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Topological and Temporal Higher-Order Functional Connectivity in Brain Connectomics: A Review of Methodologies, Developments, and Challenges

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Abstract

The human brain is a complex, integrated system defined by higher-order, multi-way interactions that are inherently simplified by traditional pairwise network models. Although a diverse array of analytical methods has been developed to address this limitation, the literature remains fragmented, lacking a unifying conceptual framework to organize these emerging developments. This review provides a comprehensive synthesis of higher-order functional connectivity (HOFC) methodologies in brain connectomics. We propose a fundamental distinction between two complementary paradigms based on their analytical outputs: Topographical HOFC and Temporal HOFC. We trace the evolution of Topographical HOFC from foundational Correlation-of-Correlations (CoC) and spatial profile similarity measures to advanced multi-view fusion frameworks and graph neural networks. Concurrently, we survey Temporal HOFC, exploring dynamic sliding-window clustering, meta-connectivity, high-resolution edge-centric models, and statistically rigorous, model-based approaches like the Matrix Variate Normal Distribution (MVND). By critically examining the conceptual, statistical, and computational challenges of these frameworks—including the biological interpretation gap, the "genuineness" of observed interactions, and the curse of dimensionality—we outline key comparative insights. Ultimately, we argue that the future of the field lies in a principled, neurobiologically grounded integration of these spatial and temporal approaches to unlock a robust, multi-level understanding of complex brain organization in health and disease.

Keywords: Higher-order functional connectivity (HOFC); Topographical HOFC; Dynamic HOFC; Edge-centric; Matrix variate normal distribution.

1. Introduction

The history of neuroscience is, in many ways, a story of successful reductionism. For decades, the mapping of specific cortical areas by pioneers like Broca and Wernicke, the dominant paradigm focused on decomposing the brain into its constituent parts, individual neurons, columns, and localized regions, to understand their specialized functions [1]. This approach has been immensely fruitful, providing the foundational knowledge upon which modern neuroscience is built. However, as our understanding of complex cognitive phenomena like consciousness, learning, and decision-making has grown, the limitations of a purely localizationist view have become increasingly apparent. It is now clear that brain activity is not an isolated phenomenon but the result of dynamic, integrated interactions among distributed neural

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populations [1–4]. This realization catalyzed the rise of network neuroscience, a powerful framework that models the brain as a graph of nodes and edges, providing a comprehensive system-level picture of its functional organization [2].

While network neuroscience represented a major step away from simple localizationism, much of its early development remained rooted in a form of relational reductionism, focusing primarily on pairwise analyses of brain connectivity. This dyadic paradigm, while computationally tractable and highly informative, inherently simplifies the complex, multi-way interactions that define a truly integrated system [5–7]. The brain, as a complex system, exhibits emergent properties where the behavior of the whole cannot be fully predicted by the sum of its pairwise parts [8]. A growing body of evidence, from physiological studies of neuromodulation to computational models, suggests that the interaction between two regions is often fundamentally altered by the concurrent activity of a third, a principle that pairwise models cannot capture [9,10]. This has motivated a new concept toward higher-order frameworks that implicitly or explicitly model interactions among more than two brain regions, extending the traditional pairwise view rather than replacing it.

Remarkable conceptual and mathematical diversity characterize this new frontier. At the foundational level of this shift, the concept of Correlation of Correlations (CoC) has emerged as a cornerstone methodology. By systematically quantifying the statistical relationship between first-order connectivity patterns (lower-order functional connectivity, or LOFC), CoC frameworks construct secondary, higher-order networks that reveal organizational properties invisible to direct time-series analyses. Depending on how this CoC principle is applied, the literature has naturally bifurcated into two primary dimensions: spatial network profiles (Topographical HOFC) [11] and dynamic temporal co-fluctuations (Temporal HOFC) [12].

The primary aim of this review is to provide a comprehensive, conceptually grounded, and up-to-date roadmap to this rapidly expanding landscape of higher-order brain connectivity. To bring coherence to a fragmented literature, we organize the existing methodologies into a unified, two-pronged taxonomy: Topographical HOFC and Temporal HOFC (Fig. 1). Rather than treating these paradigms as disconnected analytical tools, we present them as an integrated continuum of second-order brain network analysis. We first explore Topographical HOFC, tracing its evolution from simple profile similarities and network-level extensions to deep, multi-view learning architectures and graph neural networks. We then transition directly into Temporal HOFC, surveying sliding-window dHOFC clustering, meta-connectivity, parameter-free edge-centric paradigms, and culminating in the statistically rigorous Matrix Variate Normal Distribution (MVND) framework. Figure 1 provides a visual taxonomy of these frameworks, serving as a conceptual guide for the detailed methodological journey that follows.

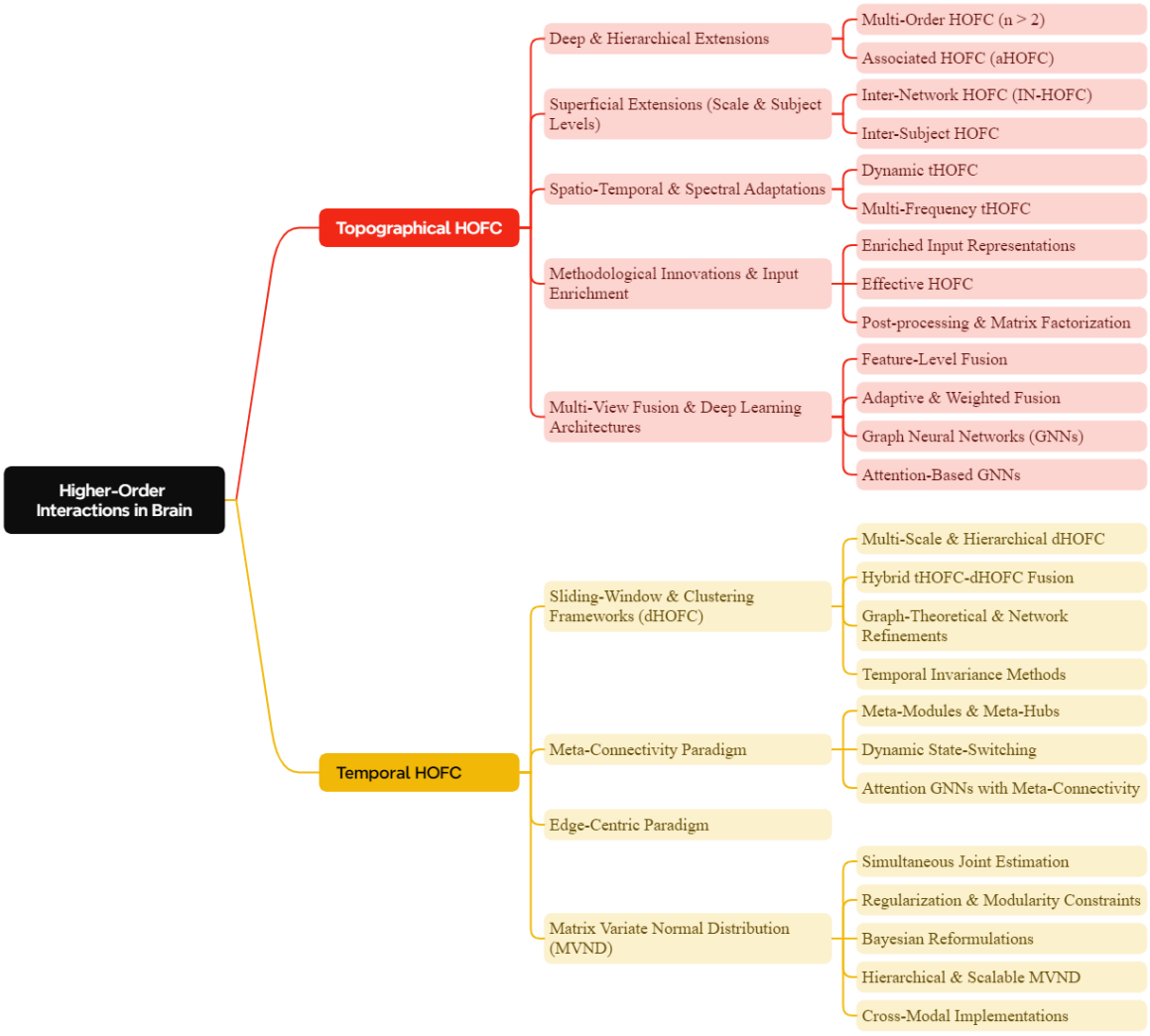

Fig. 1. A Refined Conceptual Taxonomy of Higher-Order Functional Connectivity in Brain Connectomics. This diagram illustrates the classification of HOFC methodologies covered in this review, divided into Topographical HOFC (encompassing deep, superficial, and

Following this comprehensive methodological survey, we transition from description to critique, presenting a dedicated analysis of the grand challenges and limitations that confront the field, spanning conceptual, statistical, computational, and data-related hurdles. The review concludes with a discussion of key comparative insights and a forward-looking perspective on the future directions that promise to shape this exciting frontier. We hope this structured overview will serve as an essential reference for any researcher aiming to navigate and contribute to the complex, entangled, and truly higher-order nature of the human brain.

2. Topological higher-order functional connectivity

Among the first and most influential frameworks of the CoC principle is topological HOFC. Conceptually, topological HOFC can be understood through an analogy to social networks: it measures the extent to which two brain regions share a similar community of connections or circle of friends. This method is designed

to uncover higher-level associations by evaluating the similarity of their LOFC profiles (illustrated in Fig. 2A). For each brain region, a connectivity profile is constructed, representing its Pearson correlation pattern with all other regions in the brain (equivalent to a row or column in the LOFC matrix). The similarity between any two such profiles is then computed, typically via Pearson correlation, to form the topological HOFC matrix. Unlike direct time-series correlations, topological HOFC captures second-order relationships by quantifying the degree to which two regions share similar connectivity patterns with the rest of the brain [11]. Beyond providing complementary information and demonstrating distinct predictive value relative to lower-order networks [13–17], topological HOFC enhances the characterization of complex modular architectures [11,18,19] and exhibits greater sensitivity to subtle shifts in connectivity patterns [11,16,17,20]. A schematic overview of this extraction process is illustrated in Fig. 2B.

Building upon the foundational topological HOFC framework, several studies have explored its deep extension to capture deeper and more complex inter-level relationships. One direct extension involves deriving correlations of ever-increasing order through iterative applications of the CoC procedure. In this framework, the connectivity matrix produced at one order serves as the input for computing the next, allowing for a recursive extension to orders $n > 2$. Such an approach enables the representation of more complex, hierarchical, and multilayered interactions within brain network organization [15,21]. A conceptually related development is associated HOFC (aHOFC), which was proposed to measure the similarity between a brain region's own LOFC profile and its corresponding topological HOFC profile. By quantifying this cross-level interaction, aHOFC provides a unique view of the brain's organizational hierarchy and has proven effective in diagnostic applications [13]. A schematic overview of the computation of third-order FC and aHOFC is presented in Fig. 2C and Fig. 2D, respectively.

Another major trajectory in the evolution of the topological HOFC framework has been its superficial extension, broadening its scope from individual brain regions to larger organizational units. One such formulation extends the concept to large-scale functional networks, where the connectivity profile of an entire network is derived by averaging across its constituent nodes. The correlations among these network-level profiles then yield the inter-network HOFC (IN-HOFC), providing insights into the coordination between large-scale brain systems [22]. A conceptually related approach has also been advanced at the inter-subject level, wherein the similarity of LOFC profiles across different individuals is assessed for a given brain region. Such inter-subject analyses offer a complementary perspective, enabling the detection of both shared and group-specific network architectures and thereby contributing to the characterization of common versus divergent patterns of functional organization across populations [23,24].

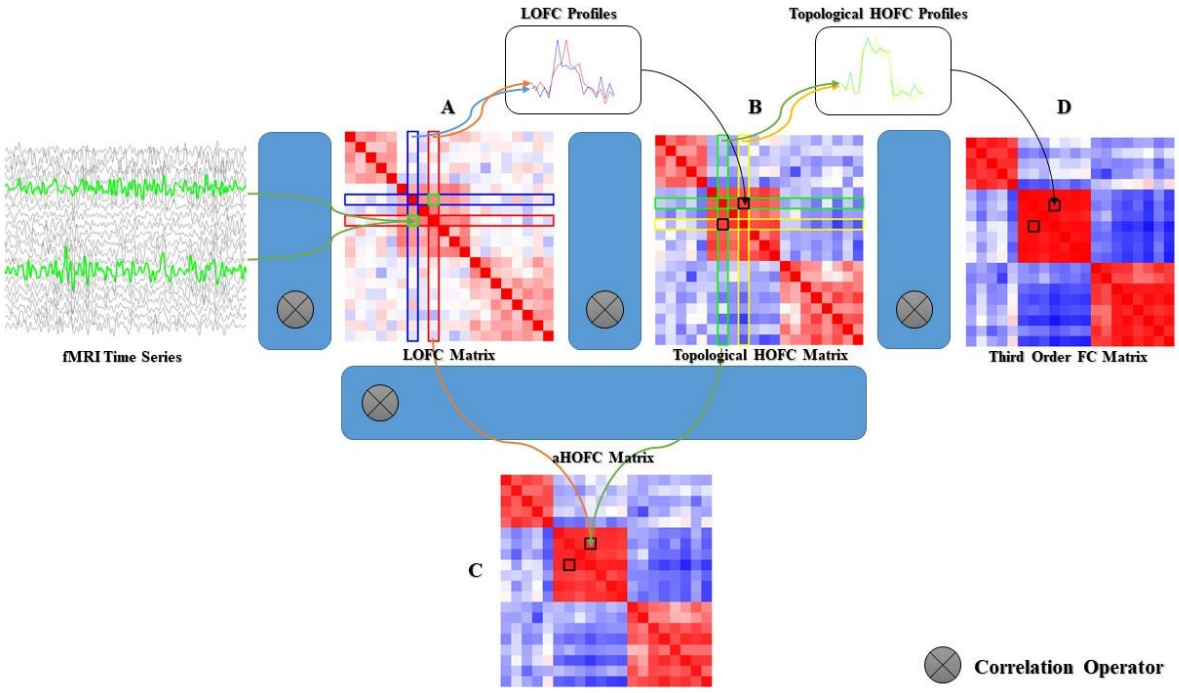

Fig. 2. Schematic illustration of Topological Higher-Order Functional Connectivity (tHOFC) and its extensions. (A) Low-Order Functional Connectivity (LOFC): Pearson correlation between the fMRI time series of any two ROIs (e.g., green traces). Each entry in this matrix represents a direct, pairwise functional connection. (B) Topological HOFC (Second-Order): The LOFC matrix serves as the input for the next level. The connectivity profile of a given ROI (e.g., the red and blue rows/columns in the LOFC matrix) represents its pattern of connections to all other brain regions. The correlation between two such profiles (e.g., red and blue traces in "LOFC Profiles") is then calculated. This second-order correlation value populates the corresponding entry in the Topological HOFC (tHOFC) matrix, capturing the similarity of connectivity patterns between the two ROIs. (C) Associated HOFC (aHOFC): This metric quantifies the cross-level interaction for a single ROI. It is computed as the correlation between that ROI's own LOFC profile (e.g., a row from the LOFC matrix) and its tHOFC profile (e.g., the corresponding row from the tHOFC matrix). The resulting aHOFC matrix captures the relationship between first- and second-order connectivity architectures. (D) Third-Order FC: The process can be iterated. By treating the tHOFC matrix as a new input, the correlation between its profiles (e.g., green and yellow traces in "Topological HOFC Profiles") is computed to generate a Third-Order FC matrix. This reveals even higher levels of network organization. The crossed circle symbol represents the correlation operator applied at each stage.

To capture the brain's non-stationary nature, the topological HOFC framework has been extended into the temporal and spectral domains. The most common approach, dynamic topological HOFC, involves dividing time series into overlapping windows, estimating LOFC within each window, and then transforming these into a sequence of time-varying topological HOFC matrices [13,25–28]. This strategy enables the temporal tracking of higher-order connectivity patterns and has been further adapted by applying it across different frequency bands to generate time-frequency-specific topological HOFC matrices, particularly in EEG studies [14,29–31]. To extract informative features from these dynamic higher-order networks, novel analytic methods have been proposed, such as the central-moment approach, which characterizes temporal correlation dynamics through higher-order statistical moments [25,32].

Recent research has increasingly focused on enhancing the topological HOFC framework through methodological innovations at various stages of the pipeline, often involving the fusion of multiple, complementary information sources. Innovations in the pre-computation stage aim to enrich the input LOFC matrix. For example, some studies construct a more comprehensive LOFC by fusing spatio-temporal features before applying the topological HOFC procedure [33], while others employ Correlation-Preserving Embedding (COPE) to learn a richer, topology-aware representation of brain regions prior to computing profile similarity [34,35]. Another innovative direction involves replacing the standard correlation-based FC with effective connectivity (EC) as the low-order network [36]. Methodological creativity is also evident in the use of novel data sources, such as incorporating White Matter (WM) BOLD fluctuations to construct cross-tissue topological HOFC networks [37], and in post-processing refinements like low-rank matrix factorization to reduce noise and enhance the modular organization of the final topological HOFC matrix [18]. An evolution of the framework involves embedding the construction of hierarchical-order networks directly within an end-to-end, task-oriented learning model. For instance, Liu et al. (2025) proposed a framework where hierarchical-order connectivity is learned iteratively using an attention mechanism, ensuring that the resulting high-order relationships are explicitly optimized for a specific predictive goal, such as amyloid-β deposition prediction [38].

One of the recent trends is the integration of topological HOFC as one of several complementary views within multi-view fusion frameworks. The underlying premise is that different FCN construction methods (e.g., Pearson correlation, sparse representation, mutual information, and topological HOFC) capture distinct aspects of neural interactions. Rather than seeking a single best representation, these studies construct a portfolio of FCNs and employ advanced fusion strategies, such as deep feature-level fusion [39], adaptively learn the fusion weights [40], joint embedding and tensor decomposition [41], or explicit separation of shared versus unique network information [42]. This multi-view philosophy has been powerfully integrated with deep learning. Graph Neural Networks (GNNs), for instance, have been used to process multi-level graphs composed of both low-order and higher-order networks, often within a joint learning framework that allows for information exchange between the different network levels [43–47]. Similarly, attention-based models are used to dynamically weigh the importance of features derived from different network views [48]. Overall, this multi-view fusion paradigm is predicated on the principle that a more holistic and robust representation of brain functional architecture can be achieved by integrating these complementary information sources. Empirical evidence consistently supports this premise, showing that fusion-based models significantly enhance the performance of downstream analyses, particularly in the classification of neurological and psychiatric disorders [41,42,45,48].

In summary, the topological HOFC framework has evolved substantially from its original formulation based on LOFC profile similarity into a diverse family of approaches. Through deep, superficial, temporal, and methodological extensions, it has been adapted to capture interactions across multiple scales, levels, and data modalities. These developments have been primarily driven by the goal of enhancing sensitivity to the brain's complex network architecture. Importantly, the application of topological HOFC and its variants has yielded significant clinical and neurobiological insights. It has consistently improved the classification and characterization of a wide range of conditions, including Alzheimer's disease and its prodromal stages [11,13,26], Parkinson's disease [17], presbycusis [16], schizophrenia [19], and autism spectrum disorder [15]. Furthermore, it has been used to predict clinical outcomes, such as post-stroke somatosensory function [20], and to provide neurobiological insights into complex theories like the integration-segregation imbalance in schizophrenia [19].

3. Temporal higher-order functional connectivity

In parallel with methods that assess the spatial similarity of connectivity patterns (topological HOFC) [11], a distinct and highly influential family of approaches quantifies higher-order interactions by examining the temporal similarity of these patterns [12,49,50]. The core principle uniting these methods is the concept of a second-order temporal correlation, and they measure how the strengths of different functional connections fluctuate together over time. The general computational workflow for this paradigm, which we term Temporal HOFC, is illustrated in Fig. 3. A useful analogy is to consider temporal HOFC as measuring conversational synchrony in a dynamic social gathering. While individual conversations (lower-order connections) fluctuate in intensity, this family of approaches identifies which pairs of conversations tend to strengthen or weaken in unison. This conceptual framework has evolved along several parallel, yet interconnected, research trajectories, often appearing under different terminologies. To provide a unified perspective, we introduce the umbrella term Temporal Higher-Order Functional Connectivity (Temporal HOFC) to encompass these methods. Key paradigms within this family include the dynamic HOFC (dHOFC) approaches [12], the concept of meta-connectivity [51], and a high-resolution edge-centric paradigm [49]. While a related concept, the Matrix Variate Normal Distribution (MVND) framework, also captures the covariance of connections, it does so through a unified statistical estimation process and will be discussed in detail in Section 3.4 [52]. In the following, we will systematically survey the evolution and application of these temporal correlation-based methods.

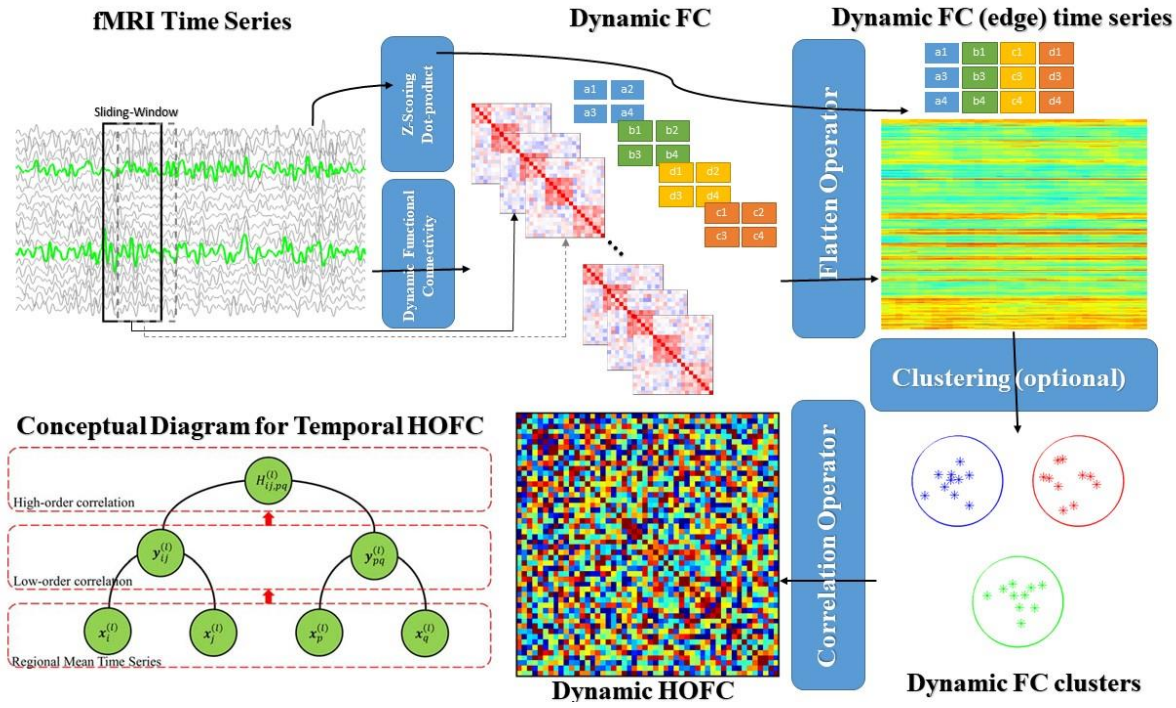

Fig. 3. Computational pipelines for Temporal Higher-Order Functional Connectivity (Temporal HOFC). In both cases, the result is a matrix of Dynamic FC (edge) time series, where each row represents the temporal fluctuation of a single pairwise connection (edge). A Flatten Operator conceptually transforms the sequence of matrices into this edge-by-time representation. Subsequently, a Correlation Operator computes the pairwise correlation between these edge time series, yielding the final Dynamic HOFC matrix. This matrix captures the second-order temporal relationships, i.e., the co-fluctuation patterns between different brain connections. As an optional intermediate step, the edge time series can be grouped using a Clustering algorithm to identify Dynamic FC clusters or "meta-modules" before computing the final correlations. The Conceptual Diagram (bottom-left [12]) summarizes this

hierarchical process, showing how high-order correlations are built upon low-order correlations, which themselves derive from the regional mean time series.

3.1. Dynamic HOFC

The first introduction of this family was dHOFC. The methodology begins by employing a sliding-window analysis on fMRI time series to generate a sequence of time-varying, low-order FC (dFC) matrices. From this sequence, the temporal trajectory of each individual connection (i.e., each edge in the low-order network) is extracted, forming a correlation time series. The final dHOFC network is then constructed by computing the Pearson correlation between these correlation time series. Conceptually, this process transforms the original pairwise edges of the LOFC into the nodes of the new dHOFC network, where the edges now represent the temporal synchrony of their fluctuations. Ultimately, dHOFC provides a higher-order representation of the brain's functional organization by mapping the underlying architecture of its temporal dynamics [12].

A direct consequence of this formulation is the curse of dimensionality; calculating correlations between all possible pairs of edges (N^2) results in a feature space on the order of N^4, which is computationally prohibitive and statistically challenging. To address this, a common and effective solution is the application of clustering algorithms [12,53–56]. In this modified pipeline, the numerous correlation time series are typically pooled across all subjects to create a common feature space and then grouped into a smaller number of clusters using methods such as hierarchical [12,55–57] or k-means [58,59] clustering. Crucially, the number of clusters is often treated as a hyper parameter, with researchers searching across a range of values to identify the optimal setting that maximizes performance on a downstream task, such as clinical classification [12,55,56]. The final dHOFC network is then computed based on the correlations between the mean time series of these clusters, significantly reducing the dimensionality while retaining the core dynamic patterns [12,53,54].

Building on this core concept, the dHOFC framework has evolved along several distinct methodological lines. One major development has been the introduction of hierarchical structures, where multi-layer dHOFC networks are constructed by systematically varying the number of clusters across layers, allowing for a multi-scale analysis of dynamic organization [60]. Another prominent trajectory involves fusing dHOFC-derived features with those from other connectivity measures, such as topological HOFC [57,61], static or dynamic low-order FC, to create a more comprehensive and powerful representation of brain function for classification tasks [62–65]. Also, the field has moved toward integrating dHOFC with Graph Neural Networks (GNNs), which can automatically learn complex topological and nodal features from these higher-order graphs, representing a significant advance over manual feature engineering [66].

Other methodological refinements have sought to improve specific stages of the dHOFC pipeline. These include the development of adaptive dFC estimation methods that move beyond the limitations of the rigid sliding window [67] and the use of central moments to derive time-invariant statistical summaries of the clustered correlation time series, thereby creating features that are robust to temporal permutations [68]. Furthermore, the dHOFC framework has proven versatile, having been successfully adapted for other imaging modalities such as EEG [69] and combined with structural methods like the Minimum Spanning Tree (MST) for feature refinement [70].

3.2. Meta-Connectivity

Closely related to the dHOFC framework is the concept of meta-connectivity (MC), a term often used to describe the correlation of dynamic functional connectivity fluctuations [51,71]. hile methodologically similar to dHOFC in its reliance on sliding-window estimates of dFC, meta-connectivity emphasizes a shift in perspective towards treating the dynamic links themselves as the primary interacting units of a complex

system. This framework has been particularly influential in characterizing the temporal organization of network dynamics beyond simple state-based models. For instance, MC analysis has revealed that brain network dynamics are not random but are organized into meta-modules, groups of functional links that co-fluctuate over time, and are coordinated by specific "meta-hubs" that act as control centers for network reconfiguration [51]. Recent applications have further leveraged this concept, for example, to identify distinct state-switching dynamics disrupted in Alzheimer's disease [50]. or to develop lightweight, attention-based Graph Neural Network (GNN) models for classifying autism spectrum disorder, where MC matrices serve as rich, higher-order edge features [72].

3.3. The Edge-Centric Paradigm

A particularly fruitful and distinct line of inquiry within the temporal HOFC family has been the edge-centric approach. This paradigm reformulates the problem by treating the dynamic edges themselves as the fundamental units of analysis, moving beyond node-centric views to directly model the interactions between pairwise connections [49,73]. The key innovation that propelled the edge-centric paradigm was the introduction of a parameter-free, high-temporal-resolution estimate of dynamic connectivity, addressing the limitations of traditional sliding-window techniques such as temporal blurring.

The cornerstone of this approach is the concept of the Edge Time Series (ETS), first proposed by Zamani Esfahlani et al. to uncover the event-driven nature of static FC [74], and formalized into a higher-order framework by Faskowitz et al. [49]. An ETS is generated for each pair of brain regions by computing the element-wise product of their respective z-scored BOLD time series [74]. The resulting value at each time point captures the instantaneous co-fluctuation of that specific edge, providing a frame-by-frame account of dynamic connectivity without the blurring effects inherent to sliding-window methods. The subsequent correlation of these ETS between different pairs of connections yields the Edge Functional Connectivity (eFC) matrix, a higher-order network where nodes represent the original connections and the new edges represent the similarity of their dynamic profiles [49]. This framework has been foundational, with its principles and applications extensively reviewed and expanded upon in subsequent work [75,76].

The development of ETS has catalyzed a rich and expanding field of research focused on the brain's fine-scale temporal dynamics, a literature too vast to comprehensively survey here. However, its foundational findings are critical for understanding the motivation behind eFC. A key discovery from the direct analysis of ETS was the identification of high-amplitude events: brief, intermittent moments of strong, brain-wide co-fluctuation that were found to be the primary drivers of the overall static functional connectivity structure [74]. This event-based perspective has proven highly insightful, and as a few illustrative examples, studies have used the spatial patterns of these events to demonstrate their link to the brain's underlying structural modularity [77]; others have used these specific temporal moments to uncover robust individual fingerprints of brain connectivity [78]; and some have leveraged the principle of instantaneous co-fluctuation to characterize the connectome profiles of discrete brain states, such as dynamic co-activation patterns (CAPs) [79]. While the direct analysis of ETS dynamics continues to be a fruitful area of research in its own right, our focus in this review is on its role as a precursor to a truly higher-order measure: the correlation between these dynamic edge profiles, known as eFC [49], forming a truly higher-order network.

The analysis of this network, most notably through the discovery of edge communities, has yielded profound insights into brain architecture. By applying clustering algorithms to the eFC matrix, researchers can identify groups of connections that exhibit similar co-fluctuation patterns over time. A key and powerful consequence of this approach is the natural emergence of overlapping modules at the node level; since a single brain region can be an endpoint for multiple edges belonging to different communities, this framework inherently reflects the multifunctional nature of brain regions [49]. This technique has been instrumental in studying the complex organization of cortical [49] or cortico-subcortical interactions [80],

uncovering the hierarchical and self-similar nature of overlapping modules [81], and understanding their development across childhood and adolescence [82]. Furthermore, the concept of edge-community entropy has been introduced as a novel metric to quantify the degree of a node's participation in these multiple communities, providing a marker for studying brain aging and cognitive specialization [83].

The richness of the information captured by the edge-centric paradigm has catalyzed a surge of successful applications in clinical and cognitive neuroscience, consistently demonstrating its power in prediction and biomarker discovery. A primary strength of the framework lies in its superior ability for subject identification and capturing individual differences. Studies have shown that eFC provides a more robust and unique fingerprint of an individual's brain compared to node-centric methods [84] and crucial for developing personalized network maps [85]. This sensitivity to individual variability has translated into powerful models for predicting behavioral and cognitive traits, such as economic risk-taking [86], loss aversion in internet gaming disorder [87], and transdiagnostic factors of depression and anxiety [88].

The edge-centric paradigm has emerged as a highly effective tool for biomarker discovery across a wide spectrum of neurological and psychiatric conditions. It has been instrumental in characterizing network alterations in neurodevelopmental disorders like autism spectrum disorder [89] and in infants with prenatal opioid exposure [73]. Similarly, it has provided novel insights into the pathophysiology of neurological conditions such as depression and anxiety comorbidity [88,90], stroke [91], multiple sclerosis [92], migraine [93], and early-stage mild cognitive impairment (eMCI) [94]. Furthermore, the framework has been applied to uncover the fundamental principles of brain organization and development, for instance by studying the temporal organization of specific circuits like corticostriatal pathways [95], and the longitudinal development of overlapping functional modules throughout childhood and adolescence [96].

The foundational concepts of the edge-centric paradigm have also inspired several methodological extensions that broaden its scope and applicability. One significant generalization moves beyond temporal co-fluctuation by defining an edge feature vector, which can encode the strength of a connection across multiple tasks, conditions, or even imaging modalities. The covariance of these feature vectors then provides a measure of higher-order relationships in multi-relational datasets [97]. In a similar spirit, Yang et al. (2023) extended the focus from temporal dynamics to population dynamics by defining the key feature of an edge as its inter-individual variability. Their work revealed a 'connectional hierarchy' in the brain, demonstrating the flexibility of the edge-centric philosophy to capture different facets of network organization [98].

3.4. Matrix Variate Normal Distribution

While the aforementioned temporal HOFC methods (such as dHOFC and edge-centric models) rely on empirical sliding-windows or heuristic element-wise products of time series, they often suffer from noise propagation and lack a rigorous generative statistical model. To address these limitations, the Matrix Variate Normal Distribution (MVND) framework holistically models the entire functional connectivity (FC) matrix as a single random statistical object. The method begins by generating a population of dynamic FC matrices, typically using a sliding-window approach on time series data [52,99,100]. This collection of dynamic matrices is then conceptualized as samples drawn from an underlying MVND. This elegant formulation allows for the simultaneous estimation of both low- and higher-order connectivity from the distribution's parameters [52]. Conceptually, this approach is closely related to the dynamic HOFC method [12], as both seek to capture the co-fluctuation of pairwise connections over time [12,52]. However, instead of using sequential correlations, the MVND framework leverages a principled statistical distribution where the mean matrix (M) represents the stable, average pairwise connections (low-order FC), and the covariance matrix (Ω) directly quantifies the higher-order relationships, or the correlations between the edges themselves [52].

The principled statistical foundation of MVND has spurred a cascade of advancements aimed at refining its robustness and theoretical rigor. Recognizing that the initial higher-order networks were often dense and noisy, Zhou et al. incorporated regularization terms into the estimation process. By adding penalties that enforce sparsity (promoting fewer, more significant connections) and modularity (favoring biologically plausible community structures), they produced more interpretable and reliable higher-order networks [101]. Further strengthening its theoretical basis, Jiang et al. proposed a Bayesian reformulation (BHM), which treats the low- and higher-order networks as latent parameters of a unified generative model, enabling more rigorous estimation [102]. To overcome the computational challenges of applying MVND to large-scale brain networks, a hierarchical strategy was developed, which partitions the brain into smaller subnetworks before integrating the results [103]. The framework's versatility is also notable, having been successfully adapted to other modalities like EEG for identifying higher-order biomarkers in depression [100] and cognitive-motor tasks [99].

4. Challenges, Limitations, and Critical Perspectives

While the previous section detailed the remarkable progress and immense potential of higher-order methods, a comprehensive review requires a critical examination of their inherent challenges and limitations. The field of higher-order brain analysis is still in a formative stage, and its methods, though mathematically elegant, are accompanied by a host of conceptual, methodological, and practical hurdles. A nuanced understanding of these challenges is not only essential for the cautious interpretation of current findings but is also crucial for guiding the future development of more robust and neurobiologically grounded approaches. This section provides a critical perspective on the field, organized around four central themes: conceptual and interpretive challenges, methodological and statistical pitfalls, computational and scalability issues, and finally, data and generalizability concerns.

4.1. Conceptual and Interpretive Challenges

In higher-order neuroscience, many of the open challenges are conceptual rather than purely computational. A recurring question concerns what these complex mathematical constructs actually represent in the biological context of the brain. Bridging the gap between mathematical abstraction and neurobiological interpretation remains a key difficulty, as discussed in recent theoretical works. This tension is reflected in the ambiguity of what higher-order measures capture and in the challenge of distinguishing genuine higher-order interactions from effects that may arise from lower-order statistical dependencies.

A primary and pervasive challenge is the biological interpretation gap. This issue manifests in two distinct facets. Many higher-order representations are abstractions whose direct physiological correlates are not immediately obvious. For instance, the precise neurobiological meaning of a COC framework remains elusive [17,24,26], and it has been noted that these features lack specific neuronal correlates at the group level [24]. Similar interpretive challenges arise in temporal higher-order and edge-centric approaches, where linking a feature back to individual brain regions is often intractable [84], complicating its interpretation [80,89].

The second facet of this gap is the lack of neurobiological generative models. The majority of current methods are descriptive and data-driven; they excel at identifying that a statistical pattern exists but offer little insight into why it exists, i.e., the underlying neural mechanisms [6]. This is a noted limitation in dynamic HOFC models [12] and in CoC-based methods that are purely data-driven [26]. Without clear generative models, it remains difficult to move from observing higher-order patterns to truly understanding their causal role in brain function.

A closely related issue is the genuineness problem: determining whether an observed higher-order statistical dependency represents a truly irreducible, synergistic interaction or is merely a manifestation of complex, lower-order (pairwise) effects. Several critical studies have demonstrated that some higher-order phenomena can be surprisingly well-replicated by null models based on static, pairwise covariance structures alone, questioning whether they provide genuinely new information [104,105].This has been most notably argued in the context of the edge-centric paradigm, where high-amplitude events and the broader eFC matrix were shown to be largely predictable from the static functional connectome [104]. This conflation of true higher-order synergy with the coincidental accumulation of pairwise effects is a general concern across many frameworks [105]. While model-based frameworks like the Matrix Variate Normal Distribution (MVND) [52] attempt to address this by imposing rigorous statistical assumptions to separate low- and higher-order connectivity, distinguishing genuine temporal co-fluctuations from static pairwise artifacts remains a central hurdle.

Furthermore, the increasing sophistication of higher-order methods often introduces a black box problem, sacrificing interpretability for predictive power. The use of clustering to reduce the dimensionality of dHOFC networks, for example, makes it difficult to trace the final predictive features back to the original brain connections, leading to a loss of neurobiological interpretability [12]. This challenge is even more pronounced in end-to-end deep learning models. While architectures that fuse multiple views of connectivity can achieve high classification accuracy, their internal decision-making processes are often opaque, making it difficult to extract clear, falsifiable biomarkers from the learned features [48].

Finally, some foundational approaches lack a solid theoretical underpinning. The intuitive CoC concept, for example, is a heuristic that has been criticized for not being grounded in a rigorous theoretical framework [104]. Similarly, a critical perspective on the edge-centric paradigm suggests that many of its dynamic features may not fully exploit the temporal structure of the data and can be reproduced by static null models, questioning the theoretical added value beyond pairwise statistics [104]. This highlights an ongoing need to bridge the gap between heuristic innovations and established theoretical principles from mathematical statistics, a direction pursued by frameworks such as the Matrix Variate Normal Distribution (MVND) [52].

4.2. Methodological and Statistical Challenges

Beyond the fundamental challenges of interpretation, the practical application of higher-order methods is fraught with significant methodological and statistical hurdles. These issues pertain to the validity, reliability, and reproducibility of the results, questioning not just what the measures mean, but whether they can be robustly and accurately estimated from complex neuroimaging data. These challenges can be broadly grouped into three categories: sensitivity to analytical choices, concerns about statistical validity, and the heavy burden of underlying model assumptions.

A primary threat to the reproducibility of higher-order research is the sensitivity of results to the parameters and heuristic choices. Many dynamic methods, for instance, rely on a sliding-window approach, where the choice of window length and step size is often a dilemma with no gold standard; shorter windows capture rapid fluctuations but are susceptible to noise, while longer windows provide more stable estimates at the cost of temporal precision [52,54,106]. Similarly, clustering-based methods like dHOFC are highly dependent on the chosen number of clusters, a hyper parameter that can severely influence the discriminative ability of the resulting network [60]. As a whole, this lack of standardized pipelines complicates the comparison of findings across studies and raises concerns about the generalizability of results.

Another statistical challenge lies in ensuring the validity of inferences and mitigating the risk of spurious findings. The hierarchical nature of many higher-order methods can lead to the accumulation of statistical error at each step of the calculation, potentially amplifying noise from the initial low-order estimates [22,101]. Moreover, the vast search space inherent in higher-order analysis creates a severe multiple comparisons problem, increasing the likelihood of detecting spurious patterns that arise from chance alone, especially with limited data [107]. Some work has questioned the statistical validity of some dynamic higher-order phenomena altogether, demonstrating that key features of the edge-centric paradigm, such as high-amplitude events, can be largely reproduced by static, Gaussian null models that lack any temporal dynamics [76,104]. This highlights a crucial need for appropriate null models and rigorous statistical testing to distinguish genuine higher-order dynamics from the complex statistical footprint of lower-order structures [108].

Finally, many higher-order methods carry a burden of model assumptions that may not always hold true for noisy and complex neural data. Information-theoretic measures, for example, often rely on the assumption of Gaussianity for tractable estimation, an assumption that is frequently violated by real neural signals, potentially leading to inaccurate estimates of synergy and redundancy [109,110]. Furthermore, methods that rely on the stationarity of time series can be biased by non-stationary noise or task-related signal changes [49]. Even the fundamental properties of fMRI data, such as strong auto-correlation, pose significant challenges for statistical inference frameworks like bootstrapping and permutation testing, complicating the assessment of statistical significance for any higher-order measure [108]. These underlying assumptions must be carefully considered when applying and interpreting the results of higher-order analyses.

4.3 Computational and Scalability Challenges

Perhaps the most significant practical barrier to the widespread adoption of higher-order methods is the profound challenge of computational and scalability issues, rooted in the combinatorial complexity and the curse of dimensionality. As analytical approaches move from pairwise (order 2) to triplet (order 3), quadruplet (order 4), and beyond, the number of potential interactions to consider grows explosively. For a network of N nodes, the number of possible k-node interactions scales as $O(N^k)$, a combinatorial explosion that quickly renders exhaustive searches computationally infeasible even for moderately sized brain networks [6,102,104,106,111–115]. This fundamental challenge manifests across nearly all higher-order paradigms, imposing severe constraints on the scale and scope of analyses.

In implicit methods, this challenge is starkly evident. The original formulation of temporal HOFC, which involves correlating all pairs of ETS, results in a feature space that scales with $O(N^4)$, a complexity that is computationally prohibitive and requires vast amounts of memory [60,104]. This has necessitated the widespread use of dimensionality reduction techniques, such as clustering ETS, as a standard but heuristic step in the pipeline [12,106].

While various strategies have been proposed to mitigate these issues, such as hierarchical partitioning in MVND [103], or utilizing dimensionality reduction techniques in dynamic HOFC [98], computational scalability remains a central and active area of research, currently limiting the application of many higher-order methods to whole-brain, high-resolution connectomes.

4.4. Data and Generalizability Challenges

Beyond the conceptual and computational hurdles, the application of higher-order methods in neuroscience is fundamentally constrained by the nature of the available data and the overarching challenge of generalizability. These practical issues directly impact the reliability of estimations and the ultimate translational potential of the findings.

A core issue is the intrinsic hunger for data that characterizes most higher-order analytical techniques. The robust estimation of multivariate dependencies requires substantially more data than pairwise measures to achieve similar statistical power. This is a particularly acute problem for statistical modeling approaches like MVND, where estimating a high-dimensional covariance matrix of edge fluctuations (Ω) from a limited number of temporal samples is often challenging and subject to high estimation variance [109]. Similarly, dynamic methods like dHOFC, which rely on short, sliding time windows, operate in a low-sample regime that can lead to unreliable estimates and an increased risk of overfitting [60,101]. This data hunger is often at odds with the inherent limitations of neuroimaging modalities like fMRI, which provide relatively short and noisy time series, creating a persistent tension between methodological sophistication and data availability.

This tension is compounded by challenges related to sample size, heterogeneity, and the generalizability of findings. Many pioneering studies in this emerging field have relied on relatively small or single-site datasets, which raises questions about the reproducibility and generalizability of their conclusions to broader populations [111]. Even when larger, multi-site datasets are used, site-specific heterogeneity can introduce significant confounds that are difficult to disentangle from true biological effects. Furthermore, the inherent noisiness of neural data means that higher-order metrics, which often involve multi-step calculations, can be particularly susceptible to noise propagation. For example, the reliability of dHOFC measures has been shown to be poor for weaker connections, which are more likely to be affected by noise [106]. Similarly, the quality of higher-order networks derived from MVND or topological HOFC is directly dependent on the reliability of the initial low-order FC estimates, which are themselves subject to noise and statistical uncertainty [34,101]. Addressing these challenges through the development of more robust estimation techniques and validation across large, diverse datasets is a critical step for moving the field of higher-order connectomics from exploratory analysis toward robust scientific and clinical application.

4.5. Synthesis of Challenges and a Comparative Overview

In summary, the journey into higher-order brain analysis, while promising, is navigated through a landscape of significant challenges. These hurdles are not uniform across the field; different methodological paradigms are susceptible to different pitfalls to varying degrees. Table 1 provides a comparative overview, summarizing the relative severity of the key conceptual, methodological, computational, and data-related challenges for each major class of methods discussed in this review.

Conceptually, the gap between mathematical abstraction and biological reality remains a universal concern, though it is perhaps most acute for complex, end-to-end deep learning models and heuristic approaches like CoC. Methodologically, methods relying on arbitrary parameter choices, such as the window length in dynamic analyses or the number of clusters in dHOFC, pose a greater threat to reproducibility. Computationally, the curse of dimensionality is a formidable barrier for nearly all paradigms, but it manifests most severely in methods that require high-dimensional feature spaces, such as unreduced edge-centric (eFC) networks and high-order covariance estimation. Finally, the need for large, high-quality datasets is a shared vulnerability, especially for data-hungry approaches like deep learning and high-dimensional statistical representations. Acknowledging this complex tapestry of strengths and weaknesses is the first step toward developing more robust, interpretable, and ultimately more useful models of the higher-order brain.

Table 1. A Comparative Overview of Challenges Across Refined Higher-Order Functional Connectivity Paradigms (✓= Moderate Challenge; ✓✓= Significant Challenge; ✓✓✓= Severe Challenge; - = Not a primary challenge / Addressed by design)

Challenge Category	Challenge	Topological HOFC	Temporal HOFC (dHOFC / MC)	Edge-Centric (eFC / ETS)	Matrix Variate Normal (MVND)
Conceptual & Interpretive	Biological Interpretation Gap	✓✓✓	✓✓✓	✓✓	✓✓
	"Genuineness" Problem	✓✓✓	✓✓✓	✓✓✓	—
	Black Box / Interpretability	✓	✓✓	✓✓	✓
Methodological & Statistical	Sensitivity to Parameters	✓	✓✓✓	✓	✓✓
	Statistical Validity & False Positives	✓✓	✓✓	✓✓	✓✓
	Burden of Model Assumptions	✓	✓	✓	✓✓✓
Computational & Scalability	Combinatorial Complexity	—	✓✓	✓✓✓	✓✓
Data & Generalizability	Hunger for Data	✓	✓✓	✓✓	✓✓✓

5. Discussion, Future Directions, and Conclusion

Our survey has traversed the vast and rapidly evolving landscape of higher-order interactions in brain network neuroscience. We have tried to chart the major methodological currents, categorizing them into two principal paradigms: topographical approaches that evaluate profile-based connectivity similarity across networks and subjects, and temporal approaches that model dynamic co-fluctuations and unified statistical distributions over time. This work has tried to reveal a rich and diverse toolkit for moving beyond the limitations of traditional pairwise analysis. Yet, it has also highlighted that the pursuit of higher-order understanding is not a linear progression toward ever-increasing complexity, but a nuanced exploration filled with conceptual challenges, methodological trade-offs, and critical open questions. This final part aims to synthesize these findings, critically discuss the overarching challenges facing the field, and outline promising directions for future research.

5.1. Synthesis and Comparative Insights

Topographical vs. Temporal HOFC (Complementary Views of the Connectome): A primary insight emerging from this review is that the topographical and temporal paradigms, while distinct in their methodological setups, exist in a complementary and convergent relationship. The choice between quantifying spatial connectivity profile similarity (the forte of topographical methods) versus modeling

dynamic, moment-to-moment co-fluctuations (the forte of temporal methods) is less a technical dichotomy and more a philosophical decision dictated by the specific research question. Crucially, these boundaries are beginning to merge. For instance, static topographical properties are increasingly used as structural or spatial priors to regularize high-dimensional temporal models like MVND, while temporal edge time series can be aggregated and clustered to reveal robust topographical network profiles. This symbiosis underscores a fundamental truth: the choice of representation shapes the achievable insights, with different formalisms capable of revealing entirely different organizational principles—such as hierarchical network integration or transient, event-driven community organization—from the very same underlying system [116].

The Complexity vs. Utility Trade-off: Is More Always Better? A second critical insight is that greater methodological complexity does not guarantee superior performance in practical applications. While higher-order models offer greater theoretical richness, their utility is context-dependent. Several studies report that simpler, lower-order models can achieve comparable or even better performance in certain clinical classification tasks. For instance, a study differentiating schizophrenia from bipolar disorder found that static functional connectivity provided greater discriminative power than dHOFC [59]. This observation is further supported by findings that the incremental benefit of adding higher-order information may diminish as the order of interaction becomes very large [117], and that for some cognitive tasks, traditional pairwise FC remains among the most effective decoding methods [118]. This complexity-utility trade-off can be attributed to several factors discussed in the previous chapter, including the high variance of higher-order estimators, the risk of overfitting in high-dimensional feature spaces, and the possibility that the most robust biomarkers for a given condition are embedded in stable, lower-order connectivity patterns.

A Common Ground (Convergent Applications in Neuroscience): Despite their methodological diversity, a striking convergence is evident in the application of higher-order methods to clinical and translational neuroscience. Across both topographical and temporal paradigms, these advanced models have consistently demonstrated an enhanced sensitivity for biomarker discovery and disease classification. Frameworks ranging from topological HOFC [11,12] to dynamic HOFC [12], meta-connectivity [50], and edge-centric networks [49] have all been successfully employed to improve the diagnosis of a wide spectrum of neurological and psychiatric conditions, including Alzheimer's disease, schizophrenia, autism, and depression. Beyond classification, these methods are also showing promise in predicting clinical outcomes and behavioral traits, offering new tools for assessing post-stroke recovery [20] or individual differences in cognitive traits like risk propensity [86]. This consistent success across different diseases and methodologies underscores a fundamental point: pathology sometimes manifests in the disruption of complex, multi-way interactions that are invisible to traditional pairwise analysis.

Unveiling Fundamental Principles of Brain Organization: In parallel, higher-order methods are providing profound new insights into the fundamental principles of brain organization and cognitive function. Dynamic approaches, particularly the edge-centric paradigm, are revolutionizing our understanding of fine-scale temporal organization by linking transient co-activation events to cognitive states and underlying structural modules [74,77]. Simultaneously, topographical HOFC frameworks have mapped the hierarchical and multi-subject organization of the connectome, while statistical approaches like MVND offer a mathematically rigorous decomposition of stable versus dynamic connection co-fluctuations over time. Collectively, these applications highlight that higher-order analysis is not merely a more complex tool, but an essential one for addressing foundational questions about how the brain's architecture gives rise to its rich functional and cognitive repertoire.

5.2 Grand Challenges and Future Directions

The maturation of higher-order neuroscience depends on addressing several grand challenges that span the conceptual to the practical. A primary challenge remains the gap between statistical observation and biological mechanism. Many current methods are descriptive, identifying that a higher-order pattern exists without explaining how it is generated by the underlying neural circuitry. The future of the field lies in moving from purely data-driven models to neurobiologically plausible generative models [119]. Such models, which could incorporate principles like oscillatory dynamics, synaptic plasticity, and neuromodulation, are needed to test hypotheses about how emergent, higher-order phenomena arise from local circuit rules [10,77].

Brain organization is inherently multi-modal and multi-scale. Future research must move towards integrating information across imaging modalities (e.g., fMRI, EEG/MEG, DTI) and spatial scales. Frameworks that can harmonize different types of relationships, such as functional co-fluctuations and structural pathways, within a unified higher-order model, like the edge covariance approach [97], represent a promising direction. This integration is critical for understanding the complex interplay between the brain's static structural scaffold and its dynamic functional repertoire.

The proliferation of novel methods has created a fragmented research landscape [118] that hinders reproducibility and widespread adoption. Unlike pairwise analysis, which is supported by numerous standardized toolboxes, many higher-order methods lack accessible, well-documented implementations. The development of comprehensive, open-source toolboxes that implement multiple higher-order techniques is a critical need. While excellent resources for specific paradigms are emerging, a unified platform would significantly accelerate progress and improve the comparability of studies.

As highlighted by several critical studies, the risk of inferring spurious higher-order structure from noise or from the complex footprint of lower-order correlations is substantial [104,108]. A major future direction must be the development and consistent application of appropriate null models and rigorous statistical inference frameworks. This includes moving beyond simplistic null models that ignore the temporal auto-correlation of neuroimaging data and developing principled methods to address the severe multiple comparisons problem inherent in any combinatorial search for higher-order patterns.

While many studies have demonstrated the potential of higher-order biomarkers, a significant gap remains between exploratory research and robust clinical translation. Future work must prioritize validation on large, diverse, and multi-site clinical datasets to ensure that identified biomarkers are generalizable and not specific to a small, homogeneous sample. Furthermore, assessing the test-retest reliability of these complex metrics is a crucial, yet often overlooked, step for establishing their suitability as stable, longitudinal markers of disease progression or treatment response [106].

5.3 Concluding Remarks

The study of higher-order interactions is fundamentally reshaping our understanding of the brain, moving us from a network of simple pairwise connections to a vision of an entangled brain defined by complex, emergent, and multi-way relationships [10]. This review has charted the diverse and innovative methodologies that form the vanguard of this new frontier. From the spatial profiling of topological connections to the fine-grained tracking of temporal co-fluctuations, these tools provide a rich vocabulary for describing the intricate architecture of brain function. However, as we have discussed, these powerful methods are not a panacea. Their application demands a critical awareness of their conceptual ambiguities, statistical pitfalls, and practical limitations. The path forward lies not in a blind pursuit of complexity, but in a thoughtful integration of these novel approaches with rigorous neurobiological grounding. By

embracing this challenge, the field of higher-order connectomics is poised to unlock profound new insights into the nature of cognition, health, and disease.

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