

Charting Higher-Order Models of Brain Function Beyond Pairwise Interactions

Corresponding Author: Professor Giovanni Petri

Parts of this Peer Review File have been redacted as indicated to remove third-party material.

This file contains all reviewer reports in order by version, followed by all author rebuttals in order by version.

Version 0:

Reviewer comments:

Reviewer #1

(Remarks to the Author)

The following comments and questions are related to the paper titled "Beyond Pairwise Interactions: Charting Higher-Order Models of Brain Function", submitted to Nature Communications.

According to the authors, the central justification for the work documented in this paper is the existence, in the literature, of a gap associated with comparative properties of higher-order interaction (HOI) metrics applied to brain connectivity models, which are traditionally derived from pairwise interaction metrics. In fact, in recent years, several HOI metrics have been proposed and applied to the aforementioned context, but there is a lack of solid references on which of these metrics would be most useful or representative for a specific purpose in this scenario. The authors then group the considered HOI metrics into two classes: the first of information-theoretic type and the second of topological type; these metrics are evaluated using resting-state and task-based fMRI data from the Human Connectome Project, producing what the authors claim to be the first large-scale evaluation within the scope outlined above.

The analysis reveals an interesting taxonomy involving redundant, synergistic, and topological HOIs, and indicates that all HOI metrics recapitulate the brain unimodal-to-transmodal hierarchy. Furthermore, it is concluded that, functionally, HOI metrics perform better than pairwise approaches in brain fingerprinting and perform equivalently in task decoding. Additionally, employing multivariate analyses, it is concluded that topological descriptors appear to play the role of key predictors of individual behavioral variability.

In what follows, I present some comments and questions that I recommend the authors carefully consider, in order to improve their paper and clarify some doubts:

1) In general, the text is well-written, being predominantly clear, well-formatted, and grammatically correct. The bibliographic references cited by the authors constitute a relevant set of related works, which support the reader regarding details that do not need to be included in the submitted manuscript. However, the text is quite dense. Although the article already has a good number of figures, I believe it would be useful if the authors elaborated an additional figure that would allow the reader to visualize the complete flow of what is addressed throughout the work.

2) Regarding the central justification for developing the work, I agree with the authors that the gap mentioned in the initial part of my text exists and is relevant. Although the paper is not a literature review, it might be worthwhile to conduct a numerical survey regarding the (supposedly growing) number of papers, over the last few years, that employ HOI metrics to model brain connectivity.

3) The authors mention that their experiments are based on third-order interactions, but that, in general, the considered metrics can be extended to higher-order interactions. I suggest that the authors include additional comments on this in their paper. Is it possible, for example, to indicate situations where it would make sense to consider fourth-order or higher interactions? What benefits could this bring and what would be the additional demand (for example, from the point of view of computational load and consequent practical feasibility)? Without something in this direction, I think one cannot naturally speak of higher-order interactions, but only of third-order interactions.

4) Is there any specific justification for choosing a cohort of 100 individuals from the HCP database? Would using a larger number of individuals improve the robustness of the evaluation regarding sensitivity to the chosen preprocessing strategies, for example?

5) It seems that certain sections of the "Discussion" section are somewhat redundant with what has already been written in previous sections of the paper; the first paragraph on page 11, for example. It is worth reviewing and checking the possibility of being more concise in the text of this section.

6) The authors do not comment on aspects related to the computational demand associated with calculating the evaluated HOI metrics. Even briefly, they could discuss this issue. Perhaps this could be especially important in situations where it makes sense to consider higher-order interactions.

7) Again, regarding the density of the material contained in the work: the figures in the paper help the reader to follow the results and are aligned with the discussions in the text. However, a kind of summary of the authors' findings would help the reader to have an overview of the conclusions reached and would enrich the work.

(Remarks on code availability)

N/A

Reviewer #2

(Remarks to the Author)

The article explores a variety of higher-order metrics, from diverse backgrounds, and compares the different metrics across a variety of settings, with an aim to understand which metrics extract which type of information, and how the different metrics compare to each other and to standard pairwise metrics. To achieve this aim the authors use fMRI data from the Human Connectome Project.

The study of higher order networks has been of great interest in recent years, with techniques for higher order analysis arising from a few different fields, in particular complex networks (hypergraphs), algebraic topology (TDA), and information theory (synergy-redundancy). This paper focuses on the latter two of these (TDA and information theory), and attempts to understand how the higher order techniques emerging from these fields compare. This is a worthwhile goal, as the higher order field is currently very fractured, due to its emergence from different fields. And thus far no other study has done such a large comparison between different HOI methods.

As a whole the article achieves this aim. Using correlation and clustering methods, they demonstrate that the metrics they consider separate into three main descriptors (redundant, topological, and synergistic), they show that certain methods are better at brain fingerprinting and other metrics are better at task decoding, thus demonstrating that the metrics capture different information and leading to a better understanding of which metrics should be used for a given analysis. A comparison to pairwise approaches is given, and it is shown that sometimes pairwise performs better and sometimes HOIs perform better, but in general they complement each other (adding to the growing body of literature supporting this). They also link their findings back to the biology, by demonstrating that these metrics capture certain biological information.

The methodology used is sound, the mathematics and techniques used are already existing methods with solid foundations, the statistical analyses and ML-based methods are all well established techniques. The conclusions drawn are well founded based on the analyses given, and provide new important insights into the field.

As with all comparative studies it is not possible to examine every metric existing in the literature. However, it would have been nice to see a few other metrics included here, as the authors claim the given metrics "provide a comprehensive lens to characterizing higher-order interdependencies". In particular, it would be nice to see other TDA techniques included beyond the authors own techniques (persistence entropy, dynamic embedding, etc), also a comparison to more pairwise metrics would be beneficial. Moreover, the study is currently a comparison between topological and information theoretic metrics (which is a worthwhile comparison), but to be truly "charting higher order models" and be a "comprehensive lens", one would like to see hypergraph metrics included. However, the article is an excellent first step in understanding how these different metrics interact.

Overall the work aims to answer an interesting question, it contributes novel noteworthy results, and new insights into the field. Thus I recommend it be accepted for publication.

The writing is excellent. A few minor comments, typos and corrections:

Page 7, paragraph 1: "restricting our analysis to transmodal cortex was almost as discriminative", it is unclear how the figure shows this, did you take all the regions of the transmodal cortex together, or do you just mean that the regions of the transmodal cortex each performed well. Also a complete list of regions included in the transmodal cortex is never given, this would be useful to add somewhere.

Table 1: The table uses the type Linear but the caption uses Classic, either works but choose one.

Page 6, paragraph 3: missing full stop after [109,112] and extra space between densities and full stop.

Page 10: Full stop missing after [17,139]

Page 14 (Homological scaffolds): K'_{ω} should be K_{ω}

References: DOI for article [85] is wrong

(Remarks on code availability)

I have not run the code, but I have looked through the supplied folder. The code looks comprehensive, there looks to be code available for each of the analyses done, along with the comments and instructions for installation. Some of the code used is existing code from previous studies, thus already well established. Some of the code looks to use datasets that are not included in what was provided, but so long as this is addressed in the final repo, that should be fine.

Version 1:

Reviewer comments:

Reviewer #1

(Remarks to the Author)

After examining the revised version of the manuscript, as well as the associated supplementary material and the authors' responses to the issues I raised in the first round of review, I consider that my concerns have been satisfactorily addressed and that, with the revisions made, the paper has been improved to the point that it can be accepted for publication in *Nature Communications*.

(Remarks on code availability)

Reviewer #2

(Remarks to the Author)

The authors have comprehensively addressed all comments. I suggested the article be accepted for publication before, the revisions have improved the work even further, thus I again suggest it be accepted for publication.

(Remarks on code availability)

No new comments

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**Beyond Pairwise Interactions: Charting Higher-Order Models of Brain
Function
(NCOMMS-25-62559-T)
Reply to the Reviewers**

February 27, 2026

General reply to the reviewers

Dear reviewers,

Thank you for the thorough and insightful review of our manuscript. We are grateful for the time and attention paid to our work. We sincerely want to thank you for your attentive comments and valuable advice, which have all been taken into consideration. We feel that our manuscript came out stronger from this constructive review process.

We provide below a list of the modifications made, followed by in-depth replies to all comments. We also provide an annotated copy of the main text, where the modifications are highlighted.

We thank you again for your time and insights.

Yours sincerely,

The authors

Detailed reply to the report of reviewer # 1

COMMENT 1.0

The following comments and questions are related to the paper titled “Beyond Pairwise Interactions: Charting Higher-Order Models of Brain Function”, submitted to Nature Communications.

According to the authors, the central justification for the work documented in this paper is the existence, in the literature, of a gap associated with comparative properties of higher-order interaction (HOI) metrics applied to brain connectivity models, which are traditionally derived from pairwise interaction metrics. In fact, in recent years, several HOI metrics have been proposed and applied to the aforementioned context, but there is a lack of solid references on which of these metrics would be most useful or representative for a specific purpose in this scenario. The authors then group the considered HOI metrics into two classes: the first of information-theoretic type and the second of topological type; these metrics are evaluated using resting-state and task-based fMRI data from the Human Connectome Project, producing what the authors claim to be the first large-scale evaluation within the scope outlined above.

The analysis reveals an interesting taxonomy involving redundant, synergistic, and topological HOIs, and indicates that all HOI metrics recapitulate the brain unimodal-to-transmodal hierarchy. Furthermore, it is concluded that, functionally, HOI metrics perform better than pairwise approaches in brain fingerprinting and perform equivalently in task decoding. Additionally, employing multivariate analyses, it is concluded that topological descriptors appear to play the role of key predictors of individual behavioral variability.

In what follows, I present some comments and questions that I recommend the authors carefully consider, in order to improve their paper and clarify some doubts:

Reply 1.0: We thank the reviewer for the comments and feedback on our manuscript. We have carefully addressed all points raised in the revised version of the manuscript, and we believe that the text is now clearer, more cohesive, and easier to follow.

COMMENT 1.1

1) In general, the text is well-written, being predominantly clear, well-formatted, and grammatically correct. The bibliographic references cited by the authors constitute a relevant set of related works, which support the reader regarding details that do not need to be included in the submitted manuscript. However, the text is quite dense. Although the article already has a good number of figures, I believe it would be useful if the authors elaborated an additional figure that would allow the reader to visualize the complete flow of what is addressed throughout the work.

Reply 1.1: We thank the reviewer for the positive assessment of the manuscript and for this helpful suggestion. In response, we have added a new schematic figure to the Supplementary Information (Supplementary Fig. S2), which illustrates the complete computational pipeline and provides a step-by-step overview of the workflow and main results of the paper. We now explicitly refer to this figure in the initial part of the manuscript to guide the reader through the structure of the paper.

Because the main text already contains a substantial number of figures — including an overview sketch of the different higher-order measures analyzed — we chose to place this additional pipeline figure in the Supplementary Information to avoid overloading the main manuscript. In parallel, we have also restructured parts of the Results and Discussion sections to improve the linearity of the narrative and reduce textual density, thereby making the paper easier to follow.

Action taken 1.1: We have added a new figure (Supplementary Fig. S2) in the supplementary and partially restructured the Introduction and Discussion sections.

For completeness, see below the new text highlighted in red:

INTRODUCTION

...

Although applications here focus on triplets for consistency and tractability, most frameworks are extensible to larger sets of regions (see Methods for a detailed description of each framework and [Supplementary Fig. S2 for an overview of the complete workflow](#)).

DISCUSSION

Recent strides in information theory and computational topology have increasingly offered novel approaches to characterize multiregional higher-order interactions (HOIs) from neuroimaging recordings [27,44,131], extending beyond standard pairwise functional connectivity (FC). Here, we addressed the lack of a systematic understanding of these diverse metrics by mapping their interrelations, biological underpinnings, and utility in brain fingerprinting, task decoding, and brain–behavior associations.

To help readers navigate this rapidly expanding field (see SI Fig. S1 for a numerical survey tracking the recent growth of HOI literature) and to summarize our full pipeline overview, from metric definitions to downstream applications, we provide a schematic in [Supplementary Fig. S2](#). Our comparative analysis, at nodal and edge-level projections, consistently reveals three families of observables: redundancy-based metrics, synergy-based metrics, and topological scaffolds (Fig. 2). In brief, we found that these computational modes align strongly with established sensorimotor-association cortical hierarchies and distinct neurochemical profiles. Furthermore, while synergy and redundancy significantly enhance subject identifiability (fingerprinting), classical pairwise FC remains optimal for decoding specific cognitive states.

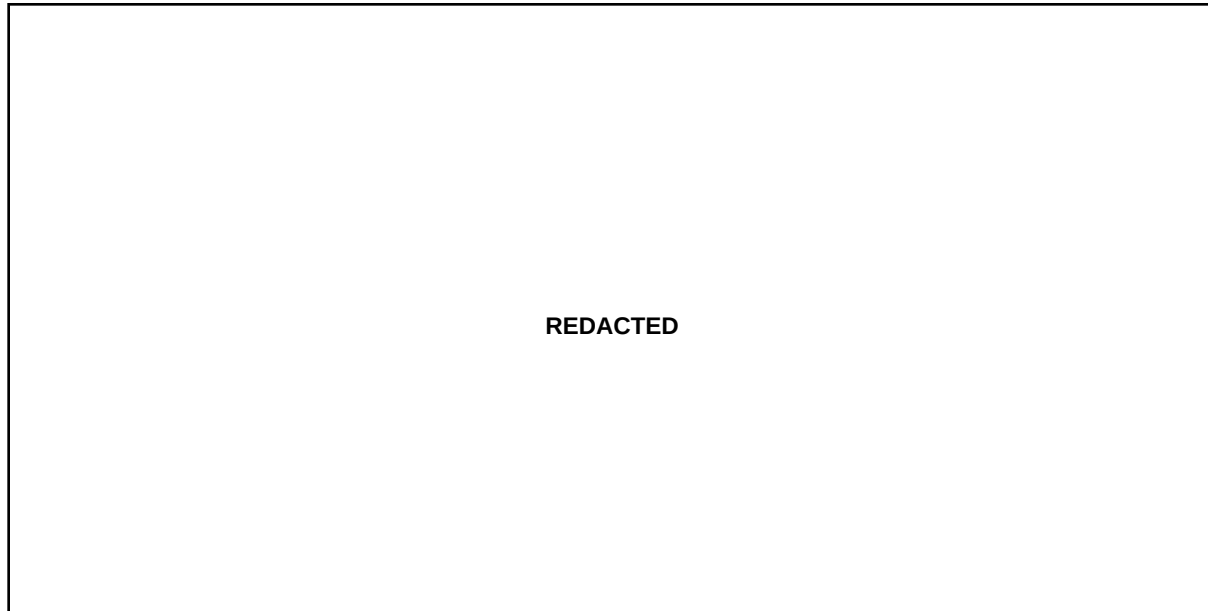


Figure S2: Schematic illustration of the comparison of the HOI framework for analyzing fMRI data. (a) fMRI data from the Human Connectome Project (HCP), comprising resting-state and seven task conditions, were parcellated using the Schaefer 100 (cortical) and Tian 16 (subcortical) atlases ($N = 116$). Regional time series were extracted to compute a pairwise baseline (Functional Connectivity, FC) and two categories of HOIs: information theory (IT) metrics (PhiID, PED, O-information, distinguishing between redundancy and synergy) and topological data analysis (TDA) metrics (static scaffolds including Frequency/Persistence, and dynamic metrics like TScaffold and triangles). (b) An edge-level similarity matrix was constructed to classify the computed metrics, revealing a dichotomy in the metric space. When projected at the nodal level, the ‘Redundancy’ cluster (including FC, Redundancy-based IT measures, and triangles) spatially aligns with metabolic gradients and unimodal cortices (visual/somatomotor areas). Conversely, the ‘synergy/topology’ cluster (including synergy-based IT measures and scaffolds) spatially aligns with neurotransmitter receptor density maps and transmodal association cortices. (c) The metrics were evaluated on two distinct prediction tasks: brain fingerprinting (identifying individuals, representing stable “traits”) and task decoding (classifying cognitive states). Results demonstrate a trade-off: HOIs and topological markers maximize individual identifiability (traits), whereas FC and redundancy-dominated measures perform optimally for state decoding. (d) (Left) A ternary plot illustrates the decomposition of FC into redundant, synergistic, and topological percentages, showing that the balance of these components varies a lot for different task conditions. (Right) Partial least squares correlation (PLSC) analysis was applied to link brain features with cognitive scores (e.g., Fluid Intelligence, Memory). The analysis reveals that topological measures explain the most variance in complex behavior compared to other metrics.

COMMENT 1.2

2) Regarding the central justification for developing the work, I agree with the authors that the gap mentioned in the initial part of my text exists and is relevant. Although the paper is not a literature review, it might be worthwhile to conduct a numerical survey regarding the (supposedly growing) number of papers, over the last few years, that employ HOI metrics to model brain connectivity.

Reply 1.2: We thank the reviewer for this constructive suggestion. We have carried out an extensive review check of the recent literature and added a new figure to the Supplementary Information (Supplementary Fig. S1), which quantifies the increasing number of publications that employ HOI metrics, both in general and specifically in brain-related studies, over the last few years. This figure clearly illustrates the growing interest in higher-order approaches. We now also briefly mention this and refer to Supplementary Fig. S1 in the revised Introduction, to strengthen the motivation and contextualization of our work.

Action taken 1.2: We added Supplementary Fig. S1, providing estimates of the number of publications regarding the HOI literature.

For completeness, see below the new text highlighted in red:

INTRODUCTION

...

However, the growing interest in HOIs and the resulting rapid development of diverse methodological frameworks — especially in information theory and topological data analysis — has led to a fragmented research landscape (see **Supplementary Fig. S1 for a quantitative trend of HOI-based brain-connectivity studies**). Existing approaches often operate in isolation, each grounded in distinct theoretical assumptions and computational principles.

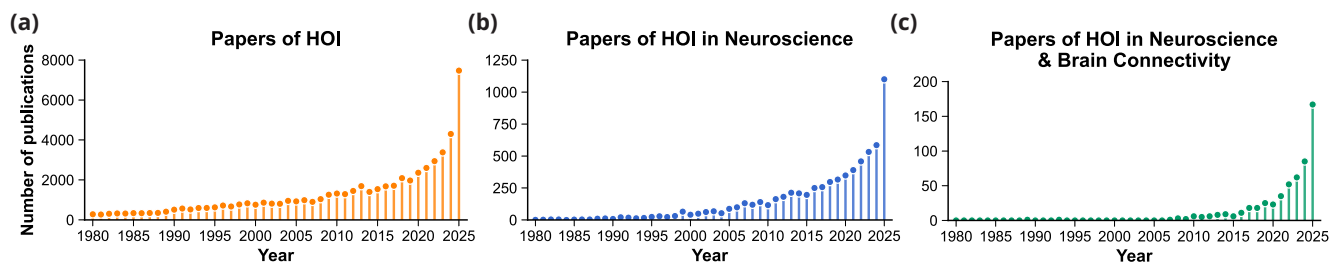


Figure S1: Temporal evolution of research interest in higher-order interactions (HOIs). The bar charts display the annual volume of scholarly publications indexed by Google Scholar between 1980 and 2025. **(a)** Total number of search results for the specific key phrase “Higher-order interactions”. **(b)** Number of publications identified using the search query “Higher-order Interactions” AND “Neuroscience”. **(c)** Number of publications identified using the search query “Higher-order Interactions” AND “Neuroscience” AND “Brain Connectivity”. The data illustrate a marked increase in relevant literature, particularly over the last decade, with an increasing usage of HOIs as novel brain connectivity over the last 5 years.

COMMENT 1.3

3) The authors mention that their experiments are based on third-order interactions, but that, in general, the considered metrics can be extended to higher-order interactions. I suggest that the authors include additional comments on this in their paper. Is it possible, for example, to indicate situations where it would make sense to consider fourth-order or higher interactions? What benefits could this bring and what would be the additional demand (for example, from the point of view of computational load and consequent practical feasibility)? Without something in this direction, I think one cannot naturally speak of higher-order interactions, but only of third-order interactions.

Reply 1.3: We thank the reviewer for this insightful comment. We completely agree that a comprehensive discussion on interactions of order $K \geq 4$, their computational feasibility, and their conceptual added value is important to justify the broader term “Higher-Order Interactions”. To address this, we have restructured part of the Discussion section and added new content to the Supplementary Material.

First, regarding the computational time and complexity, we have added a dedicated table and two new figures to the Supplementary Material (Supplementary Figures S10 and Table S1). These illustrate the computational complexity of the methods and provide empirical time estimates for running the codes on a single subject ($T = 1200$), when considering different number of ROIs $N = 10, \dots, 200$. As the number of combinations grows as $\binom{N}{K}$, exhaustive evaluation at $K = 4$ or $K = 5$ becomes computationally prohibitive for whole-brain connections.

However, we highlight that the fundamental “step change” in the physics of interacting systems occurs when moving from pairwise ($K = 2$) to triplet ($K = 3$) interactions, rather than from order 3 to order 4. In network science and dynamical systems — such as simplicial contagion models (I. Iacopini et al - <https://www.nature.com/articles/s41467-019-10431-6>), cooperation with hypergraph dynamics (A. Civilini - <https://journals.aps.org/prl/abstract/10.1103/PhysRevLett.132.167401>), or higher-order Kuramoto synchronization (P.S. Skardal et al - <https://www.nature.com/articles/s42005-020-00485-0>, A.P. Millan et al - <https://journals.aps.org/prl/abstract/10.1103/PhysRevLett.124.218301>), the inclusion of 3-body interactions is sufficient to trigger novel, emergent behaviors (e.g., explosive transitions and hysteresis) that cannot be reduced to pairs. Once triplets are introduced, higher group sizes (like $K = 4$) generally modulate these effects quantitatively but do not typically introduce entirely new qualitative dynamical regimes. Analogously, for informational properties such as synergy and redundancy, the qualitative transition occurs between order 2 and higher orders, since these quantities can not be defined at $K = 2$. Consequently, while structural differences may exist across orders higher than 3, they are expected to vary smoothly rather than exhibit abrupt qualitative changes.

Second, we have included a new plot (Supplementary Figure S11) comparing O-information computed at order 3 versus order 4, projected onto the nodal and edge levels. The high spatial correlation between the two orders confirms that $K = 3$ captures the share of the higher-order statistical synergy and redundancy present in the system, making it a robust and representative choice for studying higher-order phenomena. Notably, while redundancy shows near-perfect agreement across orders, synergy exhibits lower-but still strong ($r > 0.75$)-correlation, consistent with its definition as genuinely emergent information that is not necessarily predictable from lower-order interactions. This additional analysis suggests that analyses at $K \geq 4$ may be particularly informative when the specific goal is to probe fine-grained synergistic effects, albeit at a significantly increased computational cost.

Finally, we revised the discussion section to discuss this observations, acknowledging that the question of when it is appropriate to compute interactions of order $K \geq 4$ remains open and is an active area of research. While exhaustive whole-brain searches rapidly become computationally prohibitive, recent work has begun to explore higher-order statistics in targeted settings. In particular, preliminary results in clinical cohorts from our group suggest that, within specific functional systems, considering higher group orders $K > 3$ (e.g., for O-information) can improve discrimination between patient and control groups. However, because scaling to larger K is often not feasible in practice, we now briefly mention feasible alternatives that enable analyses at higher orders without exhaustive enumeration. Specifically, three commonly used strategies: (i) Anatomical hypotheses, reducing the effective N by pre-selecting specific functional networks or regions of interest; (ii) Sparsification: restricting candidate hyperedges to those supported by strong underlying pairwise structural or functional links; (iii) sampling, using probabilistic sampling approaches (e.g., Monte Carlo or random-walk strategies on the hypergraph) rather than exhaustive enumeration.

Action taken 1.3:

We have restructured the discussion section to include a part dedicated to higher group sizes, their significance (the 2-to-3 step change), and possible strategies for achieving them. We also refer to the novel Supplementary Figures S10-S11 and Tables S1 with time and complexity estimates, as well as the comparison between O-information at order 3 vs. order 4, explicitly referencing them in the main text.

For completeness, see below the new text highlighted in red:

DISCUSSION

...

A fundamental consideration in HOI research is the choice of interaction order. Here, we focus on third-order interac-

tions, since the 2-to-3 step, i.e., from pairwise to triplets, is the first regime where irreducible synergy and redundancy emerge beyond dyads. The same frameworks can, in principle, extend to fourth order and higher, potentially revealing broader multi-region dependencies (e.g., distributed hyper-synergies across cognitive networks). Yet, the number of candidate multiplets grows combinatorially, making exhaustive whole-brain analyses quickly infeasible. We note that the computational cost of the evaluated HOI metrics varies considerably; detailed benchmarks, including estimated time complexity for all metrics, are reported in Supplementary Tables S1 and Supplementary Figs. S10. Moreover, we quantified the added value of higher orders by comparing O-information at orders 3 and 4 (Supplementary Fig. S11). Higher orders may prove especially valuable when probing distributed cognitive systems, such as the default-mode or frontoparietal networks, where four or more regions are thought to engage in irreducible collective computation. Indeed, to overcome the computational bottleneck of exhaustive searches at these scales, future analyses can leverage targeted strategies, specifically: *(i)* anatomical pre-selection to reduce the region pool, *(ii)* structural or functional sparsification of candidate hyperedges, and *(iii)* probabilistic sampling approaches. Our findings should be considered in light of several limitations that also point toward promising directions for future work. . . .

Metric	Time Complexity	Runtime (N=200)	Dominant Computation
Functional connectivity (FC)	$O(N^2T)$	< 10 s	Correlation estimation
PhiID (Bivariate)	$O(N^2T)$	~ 20 s	Lagged covariance + pairwise atoms
Static scaffold	$O(N^2T) + O(m^3)$	~ 15 s	Single filtration + H_1 extraction
O-information (Red/Syn)	$O(N^2T + N^3)$	~ 90 s	Covariance + triplet enumeration
PED (Red/Syn)	$O(TN^3)$	~ 370 s	Triplet-wise joint-counting (binary)
Dynamic TDA (TScaff)	$O(TN^3) + T \cdot O(m_t^3)$	~ 2700 s	Per-time-point filtration + homology

Table 1: **Computational complexity and empirical runtime of network metrics.** Asymptotic time complexity for N regions and T time points, with empirical runtime obtained with a good workstation (Ryzen Threadripper 3970 with 16 cores used), processing a reference subject with $T = 1200$ and $N = 200$ ROIs. PED and dynamic TDA both scale as $O(TN^3)$ due to triplet enumeration, but dynamic TDA incurs additional per-time-point topological computation with larger constant factors. Indeed, PED uses binary discretization ($B = 2$), so the per-triplet state space is constant (2^3). For topology-based methods, m denotes the number of simplices included in the *static* filtration (e.g., vertices, edges, and triangles), and m_t denotes the number of simplices included at time point t in the *dynamic* filtration. The $O(m^3)$ and $O(m_t^3)$ terms refer to a worst-case upper bound for the matrix-reduction step used to compute persistent homology.

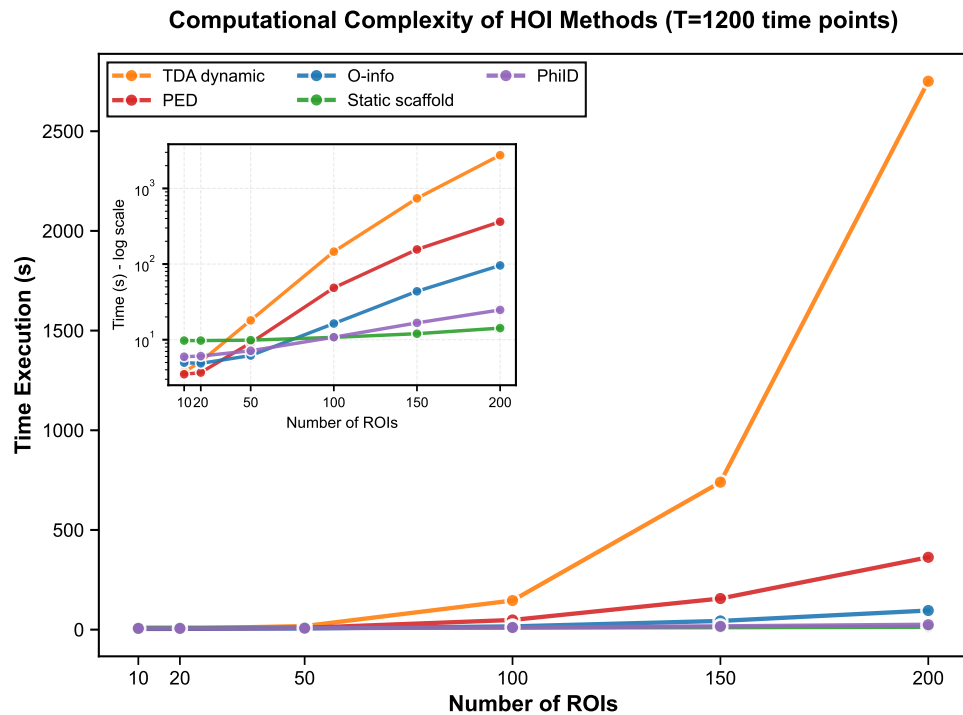


Figure S10: Execution time of HOI metrics for a representative fMRI subject. Execution time (in seconds) for computing pairwise and HOI metrics on a single subject ($T = 1200$ time points) as a function of the number of Regions of Interest (ROIs), ranging from $N = 10$ to $N = 200$. Benchmarks were performed on a Ryzen Threadripper 3970 workstation (using 16 cores). The inset (log-scale) highlights the orders of magnitude difference between the approaches. While PED and Dynamic TDA (Tsscaffold) both scale with the number of triplets ($O(TN^3)$), tsscaffold (~ 2700 s at $N = 200$) is nearly an order of magnitude slower than PED (~ 370 s). This divergence reflects the dominant computational cost: PED relies on efficient binary joint-counting ($B = 2$), whereas tsscaffold incurs an additional term $T \cdot O(m_t^3)$ representing the matrix-reduction step required to compute persistent homology at every time point (where m_t is the number of simplices in the dynamic filtration at time t). Static metrics (static scaffold, O-info) and pairwise metrics (FC, PhilID) remain computationally tractable (< 2 minutes) even at high parcellation densities ($N = 200$), scaling primarily with the initial covariance estimation ($O(N^2T)$) or static triplet enumeration. Error bars over 10 iterations are smaller than the marker size.

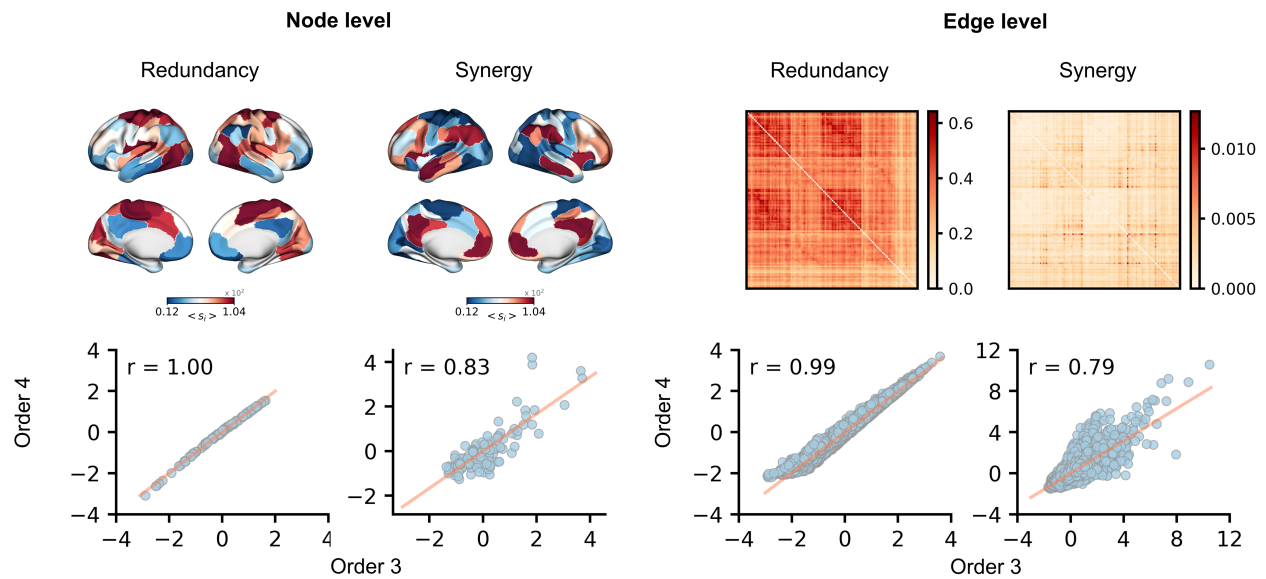


Figure S11: Consistency of redundancy and synergy across interaction orders at node and edge levels. The two top left panels show node-level maps of redundancy (left) and synergy (right) computed from order 4 interactions, displayed on the cortical surface (blue–red color scale indicates the ranking of regional mean interaction strength $\langle s_i \rangle$, computed as the sum across all quadruplets). The two top right panels show the corresponding edge-level redundancy and synergy matrices computed from order 4 interactions. Bottom panels compare order 4 versus order 3 estimates for redundancy and synergy at the node level (left) and edge level (right). Scatter plots report Pearson correlation coefficients (r), demonstrating near-perfect agreement for redundancy at both node ($r = 1.00$) and edge ($r = 0.99$) levels, and strong but reduced agreement for synergy (node: $r = 0.83$, edge: $r = 0.79$). These results indicate that redundancy patterns are highly stable across interaction orders, whereas synergy exhibits greater sensitivity to the inclusion of higher-order interactions, particularly at the edge level.

COMMENT 1.4

4) Is there any specific justification for choosing a cohort of 100 individuals from the HCP database? Would using a larger number of individuals improve the robustness of the evaluation regarding sensitivity to the chosen preprocessing strategies, for example?

Reply 1.4: We thank the Reviewer for raising this important point regarding cohort size and preprocessing sensitivity. We initially selected the 100 unrelated subjects subset of the Human Connectome Project (HCP) database because it serves as a rigorous, widely used benchmark in network neuroscience. This cohort provides high-quality acquisitions with a standardized processing stream while avoiding potential confounds related to familial structure. Furthermore, it enabled a controlled and computationally feasible comparison across the broad HOI measures used in the study.

We agree that increasing the cohort size can strengthen the robustness of these evaluations, particularly regarding sensitivity to preprocessing strategies. To partially address this in the revision, we conducted a preliminary replication using the larger 1200 subject HCP cohort (S1200, August 2025 release). Although this latest release is distributed with a different minimally preprocessed pipeline that is not directly comparable to our 100-subject cohort (as explicitly noted in the HCP guidelines), we found that the fundamental synergy-redundancy gradients and their core spatial organization were highly preserved (Supplementary Fig. S15). Moreover, the derived HOI projection patterns showed substantial agreement across datasets, yielding nodal and edge projections with Spearman correlations of $\sim 0.75 - 0.8$.

While these results strongly support the stability of the principal organization we report, conducting a fully systematic evaluation of preprocessing sensitivity at the S1200 scale is beyond the scope of the present comparative manuscript. Harmonizing pipelines across 1200 subjects for both resting-state and all seven task sessions would require downloading and processing an exceptionally large volume of data (more than 22 Tb of data). We consider this an important direction for future work and have clarified this point in the revised Limitations section of the manuscript.

Action taken 1.4: We added the S1200 replication as a new supplementary analysis (Supplementary Fig. S15) and updated the Discussion/Limitations to mention it as a robustness check, while leaving the pre-processing analyses to future investigations.

Below is the new text added in the main text and in the Supplementary Material:

DISCUSSION

Third, the relatively slow sampling of fMRI constrains inference on fast neural dynamics; integrating higher-temporal-resolution modalities such as MEG, EEG, or intracranial recordings would offer important complementary perspectives on the dynamics of HOIs [146]. Fourth, redundancy estimates are known to be sensitive to preprocessing choices; although we used established pipelines [153], we did not systematically explore variation across preprocessing strategies, parcellation schemes, or denoising approaches [154,155]. **However, to partially test robustness, we conducted a preliminary evaluation on the larger 1200-subject HCP cohort (S1200, August 2025 release). Although processed with a different, non-comparable minimally processed pipeline, as mentioned in the HCP guidelines, the fundamental synergy-redundancy gradients and their core spatial organization were highly preserved, despite some variation in the exact hierarchical clustering of the metrics (Supplementary Fig. S15). Systematically assessing these preprocessing factors in larger datasets remains an important direction for future research.**

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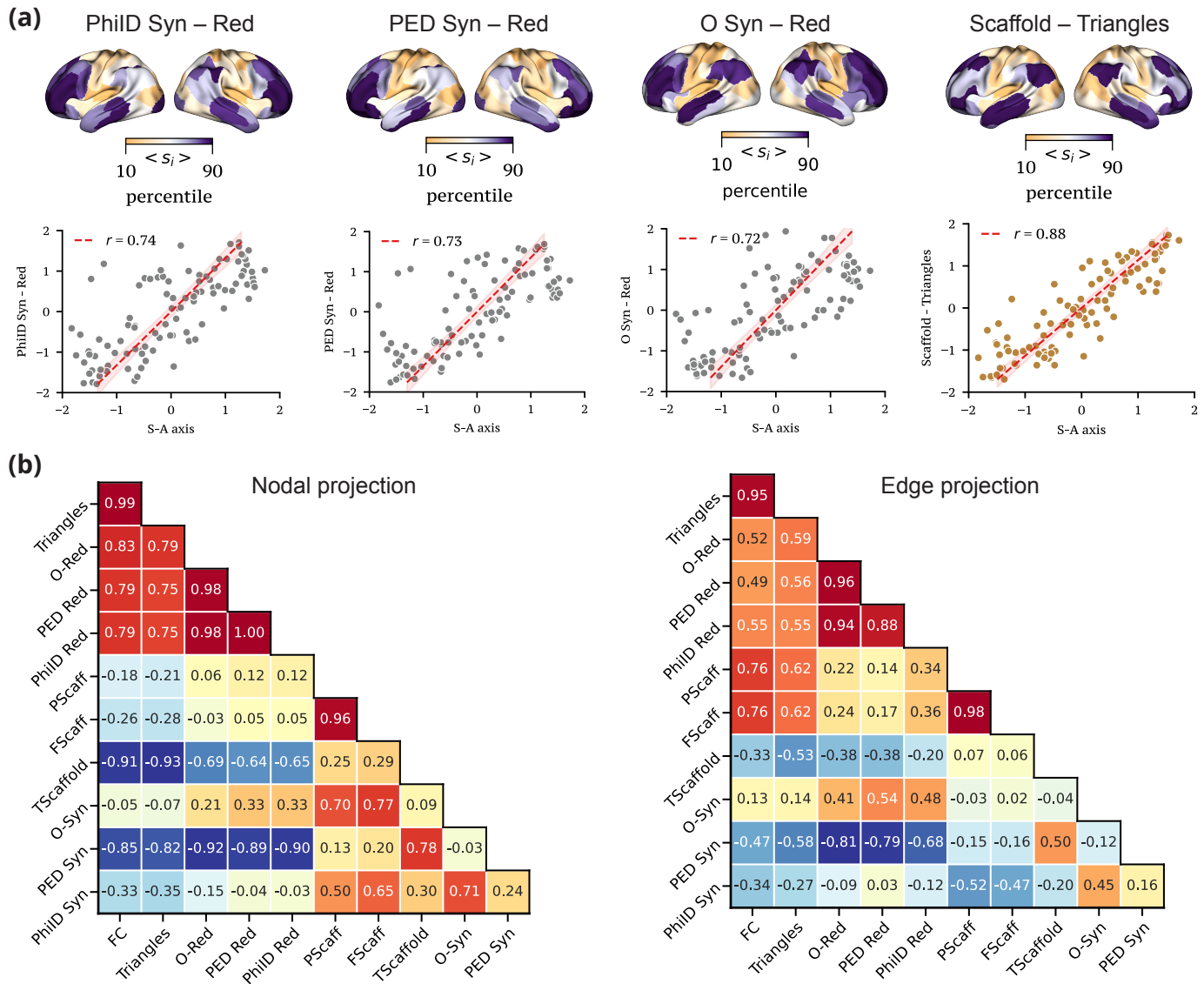


Figure S15: Replication of the synergy–redundancy cortical gradients in the HCP S1200 cohort. (a) Cortical maps of synergy–redundancy contrast for the information-theoretic frameworks (PhiID, PED, and O-information; Syn–Red) and for the temporal topological approach Scaffold–Triangles, computed on the independent HCP S1200 release (August 2025), which uses a distinct minimally preprocessed pipeline (not directly comparable to the main-text preprocessing stream). Across frameworks, the spatial organization of the synergy–redundancy axis is preserved, reproducing the unimodal–transmodal gradient reported in the main text. (b) Nodal and edge projections of the HOI metrics obtained in the S1200 cohort. Despite the different cohort size and non-comparable preprocessing, these projections show substantial agreement with the 100-subject results (Spearman’s $\rho = 0.74$ for nodal projections and $\rho = 0.78$ for edge projections), indicating that the large-scale organization of higher-order profiles is robust across HCP releases.

COMMENT 1.5

5) *It seems that certain sections of the "Discussion" section are somewhat redundant with what has already been written in previous sections of the paper; the first paragraph on page 11, for example. It is worth reviewing and checking the possibility of being more concise in the text of this section.*

Reply 1.5: In the revised manuscript, we have streamlined the discussion section to remove redundancies with earlier parts of the text as pointed out by the referee. Some parts of the Discussion are now more concise and focused on interpretation, limitations, and future directions.

At the same time, we have used this opportunity to clarify and expand points that are of broader interest but were previously underdeveloped. In particular, we now (i) discuss computational complexity more explicitly, mentioning a new table in the Supplementary Information that summarizes the computational cost of the different HOI metrics; (ii) elaborate on the challenges and opportunities of scaling the framework to higher group orders beyond three; and (iii) integrate comments on the additional analyses introduced in the revised version (e.g. further fMRI analyses and complementary HOI metrics). We believe these changes both reduce redundancy and strengthen the conceptual and practical aspects of the Discussion.

Action taken 1.5: We have shortened the opening and application-focused paragraphs of the Discussion to avoid repeating results already presented in the Results section (including the paragraph highlighted by the referee). The revised Discussion now emphasizes interpretation, limitations, and future directions, while explicitly pointing to newly added supplementary analyses (computational cost benchmarks, higher-order scaling, and additional metrics) where appropriate.

COMMENT 1.6

6) *The authors do not comment on aspects related to the computational demand associated with calculating the evaluated HOI metrics. Even briefly, they could discuss this issue. Perhaps this could be especially important in situations where it makes sense to consider higher-order interactions.*

Reply 1.6: We thank the reviewer for raising this important point. As mentioned in one of the previous comments, in the discussion of the revised manuscript, we now explicitly discuss the computational demands associated with the different HOI metrics and their implications for practical applications, especially when considering higher-order interactions.

In particular, we have included a new Table and Figure in the Supplementary Information, detailing the computational complexity of each evaluated HOI method. This table provides approximate scaling behavior as a function of system size and group order, thereby offering a concise overview of the relative costs of the various approaches and clarifying in which regimes each method is most feasible. We believe this addition addresses the reviewer's concern and offers useful guidance for readers who may wish to apply these metrics to larger or higher-order systems.

Action taken 1.6: In the revised discussion, we now consider this point more extensively and mention the analyses done and reported in the Supplementary Material.

COMMENT 1.7

7) *Again, regarding the density of the material contained in the work: the figures in the paper help the reader to follow the results and are aligned with the discussions in the text. However, a kind of summary of the authors' findings would help the reader to have an overview of the conclusions reached and would enrich the work.*

Reply 1.7: We thank the reviewer for this helpful suggestion. As mentioned in our response to an earlier comment, we have now added a full workflow figure in the Supplementary Information (Supplementary Fig. S2) to provide a visual overview of the analysis pipeline and help readers navigate the different steps of the study, providing a final summary of the results obtained.

In addition, we have strengthened the textual summarization of our findings. That is, we have rephrased part of the initial paragraphs of the Discussion to provide a more explicit, structured conclusion that highlights the main findings. We hope these additions make the overall message of the paper clearer and easier to grasp at a glance.

Action taken 1.7: We have rephrased the first part of the discussion and added a new figure in Supplementary Material (Fig. S2) to provide a visual overview of the analysis pipeline.

For completeness, we report the first part of the restructured discussion:

DISCUSSION

Recent strides in information theory and computational topology have increasingly offered novel approaches to characterize multiregional higher-order interactions (HOIs) from neuroimaging recordings [27,44,131], extending beyond standard pairwise functional connectivity (FC). Here, we addressed the lack of a systematic understanding of these diverse metrics by mapping their interrelations, biological underpinnings, and utility in brain fingerprinting, task decoding, and brain–behavior associations.

To help readers navigate this rapidly expanding field (see SI Fig. S1 for a numerical survey tracking the recent growth of HOI literature) and to summarize our full pipeline overview, from metric definitions to downstream applications, we provide a schematic in Supplementary Fig. S2. Our comparative analysis, at nodal and edge-level projections, consistently reveals three families of observables: redundancy-based metrics, synergy-based metrics, and topological scaffolds (Fig. 2). In brief, we found that these computational modes align strongly with established sensorimotor-association cortical hierarchies and distinct neurochemical profiles. Furthermore, while synergy and redundancy significantly enhance subject identifiability (fingerprinting), classical pairwise FC remains optimal for decoding specific cognitive states.

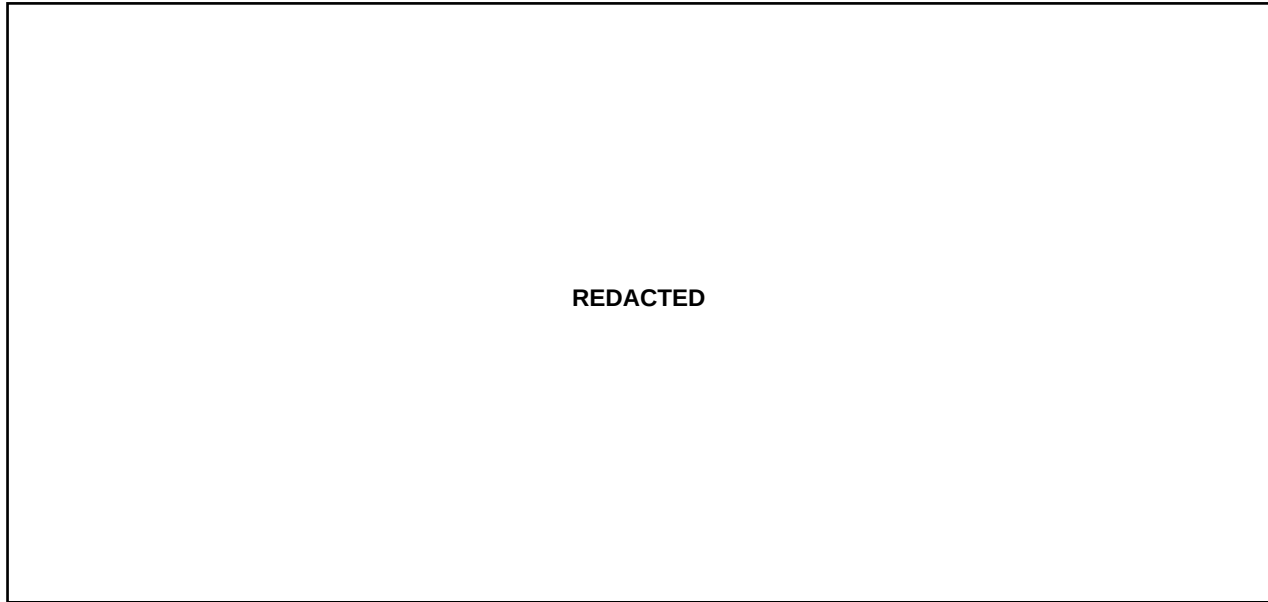


Figure S2: Schematic illustration of the comparison of the HOI framework for analyzing fMRI data. (a) fMRI data from the Human Connectome Project (HCP), comprising resting-state and seven task conditions, were parcellated using the Schaefer 100 (cortical) and Tian 16 (subcortical) atlases ($N = 116$). Regional time series were extracted to compute a pairwise baseline (Functional Connectivity, FC) and two categories of HOIs: information theory (IT) metrics (PhiID, PED, O-information, distinguishing between redundancy and synergy) and topological data analysis (TDA) metrics (static scaffolds including Frequency/Persistence, and dynamic metrics like TScaffold and triangles). (b) An edge-level similarity matrix was constructed to classify the computed metrics, revealing a dichotomy in the metric space. When projected at the nodal level, the ‘Redundancy’ cluster (including FC, Redundancy-based IT measures, and triangles) spatially aligns with metabolic gradients and unimodal cortices (visual/somatomotor areas). Conversely, the ‘synergy/topology’ cluster (including synergy-based IT measures and scaffolds) spatially aligns with neurotransmitter receptor density maps and transmodal association cortices. (c) The metrics were evaluated on two distinct prediction tasks: brain fingerprinting (identifying individuals, representing stable “traits”) and task decoding (classifying cognitive states). Results demonstrate a trade-off: HOIs and topological markers maximize individual identifiability (traits), whereas FC and redundancy-dominated measures perform optimally for state decoding. (d) (Left) A ternary plot illustrates the decomposition of FC into redundant, synergistic, and topological percentages, showing that the balance of these components varies a lot for different task conditions. (Right) Partial least squares correlation (PLSC) analysis was applied to link brain features with cognitive scores (e.g., Fluid Intelligence, Memory). The analysis reveals that topological measures explain the most variance in complex behavior compared to other metrics.

Detailed reply to the report of reviewer # 2

COMMENT 2.0

The article explores a variety of higher-order metrics, from diverse backgrounds, and compares the different metrics across a variety of settings, with an aim to understand which metrics extract which type of information, and how the different metrics compare to each other and to standard pairwise metrics. To achieve this aim the authors use fMRI data from the Human Connectome Project.

The study of higher order networks has been of great interest in recent years, with techniques for higher order analysis arising from a few different fields, in particular complex networks (hypergraphs), algebraic topology (TDA), and information theory (synergy-redundancy). This paper focuses on the latter two of these (TDA and information theory), and attempts to understand how the higher order techniques emerging from this fields compare. This is a worthwhile goal, as the higher order field is currently very fractured, due to its emergence from different fields. And thus far no other study has done such a large comparison between different HOI methods.

As a whole, the article achieves this aim. Using correlation and clustering methods, they demonstrate that the metrics they consider separate into three main descriptors (redundant, topological, and synergistic), they show that certain methods are better at brain fingerprinting and other metrics are better at task decoding, thus demonstrating that the metrics capture different information and leading to a better understanding of which metrics should be used for a given analysis. A comparison to pairwise approaches is given, and it is shown that sometimes pairwise performs better and sometimes HOIs perform better, but in general they complement each other (adding to the growing body of literature supporting this). They also link their findings back to the biology, by demonstrating that these metrics capture certain biological information.

The methodology used is sound, the mathematics and techniques used are already existing methods with solid foundations, the statistical analyses and ML-based methods are all well established techniques. The conclusions drawn are well founded based on the analyses given, and provide new important insights into the field.

Reply 2.0: We sincerely thank the reviewer for the thoughtful and very positive evaluation of our work, and for recognizing the relevance of our study for the broader higher-order interaction community.

In the revised version of the manuscript, we have carefully addressed all points raised in the reviews. In particular, we have added several new details and clarifications regarding the interpretation of our results, computational complexity of the methods, and expanded the comparison with other approaches. We have also included additional analyses and explanatory material (both in the main text and in the Supplementary Information) to make the methodological choices and results more transparent. We believe these changes further support the conclusions and improve the overall clarity and accessibility of the manuscript.

COMMENT 2.1

As with all comparative studies, it is not possible to examine every metric existing in the literature. However, it would have been nice to see a few other metrics included here, as the authors claim the given metrics "provide a comprehensive lens to characterizing higher-order interdependencies". In particular, it would be nice to see other TDA techniques included beyond the authors own techniques (persistence entropy, dynamic embedding, etc), also a comparison to more pairwise metrics would be beneficial.

Reply 2.1: We thank the reviewer for this insightful comment. In the present study, we focused on higher-order metrics that have already been applied to the analysis of brain BOLD activity, in order to ensure interpretability and relevance within the existing neuroimaging literature. As a reference pairwise metric, we employed functional connectivity, which is the most widely used pairwise approach and is commonly taken as a benchmark in the field. While the employed topological metrics are among the most established and cover both time-resolved and time-averaged analyses, we agree

that including additional metrics strengthens the manuscript.

In response, we have expanded the analysis in several ways. First, we added persistent entropy as an additional topological data analysis metric, demonstrating its ability to distinguish between different tasks. As expected, given its more global and less fine-grained nature, its classification accuracy is lower than that of the other higher-order metrics considered. Nevertheless, persistent entropy still efficiently discriminates between tasks, supporting its relevance as a complementary descriptor.

Second, we substantially expanded the comparison with pairwise approaches by including mutual information (MI), transfer entropy (TE), and precision (inverse covariance). The inclusion of MI allows us to account for general (potentially nonlinear) zero-lag statistical dependencies between pairs of regions, while TE captures directed lagged interactions, thereby introducing a temporal dimension to the pairwise comparison. Precision was added in light of recent findings demonstrating its strong performance in brain fingerprinting (<https://www.nature.com/articles/s41592-025-02704-4>), making it an important state-of-the-art benchmark for identifiability analyses. Moreover, since in this paper the evaluation of brain fingerprinting was measured as the identifiability score defined as the Cohen's D between the distribution of intra- and inter-subject correlations, we also report the score measured in this way. Finally, to address issues raised by the following comment of this review, we also added an additional hypergraph metric, SINDy, which was defined by recent literature (<https://www.nature.com/articles/s41467-025-57664-2>).

These additions allow for a more systematic and rigorous contextualization of higher-order methods, particularly in evaluating their performance in brain fingerprinting. Importantly, the higher identifiability achieved by higher-order metrics remains robust even after expanding the comparison. Specifically, after including MI, TE, and precision, the scaffold continues to exhibit the largest identifiability effect size (Cohen's d), while the Φ ID-red metric attains the highest identification rate, jointly with MI. At the network level, when performing brain fingerprinting across specific pairs of resting-state networks, higher-order metrics outperform pairwise approaches in 80 out of 108 comparisons. Together, these results confirm the consistent advantage of higher-order descriptors in capturing subject-specific structure, which is not fully accessible to pairwise statistics alone.

These additional analyses provide a more comprehensive evaluation of both TDA-based and pairwise methods, and strengthen our claim that different higher-order metrics extract distinct and complementary aspects of interdependencies in brain activity.

Finally, regarding the reviewer's suggestion of "dynamic embedding": we interpret this as likely referring to Takens/time-delay embeddings. While highly promising, applying delay-embedding-based TDA in our setting is not straightforward, because (i) fMRI has relatively slow sampling and limited time points per condition, (ii) embedding requires careful selection of delay and embedding dimension, and (iii) there is currently limited methodological consensus and relatively sparse literature on how to deploy Takens-style embeddings for whole-brain HOI mapping in fMRI in a way that is comparable across subjects and tasks. For these reasons, rather than introducing an embedding choice that would add substantial methodological degrees of freedom, we prioritized adding persistence entropy and additional pairwise baselines, which directly address the reviewer's request while maintaining comparability and interpretability across metrics.

Action taken 2.1: Persistent entropy was added as an additional topological data analysis metric, and its ability to discriminate between tasks was systematically evaluated. Mutual information and transfer entropy were also incorporated as additional pairwise metrics to extend the scope of the comparative analysis. We report the results of the new metrics in two new supplementary figures and add a few sentences in the discussion of the comparison with the recent work on pairwise metrics (Nature Methods, <https://www.nature.com/articles/s41592-025-02704-4>).

For completeness, we report below the two additional figures that are present in the supplementary:

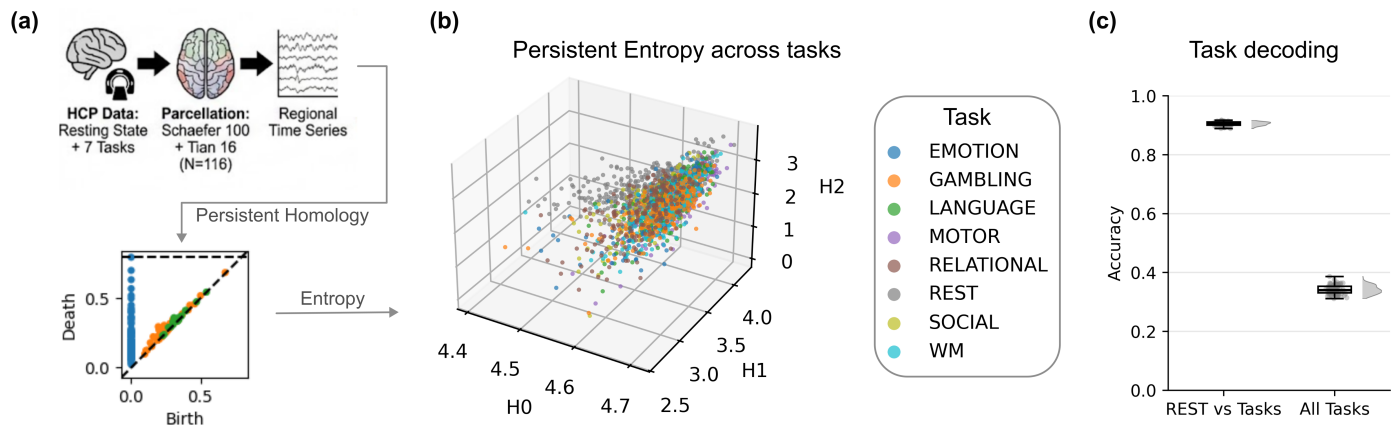


Figure S12: Persistent entropy of brain dynamics across rest and task conditions. (a) Analysis pipeline. Resting-state and task fMRI data from the Human Connectome Project (HCP) are parcellated using the Schaefer-Tian atlas ($N = 116$ regions), yielding regional time series. Persistent homology is computed on the correlation matrix obtained from the resulting functional time series, producing persistence diagrams whose topological complexity is summarized using persistent entropy. (b) Persistent entropy values across homological dimensions (H_0 , H_1 , H_2) for all subjects and conditions. Each point corresponds to a subject–task instance, colored by task. While persistent entropy values occupy a compact manifold, differences between rest and task are evident across dimensions. (c) Task decoding performance using persistent entropy features. Classification accuracy is shown for discriminating rest versus task conditions and for multiclass decoding across all tasks. Boxplots indicate the median and interquartile range across bootstrap resamples, with individual points representing bootstrap-level accuracies. Persistent entropy reliably distinguishes rest from task states and supports above-chance decoding across multiple task conditions, indicating that topological summaries capture behaviorally relevant differences in large-scale brain dynamics.

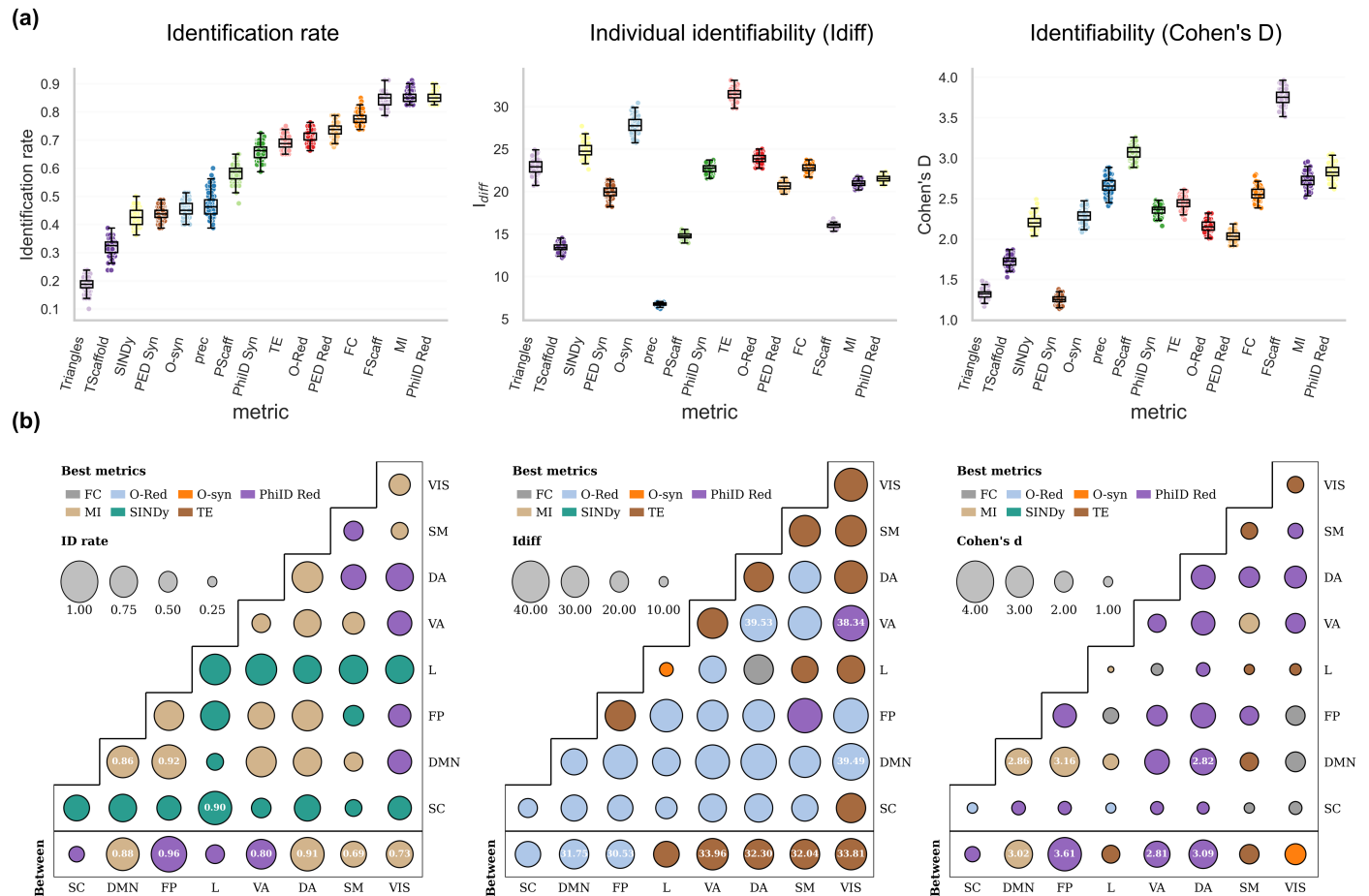


Figure S13: Extended comparison of connectivity metrics for brain fingerprinting. (a) Whole-brain fingerprinting performance evaluated across an expanded set of pairwise and higher-order metrics. Identification rate (left), individual identifiability score I_{diff} (middle), and effect size (Cohen's d , right) are reported to provide complementary assessments of brain fingerprinting. While precision, mutual information and transfer entropy improved the performance of pairwise approaches, higher-order descriptors, particularly scaffold-based and redundancy-related measures, consistently achieve greater fingerprinting scores across metrics. (b) Network-level fingerprinting performance computed within and between the seven Yeo resting-state networks. The best-performing metric varies across systems, indicating that subject-specific information is heterogeneously distributed across functional networks.

COMMENT 2.2

Moreover, the study is currently a comparison between topological and information theoretic metrics (which is a worthwhile comparison), but to be truly "charting higher order models" and be a "comprehensive lens", one would like to see hypergraph metrics included. However, the article is an excellent first step in understanding how these different metrics interact.

Reply 2.2: We thank the reviewer for this important comment. We agree that including hypergraph-based metrics can further strengthen the scope of the manuscript, as they explicitly highlight the role of higher-order representations of brain activity beyond purely informational and topological properties.

To explicitly address the reviewer's suggestion, we extended the analysis in two directions. First, we incorporated hypergraph centrality measures that have been recently generalized from pairwise networks to hypergraphs, namely H-eigenvector centrality (<https://doi.org/10.1137/18M1203031>) and Katz centrality, also referred to as α -centrality, as implemented by the python toolbox xgi (<https://xgi.readthedocs.io/en/latest/api/algorithms/xgi.algorithms.centrality.html>). These metrics provide a more nuanced characterization of node importance than simple strength (i.e., the average weight of all incident interactions, which we use to compute nodal projection in the original manuscript), as they account for the higher-order structure of hyperedges. We found that the correlation between hypergraph centralities and the strength centrality, used in the original manuscript to compute nodal projection, is consistently high across different higher-order constructions. This indicates that the nodal projections computed in the original manuscript already capture a substantial portion of the structural information encoded in the inferred hypergraphs. While a more detailed analysis the differences between distinct centrality measures could be an interesting point for future work, they are overall highly correlated with the nodal projection we used.

Second, we included an additional method for hyperedge inference based on a regression framework, namely SINDy, which estimates the joint effect of $k - 1$ variables on the future state of another region to assign weights to k -order hyperedges (<https://www.nature.com/articles/s41467-025-57664-2>). Unlike the information-theoretic and topological approaches, this method relies on sparse regression rather than information-theoretic of topological quantities. Using the same estimation procedure as in the original proposal, we found that this approach aligns closely with the redundancy-related cluster identified in our comparative analysis and shows strong fingerprinting performance, outperforming other methods in specific resting-state network pairs.

Overall, these additional analyses provide a more systematic evaluation of both (i) methods to infer hyperedges and construct hypergraph representations of brain activity, and (ii) hypergraph-based centrality measures to characterize the role of individual regions within these representations. We believe that these extensions broaden the scope of the manuscript and strengthen its contribution toward a more comprehensive framework for charting higher-order models of brain function.

Action taken 2.2: We have expanded the manuscript to explicitly include hypergraph-based analyses, with three new figures that we currently included in the supplementary materials. In particular, we (i) implemented hypergraph centrality measures recently generalized from pairwise networks and compared them to strength centrality (the one employed in the original manuscript), and (ii) incorporated SINDy as an additional hyperedge inference method based on sparse regression, independent of information-theoretic and topological frameworks. We report the correlation between hypergraph centralities and strength centrality, as well as the fingerprinting performance of SINDy at both whole-brain and network levels. These additions are now described in the Methods and Results sections and supported by new supplementary analyses, thereby broadening the scope of the manuscript toward a more explicit hypergraph representation of brain activity.

For completeness, please find below the newly added analyses in the Supplementary Material:

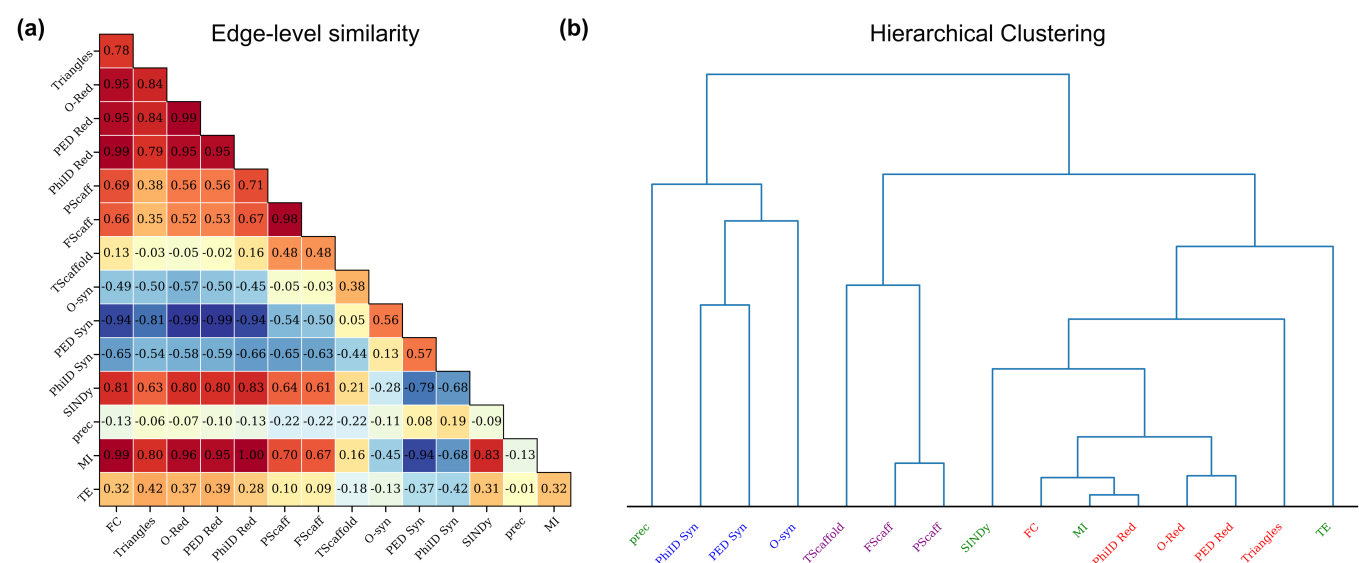


Figure S14: Edge-level similarity and hierarchical clustering, including additional higher-order and pairwise connectivity metrics. (a) Edge-level similarity matrix across all evaluated metrics, quantified using Pearson correlation between vectorized connectivity representations. Each entry reports the similarity between two metrics computed as the Spearman r across all edges. Redundancy-based measures (Red, O-Red, PED Red, Φ ID Red), together with mutual information (MI) and SINDy, show very high mutual similarity, forming a tightly correlated group. Transfer entropy (TE) and precision (prec) exhibit slightly lower correlations, with TE aligning more closely with redundancy-based metrics and precision showing greater similarity to synergy-related descriptors. (b) Hierarchical clustering dendrogram derived from the edge-level similarity matrix. The clustering confirms the presence of three main families of descriptors: redundancy-dominated metrics (including MI, SINDy, and TE), synergy-dominated metrics, and topological/scaffold-based measures. Importantly, the newly included metrics integrate consistently within the pre-existing clusters, reinforcing the robustness of the previously identified organizational structure.

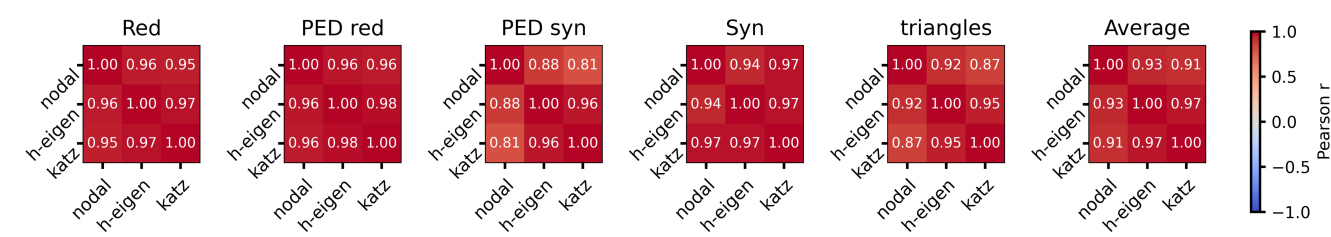


Figure S15: Comparison of hypergraph centrality measures across higher-order constructions. Pearson correlation matrices between nodal strength, H-eigenvector centrality, and Katz (α -) centrality computed on hypergraphs inferred using different higher-order metrics (Red, PED red, PED syn, Syn, triangles), together with their average across constructions. Each panel reports the pairwise correlation between centrality measures across brain regions. Across all higher-order definitions, hypergraph centralities show consistently high correlations with nodal strength and with each other ($r \approx 0.8$ – 1.0), indicating strong agreement in the ranking of regional importance. These results demonstrate that the strength-based centrality used in the main manuscript captures a substantial portion of the structural information encoded by more sophisticated hypergraph centrality formulations, while confirming the robustness of node-level characterizations across different higher-order interaction models.

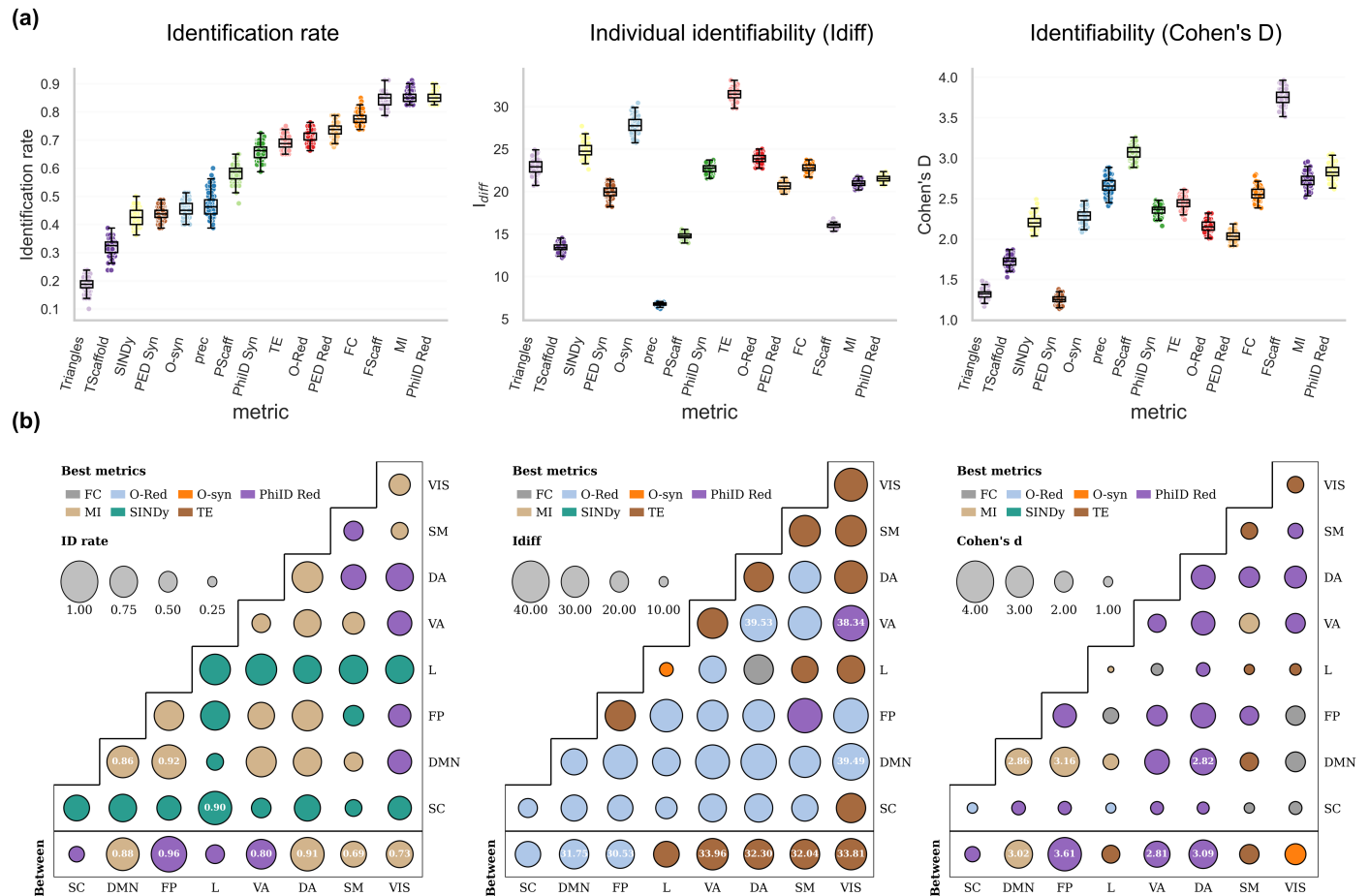


Figure S13: Extended comparison of connectivity metrics for brain fingerprinting. (a) Whole-brain fingerprinting performance evaluated across an expanded set of pairwise and higher-order metrics. Identification rate (left), individual identifiability score I_{diff} (middle), and effect size (Cohen's d , right) are reported to provide complementary assessments of brain fingerprinting. While precision, mutual information and transfer entropy improved the performance of pairwise approaches, higher-order descriptors, particularly scaffold-based and redundancy-related measures, consistently achieve greater fingerprinting scores across metrics. (b) Network-level fingerprinting performance computed within and between the seven Yeo resting-state networks. The best-performing metric varies across systems, indicating that subject-specific information is heterogeneously distributed across functional networks.

COMMENT 2.3

Overall, the work aims to answer an interesting question, it contributes novel, noteworthy results, and new insights into the field. Thus, I recommend it be accepted for publication.

Reply 2.3: We thank the reviewer for their positive evaluation and for recommending our work for publication. In the revised version of the manuscript, we have further clarified several points and added additional explanations where needed, in response to the reviewers' comments. We believe these changes strengthen the presentation and make our contributions and insights more transparent to the reader.

COMMENT 2.4

The writing is excellent. A few minor comments, typos and corrections:

Page 7, paragraph 1: "restricting our analysis to transmodal cortex was almost as discriminative", it is unclear how the figure shows this, did you take all the regions of the transmodal cortex together, or do you just mean that the regions of the transmodal cortex each performed well. Also a complete list of regions included in the transmodal cortex is never given, this would be useful to add somewhere.

Reply 2.4: We thank the reviewer for pointing out the ambiguity in that sentence. In the revised manuscript, we have removed the phrase "restricting our analysis to the transmodal cortex was almost as discriminative" from Page 7, as the wording was unclear and partially redundant with the preceding sentence.

To clarify our original intent: for brain fingerprinting, we found that considering only the functional connections of specific transmodal networks—particularly the frontoparietal (FP) and default mode network (DMN)—with all other networks yields decoding performance that is close to that obtained when using whole-brain connectivity (see the comparison of scores between Fig. 4a and Fig. 4b). We now describe this more explicitly in the Results section, avoiding the previous ambiguous formulation.

Regarding the definition of the transmodal cortex, we have clarified this in the Methods section. We explicitly state that unimodal networks correspond to VIS, SM, DA, and VA. In contrast, transmodal networks correspond to LIMBIC (L), FP, and DMN, following the standard mapping from the Schaefer parcellation to the 7-network Yeo atlas.

Action taken 2.4: In the revised version of the manuscript, we have rephrased the corresponding part of the discussion and of the methods.

COMMENT 2.4

Table 1: The table uses the type Linear but the caption uses Classic, either works but choose one.

Reply 2.4: Thanks for pointing out this inconsistency. In the revised manuscript, we have corrected the mismatch by using a consistent terminology throughout: the table and its caption now both refer to the Classic type.

COMMENT 2.5

Page 6, paragraph 3: missing full stop after [109,112] and extra space between densities and full stop.

Reply 2.5: Thanks for catching this, done.

COMMENT 2.6

Page 10: Full stop missing after [17,139];

Page 14 (Homological scaffolds): K'_ω should be $K_{\omega'}$

References: DOI for article [85] is wrong.

Reply 2.6: Reference DOI and typo are now amended in the novel version of the manuscript

COMMENT 2.7

I have not run the code, but I have looked through the supplied folder. The code looks comprehensive, there looks to be code available for each of the analyses done, along with the comments and instructions for installation. Some of the code used is existing code from previous studies, thus already well established. Some of the code looks to use datasets that are not included in what was provided, but so long as this is addressed in the final repo, that should be fine.

Reply 2.7: We thank the reviewer for examining the code and for the positive assessment. In the revised repository, which we plan , we have further improved the organization and documentation of the scripts, ensuring a clear correspondence between each analysis/figure in the manuscript and the relevant code modules.

Regarding the data, we now explicitly state in the repository that the analyses rely on Human Connectome Project (HCP) datasets, and we provide links to our existing pre-processed data, as well as links and instructions on how to obtain these data from their sources. Where possible, we have also included small illustrative or synthetic example datasets to demonstrate the workflow and allow users to test the code without restricted data.

Finally, we confirm that, upon acceptance of the paper, we will release on GitHub a complete and polished version of the code used to reproduce some of the main analyses and figures in the manuscript, accompanied by an updated README and detailed usage instructions.

Action taken 2.7: We will provide a GitHub repository with the description of the code to reproduce some of the results presented in the main text.