integration and segregation in fact map intuitively to these regimes. This result suggests that graph harmonics subsume these previous graph theory notions of integration and segregation. Together, this work espouses a framework to understand the graph Laplacian harmonics of SC which highlights the full eigenspectrum as relevant to brain function and organization.

1.5.2 Deconvolving passive diffusion to reveal novel functional organization

A simple LTI model for brain function—the network diffusion model—can account for a substantial amount of the observed functional covariance between brain regions. The network diffusion model describes signal movement through the brain as a *passive* process along concentration gradients:

if a brain region has high activation, its signal will diffuse to connected brain regions with low activation. However, in neuroscience we typically aim to study *active* rather than *passive* signals. Moreover, nearly all current work in neuroscience uses fMRI, which may contain both active and passive signal components. From these observations, two natural questions arise: 1) how can one remove the effect of passive network diffusion over the SC; and 2) what features of traditional fMRI analyses, including RSNs, principal gradients, or task-activation maps, change after eliminating this passive signal component?

In *Chapter 3: HONeD-in on Brain Activity: Deconvolving Passive Diffusion on the Structural Network from Functional Brain Signals*, I present a method to obtain what I call the Higher Order Network Diffusion-Innovation, or HONeD-in, signal. I calculate the HONeD-in signal in closed form using a HONeD operator estimated from the functional data under stationarity assumptions. I then thoroughly evaluate the resulting HONeD-in signal, showing several notable results. Specifically, HONeD-in signals 1) sparsified functional connectivity, 2) decoupled resting-state networks, 3) reorganized FC-gradients along with the RSN hierarchy, and 4) sharpened task fMRI activation maps. Together, these results suggest that some of the conventional FC structure and its resulting networks/principal gradients may in part arise from large-scale signal diffusion through SC. This work therefore not only presents a method for transforming fMRI into a new signal for future research to investigate, it also speaks to the underlying role of SC and network diffusion as a scaffold for observed brain activity and network phenomena.

1.5.3 Estimating latent structural directionality from network diffusion

Neurons have a direction: they propagate signals from dendrites near the soma, down the axon, and terminating on the dendrites of downstream neurons. Yet, a fundamental limitation with dMRI tractography is that it lacks this directional information about white matter pathways. Despite this limitation, recent work has shown that undirected structural connectivity can still reveal important hints of directional organization. Specifically, diffusion-based models can reveal systematic asymmetries in an otherwise undirected network [143, 195, 182, 73]. Meanwhile, parallel lines of

work focus on the biological link between genes and structural directionality. Biologically, genes create molecular gradients that guide axon growth [237], and genes have been shown to relate to connectivity features in SC across various species [5, 66, 4, 71, 88, 115, 52]. Together, these observations raise the possibility that a structure-function network diffusion model parameterized by gene co-expression may recover structural directionality from an undirected network.

In **Chapter 4: Gene Gradients Reveal Directed Structural Connectivity Across Species**, I present such a diffusion model, based again on the HONeD operator, that incorporates gradients of gene co-expression maps into SC via a similarity transform. I show that this approach accurately estimates directed structural connections across three non-human species, *C. elegans*, mouse, and macaque, using only a few genetic gradients. I then assess subject-specific directed structural connectivity across 770 Human Connectome Project subjects and show that the inferred directionality exhibits biologically plausible organization in sensory and thalamic circuits. I conclude by showing that the fitted directional HONeD operator admits a prediction for how brain signals “flow” through SC, thereby providing a measure I term *angular flow* (AF). This AF correlates with other directional functional connectivity estimates and its net flow reproduces the principal functional connectivity gradient. This final result is especially interesting, since the HONeD-in signal showed that the principal gradients were remodeled when network diffusion is removed, AF conversely reveals that these principal gradients appear as the predicted source-sink organization from directional diffusion over SC. Overall, this gene-informed structure-function framework provides a way to estimate and analyze both directed structural and functional connectivity in the brain.

Chapter 2

Integrative, Segregative, and Degenerate Harmonics of the Structural Connectome

2.1 Abstract

Unifying integration and segregation in the brain has been a fundamental puzzle in neuroscience ever since the conception of the “binding problem.” Here, we introduce a novel framework that places integration and segregation within a continuum based on a fundamental property of the brain—its structural connectivity graph Laplacian harmonics and a new feature we term the *gap-spectrum*. This framework organizes harmonics into three regimes—integrative, segregative, and degenerate—that together account for various group-level properties. Integrative and segregative harmonics occupy the ends of the continuum, and they share properties such as reproducibility across individuals, stability to perturbation, and involve “bottom-up” sensory networks. Degenerate harmonics are in the middle of the continuum, and they are subject-specific, flexible, and involve “top-down” networks. The proposed framework accommodates inter-subject variation, sensitivity to changes, and structure-function coupling in ways that offer promising avenues for studying cognition and consciousness in the brain.

2.2 Introduction

A central goal of systems neuroscience is to explain fundamental brain processes shared across individuals. Perhaps the most important fundamental process involves the identifying mechanisms to address the so-called “binding problem,” which asks how an *integrated* experience arises from *segregated* sensory information [167]. This philosophical question has been investigated in terms of brain function, where integration and segregation are ends of a continuum from synchrony to asynchrony, respectively [208, 67, 198]. Yet, purely functional accounts cannot explain how this integration-segregation balance emerges from the underlying biological structure. It has been proposed that white matter “structural connectivity” (SC) network topology subserves the integration-segregation balance, with integration originating from signal convergence or the “rich-club” and segregation originating from modularity [217, 197, 45]. However, graph metrics to measure these network properties in SC are incommensurable to a single integration-segregation continuum. Furthermore, characterizing what occurs between integration and segregation—the missing-middle—has not received sufficient attention. An integration-segregation continuum based on a fundamental network property is yet to be conceived for structural brain networks.

Understanding how integrative and segregative functional activity arises from SC depends on the “structure-function” relationship of brain networks—often described using graph theoretic and statistical measures [30, 13, 238, 125]. Graph Signal Processing (GSP) extends graph theoretical approaches, providing an elegant and concrete mathematical framework to describe brain function as signal diffusion through the SC [121, 1]. At GSP’s heart lies the graph Laplacian matrix and its decomposition into graph *harmonics* (eigenvectors or “gradients” [134]), reflecting orthogonal spatial patterns (wave functions) of a signal in the network, with each harmonic associated with an eigenvalue reflecting its graph frequency [37, 47]. The harmonic decomposition of the graph Laplacian is tantamount to a Fourier Transform; Laplacian harmonics form the Fourier basis that describes how hypothetical brain signals would “resonate” in the structural network, thereby linking structural graph topology to functional synchrony [121, 147]. Each harmonic is associated with an eigenvalue, and conventionally harmonics are sorted by their ascending eigenvalues.

It is therefore natural to employ the harmonic “eigenspectrum” as the organizing principle for integration and segregation, which may form the continuum we seek. This concept has recently gained currency: lower harmonics have been interpreted as integrative since they capture patterns of *global synchrony*, and higher harmonics have been interpreted as segregative since they capture *local synchrony* [177]. Just as low spatial frequencies in Fourier space represent broad and smooth gradients while high frequencies represent detailed, possibly localized, and noisy patterns, it has been observed that low harmonics reflect the global network structure and hence represent integrative activity while higher harmonics represent segregated network clusters [121, 93, 154, 158]. The lowest harmonics appear to correlate with canonical functional resting-state Networks (RSNs) [233, 236, 6] and were the most effective at predicting functional connectivity (FC) [2, 6]. Accordingly, Preti and Van De Ville [158] suggested dividing harmonics into two classes based on their participation in fMRI: the lowest harmonics were “coupled” to fMRI signal while all higher harmonics were “decoupled.” Sometimes these two regimes are also called “illiberal” and “liberal”, respectively [121]. Therefore an ascending harmonic eigenvalue ordering is a plausible means of describing the integration-segregation continuum.

However, as we show here, many aspects of the structural harmonics’ eigenspectrum make the desired integration-segregation (or “coupled-decoupled”) binary problematic and incomplete. The relationship between Laplacian eigenvalues and spatial frequency has only partial mathematical [97] and empirical [93] support. Higher harmonics in particular have been shown to break from strict frequency expectations [93]. Mathematically, graph spectra may be reasonable analogs of spatial frequencies for simpler graphs (e.g., rings and infinite or closed lattices) but not necessarily for complex networks [97, 93], such as the brain [198, 30]. The notion of low harmonics being exclusively coupled to function is also imperfect: higher harmonics also significantly contribute to functional activity, such as in MEG spectra [222, 177] and in alignment with RSNs such as the visual network [233]. Thus, both theoretical and empirical evidence suggests that the coupling-decoupling dichotomy does not neatly align with the integration-segregation continuum.

Can the Laplacian harmonic spectrum serve as an integration-segregation continuum? Do the

harmonics follow expectations for the integration-segregation continuum, such as reproducibility across individuals? What fundamental network property could distinguish integrative-versus-segregative harmonics? What represents the “missing-middle” of the continuum, and what is its relevance to the underlying biology and brain function?

In this study, we address these questions using a deep investigation of the structural harmonics’ eigenspectrum. First we develop a consensus SC to facilitate an ordering of harmonics across subjects. We seek the most informative ordering of the harmonics that simultaneously addresses the following criteria:

1. The ordering must place integration-like harmonics at one end and segregation-like harmonics at the other.
2. The ordering must reproduce as much as possible notions of spatial smoothness and sparsity.
3. The ordering should be reproducible across individuals in a predictable manner.
4. Harmonics placed similarly along the spectrum must share more properties with each other than those far apart.

We first show that the canonical ordering of harmonics by ascending eigenvalues only partially succeeds in fulfilling the above criteria, but that SC harmonics which deviate from classical Fourier expectations are not reproducible across subjects with this ordering. Then, we show that the above criteria can be met by aligning subject-specific harmonics to the group-level harmonics from the consensus SC (the mean SC across individuals). This new ordering reveals an underlying harmonic reproducibility related to the consensus “gap-spectrum,” a fundamental property of the eigenspectrum derived from spectral graph theory. Further, the gap-spectrum naturally partitions the harmonics into three distinct regimes: integrative harmonics have low eigenvalues but high spectral gaps; segregative harmonics have high eigenvalues and high spectral gaps; the “degenerate” harmonics have intermediate eigenvalues but low spectral gaps. The latter regime is so-named in analogy to degenerate modes observed in many physical systems, both classical

[186, 49, 138, 106] and quantum [99, 44]. This degenerate regime fills the “missing-middle,” has not previously been defined in brain science and is endowed with distinct functional relevance.

Together, the three regimes faithfully account for key group-level harmonic properties including spatial smoothness, sparsity, sensitivity to changes, similarity between individuals, and alignment to functional networks. Hence, a more complete stratification of harmonics requires a trichotomy—integrative, degenerate, segregative—instead of the popular integration/segregation or coupled/decoupled dichotomies. The proposed harmonic trichotomy aligns with prior graph theory accounts of integration-segregation while also revealing previously unreported structure-function relationships by explaining resting and task functional networks in a manner that is not possible within prior paradigms.

2.3 Results

Here, we present results that investigate whether SC harmonics may constitute an integration-segregation continuum in the brain. We begin by showing that harmonics deviate from strictly ascending frequencies and have an integration-to-segregation like structure. We then show that integrative and segregative harmonics are shared across individuals, which would indeed be expected for any candidate brain mechanism to resolve the binding problem. Then, using the gap-spectrum, we define integrative, segregative, and *degenerate* regimes precisely, and we further assess regime relationships to graph frequency and graph theoretical metrics. We conclude by investigating the functional relevance of the three regimes in multiple ways, including stability to changes, alignment with resting-state networks, task networks, and empirical resting-state time series.

2.3.1 SC harmonics’ spatial frequencies deviate from Graph Fourier intuitions

SC normalized Laplacian eigenvalues are similar across subjects and are close to those from the consensus SC (**Fig. 2.1A**). We also show that the lowest harmonics in the consensus SC qual-

itatively matched with those reported in prior works [228, 130, 17] and that higher harmonics are increasingly localized (**Fig. 2.1B**). Quantitatively, we investigated properties of SC harmonics related to classical Fourier intuitions, including sparsity and three spatial frequency measures: zero-cross rate, network zero-crossings [93], and roughness. First, we show that the harmonics with the highest eigenvalues are sparse (**Fig. 2.1C**). Next, based on Fourier intuitions, we may expect a monotonic relationship between harmonics’ eigenvalues and spatial frequency metrics, yet all three measures show non-monotonic relationships, with the greatest deviation for the highest eigenvalue harmonics (approximately when $\lambda \geq 1$; **Fig. 2.1C**).

These results also replicated in our independent dataset with different MRI acquisition parameters and used a different SC generation pipeline (see Supplemental Material and Supplemental Figure S11). For completeness, we also analyzed the temporal frequency characteristics of a resting-state time series projections (Supplemental Material Figure S4), finding that higher harmonics are not necessarily related to higher temporal frequency in fMRI.

Taken together, we find only partial support that SC Laplacian eigenvalues correspond to spatial frequency. While there is undoubtedly a relationship, it is not monotonic. Instead, these results suggest the presence of global “integrative” harmonics with low eigenvalues and sparse “segregative” harmonics with high eigenvalues. Additionally, this non-monotonic relationship implies that sorting all subjects harmonics by their ascending eigenvalues could result in misalignment between subjects.

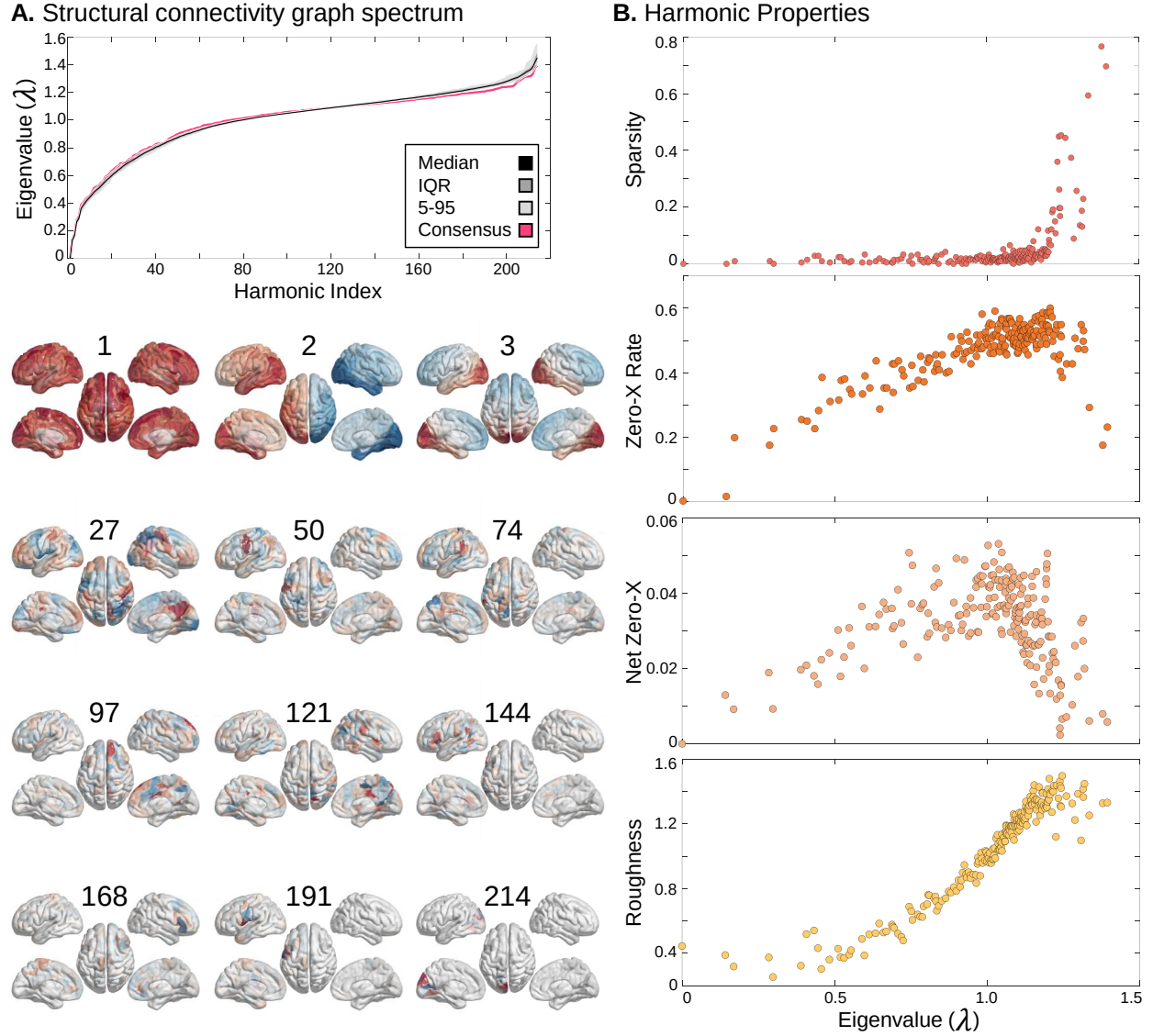


Figure 2.1: SC Harmonic Spectrum. (A) We show the normalized Laplacian eigenvalue spectrum for the SC network with 214 regions. In rose is the eigenvalue spectrum from the consensus (group-averaged) SC, and overlain on top in black is the median eigenvalue spectrum across all 50 subjects with shaded group percentiles. (B) We show several harmonics from the consensus SC with their harmonic index labeled above each plot. Notice that the harmonics become sparse and localized as eigenvalues increase. (C) We show four properties of the consensus SC harmonics: (top to bottom) sparsity, zero crossing rate, network zero crossings, and spatial roughness. The highest eigenvalue harmonics show spatial frequency characteristics that are non-monotonically related to their eigenvalues.

2.3.2 Integrative and segregative harmonics are similar across subjects

Next, we used a measure of inter-subject agreement (2.7) to test whether subjects had similar harmonics for both whole-brain (integrative) and sparse (segregative) ends of the eigenspectrum. When all subjects' harmonics are sorted by their ascending eigenvalues, we only observe high agreement for the first few harmonics (**Fig. 2.2 A & B**). However, matching harmonics to the consensus SC revealed that many subjects indeed shared harmonics at both ends of the consensus eigenspectrum (**Fig. 2.2 C & D**).

We found this result to be consistent across all Schaefer parcellation scales (Supplemental Figure S5). This result also replicated in an independent dataset with different MRI acquisition parameters, a different SC generation pipeline, and a different brain atlas (see Supplemental Material and Supplemental Figure S12). Furthermore, we evaluated the Bonferroni corrected significance between the two agreement distributions and found that nearly all harmonics showed highly significant agreement improvement after matching (Supplemental Figure S6). We then generated null-model networks with randomized edge weights from empirical SC networks and found that these randomized networks were unable to match. Empirical matching showed highly significant agreement compared to randomized harmonics (Supplemental Figure S6).

We also sought to evaluate which regions had the most inter-subject variability across harmonics, finding that sensory cortices and the orbitofrontal cortex had the least inter-subject variation while trans-modal regions had the most inter-subject variation (Supplemental Figure S7). See the Supplemental Material for other analyses on permutation length and distance (Supplemental Figure S8).

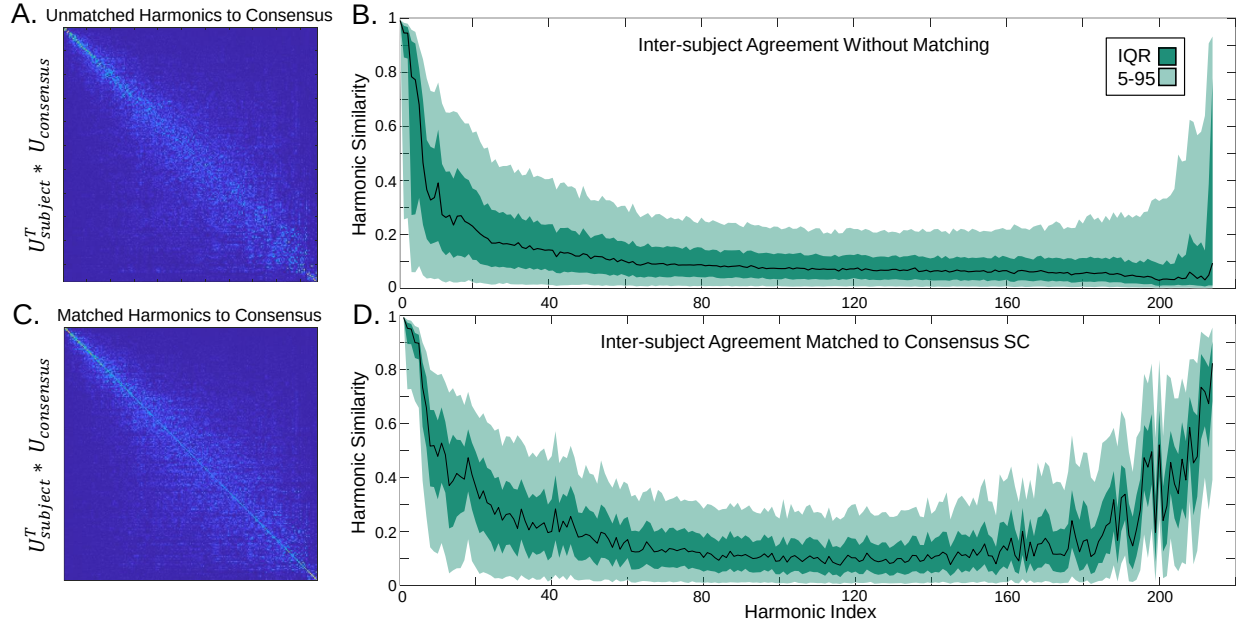


Figure 2.2: Harmonic Inter-subject Agreement. (A) Harmonics do not show a natural alignment to the consensus SC, and (B) inter-subject agreement, measured as the harmonic similarity across all combinations of subjects, showed that most subjects are misaligned for most harmonics. But (C) matching harmonics can maximize this similarity on the diagonal, and (D) following harmonic matching, we observe that subjects share many of the same integrative and segregative harmonics. In B & C, the black line indicates the median, while the shaded regions indicate the interquartile range (IQR; darker) and 5th to 95th percentiles (lighter).

2.3.3 Eigenvalue gap-spectrum as a theoretical explanation for harmonic properties

The harmonic inter-subject similarity analysis suggests there are at least three kinds of harmonics: those with low eigenvalues and high inter-subject agreement, those with high eigenvalues and high inter-subject agreement, and those with eigenvalues near $\lambda = 1$ and low inter-subject agreement.

We hypothesized that change-points in the “gap-spectrum” curvature (see Methods) would naturally partition harmonics into regimes that follow the empirical relationship with inter-subject agreement while preserving relationships with harmonic frequency. We first found regime transition points for each subject individually, then we matched subject-level harmonics to the consensus SC, and finally we determined a consensus regime assignment (**Fig. 2.3A** middle). We found the lowest regime to span harmonic 1 to 26, the central regime to span harmonic 27 to 187, and the highest regime to span 188 to 214.

Our results support the hypothesis that the gap-spectrum across subjects can indeed partition harmonic inter-subject agreement in an intuitive fashion while preserving relationships to group-level harmonic frequency (**Fig. 2.3B**; all $p < 0.05$). Based on our harmonic frequency analysis, we term the lowest regime as *integrative* since these harmonics show low-frequency whole-brain spatial configurations, and we term the highest regime *segregative* since these harmonics form segregated clusters. Now, based on the gap-spectrum analysis, we term the central regime “*degenerate*” to reflect that these harmonics have small spectral gaps characteristic to degenerate modes of a system.

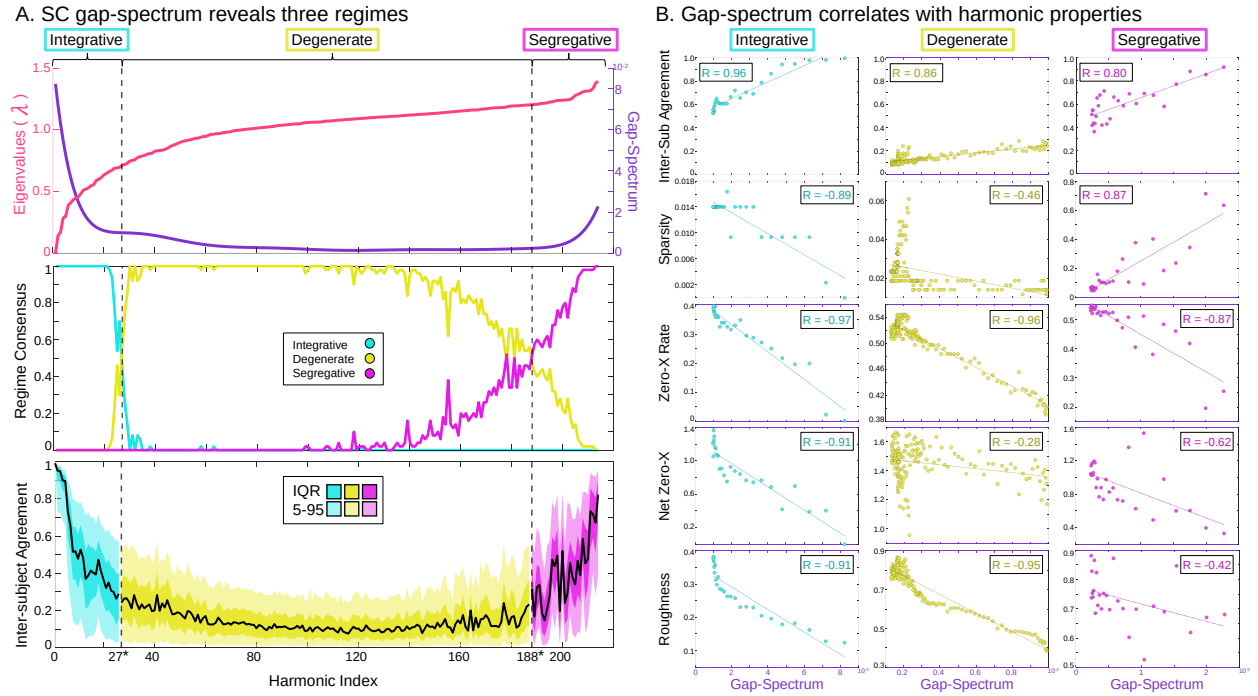


Figure 2.3: Defining Three Harmonic Regimes. (A) We show the consensus SC Laplacian eigenspectrum in rose and the analytical gap-spectrum in violet. Below this plot, we show the fraction of subjects who agree on each harmonic regime assignment. We define the final regime boundaries based on the majority crossing point. The lowest panel shows inter-subject agreement (same as shown in **Fig. 2.2D**) colored by the three regimes. (B) We show the population median values for the four harmonic frequency measures compared to the gap-spectrum. All measures show strong and significant correlations within the identified regimes and the gap-spectrum.

2.3.4 Stability of harmonics relates to the gap-spectrum

We next sought to evaluate how SC harmonics change in response to small network changes, expecting that different regimes would show different responses to perturbation. Degenerate harmonics with eigenvalues close to $\lambda = 1$ represent recurring network configurations (or “motifs”) [42], and they have mathematical “flexibility” since linear combinations of degenerate harmonics can produce another degenerate harmonic in the same eigen-subspace. Based on this theory, we hypothesized that the stability of harmonics would be related to the gap-spectrum and that degenerate harmonics would be the least stable since small perturbations could easily change the network’s motif structure.

We indeed found that degenerate harmonics were the most sensitive to perturbation while integrative and segregative harmonics were more stable (**Fig. 2.4A**). As perturbation σ increased far beyond the mean network weight, we found that all regimes approximated an exponential decay (**Fig. 2.4A** inset).

We then quantified the stability of harmonics (see Methods), and we found that stability indeed followed the same shape as the gap-spectrum (**Fig. 2.4B**). The stability of harmonics across subjects was significantly correlated with the consensus gap-spectrum (mean $r = 0.66$; all $p < 0.001$; **Fig. 2.4C**).

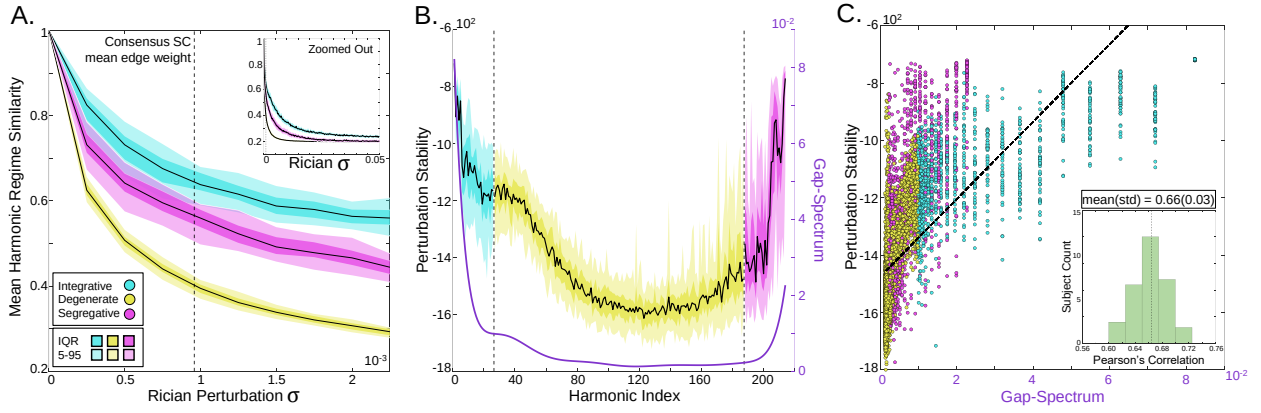


Figure 2.4: Stability of Harmonics. We perturbed the natural SC network across subjects with Rician noise over a wide range of σ (i.e., standard distribution). (A) We plot each regime-averaged intra-subject similarity between the authentic harmonics and the perturbed harmonics. The black line represents the median, while the darker and lighter shaded regions represent the IQR and 5-95 percentile range, respectively. Integrative harmonics show the most stability, segregative harmonics show intermediate stability, and degenerate harmonics show the least stability. The inset shows the same perturbation effect, but over a wider range of σ . (B) We quantify the stability of each harmonic and show that the stability follows the same general shape as the consensus gap-spectrum. (C) A scatter plot with data from all subjects and all harmonics, showing the overall relationship between the stability of harmonics and the gap-spectrum. The inset shows the distribution of subject-specific correlations between the stability of harmonics and gap-spectrum.

2.3.5 Regime-specific SC accounts for integrative and segregative graph theory metrics

We assessed whether regime-specific SC had graph theory metrics commonly related to integration and segregation. Qualitatively, the integrative SC shows broad connectivity across regions, the degenerate SC retains much of the connectivity structure from the native SC, and the segregative SC is sparse but dense in small clusters. Quantitatively, each regime SC embodies different graph metrics: 1-way ANOVAs showed significant regime-wise differences for all graph metrics (all $p \ll 0.01$, Bonferroni corrected), and post-hoc two-tailed t-tests showed that most pair-wise differences were highly significant ($p \ll 0.01$, Bonferroni corrected) (**Fig. 2.5**). Modularity was greatest for the full network and equally large for degenerate and segregative regime SC, suggesting that modularity emerges from both degenerate and segregative harmonics. Global efficiency was greatest for the integrative SC, indicating that integrative harmonics facilitate efficient information transfer through the network. Small worldness was largest for the full SC, and second largest for the degenerate SC (the difference was small but still significant $p = 7.3 \times 10^{-17}$), suggesting that degenerate harmonics account for much of the small-worldness observed in the full network. Finally, coreness was greatest for the segregative SC, revealing that segregative SC is characterized by highly clustered modules.

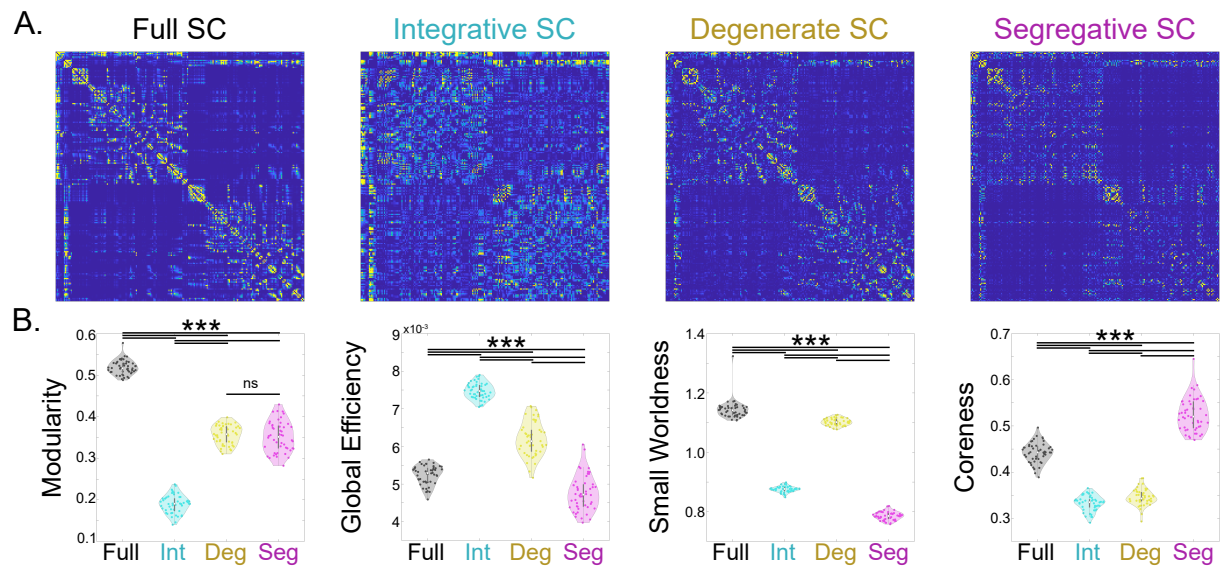
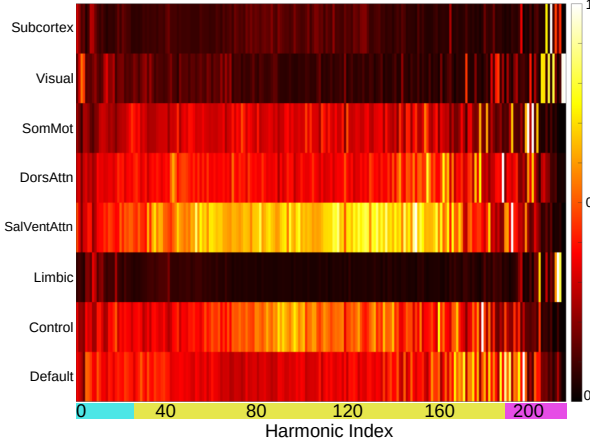


Figure 2.5: SC of Harmonic Regimes. (A) We show (left to right) the consensus SC and its decomposition into integrative SC, degenerate SC, and segregative SC. (B) Violin plots of graph theory metrics computed for the full SC and each of the low-rank SC networks. From left to right: modularity, global efficiency, small worldness, and coreness. (***) indicates $p < 0.01$, Bonferroni corrected; ns indicates non-significance).

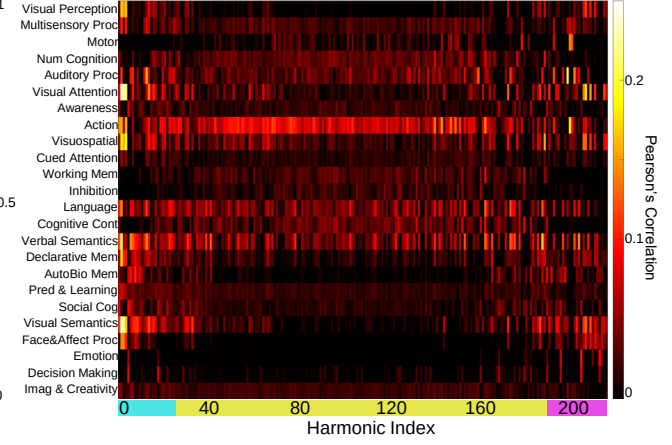
2.3.6 Harmonics have diverse participation with RSNs and functional tasks

We next assessed how SC harmonics related to functional resting-state networks (RSNs) and meta-analysis task activation maps. We found that RSNs show regime specificity across subjects (**Fig. 2.6A&C**). The ternary plot showed that the Control Network and the Salience Ventral Attention Network participated most in the degenerate regime; the Subcortex, Visual, and Limbic Networks participated most in the segregative regime; the Somatomotor and Dorsal Attention Networks participated in a balance of the degenerate and segregative regimes; and the Default Mode Network was balanced between all three regimes (**Fig. 2.6C**). RSN participation followed a similar relationship across Schaefer parcellation scales (Supplemental Material Figure S5). We further found that whole brain task activation maps correlated with SC harmonics (**Fig. 2.6B**). The ternary plot showed that tasks also had differential participation in all three harmonic regimes (**Fig. 2.6D**). For example, Prediction and Learning was mostly integrative, while Inhibition was mostly degenerate, and Emotion was mostly segregative. However, most cognitive tasks involved a balance of the three regimes, such as Language and Decision Making, having approximately 50% integrative, and between 20-30% degenerate and segregative.

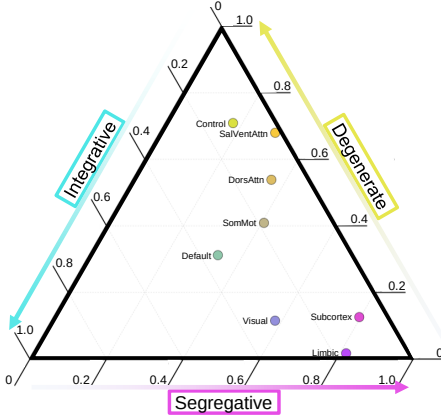
A. Resting Network Participation



B. Task Meta-Analysis Participation



C. RSN regime participation



D. Task regime participation

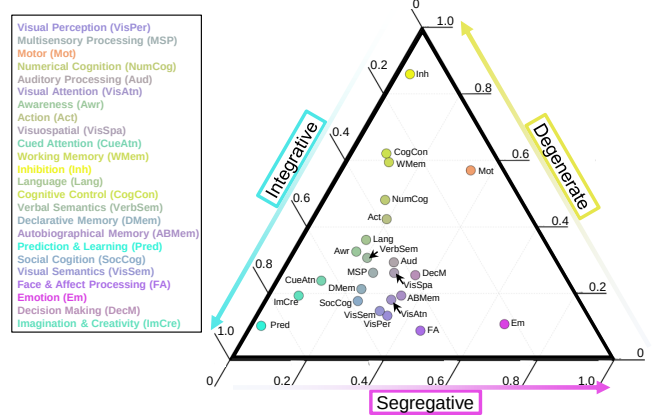


Figure 2.6: RSN and Neurosynth Coupling. We evaluated which harmonics had spatial organization that coupled with (A) resting-state functional networks (RSNs) and (B) Neurosynth task activation maps. All harmonics show spatial patterns that aligned with known functional organization. Below (C & D), we show ternary plots representing the above heat-maps as relative mixtures of each regime's participation in (C) RSNs and (D) Neurosynth task activation networks. Note that the vertices of a ternary plot represent full participation in the respective regime, and the axis ticks are slanted to indicate the direction of the axis along dashed lines. Note that the DMN, for example, is nearly at the center of the RSN ternary plot, meaning it has close to equal participation from all three regimes. Conversely, the Limbic network showed almost exclusive participation in the segregative regime. The bubbles inside the ternary plot are colored based on their proximity to each of the three vertices (cyan–integrative; yellow–degenerate; magenta–segregative).

2.3.7 Harmonic projection resting-state activity is different across regimes

Having found a relationship between harmonic regimes and known functional organizations, we hypothesized that empirical resting-state activity would also show similar regime-specific differences and relative regime contributions. We evaluated the functional characteristics of the three regimes in resting-state fMRI data projected onto the harmonic power vectors (**Fig. 2.7 A**).

We quantified three key properties of the functional projection: projection energy, temporal diversity, and spatial diversity. The regime projection energy (L2-norm squared across time) gradually decreases from low to high harmonics with no clear demarcation between regimes (**Fig. 2.7 B**). The blue triangle indicates the previously reported divide between coupled/decoupled harmonics based on the reported eigenvalue [158]; this showed that the previously identified “decoupled” regime is partially within our integrative regime and entirely within the degenerate and segregative regimes. Quantifying the spatial energy distribution across brain regions showed that integrative harmonics had a broad energy distribution across the cortex, with energy peaks located in sensory cortices; degenerate harmonics had energy weighted highest in frontoparietal and inferior temporal lobes; and segregative harmonics had sparse energy, with clusters of high energy in sensory regions, temporal poles, and ventromedial/orbitofrontal cortices (**Fig. 2.7 C**). Overall, each regime had significantly different energies, with integrative having the most, segregative having the least, and degenerate in-between (all $p \ll 0.001$; **Fig. 2.7 D**).

We next analyzed temporal diversity (sample entropy) and spatial diversity (harmonic entropy) across regimes. The average temporal diversity contained in each harmonic regime projection showed that the segregative harmonics contained the most temporal diversity compared to either integrative or degenerate regimes ($p < 0.005$; **Fig. 2.7 E**). Degenerate harmonics also had significantly more temporal diversity compared to integrative harmonics ($p < 0.05$). Regimes also showed significantly different harmonic (spatial) diversity, with the degenerate regime having the most diversity, followed by the integrative regime, and least in the segregative regime (all $p \ll 0.001$; **Fig. 2.7 F**).

Finally, we analyzed dynamics in the relative participation between regimes. We found that

resting-state function across subjects had a strong tendency to be around approximately 46.5% integrative, 33.6% degenerate, and 19.9% segregative (**Fig. 2.7 G**). With principal component analysis, we found that the degenerate regime formed the principle axis of temporal variation (**Fig. 2.7 G inset**).

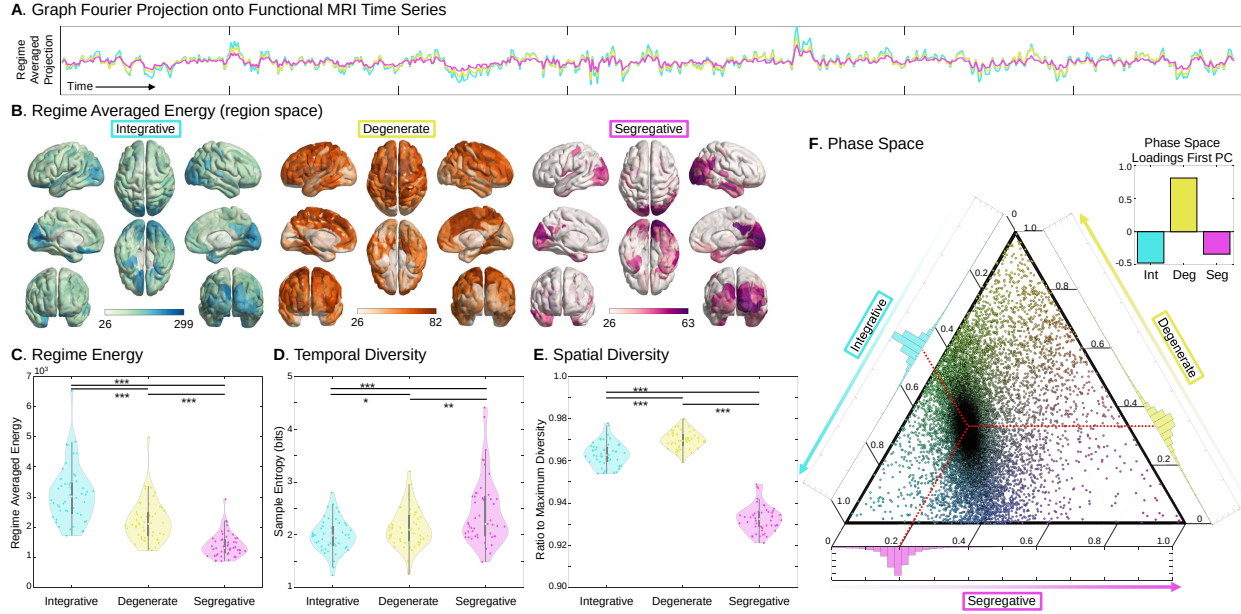


Figure 2.7: fMRI Projection. (A) We project the the resting-state functional MRI time series onto the harmonic power vectors and show the regime-averaged projection for a single subject. (B) The projection energy (L2-norm across time) across all SC harmonics. The blue triangle indicates the previously reported divide between coupled/decoupled harmonics [158]. (C) The projection energy is mapped back to region space, showing region-wise resting-state functional participation in each regime. (D) Quantifying the regime-wise projection energy showed that the integrative harmonics have the most energy per harmonic, followed by the degenerate harmonics, and least for the segregative harmonics. (E) Quantifying the harmonic signal’s temporal diversity (i.e., sample entropy) showed the opposite pattern, with segregative harmonics carrying the most bits per harmonic, followed by degenerate and integrative regimes. (F) Quantifying the harmonic diversity of each regime in the functional time series showed that many degenerate harmonics are co-active, while integrative and segregative harmonics are more specific in time. (G) With a ternary plot, we show that the brain spends most of its time in a state of 46.5% integration, 33.6% degenerate, and 19.9% segregation. The upper-right inset shows the first principal component of this distribution, indicating that most functional variation is along the degenerate axis.

2.4 Discussion

In this work, we have shown that an integration-segregation continuum in SC can be identified through its graph Laplacian harmonics and a novel feature we call the “gap-spectrum.” The gap-spectrum represents a fundamental feature of SC that naturally divides harmonics into three

regimes: integrative, degenerate and segregative. This harmonic trichotomy reveals distinct regime-specific roles for inter-subject agreement, stability of harmonics, and functional relevance. As we discuss below, this proposed integration-segregation continuum subsumes, refines, and expands upon prior work on SC harmonics and integration/segregation in brain networks, therefore unifying these previously disparate areas of network neuroscience research.

Research on the brain’s graph Laplacian harmonics is a recent but actively growing area of computational network neuroscience [121]. Brain harmonics research encourages a conceptual transformation from thinking of the brain in terms of individual regions to spatially distributed patterns of structural connectivity. Indeed, this transformation has fundamental mathematical relationships to the Fourier transform [37], and this motivates further borrowing intuitions from Fourier theory, such considering SC Laplacian eigenvalues as “spatial frequencies” [121, 6, 130]. These high eigenvalue harmonics represent bipartite-like subnetworks [42, 14, 105], which could be interpreted as a form of “high frequency” network oscillation. While these intuitions are well-motivated, our results suggest that not all Fourier intuitions perfectly apply to brain networks. Notably, we show that higher “frequency” eigenvalues don’t necessarily correspond to higher spatial frequencies, but are instead smooth across large parts of the brain except for in small, localized clusters, suggesting they are “segregative” in nature. Fourier intuitions may also suppose that these higher harmonics are noisy, yet we have found that segregative harmonics are both preserved across subjects and stable to perturbation, with both of these properties showing a relationship with the gap-spectrum. Critically, we replicated our spatial frequency and inter-subject agreement results in a separate independent dataset of 220 subjects with more diverse age demographics, imaged with different scanning parameters, processed with a different connectivity pipeline, and parceled in a different atlas, all of which strongly suggests that our findings have strong generalizability. Together, this emphasizes the need for future work to carefully evaluate the extent to which intuitions from Fourier theory apply to brain harmonics.

Despite some departures from conventional Fourier wisdom, this “graph Fourier transform” still mathematically represents how signals would propagate through a network, therefore offering

a promising way to bridge our understanding of the brain’s structure and function. In general, past work has implemented two different approaches with Laplacian harmonics to understand the brain’s function. One approach emphasizes only the lowest eigenvalue harmonics [2, 134, 6, 171]. This can be motivated for a variety of reasons such as parsimony [18], the amount of explained variance [134, 6], or as the outcome of a model [2]. However, our present work suggests that much can be gained from analyzing all harmonics, since the brain’s function across many representations—RSNs, tasks, and empirical resting-state activity—can be understood as a balance of integrative, degenerate, and segregative regimes. Interestingly, no functional networks were exclusively integrative, and the only functional network to show a near-perfect balance of the three regimes was the DMN. We speculate that this could be related to the DMN’s position at the top of the functional hierarchy [134], thereby allowing the DMN to facilitate state transitions between regimes. RSNs and tasks generally emphasize certain harmonic regimes more than others—functions related to sensation, sociality, and memory were balanced between integrative and segregative harmonics, while degenerate harmonics were related to complex “top-down” cognition, such as attention, inhibition, and working memory.

A second approach divides all SC harmonics into two categories based on their participation in resting-state fMRI time series (i.e., the equal energy split criterion) [158]. This framework identifies the lowest frequency harmonics as “coupled” and all higher harmonics as “decoupled” from function [158, 121, 94]. The coupled and decoupled components of the functional signal are commonly synthesized into a single metric known as the Structural-Decoupling Index (SDI) [158], which divides a given region’s decoupled participation by its coupled participation. SDI has proven useful, demonstrating relationships with the mechanics of cognition and behavior [158, 129, 21, 239] and could serve as a bio-marker of development [57, 145] and disease [234, 242]. Our results affirm the success of the coupling versus decoupling work while additionally suggesting a further refinement into the integrative, degenerate, and segregative trichotomy. From this new perspective, the SDI would be a measure of how much of function across the brain is weighted into degenerate and segregative harmonics versus integrative harmonics, with the effects likely driven

by the degenerate harmonics since they occupy a significant majority of the decoupled modes. Since the degenerate harmonics are also the most subject specific, SDI could be considered a metric of subject-uniqueness in function, since it is effectively normalizing by the integrative harmonics, which are most preserved across subjects. However, we emphasize that in our proposed framework *all* harmonics “couple” with function in diverse ways related to the harmonic regime. A limitation of the coupling/decoupling approach is that harmonic classification depends on their interaction with brain function rather than on an inherent feature of SC, meaning that their functional relevance is partially entangled with their classification. By defining harmonics based on the gap-spectrum inherent to SC, we can study properties of harmonics and their functional relevance independent of their classification.

Other research on the brain’s structure-function relationship seeks to explain how the structural network facilitates integration and segregation through the lens of graph metrics. The brain’s integration is interpreted as efficient signal transmission combined with signal convergence to highly connected regions, while segregation is interpreted in terms of the brain network dividing into tight-knit communities or modules with specific functions [197, 45]. However, there are two limitations with this view of integration and segregation. First, graph metrics often have an embedded (though subtle) notion of time; network efficiency, for example, measures how easily a signal can move between nodes to traverse full the network (i.e., greater efficiency implies less transmission time). Therefore, graph metrics measuring signal transmission and convergence can only account for integration in time, not in space, yet spatial integration is thought to be necessary to resolve the binding problem [140]. Second, graph metrics for integration and segregation are defined separately, and therefore, they are incommensurable to a single integration-segregation spectrum—this incommensurability is precisely the crux of the binding problem. The present work suggests an alternative view of integration and segregation as represented through graph Laplacian harmonic spectrum. These harmonics describe signal distributions in space, which resolves the first limitation, and their continuum on the eigenspectrum resolves the second limitation. Our proposed framework further reveals novel insights: integration and segregation in the human brain is similar

across subjects, stable to network changes, and is related to unimodal sensory networks. Moreover, we show that harmonic regime SC recapitulates intuitions from graph metrics measuring integration and segregation. Therefore, SC harmonics appear to subsume insights from the past frameworks while overcoming their limitations.

Using SC harmonics to define an integration-segregation spectrum also provides a natural definition for what lies between integration and segregation: the degenerate harmonics. Degenerate harmonics deviate from integration and segregation in many important ways: they are subject specific, they are sensitive to network changes, they embody the network’s small-worldness, and they relate to top-down functional networks. Degenerate harmonics have a sense of “flexibility” since they represent symmetries in the network [43], they are related to network synchronizability [124], and they can form linear combinations to produce new degenerate harmonics. This ties nicely into our finding that resting-state time series shows the greatest harmonic diversity and temporal variability in the degenerate regime, meaning that multiple degenerate harmonics are “co-active” and rapidly fluctuate on and off. This finding also aligns with recent work suggesting that FC constructed from “decoupled” harmonics are highly variable in time and may encode information in transient brain states [159]. We speculate that these functional characteristics may correspond to creating flexible linear combinations that combinatorially encoded contextual and “top-down” information. Degenerate harmonics being related to subject-specificity and frontoparietal networks also aligns with recent research on “brain fingerprinting,” which has highlighted the frontal and parietal cortices as those most related to subject uniqueness [60, 133, 216, 165, 100, 34, 33, 235, 148, 38, 116] and neural plasticity [235]. Most promisingly, Griffa et al. [81] has shown that decoupled FC (representing mostly degenerate harmonics) also contains highly unique features within frontoparietal networks useful for brain fingerprinting. Degenerate harmonics being flexible in this way also makes them an ideal substrate for neural plasticity when considering the brain’s frugal metabolic [31] and wiring cost [162] economy. These results together raise exciting possibilities for future work to use degenerate harmonics to investigate individual uniqueness and neuroplasticity.

Putting everything together, we propose that SC harmonics provide a framework to study, and perhaps help resolve, the long-standing binding problem in the philosophy of mind. In essence, the binding problem seeks to explain how the brain can bind segregated sensory channels into an integrated whole [166]. It has been shown that sensory cortices are more segregated from the rest of the brain compared to other regions [183, 184], and yet some unification of integration and segregation must be necessary to bring all senses into a single coherent precept [215]. The fundamental puzzle in the binding-problem is to find a brain mechanism that can coordinate signal flow and represent information at the global level while still leveraging regional/neuronal specializations. Such a brain mechanism should be fundamental to the brain’s structure, shared across individuals, and directly implicate sensory processing—our present work provides strong evidence that integrative and segregative SC harmonics accommodate all of these properties. It is also expected that candidate binding mechanisms should be related to states of consciousness [166]. SC harmonics again fulfill this expectation, with recent work showing that SC harmonic repertoire diversity in brain function increases while on psychedelics and decreases while sedated with propofol [130]. However, this raises a question: how do integrative and segregative harmonics interact to share information and produce this binding effect? While this question deserves careful attention in future research, we speculate that segregative harmonics may “activate” to incoming sensory stimuli, and segregative harmonics’ spatial overlap with integrative harmonics allows the signal information to spread between regimes and broadcast the newly “bound” information globally. We believe future work studying harmonics through this framework could illuminate many mechanisms of macroscopic brain function.

Of course, this work must be viewed in light of known limitations for SC harmonics. Noise, low resolution, and artifacts are common in diffusion MRI. Tractography algorithms and their associated parameters can greatly affect quality of tracts, including turning angle, stopping criteria, etc. These can have significant effects on connectome quality. Additionally, our choice of edge weights and the associated impact on the networks degree distribution may contribute to our reported results. While many prior studies have generally identified similar harmonics as shown

here [228, 121, 17], the degenerate regime may be particularly affected by these choices. Another limitation is our use of the consensus SC which was constructed from a cohort of 50 healthy young adult subjects. Future work will benefit from constructing a consensus SC with larger healthy samples, and it is presently unclear whether our findings would extend to clinical or developmental populations. With respect to our Neurosynth meta-analysis, the Neurosynth topic terms presented here were averaged across the LDA-400 list where we selected the 146 terms related to cognitive (but not illness or methodological) terms. We chose these to maximize similarity to previously published work related to SC and functional network harmonics [134, 158]. We believed that averaging correlations across many LDA terms and subjects would be more likely to eliminate findings rather than cause spurious results. Finally, we want to acknowledge an inherent tension between presenting SC harmonics as an integration-segregation continuum while also defining three discrete regimes of that continuum. The three regimes depends entirely on defining the criteria for the regimes' cut-off. We show that defining regimes based on the gap-spectrum curvature provides one way to distinguish different properties of SC harmonics, but this need not be the only effective method. Future work using Laplacian harmonics to study integration and segregation in the brain should define these regimes to fit the context of the particular scientific question being asked.

Ultimately, unifying integration and segregation into a single continuum is crucial to understanding systems-level processing in the brain. We propose a framework for this unification based on the graph Laplacian harmonics, which we show can account for an integration-segregation continuum along with a previously undefined center we term the “degenerate” harmonics. The proposed trichotomy of graph harmonics reveals previously unreported structure-function relationships in a manner that is not possible within the previous integration/segregation nor coupled/decoupled paradigms. This finding provides key biological and functional interpretations for structural brain harmonics, bringing network neuroscience closer to understanding subject-specific differences and a framework to resolve the long-standing binding problem.

2.5 Methods

2.5.1 Dataset

Data in this study come from the publicly available MICA-MICs dataset of 50 healthy young adults (23 women; mean age 29.54 years) [175]. This dataset was generated with the micapipe connectivity pipeline, and a full description of the image processing steps can be found in their articles [40, 175]. This dataset is not only of high quality, but it features cortical connectivity parcelled in the Schaefer atlas [180] at 10 different spatial resolutions (from 100 to 1000 cortical nodes), with each parcellation including an additional 6 bilateral subcortical regions and the bilateral hippocampus (14 additional nodes total). We used networks weighted by classical streamline count connectivity (hereafter “SC”) as well as the time series from resting-state functional magnetic resonance imaging (fMRI) scans (TR = 600ms, 695 time points). Most analyses were performed in MATLAB while the Neurosynth analysis was performed in Python.

Replication dataset

To ensure that our main findings were replicable, we used another dataset of SC collected with 220 healthy subjects (ages 18-75; mean(std) = 39.1 ± 16.8 ; 119 women). This replication dataset was previously used as the healthy control sample for a recent study analyzing differences in tinnitus [120]. Subjects in this replication dataset had more diverse age demographics, were imaged with different scanning parameters, were processed with a different connectivity pipeline, and were parceled in a different atlas, the Brainnetome atlas [102]. See Supplemental Material for more details.

2.5.2 Connectome harmonic analysis

For each subject’s SC, we first normalized their SC matrix to a unit Frobenius norm, then we computed the degree-normalized Laplacian:

$$\mathcal{L} = I - D^{-1/2}CD^{-1/2} \quad (2.1)$$

where I is the identity matrix, D is a diagonal degree matrix of the SC matrix (C). We then computed the eigen-decomposition of the resulting Laplacian matrix.

$$\mathcal{L} = U\Lambda U^\top \quad (2.2)$$

In (2.2), U is the orthonormal matrix of harmonics in each column and Λ is the diagonal matrix of eigenvalues associated with each harmonic. Additionally, we will henceforth use N to denote the number of regions for the SC parcellation.

Harmonic frequency analysis

Determining the precise spatial frequency of each harmonic is not straightforward since the brain’s harmonics live in the brain’s 3-dimensional space, and a 3D-FFT does not have an obvious single feature representative of the full volume’s frequency content. We instead used four measures that relate to spatial frequency and analyzed their relationship to eigenvalues. For the below measures we first apply a modest threshold ($T = \pm 0.001$) to eliminate spurious low-amplitude fluctuations around zero.

Harmonic sparsity. Harmonic sparsity is measured as the fraction of regions where the harmonic’s amplitude is zero. In classical Fourier analysis, the sparsity of all harmonics in a Fourier transform are zero (i.e., all frequencies have infinite support). Therefore, SC harmonics with high sparsity defy Fourier-based intuitions for harmonics.

Harmonic zero cross rate. We used MATLAB’s `zerocrossrate` function to measure the

rate at which the SC harmonic changes polarity (crosses zero), with high frequencies defined by a high rate of polarity switching. This measure assumes an ordering of regions such that adjacent regions are also adjacent across the harmonic’s indices. This assumption is generally appropriate, as is clear in the Regional Adjacency matrix that regions close in space are generally adjacent in the regional ordering (Supplemental Material Figure S1).

Harmonic network zero crossings. This measure of harmonic frequency was proposed by Huang et al. [93], which accounts for Laplacian harmonics being graph cuts on the network:

$$\text{Net Zero-X}(u_k) = \frac{1}{2} \sum_{i \neq j} c_{i,j} \{u_k(i)u_k(j) < 0 \mid u_k(i)^2, u_k(j)^2 > T\} \quad (2.3)$$

Descriptively, the network edges between regions with opposite signs in the harmonic are summed together, which is the graph cut weight described by the harmonic. This measure can be considered a proxy for the “frequency” of the harmonic with respect to the underlying network since higher frequencies will have less optimal (highly weighted) graph cuts. However, one known difficulty to this approach is that the areas of low harmonic amplitude fluctuate spuriously around zero, and therefore the above threshold (T) is useful to show graph cuts between regions that meaningfully participate in the harmonic. To see results across thresholds, see Supplemental Material (Figure S2).

Harmonic spatial roughness. We propose a measure for a given harmonic’s frequency that accounts for the 3-dimensional adjacency between regions. We term this measure “Spatial Roughness,” and it uses a regional adjacency matrix (A), where the entry $a_{i,j}$ is a reciprocal function of the distance between adjacent voxels in MNI space between regions i and j . Specifically,

$$a_{i,j} = \sum_k^K \frac{1}{d(i_k, j_k)} \quad (2.4)$$

In this equation, the summation is over all K voxels on the boundary between regions i and j , and $d(i_k, j_k)$ is the euclidean distance between the adjacent voxels i_k and j_k .

Our formulation for Roughness then becomes:

$$\text{Roughness}(u_i) = \|\mathcal{L}_A u_i\|_2 = \|u_i - \bar{A}u_i\|_2 \quad (2.5)$$

where $\mathcal{L}_A$ is the degree-normalized Laplacian of the regional adjacency matrix (A), u_i is the i^{th} eigenvector of the SC Laplacian, $\bar{A}$ is the degree-normalized adjacency matrix $\bar{A} = D_A^{-1/2} A D_A^{-1/2}$, and $(\|\cdot\|_2)$ is the euclidean (L2) norm of the result. The term $\|u_i - \bar{A}u_i\|_2$ captures roughness by measuring how much the harmonic signal u_i deviates from its weighted average based on the regional adjacency, effectively quantifying local signal variability. Since A is defined only within each hemisphere, we compute the Roughness separately for each hemisphere then average between them. Spatial roughness is high when adjacent regions in the brain are dissimilar in both their harmonic's signal amplitude and polarity (i.e., sign).

Harmonic matching

We computed eigenvectors for each subject's SC individually as well as for a consensus SC, which was formed by taking the average across all subject's networks, computing the normalized Laplacian (2.1), then obtaining its eigen-decomposition (2.2). We then matched each subject's eigenvectors to those of the consensus network with a bipartite matching max-flow algorithm [48] implemented in MATLAB (the `matchpairs` function). Mathematically, this function finds a permutation that maximizes the trace of $|U^T V|$, where U is the subject's eigenvectors, and V are the consensus eigenvectors. Let us define a permutation vector p such that it maximizes:

$$\max_p \sum_{i=1}^N |\langle u_{p(i)}, v_i \rangle| \quad (2.6)$$

Where $|\cdot|$ denotes an absolute value, and $u_{p(i)}$ is the column in U corresponding to the i^{th} index in the permutation p . By matching individual subjects to the consensus SC, we retain an ordering of ascending eigenvalues with respect to the consensus SC.

Note that others have recently performed eigenvector alignment using Procrustes [17]; how-

ever, we refrained from this approach to preserve as much of the subject-specific features in the harmonics as possible, since understanding the subtle harmonic variation across subjects is a key question evaluated in this work.

Inter-subject agreement

To evaluate inter-subject agreement between both unmatched and matched harmonics, we computed all possible combinations of subject-specific consensus-matched harmonic dyads ($\text{subject}_i, \text{subject}_j$) and took the absolute value of each diagonal:

$$\text{Agreement}(\text{subject}_i, \text{subject}_j) = |\text{diag}(U_{\text{subject}_i}^\top U_{\text{subject}_j})| \quad (2.7)$$

Agreement between subjects i and j is a vector in $\mathbb{R}^N$, and we computed agreement for all pairs of subjects in our dataset. Note that since these harmonics are orthonormal, subjects that share identical harmonics will have an Agreement equal to 1 for those harmonics, and fully orthogonal harmonics will have an Agreement equal to 0.

Separately from inter-subject agreement, we analyzed inter-subject variation within each region across harmonics. After matching to the consensus SC harmonics, we re-scaled subject-specific absolute-valued harmonics so that each was on the closed interval $[0, 1]$, then we took the variance across all subjects followed by the mean across all harmonics.

We replicate our primary inter-subject agreement analysis in two complementary ways. First, we replicate across parcellation resolutions with the Schaefer atlas (114-1014 parcels) in the same MICA-MICs dataset (Figure S5). Second, we replicate in an entirely separate dataset with 220 subjects processed with different MRI acquisition parameters, a different SC pipeline, and parcelled in the Brainnetome atlas with 246 regions (210 cortex plus 36 subcortex) [102] (Figure S11 & S12). This held-out dataset has been previously published here [120]. See Supplemental Material for details.

Eigenvalue gap-spectrum

In spectral graph theory, harmonic eigenvalues index different network topologies [42], and the difference (or “gap”) between ascending eigenvalues can have specific meanings—for example, the gap between the smallest and second smallest eigenvalues quantifies the network’s overall connectivity [37, 58, 196]. In general, each harmonic captures dimensions of the networks structure, and the closer two eigenvalues are to each other (i.e., the smaller their gap, the more they are degenerate), the closer the associated harmonics are to describing the same type of network configuration, i.e. network motifs [42] and symmetries [43]. More generally, the “gap” between any two eigenvalues is:

$$\text{Gap}(\lambda_i) = \min_{j \neq i} |\lambda_i - \lambda_j| \quad (2.8)$$

Spectral gaps indicate the “degeneracy” between two harmonics, where harmonics with the same eigenvalue (i.e., a gap equal to zero) are considered fully degenerate. Degenerate eigenvectors have a sense of “flexibility” since they represent symmetries in the network [43], they are related to network synchronizability [124], and they can form linear combinations to produce new degenerate eigenvectors. Here, we analyzed the SC harmonic eigenspectrum through what we’ve termed its “gap-spectrum,” which is analogous to the derivative of the ascending eigenvalues with respect to their index, and which represents a measure of harmonic degeneracy. However, because derivatives are known to amplify noise, to obtain a smooth gap-spectrum for all harmonics, we first fit an order 10 spline with 3 knots to the SC eigenvalues and then computed the first analytical spline derivative as the gap-spectrum. We hypothesized that the first-order gap-spectrum (measuring harmonic degeneracy) would be related to various properties of harmonics.

Defining harmonic regimes

We sought to define regimes of harmonics to encompass empirical group-level features across subsets of harmonics. Ideal regimes should group together integrative, degenerate, and segregative harmonics in a way that retains relationships with harmonic spatial frequency and inter-subject

agreement. Importantly, while past work has classified harmonics based on their participation in empirical functional activity [158], we sought a classification feature agnostic to brain function and instead based on a natural property of structural connectivity: the normalized Laplacian eigen-spectrum.

Since the gap-spectrum accounts for harmonic degeneracy, it becomes a natural way to classify harmonics into three regimes: those with low eigenvalues and high gap-spectrum, those with medium eigenvalues and low gap-spectrum, and those with high eigenvalues and high gap-spectrum. The simplest approach is to set a threshold on the gap-spectrum, however this choice would be somewhat arbitrary. In an attempt to impart some rigor and reproducibility, we instead sought the natural points of inflection in the gap spectrum. Specifically, we set the lower and higher bounds of the degenerate regime as the first local maximum and last local minimum in the gap-spectrum derivative (Supplemental Material Figure S9).

While it may be sufficient to classify harmonics based solely on the consensus SC eigenspectrum, we sought to ensure the classification was appropriate for all subjects by first classifying each harmonic based on the subject’s individual gap-spectrum, then we matched those subject-specific harmonics to those from the consensus SC (Equation 2.6). Therefore, for each harmonic, there was a “vote” from each subject for that harmonic’s regime classification. We defined the final “consensus regimes” based on the majority vote. We used this regime assignment for all subjects in subsequent analyses.

Stability of harmonics

We hypothesized that the stability of a harmonic to network changes would be related to the gap-spectrum. We perturbed each subject’s natural SC matrix by adding a matrix of Rician noise $R(\sigma, \nu)$ [85] with $\nu = 0$, which reduces to a Rayleigh distribution [46], and with a scale parameter σ , which is related to the distribution’s standard deviation. We chose this distribution given its

relevance to MRI imaging [85, 46]. We then define our perturbed connectivity matrix as:

$$C_\sigma = C + R(\sigma) \quad (2.9)$$

We then computed the Laplacian harmonics for each C_σ (i.e., U_σ), matched U_σ to the *same* subject's unperturbed harmonics (U) using Equation 2.6, and then computed their perturbation as:

$$P(\sigma) = |\text{diag}(U_\sigma^\top U)| \quad (2.10)$$

Thus, for each σ we obtained a measure of similarity for every harmonic across subjects. Drawing inspiration from perturbation theory and sensitivity analysis [91, 23], we can find the *stability of harmonics* as:

$$\text{Stability}(\sigma) = \frac{1}{P(\sigma)} \frac{dP(\sigma)}{d\sigma} = \frac{d}{d\sigma} \ln(P(\sigma)) \quad (2.11)$$

We evaluated this stability numerically in the range $\sigma = [0, 0.002]$ and step size $d\sigma = 2.5 \times 10^{-4}$ and finding the slope between $d\sigma$ and $\ln(P(\sigma))$. We computed stability separately for each harmonic and then compared across subjects to the gap-spectrum.

Harmonic regime SC

Given our interest in how different SC features are reflected across harmonics, we sought to analyze the graph theoretical properties of a low-rank network reconstruction of SC from a limited subset of harmonics. We hypothesized that different subsets of harmonics would embody different graph theoretical properties conventionally related to integration and segregation.

To accomplish this, consider the spectral decomposition of the graph Laplacian (2.2). To reconstitute a low-rank structural connectivity matrix, we first compute the following truncated spectral decomposition:

$$\tilde{\mathcal{L}} = \sum_{i=j}^k \lambda_i u_i u_i^\top \quad (2.12)$$

Where the interval $[j, k]$ is a subset of harmonics. Then reconstituting the underlying low-rank SC

becomes:

$$\tilde{C} = D^{1/2}(\tilde{D} - \tilde{\mathcal{L}})D^{1/2} \quad (2.13)$$

Where here D is the original diagonal degree matrix of C , and $\tilde{D} = \text{diag}(\tilde{\mathcal{L}})$. However, since the spectral summation is truncated, there will be negative weights in $\tilde{C}$ reflecting the connections that were excluded from the truncation; therefore, we threshold all $\tilde{C} < 0$ to be zero. We also provide a more detailed derivation of $\tilde{C}$ in the Supplemental Material.

To analyze the integrative and segregative properties of $\tilde{C}$ for different subsets of harmonics, we used functions implemented in the Brain Connectivity Toolbox [176] to compute the following graph theoretic measures for weighted undirected networks: efficiency, small worldness, modularity, and coreness. We use the small worldness measure [12], which is defined as:

$$\text{SmallWorldness} = \left(\frac{\chi}{\chi_r} \right) / \left(\frac{L}{L_r} \right) \quad (2.14)$$

In this equation, χ is the network's clustering coefficient, L is the network's characteristic path length, and χ_r and L_r are the clustering coefficient and characteristic path length for a randomized network, respectively. To produce randomized networks, we used the Brain Connectivity Toolbox (`null_model_und_sign`). Efficiency and small worldness capture more integrative network topologies while modularity and coreness capture segregative network topologies[45]. To analyze these network properties across regimes, we normalize each $\tilde{C}$ to give it a unit Frobenius norm, $\|\tilde{C}\|_F = 1$.

2.5.3 SC harmonics' participation in function

To investigate how harmonics are related to the brain's function, we define harmonic participation by how known functional resting-state networks, meta-analytic task networks, and empirical resting-state time series align with each harmonic's power, defined as:

$$\bar{u}_i = \frac{u_i^2}{\|u_i^2\|_2} \quad (2.15)$$

Here, the $||\cdot||_2$ denotes the L2-norm. We then concatenate these vectors into the columns of a matrix $\bar{U}$.

We use $\bar{U}$ to analyze the spatial *power* distributions of harmonics (in analogy to the “Born rule” [117]), and we analyze this “harmonic power” relationship to brain function. In other words, we ignore harmonic polarity (i.e., sign) and instead analyze how the harmonic’s power relates to 1) resting-state networks, 2) meta-analytic task networks, and 3) empirical resting-state time series. We describe each of these three functional analyses below.

Alignment with resting-state Networks

Using the Schaefer atlas, each node in the network was labeled according to the 7 canonical resting-state networks [236], with an additional label for the 14 subcortical regions (which we’ll consider analogously to the other RSNs for this analysis). To evaluate harmonic participation with RSNs, we first created a binary matrix Q with rows equal to the number of network nodes and eight columns (one row for each RSN). For each entry in Q , $q_{i,j} = 1$ if node i belongs to RSN j , and $q_{i,j} = 0$ otherwise. We then computed RSN participation matrix for each subject’s matched harmonics ($\bar{U}$) as

$$\text{RSN Participation} = \bar{U}^\top Q. \quad (2.16)$$

We are most interested in the relative participation between various RSNs, so we row-normalize the RSN Participation matrix by the maximum value in each RSN. For the participation without row-normalization, see Supplemental Material (Figure S3).

Alignment with meta-analytic task networks

To evaluate the correlation between SC harmonics with meta-analysis task activation maps, we exported the power harmonics ($\bar{U}$) from the 214 node network for each subject into NIFTI files in MNI space. We then used the `NiMARE` toolbox in Python to compute the correlation between the eigenvectors and Neurosynth task activation maps for 146 Latent Dirichlet Allocation (LDA) topics drawn from the LDA-400 set (Neurosynth version-7). We included topics related to cog-

nitive processes while we excluded topics related to methodology or clinical conditions. We then averaged subsets of the 146 topic terms to obtain 24 separate cognitive domains similar to those applied in previous meta-analysis studies using Neurosynth [134, 158]. (For a full list of LDA terms and their cognitive domain assignments, see Supplemental Material.)

Harmonic participation in resting-state fMRI time series

Finally, we analyzed the properties of harmonic power vectors in empirical resting-state fMRI time series. This projection follows a similar procedure as previous works [141, 158, 6, 130], but we instead use the power harmonics ($\bar{U}$, Equation 2.15). Given a time series ($s(t) \in \mathbb{R}^N$), we define the projection:

$$\hat{s}(t) = \bar{U}^\top s(t). \quad (2.17)$$

We refer to this as a projection “onto the harmonic power vectors.” Note that if we used U instead of $\bar{U}$ this equation would be a graph Fourier transform. To study the functional properties of the projected signals, we analyzed the signal’s energy, temporal diversity (sample entropy), spatial entropy (harmonic diversity), and temporal dynamics.

The energy of a signal ($\hat{s}_i(t)$) is defined as the L2-norm squared across time, which by Parseval’s theorem is equivalent to the integral of the signal’s spectral density [153]. We computed the energy for each time series projection signal ($\hat{s}_i$) to compare across harmonic regimes. We further assessed the regional distribution of harmonic energy by projecting the energy back into the region space.

We used a measure of temporal entropy, known as Sample Entropy (SampEn, [168, 169]), which measures the self-similarity of signal sub-sequences across time. Intuitively, this measures the signal’s temporal diversity. We used the MATLAB function `sampen` to compute the signal’s sample entropy [139]. Sample entropy requires defining a scale parameter m and a similarity tolerance parameter r . For biological signals, it has been suggested that $r = 0.2$ [169], which we have followed here. There is no standard for choosing m , but larger m accounts for more dynamics in the data, and it is recommended to be chosen to match the dynamic timescale of interest in the

signal. Accordingly, we chose $m = 5$ which corresponds to 5 TRs (i.e., 3-seconds) in the signal. Each harmonic time series $\hat{s}_i$ has one value of sample entropy, and we averaged sample entropy across regimes to evaluate whether regimes differ in their temporal diversity.

Following the measure of repertoire diversity introduced in [130], we defined a similar measure we call “harmonic diversity” for the projected time series:

$$H(t) = - \sum_i^n \frac{\hat{s}_i(t)}{\sum_i \hat{s}_i(t)} \log \left(\frac{\hat{s}_i(t)}{\sum_i \hat{s}_i(t)} \right) \quad (2.18)$$

Since this measure is influenced by the number of harmonics in a given regime, we normalized by the maximum possible diversity for each regime $\log(n)$, where n is the number of harmonics in the regime. We compute this measure of harmonic diversity within each regime, then average across time to compare across regimes.

Finally, we analyzed the dynamics of harmonics by analyzing the relative signal strength of each harmonic regime, which can be visualized in a ternary plot. We analyzed these dynamics by the mean relative contribution of each regime as well as by analyzing the first principle component to show the main axis of dynamic fluctuation.

Ternary plot analysis

Since we used the gap-spectrum to identify three regimes of harmonics, we interpreted some of the above analyses using ternary plots. Ternary plots are a visualization technique to show the relative contributions of three different phenomena in a mixture [87]. We generate ternary plots in MATLAB using the code provided here [132]. As such, the values displayed in a ternary plot are relative “quantities,” and therefore each point represents a coordinate along three dimensions that sum to 1. In our work, the quantity is the amount of participation in each of our three harmonic regimes. Importantly, the ticks on the axes of a ternary plot show the direction of the axes through the plot. We have included labels for each axis in our plots to indicate which axis corresponds to which harmonic regime, and we color data inside the ternary plot according to how close each datum is to

a mono-regime vertex. To limit the influence of spurious correlations in this analysis, we applied an 80th percentile thresholded (across all subjects) to both the RSN participation strength and Neurosynth correlations, we then averaged across subjects to obtain group-level harmonic participation maps for the RSNs and Neurosynth.

2.5.4 Statistics and reproducibility

In this study, we used three types of statistical tests: Pearson’s correlation, Analysis of Variance (ANOVA), and two-sided t-tests. For comparing harmonic properties with the gap-spectrum, we used a Pearson’s correlation and show the distribution in scatter plots with trend lines. When we compared the gap-spectrum with harmonic properties in **Fig. 2.3B**, we correlated the median value from across 50-subjects to the gap-spectrum, with the number of data-points in the correlation equal to the number of harmonics in the regime. All R-values for correlations are shown as figure insets. When we compared the stability of harmonics to the gap spectrum, we computed the Pearson’s correlation for each subject’s individual stability values compared to the gap-spectrum, which has a sample equal to the number of harmonics ($n=214$). In **Fig. 2.4C**, we show the distribution of R-values from that analysis as an inset, and a single scatter plot aggregating all values together as the main visualization. In the analyses where we compared across regimes, we first conducted a 1-way ANOVA to ensure group-level differences, then we used two-sided t-tests to determine the between-group significance. These analyses compared the full sample of 50 subjects represented by the indicated measures from different regimes. In the Supplemental Material, we show some additional statistical tests that verify the significance of the matching, in which we show the significance level as $-\log(p)$ as well as the Bonferroni-corrected significance level as a red line in the Manhattan plot. The original data and MATLAB code is provided for all primary analyses (<https://github.com/Raj-Lab-UCSF/IntDegSeg>), ensuring the complete reproducibility of our results.

2.6 Supplemental Material

2.6.1 Supplemental Section 1: Results Replication Analysis

Two of the principal findings in this work are: 1) that harmonics do not strictly correspond to spatial frequency and 2) that harmonics with low and high eigenvalues have high inter-subject agreement. To ensure that these main findings were replicable, we used another dataset of SC collected with 220 healthy subjects (ages 18 – 75; mean(std) = 39.1 ± 16.8 ; 119 women), and tested whether this dataset also showed the same relationships with harmonic spatial frequency and inter-subject agreement. This replication dataset was previously used as the healthy control sample for a recent study analyzing differences in tinnitus [120].

Our replication dataset has important differences compared to the MICA-MICs dataset:

1. The age demographics for our replication dataset are more diverse.
2. The replication dataset consisted of two different MRIs (one 3T Siemens scanner at the University of Minnesota, one 3T GE scanner at UCSF). The replication dataset followed the Human Connectome Project (HCP) protocol for structural and diffusion MRI, which is detailed elsewhere [76]. The MICA-MICs dataset does not follow the HCP protocol.
3. The SC generation pipeline was developed in-house and has systematic differences to the micapipe pipeline. The SC pipeline used for our replication dataset is described in detail here [41]. While our in-house pipeline follows many of the same steps as micapipe, perhaps the most important difference is that our pipeline is fully volumetric without mapping to the cortical surface, while micapipe requires mapping to the cortex with Freesurfer [61] before constructing connectivity. Another potentially important difference is in the streamline generation, where micapipe uses MRtrix3 [209] while our streamline generation uses DiPy [72]. Note however that both datasets used probabilistic tractography with SIFT-2 filtering.
4. The brain parcellation to define regions for SC is the Brainnetome atlas [102], which has many differences compared to the Schaefer atlas used in the MICA-MICs dataset. The

Brainnetome atlas has a total of 210 cortical regions and 36 subcortical regions, all defined volumetrically. Conversely, the micapipe pipeline Schaefer atlases have many resolution (although in the main text we focus on the 200-region parceled cortex), and it appends 14 subcortical regions defined separately from the atlas.

Despite these differences, our underlying conclusions remain unchanged: (1) SC Laplacian eigenvalues do not directly correspond to spatial frequency, with the highest eigenvalues indicating segregative harmonics (Figure S 2.8); and (2) harmonic matching shows that the integrative and segregative harmonics are well preserved across subjects while the degenerate harmonics are most subject-specific (Figure S 2.9).

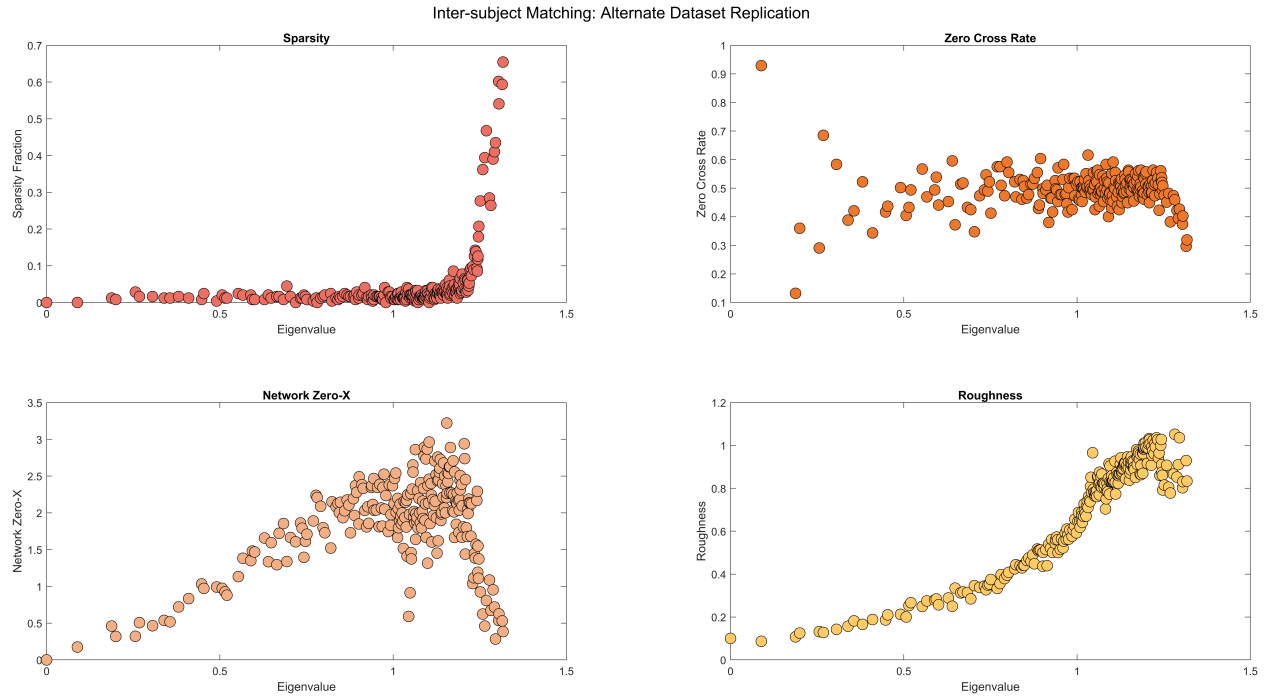


Figure 2.8: Harmonic frequency analysis of the SC consensus network generated as the mean across all 220 healthy subjects from the replication dataset.



Figure 2.9: Inter-subject agreement analysis across all 220 healthy subjects from the replication dataset.

2.6.2 Supplemental Section 2: Deriving Regime-specific (low-rank) SC

First, note that we have changed our notation from the main manuscript so that the standard Laplacian is $\mathcal{L}$ and the degree normalized Laplacian is $\check{\mathcal{L}}$, which will help clarify the following derivation.

Starting with the definition for the graph Laplacian of a network C and a diagonal matrix of network degrees D :

$$\mathcal{L} = D - C \quad (2.19)$$

The low-rank truncation of any matrix by its eigenspectrum can be given by:

$$\tilde{\mathcal{L}} = \sum_{i=j}^k \lambda_i u_i u_i^T \quad (2.20)$$

Where the interval $[j, k]$ is a subset of harmonics. Suppose we truncate the Laplacian into $M < N$ subsets (where N is the total number of network harmonics), then:

$$\mathcal{L} = \tilde{\mathcal{L}}_1 + \tilde{\mathcal{L}}_2 + \dots + \tilde{\mathcal{L}}_M \quad (2.21)$$

We'll suppose that each $\tilde{\mathcal{L}}_i$ has a Laplacian form $\tilde{\mathcal{L}}_i = \tilde{D}_i - \tilde{C}_i$, therefore:

$$\tilde{\mathcal{L}}_1 + \tilde{\mathcal{L}}_2 + \dots + \tilde{\mathcal{L}}_M = (\tilde{D}_1 - \tilde{C}_1) + (\tilde{D}_2 - \tilde{C}_2) + \dots + (\tilde{D}_M - \tilde{C}_M) \quad (2.22)$$

And then note that

$$C = \tilde{C}_1 + \tilde{C}_2 + \dots + \tilde{C}_M \quad (2.23)$$

Next, we perform the degree normalization of $\mathcal{L}$:

$$\check{\mathcal{L}} = D^{-1/2} \mathcal{L} D^{-1/2} = D^{-1/2} (\tilde{\mathcal{L}}_1 + \tilde{\mathcal{L}}_2 + \dots + \tilde{\mathcal{L}}_M) D^{-1/2} \quad (2.24)$$

And therefore

$$\check{\check{\mathcal{L}}}_i = D^{-1/2}(\check{\mathcal{L}}_i)D^{-1/2} = D^{-1/2}(\tilde{D}_i - \tilde{C}_i)D^{-1/2} = D^{-1/2}\tilde{D}_iD^{-1/2} - D^{-1/2}\tilde{C}_iD^{-1/2} \quad (2.25)$$

Recall that when we compute the low-rank degree normalized Laplacian from its harmonics, we are computing $\check{\check{\mathcal{L}}}_i$, and then $\check{\check{D}}_i = \text{diag}(\check{\check{\mathcal{L}}}_i) = D^{-1/2}\tilde{D}_iD^{-1/2}$. To find $\tilde{C}$, we must rearrange and undo the degree normalization, giving us:

$$\tilde{C}_i = D^{1/2}(\check{\check{D}}_i - \check{\check{\mathcal{L}}}_i)D^{1/2} \quad (2.26)$$

Note that $\tilde{C}_i$ now can have negative off-diagonal entries where the original C has strictly non-negative off-diagonal entries. These negative entries consist of network weights that must be canceled out in the full summation; therefore, they reflect a “negative image” of the network truncation. Our last step to recover the underlying graph representing the low-rank reconstruction is to remove all negative entries in $\tilde{C}_i$.

2.6.3 Supplemental Section 3: Supporting Figures

Regional adjacency matrix

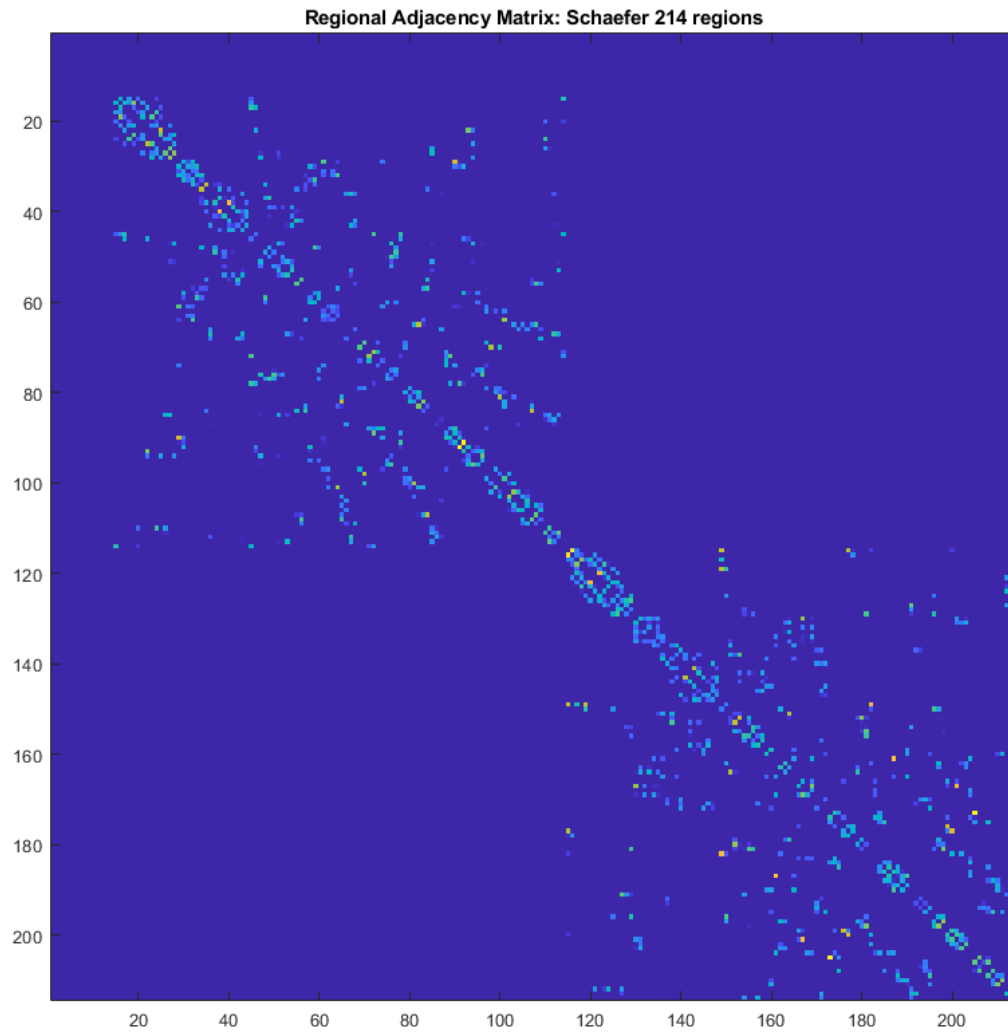


Figure 2.10: The Regional Adjacency matrix for the Schaefer 200 cortical parcellation. Entries of this matrix quantify the extent of adjacency between regions i and j . Adjacency was computed by a summation of the inverse euclidean distance between adjacent voxels. Subcortex (comprising the first 14 rows/columns) is defined to have zero adjacency.

Network zero-crossings across thresholds

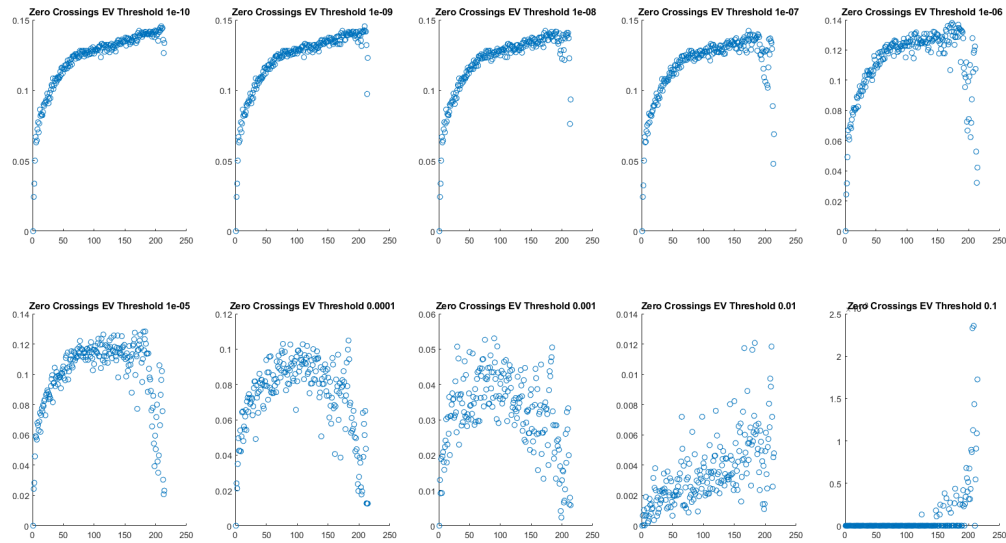


Figure 2.11: The Network Zero Crossings measure is sensitive to small fluctuations around zero (since it cares only for the sign, not magnitude, of the harmonic). For completeness, we show how this measure changes across various thresholds around zero.

Gap spectrum derivative for regime identification

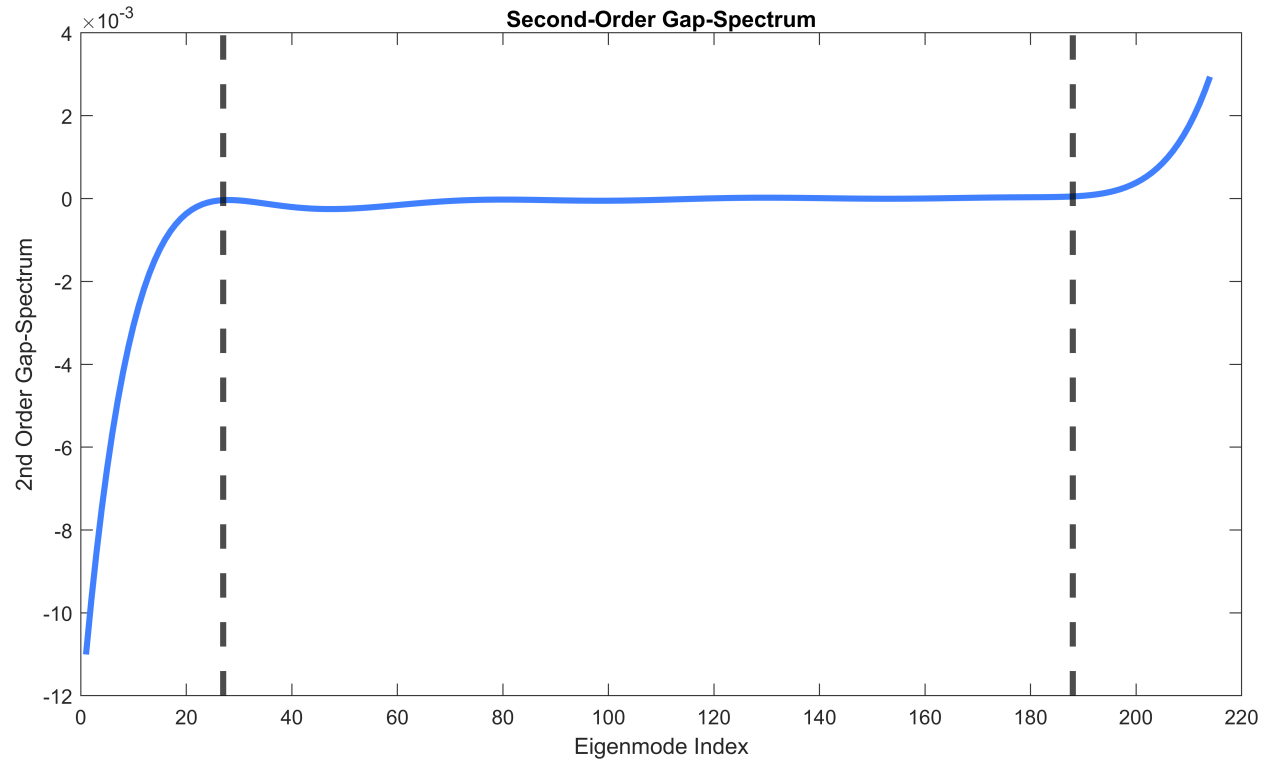


Figure 2.12: The Second-Order Gap-Spectrum, which was used to define the boundaries between the three regimes. Regime boundaries for each individual SC were identified as the first maxima (Integrative to Degenerate bound) and the last minima (Degenerate to Segregative bound). The final regime boundaries were based on the group-level boundaries after matching harmonics to the consensus SC, shown with black dashed lines.

Resting state network supplemental analysis

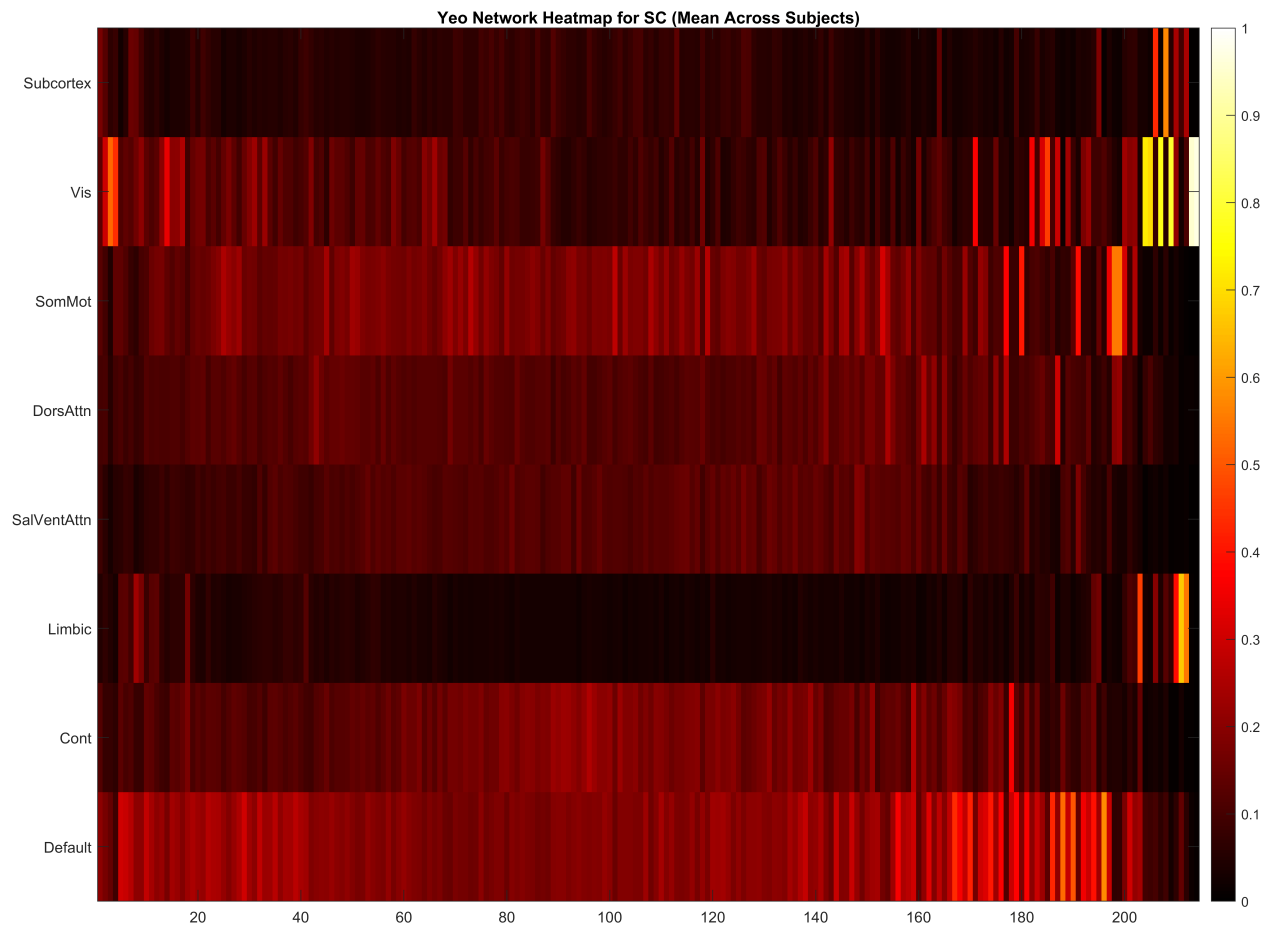


Figure 2.13: RSN participation without row-wise max-normalization.

Statistical testing of matching performance

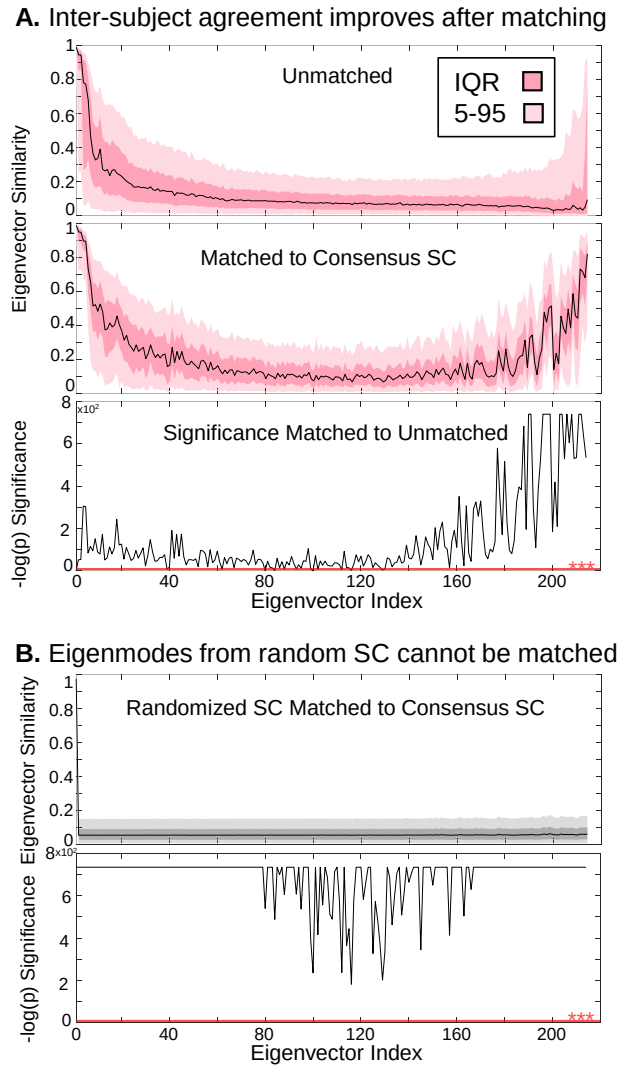


Figure 2.14: (A) Significance testing between the unmatched and matched distributions for each harmonic. The red line at the bottom of the Manhattan plot signifies the Bonferroni corrected significance threshold. All values above the red line indicate a highly significant difference between the unmatched and matched distributions. (B) Harmonics from a network with randomized edges matched to the original harmonics from the consensus SC network. The Manhattan plot beneath shows the significance between this randomized matching and the empirical matching. All subject-specific SC harmonics can match better to the consensus SC than harmonics from an edge-randomized network.

Temporal frequency supplemental analysis

Eigenmode projections onto fMRI time series have similar frequency content across the eigenspectrum

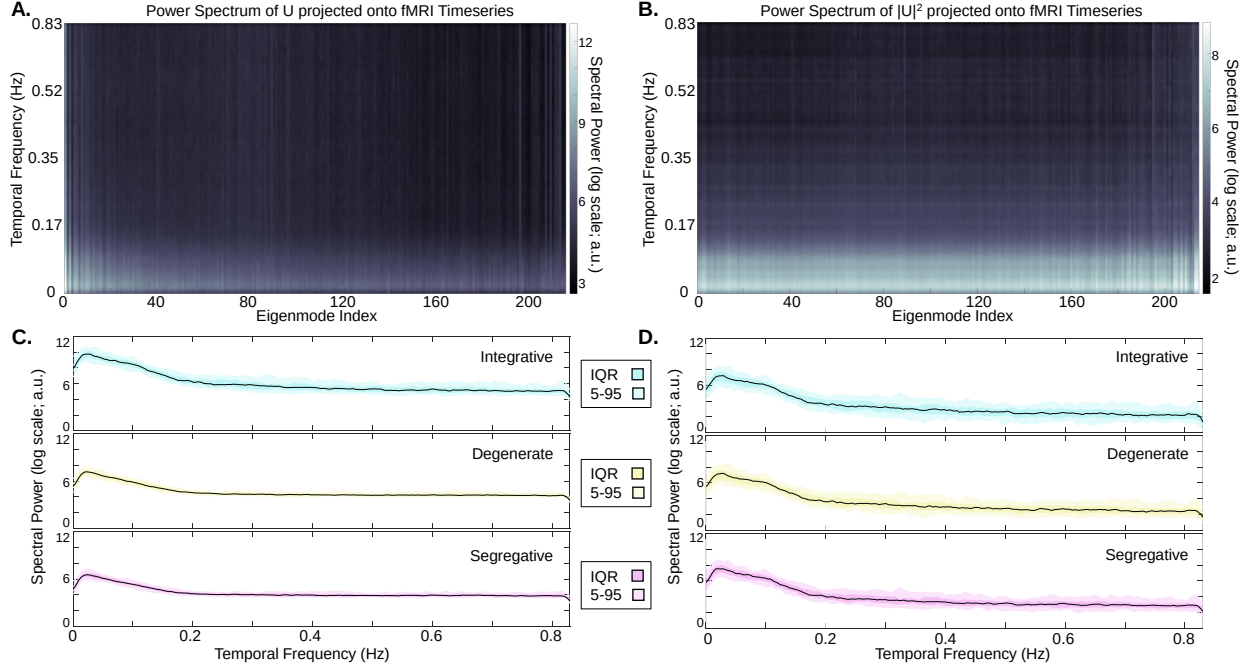


Figure 2.15: We compute measures for harmonic temporal frequency in relationship to the harmonics' participation in fMRI time series. We project the fMRI time series into the harmonic space (Graph Fourier Transform) and the harmonic power space (Equation 18 in main text). We use Welch's method to take the Fourier Transform of the resulting harmonic time series to analyze its frequency content. For completeness, we show both the spectral power for each harmonic projection using both the (A) bipolar as well as (B) power harmonic representations. (C & D) The temporal frequency characteristics are largely equivalent across all harmonics for both projections.

Inter-subject agreement across parcellation scales

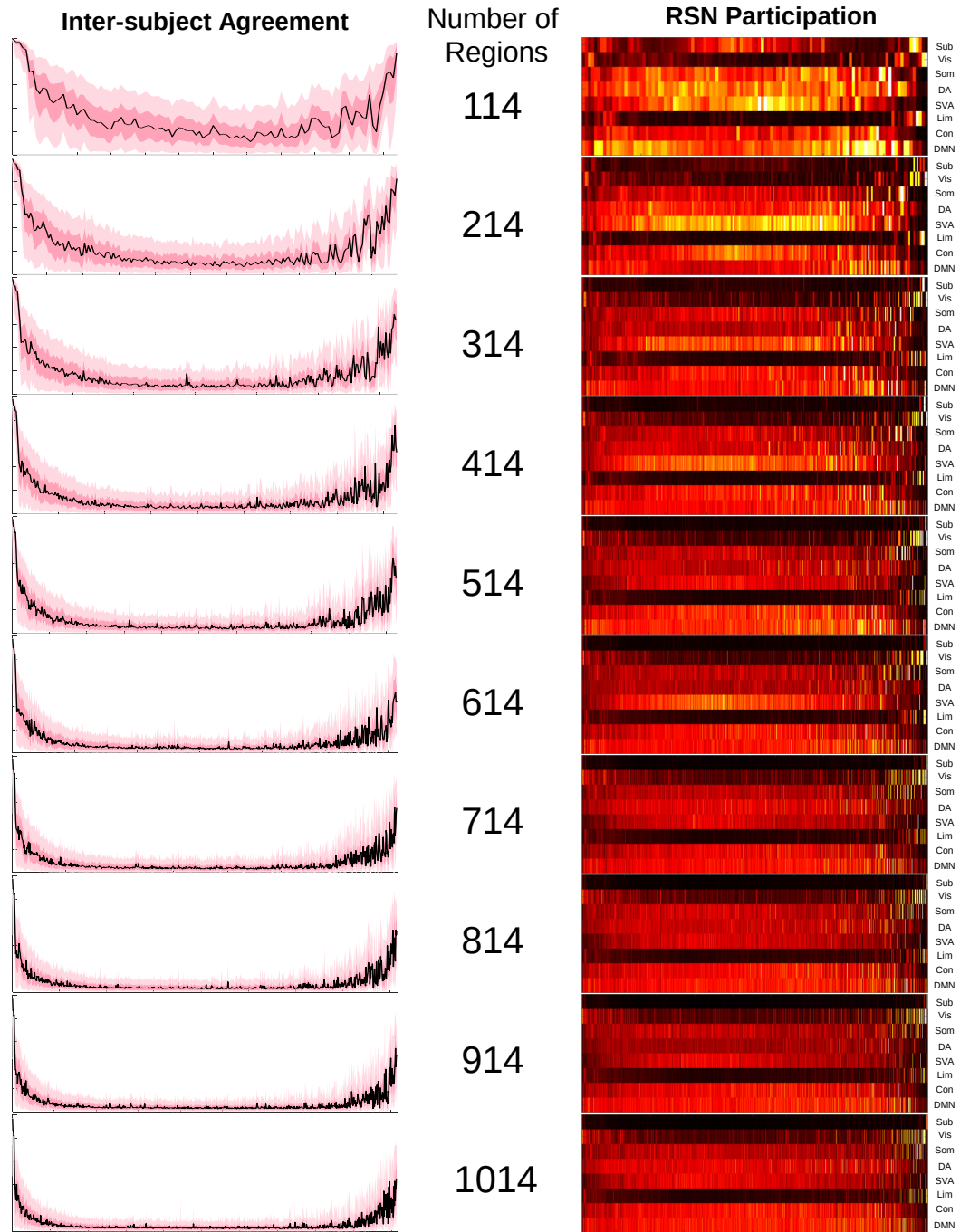


Figure 2.16: Inter-subject Agreement (left) and RSN participation (right) across all 10 Schaefer parcellation scales. General relationships at coarse parcellations qualitatively hold for fine parcellations.

Region-wise inter-subject variation

We examined which harmonics were most variable across subjects. We found that the segregative harmonics were the least variable between subjects compared to other harmonics ($p \ll 0.001$; Figure S2.17A). There was a general negative relationship between harmonic variation and mean inter-subject agreement ($r = -0.45$; $p < 0.001$; Figure S2.17A). We further found that the least harmonic variation across subjects were in the visual, somatomotor, auditory, and limbic areas (Figure S2.17B). Unexpectedly, the orbitofrontal cortex also showed low inter-subject harmonic variation. The areas with the greatest inter-subject variation were trans-modal functional network regions such as the bilateral parietal cortex and lateral prefrontal cortex (Figure S2.17B). Finally, we show the least variable Integrative and Segregative harmonics (Figure 2.17C).

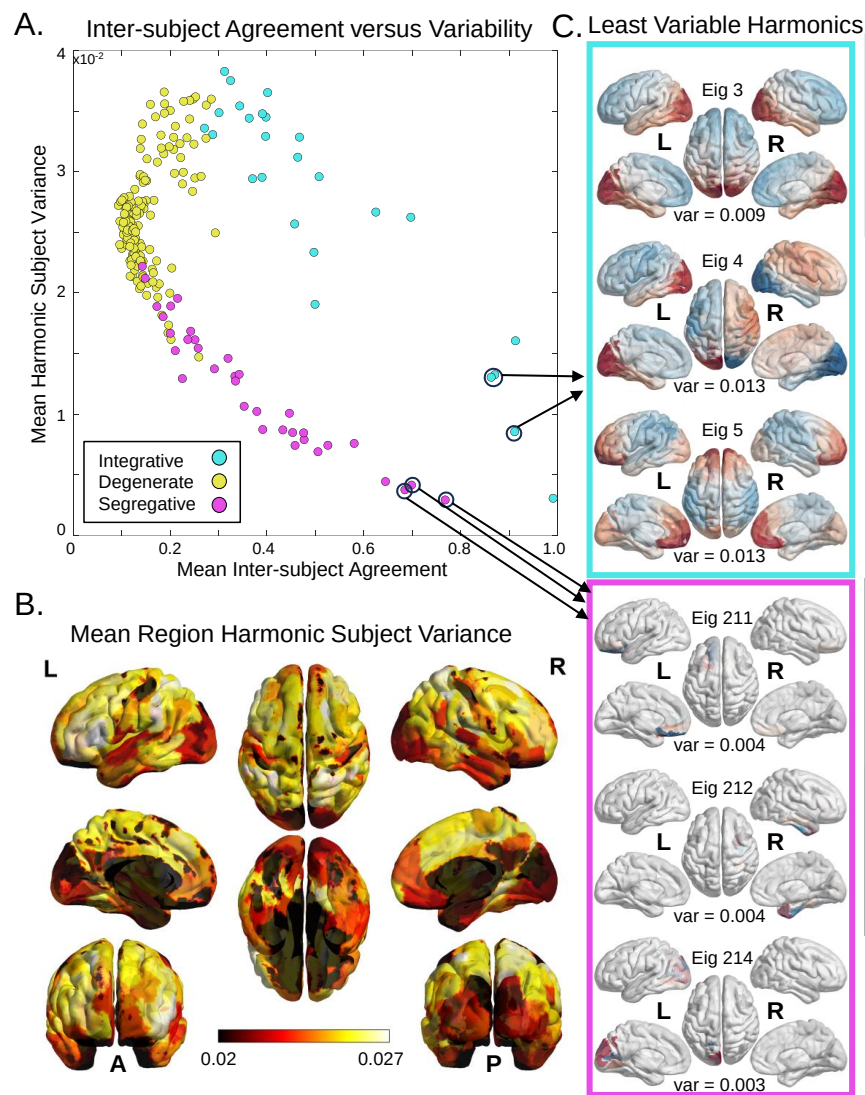


Figure 2.17: (A) The relationship between Inter-subject agreement and the variance of each harmonic across subjects. (B) Harmonic variance across subjects for each region. This shows that the sensory regions are the most similar across subjects in their harmonic representation. (C) A visualization of the least variable (i.e., most consistent) harmonics across subjects, selected from both the Integrative and Segregative regimes. (Note that the least-most variable Integrative harmonic is the trivial harmonic with eigenvalue = 0, which is not shown.)

Matching permutation distance

To further evaluate the harmonic matching, we computed the permutation length (defined as the number of column switches) for each harmonic across subjects, finding that the central harmonics required the longest permutations to match to the consensus ordering (Figure S2.18 top). We also computed the Kendall's Tau (KT) correlation, which is a measure of total permutation distance, for each subject with respect to the consensus SC (Figure S2.18 bottom), finding that overall subjects showed a matched harmonic ordering similar to the consensus SC (mean(std) KT = 0.90(0.015)).

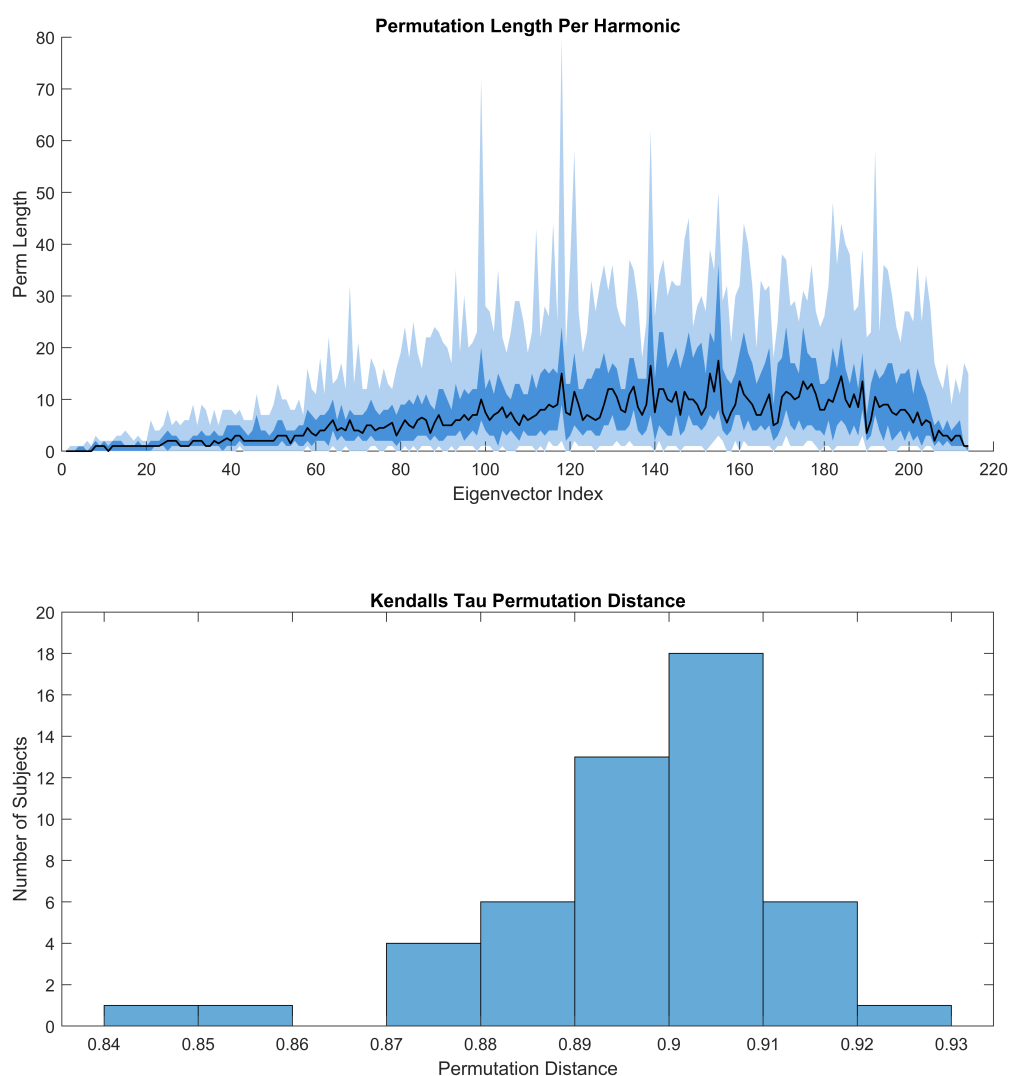


Figure 2.18: (Top) The permutation length (number of column switches) required to permute the harmonics. Darker regions denote the interquartile range (IQR) while lighter regions indicate the 5th to 95th percentile range. (Bottom) Kendall's Tau correlation between the permutation vector and an ordinal vector, which shows how far the permutation is from the consensus SC harmonic ordering.

Matching alignment with consensus

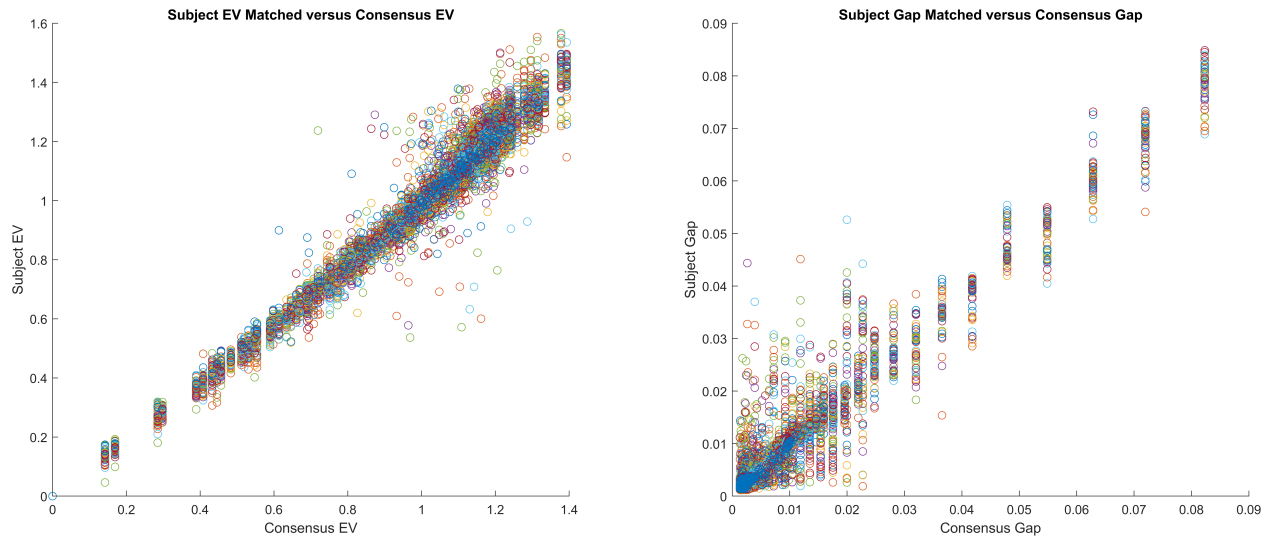


Figure 2.19: Subject-Specific eigenspectrum (left) and gap-spectrum (right) after matching compared to the consensus SC.

Chapter 3

HONeD-in on Brain Activity: Deconvolving Passive Diffusion on the Structural Network from Functional Brain Signals

3.1 Abstract

Brain regions perform distinct computations, and their signals propagate through the whole-brain white matter network. Yet, mathematical models that describe this signal propagation via *purely passive diffusion* can predict a considerable amount of the observed functional connectivity between regions. This raises a critical question: if so much functional connectivity can be explained by a *passive* process, how can we isolate the *active* process? Here, we calculate in closed-form an estimate for such an active signal in functional MRI by spatially deconvolving the effect of passive signal spread over the brain's structural connectivity using a higher-order network diffusion (HONeD) model. Across 770 Human Connectome Project subjects, we show that the resulting HONeD-innovation (HONeD-in) signal 1) sparsified functional connectivity while retaining a well-connected network, 2) restructured resting-state networks, fracturing the default mode network into two subnetworks, 3) mixed the unimodal–multimodal hierarchical organiza-

tion of networks into a circle with no clear hierarchy, and 4) sharpened the spatial profile of task-activation maps. Together, our results highlight HONeD deconvolution as a generalizable way to study resting-state and task fMRI brain signals.

3.2 Introduction

Neurons connected in a network integrate and transmit the signals they receive. When averaged over large populations, these complex nonlinear dynamics blur into macroscopic signals that are often well approximated by linear models [151]. This macroscopic signal is akin to a fluid traveling through the structural pathways between brain regions. Yet, like a fluid, we may expect that if a brain region exhibits high activity (i.e., a high ‘concentration’ of signal), then that signal should passively ‘flow’ down a concentration gradient to connected regions with less signal. This is the well-known physical process of passive diffusion. Therefore, in macroscopic brain imaging signals, we may consider two coincident types of signal movement through white matter: (1) signal moving according to *purely passive network diffusion*, and (2) signals that *cannot* be predicted by passive diffusion, which could be interpreted as *actively generated and transmitted signals*. Is it possible that our attempts to study brain activity and connectivity with macroscopic neuroimaging are in fact confounded by an ‘undercurrent’ of passive network diffusion?

The presence of such a passive diffusion-based signal in macroscopic neuroimaging has been reported in fMRI, where a significant amount of the brain’s functional connectivity (FC) can be predicted from passive diffusion along structural connectivity (SC) [1, 2]. In magnetoencephalography (MEG), related models based on network diffusion over SC are capable of predicting the brain’s frequency power spectrum [163, 222]. Related ideas appear in linear time-invariant (LTI) state-space models commonly used in network control theory, which explicitly model intrinsic linear dynamics over SC separate from external (‘exogenous’) system inputs [82–84, 109, 19]. In other signal processing contexts, such a component unexplained by the model’s intrinsic dynamics has been termed an “*innovation*” signal [144]. However, if passive network diffusion can explain

much of the macroscopic brain signal we measure, then it may be contributing substantially to canonical findings in neuroscience, including resting-state networks and task-related activations. To what extent, then, are these phenomena driven by passive diffusion rather than an active innovation signal?

The endeavor to recover these active sources of brain signal has been a long-standing pursuit in neuroscience. Early on, independent component analysis (ICA) was proposed as a method for blind source separation to recover the independent sources of brain activity [35]. ICA and other techniques, such as von Mises-Fisher clustering [236] and InfoMap [173], have been used to robustly identify whole-brain patterns of co-activation, commonly referred to as resting-state networks (RSNs), which have been treated as intrinsic network-level sources in the brain. These RSNs show remarkable stability across varying analytical techniques [181, 180] and neuroimaging modalities [36, 29, 241]. Interestingly, several studies indicate that canonical RSNs are related to and can emerge from the topology of SC itself [6, 2, 233, 192], raising the possibility that a process over SC, such as passive diffusion, lies at the heart of RSN organization. Other prior work has tried recovering innovation signals in the brain using spatio-temporal hemodynamic response function (HRF) priors (e.g., “Total Activation” [108]) or dynamical modeling with Kalman filtering [89]. Overall, the goal to recover the brain’s innovation signal is critical since our interpretations of both resting-state and task-based brain activity depend on the assumption that our neuroimaging measurements relate to what the brain is *actively* doing.

However, previous approaches to recover active innovation signals in the brain are significantly limited since they lack a physics-based model on SC. Without such a model, deriving an innovation signal is not only ill-posed, with many possible parameterizations and solutions, but also divorced from the underlying biology of white matter connectivity. What is needed is a model for passive network diffusion over SC that can be inverted in such a way that performs a *graph deconvolution*, thereby recovering the brain signals that are not blurred out by spreading over the network [55, 240, 191]. Such a graph deconvolution, grounded in the physics of passive diffusion on SC, provides a biological interpretation for the recovered innovation signal: it corresponds to a mix-

ture of computations occurring within regions and to actively transmitted signals shared between regions. A subtle but crucial point is that the recovered innovation signal can *still be constrained by the underlying SC* since the graph deconvolution *amplifies* the contribution of SC modes that *are not* related to passive signal spread governed by the physics-based model.

Here, we propose such a graph deconvolution approach using a physics-based higher-order network diffusion (HONeD) model to predict the functional MRI (fMRI) signal component attributable to passive network diffusion over SC. As we shall show below, the HONeD model fits better to empirical data, and its use prevents exponential amplification of high-frequency SC modes that arise when inverting simpler diffusion kernels. We used HONeD to deconvolve our model prediction in *closed-form* to recover the HONeD-innovation (HONeD-in) signal underlying brain activity. In the absence of ground truth, we thoroughly validate our HONeD deconvolution approach in simulation, showing that we can accurately recover $\approx 80\%$ of the original innovation signal with robustness to noise. In empirical fMRI data, we show that HONeD-in signals (1) sparsify FC and change its network topology; (2) fracture conventional RSNs into decoupled and interdigitated networks; (3) reorganize traditional RSN hierarchies in FC gradients, transforming the unimodal–multimodal divide into an organization without clear stratification; and (4) yield deblurred activation maps in task-based general linear model (GLM) analyses. These findings together suggest that dominant network phenomena in fMRI may be deeply related to the brain’s SC. HONeD deconvolution thus offers a technique to investigate brain activity in neuroimaging and ensure that our findings are not confounded by passive diffusion over structure.

3.3 Results

We start with a Linear Time-Invariant (LTI) equation $\frac{d\mathbf{x}(t)}{dt} = f(\mathcal{L}; \theta)\mathbf{x}(t) + \mathbf{z}(t)$, where the fMRI signal $\mathbf{x}(t)$ propagates via passive diffusion over the structural connectome defined by a Higher Order Network Diffusion (HONeD) model via the graph Laplacian operator $f(\mathcal{L}; \theta)$ with HONeD parameters $\theta = \{\alpha_0, \beta, \xi\}$. In closed-form, we show that we may deconvolve the effect

of passive signal diffusion over structural connectivity and recover an fMRI innovation signal as $\mathbf{z}_k = e^{-f(\mathcal{L};\theta)\Delta t}\mathbf{x}_{k+1} - \mathbf{x}_k$ (**Fig. 3.1**). Our “HONeD-innovation” (HONeD-in) signal mathematically bundles together both exogenous system input with the system actuation, thereby reflecting the most “active” component within the fMRI time course. See Methods and Materials for a thorough derivation.

Below, we first validate our HONeD-in approach in simulation, then we estimate HONeD-in signals for 770 Human Connectome Project (HCP) young adult subjects [219]. Both structural connectivity and fMRI time series were parceled into the Schaefer atlas with 500 cortical regions and an additional 14 subcortical regions [180, 157]. Model fitting performance and estimated parameters are described in Supplemental Section 2. We analyzed whether HONeD-in signals changed resting-state functional connectivity (FC) graph metrics, resting-state network structure, and FC-gradients. We conclude by assessing how HONeD-in signals changed the hemodynamic response function (HRF) and task-activation maps across six HCP fMRI tasks.

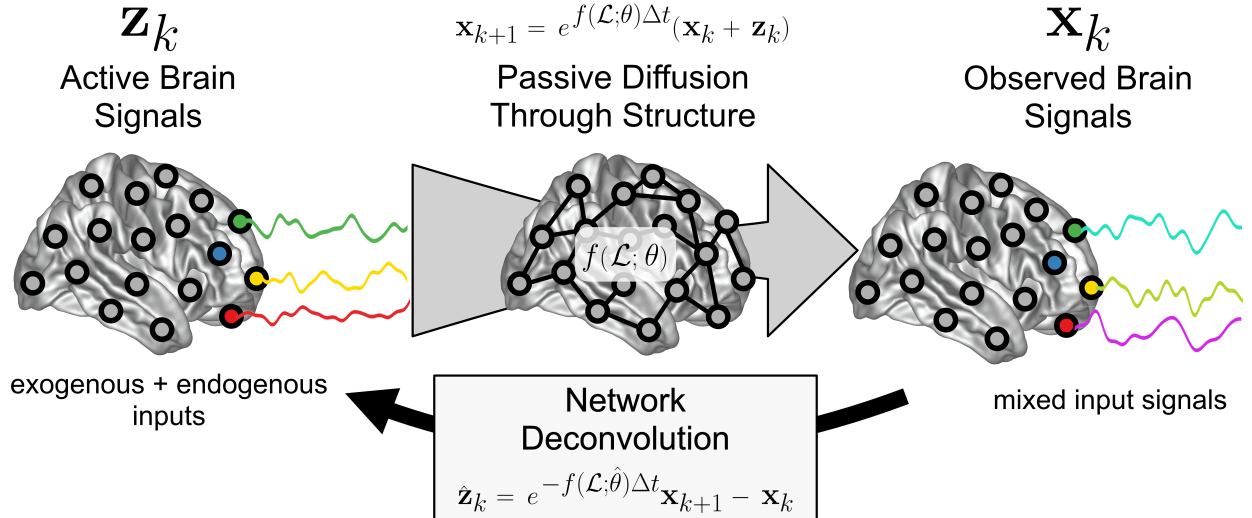


Figure 3.1: Active signals arising from exogenous and endogenous inputs mix from passive diffusion through the structural connectome (left-to-right). The goal of our approach is to model this mixing from passive diffusion with a higher order diffusion model (HONeD, $f(\mathcal{L}; \theta)$) and then deconvolve the effect from functional time series to recover an estimate for the original un-mixed signal (right-to-left).

3.3.1 Model validation

We thoroughly evaluated how well HONeD deconvolution could recover a simulated “innovation” time series and its FC after being diffused through a HONeD model (Supplemental **Fig. S3.7**). We found that under ideal conditions with subject-specific SC and no noise HONeD deconvolution recovered 78% of the original innovation time series and 89% of the FC. Using the consensus structural connectivity (SC) performed *equally well* for recovering the innovation signal, and slightly worse for FC ($\approx 88\%$). More impressively, HONeD deconvolution was highly robust to SC noise, still recovering 63% of the innovation signal and 65% of the innovation FC even when the SC edge-wise noise was double the network’s standard deviation. The degree-preserving randomization, as expected, fared worse than noise, recovering only 43% of the innovation signal and 30% of the innovation FC, emphasizing how large-scale connectivity non-trivially shapes passive diffusion-based signals. Together, these results affirm that our approach can significantly recover the majority of underlying innovation signals and FC mixed through passive diffusion over SC.

3.3.2 HONeD-in FC is a sparse connected network

After computing the HONeD-in signal, we computed its FC and compared it with “natural” FC (post-GSR) across several graph theoretical metrics. First, we found that HONeD-in FC significantly restructured the FC, increasing connections between canonical resting-state networks (RSNs) while decreasing connections within RSNs (**Fig. 3.2a & b**; edges thresholded by Bonferroni correction). We next compared the consensus FCs (shown in **Fig. 3.2a**) by their degree and edge distributions. We found that HONeD-in FC significantly *decreased* the overall degree of all nodes, and resulted in a narrower distribution with a heavier high degree tail (**Fig. 3.2c**, left). Conversely, HONeD-in FC had a significant, but subtle, *increased* edge distribution with most edges being nearly zero, and a sparse set of non-zero edges (**Fig. 3.2c**, middle). In an edge-to-edge comparison, we observe that the effect of deconvolution is to make negative edges closer to zero while acting as a soft-threshold to many high-strength edges, even converting some moderate FC connections to negative connections (**Fig. 3.2c**, right).

tween natural and HONeD-in FCs (Bonferroni corrected). In general, integrative graph metrics including rich club AUC, betweenness centrality, and clustering coefficient decreased while two segregative measures, eccentricity and characteristic path length, increased. Modularity, although typically considered a segregative measure, also decreased. All measures were also highly significantly different from both randomized networks and the noise network.¹ Overall, these results highlight how both integration and segregation is altered in HONeD-in FC, with reduced hub-based organization (lower rich club AUC and betweenness centrality), indicating less centralized information routing compared to natural FC.

3.3.3 HONeD-in FC changes resting-state networks

Since HONeD deconvolution significantly remodels FC, especially pronounced within and between RSNs, we next sought to understand the new RSN structure in HONeD-in FC.

We found empirical RSNs using the original method described by Yeo et al. [236], with von Mises-Fisher (VMF) clustering on both the natural and HONeD-in consensus (group averaged) FC and assessing the RSN organization as well as the clustering stability as also previously defined [236]. We found that 7 networks indeed offered the optimal clustering stability for both natural and HONeD-in RSNs (**Fig. 3.3d**). However, HONeD-in also had equally good stability with eight network clusters (Supplemental **Fig. S3.11**). At 7 networks, HONeD-in FC had slightly worse clustering accuracy than natural FC (Natural = 81% versus HONeD-in = 76%, $p < 10^{-36}$).

The natural FC computed from our empirical data was similar to the canonical RSN definitions, except for the Limbic network, which was temporal-lobe dominant in our clustering result (**Fig. 3.3a & b**). Meanwhile, the HONeD-in RSNs were starkly different from the canonical organization. First, the Default Mode (DMN) and Dorsal Attention (DAN) networks appear to fracture into two neighboring but distinct functional networks (**Fig. 3.3c**, DMN: Red & Pink, DAN: Light & Dark Green), both of which show remarkable similarity to previous work reporting that these

¹One exception being rich club AUC for deconvolution, which was expected due to the degree-preserving randomization.

networks decouple with highly sampled data [25]. We’ve labeled these networks DMN-A/B and DAN-A/B accordingly to align with this prior work. Next, the salience network remains intact in its core areas, however it has also expanded to invade previous somatomotor areas as well as more of the cingulate midline, dorsolateral prefrontal cortex, and both temporal poles (**Fig. 3.3c**, Purple). The control network merges with primary visual areas, suggesting the formation of a new “visual-control” network (**Fig. 3.3c**, Light Blue). The previous somatomotor network still partially resides in its canonical location, but now also includes early visual and auditory areas, transforming it into a “multi-sensory” network (**Fig. 3.3c**, Dark Blue). (For HONeD-in RSN visualizations on separate brain surfaces, see Supplemental **Fig. S3.10**). When HONeD-in FC has 8 clusters, all RSNs remain the same except for the primary visual regions along the calcarine fissure, which becomes its own 8th network (Supplemental **Fig. S3.11**).

Overall, the HONeD-in RSNs are fractured and reorganized versions of the canonical RSN structure. This significant remodeling suggests that network diffusion over structural connectivity significantly contributes to the RSN organization in fMRI. Moreover, the changes in these networks indicate that HONeD-in RSNs merge together traditional unimodal regions with multimodal regions.

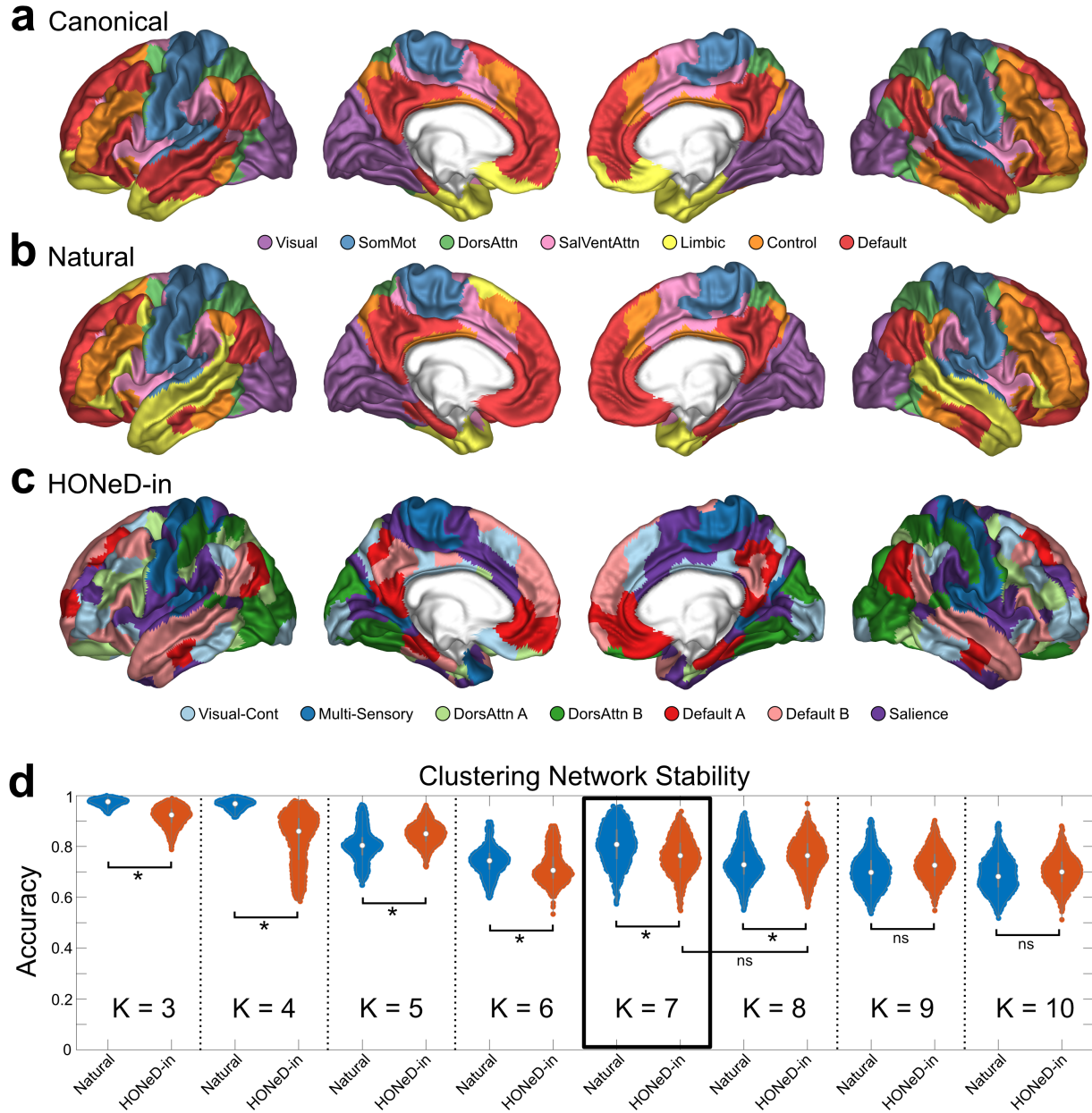


Figure 3.3: Clustering RSNs. (a) The canonical RSN definition provided by the Schaefer-500 atlas for reference, (b) the most common (mode) clustering assignment for the natural FC, and (c) the most common assignment for the HONeD-in FC. RSNs in the HONeD-in FC have a higher spatial frequency, with networks composed of semi-isolated regions from across the brain. (d) The accuracy across clustering initializations for each of the K clusters. Overall, HONeD-in RSNs are slightly but significantly less stable than natural RSNs. HONeD-in RSNs were equally stable with either 7 or 8 clusters. For RSNs plotted separately, see Supplemental **Fig. S3.10**. For the 8-network HONeD-in clustering, see Supplemental **Fig. S3.11**. (*: Bonferroni corrected significance; ns: not significant)

3.3.4 HONeD-in RSNs reorganize around new FC-gradients

Given the significant changes HONeD deconvolution imposes on RSN structure, especially the merging together of unimodal with multimodal regions, we next investigated whether these new HONeD-in RSNs had a different relationship to HONeD-in FC-gradients.

First, we assessed how HONeD deconvolution changes the FC-gradients themselves. While the natural consensus FC perfectly reproduces the original FC-gradients, the HONeD-in consensus FC gradients are restructured (**Fig. 3.4a**). These HONeD-in gradients appear to have high spatial frequency and are distributed throughout the brain with the first gradient qualitatively separating the DMN from Salience regions. Interestingly, HONeD-in gradient 2 has some similarity to the natural gradient 1, except regions are more heterogeneous in the HONeD-in gradient 2 and visual regions decouple.

To better understand FC-gradient relationships to RSNs, we plotted each brain region in the two-dimensional space spanned by the first two FC-gradients, and colored each region by its assigned RSN. The natural FC, as expected, reproduces the triangular hierarchy from previous work [134], with the DMN at one extreme of the first FC-gradient, and the visual and somatomotor networks on the other points of a triangle (**Fig. 3.4b left**). Strikingly, HONeD-in FC-gradients reorganized RSNs approximately around a circle, thus appearing to deconstruct the previous unimodal–multimodal RSN hierarchy (**Fig. 3.4b right**). Within the subspace defined by HONeD-in gradients, the DMN networks sit opposed to the Salience network, and the DAN and Multi-Sensory networks sit opposed to the Visual-Control network. Together, these results provide a second line of evidence that the previously-understood hierarchy of RSNs may arise from signal diffusion through the structural connectome, and deconvolving this diffusion dismantles the prior RSN stratification.

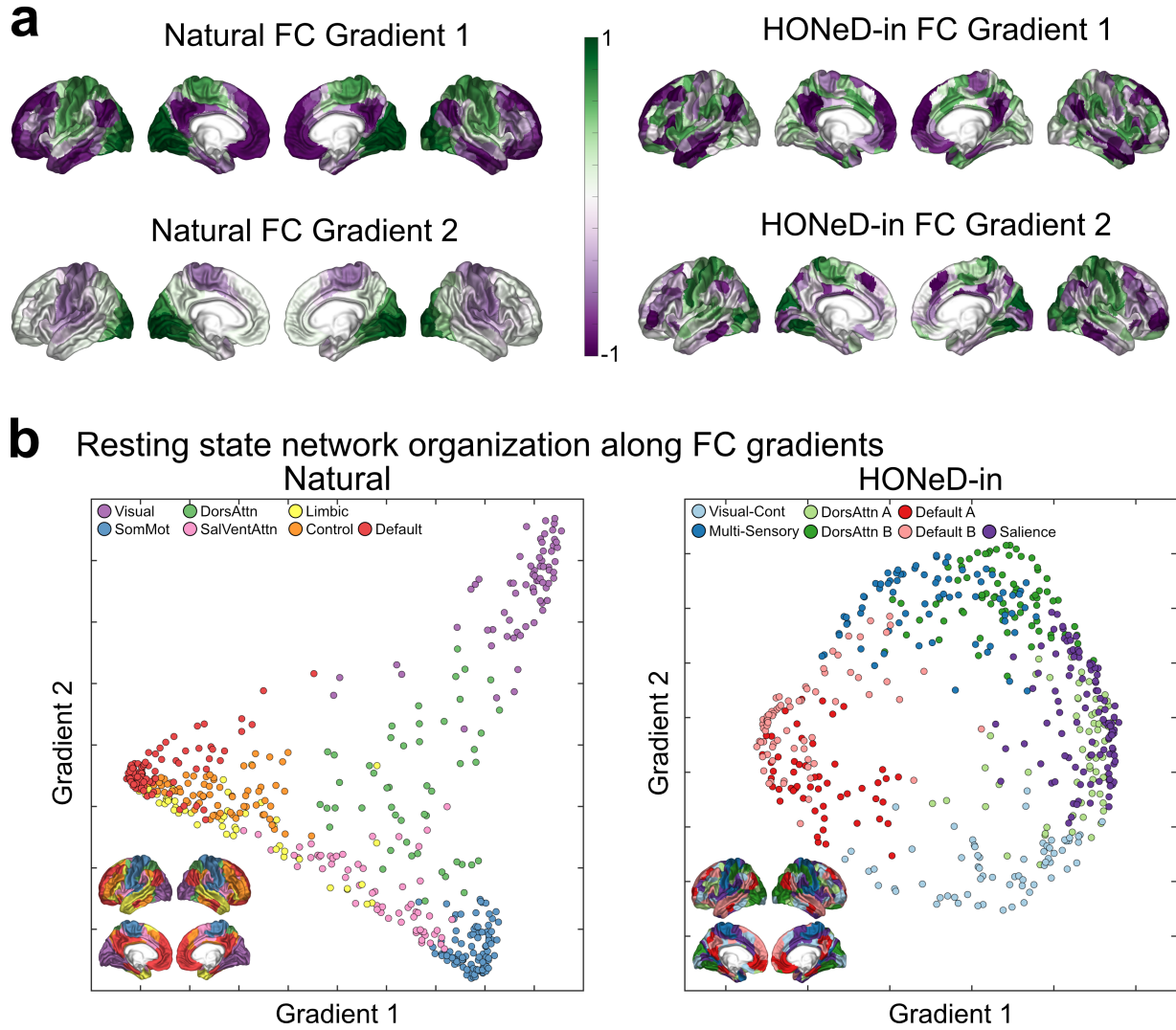


Figure 3.4: (a) The FC-gradients from natural (left) and HONeD-in (right) signals. (b) RSNs mapped onto FC-gradients derived from the natural FC (left) and HONeD-in FC (right). While the natural FC-gradients place RSNs within a hierarchy organized by a triangle, the HONeD-in FC-gradients instead map RSNs around a circle. The RSN insets are reproduced from **Fig. 3.3** for reference.

3.3.5 HONeD-in deblurs regional task activity

We first assessed whether HONeD-in signals had a different hemodynamic response function (HRF) compared to natural signals. We indeed found that the HONeD-in HRF had a stronger peak and earlier decay compared to the natural HRF, but the time to peak was unchanged (Supplemental **Fig. S3.12**). In the following GLM analyses, we used each signal’s respective HRF set.

We expected that HONeD deconvolution could be useful in increasing the activity of task-related regions while reducing the strength of signal in task-unrelated regions. However, since much of what we know about different cognitive tasks originates with fMRI, motor and language tasks represent the useful benchmarks given their well known regions of interest (ROIs) that are studied outside of fMRI through electrocorticography (ECoG) [123, 160, 210, 204].

In the right-hand motor task contrast, we observed that the natural signal power showed a strongly increased response in the hand regions of precentral gyrus (primary motor cortex) as well as the postcentral gyrus (somatosensory cortex), extending through the inferior parietal lobe (**Fig. 3.5a**). The effect of deconvolution is especially apparent in this contrast, since the strength of activity in the parietal cortex and postcentral gyrus decreases in some ROIs and eliminated entirely in others; yet, the strength in the primary motor cortex remains. Interestingly, the HONeD-in contrast also strengthens activity in the ipsilateral motor area (**Fig. 3.5a**), which has been shown to activate during similar motor tasks in ECoG literature [123, 160].

Language is another task where we have strong *a priori* ROIs from ECoG, such as the superior posterior temporal sulcus, the middle temporal gyrus, and the inferior frontal gyrus [210, 204]². In the natural contrast, there is high activation in these language areas as well as throughout the temporal lobe (**Fig. 3.5b**). The HONeD-in contrast eliminates much of this widespread activity while retaining significant activity in regions aligned with previous ECoG literature [210, 204]. Interestingly, HONeD-in contrasts also preserve activity in the right hemisphere, suggestive of

²Historically, the inferior frontal gyrus has been associated with “Broca’s” area, and the posterior superior/middle temporal gyrus has been associated with “Wernicke’s” area, although these divisions are now considered oversimplifications [211].

bihemispheric language recruitment (**Fig. 3.5b**).

While the other tasks are more challenging to interpret given their lack of ECoG as a reference, some overarching patterns persist. In general, the HONeD-in contrast represents a sparser and more spatially distributed subset of regions compared to the natural signal contrasts. Some of the regions retained in the HONeD-in contrast are suggestive: the right hand primary motor cortex (relevant to responding to each task) and primary visual areas (relevant to visually relevant tasks). Some qualitatively interesting differences include increased response in reward areas, the caudate and putamen, during the Gambling task, the appearance of theory of mind areas, the dorsomedial prefrontal cortex, right angular gyrus, and anterior temporal lobe, during the social task, and refinements in activity in ventral visual (“what”) areas during Relational and Working Memory tasks (areas circled in **Fig. 3.5c-f**). However, given the qualitative nature of this analysis without external reference, we refrain from too much speculation about these changes.

3.4 Discussion

Disentangling the role of passive signal diffusion from driving signals in the brain is critical to interpreting macroscale neuroimaging recordings. Here, we developed a method to estimate such a driving signal in closed-form using a higher-order network diffusion (HONeD) model over the structural connectome (SC). The resulting “innovation” (HONeD-in) fMRI signals had significantly altered correlational and hierarchical properties. Specifically, HONeD-in signals 1) sparsified functional connectivity (FC), 2) decoupled resting-state networks (RSNs), 3) reorganized FC-gradients along with the RSN hierarchy, and 4) sharpened task fMRI activation maps. Together, these results suggest that some of the conventional FC structure may be an epiphenomenon of large-scale signal diffusion through SC.

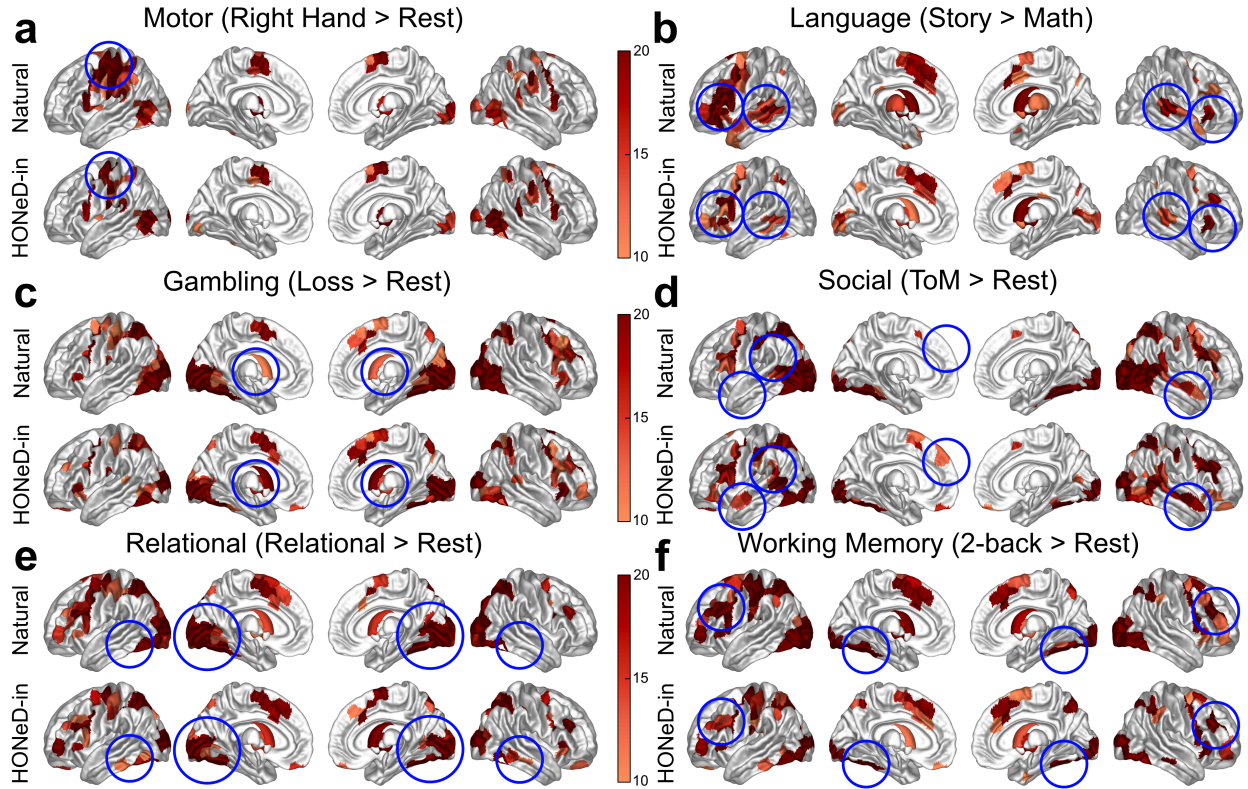


Figure 3.5: The GLM task contrast for six Human Connectome Project tasks. Task contrasts include (a) Motor (Right Hand > Rest) (b) Language (Story > Math) (c) Gambling (Loss > Rest) (d) Social (Theory of Mind > Rest), (e) Relational (Relational > Rest), and (f) Working Memory (2-back > Rest). In general, HONeD deconvolution appears to “deblur” the activation maps across tasks. For example, the motor cortex activity becomes more restricted to right hand and finger areas during the right finger-tapping motor task (a). Similarly for the language task (b), the HONeD-in signal refines activity around the inferior frontal gyri (Broca’s area) and in well-known language areas in the temporal lobe. The ability for HONeD deconvolution to elevate specificity in activated regions across tasks is nicely portrayed by activity in the primary visual area (V1), where many of the tasks display a significant activity throughout the visual cortex, but the HONeD-in signal tends to refine this signal to V1, with expanded activity during especially visually demanding tasks—Gambling (c), Relational (e) and Working Memory (f). General areas of interesting differences are circled in blue. The color bar is in terms of the test-statistic from the group-level analysis under a Student’s t-test.

3.4.1 Passive signal diffusion through SC may confound fMRI

FC from fMRI and SC from dMRI are commonly treated as fundamentally distinct and challenging to reconcile; yet, recent structure-function modeling efforts have made great progress in understanding how FC may arise from SC [63]. Since FC is a statistical measure of covariance between functional time series across regions, SC-FC models are motivated by the hope of endowing FC with biophysical interpretations related to classical neuronal signal propagation along SC. These efforts are especially salient in the active research on complex and nonlinear neural mass models in fMRI [179, 103, 170, 53]. However, the surprising success of simple linear SC-FC models at the macroscopic scale [151], such as the network diffusion-based models [1, 2, 163, 222], suggests that the typical measurements of FC may be confounded by passive signal diffusion over SC. Therefore, HONeD deconvolution seeks to recover an FC that reflects an ‘active’ innovation signal covariance. Although there is no ground-truth to assess our method against, our simulation analyses strongly support HONeD deconvolution as an approach that can recover an underlying structured innovation signal blurred out by passive diffusion over SC (Supplemental **Fig. S3.7**). This provides a principled basis for interpreting the following empirical changes we observed after HONeD deconvolution.

3.4.2 HONeD deconvolution restructures FC and the unimodal–multimodal divide

A pronounced effect of HONeD deconvolution was a global sparsification of FC. HONeD-in FC showed decreased centrality metrics, including Rich Club and betweenness centrality, alongside decreased modularity and increased eccentricity (**Fig. 3.2d**), suggesting a less hub-dominated and less hierarchically centralized topology. The high network density of FC has been a known challenge in the field of resting-state fMRI connectivity, and approaches to address this issue have included global signal regression (GSR) [122], percolation thresholds [22, 149], or regularization [243]. However, HONeD deconvolution’s advantage over these alternative approaches is that the

sparsification arises from a biophysical description of the signal that is being eliminated, rather than a statistical description (e.g. GSR) or a mere pruning of weak edges, which could themselves be meaningful.

Consistent with this global reduction in signal covariance, we found that some of the traditional RSN structure breaks apart. Of particular note were the default mode (DMN) and dorsal attention (DAN) networks, each decoupling into two interdigitated networks (**Fig. 3.3**). The newly fractured DMN-A was generally posterior and inferior to DMN-B. Meanwhile, DAN-A occupied more frontal areas while DAN-B involved occipital areas, with both interlocking in the superior parietal cortex. We borrowed these A/B division labels from previous work showing remarkably similar RSN decoupling when deeply sampling individual subjects [25, 26]. One difference from this previous work is that we did not observe a specific language network—instead, language areas belonged to DMN-B, which may be a result of our relatively large parcels and that the language network and DMN-B are intermixed through the temporal lobe [26]. Together, our analysis suggests that diffusion through SC may blur together these parallel networks in a way that can only be decoupled with enough resting-state scan time. HONeD deconvolution may help pull apart these parallel networks, providing a new way to study their relevance in fMRI with relatively less data.

Besides fracturing RSNs, HONeD deconvolution also deconstructed the traditional unimodal and multimodal dichotomy in FC. The salience network invaded somatomotor areas seeming to align with the recently proposed integrate-isolate model of the motor homunculus [79], which suggests that the salience network may mediate their proposed action and body representations in a fitting alignment to its role in interoception [111]. The control network reorganizing to include primary visual regions has intriguing parallels with recent work showing a close relationship between control and visual areas during working memory [150]. Instead of a strictly somatomotor network, a new “multi-sensory” network emerged, joining together somatomotor, auditory, and peripheral visual regions (**Fig. 3.3c**). More than just merging unimodal and multimodal regions in RSNs, HONeD deconvolution in fact dismantled the previous unimodal to multimodal hierarchy along FC-gradients [134]. Instead, our new FC-gradients placed RSNs around a circle, with DMN

opposed to the salience and DAN-A networks, and with the visual-control network opposed to the multi-sensory and DAN-B networks (**Fig. 3.4b**). Together, these findings suggest that dominant network phenomena in fMRI, including RSN organization and unimodal–multimodal dichotomies, may be deeply related to the brain’s SC, highlighting HONeD deconvolution’s potential to investigate these phenomena from a new perspective.

3.4.3 Implications for task fMRI

Analyzing HONeD-in signals could be especially relevant to task fMRI, where the brain is receiving structured input and generating endogenous computations in response to specific tasks. We found that the GLM-based activation maps from the HONeD-in signal were sparser than activation maps from the natural signal, suggesting that HONeD deconvolution helped to “deblur” these activation maps (**Fig. 3.5**). It has long been understood that fMRI signals during tasks show strong spatial autocorrelation resulting in large clusters of significant activity [68, 51]. One important source of spatial autocorrelation could arise from passive signal diffusion through white matter, thus blurring the signal effects across regions. HONeD deconvolution precisely aims to correct for this blurring effect, and we indeed observe that the HONeD-in signal reduces large clusters of activity to smaller, spatially separated clusters. In general, we found that regions remaining in HONeD-in activation maps aligned well with the electrophysiology literature on finger movement and language processing [123, 160, 210, 204]. Importantly, HONeD deconvolution did not just sparsify activation maps, but also elevated the activity of important regions. One example was during the theory of mind task where HONeD-in activity increased in the dorsomedial prefrontal cortex and anterior temporal cortex, which are both known to be strongly related to theory of mind [221, 200]. Given how HONeD deconvolution reweights the importance of different regions during tasks, it may provide a useful tool for analyzing task fMRI and localizing task-relevant brain regions.

3.4.4 Relationship to prior approaches

Several approaches in computational neuroscience share conceptual similarities with HONeD deconvolution. Independent component analysis (ICA) to perform blind source separation was among the earliest methods to search for independent sources of brain activity [35]. Dynamic causal modeling (DCM) takes a different perspective, aiming to find effective (directed) regional relationships in the brain that depend on differences between time-steps [69]. Another approach aims to enhance high-frequency features in fMRI data by isolating the bottom “minor” components of task fMRI time series, thereby creating a “connectome caricature” that improves fingerprinting accuracy [172]. These approaches, however, are statistical in nature and rely solely on the fMRI data without explicit reference to the underlying SC. Network control theory overcomes this limitation by incorporating SC directly to quantify the controllability of different regions and transitions between brain states, and it leverages the same mathematical framework that underlies our derivation of the HONeD-in signal [84, 109]. Another SC-based approach uses graph filtering to extract the high-frequency eigenvectors of the SC Laplacian [81], analogous to the connectome caricature, but instead emphasizing high-frequency *structural* components. HONeD deconvolution nevertheless stands out among these approaches because it provides a closed-form, physics-informed inversion of diffusion on the SC, directly solving for an fMRI innovation signal. In this light, HONeD deconvolution is analogous to the residual of an “interaction picture” in physics, where a simple and well-understood part of the system is removed to reveal more complex dynamics [127]. What remains after HONeD deconvolution is not necessarily a signal untethered from structure: HONeD-in signals isolate the part of the signal that *cannot be predicted by passive diffusion* over the SC, but whose *subsequent propagation* can still be mediated by that same connectome.

Limitations and future directions

One possible concern is that HONeD deconvolution rests in part on obtaining an accurate structural connectome. There are many known limitations with estimating white matter connectivity [101], yet we believe this is not as significant of a limitation as it may first appear. We showed that

a consensus SC recovers the innovation signal with as much fidelity as the subject-specific SC, which indicates that many of the highly detailed and subject-specific connections that may be challenging to estimate are not as relevant to HONeD deconvolution. While small variations in SC may not be a significant challenge, the number of brain regions defined for SC and fMRI may prove to be more challenging. We used the Schaefer-500 atlas since it was high-resolution, but still computationally tractable. Task fMRI typically analyzes regional activity at a voxel or vertex level, so extending HONeD to high resolution data would be an important future direction. Another theoretical limitation is that HONeD in its present form assumes that the innovation signal is not correlated across harmonics. However, while harmonics are orthogonal in space, they may not be independent from each other in time. Correlations between harmonics would erode the ability for HONeD-in signals to capture the true innovation signal. Additionally, our HONeD-in signal presently includes the actuation matrix (B) in the LTI equation. Using the HONeD-in signal estimates to further recover such an “effective connectivity” matrix could be an interesting area for future work. Finally, we acknowledge that while our results show evidence of HONeD-in signals sharpening task-evoked activation maps, since all possible reference maps originate from previous fMRI analyses inherently convolved with passive diffusion through structure, it remains an open question whether the HONeD-in activation maps indeed reflect a “truer” description for the brain regions relevant to any given task. Accordingly, we have refrained from making such a claim, and in fact, the ground truth of any fMRI task-evoked activation map is generally not accessible without intervention-based approaches.

3.4.5 Conclusion

Our HONeD-in approach reveals an underlying “innovation” signal that substantially remodels fMRI signals. The HONeD-in signal has sparser but still well-connected FC, reorganizes resting-state networks, mixes unimodal and multimodal regions, and spatially sharpens task-evoked activity. Overall, HONeD deconvolution shows significant promise as a new approach to studying cognitive neuroscience and diseases with functional MRI.

3.5 Methods

3.5.1 Theory

In the following, we describe the theoretical foundation for estimating HONeD-in.

General linear time-invariant model for brain activity

In the study of Linear Time-Invariant (LTI) systems, a general state-space equation for how a signal behaves in a system can be written as:

$$\frac{d\mathbf{x}(t)}{dt} = A\mathbf{x}(t) + B\mathbf{u}(t) \quad (3.1)$$

Here, $\mathbf{x}(t) \in \mathbb{R}^n$ is a vector specifying the state of the system’s signal across n nodes, $A \in \mathbb{R}^{n \times n}$ is a state transition matrix (i.e., the system’s “internal dynamics”), $\mathbf{u}(t) \in \mathbb{R}^m$ is a vector specifying the exogenous input into the system at m inputs, and $B \in \mathbb{R}^{n \times m}$ is an actuation matrix that specifies how the input distributes through the system. In neuroscience, this equation is commonly invoked when studying network control theory, where the internal system dynamics A can be taken as the structural connectivity (SC), and certain aggregate properties of B and/or $\mathbf{u}(t)$ are estimated [82, 109].

Here, we leverage this framework to model intrinsic brain dynamics as diffusion over structural connectivity.

The graph Laplacian and higher-order network diffusion

We construct the state matrix A using the *graph Laplacian*, making A a physics-based operator for network diffusion. A full first-principles derivation and explication for the relationship between the graph Laplacian and the physics of signal diffusion has been well documented [154, 1]. For completeness, we will provide an abbreviated description here.

Consider the brain’s structural connectivity matrix ($C \in \mathbb{R}^{n \times n}$), where each row/column rep-

resents a single brain region of interest (ROI) and the matrix entry (C_{ij}) corresponds to the connectivity strength between regions i and j . Then the way in which a signal can be expected to change under passive diffusion is $\frac{dx_i(t)}{dt} = -\beta(x_i(t) - \frac{1}{\sqrt{D_{ii}}} \sum_j \frac{1}{\sqrt{D_{jj}}} C_{ij} x_j(t)) + \sum_j B_{ij} u_j(t)$, where $D_{ii} = \sum_j C_{ij}$ corresponds to the amount of connectivity (degree) at a given region i . Vectorizing this equation reveals the degree normalized graph Laplacian:

$$\frac{d\mathbf{x}(t)}{dt} = -\beta(I - D^{-1/2}CD^{-1/2})\mathbf{x}(t) + B\mathbf{u}(t) = -\beta\mathcal{L}\mathbf{x}(t) + B\mathbf{u}(t) \quad (3.2)$$

The graph Laplacian ($\mathcal{L} \in \mathbb{R}^{n \times n}$) is a graph analogue to the Laplace-Beltrami operator for manifolds [104], and it is deeply related to the physics of diffusion over networks [154].

However, note that the above case is in fact a specific linearized truncation of a more general way to specify diffusion through a network. Instead of considering merely $-\beta\mathcal{L}$ as the operator for diffusion, we can generalize this operator to be of the form

$$f(\mathcal{L}; \theta) = \sum_{p=0}^P \theta_p \mathcal{L}^p \quad (3.3)$$

Here, P is the order of the Taylor series approximation for a generalized “higher-order network diffusion” (HONeD) operator, and $\theta \in \mathbb{R}^{P+1}$ is the vector of HONeD parameters. A key advantage of this generalized form is that it accounts for multi-step pathways through the brain’s structural network³ [16, 39].

It is relevant to note that $\mathcal{L}$ being diagonalizable ($\mathcal{L} = U\Lambda U^\top$) with orthogonal eigenvectors (hereafter called “harmonics”) U and eigenvalues Λ means that any polynomial function of this matrix can be written as a function of its eigenvalues⁴:

$$f(\mathcal{L}; \theta) = Uf(\Lambda; \theta)U^\top \quad (3.4)$$

³The p -th power of any graph’s adjacency matrix, $G^p \forall p \in \mathbb{N}$, computes the movement through the graph after p -steps.

⁴Note that $f(\Lambda; \theta)_{kk} = \sum_p \theta_p \lambda_k^p$ becomes a scalar function.

The graph Laplacian harmonics can be interpreted as standing waves sustained on the structure of the network. Decomposing the Laplacian into its harmonics provides an intuitive and computationally useful way to fit the parameters (θ_p) of the HONeD operator, which we'll describe in detail below.

With our HONeD operator in hand, let's return to the LTI model and derive the HONeD-innovation (HONeD-in) signal. Henceforth, we specify $A = f(\mathcal{L}; \theta)$ such that the internal system dynamics is governed by the physics-based HONeD diffusion operator over SC.

Deriving the innovation signal

In this work, we seek to estimate a signal $\mathbf{z}(t) = B\mathbf{u}(t)$, since B and $\mathbf{u}(t)$ are not individually identifiable, and therefore our estimate bundles together the exogenous system input $\mathbf{u}$ with the system actuation B . Hence, our differential equation takes the form:

$$\frac{d\mathbf{x}(t)}{dt} = f(\mathcal{L}; \theta)\mathbf{x}(t) + \mathbf{z}(t)$$

The solution to this inhomogeneous ODE is:

$$\mathbf{x}(t) = e^{f(\mathcal{L}; \theta)t} \mathbf{x}_0 + \int_0^t e^{f(\mathcal{L}; \theta)(t-\tau)} \mathbf{z}(\tau) d\tau \quad (3.5)$$

Here, we assume that the innovation signal behaves like a Dirac delta function of the form $\mathbf{z}(t) = \sum_k \mathbf{z}_k \delta(t - t_k)$ with $t_k = k\Delta t$, which is a sparse signal in time, and where we assume the convention where each pulse is the beginning of each TR. Assuming the innovation signal behaves like a delta function is aligned with previous work on estimating innovation signals in fMRI [108] ⁵. Using this formulation, we show that we can calculate the HONeD-in signal in discrete time as:

$$\mathbf{z}_k = e^{-f(\mathcal{L}; \theta)\Delta t} \mathbf{x}_{k+1} - \mathbf{x}_k \quad (3.6)$$

⁵Note that this assumed structure of the innovation signal may not be valid across all neuroimaging modalities.

For a thorough mathematical derivation, see Supplemental Section 1. However, this closed-form equation requires knowing the correct *parameterization* (θ) for HONeD $f(\mathcal{L}; \theta)$. Hence, we next show how we estimate the HONeD parameters under a homogeneous passive diffusion model.

Estimating HONeD parameters

To approximate the effect of homogeneous passive diffusion, we take the general LTI equation, but without any specific exogenous drive: $\frac{d\mathbf{x}(t)}{dt} = f(\mathcal{L})\mathbf{x}(t)$, which has the solution $\mathbf{x}(t) = e^{f(\mathcal{L})t}\mathbf{x}_0 = Ue^{f(\Lambda)t}U^\top\mathbf{x}_0$.⁶ Importantly, this model makes a different assumption about the initial condition of the system—the homogeneous HONeD model treats the “initial condition” as an independent and identically distributed (i.i.d.) Gaussian random variable such that $\mathbb{E}[\mathbf{x}_0\mathbf{x}_0^\top] = I$.⁷

We use this homogeneous HONeD model to predict the covariance of fMRI signals during resting-state:

$$\langle \mathbf{x}(t)\mathbf{x}(t)^\top \rangle_t = Ue^{f(\Lambda)t}U^\top \mathbb{E}[\mathbf{x}_0\mathbf{x}_0^\top] Ue^{f(\Lambda)t}U^\top = Ue^{2f(\Lambda)t}U^\top \quad (3.7)$$

We wrote this model prediction in terms of the Laplacian’s harmonic decomposition to highlight how HONeD also *predicts the shape of harmonic power*. Specifically, let us define $X_i(t) = U_i^\top \mathbf{x}(t)$ as the projection of the time series to the space of the i^{th} graph harmonic (Supplemental Section 3.8) and graph harmonic power as $\langle X_i(t)^2 \rangle_t = U_i^\top \langle \mathbf{x}(t)\mathbf{x}(t)^\top \rangle_t U_i$. Then our model, equation (3.7), can be evaluated as a scalar function:

$$\langle X_i(t)^2 \rangle_t = e^{2f(\lambda_i)t} \quad (3.8)$$

To fit HONeD to empirical fMRI, we solve a constrained least-squares regression problem on the log-transformed harmonic power: $f(\lambda_i; \theta) = \frac{1}{2} \log(\langle X_i(t)^2 \rangle_t)$. Since least-squares fitting to polynomials is a convex quadratic optimization problem with globally optimal solutions, this model formulation is both fast to solve and comes with minima guarantees [24]. Additionally, we

⁶Note that the *homogeneous* diffusion time (t) becomes absorbed within the HONeD parameters θ .

⁷This statistical expectation is because HONeD describes a stochastic processes driven by a random input $\mathbf{x}_0$, meaning we define its theoretical average properties rather than an exact signal. This is justified by the ergodic hypothesis and the assumption that the underlying process is stationary (i.e., statistically stable).

fit the HONeD model with a constraint that the polynomial be non-decreasing at the largest eigenvalue ($\lambda_{\max}$), meaning that its derivative is non-negative. This constraint ensures that inverting the HONeD kernel does not overly amplify the highest eigenvalue harmonics. Thus, we use the following optimization function to estimate the subject-specific HONeD parameters ($\hat{\theta}$) in harmonic space:

$$\hat{\theta} = \arg \min_{\theta \in \mathbb{R}^{P+1}} \sum_{i=1}^n \left(\sum_{p=0}^P \theta_p \lambda_i^p - \frac{1}{2} \log(\langle X_i(t)^2 \rangle_t) \right)^2$$

We constrain the optimization so that $\sum_{p=1}^P p \theta_p \lambda_{\max}^{p-1} \geq 0$. So far, we have kept the form of HONeD general, but in practice we must choose a polynomial order. For the current work, we chose to limit HONeD to two steps ($P = 2$) through the network, since previous work has shown that two steps through SC nearly saturate SC's ability to predict functional connectivity [16], and we verified that two-step diffusion was also optimal for HONeD in this dataset (Supplemental **Fig. S3.9**). Therefore, the HONeD operator for the present work becomes

$$f(\mathcal{L}; \theta) = \alpha_0 I - \beta \mathcal{L} + \xi \mathcal{L}^2 \quad (3.9)$$

We denote the terms from the Taylor expansion $\theta_0 = \alpha_0$, $\theta_1 = -\beta$, and $\theta_2 = \xi$ for ease of referencing. Since empirical work has shown that $\theta_1 < 0$, we reference $\theta_1 = -\beta$ to make θ_1 's empirical negativity clear and to align terminology with previous network diffusion model work [1, 2, 158]. By fitting the HONeD model to the empirical harmonic power, we estimate subject-specific parameters $\hat{\theta} = \{\hat{\alpha}_0, \hat{\beta}, \hat{\xi}\}$, which we describe in detail below. An overview of the study theory is provided in Supplemental **Fig. S3.8**.

Estimating the HONeD-in signal

Having inferred the parameters of the homogeneous HONeD model, we finally estimate the HONeD-innovation (HONeD-in) signal as

$$\hat{\mathbf{z}}_k = e^{-f(\mathcal{L}; \hat{\theta}) \Delta t} \mathbf{x}_{k+1} - \mathbf{x}_k \quad (3.10)$$

In words, at each fMRI sample, the HONeD-in signal is obtained by “unwinding” the system defined by our HONeD operator, then comparing with the previous state. As such, $\hat{\mathbf{z}}_k$ is estimated as a *graph-deconvolution*.

3.5.2 Dataset and processing

We used 770 subjects from the Human Connectome Project (HCP) Young Adult dataset in this study [219]⁸. We included all HCP subjects that had both diffusion and functional MRI, and excluded subjects with quality control issues. Unprocessed HCP data were downloaded and organized into BIDS format. Anatomical scans were collected with an MPRAGE T1-weighted sequence. Functional MRI (fMRI) data included four 15-minute rest sessions and two task sessions for six tasks (Motor, Language, Gambling, Social, Relational, and Working Memory), all with a repetition time (TR) of 720 ms. Additionally, we used the pre-processed diffusion tensor imaging (DTI) data made available by HCP, which includes merging high fidelity directions across multiple multi-shell DTI acquisitions ($b = 1000, 2000, \& 3000$) and correcting for phase-encoding polarity distortion [77]. We applied a state-of-the-art image processing pipeline, micapipe [40], which processes the anatomical, functional, and diffusion MRI data in a coherent framework to produce subject-specific structural connectivity and functional regional time series in the Schaefer atlas with 500 cortical regions [180], each with connectivity to an additional 14 subcortical regions [157].

The structural connectivity was computed using MRtrix3 and probabilistic tractography, generating 10 million streamlines throughout the gray matter white matter interface (maximum tract length = 400, minimum length = 10, cutoff = 0.06, step = 0.5, angle curvature = 22.5°) using the iFOD2 algorithm and 3-tissue anatomically constrained tractography [40]. Tractograms were filtered using SIFT2 [194], reweighting streamlines by cross-sectional multipliers to provide con-

⁸Data were provided by the Human Connectome Project, WU-Minn Consortium (Principal Investigators: David Van Essen and Kamil Ugurbil; 1U54MH091657) funded by the 16 NIH Institutes and Centers that support the NIH Blueprint for Neuroscience Research; and by the McDonnell Center for Systems Neuroscience at Washington University. Ethical approval was not required as confirmed by the license attached with the open access data.

nection densities that are biologically valid measures of fiber connectivity.

The fMRI underwent image re-orientation, motion and distortion correction, and nuisance signal regression (white matter, cerebrospinal fluid (CSF), and frame-wise displacement spikes). Volumetric time series were mapped to the native FreeSurfer space using boundary-based registration [80]. Vertex-level time series were averaged into parcels defined by the Schaefer atlas with 500 cortical regions [180]. Parcel-level time series were bandpass filtered to be less than 0.1Hz, then underwent global signal regression (GSR). We computed the FC as the Fisher Z-transform of Pearson correlations between parcel-level time series [62, 218].

3.5.3 Simulation analysis

We evaluated our HONeD deconvolution method by creating a “ground-truth” innovation signal by randomly permuting region order in empirical fMRI time series following GSR. Since HONeD is based on propagation over SC, we randomly shuffle fMRI time series to destroy its spatial correspondence with SC but retain all natural fMRI statistics and correlations between signals, making it a structured innovation signal. Then, we run this innovation signal through the LTI equation using the HONeD operator, equation (3.9), and Euler integration to generate a simulated “natural” signal 1000 times. Since network diffusion imposes a global signal⁹, we perform GSR on the simulated “natural” signal and then fit our HONeD model to the post-GSR “natural” time series to estimate the innovation signal.

We determined how well HONeD deconvolution recovered the ground-truth innovation signal by computing two complementary metrics of signal recovery, normalized by the HONeD simulated “natural” signal. In the following, $\tilde{\mathbf{z}}_{\text{true}}$ is the ground-truth innovation signal entered into the HONeD ODE, $\tilde{\mathbf{x}}_{\text{“natural”}}$ is the simulated signal after running the ground truth signal through the HONeD ODE, and $\tilde{\mathbf{z}}_{\text{deconv}}$ is the estimated deconvolved innovation signal.

⁹This global signal is generated by the first eigenmode ($\lambda_0 = 0$), which is the ‘DC’ mode and related to the SC’s degree distribution.

First, we computed a normalized mean squared error (MSE) as:

$$\text{Recovered Signal \%} = \frac{\text{MSE}(\tilde{\mathbf{x}}^{\text{“natural”}}, \tilde{\mathbf{z}}_{\text{true}}) - \text{MSE}(\tilde{\mathbf{z}}_{\text{deconv}}, \tilde{\mathbf{z}}_{\text{true}})}{\text{MSE}(\tilde{\mathbf{x}}^{\text{“natural”}}, \tilde{\mathbf{z}}_{\text{true}})} \times 100$$

Second, we computed an analogous measure for FC:

$$\text{Recovered Innovation FC \%} = \frac{R_d - R_n}{1 - R_n} \times 100$$

where $R_d = \text{corr}(\text{FC}_{\text{true}}, \text{FC}_{\text{deconv}})$ and $R_n = \text{corr}(\text{FC}_{\text{true}}, \text{FC}^{\text{“natural”}})$, where again FC_{true} is the functional connectivity computed from the ground-truth innovation signal $\tilde{\mathbf{z}}_{\text{true}}$. We also evaluated how well HONeD parameters were recovered and how optimal HONeD deconvolution behaves around the ground-truth parameters.

We leveraged this simulation to thoroughly evaluate the performance of HONeD deconvolution across a variety of conditions. To assess the optimal performance, we used the subject-specific SC in both the simulation and the HONeD filter estimation. To test generalizability of HONeD in cases where subject-specific SC may not be available, we estimated the HONeD filter using a consensus SC (i.e., mean across all 770 HCP subjects). To evaluate HONeD deconvolution’s robustness to SC estimation error, we added random Rician noise to subject-specific SC. We scaled the standard deviation of the Rician distribution to the standard deviation of the original SC edge weight distribution. We evaluated Rician noise at the following scales: $\sigma = \{0.25, 0.5, 1, 2\}$ (e.g., when $\sigma = 1$, the Rician standard deviation matches the empirical SC’s standard deviation). Similarly, we evaluated HONeD deconvolution’s robustness to additive Gaussian noise by first z-scoring the HONeD-generated “natural” fMRI signal then adding Gaussian noise with the same noise scales: $\sigma = \{0.25, 0.5, 1, 2\}$. We also evaluated how HONeD deconvolution performed using a randomized SC, which rewired empirical SC edges at least 5 times, only preserving the network’s binary degree distribution and connectedness [176]. Since HONeD introduces a global signal into the data, meaning also that HONeD deconvolution performs a type of GSR, we compared the ground truth innovation signal and FC to the simulated post-GSR “natural” signal, thereby testing whether

GSR recovers any innovation signal or FC structure.

3.5.4 Graph theoretical analyses

Recall that HONeD predicts the amount of fMRI signal governed by passive diffusion driven by i.i.d. Gaussian white noise. If passive diffusion with uniform actuation ($B = I$) is all there is to brain connectivity, the HONeD-in signal should have an FC that approximates the identity matrix with no structure in its network connectivity. Therefore, to evaluate whether the HONeD-in signal *does* in fact have meaningful network structure, we analyzed the graph theoretical properties of the “HONeD-in FC” and compared them to the same graph metrics from the post-GSR “natural FC,” as well as network randomized versions of the empirical networks and a network composed of only Gaussian noise. To align with traditional network neuroscience approaches, we computed the Pearson correlation between each region’s time series, then performed the Fisher Z-transform to obtain FC [62, 218]. For all graph theoretical analyses, we used only the positive FC edges, discarding all negative connections.

We compared natural to HONeD-in FC across traditional graph metric properties using the brain connectivity toolbox [176]. These metrics were modularity, mean clustering coefficient, mean betweenness centrality, mean eccentricity, the rich club (area under curve), and characteristic path length (CPL). These measures index a wide array of graph topological properties, especially the integrative and segregative network topology. Broadly, rich club AUC, betweenness centrality, and clustering coefficient indicate more integration while modularity, eccentricity, and CPL indicate more segregation [45]. Since HONeD deconvolution suppresses the integrative harmonics [192], we predicted that HONeD-in FC should show decreases in measures of network integration, resulting in a sparse network.

3.5.5 Resting-state network and FC-gradient analyses

Functional resting-state networks (RSNs) have become a cornerstone of neuroscience research. RSNs have previously been identified using von Mises-Fisher clustering on consensus FC [236,

180]. Therefore, we also evaluated the effect of HONeD deconvolution on the identification of these networks. We replicated this previous approach by performing von Mises-Fisher clustering with 7 clusters on the natural and HONeD-in consensus FCs with only positive edges across 10,000 initializations [98, 9, 110]. In this study, we are using the HCP dataset, which was the original dataset used to identify these networks in the Schaefer atlas [180]. Although the pre-processing differences may result in variation, we expect the natural FCs to align well with the canonical organization. We assessed the clustering performance with cross-validation [236]. That is, we identified RSNs using randomly selected half of the brain’s regions, then we predicted the RSN assignment using the Euclidean distance to the nearest centroid. We re-ran this cross-validation 1000 times for each clustering order (K). This yielded an accuracy distribution which we used as our measure of clustering stability.

Moreover, there has been much work investigating the properties of “functional gradients,” which are the Laplacian diffusion map eigenvectors of FC originally described by Margulies et al [134]. This seminal work showed that these gradients intimately relate to RSNs: the first principle gradient organized a multimodal to unimodal hierarchy from the default-mode network (DMN) to visual/motor areas; the second gradient further separated the visual and motor cortices. To assess whether HONeD-in signals alter this hierarchy, we computed two FC-gradients for both the natural and HONeD-in consensus FC and evaluated whether FC-gradients were left unchanged by removing the effect of passive signal diffusion through SC. Then, we investigated how brain regions and RSNs derived from the HONeD-in FC organized around HONeD-in FC Gradients.

3.5.6 Task-contrast analysis

We assessed how HONeD deconvolution influenced the activity across different HCP tasks. We followed a traditional approach taken in task fMRI studies by convolving a canonical hemodynamic response function (HRF) with the time-wise binary vector indicating task-blocks of interest. The form of the HRF was estimated for each subject directly from the data using the resting-state time series using the rsHRF package [232]. Since HONeD deconvolution may change the shape of

the HRF, we estimated these HRFs separately for the natural and HONeD-in signals. We then used a general linear model (GLM) to compute the association between each parceled region’s time series and the HRF-convolved response time series with 1-step autoregressive prewhitening, which controls for temporal autocorrelation [68]. We computed region-wise contrast in the regression weights from the GLM for each subject as a first-level analysis (i.e., $\Delta b = b_{\text{task}} - b_{\text{rest}}$)¹⁰, followed by a second-level analysis as a univariate t-test across all beta weight contrasts across subjects, using Bonferroni correction for multiple comparisons [50]. This produced test-statistic maps that we used to evaluate the differences in “regional activity” between the natural and HONeD-in signals. Note that, unlike traditional fMRI task-based analyses, we assessed the task activations using the post-GSR signal to ensure an appropriate comparison with other results.

¹⁰This ‘ b ’ is unrelated to the diffusion depth parameter (β) in the HONeD model.

3.6 Supplemental Material

3.6.1 Supplemental Section 1: Deriving the HONeD-innovation Signal

The solution to our LTI system inhomogeneous ODE is:

$$\mathbf{x}(t) = e^{f(\mathcal{L})t} \mathbf{x}_0 + \int_0^t e^{f(\mathcal{L})(t-\tau)} \mathbf{z}(\tau) d\tau \quad (3.11)$$

Recall that our higher-order network diffusion (HONeD) model is represented by $f(\mathcal{L})$, corresponding to the brain's internal dynamics. Here, we assume that the innovation signal behaves like a Dirac delta function of the form $\mathbf{z}(t) = \sum_s \mathbf{z}_s \delta(t - t_s)$ with $t_s = s\Delta t$ such that our sampling interval is $\Delta t = t_{s+1} - t_s \forall s$, which is the signal TR on a uniform sampling grid and where s is a dummy index for the summation. Substituting this impulse train into the solution gives the following:

$$\begin{aligned} \mathbf{x}(t) &= e^{f(\mathcal{L})t} \mathbf{x}_0 + \int_0^t e^{f(\mathcal{L})(t-\tau)} \sum_s \mathbf{z}_s \delta(\tau - t_s) d\tau \\ \mathbf{x}(t) &= e^{f(\mathcal{L})t} \mathbf{x}_0 + \sum_s \int_0^t e^{f(\mathcal{L})(t-\tau)} \mathbf{z}_s \delta(\tau - t_s) d\tau \\ \mathbf{x}(t) &= e^{f(\mathcal{L})t} \mathbf{x}_0 + \sum_{s: 0 \leq t_s \leq t} e^{f(\mathcal{L})(t-t_s)} \mathbf{z}_s \end{aligned} \quad (3.12)$$

Next, we can write the above equation (3.12) in discrete time using the following update rule:

$$\mathbf{x}_{k+1} = e^{f(\mathcal{L})(t_{k+1}-t_0)} \mathbf{x}_0 + \sum_{s=0}^k e^{f(\mathcal{L})(t_{k+1}-t_s)} \mathbf{z}_s \quad (3.13)$$

Because an impulse train input $\mathbf{z}(t) = \sum_k \mathbf{z}_k \delta(t - t_k)$ generally induces jump discontinuities in the state $\mathbf{x}(t)$ at the impulse times $\{t_k\}$, the value $\mathbf{x}(t_k)$ is ambiguous unless a left/right limit convention is specified. Throughout, we define the sampled state at time t_k to be the left-limit

$$\mathbf{x}_k := \mathbf{x}(t_k^-),$$

i.e., the state immediately *before* the impulse at t_k . Under this convention, the impulse produces an instantaneous jump

$$\mathbf{x}(t_k^+) = \mathbf{x}(t_k^-) + \mathbf{z}_k = \mathbf{x}_k + \mathbf{z}_k,$$

and the state then evolves homogeneously over the interval (t_k, t_{k+1}) . In other words, we assume that the sampling of $\mathbf{x}_k$ happens just before the following innovation signal $\mathbf{z}_k$ in the pulse train at time t_k . Without loss of generality, we take $t_0 = 0$. In the following, we will evaluate this update rule for the first two cases and then provide the closed form expression.

Let $k = 0$:

$$\mathbf{x}_1 = e^{f(\mathcal{L})(t_1-t_0)}\mathbf{x}_0 + e^{f(\mathcal{L})(t_1-t_0)}\mathbf{z}_0$$

$$\mathbf{x}_1 = e^{f(\mathcal{L})\Delta t}\mathbf{x}_0 + e^{f(\mathcal{L})\Delta t}\mathbf{z}_0$$

$$\mathbf{x}_1 = e^{f(\mathcal{L})\Delta t}(\mathbf{x}_0 + \mathbf{z}_0)$$

$$\mathbf{z}_0 = e^{-f(\mathcal{L})\Delta t}\mathbf{x}_1 - \mathbf{x}_0$$

Let $k = 1$:

$$\mathbf{x}_2 = e^{f(\mathcal{L})(t_2-t_0)}\mathbf{x}_0 + e^{f(\mathcal{L})(t_2-t_0)}\mathbf{z}_0 + e^{f(\mathcal{L})(t_2-t_1)}\mathbf{z}_1$$

$$\mathbf{x}_2 = e^{f(\mathcal{L})2\Delta t}\mathbf{x}_0 + e^{f(\mathcal{L})2\Delta t}(e^{-f(\mathcal{L})\Delta t}\mathbf{x}_1 - \mathbf{x}_0) + e^{f(\mathcal{L})\Delta t}\mathbf{z}_1$$

$$\mathbf{x}_2 = e^{f(\mathcal{L})2\Delta t}\mathbf{x}_0 + e^{f(\mathcal{L})\Delta t}\mathbf{x}_1 - e^{f(\mathcal{L})2\Delta t}\mathbf{x}_0 + e^{f(\mathcal{L})\Delta t}\mathbf{z}_1$$

$$\mathbf{x}_2 = e^{f(\mathcal{L})\Delta t}\mathbf{x}_1 + e^{f(\mathcal{L})\Delta t}\mathbf{z}_1$$

$$\mathbf{x}_2 = e^{f(\mathcal{L})\Delta t}(\mathbf{x}_1 + \mathbf{z}_1)$$

$$\mathbf{z}_1 = e^{-f(\mathcal{L})\Delta t}\mathbf{x}_2 - \mathbf{x}_1$$

This pattern continues such that the closed form expression for the HONeD-innovation signal at any time t_k is:

$$\mathbf{z}_k = e^{-f(\mathcal{L})\Delta t}\mathbf{x}_{k+1} - \mathbf{x}_k \tag{3.14}$$

3.6.2 Supplemental Section 2: HONeD model Fitting and Simulation

HONeD fitting performance

We found that an order-2 HONeD operator provided the best improvement on harmonic prediction given our model constraints (Supplemental Figure 3.9). The homogeneous HONeD model fit well to the empirical harmonic power across subjects in both mean squared error ($\text{MSE} = 0.14(\pm 0.03)$) and Pearson correlation ($R = 0.85(\pm 0.02)$). HONeD passive diffusion parameters across all 770 HCP subjects were $\beta = 2.98(\pm 0.26)$ and $\xi = 1.07(\pm 0.11)$ (Supplemental Figure 3.6).

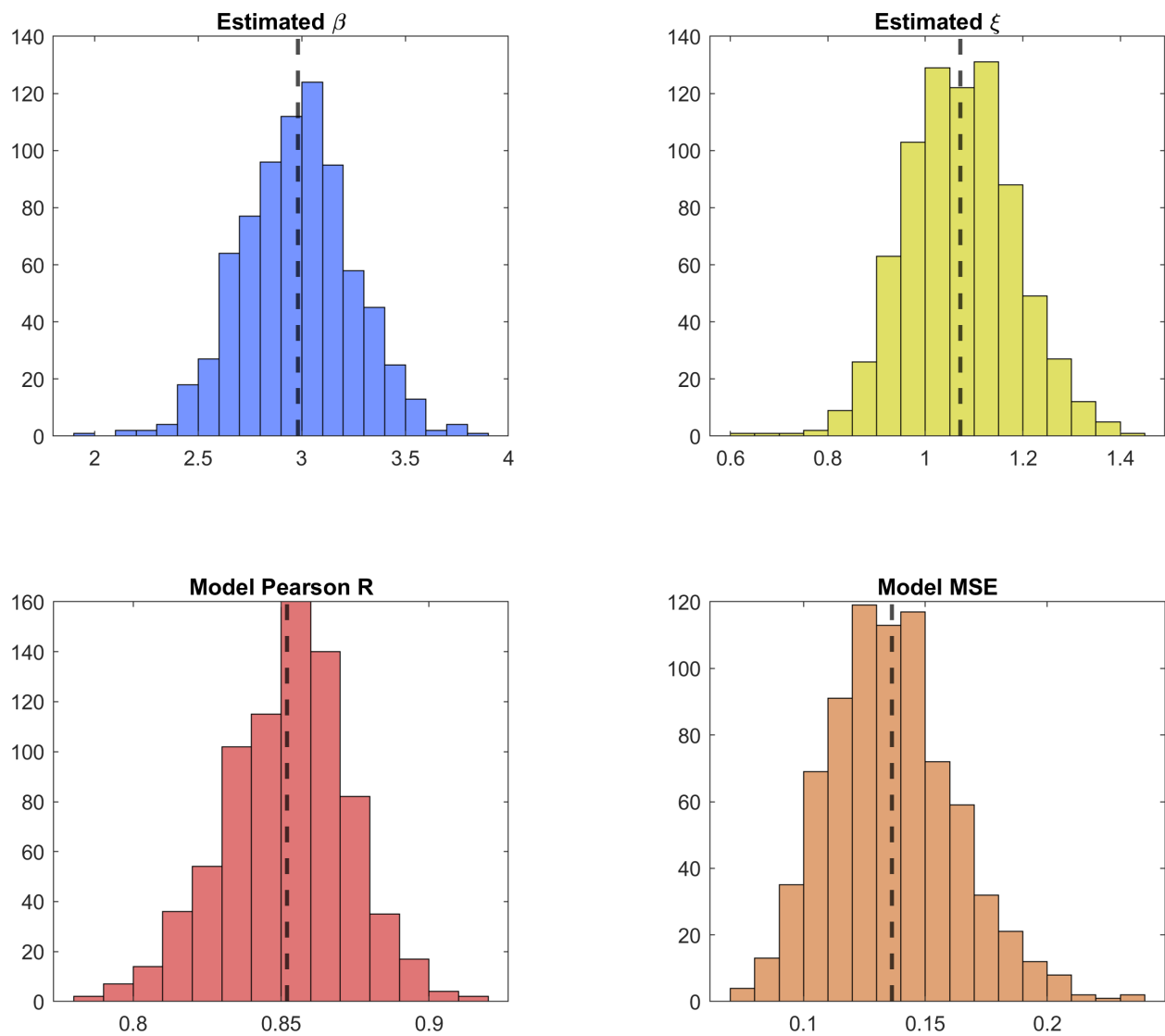


Figure 3.6: Empirical HONeD Parameter Fits. The estimated HONeD parameters, and model performance metrics (Pearson's R and MSE) between the predicted and empirical graph harmonic power, across the 770 HCP subjects included in this study.

HONeD deconvolution simulation

We found that HONeD deconvolution was well-posed under simulations following the HONeD model. Our method for estimating HONeD parameters predicts close to the ground-truth simulated parameters on average (True $\beta = 3$, Estimated $\hat{\beta} = 2.88(\pm 0.20)$; True $\xi = 1.2$, Estimated $\hat{\xi} = 1.29(\pm 0.11)$; Figure 3.7a & b). We also evaluated whether the true parameters were indeed the optimal parameters for the deconvolution. We found that there was a range of ideal deconvolution parameters, and that the true parameters were indeed near the center of this range (Figure 3.7c). Since β and ξ can create similar deconvolution filter shapes when they change together, it makes sense that a range of correlated parameters can identify equally good deconvolution estimates.

We next evaluated how well HONeD deconvolution could recover the original time series and FC across a range of conditions (Figure 3.7d & e). Unsurprisingly, subject-specific SC with no noise performed best, recovering 78% of the innovation time series and 89% of the FC. Using the consensus structural connectivity (SC) performed equally well for recovering the innovation signal, and slightly worse for FC ($\approx 88\%$). More impressively, HONeD deconvolution was highly robust to SC noise, still recovering 63% of the innovation signal and 65% of the innovation FC even when the SC edge-wise noise was double the network's standard deviation. The degree-preserving randomization, as expected, fared worse than noise, recovering only 43% of the innovation signal and 30% of the innovation FC. HONeD deconvolution was moderately robust to additive white noise: noise at half the signal's standard deviation still recovered 58% of the innovation signal and 75% of the FC. The innovation signal was not recoverable when time series noise was twice the signal's standard deviation. We finally evaluated how well only performing global signal regression (GSR) contributed to recovering the innovation signal. We found that GSR only recovered 30% of both the ground truth innovation signal the ground truth innovation FC.

Together, these results affirm that fitting HONeD can closely estimate the diffusion coefficients arising from signal propagation through SC, with robustness to noise sources, and significant recovery of underlying innovation signals and their covariance.

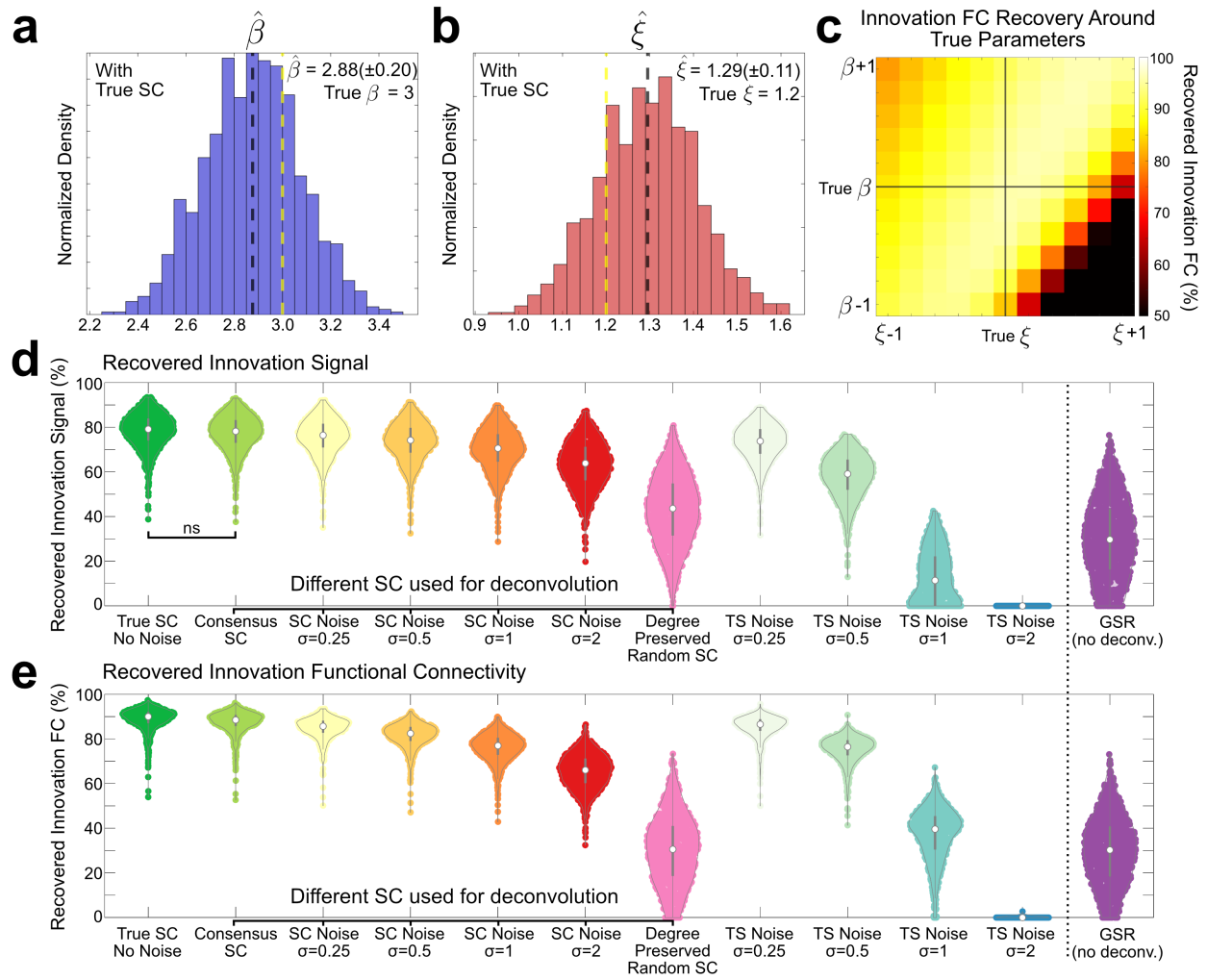


Figure 3.7: HONeD Simulation Results. (a & b) The distributions of estimated $\hat{\beta}$ and $\hat{\xi}$. The dashed black line indicates the sample mean while the dashed yellow line indicates the simulated ground-truth value. (c) A heatmap showing how variations around the ground truth parameters influence the recovery between ground truth innovation FC and the deconvolved innovation FC. (d) Violin plots showing the Recovered Innovation Signal (%) across different simulation conditions, and (e) shows the Recovered Innovation FC (%). For visualization, we set all negative recovery values to zero. Both showcase HONeD deconvolution robustness to noise and clear improvement over GSR alone. We labeled all pair-wise comparisons that were non-significant (ns) under a Student's t-test. Where violins are not labeled, pairwise distributions are significantly different after Bonferroni correction.

3.6.3 Supplemental Section 3: Supplemental Figures

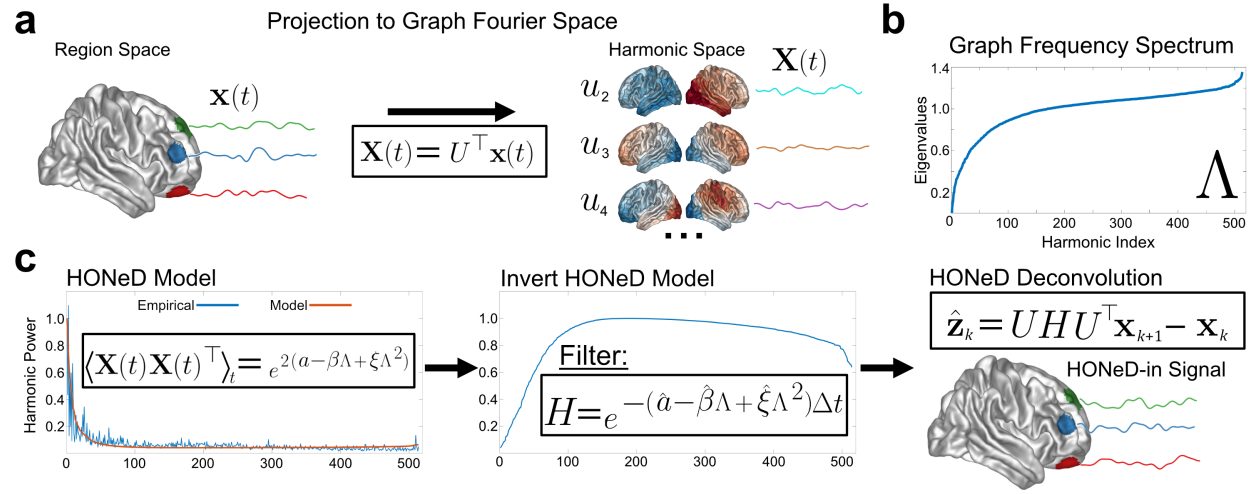


Figure 3.8: Technical HONeD-in Overview. (a) A depiction of the Graph Fourier Transform taking signals in region space and projecting them into the harmonic space. (b) The graph frequency spectrum (i.e., Laplacian eigenvalues), which are used to compute the HONeD model prediction. (c) The HONeD model fits to the empirical harmonic signal power. This prediction is inverted to create the HONeD filter which is subsequently applied to the original time series to obtain the estimated HONeD-innovation signal $\hat{\mathbf{z}}_k$. (Notation: bold denotes time series signals, lower-case denotes region space signals, and upper-case denotes harmonic space signals.)

$$\text{Fit Improvement}(k) = \frac{\epsilon_{k-1} - \epsilon_k}{\epsilon_{k-1}} \times 100 \quad (3.15)$$

Where ϵ_k is the mean squared error for the k^{th} model order's fit to harmonic power.

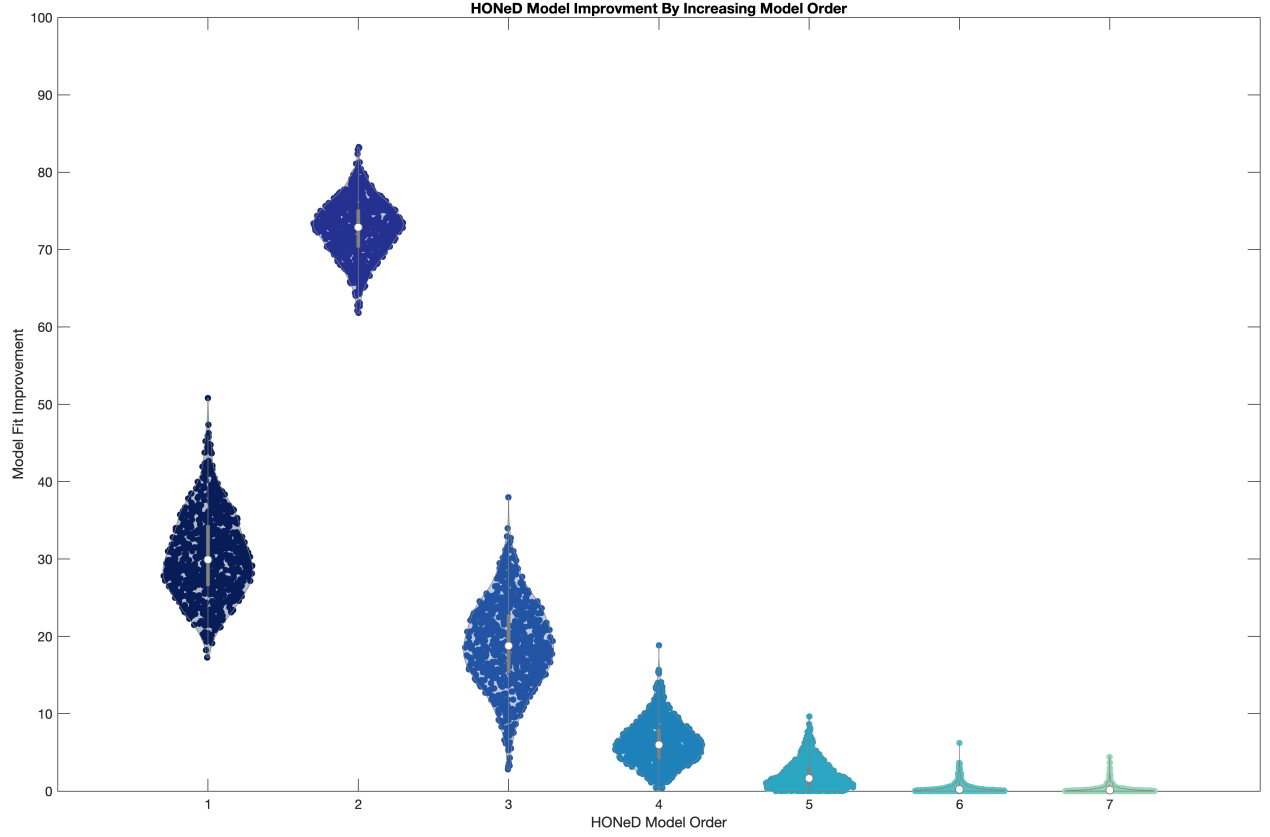


Figure 3.9: Choosing the Model Order. We show the empirical HONeD model fitting improvement in the HCP dataset across varying model orders. Fit improvement is measured in percent and is given by equation 3.15. The HONeD order = 2 offered the greatest improvement.

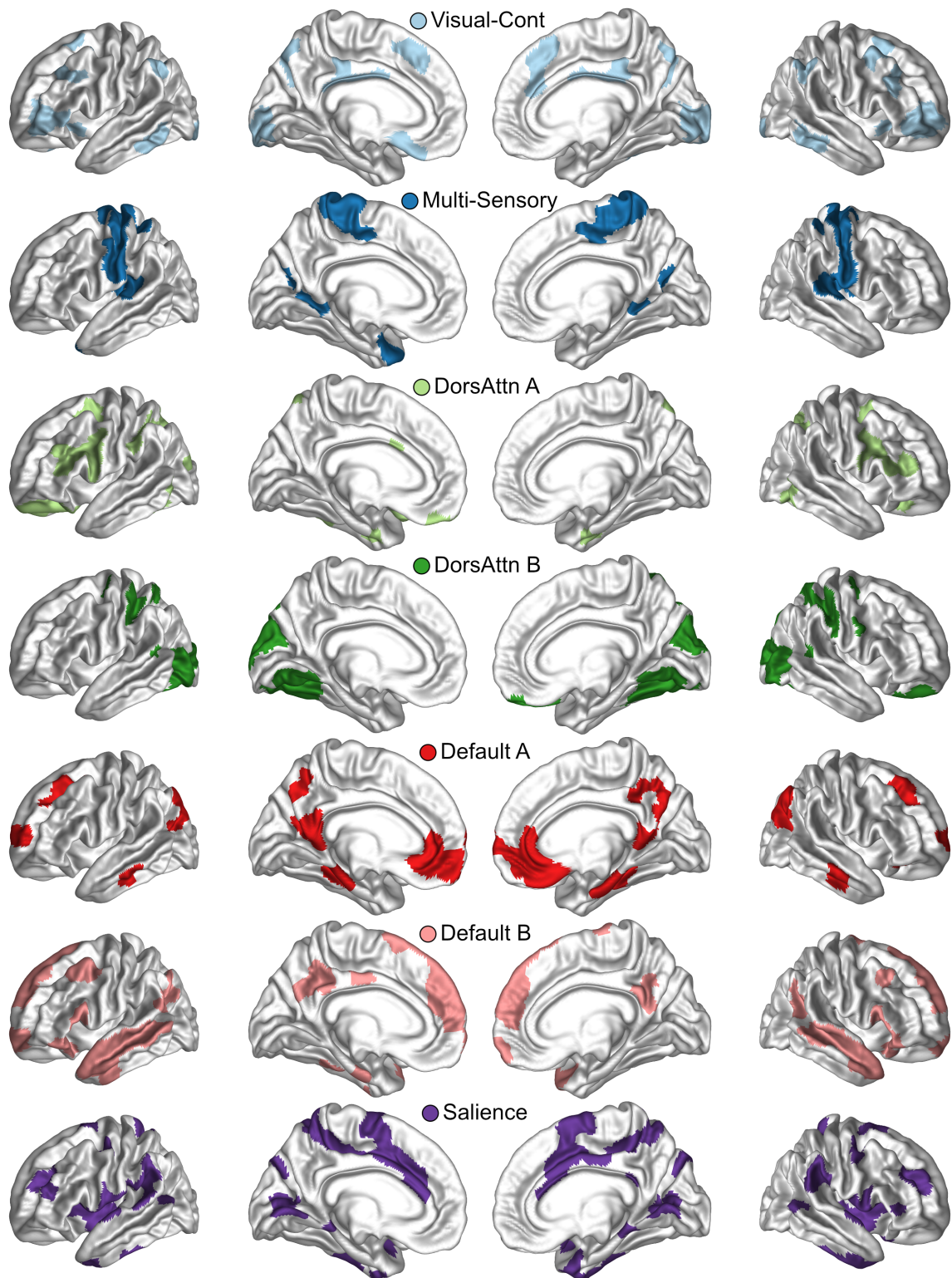
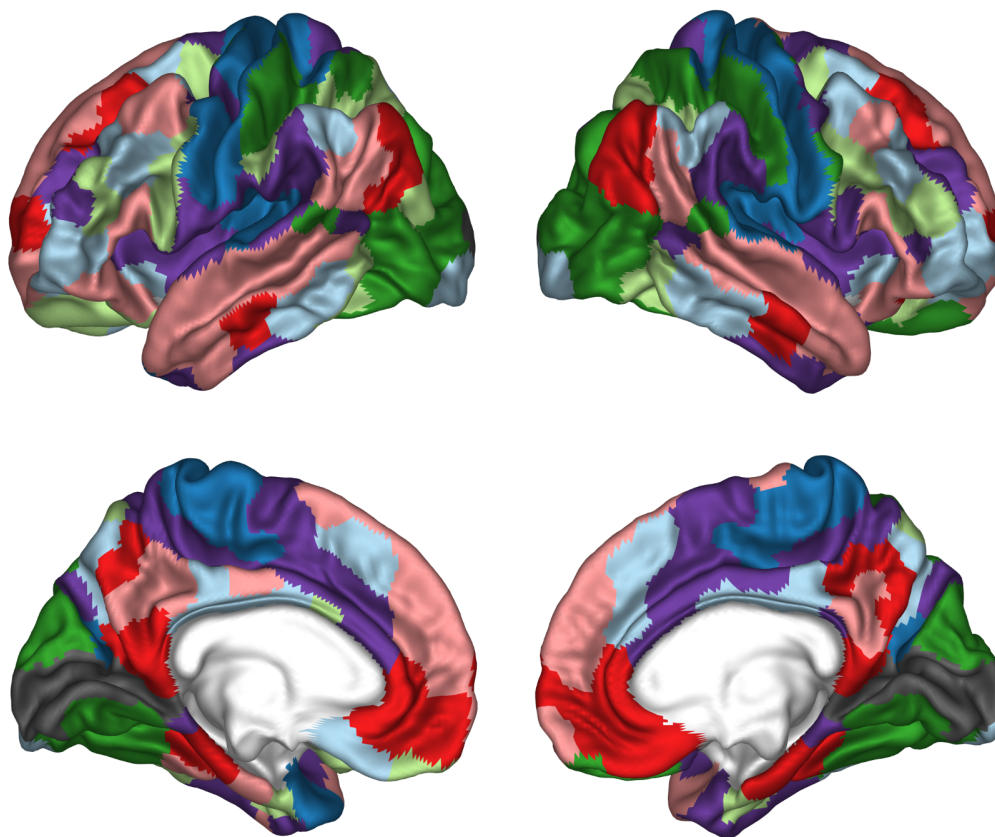


Figure 3.10: HONeD-in RSNs Shown Individually. The HONeD-in RSNs shown in Figure 3c plotted on separate brains, with the lateral views rotated 10° for a view of RSN arrangement around gyri.



HONeD-in RSNs with 8 Clusters

- Primary Visual ● Visual-Cont ● Multi-Sensory ● Salience
- DorsAttn A ● DorsAttn B ● Default A ● Default B

Figure 3.11: Eight RSN Solution. The 8-network solution for von Mises Fisher clustering on HONeD-in FC, which was equally stable to the 7-network solution (shown in Figure 3d). RSNs are identical to the 7-network case except for regions around the primary visual areas in the calcarine fissure, which form their own network. Note that the new visual-control network still occupies primary visual areas at the posterior-most end of the visual cortex.

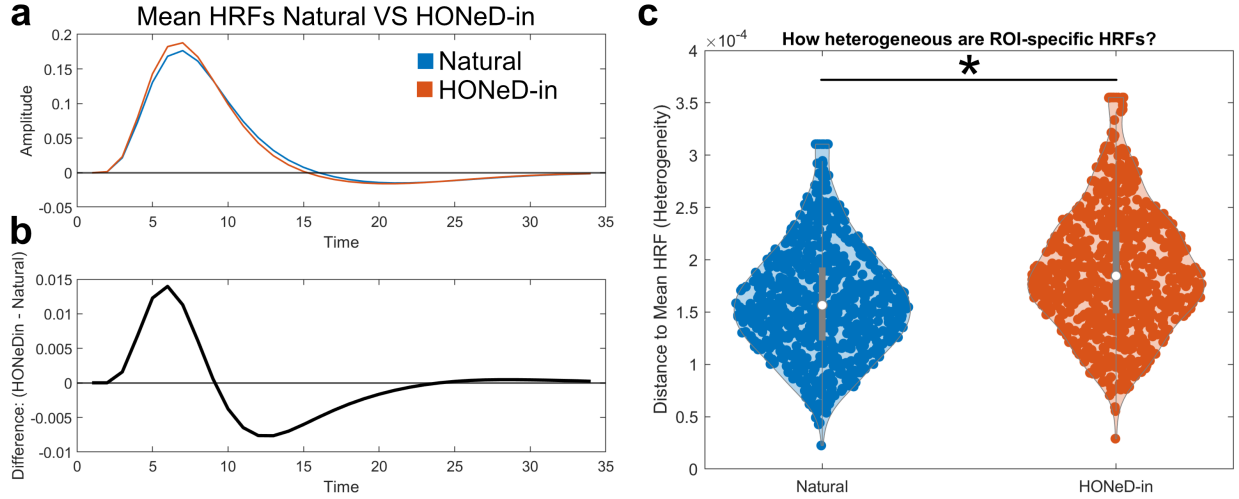


Figure 3.12: HONeD-in HRF Changes. (a) The subject mean estimated hemodynamic response function (HRF) for the natural signal (blue) compared to the HONeD-in signal (orange). (b) The difference between the HONeD-in and natural HRFs, showing that HONeD-in HRF has both a stronger peak and earlier decay compared to natural HRFs. The differences in HRFs were highly statistically significant using cluster-based analysis at all time points ($p_{\text{permutation}} = 0$). (c) We evaluated whether region-specific HRFs were more heterogeneous for HONeD-in signals by computing the Euclidean distance between each region-specific HRF and the global mean HRF. HONeD-in HRFs were significantly more heterogeneous than natural HRFs (Student's t-test: $p < 10^{-22}$).

Chapter 4

Gene Gradients Reveal Directed Structural Connectivity Across Species

4.1 Abstract

Diffusion MRI (dMRI) tractography is widely used to estimate structural connectivity (SC) between brain regions *in vivo*, but it cannot determine the direction of white matter pathways. Here, we introduce a structure-function computational model that combines dMRI-derived SC, gene co-expression gradients, and functional activity data to infer structural directionality. Our model accurately predicts ground-truth directionality in *C. elegans* ($r = 0.70$), mouse ($r = 0.57$), and macaque ($r = 0.46$). We then inferred directionality across 770 healthy young adults from the Human Connectome Project. Predicted directionality reproduced established asymmetries between the primary sensory areas and the thalamus and revealed distinct gene ontologies associated with network sources and sinks. Finally, we show how directed SC implies a model-based measure of directed functional connectivity, termed “angular flow” (AF). Regional AF net flow recapitulated the principal gradient of functional connectivity, suggesting that the canonical unimodal–multimodal hierarchy may arise from a source–sink organization of signal flow across the brain. This computational framework linking gene expression, structural directionality, and brain func-

tion enables future studies on gene-structure-function interactions in both health and disease.

4.2 Introduction

Mapping whole-brain structural connectivity (SC) is a central goal in neuroscience. The first completely mapped “connectome” was in the nematode, *Caenorhabditis elegans*, comprising 302 neurons [229]. Critically, this connectome is *directional*—it establishes which neurons transmit to others. Highly detailed directed connectomes have enabled computational models that provide deep mechanistic insights into brain processing and support large-scale *in silico* simulation of brains and behavior [189]. In mammals, however, whole-brain single-cell wiring diagrams remain inaccessible. Instead, invasive tract-tracing studies have been used to map regional directed connectivity in mice and non-human primates [152, 8], but these techniques are not suited for mapping human connectivity. As a result, present efforts to map human SC rely largely on diffusion magnetic resonance imaging (dMRI) tractography, which can measure the strength of connections between regions, but not the directionality. Therefore, neuroscience is in need of a framework to estimate structural directionality by other means.

A biological link between genes and SC suggests their potential utility for estimating directionality. Molecular gradients are well known to guide axon development [237], and regional gene-expression patterns are systematically related to macroscale brain connectivity [5]. Early work in rodents found that brain regions with similar gene expression profiles tend to have similar connectivity profiles, and that connected regions tend to exhibit greater co-expression than unconnected regions [66]. Gene expression also relates to structural hub organization: studies in *C. elegans* and mouse have identified distinctive transcriptional signatures of hub connectivity and elevated gene expression similarity between hubs [4, 71]. Similar relationships have been observed in humans, where regional gene expression and inter-region co-expression are significantly associated with both structural and functional connectivity [78, 88, 224]. Gene-expression topographies also mirror large-scale cortical network organization, consistent with a role in long-range cortic-

ocortical connectivity [115]. Importantly, studies in mouse have identified relationships between gene-expression and cell-type distributions and the direction of source-target axonal connectivity [52, 203]. Together, these findings suggest that gene co-expression maps may also contain latent information about directed SC.

Network diffusion models over the SC have also shown potential to reveal hints of latent directionality. Asymmetric communication emerges when signaling is modeled as a diffusive process on the network [143, 176]. Extending this idea to the whole-brain, decentralized communication measures including diffusion efficiency were used to infer group-level sender–receiver asymmetries from undirected structural connectomes [182]. More generally, network diffusion models relate correlations between brain signals to passive signal propagation through SC [1, 2, 63, 73]. Simulated asymmetric, afferent-normalized diffusion over structural networks has been shown to better constrain effective connectivity than conventional anatomical connectivity alone [195]. Similarly, noise-diffusion models often leverage the *Lyapunov Equation*, which describes the stationary covariance of a linear stochastic differential equation and has been used to infer directed effective connectivity from time-shifted functional covariance [73]. Therefore, network diffusion may also reflect latent directional information embedded in the way brain signals propagate across structural networks.

Together, these observations raise the possibility that combining gene expression and network diffusion models into a single genetically informed structure-function model could provide a more robust biophysically constrained scaffold for estimating the brain’s directed SC. Here, we introduce such a gene-structure-function model based on two hypotheses: 1) gene co-expression patterns can provide a parsimonious parameterization for directionality, and 2) there exists latent directional information contained in the undirected covariance of brain signals. Specifically, we construct a node-level metric from a parsimonious linear combination of gene expression principal components that together impose edge-level directionality throughout SC. We then learn the weights of these gene gradients by minimizing the Lyapunov Equation, which fits the model under the assumption that empirical zero-lag functional connectivity is stationary. The result of our model

fitting provides a prediction for the directed SC.

We found that our genetically informed structure-function model accurately estimates directed structural connections, using only a few gene gradients, across species where ground-truth directed connectivity is available (*C. elegans*, mouse, and macaque). In humans, since we lack ground-truth directionality, we used test-retest reliability to identify the optimal number of gene gradients. We then predicted subject-specific directed SC across all 770 Human Connectome Project subjects and analyzed both the predicted gene ontology relationships and directed structural pathways. We assessed the overall directional bias of structural connections, finding local directional motifs in each primary sensory area. Interestingly, our gene-structure-function model implies a *functional* directionality that recapitulates the traditional unimodal-multimodal functional gradient [134], suggesting that this gradient may originate from signal flow through SC. Together, our results establish a biologically constrained framework for recovering directed SC *in vivo*, linking gene expression, anatomical directionality, and large-scale functional hierarchy within one unified model.

4.3 Results

To infer structural directionality, we developed a model that constrains regional source–sink organization to a low-dimensional basis of gene co-expression gradients (**Fig. 4.1**). A weighted linear combination of these gradients defines a latent source–sink bias for each brain region, which transforms an undirected structural connectome (SC) into a predicted directed SC. We infer the gradient weights, together with three higher-order network diffusion parameters, with by fitting the model-implied steady-state covariance to the empirical zero-lag functional connectivity matrix through the Lyapunov equation (see Methods). Thus, the model estimates structural directionality from gene-expression gradients and symmetric structural and functional connectivity, without fitting to an empirical measure of functional directionality.

We first validated our directionality inference approach against ground-truth connectomes from three species: *C. elegans*, mouse, and macaque. We then applied the same approach to infer

human structural directionality in the Schaefer-400 atlas with 14 subcortical regions [180, 157], using test–retest fingerprinting to identify the optimal number of gene gradients. We examined the model-predicted human directed SC in terms of regional sinks/sources and directional relationships between resting-state networks. Using the estimated directed SC, we then derived *angular flow* (AF), a model-implied directed functional connectivity constrained by SC. We compared AF with lagged-FC, regression dynamic causal modeling (rDCM), and Granger causality (GC) estimated from human fMRI [69, 10]. Finally, we assessed the relationship between AF net flow and the principal gradient of undirected functional connectivity [134].

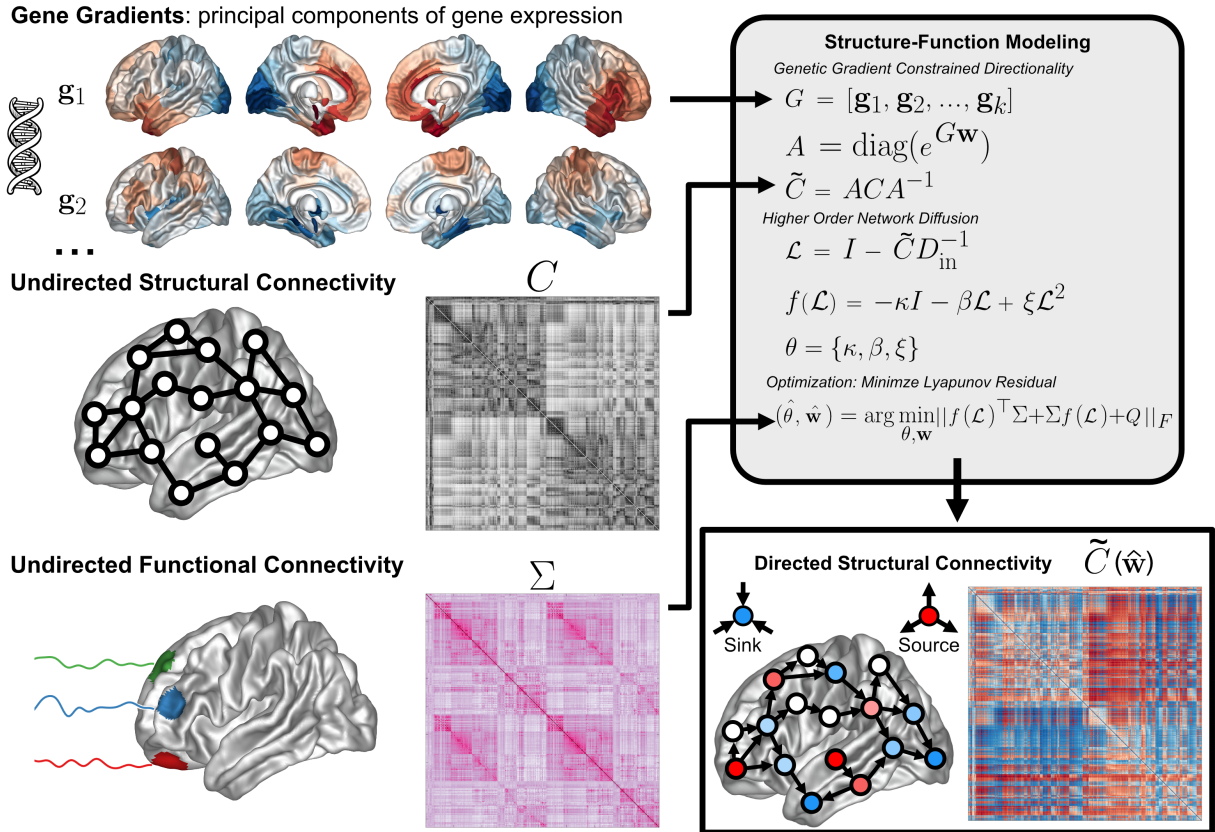


Figure 4.1: Method Overview. We estimate a node-level *asymmetry metric* using a linear combination of gene gradients (Gw). This asymmetry metric is assembled into an asymmetry matrix (A), which is used in a similarity transform on the undirected structural connectivity (C) to produce our directed SC ($\tilde{C}$). We estimate the optimal model parameters ($\{\theta, w\}$) by fitting a higher-order network diffusion model to functional connectivity (Σ) using the residual of the Lyapunov equation. The final predicted SC uses the optimal gene gradient weights: $\tilde{C}(\hat{w})$. Throughout, we follow the convention that network sinks are blue while sources are red.

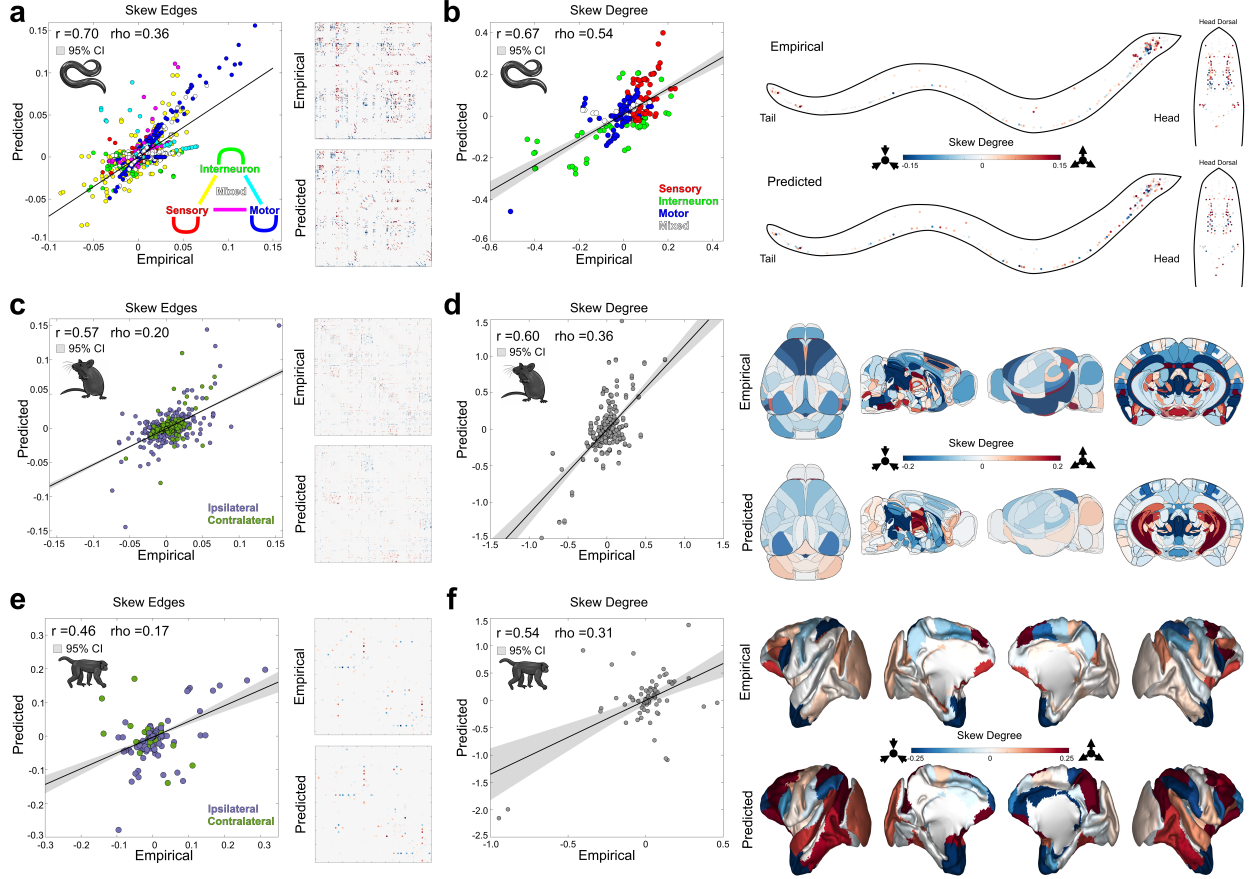


Figure 4.2: Cross-Species Validation. Comparison of directionality model predictions against ground-truth directed connectivity from three species: *C. elegans* (a & b), Mouse (c & d), and Macaque (e & f). For each species, we show the correlation between observed and predicted skew edges (a, c, e), and the corresponding skew connectivity matrices to the right of the scatter plots. For *C. elegans*, we color each connection by whether the neuron function is sensory (red), motor (blue), an interneuron (green), or of mixed-identity (white). When connections linked neurons of different types, we colored that connection as an intermediate color between the base colors. For mouse and macaque comparisons, we colored ipsilateral edges purple and contralateral edges dark green. We additionally show the skew degrees (b, d, f), which are the row-sums of the skew connectivity matrix ($D_{\text{skew}} = D_{\text{out}} - D_{\text{in}}$), both as a scatter plot and plotted in brain/body spaces on the right. For each scatter plot, we provide both the Pearson r and Spearman ρ correlations, all highly significant ($p \ll 0.001$), as well as the linear regression best fit lines with a shaded 95% confidence interval. We show the skew edge correlation results across different numbers of gene gradients in Supplemental Fig. S 4.6. We also show the empirical SC and FC used to fit the model in Supplemental Fig. S 4.7

4.3.1 Gene co-expression gradients predict directionality in non-human species

To validate against our three non-human species, we symmetrized the empirical ground-truth directed connectomes, $C_{\text{sym}} = (C_{\text{emp}} + C_{\text{emp}}^T)/2$, and entered this symmetric matrix, species-specific gene gradients, and the symmetric functional connectivity data into our model. We then compared only the skew (i.e., purely directional) components of the empirical and predicted structural networks, $C_{\text{skew}} = (C - C^T)/2$.

Model-predicted directionality significantly correlated with ground-truth directed edges in all three species. Our model-predicted directionality correlated with neuron-to-neuron synaptic directionality in *C. elegans* ($r = 0.70$), tracer-based directionality in mouse ($r = 0.57$), and tracer-based directionality in macaque ($r = 0.46$) (all $p \ll 0.001$, **Fig. 4.2 a, c, & e**). This correspondence remained significant under rank correlation and when evaluating network skew-degrees (**Fig. 4.2 b, d, & f**, see Supplemental Section 1 for exact statistics). We found that our model predicted edge-level directionality similarly well within and between hemispheres in *C. elegans* ($r_{\text{ipsi}} = 0.64$, $r_{\text{contra}} = 0.57$) and in mouse ($r_{\text{ipsi}} = 0.57$, $r_{\text{contra}} = 0.59$). However, for macaque directionality, only ipsilateral connections were accurate while contralateral connections, which were far fewer in number, were predicted in the opposite direction ($r_{\text{ipsi}} = 0.64$, $r_{\text{contra}} = -0.55$). We note that the macaque data may have significant limitations, including poor spatial resolution and very few gene expression maps (see Methods), which together may influence the observed results [131]. Nevertheless, these cross-species validations provide strong evidence that the model recovers substantial directional structure under favorable data conditions, while highlighting possible limitations in estimating contralateral directionality from sparse or incomplete data.

In our cross-species study the optimal number of gene gradients differed across species (*C. elegans*: $k = 3$; Mouse: $k = 5$; Macaque: $k = 1$; Supplemental **Fig. 4.6**), each corresponding to different amounts of explained variance (*C. elegans*: 13%; Mouse: 44%; Macaque: 36%; Supplemental **Fig. 4.6**).

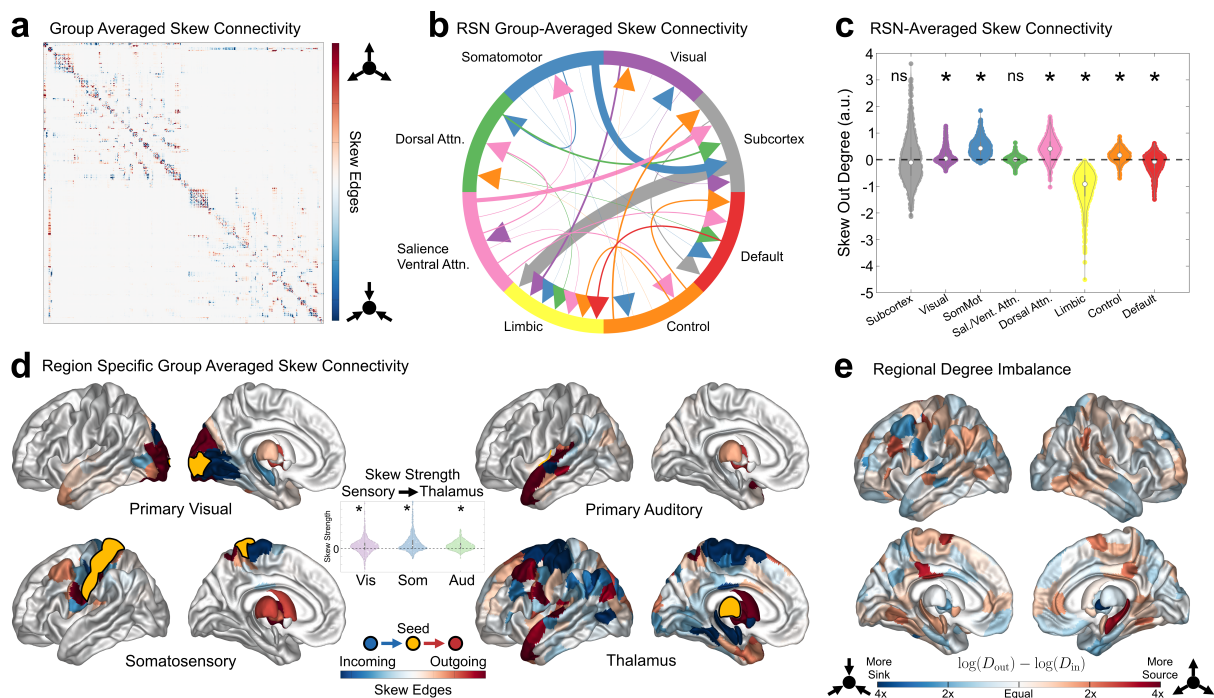


Figure 4.3: Human Estimated Structural Directionality. (a) The skew component of the group-averaged predicted SC. (b) Significant skew connectivity between resting-state networks. (c) Group-level skew out-degree of each RSN. (d) Select rows from the skew connectome for the primary sensory areas and thalamus showing directional bias between primary and higher-order processing areas. The yellow ROI indicates the exact region(s) we evaluated. The inset shows the group-level weights from each primary sensory area to the thalamus. All distributions were significantly positive, indicating net anatomical feedback connectivity to the thalamus. (HG: Heschl’s Gyrus) (e) The overall degree imbalance for each brain region from the group-averaged SC. The color map is on a $\log_2$ scale reflecting a multiplicative difference in out- versus in-degrees. Statistical tests were evaluated with a t-test, where $*:p < 0.01$, Bonferroni corrected. We show the fingerprinting and external dataset robustness results in the Supplemental Figs. S 4.8 and S 4.9, respectively.

4.3.2 Model-inferred human structural directionality

Because human structural directionality lacks direct ground-truth, we chose the number of gene gradients based on test-retest fingerprinting analysis on the predicted asymmetry metric (Gw). This implicitly hypothesizes that our model should yield directed SC estimates that are both replicable within subjects and discriminative between subjects. We evaluated test-retest fingerprinting for both 34 HCP test-retest subjects, each with two separate visits, and 724 HCP subjects, each with resting-state fMRI scans split into two equally sized ≈ 30 -minute blocks. We found that human asymmetry parameters had the overall best test-retest reliability ($ICC = 0.51 \pm 0.03$, Discriminability = 0.77, Supplemental **Fig. S 4.8**) when using $k = 5$ gene gradients, which together explained 59% of gene co-expression variance (See Supplemental Section 1 for details). Our model

predictions at $k = 5$ gene gradients also replicated in an external dataset ($r = 0.63, p < 0.01$, Supplemental **Fig. S 4.9**) [175]. Therefore, our subsequent results report the model with $k = 5$ gene gradients.

We show in **Fig. 4.3a** the group-averaged skew-directionality inferred by our model. We first investigated directionality between resting-state networks (RSNs). We found that many RSNs—Control, Salience, Dorsal Attention, Somatomotor, and Visual—were all strongly directed toward the subcortex (**Fig. 4.3b**); conversely, the subcortex had the strongest inter-RSN directionality toward the Limbic network. We evaluated the overall skew out-degree for each RSN across subjects. This showed that the Somatomotor and Salience Ventral Attention networks were the most prominent RSN-level sources, with the Visual and Control networks also showing a slight but significant group-level bias toward being net-sources (**Fig. 4.3c**). In contrast, the Limbic and Default networks were net-sinks, with the Limbic network having the most decisive directionality across all subjects (**Fig. 4.3c**). The Subcortical and Dorsal Attention networks did not show a significant source or sink bias at the group level, although subcortex directionality varied considerably across subjects (**Fig. 4.3c**). Since these networks tend to have both source- and sink-oriented connectivity, averaging across them negates the network-level bias.

Significant work in animal models has suggested that anatomical feedback connectivity from primary sensory areas to the thalamus largely outnumbers anatomical feedforward pathways from thalamus to sensory cortices [28, 3]. Therefore, we sought to evaluate and quantify our model-inferred directionality in each of three primary sensory cortices: visual, somatosensory, and auditory. Our model’s predictions align with this previous work, showing group-level bias in anatomical pathways from all three primary sensory areas to the thalamus (**Fig. 4.3d**, $p \ll 0.001$). Additionally, each primary sensory area had distinct patterns of connectivity to other nearby areas. Primary visual areas showed both feedback and feedforward connectivity to distinct areas of both dorsal and ventral visual streams (**Fig. 4.3d**). Primary visual areas also showed significant incoming connections from the hippocampus (**Fig. 4.3d**). Within the somatosensory cortex, the model predicted general incoming connectivity from nearby motor areas and outgoing connectivity to

more distant higher-level attention areas (**Fig. 4.3d**). The primary auditory cortex on Heschl's Gyrus (HG) showed nearly the reversed pattern: stronger outgoing connectivity to nearby regions, and more distant incoming connectivity from higher-level areas (**Fig. 4.3d**). Finally, the thalamus displayed strong directional preferences throughout the cortex and subcortex, which appear suggestive of corticothalamocortical (CTC) circuits [188].

While the above analyses assess the skew connectivity, measuring each node's degree imbalance is a way of quantifying the overall multiplicative difference between connections leaving versus entering the region. Across the brain, we found that most regions varied in their degree imbalance within a factor of 2, with some regions, including the hippocampus and pallidum, having as much as a 4-fold degree imbalance (**Fig. 4.3e**). Here, the thalamus showed a slight sink-bias, indicating that while its connectivity with sensory areas is significantly sink-like, its connectivity in general may be more balanced. The strongest network sinks included the hippocampus, temporoparietal junction, anterior cingulate, and posterior cingulate while the strongest network sources were the pallidum, temporal poles and ventromedial prefrontal cortices (**Fig. 4.3e**). Although the magnitude of directionality differed, there remained a distinct qualitative symmetry between homologous regions.

4.3.3 Sinks and sources suggest distinct gene ontologies

To assess the biological plausibility of our model-inferred directed human SC, we investigated whether our model-predicted asymmetry metric implicated genes with interpretable ontologies. We calculated the cosine similarity between our consensus-fit asymmetry metric and each of the 15,633 gene expression maps. Using the top 1,000 genes aligned with sinks or sources, respectively, we evaluated their gene ontologies with statistical comparisons to both our pool of 15,633 genes as well as to a null distribution defined by a spatial-autocorrelation (SA) preserving random rotation of the empirical map [32, 112] (see Methods for details). We calculated the "Enrichment Ratio" as the empirical number of genes related to the gene ontology term normalized by the mean number of genes across all SA-null maps associated with the same term.

We found that genes aligned in the sink-direction and genes aligned in the source-direction were associated with different gene ontology terms. Sink-aligned genes were enriched for ontologies related to protein synthesis, translation, and endoplasmic reticulum (ER) processing and quality control (**Fig. 4.4c**). The sink-axis was also enriched with genes related broadly to neural development and axon guidance, including regulation of SLIT and ROBO expression, as well as immune and broad disease- and infection-associated pathways (**Fig. 4.4c**). In contrast, source-aligned genes showed significant enrichment for ontology profiles related to the cellular structural constituents, including filaments and keratinization, as well as chemosensory receptor activity and G protein-coupled receptor signaling (**Fig. 4.4c**). Together, these results suggest a model-informed hypothesis in which sink-biased regions are enriched for molecular programs related to protein processing and developmental guidance cues, whereas source-biased regions are enriched for cytoskeletal and receptor-related programs that may support cellular responsiveness to such molecular landscapes.

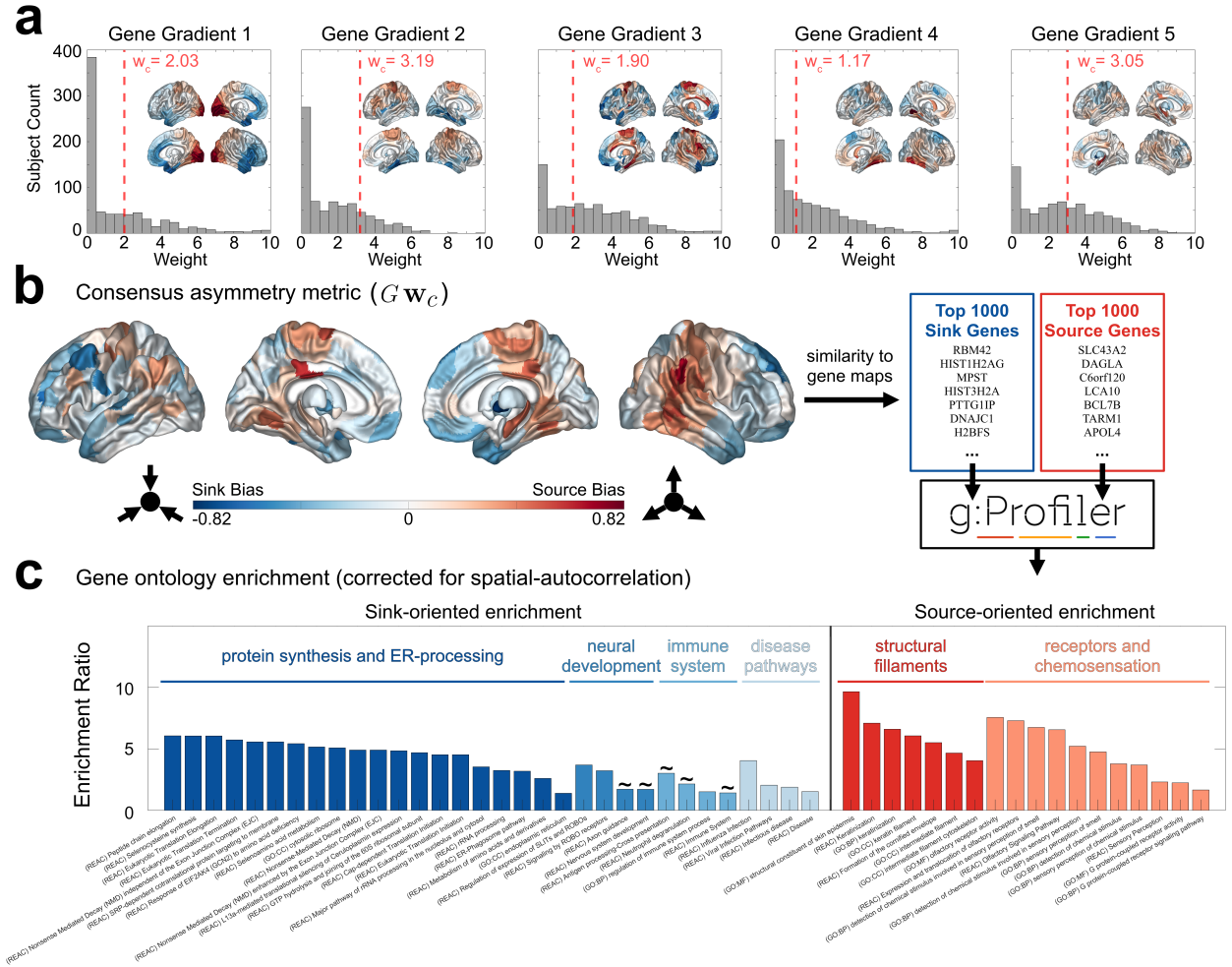


Figure 4.4: Model-Predicted Gene Ontologies. (a) The model-predicted gene gradient weights across all subjects (gray) and the weight parameters for the model fit to the consensus SC and FC (dashed red line). Each gene gradient used in the model is shown as an inset on the respective histogram. (b) The model-predicted node-level asymmetry metric for the consensus fit (i.e., the linear combination of gene gradients, Gw_c). Regions colored blue are biased toward receiving connections whereas regions colored red are biased toward sending out connections. We used the cosine similarity between this asymmetry metric and each gene map to extract the 1000 most sink- and source-aligned genes for input to g:Profiler. (c) A gene ontology enrichment analysis, corrected for spatial autocorrelation. We show all FDR-corrected significant gene ontology terms for the sinks (blue) or sources (red). Subsequent statistical testing compared these terms against a spatial-autocorrelation (SA) preserving null models. The “Enrichment Ratio” for a term is the empirical number of genes related to the term normalized by the mean number of genes across all SA-null maps associated with the same term (Equation 4.12). Gene ontology terms with a ~ were statistically significant (FDR $p < 0.05$) under the g:Profiler general ontology analysis, but trending ($0.05 < p < 0.1$) under the SA-null distribution; all other terms were significant under both.

4.3.4 Angular flow relates directed structure to directed function

Combining the previously fit directed SC operator with empirical functional covariance implies a model-based measure of directed functional flow, which we term “angular flow” (AF). We assessed whether AF offers complementary directional information to conventional causal discovery met-

rics in humans by comparing with lagged-FC, regression dynamic causal modeling (rDCM), and Granger causality (GC). To keep these metrics well-posed and tractable, we ran our comparisons in the Schaefer 100 atlas with 14 subcortical regions.

We found that all three causal discovery methods significantly correlated with AF (Lagged-FC: $r = 0.34$; rDCM: $r = 0.11$; GC: $r = 0.22$; all $p \ll 0.001$; **Fig. 4.5b**), and these results remained significant under rank correlation (see Supplemental Section 1). This provides convergent evidence that AF captures a broad directional bias shared, albeit weakly, by other causal discovery methods, but not reducible to any of them.

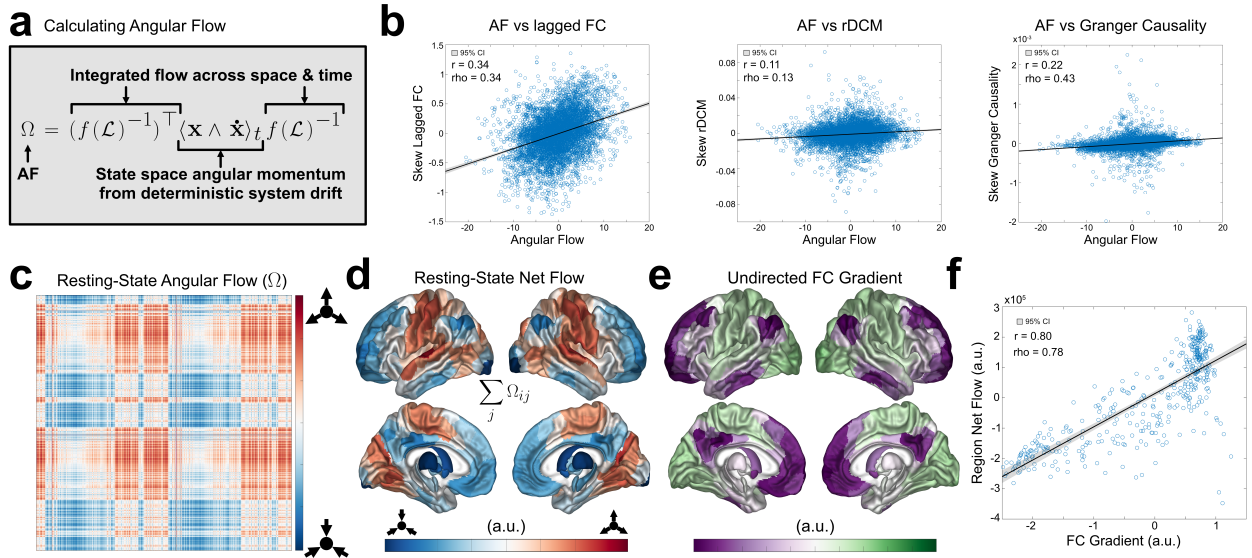


Figure 4.5: Angular Flow. (a) The AF equation, which emphasizes its relationship to both flow through the network and the brain’s angular momentum. (b) The comparisons between AF and (left-to-right) the human lagged-FC, rDCM, and GC, respectively (all in the Schaefer-100 atlas). (c) The angular flow (AF) during resting-state fMRI, averaged across subjects. (d) The sum along each row of AF to obtain the network’s net flow. (e) The first principal gradient of the group-averaged functional connectivity. (f) A scatter plot comparing (d) with (e), showing a highly significant correlation ($r = 0.8$, $p_{\text{spin}} \ll 0.001$). The null-distribution for the spin test is shown in Supplemental **Fig. 4.11**; the underlying diffusion operator is shown in Supplemental **Fig. 4.12**.

AF during resting-state fMRI showed distinct sink/source relationships between RSNs. Source RSNs consisted of the visual, somatomotor, dorsal attention, and salience/ventral attention networks; meanwhile, sink RSNs consisted of the default, control, limbic, and subcortical networks (**Fig. 4.5c-e**). Moreover, AF had regional net flow that strongly correlated with the principal functional connectivity gradient ($r = 0.80$, $p_{\text{spin}} \ll 0.001$; **Fig. 4.5f**) [134]. This correspondence could not be trivially reduced to the underlying diffusion operator ($r = 0.04$, Supplemental **Fig. 4.12**),

which suggests that the emergence of the principal gradient was a synergistic interaction of the diffusion operator acting on the empirical signal covariance. We also found that subject-specific AF calculations with directed SC outperformed the same calculation with undirected (symmetric) SC and the empirical lagged-FC ($p < 0.001$; Supplemental **Fig. 4.13**), highlighting the primacy of the directed SC in mediating this structure-function relationship.

4.4 Discussion

Inferring directed structural connectivity (SC) at the macroscale remains a central challenge in network neuroscience. Here, we constrain directionality to a low-dimensional basis of gene co-expression gradients and fit their contributions using a structure-function model. The model recovered significant directional organization across three non-human species (**Fig. 4.2**), and, in humans, produced reliable subject-specific estimates with biologically interpretable sink-source organization and gene ontologies (**Figs. 4.3 & 4.4**). The model operator also implied a measure of functional “angular flow” (AF) through SC that recapitulates the principal gradient of functional connectivity (**Fig. 4.5**). Together, these findings link regional gene expression, anatomical directionality, and large-scale signal flow within a unified framework.

4.4.1 Gene gradients constrain structural directionality

A central implication of these results is that gene co-expression gradients define a low-dimensional biological manifold for network directionality. Although prior work has suggested links between genes and structural connectivity, it has generally lacked a model to relate them [66, 115, 5, 52, 203]. Here, we provide such a genetically informed structure-function model, which suggests that genes impose a directional bias at both neuronal and regional levels. Past work on structure-function modeling has argued that lagged functional connectivity is necessary for SC directionality to be identifiable [73]. However, our results point to gene expression as a parsimonious and biologically plausible constraint from which directional properties can emerge even for zero-lag covari-

ance. This constraint collapses an otherwise underdetermined n^2 -dimensional edge-direction problem into a low-dimensional node-level parameterization, making directionality estimation tractable and empirically testable.

4.4.2 Model predictions align with biological evidence

Our model’s ability to estimate non-human directed SC across *C. elegans*, mouse, and macaque suggests that the relationship between gene gradients and structural directionality is conserved across both phylogeny and brain scales. However, given a lack of ground-truth in humans, it is important to approach interpreting the human directed SC with caution. The discussion below should be considered as an exploration of model-driven hypotheses rather than definitive results on white matter directionality as such.

One way to biologically interpret our model prediction is to assess how it relates to well-studied anatomical pathways in non-humans. There is considerable scientific discussion on the role and quantity of feedback versus feedforward connectivity between sensory areas and the thalamus [28, 3]. While corticothalamic connectivity is generally reciprocal, evidence suggests a bias toward more corticothalamic projections across sensory modalities [146, 220, 230, 174]. Our model similarly showed corticothalamic bias in primary sensory areas, and is therefore broadly consistent with prior non-human anatomy literature (**Fig. 4.3**). Feedback connectivity from higher-level sensory areas to primary sensory areas is also well documented [137, 114], and was also observed in our model predictions (**Fig. 4.3**). At the network level, subcortical and cortical limbic systems were prominent sinks, which aligns with previous hypotheses that these regions are targets of top-down allostasis-driven predictions [11]. However, our model did not simply predict the thalamus as a global sink, but instead predicted patterned bidirectional connections throughout the cortex, suggestive of corticothalamocortical circuits [188]. While it is reassuring that the model appears generally aligned with previous research, it is crucial not to over-interpret model predictions and instead recognize that these predictions are merely hypotheses to guide future empirical work.

Another way to biologically interpret our model prediction is to assess what it implies about the underlying gene expression ontologies related to directionality. Our model predicted sink-biased regions that were enriched for genes involved in protein synthesis and neural development and source-biased regions enriched for cellular intermediate filaments and chemosensory receptors (**Fig. 4.4**). One especially interesting result was the model-predicted enrichment for SLIT and ROBO gene regulation, which are genes well documented to code for molecular gradients that can either attract or repel growing axons in the brain [206, 126, 190, 178, 135]. Meanwhile, intermediate filaments are broadly involved in cell and tissue mechanics, contributing to mechanical stability, cytoarchitecture, cell-shape regulation/remodeling, and cell migration [96, 118], which is biologically appropriate for source-biased regions. Chemosensory olfactory receptor (OR) enrichment was also significantly related to source-biased regions, which aligns with previous work showing that OR expression helps guide axon growth in olfactory circuits [202, 54] and have significant ectopic expression [107]. Contextualized by this literature, our model therefore suggests the hypothesis that sink-biased regions may contribute molecular guidance landscapes, while source-biased regions may be enriched in receptor and cytoskeletal programs that support sensing and responding to such landscapes.

4.4.3 The structure-function relationship reveals latent directionality across scales

The present work adds to a growing literature showing that structural information can impose strong constraints on functional organization, especially within linear models [1, 2, 16, 195, 151]. That our model can approximate ground-truth directed SC by fitting to undirected functional connectivity supports the broader view that a *directed* SC provides a macroscopically linear scaffold for brain function with observable consequences.

Somewhat surprisingly, we found that our linear graph diffusion model was effective in fitting to *C. elegans* data and accurately recovering the underlying synaptic directionality (**Fig. 4.2**). This suggests that even a relatively small network of neurons with highly nonlinear dynamics may

still have a form of macroscopic linearity that our model can observe. This is especially notable because previous work studying signal propagation in *C. elegans* showed that SC poorly predicted functional signaling when using a neural mass model [164]. Although this current work does not yet fully resolve the SC-FC misalignment tension in *C. elegans*, these findings suggest the potential for linear structure-function relationships in the brain to remain relevant even within relatively small neural populations.

4.4.4 Angular flow as a natural extension of a directed SC

Modern directionality estimates in human neuroscience typically estimate a notion of causality either by the predictability of signals between brain regions, such as in Granger causality [185, 10], or by model-based approaches such as dynamic causal modeling [65]. However, estimating these measures is computationally challenging and increasingly ill-posed with large networks [65], and they generally are not informed by the biophysics of the underlying SC. Even DCM, which has the potential to be constrained by SC, does so only in a binary fashion without SC weights.

Here, we introduce angular flow (AF) as a complementary measure for directionality. AF has the key advantage of being based on a generative model leveraging all the information contained in SC to predict the net flow of signal between two regions. While prior methods aim to estimate a pairwise causality between brain regions, AF analytically calculates the aggregate observed signal movement through SC and across time. In humans, our AF measure somewhat correlated with lagged-FC, rDCM, and multivariate Granger causality, suggesting that they share some directional information despite their differences (**Fig. 4.5**). AF also complements our view of directionality from purely anatomical connectivity. For example, while the thalamus is only slightly sink-biased in the modeled SC (**Fig. 4.3**), once we factor in the dynamics of empirically observed function, the thalamus becomes the strongest network sink of the brain (**Fig. 4.5**). This example highlights an important distinction between a purely pairwise directional scaffold and the total dynamical flow through that scaffolding.

AF may also explain the emergence of the unimodal-multimodal principal functional gradient

in undirected functional connectivity. Since its first description by Margulies et al. [134], much work has emphasized the primacy of this unimodal-multimodal gradient in the brain [95]. Previous work has related this principal gradient to the brain’s structure-function relationship, even when SC-FC coupling is defined in several distinct ways [156, 158, 15, 226]. AF extends and refines these insights by suggesting that the unimodal-multimodal gradient arises from the net flow of brain signals through the directed SC from unimodal to multimodal cortical areas (**Fig. 4.5**). Importantly, lagged-FC failed to recover this relationship (Supplemental **Fig. 4.13**), emphasizing the role of the structure-function model in revealing this correspondence. This result dovetails with our prior work on network deconvolution [193]: when passive network diffusion over SC is removed from fMRI, functional gradients become remodeled; when directional diffusion is estimated on empirical brain signals, the functional gradient reappears as the pattern of net flow through structure.

4.4.5 Limitations and future work

These results should be interpreted with appropriate caution. Human directed SC here remains a model prediction rather than a directly observed anatomical measure. The non-human validations are limited by the availability of only one consensus ground-truth per species, and those ground-truth datasets differ in completeness, scale, and biological meaning. The model also depends on how regional gene expression maps are estimated, including which parcellation is chosen, which genes are available, and how missing tissue is interpolated. These ground-truth limitations were especially relevant for the macaque data, where directionality was consolidated by CoCoMac across many separate studies and both the gene spatial coverage and diversity were highly limited. We speculate that these issues may explain why the macaque model only used one genetic gradient, and why the prediction itself was the weakest of the three ground-truth analyses.

Methodologically, our directionality parameterization is effective but still bespoke: a diagonal similarity transform is mathematically convenient and biologically suggestive, yet it is not itself a mechanistic developmental model of axonal targeting. Likewise, the fitted diffusion operator

is linear and stable, which likely restricts the space of recoverable directed dynamics even as it guards against overfitting. Our AF measure inherits these assumptions and introduces an additional interpretational caveat: an inhibitory influence between two regions may be partially conflated with a reversed directionality. Future work should therefore consider testing alternative generative mechanisms for genetically influenced asymmetry and assessing the behavioral relevance of task-based changes in AF.

4.5 Conclusion

We introduced a genetically informed structure-function model for recovering directed structural connectivity and validated it against ground-truth connectomes in *C. elegans*, mouse, and macaque. Applied to humans, the model revealed biologically interpretable source–sink organization and enabled a structurally informed measure of directed functional flow, termed angular flow (AF). AF recapitulated the principal functional connectivity gradient, linking molecular organization, anatomical directionality, and large-scale functional hierarchy within a unified framework. Overall, this framework provides a fundamentally new way to estimate and analyze both directed structural and functional connectivity in the brain.

4.6 Materials and Methods

4.6.1 Theory

Here, we describe the structure-function model used to predict directed structural connectivity. In essence, our model predicts that resting-state functional covariance is close to a stationary covariance, which we formalize using the Lyapunov Equation within a multivariate Ornstein–Uhlenbeck (MOU) process. The model operator that governs the brain’s internal dynamics over the structural connectome is a higher-order (i.e., polysynaptic) network diffusion model. Our goal is to find a node-level directionality bias, parameterized by gene gradients, that optimizes this station-

ary structure-function alignment. In the following, we construct this structure-function model by first parameterizing structural directionality with gene gradients, then introducing the higher-order graph Laplacian operator, and finally relating the resulting dynamics to stationary empirical covariance.

Parameterizing directionality with gene gradients

We first obtained gene expression maps ($E \in \mathbb{R}^{m \times n}$) for all n brain regions (or neurons in the *C. elegans* case), z-scored each map, then calculated the principal components as the eigen-decomposition of the gene expression covariance matrix ($E^\top E = G\Lambda_E G^\top$). Hereafter, we term these principal components “gene gradients”. Using the gene gradients associated with the k largest eigenvalues ($G^{(k)} \in \mathbb{R}^{n \times k}$), we imposed directionality by constructing a node-wise *asymmetry metric* as a linear combination of genetic gradient basis vectors with weights ($\mathbf{w} \in \mathbb{R}^{k \times 1}$): $G^{(k)}\mathbf{w}$. This asymmetry metric is built into a diagonal positive-definite matrix $A = \text{diag}(e^{G^{(k)}\mathbf{w}})$ which induces a similarity transform on our undirected structural connectivity matrix $C \in \mathbb{R}^{n \times n}$:

$$\tilde{C}(\mathbf{w}) = ACA^{-1} \quad (4.1)$$

Element-wise, this is $\tilde{C}_{ij} = \frac{A_{ii}}{A_{jj}}C_{ij} = C_{ij}e^{(G^{(k)}\mathbf{w})_i - (G^{(k)}\mathbf{w})_j}$, making it clear that each entry in C is multiplied by an asymmetry factor given by the diagonal of A ¹. This means that our model preserves all non-zero edges, and the model will not add new edges that were not present in the original connectome. Throughout, we follow the convention that $\tilde{C}_{ij}$ indicates a directed connection from node i to node j . In the directed network $\tilde{C}$, we may calculate the *out-degree* ($D_{\text{out}} = \text{diag}(\sum_j \tilde{C}_{ij})$) and the *in-degree* ($D_{\text{in}} = \text{diag}(\sum_i \tilde{C}_{ij})$) representing how strongly that region transmits or receives connections, respectively.

¹This parameterization is invariant under a constant shift (i.e., the metric has an invariant geometric mean). *Proof:* Consider the transformation $A \mapsto \hat{A} \equiv sA$ for any scalar $s > 0$. Then $\hat{A}C\hat{A}^{-1} = (sA)C(sA)^{-1} = (sA)C(s^{-1}A^{-1}) = ACA^{-1}$. Equivalently in log coordinates, $\hat{A} = \text{diag}(se^{G\mathbf{w}}) = \text{diag}(e^{(\log s) + G\mathbf{w}})$, and $\tilde{C}_{ij} = C_{ij}e^{\log s + (G\mathbf{w})_i - \log s - (G\mathbf{w})_j} = C_{ij}e^{(G\mathbf{w})_i - (G\mathbf{w})_j}$.

Directed graph Laplacian

The graph Laplacian is a graph analogue to the Laplace-Beltrami operator for manifolds [104]. It is critical to modeling how signals move through networks, and it is the heart of graph diffusion models. Here, we chose to use the column-stochastic Laplacian:

$$\mathcal{L}(\mathbf{w}) = I - \tilde{C}(\mathbf{w})D_{\text{in}}^{-1} \quad (4.2)$$

The graph Laplacian normalizes each node by the network’s in-degree, thereby assuming that each brain region changes its signal based on the weighted average of all incoming signals. We chose this specific Laplacian normalization based on previous work demonstrating that in-degree normalized networks outperform other normalization strategies when predicting directed functional connectivity [195].

The higher-order network diffusion (HONeD) model

Prior work, including our own, has generalized the network diffusion model on networks to account for multi-step connections through SC [193, 16, 195]. Here, we again leverage higher-order network diffusion (HONeD) as our structure-function model operator to identify SC directionality. We define our diffusion operator as:

$$f(\mathcal{L}(\mathbf{w}); \theta) = \sum_{p=0}^P \theta_p \mathcal{L}^p \quad (4.3)$$

Here, P is the order of the Taylor series approximation, and $\mathcal{L}$ is the directed graph Laplacian of structural connectivity. As in past work, we chose to limit the network diffusion model to two steps ($\mathcal{L}^2$) through the network² [193, 16]. Therefore, the HONeD operator for the present work becomes

$$f(\mathcal{L}(\mathbf{w}); \theta) = -\kappa I - \beta \mathcal{L} + \xi \mathcal{L}^2 \quad (4.4)$$

²The matrix power of a graph’s adjacency matrix, $G^n \forall n \in \mathbb{N}$, encodes walks of length n on the graph.

Here, we denote the terms from the Taylor expansion $\theta_0 = -\kappa$, $\theta_1 = -\beta$, and $\theta_2 = \xi$ for ease of referencing. Written in this way, κ , β , and ξ are all constrained to maintain model stability and identifiability. In the following, we use $f(\mathcal{L})$ as a shorthand for this parameterized function of the graph Laplacian.

Predicting structural directionality with HONeD

Network diffusion may be well-suited to identifying directionality since its influence on brain signal covariance should remain stable across long time scales. HONeD can be expressed as the drift operator of a structurally constrained multivariate Ornstein–Uhlenbeck (MOU) process, or equivalently a linear time-invariant (LTI) graph-diffusion system driven by stochastic input [73, 75, 1, 214]. In this model, we consider a brain signal $\mathbf{x}(t) \in \mathbb{R}^n$ with an actuation matrix $B \in \mathbb{R}^{n \times \ell}$ and a stochastic driving signal $\epsilon(t) \in \mathbb{R}^\ell$: $\frac{d\mathbf{x}(t)}{dt} = f(\mathcal{L})^\top \mathbf{x}(t) + B\epsilon(t)$ ³.

This MOU process can be shown to have a relationship to the change in the instantaneous signal covariance $\Sigma(t) = \mathbf{x}(t)\mathbf{x}(t)^\top$ (whose expectation approximates a stationary covariance) with the Lyapunov equation [7]:

$$f(\mathcal{L})^\top \Sigma(t) + \Sigma(t)f(\mathcal{L}) + Q = \dot{\Sigma}(t) \quad (4.5)$$

Commonly, the Lyapunov equation is solved at steady state where $\dot{\Sigma}(t) = 0$ denotes the time derivative of instantaneous covariance [73]. At steady state, this derivative is zero. We approximate the stationary covariance with the sample covariance $\Sigma = \mathbb{E}[\mathbf{x}(t)\mathbf{x}(t)^\top] = \frac{1}{T} \sum_{t=1}^T \mathbf{x}(t)\mathbf{x}(t)^\top$, and with the noise covariance $Q = B \mathbb{E}[\epsilon(t)\epsilon(t)^\top]B^\top \propto I$. For a thorough derivation, see Supplemental Section 2. By estimating the sample covariance of brain signals as Σ , we can leverage the Lyapunov equation to define a cost function for our model:

$$(\hat{\theta}, \hat{\mathbf{w}}) = \arg \min_{\theta, \mathbf{w}} \|f(\mathcal{L})^\top \Sigma + \Sigma f(\mathcal{L}) + Q\|_{\text{Fro}} \quad (4.6)$$

With this cost function, we acknowledge that the brain is not fully stationary, so we instead find the

³For ease of notation, we abbreviate the model $f(\mathcal{L}; \theta; \mathbf{w}) \equiv f(\mathcal{L})$. While we include the mathematical details with the actuation matrix (B) for completeness, the properties of B are neither explored in nor relevant to this work.

optimal model parameters ($\{\hat{\theta}, \hat{\mathbf{w}}\}$) that bring the system as close to a stationary state as possible. When fitting the model, we chose Q to be the diagonal of the empirical covariance (Σ). Using these optimal values, we constructed a directed $f(\mathcal{L})$ that best describes the observed stationary diffusion process in the brain.

Predicting functional directionality with structural directionality

Once our directed HONeD operator has been fit to empirical data, we can then leverage that same operator with the same parameters to better understand the directionality of functional brain signals.

We approach this notion of *functional* directionality using a conceptual framework similar to previous work by considering the time lags in the system. More precisely, our model predicts that $\mathbf{x}(t + \tau) = e^{f(\mathcal{L})^\top \tau} \mathbf{x}(t) + \eta_\tau(t)$, where $\eta_\tau(t) = \int_0^\tau e^{f(\mathcal{L})^\top (\tau-s)} B d\epsilon(t + s)$ is the future white noise accumulated after time t . This yields a prediction for the time-lagged covariance:

$$\tilde{\Sigma}(\tau) = \mathbb{E}[\mathbf{x}(t)\mathbf{x}(t + \tau)^\top] = \Sigma e^{f(\mathcal{L})\tau} + \mathbb{E}[\mathbf{x}(t)\eta_\tau(t)^\top] \quad (4.7)$$

Then $\tilde{\Sigma}(\tau)_{ij}$ quantifies how fluctuations in region i at time t covary with region j at time $t + \tau$.⁴ Here, we assume that the white noise is independent of the current state, causing the second term to vanish: $\mathbb{E}[\mathbf{x}(t)\eta_\tau(t)^\top] = 0$. Now we will define the total flow (F) of functional signals through all paths in the structural connectome as the integral across all lags:

$$F = \int_0^\infty \tilde{\Sigma}(\tau) d\tau = \Sigma \int_0^\infty e^{f(\mathcal{L})\tau} d\tau = -\Sigma f(\mathcal{L})^{-1} \quad (4.8)$$

This uses the identity $\int_0^\infty e^{f(\mathcal{L})\tau} d\tau = -f(\mathcal{L})^{-1}$, which holds whenever $f(\mathcal{L})$ is Hurwitz.⁵ The matrix $-f(\mathcal{L})^{-1}$ is the time-integrated evolution operator for the system, and it bears some similarity

⁴To keep our directionality convention homogeneous across networks, we used the transpose of the traditional dynamic causal model (DCM) framework where $\Sigma(\tau)_{ij} = \mathbb{E}[\mathbf{x}(t + \tau)\mathbf{x}(t)^\top]$ implies a directed connection from j to i .

⁵Note that in our HONeD model, $f(\mathcal{L})$ is constrained to be Hurwitz.

to previously defined measures of flow based on a different framing for a linear dynamical MOU process [74]. Therefore, F can also be viewed as a form of “flow” in the sense that it casts the empirical covariance (conventionally known as “functional connectivity”) through the directed SC operator integrated *across all time*, reflecting the aggregate flow of signal from any region i to region j across all possible network paths.

Deriving the brain signal’s angular momentum

In this section, we show that this hybridization between the empirical brain function and the model operator has a fundamental relationship to a form of angular momentum in the brain. To show this relationship, first consider the purely directional, anti-symmetric component of F :

$$\Omega = F - F^\top = (f(\mathcal{L})^{-1})^\top \Sigma - \Sigma f(\mathcal{L})^{-1} \quad (4.9)$$

When we factor out the time-integrated operator from both sides, it reveals a relationship to an *angular momentum*-like bivector of the brain signal’s state space:

$$\begin{aligned} \Omega &= (f(\mathcal{L})^{-1})^\top \Sigma - \Sigma f(\mathcal{L})^{-1} \\ &= (f(\mathcal{L})^{-1})^\top (\Sigma f(\mathcal{L}) - f(\mathcal{L})^\top \Sigma) f(\mathcal{L})^{-1} \\ &= (f(\mathcal{L})^{-1})^\top \langle \mathbf{x}(t) \dot{\mathbf{x}}(t)^\top - \dot{\mathbf{x}}(t) \mathbf{x}(t)^\top \rangle_t f(\mathcal{L})^{-1} \\ &= (f(\mathcal{L})^{-1})^\top \langle \mathbf{x} \wedge \dot{\mathbf{x}} \rangle_t f(\mathcal{L})^{-1} \end{aligned} \quad (4.10)$$

Here, $\mathbf{x} \wedge \dot{\mathbf{x}}$ can be interpreted as an angular momentum bivector, analogous to classical angular momentum in physics.⁶ We take $\dot{\mathbf{x}}(t) = f(\mathcal{L})^\top \mathbf{x}(t)$ to be the fully deterministic drift without noise. Given its origin as the antisymmetric component of covariance-weighted integrated flow, and its formal relationship to a state-space angular momentum bivector, we refer to this quantity as

⁶The wedge symbol ($\wedge$) denotes the exterior product, also called the wedge product. Given two vectors, it produces an antisymmetric matrix that encodes the oriented area spanned by those vectors. In classical mechanics, angular momentum can be written as $L = r \wedge p$, where r is the position and $p = m\dot{r}$ is the momentum. In three dimensions, this bivector is equivalent via the Hodge-dual to the more familiar angular momentum vector $r \times p$.

angular flow (AF). Therefore, AF has the interpretation of transforming the net state-space angular momentum through the time-integrated system dynamics.

Using AF, we may calculate the net flow for each brain region as $\sum_j \Omega_{ij} = \sum_j F_{ij} - F_{ji}$, which is positive if there is net flow moving *out* of a region, and negative if there is net flow *into* a region. In this sense, $\sum_j \Omega_{ij}$ is analogous to the graph divergence of an antisymmetric edge-flow field, where Ω can be viewed as a discrete 1-cochain on the network.

It is worth emphasizing again that AF is *not* purely an SC-based prediction for functional connectivity, nor is it a trivial reproduction of the original signal covariance (Σ). Instead, it is an object that hybridizes the prediction of a directed structural operator governing brain signal flow and the empirically observed signal covariance itself. Since it is derived from the HONeD operator, it inherits the constraints imposed by diffusion through SC when calculating the asymmetric flow between regions. AF also does *not* imply a notion of pairwise causality; rather, it implies a whole-brain ‘tilt’ of signal flow through the entire network between any two brain regions across time.

4.6.2 Non-human datasets and processing

Caenorhabditis elegans dataset

We leveraged the publicly available *C. elegans* dataset provided by `wormatlas`, which includes recordings from 300 neurons imaged from 113 individuals [164]. In particular, it includes a directed neuron-to-neuron structural connectome [229, 231], single-cell transcriptomics for 13,669 genes [205], and neuron-level Ca^{2+} fluorescence imaging time series where optogenetic stimulation was applied to single cells [164]. The final *C. elegans* connectomes reflected structural synaptic connectivity between 296 cells, where 4 cells were excluded since they lacked any empirically observed synaptic connections. We took the empirical ground-truth neuron-to-neuron structural connectome and symmetrized it as $C_{\text{sym}} = (C + C^\top)/2$, thereby destroying all directional information, before entering it into our directionality model. For an approximation of the signal covariance between neurons, we used the empirical preprocessed Ca^{2+} imaging time series across all 113 individuals and calculated $\Sigma_{ij} = \langle \mathbf{x}_i(t) \mathbf{x}_j(t) \rangle_t \quad \forall t \mid \mathbf{x}_i(t), \mathbf{x}_j(t) \neq 0$. Since each cell

had its own transcriptomic profile, we calculated the principal components of the full matrix and used the first k largest principal components in our model (see Theory section for mathematical details).

Mouse dataset

The Allen Mouse Brain Connectivity Atlas, the first whole-brain mouse connectome, was published and made publicly available in a landmark study by the Allen Brain Institute [152]. They used an anterograde tracer with 469 image sets to identify directed structural connections between 213 regions across the entire mouse brain. Each region was assessed for either ipsilateral or contralateral connectivity, meaning that left and right homologs were used together in directional estimations. Therefore, to construct a whole-brain connectome with 426 regions to serve as ground-truth, we assumed that left-right homologous regions had equivalent ipsilateral/contralateral directionality. Region-level gene expression data came from the coronal series of the in situ hybridization (ISH)-based Allen Gene Expression Atlas (AGEA) with 4083 genes [119].

Preprocessed functional MRI data were obtained from nine mice (age: 9 ± 0.05 months) with a total of 40 minutes of resting-state fMRI scan time for each mouse [207]. Preprocessed fMRI and anatomical images were provided already registered to the Australian Mouse Brain Mapping Consortium (AMBMC) MRI template. We then registered the Allen Brain structural template at $10 \mu\text{m}$ to the AMBMC mean fMRI volumes using Advanced Normalization Tools (ANTs) with linear interpolation in Python. We then used this transform between spaces to map the Allen Brain atlas with 426 regions to the AMBMC space with generic label interpolation. With the atlas in AMBMC space, we used nilearn to calculate the mean time series for all regions.

Macaque dataset

For the non-human primate dataset, we used an OpenNeuro macaque dataset that includes fMRI time series from nine macaques (eight *Macaca mulatta*, one *Macaca fascicularis*) and a dMRI-derived consensus SC parceled in the RM atlas with 82 cortical brain regions [187]. Notably, the

SC was directed, with directionality coming from aggregating results from tracer-based studies in the CoCoMac dataset [201]. This tracer-based directionality was treated as a ground-truth to which we compared our model performance. When entering this connectome into our directionality model, we symmetrized the macaque connectome (C_M) as $C_{M,\text{sym}} = (C_M + C_M^\top)/2$. The preprocessed fMRI time series were obtained in a standardized F99 volumetric space after confound regression, and we parceled the time series by averaging all voxels in each region using the macaque volumetric RM atlas. Macaques were lightly anesthetized before their scanning session, and anesthesia was maintained using 1–1.5% isoflurane during image acquisition [187]. For full acquisition and processing details, see Shen et al. [187]. Region-wise transcriptomics was obtained from a publicly available dataset with 131 genes [131].

Statistical comparisons to ground-truth connectomes

When comparing model predictions to the ground-truth in the above non-human species, we calculated the Pearson correlation between the empirical and predicted skew connectivity matrices, $C_{\text{skew}} = (C - C^\top)/2$, as well as empirical and predicted skew degrees, $D_{\text{skew}} = D_{\text{out}} - D_{\text{in}}$. We used only non-zero edges since the absence of an empirically reported directed edge does not necessarily reflect a true absence of directed connectivity between observed brain regions. When p-values were below computer precision, we denoted them as $p \ll 0.001$.

4.6.3 Human dataset and processing

We used 770 subjects from the Human Connectome Project (HCP) Young Adult dataset in this study [219]⁷. We excluded all HCP subjects that had documented quality control issues. Unprocessed HCP data were downloaded and organized into BIDS format. Anatomical scans were collected with an MPRAGE T1-weighted sequence. Functional MRI (fMRI) data included four

⁷Data were provided by the Human Connectome Project, WU-Minn Consortium (Principal Investigators: David Van Essen and Kamil Ugurbil; 1U54MH091657) funded by the 16 NIH Institutes and Centers that support the NIH Blueprint for Neuroscience Research; and by the McDonnell Center for Systems Neuroscience at Washington University. Ethical approval was not required as confirmed by the license attached with the open access data.

15-minute rest sessions and two task sessions for six tasks (Motor, Language, Gambling, Social, Relational, and Working Memory), all with a repetition time (TR) of 720 ms. Additionally, we used the pre-processed diffusion tensor imaging (DTI) data made available by HCP, which includes merging high-fidelity directions across multiple multi-shell DTI acquisitions ($b = 1000$, 2000 , & 3000) and correcting for phase-encoding polarity distortion [77]. We applied a state-of-the-art image processing pipeline, micapipe [40], which processes the anatomical, functional, and diffusion MRI data in a coherent framework to produce subject-specific structural connectivity and functional regional time series in the Schaefer atlas with 400 cortical regions [180], each with connectivity to an additional 14 subcortical regions [157]. Regional expression maps for 15,633 genes were obtained using the *abagen* toolbox in our same parcellation space with linear distance-based interpolation for any missing regions [136, 90].

The structural connectivity was computed using MRtrix3 and probabilistic tractography, generating 10 million streamlines throughout the gray matter white matter interface (maximum tract length = 400, minimum length = 10, cutoff = 0.06, step = 0.5, angle curvature = 22.5°) using the iFOD2 algorithm and 3-tissue anatomically constrained tractography [40]. Tractograms were filtered using SIFT2 [194], reweighting streamlines by cross-sectional multipliers to provide connection densities that are biologically valid measures of fiber connectivity.

The fMRI underwent image re-orientation, motion and distortion correction, and nuisance signal regression (white matter, cerebrospinal fluid (CSF), and frame-wise displacement spikes). Volumetric time series were mapped to the native Freesurfer space using boundary-based registration [80]. Vertex-level time series were averaged into parcels defined by the Schaefer atlas with 400 cortical regions [180]. Parcel-level time series were low-pass filtered to be less than 0.1 Hz. We computed the functional connectivity (FC) as the Pearson correlation matrix between parcel-level time series.

To estimate directed SC, we first ran our fingerprinting analyses (see below) to identify the optimal number of gene gradients. We fit subject-specific parameters in a hierarchical fashion. First, we fit a single model to the consensus SC and functional covariance to determine which sign

each gene gradient should take. Since it is biologically implausible that gene gradients should operate with opposite polarity across brains in the same species, we fit subject-specific directionality models where gene gradient weights were constrained to have the same sign as the consensus result.

As an additional robustness analysis, we ran our model on an external public dataset, the MICA-MICs dataset [175]. This dataset is high-quality, and it uses the same processing pipeline we implemented on the HCP data, helping to ensure comparability between data processing.

4.6.4 HCP fingerprinting analysis

We used test-retest fingerprinting analysis to optimize the number of gene maps for directionality prediction. That is, we sought the fewest gene maps that produced an asymmetry metric (Gw) with the best overall test-retest performance across three metrics: Intraclass Correlation Coefficient (ICC), Discriminability, and Top-1 Identification [60, 27]. For this purpose, we used two complementary approaches with the HCP dataset. First, we evaluated these metrics on $n = 34$ subjects from the HCP Test-Retest dataset; both test and retest have subject-specific SCs and 1 hour of scan time with the separation between scans being approximately 4 months. Second, we evaluated these metrics by splitting the fMRI time series into two ≈ 30 -minute blocks using the full HCP dataset in subjects with the full 1 hour of scan time $n = 724$.

We estimated feature-wise ICC (one-way, single-measures): for each feature, the $N \times 2$ subject-by-session matrix was input to a variance-components ICC:

$$ICC = \frac{MS_b - MS_w}{MS_b + MS_w} \quad (4.11)$$

Here, MS_b and MS_w are the between-subjects and within-subjects mean squares, respectively. Uncertainty was quantified by nonparametric bootstrap resampling of subjects (1000 samples, with replacement) and was calculated as the 95% confidence interval for each feature's ICC.

Second, we quantified multivariate discriminability between test and retest datasets. For each

subject, we formed the Euclidean distance between that subject’s feature vector in the test (session-1) and retest (session-2), which corresponds to the “same-subject” distance, and compared it to the distances between that session-1 vector and all other subjects’ session-2 vectors, which correspond to the “different-subject” distances. Discriminability is defined as the proportion of pairwise comparisons in which the same-subject distance was smaller than the different-subject distance (i.e., the probability that a subject is closer to themselves than others across the two sessions). Statistical significance was assessed by a label-permutation test that randomly permuted subject indices in session-2 (5000 permutations) to generate a null distribution of the discriminability statistic. The permutation p-value was obtained as the proportion of the null distribution that was more than the observed discriminability across subjects.

Third, we quantified Top-1 identification accuracy following a connectome fingerprinting framework [60]. Let $Y^{(1)}, Y^{(2)} \in \mathbb{R}^{N \times P}$ denote the subject-by-feature matrices from session 1 and session 2, respectively. We computed the Pearson correlations between all subject pairs across sessions and, for each subject, identified the single best-matching subject in the opposite session as the one with the maximal correlation. Identification accuracy was computed in both directions, and the final Top-1 score was defined as the average proportion of correct identifications across the two directions. Statistical significance was assessed with a label permutation test (5000 permutations), in which subject labels in one session were randomly permuted to generate a null distribution of Top-1 accuracy. To estimate feature importance for identification, we additionally computed a Finn-style differential power for each feature, based on the extent to which within-subject cross-session products exceeded between-subject cross-session products after feature-wise z-scoring across subjects in each session [60].

4.6.5 Human gene ontology analysis

After settling on the number of gene gradients (k) to use in our analysis, we used the asymmetry metric obtained from fitting the consensus (group-averaged) structural connectome to the consensus functional connectome: $g^* = G^{(k)}\mathbf{w}$. We then calculated the cosine similarity between each

gene expression map $E_i \in \mathbb{R}^n$ and the identified asymmetry metric g^* as $\frac{\langle E_i, g^* \rangle}{\|E_i\|_2 \|g^*\|_2} \in \mathbb{R}$. That is, for every gene, we obtained a measure of how well that gene is aligned (or anti-aligned) with the asymmetry metric. When the gene expression is aligned (anti-aligned) with g^* we classified it as source-biased (sink-biased), since the expression is high (low) where the asymmetry metric is positive (negative).

To evaluate the distinct gene ontologies of source- and sink-biased genes, we extracted the top 1,000 source- and sink-biased genes, respectively, and entered them into the g:Profiler web-based interface [112]. We specified the gene universe “background” to be precisely the full list of genes within the Allen Human Brain Atlas (i.e., 15,633 genes in our dataset). This provides a list of significant ($p < 0.05$, after FDR correction) gene ontology terms where the significance is based on a random sampling of our background. For interpretability, we limited our database search to the “GO” databases and the “Reactome” database. For each significant gene ontology term, g:Profiler provides an *intersection*, which is the number of genes from our empirical input gene set that was part of the term. Let the cardinality of the term intersection be denoted $|S|$.

Since brain maps tend to be spatially autocorrelated (SA), it is imperative to run another level of statistical analyses on the g:Profiler results based on a SA-null distribution [32]. Therefore, we used a Moran spectral randomization spin-test on the cortical map with 1,000 permutations [225, 227], and entered each of these maps into g:Profiler while exporting all results (including non-significant results) to compare against our empirical map results. Therefore, for each SA-null map, we have another measure of the gene ontology term intersection. Using these SA-null distributions, we can then calculate for each empirical term a SA-corrected p-value and a measure of SA-corrected enrichment:

$$\text{Enrichment Ratio} = \frac{|S|_{\text{true}}}{\frac{1}{1000} \sum_j^{1000} |S|_{\text{null}}^{(j)}} \quad (4.12)$$

That is, the enrichment ratio calculates how many more genes, on average, appear in our true expression map compared to a SA-null-corrected background. In our results, we showed all terms that were significantly enriched relative to the background as determined by g:Profiler and we

plot their Enrichment Ratios compared to the SA-null distribution. Some terms were significant according to the generic background but only trending ($0.05 < p_{\text{spin}} < 0.1$) after calculating the SA-corrected p-value. We label these terms with a tilde ($\sim$).

Since many terms are not independent of each other (i.e., both terms may describe closely related gene ontologies with nearly the same sets of genes), we grouped terms together based on a biological category after carefully evaluating each term’s biological relevance. This grouping should be considered an interpretive step and is not itself an outcome of the g:Profiler analysis.

4.6.6 Network source and sink analysis

To explore the source and sink organization of our estimated directed SC, we first assessed the skew connectivity, defined as $\tilde{C}_{\text{skew}} = (\tilde{C} - \tilde{C}^\top)/2$. We used the rows of $\tilde{C}_{\text{skew}}$ to visualize and qualitatively assess skew connectivity (i.e., the outgoing versus incoming structural relationships) within primary sensory areas and the thalamus. To summarize these skew edges across resting-state networks, we calculated $\tilde{C}_{\text{skew}}^{(R)} = R^\top \tilde{C}_{\text{skew}} R$, where $R = [r_1, r_2, \dots, r_m]$ given $r_i \in \{0, 1\}^{N \times 1}$.

Additionally, we investigated the overall degree imbalance of each node as the log ratio of out versus in degrees:

$$D_{\text{imbalance}} = \log_2(D_{\text{out}}) - \log_2(D_{\text{in}}) \quad (4.13)$$

A positive degree imbalance indicates that the node has stronger outgoing connections than incoming connections, while a negative degree imbalance suggests the reverse. This measure reflects a multiplicative relationship in the out-versus-in relationship that can emphasize the sources or sinks that may have relatively few connections but are highly biased in their directionality.

4.6.7 Angular flow analysis

Our directed SC and HONeD model imply a way to augment zero-lag functional covariance into a measure of functional “flow” through SC, which we term “angular flow” (AF). We compared AF against traditional directed/effective connectivity metrics in the Schaefer-100 atlas with 14

subcortical regions [180, 157]; namely lagged-FC, regression dynamic causal modeling (rDCM), and multivariate Granger causality (GC) [70, 10]. SC directionality for the 114-region atlas was identified for every subject using $k = 5$ gene gradients to keep the results homogeneous with the rest of the analyses. We calculated lagged-FC as the average sample (lagged) covariance across 10 lags. For rDCM and GC, we used established toolboxes [70, 10]. We statistically compared AF to these other directed functional connectivity metrics with both Pearson and Spearman correlations, reported together. When p-values were below computer precision, we denoted them as being $p \ll 0.001$. When running comparisons, we used only the upper-triangular entries of the respective measure’s skew matrix.

When assessing resting-state connectivity, we evaluated the net flow for each node: $\sum_j \Omega_{ij}$ ⁸. Meanwhile, the resting-state functional connectivity principal gradient was calculated as the first non-trivial eigenvector of the Laplacian diffusion embedding in the same way as previous work [134]. We correlated these two maps with a Pearson correlation, then we evaluated its significance using a distance-dependent Moran spectral randomization spin-test on the cortical maps with 100,000 permutations [225, 227].

We also assessed whether this alignment between AF and the principal FC gradient was greater when calculating AF using a directed SC compared to a symmetric (undirected) SC. We also sought to compare whether simple lagged-FC had net flow that significantly aligned with the same principal FC gradient across subjects. Alignment was calculated using a Pearson correlation. We compared each of these distributions with a two-sample t-test.

⁸Taking the sum of the AF along each row is equivalent to calculating the difference between the out-degree and in-degree of the flow connectivity $F = -\Sigma f(\mathcal{L})^{-1}$.

4.7 Supplemental Material

4.7.1 Section 1: Extended Results and Figures

Extended Statistics of Cross-Species Validation

To ensure results were not entirely driven by outlier edges, we also computed the Spearman's ρ as a non-parametric correlation, which also showed robust positive correspondence between the model prediction and ground truth skew connectivity (*C. elegans*: $\rho = 0.36$; Mouse: $\rho = 0.20$; Macaque: $\rho = 0.14$; all $p \ll 0.001$). We found similarly promising results when correlating the skew degree of empirical versus predicted networks (Pearson's r — *C. elegans*: $r = 0.67$; Mouse: $r = 0.60$; Macaque: $r = 0.54$; Spearman's ρ — *C. elegans*: $\rho = 0.54$; Mouse: $\rho = 0.36$; Macaque: $\rho = 0.31$; all $p \ll 0.001$).

Identifying the optimal k in Cross-Species Validation

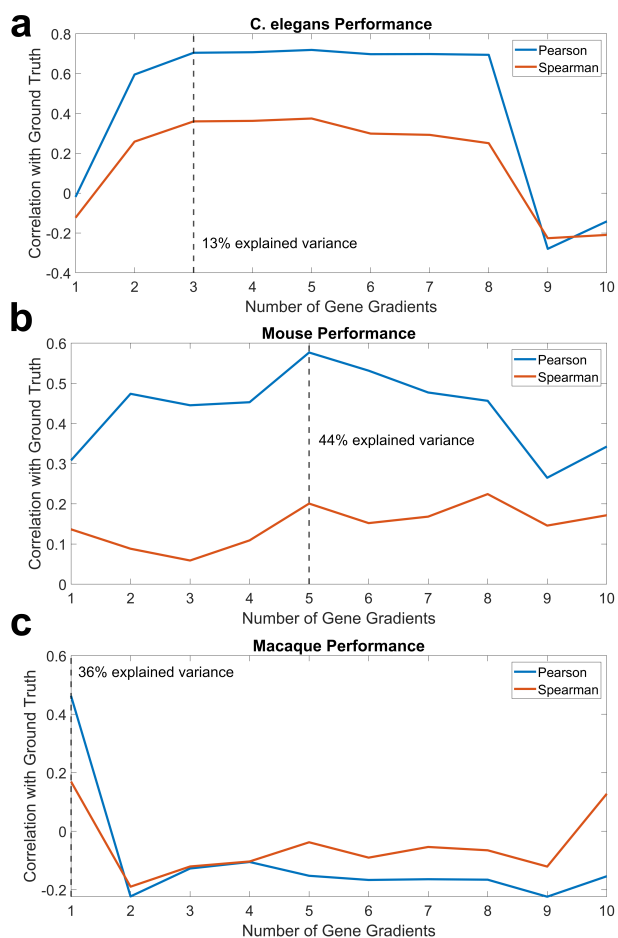


Figure 4.6: We evaluated the correlation between model-predicted and ground-truth directed (skew) connectivity with different numbers of gene gradients (k) ranging from 1 to 10. **(a)** *C. elegans* showed the best alignment with ground-truth at $k = 3$; **(b)** mouse showed the best alignment at $k = 5$; **(c)** macaque showed the best alignment at $k = 1$. The main results for the cross-species analysis are shown in **Fig. 4.2**.

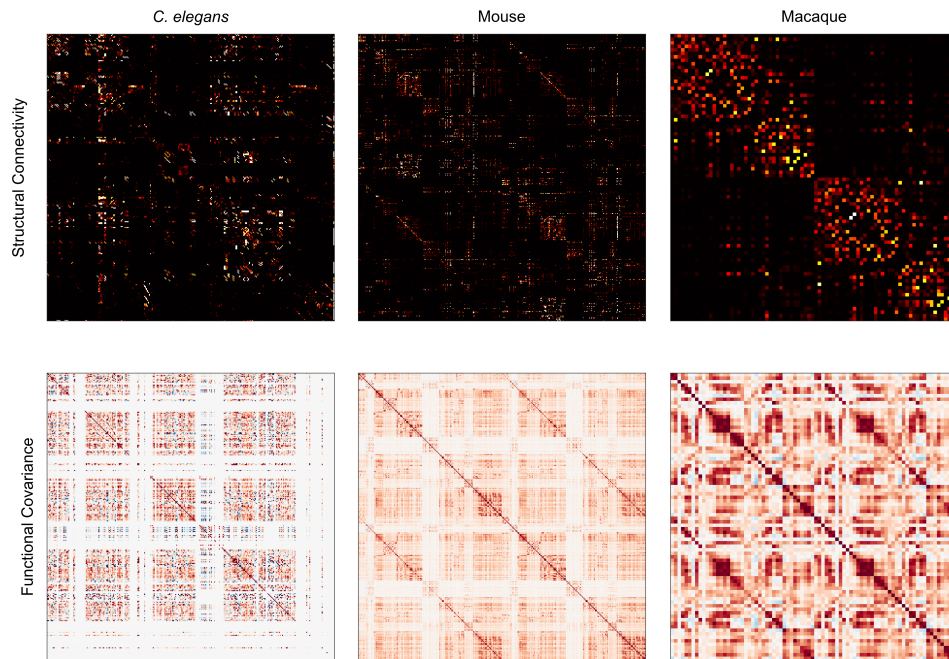


Figure 4.7: We visualize the structural connectivity and functional covariance matrices used to fit the directionality model for each species. The main results for the cross-species analysis are shown in **Fig. 4.2**.

Human Fingerprinting and Replication

For the 34 test-retest dataset (Supplemental **Fig. S 4.8a**), $k = 5$ gene gradients showed a peak in ICC (0.46 ± 0.11), significant Discriminability (0.73 $p_{\text{perm}} = 0$), and significant Top-1 Identification (28% , $p_{\text{perm}} < 0.001$). For the 724 split fMRI subjects (Supplemental **Fig. S 4.8b**), we similarly found that $k = 5$ gene gradients had high ICC (0.51 ± 0.03), significant Discriminability (0.77 , $p_{\text{perm}} < 0.001$), and a modest but significant Top-1 Identification (3% , $p_{\text{perm}} < 0.001$) (Supplemental **Fig. S 4.8b**). The most subject-specific identifiable regions in both datasets involved cingulate regions, left ventral prefrontal cortex, left inferior temporal gyri, and the hippocampus.

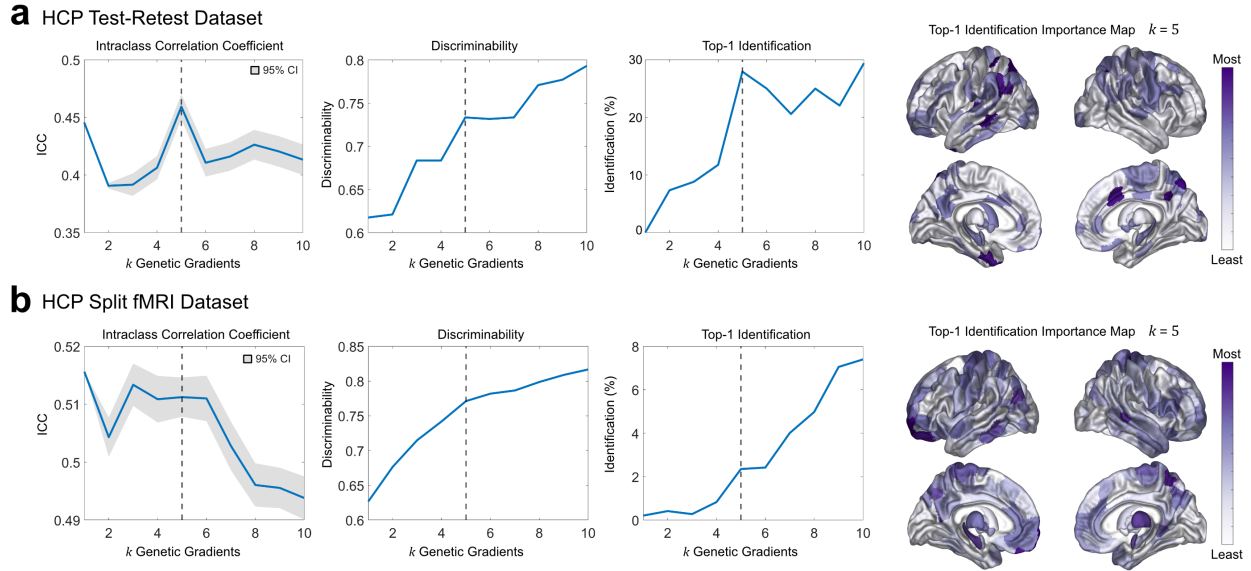


Figure 4.8: Human Asymmetry Test-Retest Fingerprinting. Fingerprinting on the fitted asymmetry metric for the (a) HCP Test-Retest dataset ($n = 34$), and (b) HCP split fMRI dataset ($n = 724$). We show (left to right) Intraclass Correlation Coefficient (ICC) with the 95% confidence interval shaded around the mean, the Discriminability score (all significant $p_{\text{perm}} = 0$), the Top-1 Identification metric (%), and the Top-1 Identification regional-importance map. The main results for the human analysis are shown in **Fig. 4.3**.

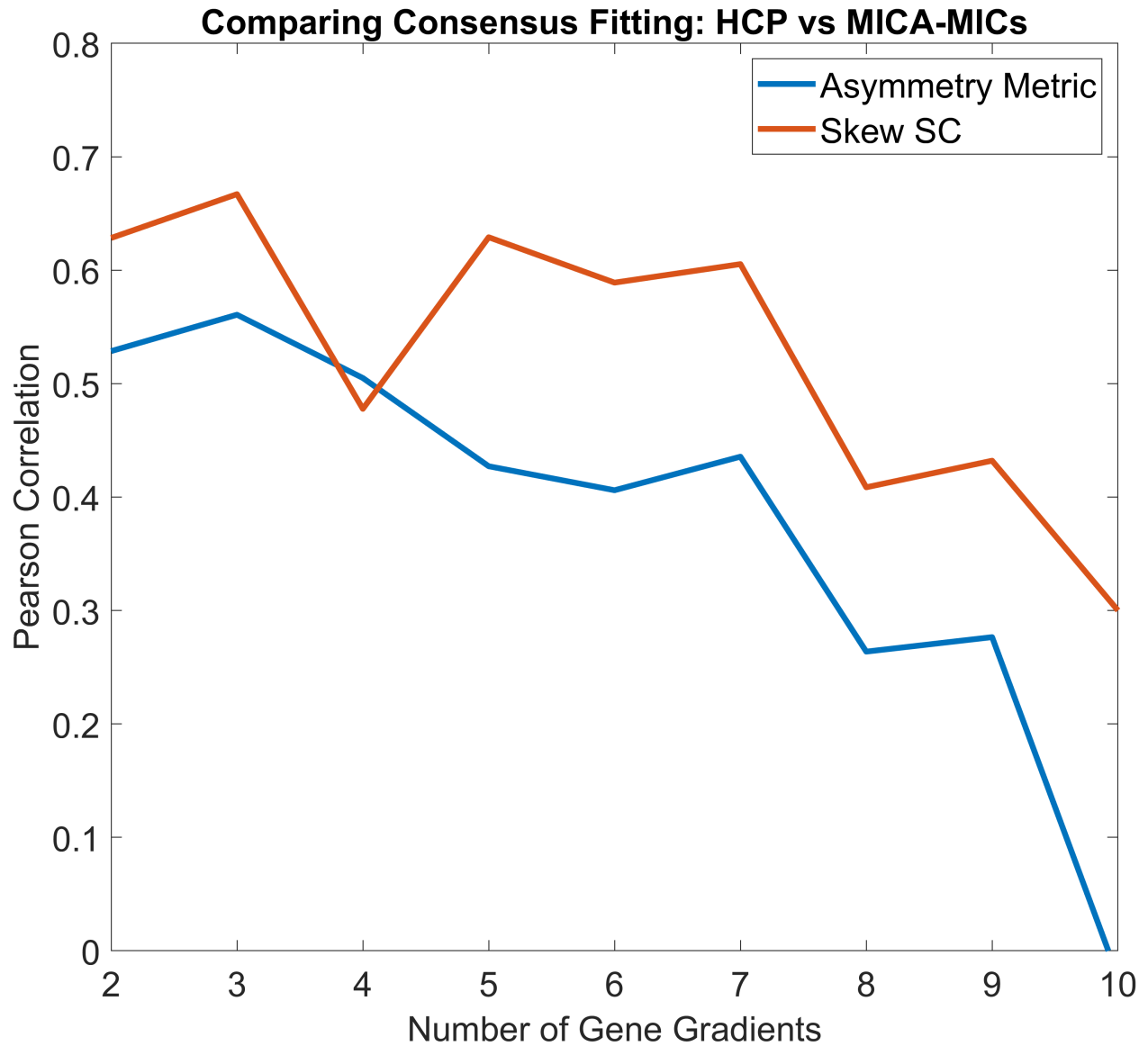


Figure 4.9: Human Directed SC Replication Dataset. We evaluated our model on the consensus connectome from the MICA-MICs dataset as an external validation. We evaluated the correlation between the predicted skew connectivity in the Schaefer-400 atlas for each dataset as well as the identified asymmetry metric. The main results for the human analysis are shown in **Fig. 4.3**.

Extended Angular Flow Results

Statistical Comparison to Causal Discovery Methods: Lagged-FC significantly correlated with AF ($r = 0.34$, $p \ll 0.001$, Spearman $\rho = 0.34$, $p \ll 0.001$; **Fig. 4.5b**). We observed that GC had the strongest non-parametric relationship with AF ($r = 0.22$, $p \ll 0.001$, Spearman $\rho = 0.43$, $p \ll 0.001$; **Fig. 4.5b**) while rDCM showed more moderate but still significant correlations ($r = 0.11$, $p \ll 0.001$, Spearman $\rho = 0.13$, $p \ll 0.001$; **Fig. 4.5b**). Interestingly, GC and rDCM were negatively correlated by Pearson correlation but not by Spearman correlation, suggesting little monotonic relationship despite the Pearson association ($r = -0.21$, $p \ll 0.001$, Spearman $\rho = -0.0037$, $p = 0.77$; Supplemental **Fig. 4.10**).

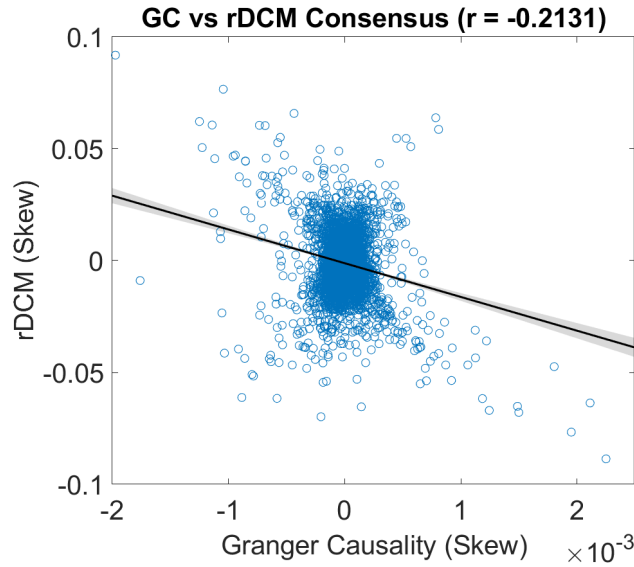


Figure 4.10: A comparison of the consensus rDCM skew-connectivity versus GC skew-connectivity. The main results for the AF analyses are shown in **Fig. 4.5**.

Spin Test for AF Net-Flow and Principal Gradient:

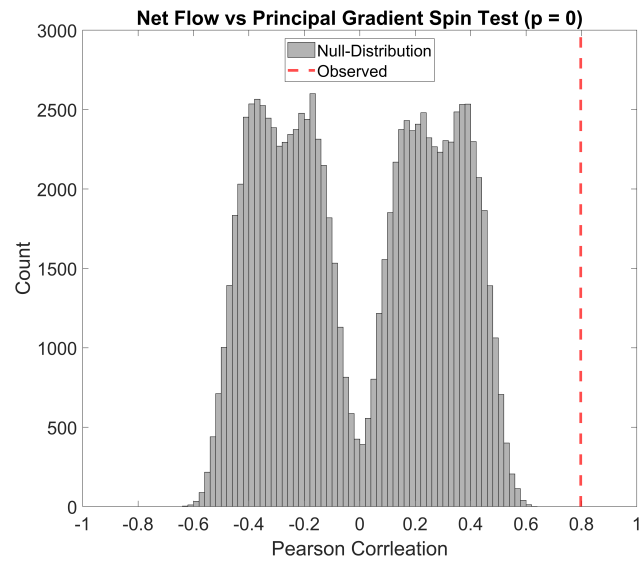


Figure 4.11: Spin-test results comparing the first principal gradient of undirected connectivity to the AF net-flow. The main results for the human AF analyses are shown in **Fig. 4.5**.

Graph Laplacian Flow Operator:

Laplacian Flow Operator Skew Degree: $\sum_j f(\mathcal{L})_{ji}^{-1} - f(\mathcal{L})_{ij}^{-1}$ Correlation with Principal FC Gradient: $r = 0.04$

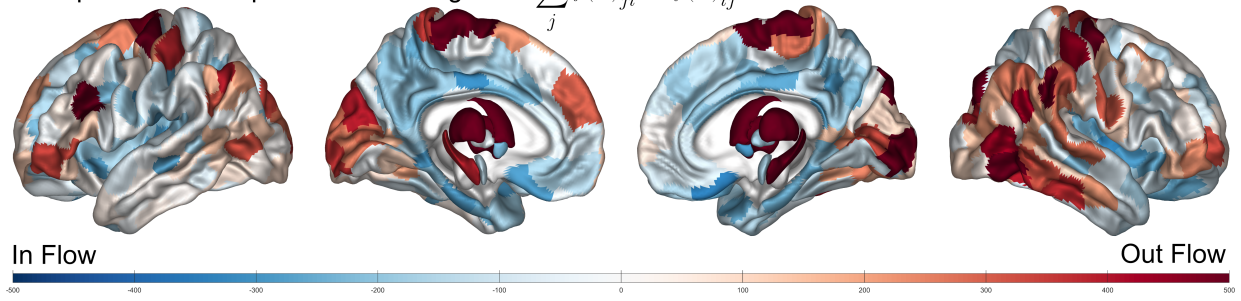


Figure 4.12: The net flow of the modeled diffusion operator in isolation. The main results for the AF analyses are shown in **Fig. 4.5**.

Comparing Alignment with FC Gradient Across Cases:

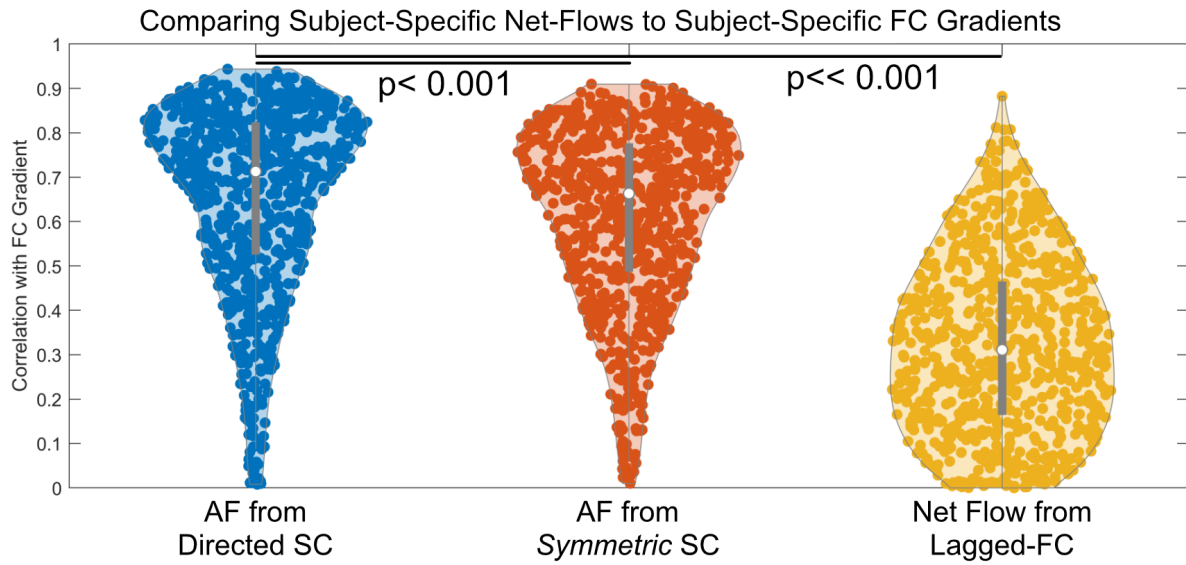


Figure 4.13: We statistically compared the predicted AF net-flow when calculated with the directed SC versus the original symmetric SC ($p < 0.001$), as well as against the net flow from the conventional lagged-FC. All comparisons were performed in the Schaefer 400 atlas. The main results for the AF analyses are shown in **Fig. 4.5**.

4.7.2 Section 2: Derivation of the Lyapunov Objective for Predicting Structural Directionality

Linear stochastic dynamics

We begin with a continuous-time linear stochastic model for the evolution of brain activity

$$d\mathbf{x}(t) = A\mathbf{x}(t) dt + B d\boldsymbol{\epsilon}(t), \quad (4.14)$$

where $\mathbf{x}(t) \in \mathbb{R}^n$ is the vector of regional brain activity, $A \in \mathbb{R}^{n \times n}$ is the linear dynamics operator, $B \in \mathbb{R}^{n \times r}$ maps stochastic inputs into the observed state space, and $d\boldsymbol{\epsilon}(t)$ is a vector of Wiener-process increments satisfying

$$\mathbb{E}[d\boldsymbol{\epsilon}(t)] = 0, \quad \mathbb{E}[d\boldsymbol{\epsilon}(t)d\boldsymbol{\epsilon}(t)^\top] = Q_\epsilon dt. \quad (4.15)$$

In our case, the deterministic dynamics are specified by the HONeD operator, so that

$$A = f(\mathcal{L})^\top, \quad f(\mathcal{L}) = -\kappa I - \beta \mathcal{L} + \xi \mathcal{L}^2, \quad (4.16)$$

where $\mathcal{L}$ is the directed graph Laplacian and $\theta = \{\kappa, \beta, \xi\}$ denotes the diffusion parameters. The transpose appears because we write the state equation in the column-vector convention $\dot{\mathbf{x}}(t) = f(\mathcal{L})^\top \mathbf{x}(t)$. For ease of notation, we abbreviate $f(\mathcal{L}; \theta; \mathbf{w}) \equiv f(\mathcal{L})$, where $\mathbf{w}$ denotes the parameters controlling structural directionality.

The effective covariance of the stochastic drive is

$$Q = BQ_\epsilon B^\top. \quad (4.17)$$

In the analyses below, we use an isotropic innovation model,

$$Q \propto I, \quad (4.18)$$

which assumes that unresolved local fluctuations inject variance into each region without imposing a preferred large-scale covariance structure. This choice is useful because the goal is to test whether the directed structural operator itself can explain the observed covariance structure, rather than allowing a flexible noise covariance to absorb that structure.

From state dynamics to covariance dynamics

The empirical functional covariance is modeled as the expected second moment

$$\Sigma(t) = \mathbb{E}[\mathbf{x}(t)\mathbf{x}(t)^\top]. \quad (4.19)$$

Since the data are mean-centered, this second moment is equivalent to the covariance. We now derive the differential equation governing $\Sigma(t)$.

First, define the instantaneous outer product

$$S(t) = \mathbf{x}(t)\mathbf{x}(t)^\top. \quad (4.20)$$

Using the stochastic product rule, also known as Itô's product rule,

$$dS(t) = d\mathbf{x}(t) \mathbf{x}(t)^\top + \mathbf{x}(t) d\mathbf{x}(t)^\top + d\mathbf{x}(t) d\mathbf{x}(t)^\top. \quad (4.21)$$

Substituting the stochastic dynamics from Eq. (4.14) gives

$$\begin{aligned} dS(t) &= (A\mathbf{x}(t) dt + B d\boldsymbol{\epsilon}(t)) \mathbf{x}(t)^\top \\ &\quad + \mathbf{x}(t) (A\mathbf{x}(t) dt + B d\boldsymbol{\epsilon}(t))^\top \\ &\quad + (B d\boldsymbol{\epsilon}(t)) (B d\boldsymbol{\epsilon}(t))^\top. \end{aligned} \quad (4.22)$$

Expanding the first two terms,

$$\begin{aligned}
dS(t) &= A\mathbf{x}(t)\mathbf{x}(t)^\top dt + B d\boldsymbol{\epsilon}(t)\mathbf{x}(t)^\top \\
&\quad + \mathbf{x}(t)\mathbf{x}(t)^\top A^\top dt + \mathbf{x}(t)d\boldsymbol{\epsilon}(t)^\top B^\top \\
&\quad + B d\boldsymbol{\epsilon}(t)d\boldsymbol{\epsilon}(t)^\top B^\top.
\end{aligned} \tag{4.23}$$

Taking expectations, the terms that are linear in $d\boldsymbol{\epsilon}(t)$ vanish because the Wiener increments have zero mean and are independent of the present state. Therefore,

$$\begin{aligned}
\mathbb{E}[dS(t)] &= A \mathbb{E}[\mathbf{x}(t)\mathbf{x}(t)^\top] dt + \mathbb{E}[\mathbf{x}(t)\mathbf{x}(t)^\top] A^\top dt \\
&\quad + B \mathbb{E}[d\boldsymbol{\epsilon}(t)d\boldsymbol{\epsilon}(t)^\top] B^\top.
\end{aligned} \tag{4.24}$$

Using the definitions of $\Sigma(t)$ and $Q = BQ_\epsilon B^\top$, we obtain

$$d\Sigma(t) = A\Sigma(t) dt + \Sigma(t)A^\top dt + Q dt. \tag{4.25}$$

Dividing by dt gives the continuous-time differential Lyapunov equation

$$\dot{\Sigma}(t) = A\Sigma(t) + \Sigma(t)A^\top + Q. \tag{4.26}$$

Substituting $A = f(\mathcal{L})^\top$, Eq. (4.26) becomes

$$\dot{\Sigma}(t) = f(\mathcal{L})^\top \Sigma(t) + \Sigma(t)f(\mathcal{L}) + Q. \tag{4.27}$$

This is the Lyapunov equation used in our structural directionality objective.

Steady-state covariance constraint

If the linear dynamics are stable, meaning that the eigenvalues of $A = f(\mathcal{L})^\top$ have negative real part, then the covariance converges toward a stationary covariance Σ . At stationarity,

$$\dot{\Sigma}(t) = 0, \quad (4.28)$$

so Eq. (4.27) reduces to the algebraic Lyapunov equation

$$f(\mathcal{L})^\top \Sigma + \Sigma f(\mathcal{L}) + Q = 0. \quad (4.29)$$

This equation expresses a balance between two contributions. The terms

$$f(\mathcal{L})^\top \Sigma + \Sigma f(\mathcal{L})$$

describe how the deterministic network dynamics dissipate, redistribute, or amplify covariance, whereas Q describes the covariance injected by stochastic innovations. At steady state, the observed covariance is one for which deterministic dissipation and stochastic injection are balanced.

Chapter 5

Conclusion

Understanding how a relatively unchanging white matter network facilitates a dynamic repertoire of brain function is a central problem in computational neuroscience. Resolving this structure-function problem is critical because it bridges underlying neuronal biology and the emergent properties of the brain as a whole. Insights into this relationship may therefore reshape our understanding of the neural mechanisms underlying cognition, behavior, and disease.

In this work, I have described three investigations into the structure-function problem, each of which illuminates a different aspect of how brain structure and function are related. Together, these works offer a perspective on what a unified structure-function mechanism might look like and demonstrate how structure-function models can integrate imaging modalities to recover information unavailable from any single modality in isolation. Below, I summarize and synthesize these works, demonstrating how they braid together to form a larger argument about the structure-function relationship in the brain. Then, I conclude by considering what future work can be done using these insights.

5.1 Synthesizing across results

Chapter 2 shows that the graph Laplacian harmonics of the structural connectome (SC) exhibit a consistent organization across subjects and map onto an integration-segregation spectrum in the

brain. Harmonics belonging to different parts of this integration-segregation spectrum display different properties related to their group-level agreement, spatial alignment, graph-theoretical metrics, and functional relevance. Importantly, this work urges us to consider the functional and behavioral relevance of all harmonics rather than merely considering them as a means for dimensionality reduction, as if they reflected a form of principal component analysis. Instead, Laplacian harmonics can define distinct structural subspaces that may support different forms of network-level computation in the brain.

Chapter 3 introduces a way to estimate an “innovation” signal in fMRI data based on amplifying the brain signal’s energy in higher spatial frequency harmonics by inverting a higher-order network diffusion (HONeD) model. This analysis revealed extensively reorganized HONeD-in functional networks that nevertheless retained rich, nonrandom structure. This analysis again emphasized the relevance of considering the full harmonic spectrum, showing how even harmonics with disproportionately low signal power in the original fMRI time series may nevertheless contain rich and non-random functional organization. Moreover, HONeD-in signals remodeled the organization of resting state networks (RSNs), functional gradients, and task activation, thereby demonstrating how these network- and region-level features in fMRI may be at least partially influenced by passive diffusion through SC.

Chapter 4 takes the reverse approach, where instead of removing the passive diffusion signal in fMRI, I leverage it to estimate directional information in the original structural connectivity. This analysis again highlights the mutual interplay between structure and function, but critically it also introduces a third modality: transcriptional gene expression. Thus, this work presents a gene-informed structure-function framework in which region-wise transcriptional heterogeneity can be parameterized inside the model to learn about gene-brain relationships. The model received support from analyses across three nonhuman species and, in humans, produced relatively stable subject-specific phenotypes with biologically plausible gene-ontology associations. These analyses therefore complement HONeD-in, showing the power of leveraging the brain’s signal diffusion to learn about other biological features that may be generalized across both spatial and phylo-

genetic scales. The directional connectomes estimated by this approach can then be leveraged in a variety of future studies that aim to understand how directionality influences brain function, controllability, and disease progression.

Taken together, these chapters support a common view: the graph Laplacian of the structural connectome provides a mathematically coherent language for describing how anatomy constrains functional organization. The graph Laplacian articulates this language in the form of its harmonics—the standing waves that live on the scaffolding of the brain. These harmonics reflect the physics of signal movement through the system, and the full harmonic spectrum may be leveraged to understand the brain’s structure-function relationship. Harmonics organize across humans who generally share both the lowest and highest frequency graph harmonics and tend to disproportionately involve sensory/unimodal brain regions. While the lowest-frequency *integrative* harmonics are most related to passive diffusion in the brain, the intermediate-frequency *degenerate* and high-frequency *segregative* harmonics carry components of activity related to the brain’s *innovation* signal. This innovation signal can be estimated by inverting a HONeD model, and it may be interpreted as the endogenous and exogenous signals produced within the system.

Studying this HONeD-in signal reveals how conventional RSNs may partly reflect the diffusion-mediated blurring of endogenously generated networks that combine unimodal and multimodal processing. Functional gradients, too, may be a reflection of signal movement through an underlying structural network. When the passive diffusion over SC is removed, functional gradients remodel in a way that eliminates their apparent hierarchy—all RSNs become balanced around a circle defined by the deconvolved HONeD-in gradients. This hypothesis, that functional gradients are shaped by flow through SC, is further supported by identifying the net flow through a *directed* SC. This net flow reveals that the principal functional gradient can be reconceived as the flow of signal from traditionally unimodal networks to multimodal networks. Thus, the unimodal-multimodal divide can be described in terms of a source-sink relationship mediated by passive diffusion through SC.

More generally, this work suggests that passive diffusion through SC may be a consistent as-

pect of brain function, extending even to small-scale brains and across different species. The finding that synaptic directionality in *C. elegans* can be partially recovered by its functional connectivity suggests that the strongly nonlinear microscopic neural dynamics may nevertheless give rise to emergent macroscopic linearity described by the graph Laplacian. These results together demonstrate the utility of structure-function models to relate different imaging modalities and provide insight into how macroscopically observed emergent activity may arise from simple physical processes constrained by brain structure.

5.2 Future work

These results ultimately argue in favor of analyzing the brain's function through the lens of its structure, using the SC graph Laplacian and its harmonics as a language to define connectivity that may offer deeper insights than the correlation of brain signals alone.

First, future work should not treat graph harmonics like a form of principal component analysis or as a mere dimensionality reduction technique. Although certain regimes of harmonics may be more relevant than others when answering different scientific questions, all harmonics have an interpretability endowed by their topological organization, consistency across subjects, and fundamental relationship to the physics of the system. For example, work focusing on response to sensory stimuli may benefit from a careful investigation of the behavior of the segregative harmonics, while work focusing on cognitive control and attention-oriented tasks may benefit from assessing the collective dynamics of degenerate harmonics. Since these harmonics have an embedded notion of SC, studying the functional dynamics of these harmonics allows for a form of connectivity analysis that moves from purely statistical descriptions of brain connections to a description instantiated in the underlying biology. Indeed, some recent work has leveraged our approach to investigate brain dynamics during cognitive tasks in precisely this way, showing that all harmonics have dynamical responses to various tasks that depend on whether harmonics are integrative, segregative, or degenerate [20]. I believe this reflects the beginning of a rich area of harmonics-based

analyses, privileging the dynamics of different harmonic families from across the full spectrum rather than viewing Laplacian harmonics as merely a form low-dimensional embedding.

Future work that aims to investigate relationships in correlation-based functional connectivity should carefully evaluate whether reported results hold after deconvolving the effect of passive diffusion over SC. For instance, some work has suggested that tauopathies in AD may propagate along functional connectivity networks [64], yet the work I have presented here motivates a reassessment of how such relationships should be interpreted. It is possible that some apparent relationships between FC and brain pathology arise because FC reflects passive diffusion through SC, rather than because correlation-based FC independently defines the relevant propagation pathways. This ties back to the dichotomy of perspectives I introduced at the very beginning of this dissertation—computational neuroscience is at its best when it is both theoretically rich and biologically grounded. How exactly functional correlations could relate to the spread of molecules through the brain remains unclear; more specifically, this highlights a potential mismatch between what a computational or statistical description of the system can say in isolation (i.e., FC alone) versus what a hybridized SC-FC framework can say when it more directly unifies computational theory with biology.

Another, more general, future direction in this same vein is to carefully evaluate situations in which the functional dynamics observed in neuroimaging appear to blur together. This is especially relevant for fMRI analyses that aim to identify task-related brain regions. As I’ve shown with HONeD-in signals, task contrasts using the HONeD-in signal can both eliminate and elevate significance in different brain regions, depending on the context. One important next step for the HONeD-in framework is to extend and validate the method on high-resolution brain imaging so that HONeD-in signals need not be entangled with arbitrary parcellation choices. This may further allow for new brain atlases based on local HONeD-in signal features, since current parcellations may also be partially blurred by the fMRI signals from which they are derived.

Finally, there is significant potential to leverage an estimated directed SC in future work. Potential applications include studying how directionality changes across the lifespan; characterizing

white-matter pathways such as the arcuate fasciculus; determining whether directionality changes under various forms of medical or therapeutic interventions; and testing whether a directed SC better predicts the spread of pathology in dementia and other network-mediated diseases. Although appropriate caution is warranted given that ground-truth estimates of directionality in humans are still inaccessible, there remains potential for even an approximate directional SC to influence the study of the brain. Moreover, a directed SC mathematically motivates a new form of functional connectivity based on angular flow through the network, representing another step toward an FC measure rooted in the underlying biology rather than defined purely by statistical association. It also provides a way to decouple notions of directionality from implications of causality—the flow of signal through SC is a physical description of signal behavior that need not imply casual inference. This will help future work articulate brain-behavior relationships not in terms of pairwise relationships between regions, but in terms of the net flow of signals through the biological network.

Taken together, this dissertation argues that the structure-function problem is not merely a question of linking anatomy to activity, but of learning to read brain function in the language written by the structural connectome itself.

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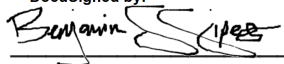
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