

Investigating brain connectivity from a signal processing perspective

Alexandra Tsipourakis¹, Marco Agostino Deriu^{1,*}

¹Politecnico di Torino, Department of Mechanical and Aerospace Engineering, PolitoBIOMed Lab, Corso Duca degli Abruzzi 24, Turin 10129, Italy

*Correspondence: marco.deri@polito.it
DOI: <https://doi.org/10.56280/1702827275>



This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>)

Received: 3 June 2025

Accepted: 29 June 2025

Online Published: 30 June 2025

Abstract

Understanding brain connectivity is crucial for deciphering both neural function and dysfunction. This review highlights the key signal-processing methods used to analyze brain connectivity, including techniques such as Fourier transforms, wavelet analysis, and graph-theoretical approaches. Applications of these techniques across various neuroimaging and electrophysiological modalities, including electroencephalography (EEG), magnetoencephalography (MEG), and functional magnetic resonance imaging (fMRI), are examined. Additionally, challenges such as noise reduction, signal non-stationarity, and computational complexity are addressed. By bridging neuroscience and signal processing, this review aims to provide insights into the strengths and limitations of both traditional and cutting-edge signal-processing methods for studying brain connectivity while also highlighting potential future research directions.

Keywords: Brain connectivity, signal processing, neuroscience, machine learning, EEG, MEG

1. Introduction

The human brain is a highly complex organ, responsible for all cognitive, sensory, and motor functions that define human behavior. It regulates processes such as muscle control, perception, memory and abstract thought, integrating billions of neurons into highly specialized networks, serving as the central processing unit for all bodily and cognitive functions (Sultana et al., 2024). Structurally, it is composed of three main parts: the cerebrum, the cerebellum, and the brainstem. Functionally, it depends on neurons, the specialized cells responsible for transmitting and receiving nerve impulses. Neurons never function in isolation; they are organized into groups, namely neural circuits, that process specific kinds of information, forming the basis of neural communication within the brain and its several regions (Stiles & Jernigan, 2010).

The mechanisms hidden behind neural communication can be primarily categorized into electrical and chemical signaling. The interaction between electrochemical signals, ensures the efficient and dynamic functioning of the brains' neural circuits (Pereda, 2014).

The brain, as an extraordinarily complex organ, is also subject to dysfunction. Disruptions in neural communication can lead to the development of neurological disorders ranging from common conditions such as Parkinson's disease and epilepsy to less prevalent ones (Wang & Michaelis, 2010). These abnormalities, which affect the way brain regions communicate, can be assessed, and investigated through the lens of brain signal analysis.

To interpret brain signals, many advancements have been made in recent years, opening new pathways for decoding the brains' inner workings. Researchers now employ sophisticated analytical tools to study brain connectivity across multiple scales, from individual neurons and microcircuits to full-scale neural networks (Scholtens et al., 2022). The growing research field encompassing these studies, neuroscience, seeks not only to map these connections, but also to understand *how* dynamic patterns of neural activity give rise to cognition, behavior, and disease.

Several approaches to modelling the human brain have been developed over the years, but the most frequently

utilized concepts and methods are those derived from graph theory in mathematical modelling. In this context, brain regions are conceptualized as *nodes*, whereas the connections between them, whether anatomical or functional, are represented as *edges* (Sporns, 2018). Building on this concept, researchers distinguish among three primary types of brain connectivity: structural, functional, and effective (Babaeeghazvini et al., 2021; Friston, 2011).

Structural (or neuroanatomical) connectivity refers to the structural links, such as synapses or fiber pathways, at the microscopic scale of neurons. This connectivity type is often mapped with the use of techniques such as diffusion tensor imaging (DTI), with which the pathways of white matter tracts in the brain can be visualized, forming the *anatomical framework* for neuronal communication (Basser, 1995).

Functional connectivity describes the statistical dependencies and temporal correlations between spatially separated neuronal units or brain regions (Friston, 1994). It is concerned with the patterns of coactivation and synchronization between different brain areas, even if these areas are not *directly* connected. This type of connectivity is frequently measured through non-invasive imaging techniques like functional magnetic resonance imaging (fMRI) (Chen & Glover, 2015) or electroencephalography (EEG) (Berger, 1929) to reveal dynamic patterns of interaction while the subject is either resting or performing a specific task.

Finally, effective connectivity goes beyond describing the patterns of correlation or association to infer *directional* influence and causal interactions between brain regions (Friston, 1994). It aims to understand how neuronal systems are correlated and examine the mechanisms of these interactions. Effective connectivity can be studied through models that estimate the influence one neural unit exerts over another, accounting for the *direction* and *causal effect* of these interactions. Techniques such as Granger causality analysis (Shojaie & Fox, 2022a) or dynamic causal modelling (DCM) (Friston et al., 2003a) are often employed to explore effective connectivity, providing insights into the operational architecture of the brain's functional networks.

To study deeper neural connections at the microscale level, the concept of cellular brain connectivity is employed (Giacopelli et al., 2021), which studies the structural organization and branching patterns of individual neurons, particularly the dendritic and

axonal arbors, that enable synaptic communication and the integration of neural signals within local neural circuits. It includes features such as dendritic tree complexity, spine density, and synaptic input capacity. This microscale architecture underlies how neurons receive and process information and is thought to reflect broader principles of brain organization across scales (Scholtens et al., 2022).

Together, these connectivity categories provide a complete framework for understanding the complex interplay between the brain's structure and function, as well as the dynamic processes that underlie human cognition and behavior.

2. Signal processing: tools, techniques, and their diagnostic value

After defining brain connectivity, the focus now shifts to *how* this network information can be extracted from raw neural recordings. Signal-processing pipelines, from acquisition to advanced analytics, allow us to quantify the coordination and causality among brain regions, revealing patterns that are imperceptible to the naked eye.

Clinically, the development of connectivity measures has enabled researchers to move beyond lesion localization and into a network-level view of disease. Common diseases such as epilepsy, Alzheimer's, schizophrenia and autism have been found to display characteristic disruptions in connectivity topology and dynamics (Bassett & Bullmore, 2009; Fornito et al., 2015). Early brain network biomarkers support pre-symptomatic diagnosis and therapy planning, which is essential, especially in cases where disease assessment is inherently complicated (e.g., paediatric cerebral-palsy risk, dementia in older patients (Merhar et al., 2020; van 't Westende et al., 2022)), while also connectivity-guided neuromodulation techniques are emerging as targeted, personalized interventions (Tsipourakis et al., 2024).

Moreover, advances in signal processing have made it possible not only to visualize but also to quantify these connectivity anomalies. As a result, brain scans are now used not only to localize lesions but also to analyze entire brain networks, transforming diagnostics from a static to a dynamic system-level paradigm. To study these interactions, modern neuroscience employs a wide range of signal processing techniques applied to both structural and functional data. These techniques aim to extract meaningful information from raw brain

Table 1 Summarizes principal signal acquisition techniques employed in neuroscience to investigate brain connectivity.

Method	Description	Connectivity Type	Temporal Resolution	Spatial Resolution	Invasiveness (*)	Main Applications
EEG (Electroencephalography)	Measures electrical activity via scalp electrodes.	Functional, Effective	High (ms)	Low (cm)	0	Seizure detection (epilepsy research), sleep studies, BCI
MEG (Magnetoencephalography)	Detects magnetic fields from neuronal activity.	Functional, Effective	High (ms)	Moderate (mm)	0	Functional mapping, epilepsy localization
fMRI (Functional Magnetic Resonance Imaging)	Measures BOLD signals reflecting neural activity.	Functional, Structural	Low (s)	High (mm)	0	Cognitive neuroscience, brain mapping
NIRS (Near-Infrared Spectroscopy)	Measures hemodynamic responses using near-infrared light.	Functional	Low (~s)	Low to Moderate (cm)	0	Portable monitoring, infant studies
ECoG (Electrocorticography)	Records electrical activity directly from the cortical surface.	Functional, Effective	High (ms)	High (mm)	1	Pre-surgical mapping, epilepsy treatment
Single-Unit Recording	Measures action potentials from individual neurons.	Cellular	Very High (μs –ms)	Very High (μm)	2	Neuroscience research, animal models

*Invasiveness: 0 = non-invasive, 1 = invasive, 2 = highly invasive

signals, often noisy and complex, using mathematical models, statistical analysis, and nowadays, also machine learning algorithms. This work sheds light on how brain connectivity is studied through signal processing. It first elaborates on the various signal acquisition techniques utilized, followed by a discussion of the mathematical methods used to process brain signals.

Numerous methods for signal acquisition have been developed, each of them aiming to highlight different aspects of brain signals, as detailed in Table 1. Fundamentally, these methods differ in their spatial and

temporal resolution, invasiveness and the type of interaction they probe. **Table 1**, highlights some widely used modalities, organized by their principal connectivity domain, characteristics and main applications.

Table 1 summarizes the principal signal acquisition methods employed in neuroscience to investigate brain connectivity. Each method is categorized by its suitability for exploring the various types of connectivity, and key technical specifications, including temporal and spatial resolution, invasiveness, and main applications, are presented. In more detail, non-invasive techniques, such as EEG, MEG, fMRI,

and NIRS, record brain activity from outside the skull and are widely used in both research and clinical settings due to their relative safety. In contrast, invasive methods such as ECoG and single-unit recording require surgical intervention and are typically restricted to clinical monitoring or animal studies, offering higher resolution at the cost of increased risk. EEG is a non-invasive technique that records electrical activity from the scalp using electrodes applied with conductive gel or saline. While convenient and well-suited for long-term monitoring, EEG signals are distorted by the electrical properties of the scalp and skull, which can reduce spatial precision (Antonakakis et al., 2020).

Despite this, EEG remains valuable for its high temporal resolution, ease of use, and suitability for studying chronic conditions like epilepsy, Alzheimer's, and Parkinson's disease. In contrast, invasive electrophysiological methods, such as electrocorticography (ECoG) and single-unit recordings, place electrodes directly on or within the brain, bypassing the distorting layers and enabling much higher spatial and temporal resolution (Buzsáki, 2004; Nicolelis, 2003). These approaches offer detailed insight into local neural activity but require surgery and are not ideal for long-term human use.

Beyond EEG, several other neuroimaging modalities provide different insights into brain activity. Magnetoencephalography (MEG) detects the magnetic fields generated by neuronal currents, offering temporal resolution similar to that of EEG but with improved spatial localization, albeit requiring magnetically shielded environments for accurate measurement. Functional magnetic resonance imaging (fMRI), by contrast, captures brain activity indirectly through hemodynamic responses, achieving high spatial resolution suitable for mapping functional networks; however, the sluggish nature of blood flow changes constrains its temporal resolution. Near-infrared spectroscopy (NIRS) provides a more portable and non-invasive alternative to fMRI, measuring cortical hemodynamics through light absorption. While less precise in both spatial and temporal dimensions, NIRS is valuable for studies requiring mobility or accessibility outside traditional imaging environments.

On the invasive end of the spectrum, electrocorticography (ECoG) records neural signals directly from the cortical surface, striking a strong balance between spatial and temporal resolution, and is sometimes used in pre-surgical evaluation of epilepsy. For even finer detail, single-unit recordings employ microelectrodes inserted into brain tissue to isolate

action potentials from individual neurons. Though technically demanding and primarily limited to animal models or intraoperative contexts, this method provides unmatched cellular-level resolution. These methods provide the foundational data from which brain connectivity is inferred and analyzed, forming the basis for the application of advanced signal processing techniques.

3. Brain frequency bands

Time-domain signals alone often obscure the strength and significance of underlying neural processes. For this reason, frequency-domain analysis is used to reveal important neural activity by isolating rhythmic components associated with brain function. Hans Berger, who developed EEG, first recorded human EEG rhythms in the 1920s, identifying an 8-13 Hz 'alpha' rhythm, originally termed the 'primary' rhythm and noting faster 'beta' waves, marking the conceptual origin of canonical frequency bands (Berger, 1929). Neural activity typically spans frequencies from approximately 0 to 100 Hz, which are categorized as follows in Table 2, where delta (δ , 0.5-4 Hz), theta (θ , 4-8 Hz), alpha (α , 8-13 Hz), beta (β , 13-30 Hz), and gamma (γ , >30 Hz), which includes all frequencies above 30 Hz and is associated with higher-order cognitive functions such as perception and consciousness (Buzsáki & Wang, 2012).

Table 2 Brain signal activity frequencies.

Band Name	Symbol	Frequency Range	Associated Functions
Delta	δ	0.5-4 Hz	Deep sleep, unconscious processes
Theta	θ	4-8 Hz	Drowsiness, meditation, memory encoding
Alpha	α	8-13 Hz	Relaxed wakefulness, closed eyes
Beta	β	13-30 Hz	Active thinking, attention, motor behavior
Gamma	γ	30-100+ Hz	Perception, consciousness, high-level cognition

The need to interpret these frequency bands has driven the development of numerous connectivity analysis

methods and mathematical models, which are used to preprocess, analyze, and interpret brain signals.

3.1 EEG and MEG analysis in the frequency space

Building on the discussed acquisition techniques and their associated frequency bands, neural data exhibit diverse temporal and spatial characteristics, requiring tailored analytical strategies for correct interpretation. As shown in **Table 1** EEG and MEG both record fast-changing signals in the millisecond range, reflecting real-time neural dynamics. EEG captures voltage fluctuations on the scalp resulting from postsynaptic potentials, while MEG detects the magnetic fields produced by these same neural currents, offering better spatial localization due to minimal distortion from the skull and scalp (Gross et al., 2013). Analysis of EEG and MEG data often begins with time-frequency decomposition using techniques such as the Fourier transform or wavelet transform, enabling researchers to study neural oscillations across frequency bands. For stimulus-related experiments, event-related potential (ERP) analysis is commonly used in EEG, whereas MEG typically employs beamforming and other source localization techniques to identify the origin of neural activity (Gross et al., 2013). Both EEG and MEG also make extensive use of independent component analysis (ICA) to isolate neural sources from physiological and environmental artifacts (Delorme & Makeig, 2004). In network-level studies, functional connectivity metrics such as phase-locking value, coherence, and Granger causality are increasingly used in both modalities (Bastos & Schoffelen, 2015).

3.2 fMRI and fNIRS

In contrast, fMRI and fNIRS measure slower, indirect indicators of brain activity based on cerebral blood flow and oxygenation. fMRI relies on the blood-oxygen-level-dependent (BOLD) signal (Hillman, 2014) and provides high spatial resolution, typically in the millimeter range, but limited temporal resolution due to the slow hemodynamic response (~2–6 seconds delay) (Friston et al., 2003). Its core analytical tool is the general linear model (GLM), which enables researchers to identify brain regions activated by experimental tasks (Pedregosa et al., 2013). Additional techniques such as ICA and functional connectivity mapping are widely applied in resting-state and task-based designs (Smith et al., 2009). Multivoxel pattern analysis fNIRS, while also hemodynamic, uses near-infrared light to infer changes in oxygenated and deoxygenated hemoglobin. It shares many of fMRI's analytical approaches, especially GLM and block averaging, but

is better suited to portable and developmental research due to its ease of use and tolerance for movement (Ferrari & Quaresima, 2012). However, its lower spatial resolution and susceptibility to superficial signal contamination require careful preprocessing, often involving wavelet filtering to remove motion artifacts (Cooper et al., 2012).

Ultimately, the nature of the recorded signal, whether electrical, magnetic, or hemodynamic, also determines the appropriate analytical tools, the trade-offs between temporal and spatial resolution, and the type of insights each modality can provide. It is essential to understand and distinguish the strengths and limitations of each method, and then select the one that is best suited for each research goal. When human subjects are involved, the priority must be to minimize risk and ensure their comfort throughout the procedure, not only for the respect of the subjects, but also to obtain signals as clearly as possible. Signal acquisition research should focus not only on data quality but also on optimizing the methods by which signals are captured, in ways that enhance both participant safety and the overall integrity of the research protocol.

4. Challenges in brain signal analysis

The preceding analysis highlights the inherent complexity of neural signal acquisition, presenting several methodological and technical challenges. Addressing them requires not only the refinement of acquisition hardware and protocol design but also the application of rigorous mathematical and statistical frameworks. This section outlines the principal analytical techniques employed in the study of brain connectivity signals.

4.1 Methods for signal analysis and data manipulation

Figure 1 illustrates the end-to-end pipeline for analyzing neurophysiological data to estimate brain connectivity and support patient treatment decisions, utilizing advanced computational techniques while addressing potential signal quality issues. The core steps, which include signal acquisition, preprocessing, traditionally used in neuroscience research. In contrast, components highlighted in green represent the most recent methodological advancements, which include the integration of ML, DL and XAI techniques. These modern tools serve two major purposes: (i) enhancing traditional preprocessing through automated, data-driven denoising (e.g., CNNs, autoencoders); and (ii)

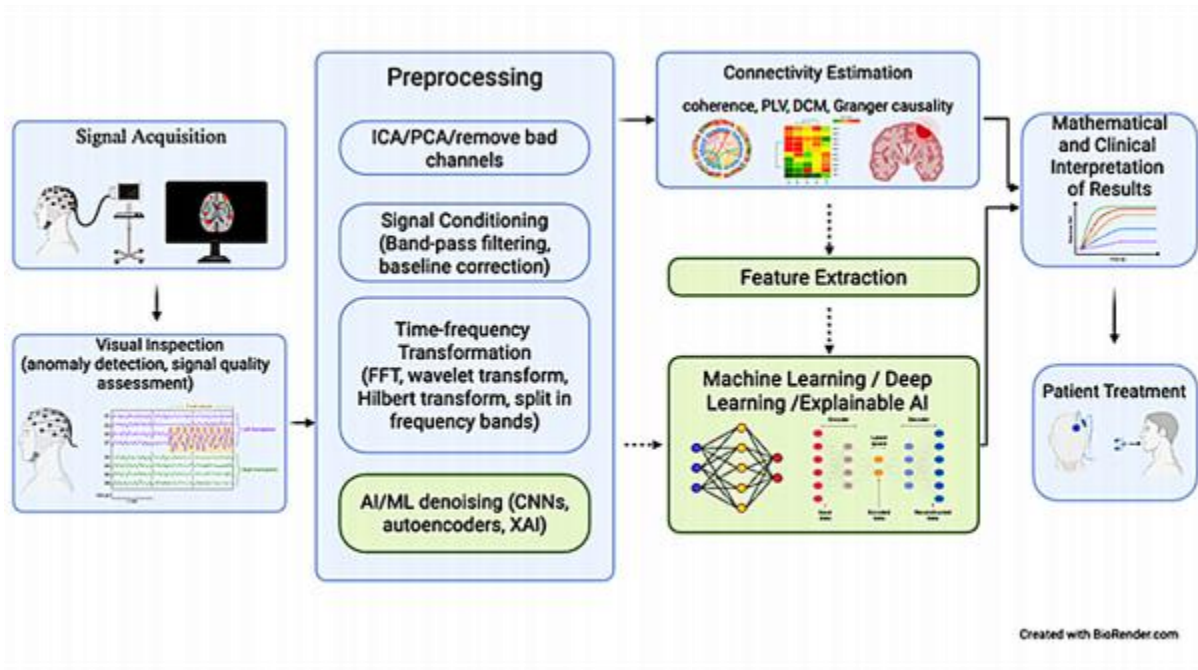


Figure 1 Pipeline for studying brain connectivity. This figure illustrates a typical, end-to-end workflow for analyzing neurophysiological signals to estimate brain connectivity. In more detail, components shown in blue represent classical methods employed in standard connectivity assessment pipelines, while those in green highlight recent advancements involving the integration of ML methods. The process begins with signal acquisition from neurophysiological modalities (e.g., EEG or MEG), followed by visual inspection for anomaly detection and assessment of signal quality. Preprocessing steps include artifact removal (e.g., via ICA or PCA), signal conditioning through band-pass filtering and baseline correction, and time-frequency transformation using methods such as FFT, wavelet transform, or Hilbert transform, as discussed in the manuscript. To automate these steps, AI-based denoising approaches (e.g., convolutional neural networks, autoencoders, and explainable AI techniques) can also be employed, either as an alternative or to complement traditional preprocessing methods. Following preprocessing, the pipeline proceeds to connectivity estimation, which typically refers to functional or effective connectivity, and can be assessed through various statistical metrics (e.g., coherence, phase-locking value (PLV), dynamic causal modeling (DCM), and Granger causality). Then, if ML methods are applied, relevant connectivity features are extracted and used as inputs to machine learning (ML) or deep learning (DL) models to evaluate connectivity. The final steps of the pipeline always involve interpreting the results into explainable solutions that provide both mathematical and clinical insights into brain dynamics, ultimately contributing to informed patient treatment strategies.

enabling more powerful and interpretable feature extraction and classification from connectivity data. By complementing classical signal processing with AI-based models, researchers can improve robustness, scalability, and clinical applicability of brain connectivity analyses.

4.1.1. Preprocessing

Preprocessing is a critical step in brain signal analysis, as raw neural recordings are inherently contaminated by various types of noise and artifacts that can hide meaningful activity. These distortions mainly arise from physiological sources (e.g., eye blinks, muscle contractions, cardiac rhythms) and external sources (e.g., electrical interference, movement), and must be mitigated to ensure the validity of subsequent

connectivity analyses (Bullock et al., 2021; Islam et al., 2016; Muthukumaraswamy, 2013).

The first preprocessing step typically involves bandpass filtering, which isolates frequency components of interest (e.g., 0.5-50 Hz in EEG) while excluding slow drifts and high-frequency noise. More specifically, limiting analysis above 0.5 and below 50 Hz is common because in these frequency ranges, signals are more susceptible to noise and artifacts, and less consistently measured across different recording systems. Furthermore, EEG signals often contain powerline interference, which manifests as narrowband noise centered at 50 Hz in Europe and 60 Hz in North America. To mitigate this, notch filters are typically applied to suppress these specific frequencies during preprocessing, removing powerline interference (Islam et al., 2016; Luck, 2014; Muthukumaraswamy, 2013).

To further address non-neural artifacts, methods like ICA or Principal Component Analysis (PCA) are used. These algorithms decompose multichannel signals into statistically independent or orthogonal components, enabling the identification and removal of artifact-related components (or channels, in the case of EEG) such as eye movements or heartbeat artifacts (Chaumon et al., 2015; Delorme and Makeig, 2004).

Baseline correction and re-referencing (e.g., average or linked-ear references in EEG) are also commonly applied to improve signal comparability across trials or electrodes. Specifically, in fMRI, motion correction algorithms are employed to adjust for head movement across volumes, typically using realignment procedures (Friston et al., 1996). For functional near-infrared spectroscopy (fNIRS), wavelet filtering is frequently used to remove motion artifacts (Cooper et al., 2012).

Preprocessing pipelines are now implemented in toolboxes for various programming languages, such as EEGLAB (Delorme and Makeig, 2004), MNE-Python (Gramfort et al., 2013), FieldTrip, or SPM, which standardizes these steps and allows for reproducible, quality-controlled signal preparation.

4.1.2 Time-Frequency Analysis

Time-frequency analysis plays a pivotal role in uncovering the dynamic oscillatory behavior of brain activity. Unlike time-domain or frequency-domain approaches, time-frequency methods offer insight into how spectral content evolves, making them well-suited for studying transient and non-stationary brain signals, such as those recorded through EEG or MEG. The most fundamental tool in this domain is the Fourier Transform (FT), which decomposes signals into their constituent sine and cosine components to identify dominant frequencies. However, standard Fourier analysis assumes signal stationarity and offers no temporal resolution, limiting its applicability to rapidly changing brain dynamics. To overcome this, the Short-Time Fourier Transform (STFT) was introduced. It applies the Fourier Transform within a sliding time window, enabling for partial time localization. However, the trade-off between time and frequency resolution remains fixed due to the constant window size (Bruns, 2004).

A more flexible approach is the Wavelet Transform (WT), which uses scalable, time-localized wavelets as basic functions (Morlet et al., 1982). Wavelets adapt their resolution across frequencies, offering high temporal resolution for fast oscillations (e.g., gamma

and high frequency resolution for slow rhythms (e.g., delta). This makes WT particularly effective for characterizing cognitive processes such as attention, working memory, and motor planning. Finally, another powerful technique is the Hilbert Transform, often combined with bandpass filtering to compute amplitude envelopes and instantaneous phase, which are essential for analyzing phase synchrony and amplitude coupling between brain regions (Le Van Quyen et al., 2001). These time-frequency methods form the backbone of connectivity analyses that rely on oscillatory dynamics, such as phase-locking value (PLV) or cross-frequency coupling (CFC). Their application to signal analysis enables researchers to bridge the gap between raw neural activity and interpretable patterns of brain network interaction.

4.2 From classical signal tools to modern connectivity analysis

Built upon the aforementioned foundational signal processing methods, current approaches to brain connectivity, such as coherence, phase-locking value, and Granger causality (Baccalá & Sameshima, 2001; Fries, 2005; Shojaie & Fox, 2022b) enable researchers to quantify both synchronous and causal interactions between neural regions.

These methods have been instrumental in advancing understanding of the brain's dynamic architecture. For instance, phase synchrony analyses have revealed how large-scale neural oscillations coordinate cognition, including working memory, attention, and perception (Fries, 2005). Granger causality and dynamic causal modeling have uncovered directed influences between regions during language processing, motor planning, and even during resting-state activity (Brovelli et al., 2004; Friston et al., 2003a). Functional connectivity analysis using EEG and fMRI, as the combination of EEG and MEG for effective connectivity studies, have shaped the panorama for defining key resting-state networks, including the default mode network (Raichle et al., 2001) and have shed light on neurological disorders, from sleep disorders to epilepsy, Alzheimer's disease, and schizophrenia by identifying abnormal patterns of synchronization and network breakdown (Fornito et al., 2015; Politof et al., 2019; Stam, 2014).

The success of these methods highlights their crucial role in neuroscience, offering valuable insights into how complex behaviors and pathologies emerge from the interplay of distributed neural interactions. However, these methods are deeply rooted in complex

statistics, so their implementation often involves very technical, multi-step pipelines, which are also sensitive to preprocessing quality and signal variability. To address these challenges, Machine Learning (ML) approaches are increasingly being used to complement traditional methods (Mohammadi & Karwowski, 2025). In the realm of artifact removal, studies have shown that deep neural networks can outperform conventional denoising techniques (Fabietti et al., 2022): for example, recurrent neural networks have effectively removed ballistocardiogram artifacts in concurrent EEG-fMRI recordings (McIntosh et al., 2021), and convolutional neural networks have reduced ocular and muscular noise with high fidelity. Broader reviews confirm that ML classifiers and autoencoders streamline artifact handling while preserving neural signal quality (Chuang et al., 2022; Saba-Sadiya et al., 2021).

Beyond denoising, ML has also been successfully applied to connectivity-based classification and decoding (Bhavna et al., 2024). A recent study used effective connectivity features extracted from EEG to distinguish levels of mental workload, demonstrating how ML can enhance interpretability of brain networks in practical scenarios (Safari et al., 2024). These applications underscore how ML empowers researchers to navigate nonlinear dynamics, high-dimensional datasets, and cross-frequency interaction areas where traditional methods struggle to complement rather than replace classical signal-processing frameworks.

5. Conclusions

The investigation of brain connectivity via signal processing has profoundly shaped the understanding of neural communication, enabling the quantification of both functional and effective interactions across spatial and temporal scales. Classical methodologies, which mostly rely on spectral analysis, synchrony measures, and causal inference, have offered reliable frameworks for examining the neural basis of cognition and behavior. These tools have proven invaluable for studying both healthy and clinical populations, revealing how disrupted connectivity patterns underlie various neurological and psychiatric disorders.

Further steps can be made to deepen the understanding of the brain. Starting from the electronics, portable and robust solutions should be created to provide comfortable setups in which signal acquisition can be performed in correct setups, with the least possible bias to the subjects.

As for signal processing, besides the classical methods described in the present work, the incorporation of Machine Learning approaches has recently expanded the analytical repertoire available to researchers in the field, providing novel means of modeling complex, high-dimensional data and offering new perspectives on signal interpretation and classification.

Despite these advancements, several challenges remain unresolved, motivating the pursuit of more integrated and adaptive methodologies. One important direction for future work is the integration of multimodal data sources, such as the fusion of EEG and fMRI, or the combination of anatomical and functional imaging modalities. Such approaches hold the promise of unifying the complementary strengths of different techniques, high temporal resolution with high spatial precision, enabling a more comprehensive representation of brain dynamics across scales. Another critical frontier involves improving the interpretability of ML models applied to neural data.

While these models often achieve high predictive performance, their lack of transparency can limit their utility in scientific and clinical contexts. The development of explainable AI techniques, such as attention mechanisms or interpretable latent spaces, may provide a means of translating learned representations into neurobiologically meaningful insights, thereby enhancing both trust and usability in clinical applications.

In parallel, as priorly mentioned, there is growing interest in the use of AI for signal quality enhancement, especially in the domain of artifact correction. As can be deduced from the provided analysis, traditional preprocessing pipelines heavily depend on manual calibration and fixed statistical assumptions, which often lead to the misinterpretation of neural signals and introduce significant subjectivity into each researcher's results, thereby reducing the reliability of any clinical practice tools. Emerging deep learning models, including autoencoders and convolutional neural networks (CNNs), have demonstrated considerable potential for directly learning to suppress complex, non-stationary noise from data.

The integration of such methods into real-time or portable neural interfaces could significantly improve signal fidelity, especially in noisy or uncontrolled environments. Steps are being made in that direction, which are set to revolutionize the way we study neural signals and human cognition.

As signal processing and ML continue to converge, the field stands at a critical juncture. The challenge ahead lies not only in refining technical performance but also in ensuring that the resulting models remain interpretable, generalizable, and grounded in neuroscientific theory. Addressing these challenges will be essential for translating connectivity analyses into meaningful tools for understanding the brain and preventing or treating its disorders.

Conflict of Interest Statement

The authors declare no conflict of interest.

Funding Statement

The present research was carried out as part of the PARENT and GALATEA projects. PARENT received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie Innovative Training Network, Grant Agreement No. 956394 (<https://parenth2020.com/>). The GALATEA project has received funding from the European Union's Horizon Europe research and innovation programme under the Marie Skłodowska-Curie Grant Agreement No. 101183057 (<https://galateahe.eu/>).

References

- Antonakakis, M., Schrader, S., Aydin, Ü., Khan, A., Gross, J., Zervakis, M., Rampp, S. & Wolters, C.H. (2020) Inter-subject variability of skull conductivity and thickness in calibrated realistic head models. *NeuroImage* **223**, 117353.
- Babaeeghazvini, P., Rueda-Delgado, L.M., Gooijers, J., Swinnen, S.P. & Daffertshofer, A. (2021) Brain structural and functional connectivity: A review of combined works of diffusion magnetic resonance imaging and electro-encephalography. *Frontiers in Human Neuroscience* **15**, 721206.
- Baccalá, L.A. & Sameshima, K. (2001) Partial directed coherence: A new concept in neural structure determination. *Biological Cybernetics* **84**, 463–474.
- Basser, P.J. (1995) Inferring microstructural features and the physiological state of tissues from diffusion-weighted images. *NMR in Biomedicine* **8**, 333–344.
- Bassett, D.S. & Bullmore, E.T. (2009) Human brain networks in health and disease. *Current Opinion in Neurology* **22**, 340–347.
- Bastos, A.M. & Schoffelen, J.-M. (2015) A tutorial review of functional connectivity analysis methods and their interpretational pitfalls. *Frontiers in Systems Neuroscience* **9**, 175.
- Berger, H. (1929) Über das Elektrenkephalogramm des Menschen. *Archiv für Psychiatrie und Nervenkrankheiten* **87**, 527–570.
- Bhavna, K., Akhter, A., Banerjee, R. & Roy, D. (2024) Explainable deep-learning framework: Decoding brain states and prediction of individual performance in false-beliefs task at early childhood stage. *Frontiers in Neuroinformatics* **18**, 1392661.
- Brovelli, A., Ding, M., Ledberg, A., Chen, Y., Nakamura, R. & Bressler, S.L. (2004) Beta oscillations in a large-scale sensorimotor cortical network: Directional influences revealed by Granger causality. *Proceedings of the National Academy of Sciences (USA)* **101**, 9849–9854.
- Bruns, A. (2004) Fourier-, Hilbert- and wavelet-based signal analysis: Are they really different approaches? *Journal of Neuroscience Methods* **137**, 321–332.
- Bullock, M., Jackson, G.D. & Abbott, D.F. (2021) Artifact reduction in simultaneous EEG-fMRI: A systematic review of methods and contemporary usage. *Frontiers in Neurology* **12**, 622719.
- Buzsáki, G. & Wang, X.-J. (2012) Mechanisms of gamma oscillations. *Annual Review of Neuroscience* **35**, 203–225.
- Buzsáki, G. (2004) Large-scale recording of neuronal ensembles. *Nature Neuroscience* **7**, 446–451.
- Chaumon, M., Bishop, D.V.M. & Busch, N.A. (2015) A practical guide to the selection of independent components of the electroencephalogram for artifact correction. *Journal of Neuroscience Methods* **250**, 47–63.
- Chen, J.E. & Glover, G.H. (2015) Functional magnetic resonance imaging methods. *Neuropsychology Review* **25**, 289–313.
- Chuang, C.-H., Chang, K.-Y., Huang, C.-S. & Jung, T.-P. (2022) IC-U-Net: AU-Net-based denoising autoencoder using mixtures of independent components for automatic EEG artifact removal. *NeuroImage* **263**, 119586.
- Cooper, R., Selb, J., Gagnon, L., Phillip, D., Schytz, H.W., Iversen, H.K., Ashina, M. & Boas, D.A. (2012) A systematic comparison of motion artifact correction techniques for functional near-infrared spectroscopy. *Frontiers in Neuroscience* **6**, 147.
- Delorme, A. & Makeig, S. (2004) EEGLAB: An open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of Neuroscience Methods* **134**, 9–21.
- Fabietti, M., Mahmud, M., Lotfi, A. & Kaiser, M.S. (2022) ABOT: An open-source online benchmarking tool for machine learning-based artefact detection and removal methods from neuronal signals. *Brain Informatics* **9**, 19.
- Ferrari, M. & Quaresima, V. (2012) A brief review on the history of human functional near-infrared spectroscopy (fNIRS) development and fields of application. *NeuroImage* **63**, 921–935.
- Fornito, A., Zalesky, A. & Breakspear, M. (2015) The connectomics of brain disorders. *Nature Reviews Neuroscience* **16**, 159–172.
- Fries, P. (2005) A mechanism for cognitive dynamics: Neuronal communication through neuronal coherence. *Trends in Cognitive Sciences* **9**, 474–480.

- Friston, K.J. (1994) Functional and effective connectivity in neuroimaging: A synthesis. *Human Brain Mapping* **2**, 56–78.
- Friston, K.J. (2011) Functional and effective connectivity: A review. *Brain Connectivity* **1**, 13–36.
- Friston, K.J., Harrison, L. & Penny, W. (2003) Dynamic causal modelling. *NeuroImage* **19**, 1273–1302.
- Friston, K.J., Williams, S., Howard, R., Frackowiak, R.S.J. & Turner, R. (1996) Movement-related effects in fMRI time-series. *Magnetic Resonance in Medicine* **35**, 346–355.
- Giacopelli, G., Tegolo, D., Spera, E. & Migliore, M. (2021) On the structural connectivity of large-scale models of brain networks at cellular level. *Scientific Reports* **11**, 4345.
- Gramfort, A., Luessi, M., Larson, E., Engemann, D.A., Strohmeier, D., Brodbeck, C., Goj, R., Jas, M., Brooks, T., Parkkonen, L. & Hämäläinen, M. (2013) MEG and EEG data analysis with MNE-Python. *Frontiers in Neuroscience* **7**, 267.
- Gross, J., Baillet, S., Barnes, G.R., Henson, R.N., Hillebrand, A., Jensen, O., Jerbi, K., Litvak, V., Maess, B., Oostenveld, R., Parkkonen, L., Taylor, J.R., van Wassenhove, V., Wibral, M. & Schoffelen, J.-M. (2013) Good practice for conducting and reporting MEG research. *NeuroImage* **65**, 349–363.
- Hillman, E.M.C. (2014) Coupling mechanism and significance of the BOLD signal: A status report. *Annual Review of Neuroscience* **37**, 161–181.
- Islam, M.K., Rastegarnia, A. & Yang, Z. (2016) Methods for artifact detection and removal from scalp EEG: A review. *Neurophysiologie Clinique/Clinical Neurophysiology* **46**, 287–305.
- Le Van Quyen, M., Foucher, J., Lachaux, J.-P., Rodriguez, E., Lutz, A., Martinerie, J. & Varela, F.J. (2001) Comparison of Hilbert transform and wavelet methods for the analysis of neuronal synchrony. *Journal of Neuroscience Methods* **111**, 83–98.
- Luck, S.J., 2014. *An Introduction to the Event-Related Potential Technique*. 2nd ed. Cambridge, MA: MIT Press.
- McIntosh, J.R., Yao, J., Hong, L., Faller, J. & Sajda, P. (2021) Ballistocardiogram artifact reduction in simultaneous EEG-fMRI using deep learning. *IEEE Transactions on Biomedical Engineering* **68**, 78–89.
- Merhar, S.L., Gozdas, E., Tkach, J.A., Parikh, N.A., Kline-Fath, B.M., He, L., Yuan, W., Altaye, M., Leach, J.L. & Holland, S.K. (2020) Neonatal functional and structural connectivity are associated with cerebral palsy at age 2. *American Journal of Perinatology* **37**, 137–145.
- Mohammadi, H. & Karwowski, W. (2025) Graph neural networks in brain connectivity studies: Methods, challenges, and future directions. *Brain Sciences* **15**, 17.
- Morlet, J., Arens, G., Fourgeau, E. & Giard, D. (1982) Wave propagation and sampling theory; Part I, complex signal and scattering in multilayered media. *Geophysics* **47**, 203–221.
- Muthukumaraswamy, S. (2013) High-frequency brain activity and muscle artifacts in MEG/EEG: A review and recommendations. *Frontiers in Human Neuroscience* **7**, 138.
- Nicoletis, M.A.L. (2003) Brain-machine interfaces to restore motor function and probe neural circuits. *Nature Reviews Neuroscience* **4**, 417–422.
- Norman, K.A., Polyn, S.M., Detre, G.J. & Haxby, J.V. (2006) Beyond mind-reading: multi-voxel pattern analysis of fMRI data. *Trends in Cognitive Sciences* **10**, 424–430.
- Pedregosa, F., Eickenberg, M., Thirion, B. & Gramfort, A. (2013) HRF Estimation Improves Sensitivity of fMRI Encoding and Decoding Models, In, *Presented at the 2013 International Workshop on Pattern Recognition in Neuroimaging*, pp. 165–169.
- Pereda, A.E. (2014) Electrical synapses and their functional interactions with chemical synapses. *Nature Reviews Neuroscience* **15**, 250–263.
- Politof, K., Antonakakis, M., Wollbrink, A., Zervakis, M. & Wolters, C.H. (2019) Effective Connectivity in the Primary Somatosensory Network using Combined EEG and MEG, In, *Presented at the 2019 IEEE 19th International Conference on Bioinformatics and Bioengineering (BIBE)*, pp. 593–597.
- Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A. & Shulman, G.L. (2001) A default mode of brain function. *Proceedings of the National Academy of Sciences (USA)* **98**, 676–682.
- Saba-Sadiya, S., Chantland, E., Alhanai, T., Liu, T. & Ghassemi, M.M. (2021) Unsupervised EEG artifact detection and correction. *Frontiers in Digital Health* **2**, 608920.
- Safari, M., Shalhaf, R., Bagherzadeh, S. & Shalhaf, A. (2024) Classification of mental workload using brain connectivity and machine learning on electroencephalogram data. *Scientific Reports* **14**, 9153.
- Scholtens, L.H., Pijnenburg, R., de Lange, S.C., Huitinga, I., van den Heuvel, M.P. & Netherlands Brain Bank (2022) Common microscale and macroscale principles of connectivity in the human brain. *Journal of Neuroscience* **42**, 4147–4163.
- Shojaie, A. & Fox, E.B. (2022a) Granger causality: a review and recent advances. *Annual Review of Statistics & Its Application* **9**, 289–319.
- Shojaie, A. & Fox, E.B. (2022b) Granger causality: a review and recent advances. *Annual Review of Statistics & Its Application* **9**, 289–319.
- Smith, S.M., Fox, P.T., Miller, K.L., Glahn, D.C., Fox, P.M., Mackay, C.E., Filippini, N., Watkins, K.E., Toro, R., Laird, A.R., & Beckmann, C.F. (2009) Correspondence of the brain's functional architecture during activation and rest. *Proceedings of the National Academy of Sciences (USA)* **106**, 13040–13045.

- Sporns, O. (2018) Graph theory methods: applications in brain networks. *Dialogues in Clinical Neuroscience* **20**, 111–121.
- Stam, C.J. (2014) Modern network science of neurological disorders. *Nature Reviews Neuroscience* **15**, 683–695.
- Stiles, J. & Jernigan, T.L. (2010) The Basics of Brain Development. *Neuropsychology Review* **20**, 327–348.
- Sultana, O.F., Bandaru, M., Islam, M.A. & Reddy, P.H. (2024) Unraveling the complexity of human brain: Structure, function in healthy and disease states. *Ageing Research Reviews* **100**, 102414.
- Tsipourakis, A., Antonakakis, M., Kaiser, F., Rampp, S., Kovac, S., Kellinghaus, C., Möddel, G., Wolters, C.H. & Zervakis, M. (2024) The Effect of Multi-Channel tDCS on the Directed Connectivity Patterns of a Case with Focal Epilepsy Using a Multi-Feature Machine Learning Evaluation. In, *Presented at the 2024 IEEE 24th International Conference on Bioinformatics and Bioengineering (BIBE)*, pp. 1–8.
- van 't Westende, C., Geraedts, V.J., van Ramesdonk, T., Dudink, J., Schoonmade, L.J., van der Knaap, M.S., Stam, C.J. & van de Pol, L.A. (2022) Neonatal quantitative electroencephalography and long-term outcomes: a systematic review. *Developmental Medicine & Child Neurology* **64**, 413–420
- Wang, X. & Michaelis, E.K. (2010) Selective neuronal vulnerability to oxidative stress in the brain. *Frontiers in Aging Neuroscience* **2**, 12.