



Technical University of Crete

School of Electrical and Computer Engineering
Digital Image and Signal Processing Laboratory

**BRAIN FUNCTIONAL NETWORK ALTERATIONS OF
MILD TRAUMATIC BRAIN INJURIES UTILIZING FINITE
ELEMENT REALISTIC HEAD MODELING AND
EEG/MEG**

Master's Thesis

Konstantinos Politof

Diploma committee:

Supervisor: Prof. Michael Zervakis (Technical University of Crete)

Prof. Athanasios Liavas (Technical University of Crete)

Prof. Carsten Hermann Wolters (University of Münster, Institute for Biomagnetism and Biosignalanalysis IBB)

CHANIA, SEP 2025

.....
Konstantinos Politof

Electrical and Computer Engineer
Technical University of Crete

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ACKNOWLEDGEMENTS

First and foremost, I would like to express my sincere gratitude to my academic advisor, Professor Michael Zervakis, for his invaluable guidance, continuous support, and insightful feedback throughout the duration of this Master's thesis. His mentorship has been instrumental in shaping both the direction and quality of this work.

I am also grateful to Professor Zouridakis George (Department of Engineering Technology, University of Houston, USA) for kindly providing the dataset used in this study.

I would also like to extend my appreciation to Professor Carsten Hermann Wolters from the University of Münster (Institute for Biomagnetism and Biosignalanalysis, IBB) and to Professor Athanasios Liavas for their involvement in this Master's thesis. Their willingness to contribute their expertise and serve on the examination committee is sincerely appreciated. Their constructive comments and academic insight have significantly enriched the scientific quality of this study.

Furthermore, I would like to acknowledge Dr. Marios Antonakakis, postdoctoral researcher at the Technical University of Crete, for his substantial contribution to the technical aspects of this work and for his consistent support and patience throughout the research process.

Finally, I extend my heartfelt appreciation to my family, my mother Kallia, my father Manolis, my stepfather Michalis, and to my fiancée Stella, for their unwavering encouragement, emotional support, and belief in my academic journey. I am also thankful to my friends who have been a source of strength and motivation during the course of my studies.

ABSTRACT

Motivation: Mild traumatic brain injury (mTBI) induces subtle neural changes that are often undetected by traditional neuroimaging techniques. Due to variability in findings across studies using EEG and MEG functional modalities, there is an increasing need for a spatiotemporally detailed pipeline to analyze functional data for accurately characterizing of mTBI assessment.

Objective: To develop and apply a personalized, multimodal analytic pipeline that integrates neurosource-driven EEG and MEG data to investigate functional brain dynamics, with the aim of supporting diagnosis and monitoring recovery in individuals with mTBI during the subacute phase (2–4 weeks post-injury).

Methods: After a detailed preprocessing pipeline, three-minute segments of artifact-free resting-state EEG and MEG data were analyzed from individuals with mTBI during the subacute recovery phase, as well as from orthopedic control (OC) participants. Source localization was conducted using anatomically realistic, subject-specific head models generated through the combination of a new segmentation pipeline and the Finite Element Method (FEM). The realistically head volume conductor was then serve the base of the estimation of the neural activity using a Linearly Constrained Minimum Variance (LCMV) beamformer to improve spatial accuracy. Through the new segmentation pipeline, the cortex was divided into 94 regions of interest (ROI) selected from the AAL3 atlas. For each ROI, representative time series were extracted from the source-level signals and filtered into delta, theta, and alpha frequency rhythms. Dynamic Functional Connectivity Graphs (DFCGs) was estimated via amplitude envelope correlations using the Hilbert transform. The DFCGs were then filtered using Orthogonal Minimal Spanning Trees (OMST) to reduce spurious node connections. In the final step, the degree of DFCGs were converted to symbolic time series via the Neural-Gas (NG) algorithm and the Complexity Index (CI) was computed to quantify the richness and variability of neural dynamics across delta, theta, and alpha frequency bands.

Results: The CI in the theta band (4–8 Hz) consistently reflected functional brain alterations and recovery following mTBI. Reductions in CI were observed across both EEG and MEG modalities, highlighting theta-band CI as a potential biomarker for early diagnosis and longitudinal monitoring of mTBI recovery.

Novelty: This study introduces a multimodal, source-level pipeline that combines advanced head modeling with dynamic connectivity metrics to sensitively track mTBI-related brain alterations during the subacute phase, offering novel insights into neural recovery and identifying potential biomarkers for diagnosis and prognosis.

Keywords: Mild traumatic brain injury, Electroencephalography, Magnetoencephalography, Finite Element Method, Linear Constraint Minimum Variance beamformer, Dynamic Functional Connectivity analysis & Complexity Index.

ΠΕΡΙΛΗΨΗ

Κίνητρο: Η ήπια τραυματική εγκεφαλική βλάβη (mTBI) προκαλεί ανεπαίσθητες νευρολογικές μεταβολές, που συχνά δεν ανιχνεύονται από τις παραδοσιακές τεχνικές νευροαπεικόνισης. Λόγω της διακύμανσης των ευρημάτων μεταξύ των μελετών που χρησιμοποιούν λειτουργικές μεθόδους EEG και MEG, καθίσταται αναγκαία η ανάπτυξη μιας τυποποιημένης αναλυτικής διαδικασίας που θα επιτρέπει την αξιόπιστη αξιολόγηση των λειτουργικών δεδομένων και θα ενισχύει τη διαγνωστική ακρίβεια και την παρακολούθηση της ανάρρωσης σε ασθενείς με mTBI.

Σκοπός: Η ανάπτυξη και εφαρμογή μιας εξατομικευμένης, πολυτροπικής αναλυτικής μεθοδολογίας που ενσωματώνει δεδομένα EEG και MEG σε επίπεδο πηγής για τη διερεύνηση της λειτουργικής δραστηριότητας του εγκεφάλου, με στόχο την υποστήριξη της διάγνωσης και παρακολούθησης της ανάρρωσης ατόμων με mTBI κατά τη διάρκεια της υποξείας περιόδου (2–4 εβδομάδες μετά τον τραυματισμό).

Μέθοδοι: Μετά από μια λεπτομερή διαδικασία προεπεξεργασίας, αναλύθηκαν τρία λεπτά καθαρών από θορύβους καταγραφών EEG και MEG σε κατάσταση ηρεμίας από άτομα με mTBI κατά τη φάση της υποξείας ανάρρωσης, καθώς και από συμμετέχοντες με ορθοπεδικούς τραυματισμούς (OC). Ο εντοπισμός της νευρωνικής δραστηριότητας πραγματοποιήθηκε χρησιμοποιώντας ρεαλιστικά, εξατομικευμένα ανατομικά μοντέλα κεφαλής, τα οποία δημιουργήθηκαν μέσω μιας νέας διαδικασίας τμηματοποίησης σε συνδυασμό με τη μέθοδο πεπερασμένων χτοιχείων (FEM). Ο ρεαλιστικός όγκος αγωγιμότητας της κεφαλής αποτέλεσε τη βάση για την εκτίμηση της νευρωνικής δραστηριότητας με τη χρήση της μεθόδου Linearly Constrained Minimum Variance (LCMV) beamformer, με σκοπό τη βελτίωση της χωρικής ακρίβειας. Μέσω της νέας διαδικασίας τμηματοποίησης, ο φλοιός του εγκεφάλου χωρίστηκε σε 94 περιοχές ενδιαφέροντος (ROI), επιλεγμένες από το πρότυπο AAL3. Για κάθε περιοχή ROI, εξήχθησαν αντιπροσωπευτικές χρονοσειρές από τα σήματα στο επίπεδο της πηγής και φιλτραρίστηκαν σε ρυθμούς συχνότητας δέλτα, θήτα και άλφα. Οι δυναμικοί γράφοι λειτουργικής συνδεσιμότητας (DFCGs) υπολογίστηκαν μέσω συσχετισμών περιβλήματος πλάτους χρησιμοποιώντας τον μετασχηματισμό Hilbert. Στη συνέχεια, οι DFCGs φιλτραρίστηκαν με τη μέθοδο Orthogonal Minimal Spanning Trees (OMST), ώστε να μειωθούν οι ψευδείς συνδέσεις μεταξύ κόμβων. Στο τελικό βήμα, ο βαθμός (degree) των DFCGs μετατράπηκε σε συμβολικές χρονοσειρές μέσω του αλγορίθμου Neural-Gas (NG) και υπολογίστηκε ο Δείκτης Πολυπλοκότητας (CI), για την ποσοτικοποίηση του πλούτου και της μεταβλητότητας της νευρωνικής δυναμικής στις συχνотικές ζώνες δέλτα, θήτα και άλφα.

Αποτελέσματα: Ο δείκτης CI στη συχνотική ζώνη θήτα (4–8 Hz) αποτυπώνει με συνέπεια τις λειτουργικές μεταβολές του εγκεφάλου και τη διαδικασία ανάρρωσης μετά από ήπιο τραυματισμό του εγκεφάλου. Σημειώθηκαν σημαντικές μειώσεις του CI και στα δύο εγκεφαλογραφικά μέσα, EEG και MEG, υποδηλώνοντας ότι ο CI στη ζώνη θήτα δύναται να λειτουργήσει ως αξιόπιστος βιοδείκτης για την έγκαιρη διάγνωση και την παρακολούθηση της μακροχρόνιας αποκατάστασης μετά από mTBI.

Καινοτομία: Αυτή η μελέτη παρουσιάζει μια πολυτροπική αναλυτική προσέγγιση σε επίπεδο πηγής, η οποία συνδυάζει ρεαλιστικά, υποκείμενα-ειδικά μοντέλα κεφαλής με δυναμικές μετρήσεις λειτουργικής συνδεσιμότητας, επιτρέποντας την ευαίσθητη παρακολούθηση εγκεφαλικών διαταραχών που σχετίζονται με mTBI κατά τη φάση της υποξείας ανάρρωσης. Η προσέγγιση αυτή προσφέρει νέες γνώσεις στη νευρολογική ανάρρωση και συμβάλλει στην ταυτοποίηση πιθανών βιοδεικτών για διάγνωση και πρόγνωση.

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CHAPTER 1: INTRODUCTION

1.1 MOTIVATION

Mild traumatic brain injury (mTBI) remains a significant public health concern, with diagnosis and monitoring posing substantial clinical challenges. Conventional neuroimaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI), frequently fail to detect the subtle neuropathological alterations associated with mTBI, as the injury predominantly affects brain function rather than structure. Clinical assessment is further complicated by the often nonspecific and subjective nature of reported symptoms, such as fatigue, confusion, or dizziness, which can be vague, inconsistent, or influenced by recall bias. As a result, there is a pressing need for the widespread clinical implementation of reliable methods capable of capturing neurophysiological alterations in patients with mTBI, thereby facilitating early diagnosis and longitudinal monitoring of recovery. In recent years, magnetoencephalography (MEG) and electroencephalography (EEG) have emerged as promising modalities for assessing functional brain alterations in mTBI due to their excellent temporal resolution and, in the case of MEG, enhanced spatial localization capabilities. However, the translation of these techniques into clinical practice has been hindered by methodological heterogeneity across studies and a scarcity of longitudinal research focusing on the early recovery period. To address these limitations, the present thesis proposes a novel, multimodal, source-level pipeline that integrates EEG and MEG functional recordings with anatomically realistic, subject-specific head models. It combines advanced head modeling with dynamic connectivity metrics to sensitively track mTBI-related brain alterations during the subacute phase, thereby offering novel insights into neural recovery and identifying potential biomarkers for diagnosis.

1.2 RELATED WORK

Non-invasive diagnosis and monitoring including biomarkers and standardized protocols for the recovery in patients with mTBI has gain high interest in the last decade (Arakaki, et al., 2018; Allen, et al., 2021; Proskovec, et al., 2020; Huang, et al., 2017; Antonakakis, et al., 2020). In this regard, traditional imaging methods, such as computed CT and MRI, often fail to detect the brain alterations characteristic of mTBI, as the injury primarily affects brain function rather than structure. Diagnosis is further complicated by the fact that mTBI events are frequently unwitnessed or appear minor, making it unclear whether a significant injury has occurred. Moreover, diagnosis often relies on patients' subjective reports of symptoms such as dizziness, confusion, or fatigue, which can be vague, inconsistent, or influenced by recall bias (Peitz, et al., 2021; Huang, et al., 2017). These symptoms also commonly overlap with other conditions like anxiety, depression, or sleep disturbances, making differential diagnosis difficult. Additionally, the presentation and progression of mTBI symptoms can vary widely between individuals, and over time further challenging standardized clinical assessment. EEG and MEG provide promising avenues for evaluation, offering high temporal resolution and, in the case of MEG, precise spatial localization, making them useful tools for detecting functional brain changes in mTBI.

Recently, Li and colleagues (Li, et al., 2018) examined whether source connectivity analysis of resting-state MEG activity can differentiate mTBI patients from controls. Thirteen mTBI subjects and eight orthopedic controls were recruited. Connectivity analysis was performed at the source level using the Granger causality index, applied to the averaged activation time series of each atlas-defined region of interest (ROI). Analyzing data from three sessions, it found that mTBI patients show a higher number and stronger brain connections, particularly in areas related to memory, perception, and emotion. These differences decreased over time, indicating patient improvement. The results suggest that connectivity analysis could serve as a reliable biomarker for diagnosing and assessing mTBI recovery. The produced raw recordings utilized in their study are also employed in this Thesis.

The (Antonakakis, et al., 2020) deploys Dynamic Functional Connectivity (DFC) analysis of MEG resting-state recordings to examine brain activity changes in mTBI. It focuses on 90 brain regions, reconstructing activity across multiple frequency bands using beamforming. Imaginary Phase-locking (iPLV) DFC graphs from 30 mTBI patients and 50 healthy controls are analyzed to identify network microstates (NMstates). The study suggests that frequency-dependent connectomic markers could serve as indicators for assessing mTBI recovery.

The above example studies are also part in the most representative review paper (Allen, et al., 2021) for MEG-based biomarkers in mTBI diagnosis. Allen and colleagues (Allen, et al., 2021) conducted a systematic review of 37 studies to evaluate MEG as an imaging biomarker for mTBI. The review focused on spectral and connectivity analyses across key frequency bands, examining power changes in spectral analysis and functional connectivity in brain regions. It emphasized resting-state low-frequency power and connectivity alterations as potential biomarkers for mTBI. At present, this review does not provide sufficient evidence to support the routine clinical application of MEG in mTBI, primarily due to variability across studies and a lack of robust supporting data. However, it highlights two potential biomarkers, resting-state low-frequency power and connectivity changes across all frequency bands, that may offer diagnostic and prognostic value.

Very recently, this study (Ueda, et al., 2025) examined resting-state EEG activity and brain network characteristics in mTBI patients and their relationship with neurocognitive function (NCF). Twenty-six mTBI patients and twenty-one age- and sex-matched healthy controls were assessed. Cortical current source density (CSD) distribution was examined using exact low-resolution brain electromagnetic tomography (eLORETA), and functional connectivity was assessed using Lagged Phase Synchronization (LPS) between pairs of 24 cortical ROIs across five frequency bands. Although this study did not find evidence supporting the use of resting-state EEG for directly identifying mTBI, the results indicate potential for these measures to serve as biomarkers for NCF impairments. Resting-state EEG may be valuable for understanding cognitive decline mechanisms following mTBI.

Last but not least, an updated review study conducted by Mavroudis and colleagues (Mavroudis, et al., 2025) including 25 studies to evaluate their methodologies, assessed parameters, and the clinical implications of using MEG for diagnosis, assessment and monitoring of mTBI. Due to heterogeneity across the studies, a narrative synthesis was conducted, emphasizing key aspects: MEG biomarkers associated with cognitive dysfunction, disruptions in neural connectivity, particularly within the default mode network (DMN), and MEG's potential for tracking brain recovery over time. In conclusion, MEG demonstrates considerable promise for diagnosing and monitoring mTBI, as it facilitates the detection of abnormal brain oscillations and connectivity disturbances, offering valuable insights into the neural mechanisms and long-term consequences of mTBI-related brain injury.

Although the above-mentioned recent research has demonstrated the potential of MEG and EEG in identifying functional biomarkers for mTBI, progress toward clinical translation remains limited by methodological inconsistencies, the lack of personalized modeling, and a shortage of longitudinal studies. Few studies have examined the recovery trajectory during the crucial early post-injury window, incorporated orthopedic controls (OC) to isolate brain-specific effects, or employed both modalities within a unified and individualized analysis framework. Addressing these gaps, the present thesis proposes a

novel and comprehensive pipeline employs a DFC analysis that builds upon the approach of (Antonakakis, et al., 2020), integrating functional EEG and MEG recordings with subject-specific anatomical head models constructed using the Finite Element Method (FEM). In addition, this study focuses on data collected between the second- and fourth-weeks post-injury, a critical yet underexplored recovery period, and includes OC participants to distinguish brain-specific alterations attributable to mTBI. The investigated frequency bands of interest following (Allen, et al., 2021; Mavroudis, et al., 2025) include the low frequency content, i.e., δ (0.5–4 Hz), θ (4–8 Hz), and α (8–13 Hz). This work offers a multimodal approach that incorporates individually constructed anatomical models to enhance our understanding of early functional recovery in mTBI.

1.3 CONTRIBUTION

This study introduces a novel and comprehensive multimodal pipeline designed to advance the understanding of mTBI through an integrative, individualized framework. Specifically, it combines functional information from EEG or MEG recordings with subject-specific head models constructed using combination of a new segmentation pipeline and the FEM, substantially enhancing the accuracy of source localization. The pipeline incorporates DFC analysis to examine neural dynamics at the source level across δ , θ , and α frequency bands. A key innovation lies in the focus on the subacute recovery period, between the second- and fourth- weeks post-injury, an underexplored yet critical window for understanding early functional changes. Furthermore, the inclusion of OC participants allows for the differentiation of brain-specific alterations from general trauma-related effects. Collectively, this work contributes a personalized, temporally targeted, and methodologically rigorous framework that enhances the potential for identifying clinically relevant biomarkers and deepens our understanding of mTBI recovery trajectories.

Key Aspects of the Study:

- **Subject-Specific Analysis:** Integration of functional data from EEG/MEG with individualized anatomical features to construct realistic head models using FEM.
- **DFC Analysis:** Assesses neural dynamics at the source level across δ (0.5–4 Hz), θ (4–8 Hz), and α (8–13 Hz) frequency bands to explore functional brain changes.
- **Recovery Assessment:** Evaluation of neural changes during the critical subacute phase, specifically between the second- and fourth- weeks post-injury.
- **Comparative analysis:** Evaluates mTBI participants at two critical post-injury time points and compares them with OC subjects to isolate brain-specific alterations from general trauma-related effects.

1.4 STRUCTURE OF CURRENT STUDY

Chapter 2 provides the theoretical background necessary for understanding this study. Section 2.1 discusses the anatomy of the human brain relevant to functional brain analysis. Sections 2.2 elaborate on non-invasive brain measurements, focusing on EEG and MEG, and offer a comparative analysis between the two modalities. Section 2.3 introduces mTBI, laying the foundation for understanding the neurological context of this study.

Chapter 3 details the methodological framework adopted for the analysis of functional brain networks. Section 3.2 describes the preprocessing pipeline, including artifact detection, elimination, and correction techniques necessary for cleaning EEG/MEG data. Section 3.3 introduces source analysis, beginning with a conceptual overview and proceeding with the mathematical formulation of the forward and inverse problems required for source localization. Section 3.4 explains the methods used for connectivity analysis among brain regions, specifically focusing on the Hilbert Transform, Orthogonal Minimal Spanning Trees (OMST), Neural-Gas clustering, and the Complexity Index (CI).

Chapter 4 presents the implementation of the methodologies and the results derived from them. Section 4.1 describes the experimental setup. Section 4.2 outlines the preprocessing procedures performed on the EEG/MEG data. Section 4.3 includes the implementation of source localization techniques (both forward and inverse solutions) using realistic head modeling. Section 4.4 discusses the extraction of DFC patterns from the source-level data and their graphical representation for further interpretation.

Chapter 5 discusses the findings of the study, draws conclusions, and proposes directions for future research. Sections 5.1 through 5.3 summarize the results, reflect on their significance in the context of mTBI assessment, and outline potential improvements and extensions of the current work.

CHAPTER 2: THEORETICAL BACKGROUND

2.1 ANATOMY OF THE HUMAN BRAIN

The nervous system (NS) (Purves, et al., 2004) comprises an extensive network of billions of neurons responsible for transmitting and processing information, which is vital for the proper functionality of the human body. The three primary functions of the nervous system are sensory input, integration, and motor output. Sensory input is responsible for detecting both external and internal stimuli within the body. Specialized sensory receptors recognize various stimuli, such as temperature, pain, pressure, light, sound, taste, and smell. Subsequently, the integration function involves the analysis and the interpretation of these inputs, enabling the system to make decisions and generates the appropriate response of the body to the stimulus, which is known as motor output. Furthermore, the nervous system is divided into two principal systems (Figure 2. 1): the central nervous system (CNS) and the peripheral nervous system (PNS). The CNS comprises the brain and the spinal cord and is responsible for coordinating the analysis and management of sensory and motor information. The PNS is composed of cranial and spinal nerves and connects

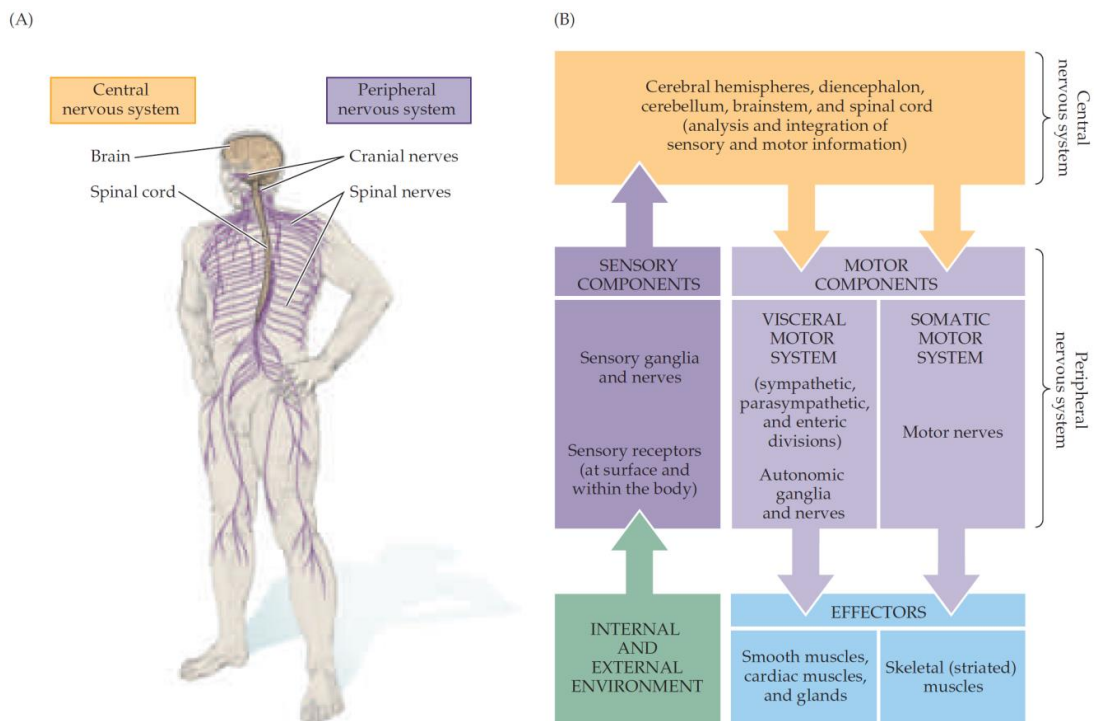


Figure 2. 1: a) The central and the peripheral nervous system and b) their interactions, adapted from (Purves, et al., 2004).

the CNS with the rest of the body. The human brain is part of the CNS and is responsible for the most crucial functions of humans. To safeguard this vital organ from injuries, the human head comprises several protective layers (Figure 2. 2). In summary, the main protective layers for the brain include the skin, skull (hard-spongiform-hard layers) and cerebrospinal fluid (CSF), which flows under the arachnoid mater, as shown in figure below.

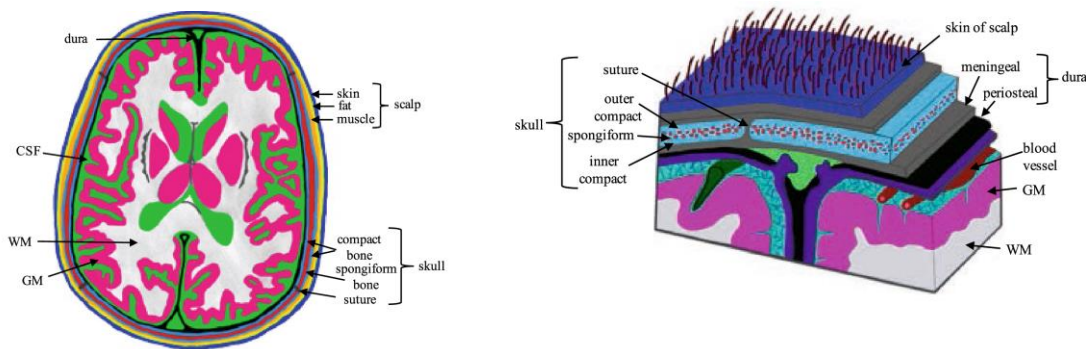


Figure 2. 2: The protective layers of the human head. In this work we focus on the scalp, skull, CSF, gray and white matter (GM & WM), adapted from (McCann, et al., 2019).

The brain consists of four primary regions: the cerebrum, diencephalon, brainstem and cerebellum. The cerebrum is further subdivided into two hemispheres, the right and the left, which are separated by the longitudinal fissure and primarily connected by the corpus callosum. Each cerebral hemisphere controls the contralateral side of the body, meaning that the left hemisphere governs the right side, and vice versa. Within the cerebral hemispheres, there are two distinct layers: an outer layer of gray matter known as the cerebral cortex and an inner layer of white matter. Gray matter derives its name from its high concentration of neuronal cell bodies and dendrites along with other structures. Apart from the cerebral cortex, gray matter can also be found in the inner part of the spinal cord. The neurons in the gray matter (GM) of the cerebral cortex are organized vertically into six layers (Figure 2. 4). The white matter (WM) is mainly formed by a network of nerve tracts, which are bundles of axons with a common direction. There are three primary categories of nerve fiber in the central nervous system, each distinguishable by the regions they connect (Figure 2. 5):

- Projection fibers connect different parts of the hemispheres with spinal cord or lower brain (e.g., thalamus). They can be efferent (i.e., descending) when carrying motor information from the cerebral cortex to the lower regions of the brain or spinal cord, or afferent (i.e., ascending) when transmitting sensory information in the opposite direction of efferent signals.
- Association fibers transmit information between various parts of the gray matter within the same cerebral hemisphere.
- Commissural fibers connect and transmit information between the two cerebral hemispheres (e.g., corpus callosum).
- Each hemisphere of the cerebral cortex is divided into four lobes (Figure 2. 3), each lobe has distinct functionalities:
- The Frontal lobe, located at the front of the brain, controls movement, speech and higher cognitive functions, including thinking, planning, decision-making, and problem-solving, memory and, attention. Posterior to the frontal lobe is the primary motor cortex, responsible for controlling muscle movements.
- The Parietal lobe, situated behind the frontal lobe, is associated with the processing of sensory information like the sense of touch, pain, and temperature. Anterior to the parietal lobe is the primary somatosensory cortex, which receives and processes sensory information from the body.
- The Temporal lobe, positioned sideways of the brain and underneath the frontal and parietal lobes, is associated with auditory processing, long-term memory, and language comprehension.
- The Occipital lobe, located at the back of the brain behind the parietal lobe, and receives and interprets most of the visual information.

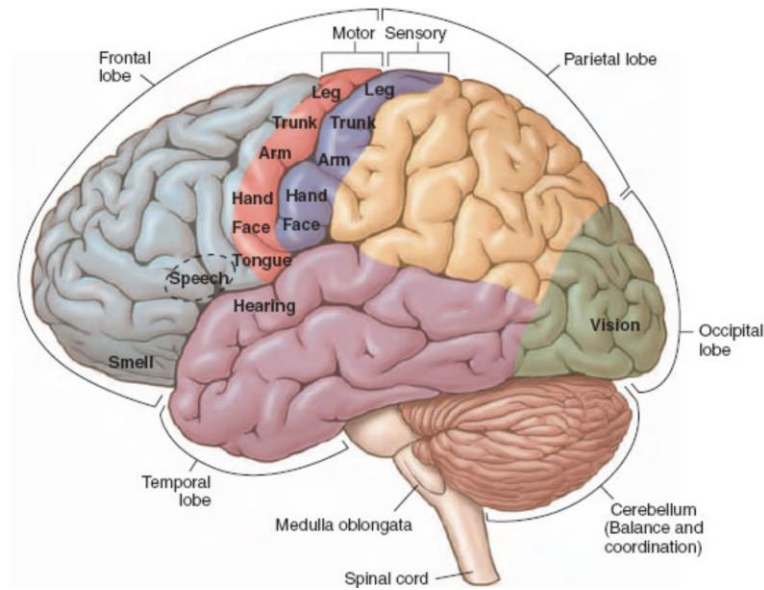


Figure 2. 3: The lobes of the left cerebral hemisphere, the primary motor and sensory cortex, brainstem and the cerebellum (adapted from biocyclopedia.com)

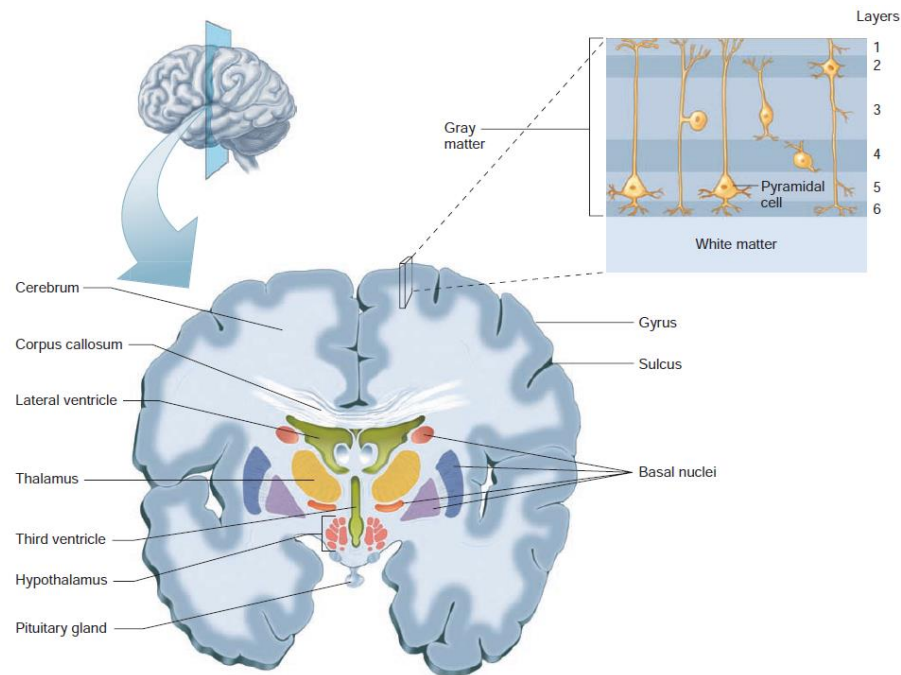


Figure 2. 4: Frontal slice of brain showing interior structures (e.g., thalamus) and the six layers of gray matter, adapted from (Widmaier, et al., 2008).

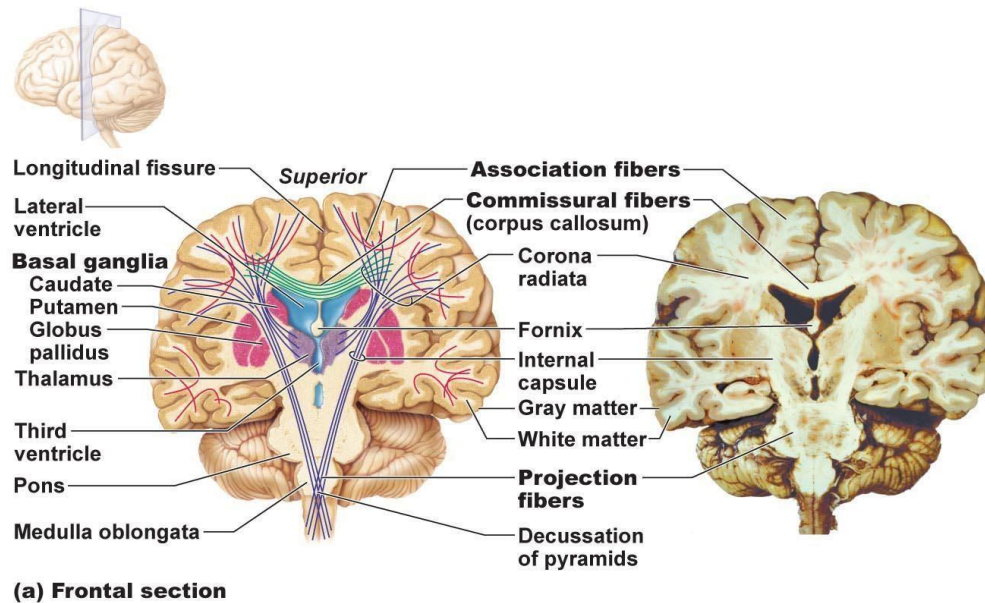


Figure 2. 5: The different types of fiber (projection, commissural and association) inside the white matter of brain (adapted from 2011 Pearson Education, Inc.)

2.2 NON-INVASIVE BRAIN MEASUREMENTS

Non-invasive measurements allow for the exploration of both the functional and anatomical aspects of the human brain. Their patient-friendly nature has led to a higher prevalence of research in biomedical field compared to invasive procedures, which require surgical interventions. This study focusses on the functionality of the electric potential and the magnetic field, which recorded by electroencephalography (EEG) and magnetoencephalography (MEG), respectively. Additionally, magnetic resonance imaging (MRI) provides insights into the anatomical features of the human head and its internal brain tissues. The collective use of EEG, MEG, and MRI offers both high temporal and spatial resolution, enabling a precise exploration of the complexities of brain functionality. This section will provide further analysis of EEG, MEG and their comparison.

2.2.1 ELECTROENCEPHALOGRAPH

The EEG electrodes (Sanei & Chambers, 2007) attach at the scalp (Figure 2. 6 a) and measure the electrical activity over a period of time. In comparison to other methods like MEG, the EEG offers a cost-effective solution for the diagnosing and monitoring of various neurological conditions, such as epilepsy, sleep disorders. This affordability makes it the prevailing choice for conducting multichannel brain recordings. The positioning of these electrodes adheres to international systems, such as the 10-20 system and its extensions, like the 10-10 system. For instance, the 10-20 system has 21 electrodes (Figure 2. 6 b) that are placed with intervals at 10% or 20% of constant distances measured by anatomic landmarks on the skull. These landmarks are the nasion (Nz), the inion (Iz) and the left and right pre-auricular points (A1 and A2). Each EEG channel records the corresponding electrical potential on the scalp, representing the voltage difference between an electrode and a reference point, measured in microvolts (μV). The choice of reference, determined by the montage we select (e.g., it could be another electrode or a common average reference), is crucial for emphasizing specific characteristics of our data.

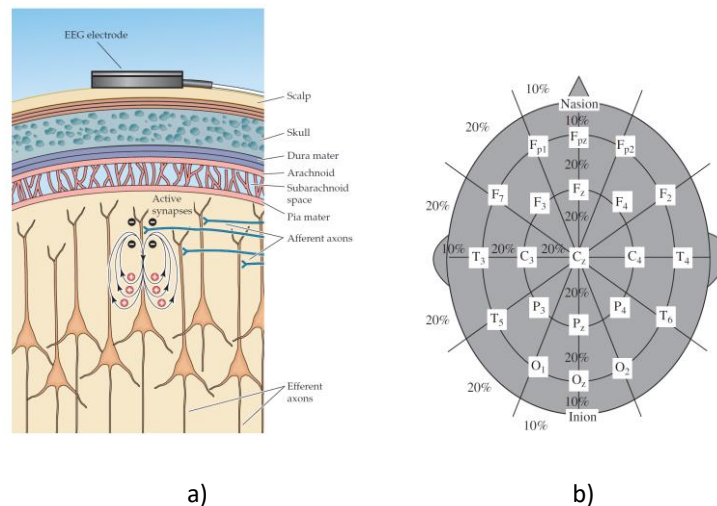


Figure 2. 6: a) The EEG electrode on the scalp adapted from (Purves, et al., 2004) and b) The 10-20 system with 21 electrodes adapted from (Sanei & Chambers, 2007).

2.2.2 MAGNETOENCEPHALOGRAPHY

The MEG (Hämäläinen, et al., 1993) exclusively records the brain's magnetic field that extends beyond the head, as illustrated in Figure 2. 7 b. This magnetic field, originating from the synchronous perpendicular electrical activation of the neurons, is relatively weak and falls within the femtotesla (fT) range. The MEG exhibits high sensitivity to external magnetic fields that do not originate within the brain. For instance, the Earth's static

geomagnetic field surpasses the brain's magnetic fields by a magnitude of eight to nine orders or noise present in laboratory settings, often stemming from electronic devices, is significantly higher. To eliminate the external disturbances, the MEG system is situated within a magnetically shielded room, as shown in Figure 2. 7 a. The participants can be in either sitting or lying position, placing their head as closely as feasible to the curved section of the MEG system, where the sensors are located. In Figure 2. 7 a, an experiment is depicted, involving simultaneous EEG and MEG measurements, during which the subject is exposed to various stimuli, such as auditory, visual, or tactile inputs.

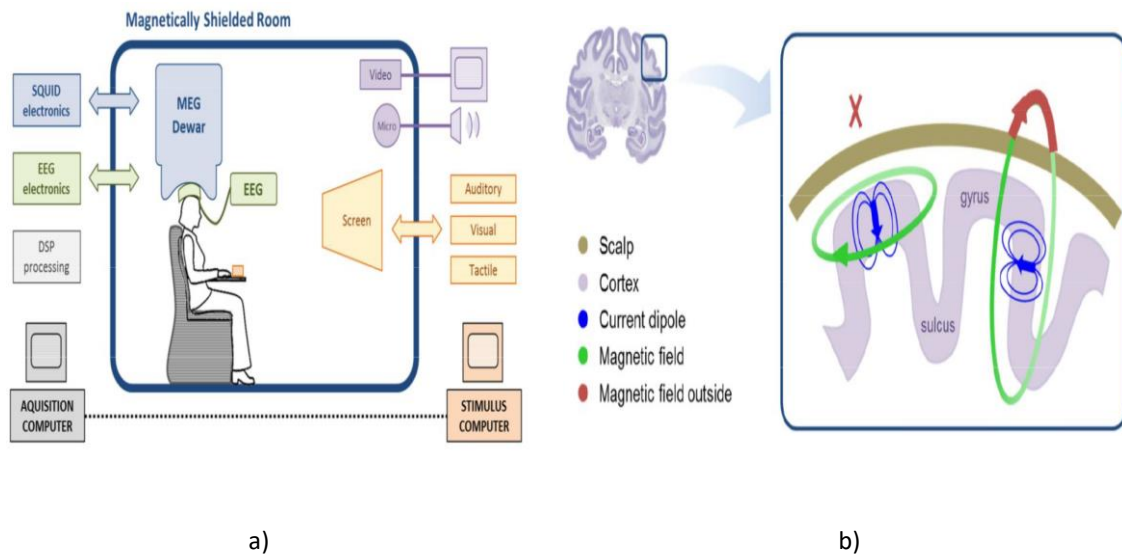


Figure 2. 7: a) The MEG system combined with the EEG system, adapted from (Galán, 2013) and b) Only the magnetic field that pass through outside the head can be detected by the MEG, adapted from (Galán, 2013).

2.2.3 COMPARISON BETWEEN EEG AND MEG

The brain activity (Hämäläinen, et al., 1993; Sanei & Chambers, 2007; Aydin, et al., 2014) generates an electric potential and a perpendicular magnetic field that both originate from the same electrical source (Figure 2. 8). These phenomena can be measured by EEG and MEG, respectively. The advantage of these modalities lies in their higher temporal resolution, typically within a range of one to a few milliseconds (ms), despite their limitation in spatial resolution. Their spatial resolution is directly linked to the number of electrodes or sensors utilized for data acquisition. MEG exhibits greater sensitivity to superficial sources positioned tangentially to the skull, which are located near to the sensors (Figure 2. 7 b). In contrast, the EEG is capable of detecting activities from sources with any orientation, including both tangential and radial orientations, even when the source is

situated deep within the brain. However, neither modality can detect sources with suppressed activations within the brain, often referred to as "silent sources". The anisotropy of the skull and the white matter significantly impacts the EEG measurements in comparison with MEG, because the magnetic field is almost unaffected to their effect. Additionally, the preparation time for MEG measurements is typically shorter in comparison to EEG, as the latter necessitates ensuring the proper contact between the scalp and the electrodes. Long-term recordings can be conducted with EEG, but this is not typically feasible with MEG, as it requires the subject to remain immobile. Moreover, EEG is more cost-effective than MEG due to the costly installations required for the latter, such as shielded rooms, and ongoing maintenance expenses. In conclusion, when comparing these recording methods, it becomes evident that EEG and MEG offer complementary information. Therefore, the combination of both modalities through simultaneous recording (EMEG) provides more precise findings.

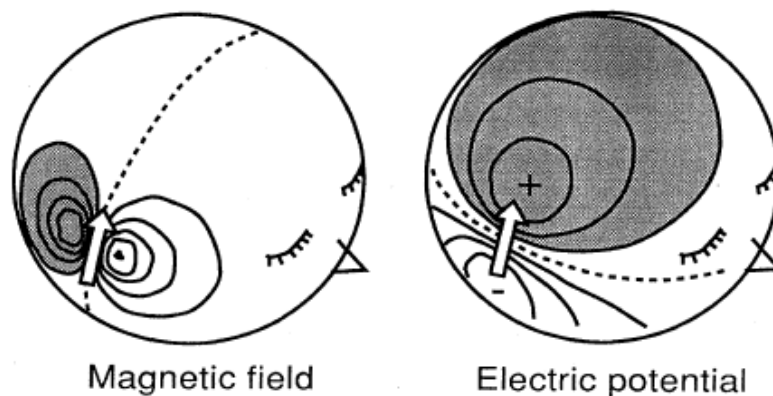


Figure 2. 8: The electric potential and magnetic field that are produced by the same electrical source (white arrow, adapted from (Hämäläinen, et al., 1993)).

2.3 MILD TRAUMATIC BRAIN INJURY

Mild traumatic brain injury (mTBI), also referred to as concussion (Proskovec, et al., 2020; Huang, et al., 2017; Proskovec, et al., 2020; Peitz, et al., 2021; Antonakakis, et al., 2020), represents the majority of the head injuries and typically results from a sudden jolt or blow to the head or body (Figure 2. 9). These injuries often occur due to incidents such as motor vehicle accidents, sports-related injuries and falls. Patients with mTBI may experience a range of issues that impact physical, cognitive, emotional, sleep, and behavioral functioning (Figure 2. 10). While symptoms typically resolve within a few days or weeks, some individuals experience persistent symptoms lasting three months or more,

which are then classified as post-concussive symptoms (PCS). Conventional neuroimaging techniques, including CT, acute MRI, and functional MRI (fMRI) often struggle to detect physiological changes in mTBI patients due to their low sensitivity. In cases where mTBI is accompanied by diffuse/traumatic axonal injury (DAI), as shown in Figure 2. 11, diffusion MRI (dMRI) techniques, which provide insights into white matter tracts, have demonstrated promising results in distinguishing mTBI patients from non-injured individuals. The common approach to diagnosing mTBI relies on clinical assessment and the presence of characteristic symptoms. EEG and MEG are valuable tools for mTBI analysis due to their high temporal resolution ($< 1\text{ ms}$), with MEG offering the additional benefit of a large number of sensors and good spatial localization accuracy (2–3 mm).

Numerous studies (Allen, et al., 2021; Mavroudis, et al., 2025; Peitz, et al., 2021) have focused on the detection and characterization of brain abnormalities through EEG and MEG connectivity analyses. MEG, in particular, is highly sensitive to abnormal slow-wave activity in mTBI patients and is increasingly used to examine network-level integration in the brain. The high-resolution temporal, spatial, and spectral properties of MEG make it a powerful tool for precisely quantifying the subtle neurophysiological aberrations associated with mTBI, which can then be translated into biomarkers. Despite the lack of structural damage typically seen in standard imaging studies like CT scans or MRIs, mTBI is characterized by temporary alterations in consciousness and cognitive function. These changes may not be detectable through conventional imaging techniques, highlighting the importance of EEG and MEG in advancing the understanding of mTBI and its effects on brain function.

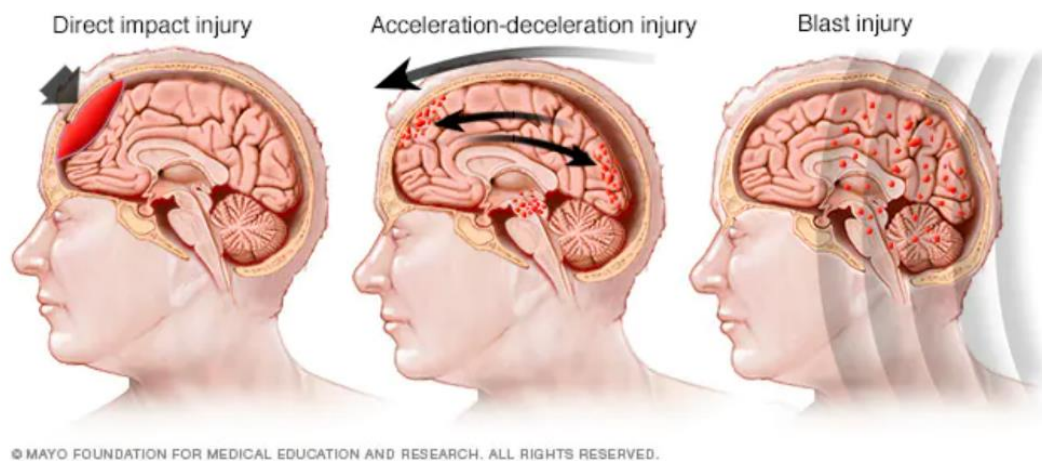


Figure 2. 9: Common injuries that cause concussion (adapted from, mayoclinic.org)



Figure 2. 10: The sign and the symptoms of a concussion (adapted from noahhelps.org)

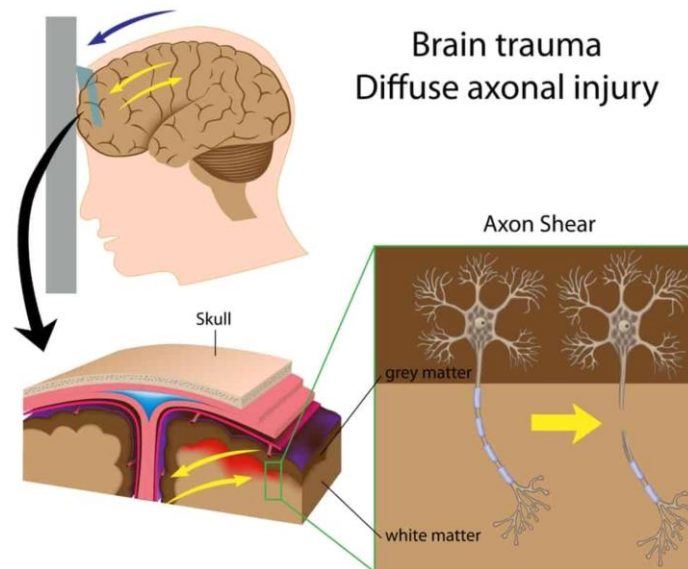


Figure 2. 11: Illustration of diffuse/traumatic axonal injury (DAI), adapted from propelphysiotherapy.com

CHAPTER 3: METHODS

3.1 SUMMARY OF CHAPTER

This chapter outlines the methodologies employed in this thesis to investigate brain activity and connectivity. It begins with a detailed preprocessing phase, which includes Artifact Detection and Elimination (3.2.1) and Artifact Correction (3.2.2), ensuring the integrity and accuracy of the data before analysis. Following preprocessing, Source Analysis (3.3) is introduced, providing insight into the techniques used to localize and interpret the sources of brain signals. The Forward Solution (3.3.2.1) is addressed through various head volume conductor models, which simulate the propagation of brain activity through the head's complex structures. Subsequently, the Inverse Solution (3.3.3) is explored, focusing on the methods for reconstructing the sources of activity using linear constraint minimum variance beamforming. Finally, the chapter explores Connectivity Analysis (3.4), focusing on the dynamic interactions between brain regions. Using the Neural Gas (NG) symbolization approach, symbolic time series (STS) are generated followed by Complexity Index (CI) estimation to quantify the diversity of those sequences. Together, these methodologies provide a robust framework for understanding brain activity and its network dynamics.

The pipeline steps are illustrated in Figure 3. 1, which shows the preparation of initial MRI, EEG, or MEG data, ultimately leading to the extraction of useful brain activity. Figure 3. 2 presents the subsequent phase of the pipeline, focusing on the DFC analysis which is derived from the representative signals of each region within the brain atlas. These stages facilitate the analysis of brain functional network alterations in mTBIs, enabling a comprehensive understanding of dynamic changes and interactions in response to injury through the use of finite element realistic head modeling combined with EEG or MEG data.

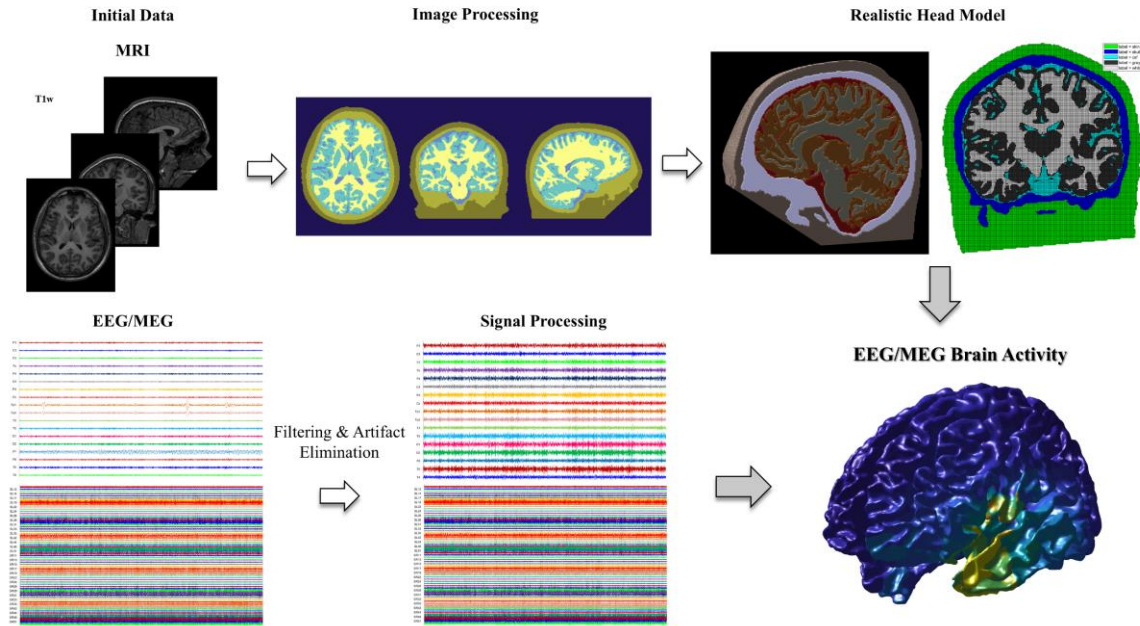


Figure 3. 1: Overview of the initial processing pipeline, starting with MRI and EEG/MEG data acquisition. The MRI is used to generate tissue masks for five compartments (scalp, skull, CSF, WM, and GM), which are then used to construct a realistic head model. Simultaneously, EEG or MEG data undergo filtering and artifact removal. Finally, brain activity is estimated by combining the artifact-free signals with the realistic head model.

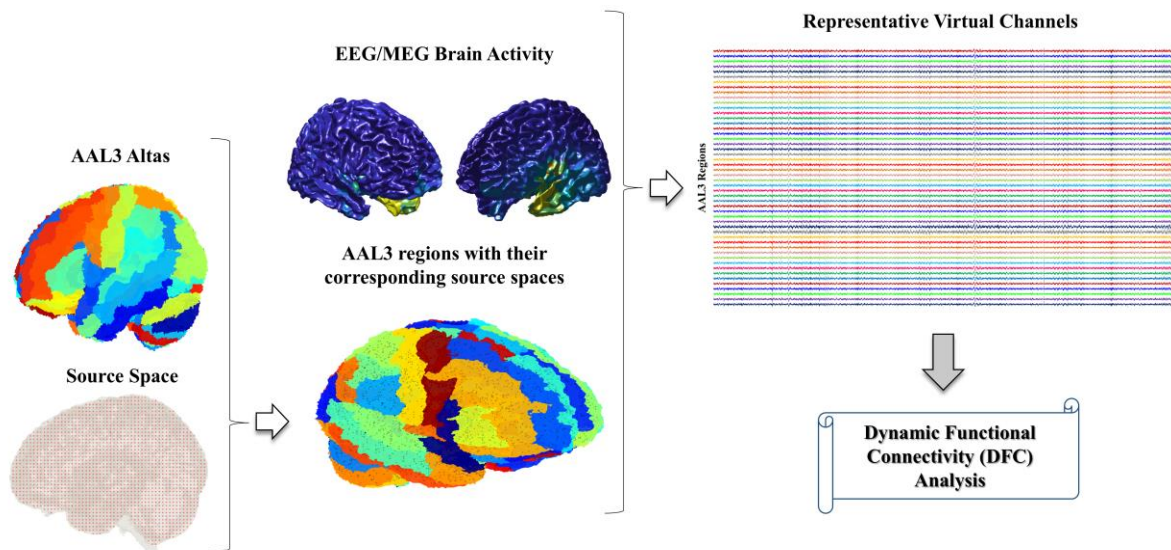


Figure 3. 2: The second stage of the pipeline consists of mapping source space points to anatomical regions, extracting representative brain source signals from each atlas region, and performing dynamic functional connectivity DFC analysis

3.2 PREPROCESSING

Starting with the noise reduction process (Politof, et al., 2019, a; Politof, et al., 2021; Sanei & Chambers, 2007), this pipeline applies a 5th-order band-pass Butterworth filter from 0.5 to 100 Hz to EEG and MEG signals to retain frequencies of interest. A Notch filter is used to eliminate power line noise (PLN) harmonics at 60 Hz, following the American standard. Additionally, visual inspection is performed to reject bad channels. Subsequently, it is essential to identify and mitigate external signals, such as electrophysiological artifacts and various types of noise, as these can significantly impact the quality and interpretation of the data. To address this, an automated procedure is implemented to detect and either eliminate or correct these artifacts. The preparation of the T1-weighted MRI sequences will be further analyzed during the construction of the head model in the chapter on the forward problem.

3.2.1 ARTIFACT DETECTION AND ELIMINATION

The EEG/MEG signals are a mixing of the unknown brain sources and various artifact sources, including electrophysiological activity from the eyes, heart, and muscles, as well as subject movements and environmental noise. Independent Component Analysis (ICA) (Hyvärinen & Oja, 2000; Hyvärinen, et al., 2001; Politof, 2019, b) is used to disentangle these mixed signals into independent components (ICs), which serve as estimations of the unknown independent sources from the observed multivariate signal. Let X represent the observed data recorded from the sensors. Through an unknown mixing matrix A , the independent sources S are mixed to produce the observed data X :

$$X = AS \quad (3.1)$$

where the dimensions are as follows:

- $X \in \mathcal{R}^{chs \times samples}$ (observed data),
- $A \in \mathcal{R}^{chs \times comps}$ (mixing matrix),
- $S \in \mathcal{R}^{comps \times samples}$ (independent sources).

Here, *chs* refers to the number of EEG/MEG channels, *comps* represent the source components, and *samples* denote the discrete time points. The ICA method estimates the ICs along with an unmixing matrix W using the equation:

$$ICs = WX \quad (3.2)$$

where the dimensions are:

- $W \in \mathcal{R}^{comps \times chs}$ (unmixing matrix),
- $ICs \in \mathcal{R}^{comps \times samples}$ (independent components).

To successfully separate the ICs, the following ICA assumptions must be considered:

- The X should be a linear combination of statistically independent sources S that have either non-Gaussian or at least one Gaussian distribution.
- The observed data X should be standardized transformed that is unit variance and zero mean and also be whitened (uncorrelated) using the principal component analysis (PCA).
- The mixing matrix A must be full-rank.

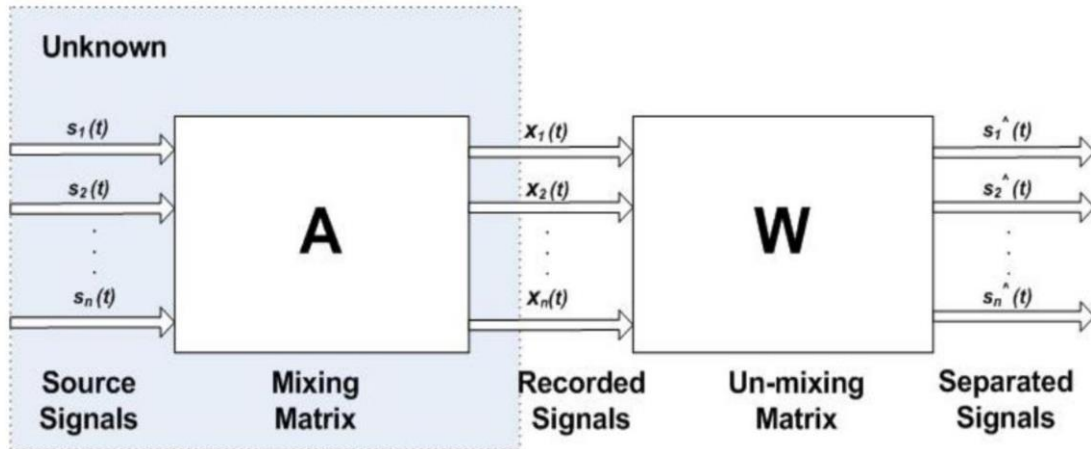


Figure 3. 3: The illustration shows the process from unknown sources to recorded signals, and then to the estimation of the sources (adapted from Ganesh R. Naik and Dinesh K Kumar, 2009)

Artifact detection is performed through an iterative process that assesses whether an independent component exceeds a specific z-score threshold for each of four metrics (Antonakakis, et al., 2013): kurtosis, skewness, and the root mean squared value of Shannon and Rényi entropy. This process identifies activities that can be characterized as outliers, deviating from the typical neural activity. Furthermore, if an independent component shows a strong correlation with the EOG or ECG signal, it is classified as an ocular or cardiac artifact, respectively. All components identified as artifacts are excluded, except for those correlated with ocular activity.

3.2.2 ARTIFACT CORRECTION

If an Indented Component (IC) is labeled as an artifact component with ocular activity, the correction of this signal is performed using the Empirical Mode Decomposition (EMD) (Lindsen & Bhattacharya, 2010; Zeng, et al., 2013; Patel, et al., 2016; Nguyen, et al., 2024). Ocular artifacts, caused by eye blinks and movements, primarily contaminate the frontal lobe, exhibiting higher amplitude characteristics and predominantly affecting the lower frequencies of brain signals. These artifacts can significantly distort EEG/MEG data, making it challenging to analyze neural activity accurately. The EMD is an adaptive technique that decomposes the signal into a sum of Intrinsic Mode Functions (IMFs).

EMD Processing Steps:

- (1) Given a signal $S(t)$, identify all local maxima and minima.
 - (2) Interpolate between maxima to estimate the upper envelope $S_{up}(t)$ and between minima to estimate the lower envelope $S_{low}(t)$.
 - (3) Compute the mean of the two envelopes, $m(t) = (S_{up}(t) + S_{low}(t))/2$, and subtract it from the data: $d(t) = S(t) - m(t)$.
 - (4) Repeat step (1) - (3) on $d(t)$ until a stopping criterion is fulfilled.
-

The signal $S(t)$ can be decomposed as:

$$S(t) = \sum_{m=1}^M IMF_M(t) + r(t) \quad (3.3)$$

where:

- $IMF_M(t)$ represents the m-th Intrinsic Mode Function.
- $r(t)$ is the residual signal.
- M is the total number of IMFs.

For the resulting IMFs to be valid, the following criteria must be satisfied:

- a. The number of extrema (peaks and troughs) and zero-crossings must be equal or differ by at most one.
- b. The mean of the envelope (defined by local maxima and minima) at any point should be zero, meaning the envelopes must be symmetric around zero.

The slow oscillations induced by ocular activity are typically captured by higher-order IMFs, which correspond to the low-frequency components of the signal. To clean the signal, it is essential to identify and remove the contaminated IMFs. This can be achieved through various techniques such as regression and thresholding methods. Once the artifact-dominated IMFs are removed, the clean IC signal can be reconstructed by summing the

remaining, artifact-free IMFs along with the residual signal. This process ensures that the neural activity is preserved while effectively eliminating the ocular artifacts, making EMD a powerful tool for EEG/MEG preprocessing.

The final step of preprocessing to acquire clean data involves back-projecting the artifact-free ICs, along with the corrected ICs from ocular activity, as shown in the following figure:

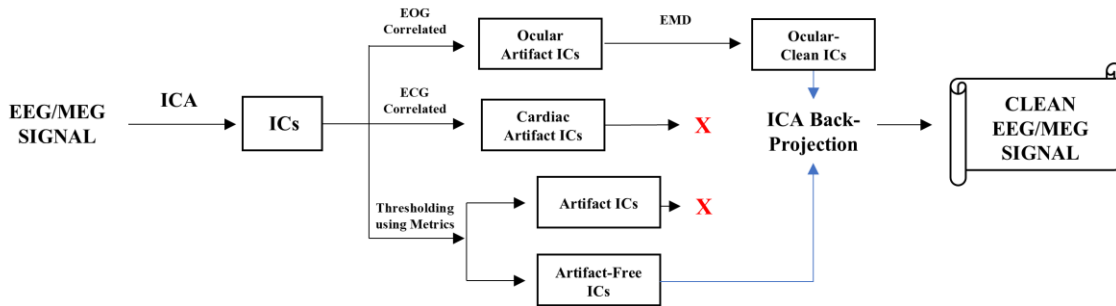


Figure 3. 4: Diagram illustrating the process of handling artifacts to acquire clean data.

3.3 SOURCE ANALYSIS

3.3.1 INTRODUCTION OF SOURCE ANALYSIS

The source localization problem is a critical challenge in neuroimaging and brain research, aiming to identify the location and characteristics of neural sources that generate electrical activity in the brain. Specifically, the goal is to estimate the position and dipole moment of the unknown neural source(s) based on external measurements, which are typically recorded through non-invasive techniques such as EEG, MEG, or their combined form, EMEG. The source localization problem is divided into two main categories: the forward problem and the inverse problem.

The forward problem (Hallez, et al., 2007; Brette & Destexhe, 2012; Vorwerk, et al., 2014) involves predicting the distribution of measured signals, such as electric potential or magnetic field, across all recording channels for each possible neural source (dipole). This is accomplished through a head volume conductor model that represents the electromagnetic properties of the human brain. The sources are located within the source space (or source model), which includes all potential positions within the brain, particularly in regions such as the gray matter, where neural activity is likely to originate. Each source

is defined by its spatial coordinates (position) and dipole moment, which consists of both amplitude and orientation.

The lead-field matrix L (also referred to as the gain matrix G) represents the forward solution by describing how each neural source contributes to the observed measurements at the sensors. It establishes a linear relationship between the source activity and the resulting electric or magnetic field recorded by EEG or MEG. Mathematically, in the absence of noise, this relationship can be expressed as:

$$X_{est} = LS \quad (3.4)$$

where $X_{obs} \in \mathcal{R}^{chs \times samples}$ represents the estimated observed measurements, $L \in \mathcal{R}^{chs \times q}$ is the lead-field matrix, and $S \in \mathcal{R}^q \times samples$ denotes the source magnitudes (dipoles). The parameter q is defined as $q = k$, where k represents the number of locations in the source space. In a Cartesian coordinate system, this implies that q belongs to $\mathcal{R}^{3 \times k}$, accounting for the three spatial components (x, y, z) of each dipole at k distinct source positions. For example, considering N measurement channels, k dipoles, and a single time sample, the observed measurements can be expressed as:

$$X_{obs} = \begin{bmatrix} X_{obs}(r_1) \\ \vdots \\ X_{obs}(r_N) \end{bmatrix} = \begin{bmatrix} l(r_1, r_{sour1}) & \cdots & l(r_1, r_{sourk}) \\ \vdots & \ddots & \vdots \\ l(r_N, r_{sour1}) & \cdots & l(r_N, r_{sourk}) \end{bmatrix} \begin{bmatrix} m_1 \\ \vdots \\ m_k \end{bmatrix} \quad (3.5)$$

where $r_1 \cdots r_N$ denote the positions of the measurement channels, $r_{sour1} \cdots r_{sourk}$ represent the locations of the dipoles within the brain, and each dipole moment is given by $m_i = d_i \vec{e}_i$, for $i = 1 \dots k$ where d_i is the dipole magnitude and $\vec{e}_i$ is the unit orientation vector. To solve the forward problem and compute the lead-field matrix, it is necessary to have the head model, the source space, and the positions of the channels (electrodes or sensors). These elements must be aligned within a common coordinate system (such as fiducial points) and employ consistent units.

The inverse problem (Grech, et al., 2008; Brette & Destexhe, 2012) is considered ill-posed because a single set of observed data may correspond to multiple potential solutions, given the large disparity between the number of sources and channels (sources $\gg$ channels). To tackle this challenge, two primary approaches are commonly used: parametric and non-parametric methods. The parametric approach reduces the number of sources to constrain the problem, using techniques that estimate both the dipole's position and moment. However, the inclusion of position estimation adds non-linearity, making the solution more complex. Beamforming is an example of a parametric method. In contrast, non-parametric methods focus on estimating the moments of sources within a predefined source space, leading to a linear problem. Techniques such as MNE and sLORETA are examples of non-parametric methods. Additionally, regularization is applied in non-parametric approaches to transform the ill-posed problem into a well-posed one.

The inverse problem utilizes the lead-field matrix L derived from the forward solution and the original observed data (from EEG/MEG/EMEG) to determine the unknown source(s). The relationship is expressed as:

$$S = L^{-1}X_{orig} \quad (3.6)$$

where the $X_{orig} \in \mathcal{R}^{chs \times samples}$ represents the original data. In practice, noise cannot be entirely removed, so the forward equation is adjusted to:

$$X_{est} = LS + n \quad (3.7)$$

Consequently, the inverse solution provides an estimate of the source(s) as:

$$\hat{S} = L^{-1}X_{orig} \quad (3.8)$$

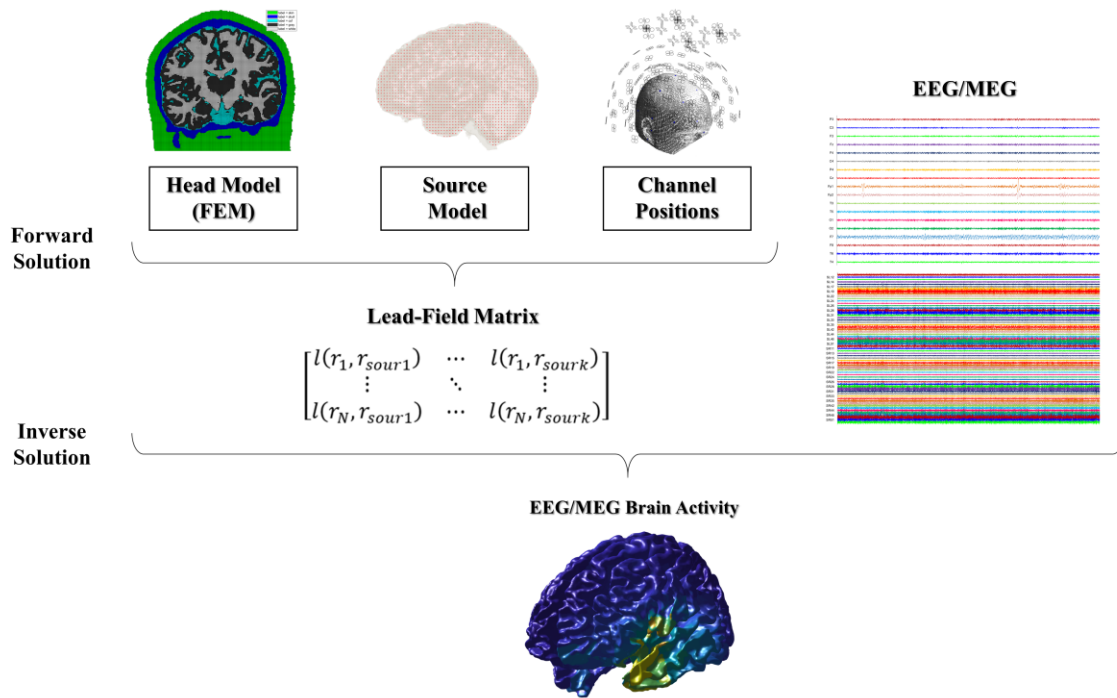


Figure 3. 5: Illustration of Forward and Inverse Problem Solutions

3.3.2 MATHEMATICAL BACKGROUND FOR THE FORWARD PROBLEM

The forward problem involves modeling how electrical or magnetic fields propagate from a given neural source to the measurement sensors. This source can be modeled using the equivalent current dipole (ECD) (Hämäläinen, et al., 1993; Halles, et al., 2007), which represents the synchronized electrical activity of a large cluster of neurons within a localized region of the brain. Assume that the ECD Q is mathematically defined at a specific time instant with the following parameters: position r_Q , magnitude d_Q and orientation $\vec{e}_Q$. The dipole moment $\mathbf{m}_Q$ is formed by the product of the magnitude and orientation, i.e., $\mathbf{m}_Q = d_Q \vec{e}_Q$. The unit vector $\vec{e}_Q$ represents the direction of the dipole, pointing from the sink to the source.

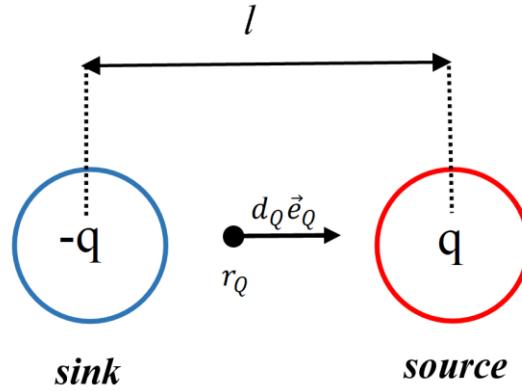


Figure 3. 6: The dipole moment for a time instant (Politof, 2019, b).

The current density $\mathbf{J}$ generated by ECD at position r_Q consists of both primary and passive (or secondary) components. The primary current density $\mathbf{J}_Q^{pr}(r_Q)$ corresponds to the primary current $\mathbf{I}_{pr}$, which flows across a tiny volume over a distance l from sink to source. The passive current density is defined by the Ohm's law as the product of the medium's conductivity σ (e.g., scalp or brain) and the electric field $\mathbf{E}$ present within that medium and expressed as $\mathbf{J}^{pas}(r_Q) = \sigma \mathbf{E}$. The human head compartments can be classified into two categories based on their conductivity σ : isotropic and anisotropic. Isotropic compartments, such as the scalp and CSF, allow current to flow equally in all directions. In contrast, anisotropic compartments, like the skull, gray matter, and white matter, have varying conductivity depending on the direction. The conductivity for isotropic regions is scalar, whereas for anisotropic regions, it is represented by a directional matrix (Wolters, et al., 2006; Halles, et al., 2007; Dannhauer, et al., 2011; Vorwerk, et al., 2014). Due to the absence of diffusion tensor imaging (DTI) sequences, this study assumes

the conductivity of the head compartments to be isotropic, assigning a constant value to each compartment.

To calculate the electric field $\mathbf{E}$ and the magnetic induction $\mathbf{B}$, a quasi-static approximation of Maxwell's equations is employed (Hämäläinen, et al., 1993; Wolters & Munck, 2007; Brette & Destexhe, 2012; Vorwerk, et al., 2014). This approach expresses the electric field $\mathbf{E}$ as the gradient of the electric potential V as:

$$\mathbf{E} = -\nabla V \quad (3.9)$$

$$\nabla \times \mathbf{B} = \mu_0 \mathbf{J}, \quad (3.10)$$

where the μ_0 is magnetic permeability

$$\mathbf{J} = \mathbf{J}^{pr} + \sigma \mathbf{E} \quad (3.11)$$

The nabla symbol (∇) represents the three-dimensional gradient operator, while $\nabla \cdot$ and $\nabla \times$ correspond to the divergence and curl vector operators, respectively.

Combine the equation 3.9 and 3.11 with continuity equation for current $\nabla \cdot \mathbf{J} = 0$ yields a differential equation for V :

$$\nabla \cdot (\sigma(\nabla V)) = -\nabla \cdot \mathbf{J}^{pr} \quad (3.12)$$

This equation models how current sources inside the brain (source space) produce measurable scalp potentials and is solved to compute V for given sources and conductivities. The solution can be analytical or numerical depending on the complexity of the head model. Knowing the electric potential V allows the calculation of the electric field $\mathbf{E}$ and subsequently the passive current density $\mathbf{J}^{pas} = \sigma \mathbf{E}$. The magnetic field $\mathbf{B}$ can be computed by applying the Biot-Savart law (Hämäläinen, et al., 1993; Wolters & Munck, 2007; Vallaghé, 2008; Brette & Destexhe, 2012; Vorwerk, et al., 2014; Piastra, et al., 2018):

$$\mathbf{B}(\mathbf{r}) = \frac{\mu_0}{4\pi} \int_{\mathbb{R}^3} \mathbf{J}(\mathbf{r}') \times \frac{(\mathbf{r} - \mathbf{r}')}{\|\mathbf{r} - \mathbf{r}'\|^3} d\mathbf{r}' \quad (3.13)$$

In accordance with the equation $\mathbf{J} = \mathbf{J}^{pr} + \mathbf{J}^{pas} = \mathbf{J}^{pr} - \sigma(\nabla V)$, the magnetic field can be expressed as the sum of two components:

$$\begin{aligned} \mathbf{B}(\mathbf{r}) &= \mathbf{B}^{pr}(\mathbf{r}) + \mathbf{B}^{pas}(\mathbf{r}) \\ &= \frac{\mu_0}{4\pi} \int_{\mathbb{R}^3} \mathbf{J}^{pr}(\mathbf{r}') \times \frac{(\mathbf{r} - \mathbf{r}')}{\|\mathbf{r} - \mathbf{r}'\|^3} d\mathbf{r}' - \frac{\mu_0}{4\pi} \int_{\mathbb{R}^3} \sigma(\nabla V(\mathbf{r}')) \times \frac{(\mathbf{r} - \mathbf{r}')}{\|\mathbf{r} - \mathbf{r}'\|^3} d\mathbf{r}' \end{aligned} \quad (3.14)$$

The $\mathbf{B}(\mathbf{r})$ denotes the magnetic field measured outside the brain at the location $\mathbf{r}$, which is generated by the primary current with current density $\mathbf{J}(\mathbf{r}')$ at the point $\mathbf{r}'$ within the brain. Additionally, the passive magnetic field is contributed by the passive current resulting from the electric field gradient, influenced by the conductivity of the medium.

3.3.2.1 FORWARD SOLUTION

The forward problem in EEG and MEG can be solved using either analytical or numerical approaches, depending on the complexity of the head model and the required level of accuracy. The result of these approaches is the calculation of the electric or magnetic field distribution generated by neural sources within the brain, which is subsequently measured at the scalp or by sensors placed around the head.

Analytical solutions, such as the overlapping spheres model (Frank, 1952; Hallez, et al., 2007; Wolters & Munck, 2007; Brette & Destexhe, 2012), offer computationally efficient approximations of the head by representing it as a set of concentric spheres with homogeneous conductivity. The three-sphere model is a basic representation in which the outer layer corresponds to the scalp, the middle layer to the skull, and the innermost layer to the brain. To increase anatomical accuracy, the model can be extended to four- and five-sphere models. The four-sphere model introduces an additional layer for the CSF situated between the brain and skull, while the five-sphere model further divides the brain into separate gray and white matter compartments. However, they fail to accurately capture the true anatomical features of the head, and they overlook the anisotropy present in the skull and white matter, leading to considerable inaccuracies in the model.

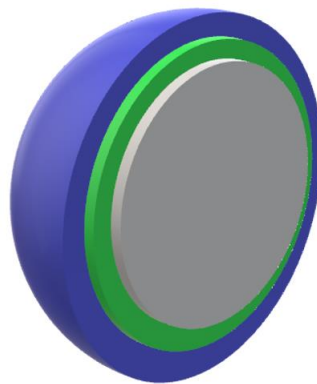


Figure 3. 7: The three-layer concentric spherical head model, where the outermost, middle, and innermost spheres represent the scalp, skull, and brain, respectively, adapted from (Politof, 2019, b).

Numerical methods, including the Boundary Element Method (BEM) and the Finite Element Method (FEM), offer more precise solutions by incorporating realistic head

geometries and inhomogeneous conductivity distributions. BEM (Hallez, et al., 2007; Wolters & Munck, 2007; Brette & Destexhe, 2012) is widely used for EEG and MEG forward modeling, offers a more efficient approach by discretizing only the boundary surfaces between distinct tissue compartments, thereby reducing computational demands. In a typical BEM implementation, such as the three-compartment head model comprising the scalp, skull, and brain, the interfaces between compartments are represented by triangular boundary elements. These elements allow for the calculation of electric potential differences between the compartments, assuming each is a homogeneous and isotropic volume conductor. The homogeneous condition implies that the conductivity is uniform throughout the entire volume. The isotropic condition holds when the current flows equally in all directions, meaning that the conductivity is the same regardless of the direction of current flow. While these simplifications improve the computational efficiency of solving the forward problem, they also introduce limitations. Specifically, the isotropic assumption fails to account for the anisotropy present in the skull and white matter, where current flow is directionally dependent due to variations in conductivity. For example, the skull demonstrates anisotropy across its three layers (hard, spongiform, and hard), and the white matter exhibits anisotropic properties within nerve fibers, with the primary fiber orientation further influencing conductivity variations.

The FEM (Wolters, et al., 2006; Hallez, et al., 2007; Rullmann, et al., 2009; Aydin, et al., 2014; Vorwerk, et al., 2019; Wolters, et al., 2004) models the internal volume of the head by subdividing it into finite elements, typically tetrahedrons or hexahedrons. The potential is computed at the vertices of these elements, allowing for the representation of inhomogeneities such as CSF, gray and white matter, and the layered structure of the skull (compacta-spongiosa-compacta), as well as brain anisotropy within the head volume conductor (Dannhauer, et al., 2011). This method supports high-resolution modeling, even down to 1 mm or less. The compartments modeled include the scalp, skull compacta, skull spongiosa, CSF, gray matter, and white matter. While FEM's primary disadvantage is its relatively high computational cost compared to other methods, this is no longer a major limitation due to advances in computational power (Wolters & Munck, 2007; Brette & Destexhe, 2012).

The selection between analytical and numerical approaches for solving the forward problem in EEG and MEG modeling depends on balancing computational efficiency with anatomical accuracy. While analytical methods are often quicker, numerical techniques, such as the FEM, are preferred for more complex, individualized head models due to their ability to provide higher anatomical fidelity. In this study, the realistic head model is constructed using FEM with hexahedral elements, resulting in a high-resolution representation of the head. Due to the limitation of not having access to T2-weighted (T2w) and DTI sequences, the head model is simplified and divided into five compartments: skin,

skull, CSF, gray matter, and white matter, with each compartment assigned specific conductivity values.

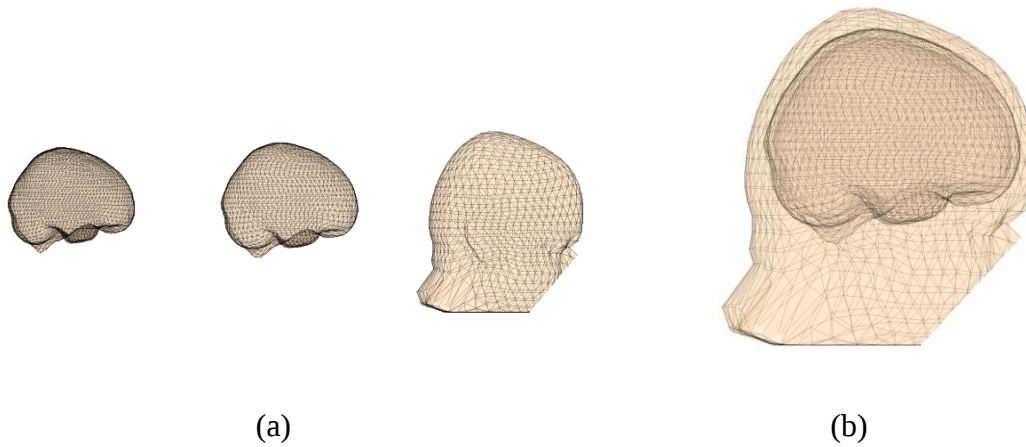


Figure 3. 8: The Boundary Element Method (BEM) model with three distinct compartments, generated using the FieldTrip toolbox. (a) The individual compartments, from left to right, represent the brain, skull, and scalp. (b) A visualization of all compartments combined, adapted from (Politof, 2019, b).

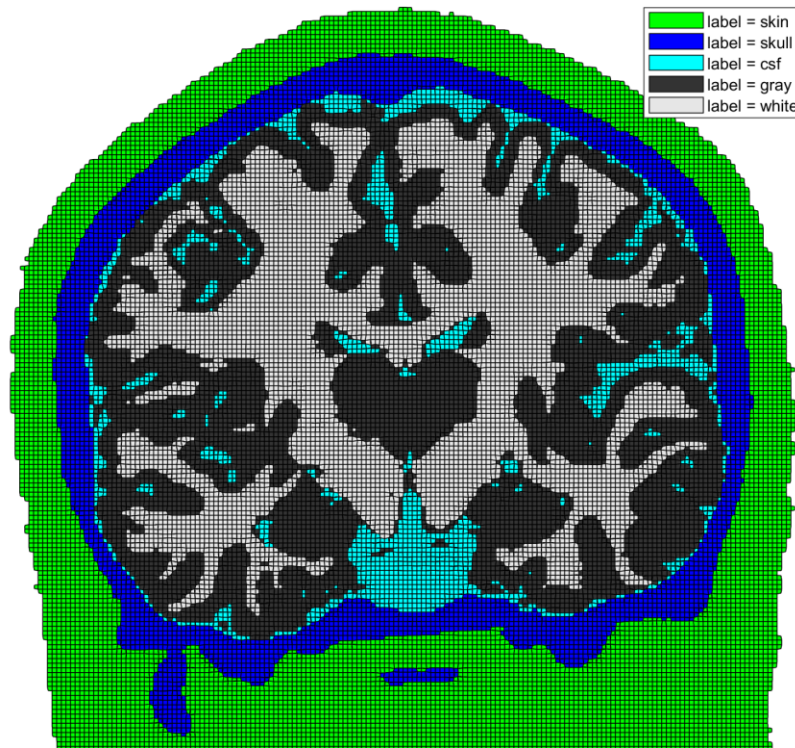


Figure 3. 9: The Finite Element Method (FEM) model utilizing hexahedral elements, consisting of five compartments: skin, skull, cerebrospinal fluid (CSF), gray matter, and white matter.

3.3.3 INVERSE SOLUTION

The observed measurement data X_{obs} obtained from EEG, MEG, or EMEG are a mixture of unknown neural source(s) S and can be expressed in a linear form as:

$$X_{obs} = LS + n \quad (3.15)$$

where L is the lead-field matrix that describes how neural sources contribute to the recorded signals, and n represents measurement noise. The objective of the inverse problem is to estimate the parameters of these neural sources S , including their location, orientation, and strength, from the measured data X_{obs} .

The Beamforming Approach is a parametric technique used to solve the inverse problem (Grech, et al., 2008). It is a spatial filtering method that aims to estimate neural source activity by optimizing a set of spatial filters. The beamformer applies a spatial filter to the sensor data at each time point t to extract the estimated activity of a target source:

$$\hat{S}(t) = W^T X_{obs}(t) \quad (3.16)$$

where W^T is the spatial filter matrix. This approach enhances sensitivity to the source of interest while simultaneously minimizing contributions from noise and other interfering sources. Specifically, when the location of interest is r_{sour} , the spatial filter is designed to satisfy the following condition:

$$W^T(r_{sour})L(r) = \begin{cases} \mathbf{I}, & \|r - r_{sour}\| \leq \delta \\ 0, & \|r - r_{sour}\| > \delta \end{cases} \quad (3.17)$$

where $\mathbf{I}$ represents the identity matrix and δ is a small distance around the source. This study employs Linear Constraint Minimum Variance (LCMV) beamformer (Veen, et al., 1997; Darvas, et al., 2004; Grech, et al., 2008; Jaiswal, et al., 2020), in which the spatial filters are computed to minimize the output energy $W^T C_X W$, under the constraint that only the dipole r_{sour} is active at that time. By setting $\delta = 0$, the filter enforces strict suppression of all other sources. The corresponding optimization problem is:

$$\min_{W^T} (Tr(W^T C_X W)) \text{ subject to } W^T(r_{sour})L(r_{sour}) = \mathbf{I} \quad (3.18)$$

with C_X is the covariance of the observed measurement data. Beamforming techniques, like LCMV, offer key advantages. They are data-adaptive, optimizing filters to suppress noise based on the observed signals. Additionally, they do not require prior assumptions about the number of active sources, making them ideal for exploratory analysis.

3.4 CONNECTIVITY ANALYSIS

Following source analysis, representative time series are extracted for each region of interest (ROI), based on the pipeline described by (Antonakakis, et al., 2020). This procedure will be explained in detail in Chapter 4. The next step involves constructing dynamic functional connectivity graphs (DFCGs) for each frequency band, capturing the time-varying interactions among brain regions. Functional connectivity is estimated by computing the correlation between pairs of ROI time series, using the amplitude envelopes obtained via the Hilbert transform. This method captures the dynamics of amplitude-to-amplitude coupling over time. Topological filtering is then applied to the resulting correlation matrices using the orthogonal minimal spanning tree (OMST) algorithm, which enhances the interpretability of the functional connectivity graphs by preserving the most dominant and biologically meaningful connections while minimizing noise and irrelevant links. Subsequently, the degree of the graph for each ROI at each timestamp is calculated by summing the values in each row of the functional connectivity graph. For each group of subjects, the Neural Gas (NG) algorithm is employed to model and compress the dynamic connectivity profiles into symbolic representations. By mapping high-dimensional functional connectivity data to a finite set of representative codebook vectors, the NG algorithm facilitates the generation of symbolic time series (STS). Finally, to characterize the complexity and richness of these symbolic sequences, the Complexity Index (CI) is computed for each subject separately. The CI quantifies the diversity of the symbolic patterns within the STS by measuring the number of distinct subword patterns across varying lengths.

3.4.1 ENVELOPE OF HILBERT TRANSFORMATION

The Hilbert transform (Boashash, 1992) is a mathematical operation that provides a way to extract the analytic signal $z(t)$ given a real-valued signal $x(t)$:

$$z(t) = x(t) + jH[x(t)] \quad (3.19)$$

where $H[x(t)]$ is the Hilbert transform of $x(t)$. The envelope $env(t)$ of the signal is the magnitude of the analytic signal:

$$env(t) = |z(t)| = \sqrt{x(t)^2 + H[x(t)]^2} \quad (3.20)$$

This envelope represents the time-varying amplitude of the signal, capturing fluctuations in intensity while preserving the phase information from the original signal. The envelope is particularly useful for analyzing modulations in oscillatory signals, such as in neural activity or other time-series data.

3.4.2 ORTHOGONAL MINIMAL SPANNING TREES

The Orthogonal Minimal Spanning Trees (OMSTs) (Dimitriadis, et al., 2017, a; Dimitriadis, et al., 2017, b) algorithm is a data-driven topological filtering technique designed to preserve the fundamental structure of the functional connectivity graph. It achieves this by enforcing network sparsity while maintaining biologically plausible connections, thereby enhancing both the interpretability and reliability of the resulting network representations. In more detail, a spanning tree is a subgraph that connects all N nodes of a given graph with exactly $N - 1$ edges, ensuring that there are no cycles and the graph remains connected. A Minimum Spanning Tree (MST) of a connected weighted graph is defined as the spanning tree that minimizes the total sum of edge weights. In other words, it identifies the most efficient set of connections that links all nodes with the least possible cumulative cost. In large-scale brain networks comprising hundreds of nodes, the MST results in a highly sparse structure that may fail to accurately reflect the true underlying topology, potentially reducing its effectiveness in distinguishing between different groups (e.g. mTBIs and Orthopedic Controls). The OMST method extends the MST concept by iteratively constructing multiple, non-overlapping MSTs from the original functional connectivity graph using the Kruskal's algorithm, with each tree comprising distinct sets of edges. In the iterative OMST process:

- The 1st MST runs at the original network.
- The $(k + 1)^{th}$ MST is computed on the network after all connections used in the previous k MSTs have been removed (i.e., share no common edges). Thus, the $(k + 1)^{th}$ MST is constructed to be orthogonal to all preceding MSTs.
- This procedure is repeated until no more MSTs can be constructed due to the absence of remaining edges or a predefined number of MSTs is reached.

Orthogonality means that the MSTs capture distinct, non-overlapping parts of the graph's structure, ensuring no redundancy. The resulting filtered connectivity graph is derived by sequentially adding MSTs until the trade-off between global efficiency and wiring cost (i.e., Global Cost Efficiency) is maximized, thereby preserving the most dominant interactions. This graph is then used for further analysis, such as calculating graph-theoretic metrics (e.g., node degree).

3.4.3 NEURAL – GAS

The Neural – Gas (NG) algorithm (Martinetz, et al., 1993; Antonakakis, et al., 2019; Antonakakis, et al., 2020) is a self-organizing neural network designed for clustering and serves as an efficient approximation technique for vector quantization, offering a topology-preserving alternative to traditional methods such as k-means. The NG algorithm maps high-dimensional input vectors $\{v_1, \dots, v_V\}$ to a finite set of representative codebook vectors (or prototypes) $\{w_1, \dots, w_M\}$, where M is the number of representative symbols (i.e. M number of clusters), forming a codebook. It iteratively adapts a set of vectors $\{w_1, \dots, w_M\}$ to capture the structure of the input dataset $\{v_1, \dots, v_V\}$. The first step is to assign initial random values to prototype vectors w . At each iteration, the distance between each input vector v and all codebook vectors is computed, and then the codebook vectors are ranked according to their distance to v . At each iteration, compute the distance between a vector v and all codebook vectors, then rank the codebook vectors according to their distance to v . Each codebook vector w_i is then updated according to the following rule:

$$\Delta w_i = \epsilon e^{-k_i/\lambda} (v - w_i) \quad (3.21)$$

where,

- k_i is the rank of w_i with respect to its distance to v , $k = 0, \dots, M - 1$,
- ϵ is the learning rate,
- λ is the neighborhood parameter, controlling how broadly the update affects the neurons.

This process allows a relatively small set of M codebook vectors to efficiently represent a much larger high-dimensional dataset, while preserving essential structural information. The distortion error (DE) quantifies the normalized reconstruction loss, serving as a key metric for evaluating the quality of vector quantization. As M increases, DE typically decreases, indicating a closer approximation to the original data distribution. The distortion error is expressed as:

$$DE = \frac{\sum_{t=1}^N \|v(t) - v_{rec}(t)\|^2}{\sum_{t=1}^N \|v(t) - \bar{v}\|^2} \quad (3.22)$$

where,

- $\bar{v} = \frac{1}{N} \sum_{t=1}^N v(t)$ is the mean of all input vectors,

- N is the total number of data points, computed as the number of timestamps T multiplied by the number of subjects in the group.

This process continues until the DE falls below a predefined threshold, ensuring convergence toward an optimal reconstruction and consequently improving the quality of the encoding. Upon completion of the process, the optimal number of clusters is determined, and the output of the NG algorithm is the symbolic time series (STS), consisting of symbols $1, \dots, M$.

3.4.4 COMPLEXITY INDEX

The Complexity Index (CI) (Janson, et al., 2004; Antonakakis, et al., 2019) of a sequence is defined as the sum of the numbers of all distinct substrings (also referred to as subwords) present in a string, considering subwords of lengths $l = 1, \dots, n$, where n denotes the maximum subword length. In the present study, the CI for the STS generated by the Neural Gas algorithm is given by:

$$CI(STS) = \sum_{l=1}^n c^l(STS) \quad (3.23)$$

where $c^l(s)$ denotes the complexity function of a string s , defined as the number of distinct substrings of length l . For example, consider the sequence $s = "A B A B A C"$:

- For $l = 3$, $c^3(x) = 3$, corresponding to the three distinct substrings: "ABA", "BAB", and "BAC".
- For $l = 5$, $c^5(x) = 2$, corresponding to the two distinct substrings: "ABABA" and "BABAC".

A low complexity index indicates a sequence with many repeated substrings, while a high complexity index reflects diverse, information-rich strings with minimal repetition. For instance, consider the two sequences, $s_1 = "A A A A"$ and $s_2 = "A B A D"$, for which the complexity indices are $CI_1 = 3$ and $CI_2 = 8$ when $n = 3$, respectively. Furthermore, to facilitate the comparison of sequences of different lengths, the complexity measure is normalized by dividing it by the mean complexity computed from a set of random sequences of the same length, where each symbol appears with equal probability.

CHAPTER 4: METHODOLOGY AND RESULTS

4.1 EXPERIMENT SETUP

Three mTBI subjects (3 male, average age 25.6 ± 9.2) and three orthopedic controls (2 male, 1 female, average age 28.6 ± 7.2). The orthopedic control group consisted of individuals with minor orthopedic or extremity injuries who did not sustain head injury. The table below provides general information about the subjects, including gender, age, details about the injury, and recording dates. Data collection took place at the Huntington Medical Research Institutes (HMRI) in Pasadena, CA, USA. Exclusion criteria for the study included a personal history of neurological or psychiatric illness, serious medical condition, and drug or alcohol addiction. The study protocol was approved by the appropriate institutional review boards at HMRI and the University of Houston, and written informed consent was obtained from all participants in the study.

Approximately 5 minutes of continuous EEG and MEG resting-state activities were obtained while the subjects' eyes were closed. The dry electrode EEG system (Wearable Sensing, San Diego, CA) consists of 21 channels for EEG and two additional channels to record electrooculogram (EOG) and electrocardiogram (ECG) activity to monitor eye and cardiac artifacts. The sampling rate for EEG was 300 Hz. The CTF MEG system (MEG International Services Ltd., Coquitlam, BC, Canada) was comprised of 66 axial gradiometer sensors and 31 additional channels that can be used for noise reduction. Data were collected at a sampling rate of 625 Hz and bandpass filtered between 0.1–200 Hz using hardware. The anatomical characteristics of the subject were included at T1-weighted (T1w) MRI sequences scanned by a Siemens MAGNETOM Prisma 3T scanner.

In the current study, data for the three mTBI subjects were collected at two separate visits: two weeks and one month after the injury occurred. For the Orthopedic Control subjects, data collection was conducted during a single visit, within a range of one day to two weeks after the injury occurred. As shown in the table below:

Table I. General Information for mTBI and Orthopedic Control subjects.

mTBI/OC	Gender (Age)	Location	Injury		Recording Dates	
			Type	Date	mTBI	
					Two Weeks	One Month
mTBI_1	Male (18)	Head left front	Motorcycle	20/11/2014	03/12/2014	22/12/2014
mTBI_2	Male (36)	Head right side	Fall on concrete	09/01/2015	23/01/2015	10/02/2015
mTBI_3	Male (23)	Head right front	Car accident	17/11/2014	01/12/2014	15/12/2014
OC_1	Female (37)	Right forearm	Fall on floor	03/02/2015	04/02/2015	
OC_2	Male (25)	Right ankle	Basketball	08/02/2015	11/02/2015	
OC_3	Male (24)	Left knee, thigh	Motorcycle	10/03/2015	24/03/2015	

4.2 PREPROCESSING

The preprocessing steps are executed using the high-level FieldTrip toolbox in MATLAB (Oostenveld, et al., 2011), which is an open-source software for analyzing the EEG and MEG data. The preprocessing outcome is three minutes of artifact-free EEG and MEG activities. Firstly, the MEG data are downsampled to make them comparable with the EEG data, as the later have lower sample frequency at 300 Hz, using the function *ft_resampleddata*. The first steps involve applying a 5th-order band-pass Butterworth filter ranging from 0.5 to 100 Hz to retain the frequency of interest, a Notch filter for elimination the power line noise at 60 Hz and re-reference of EEG data to common average reference using the *ft_preprocessing* function. Additionally, the visual inspection and rejection of the bad channels for each modality are performed using *ft_databrowser* and *ft_rejectvisual* (Figure 4. 1 and Figure 4. 2). The former function displays all channels in a chosen view mode, allowing the detection of bad channels that are characterized by abnormal amplitude fluctuation and the latter provides a visual means to investigate the bad channels as outliers by identifying them using metrics like z-value, kurtosis and variance. Subsequently, performing ICA with the *ft_componentanalysis* and selecting the number of components in order to retain useful information of the data equal or greater than 95%. Divide the 3 min components, including EOG and ECG signals into 0.5 second segments. If a component has a mean segments absolute correlation value equal or greater than 50% with EOG or ECG signal, it is characterized as artifact. If a component label as an ocular artifact, EMD is applied in segments of 10 seconds. For each segment, we preserve the minimum intrinsic mode functions where their back projection signal has an absolute correlation value equal or greater than 55% of initial component segment (Figure 4. 3). For each IC, we calculate the metrics kurtosis, skewness and root mean squared value of Shannon and Rényi entropy, generating a vector with component values for each metric. Then, we compute the absolute value of the z-score for each metric vector. If any component's absolute z-score exceeds a value of 2, is considered as an artifact and is removed from the vector. This process is repeated until all remaining values fall below the threshold of 2. Finally, the ocular-free components and the non-artifact components are back projected to generate the clean EEG or MEG data.

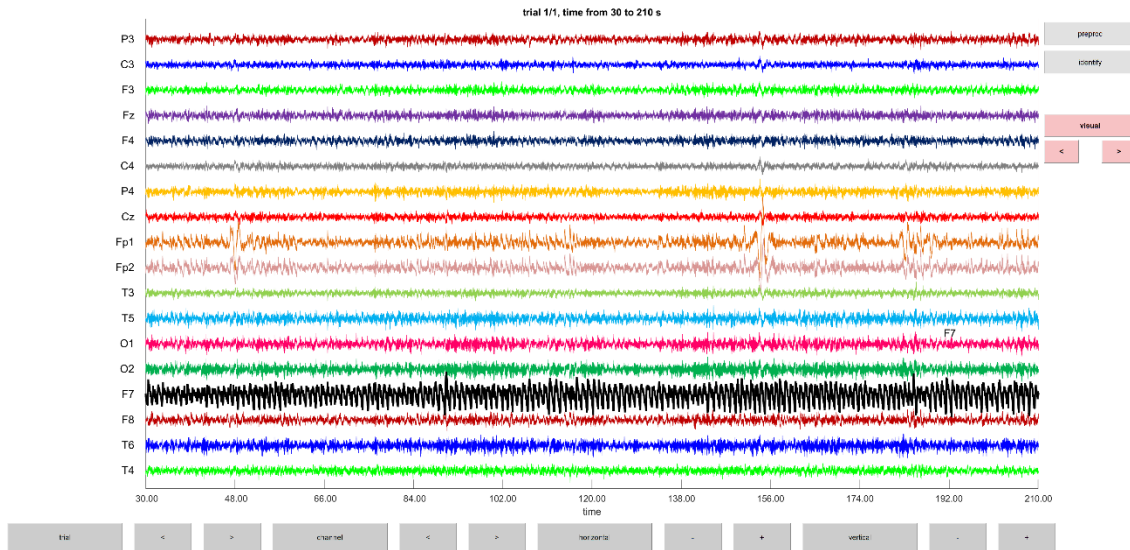


Figure 4. 1: Visual detection of the bad channel F7 at EEG data, which has abnormal amplitude fluctuation, using the ft_databrowser.

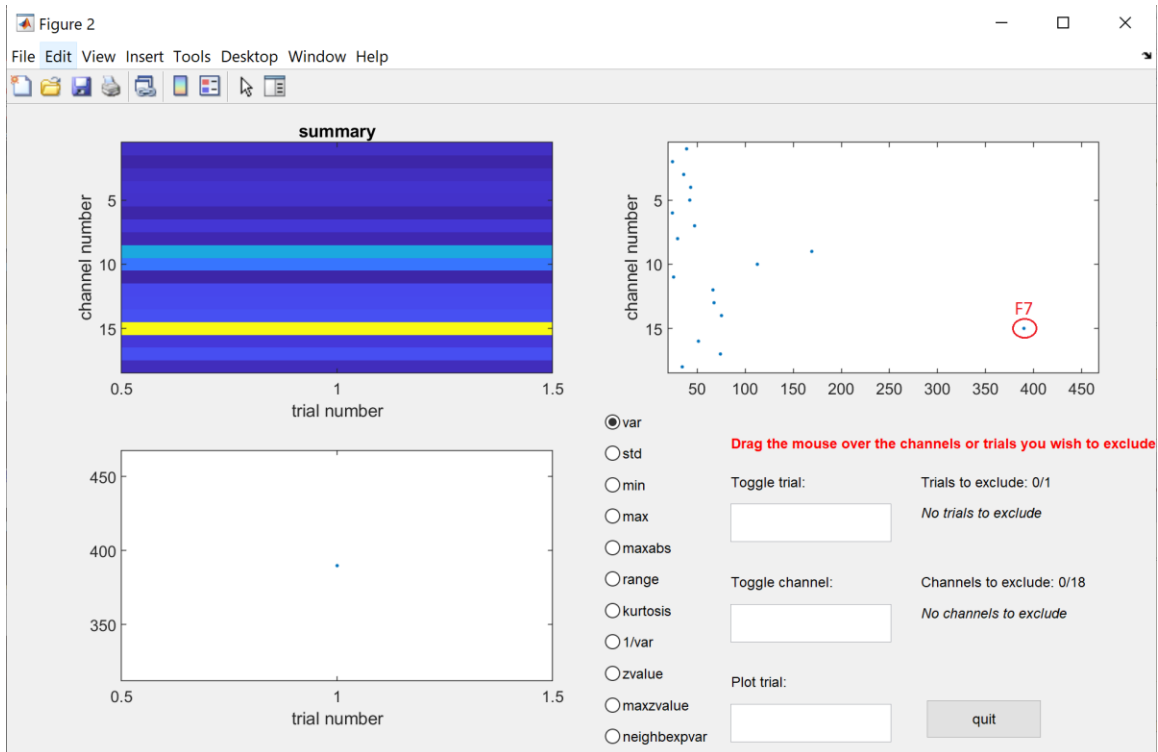


Figure 4. 2: Visual inspection and rejection of the bad channels (e.g., the bad channel F7) with the metrics z-value, kurtosis and variance using the ft_rejectvisual.

Empirical Mode Decomposition

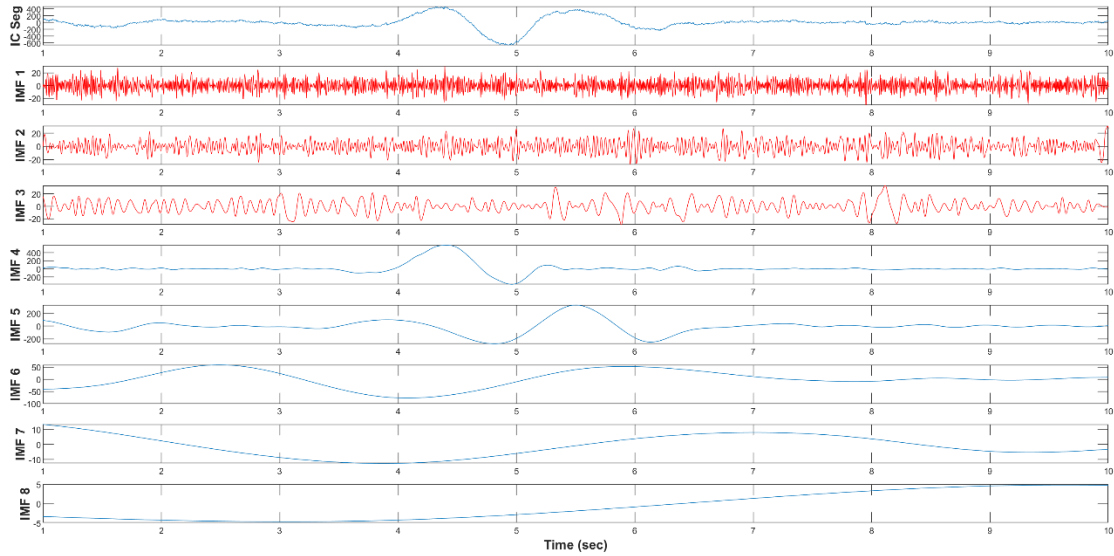


Figure 4. 3: Applying EMD to the segment of independent component (first row), which labeled as ocular artifact. The three first IMF 1-3 (shown in red) are then utilized to back-project the ocular-free artifact signal.

4.3 SOURCE ANALYSIS

This section focuses on extracting resting-state brain activity for each subject in the study, and for each visit in the case of mTBI subjects by applying source analysis on EEG and MEG data. The source analysis comprises two main steps (Figure 4. 4): the forward and the inverse solutions. The former computes the lead-field, which is a requirement for the inverse solution, using the head model, source model, and the positions of electrodes or sensors as inputs. In this study, the realistic head model is constructed using the FEM with hexahedral elements and consists of five compartments (skin, skull, CSF, gray matter, and white matter), each assigned a predetermined conductivity value. A Venant source model (Vorwerk, et al., 2014; Munck, et al., 2012) with a 3 mm resolution is simulated at the center of the gray matter compartment using the SimBioInterface package (Wolters, et al., 2007). Finally, the inverse solution uses the 3-minute artifact-free EEG or MEG data and the corresponding lead-field as inputs in order to extract the brain activity. The LCMV beamforming method is employed to solve the inverse problem and compute the power at each source point by optimizing weights assigned to sensor signals under specific constraints, with a regularization parameter λ set to 5 per cent.

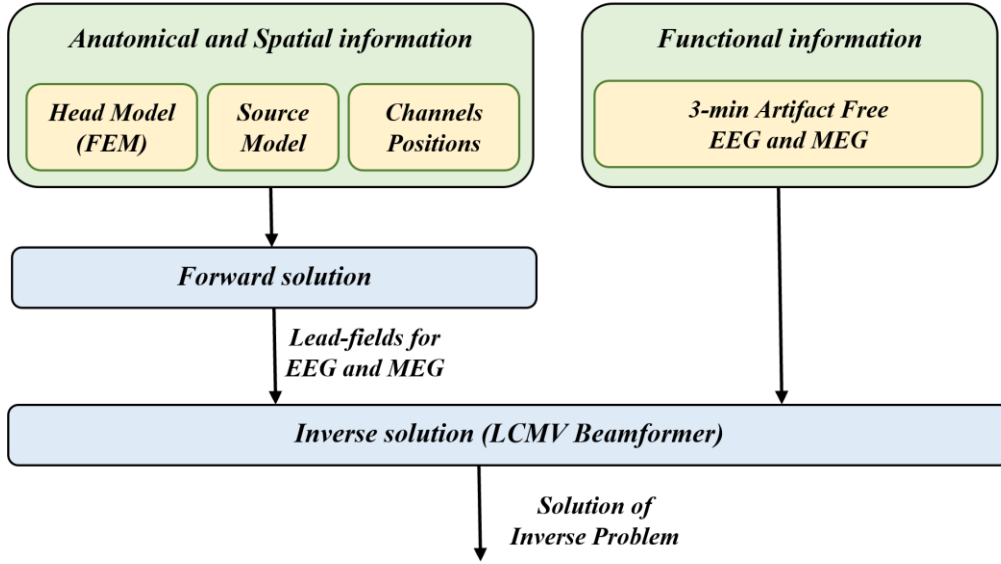


Figure 4. 4: Schematic representation of the source localization process in our implementation, illustrating the key steps and methodologies involved in mapping neural activity.

4.3.1. FORWARD SOLUTION

The production of the lead-fields for EEG and MEG is achieved for each subject by solving the forward problem, which requires the head model, the source space, and the channel positions as input. The solution to the forward problem was accomplished using a combination of Windows and Linux operation system, MATLAB R2020a along with open-source software tools. Facial features were removed from the MRI data to preserve participant anonymity. The first step of the pipeline is to compute the head model, which will consist of a five- compartments mesh (scalp, skull, cerebrospinal fluid (CSF), white and gray matter (WM & GM)). These compartments are derived from T1w MRI sequences. In the Windows environment using the high-level FieldTrip ver. 20210311 (Oostenveld, et al., 2011), along with the software toolboxes SPM12¹ as external tool of FieldTrip and the CAT12 (Gaser, et al., 2024), which is an extension to SPM12. First, using FieldTrip functions, the T1-weighted sequences were read with *ft_read_mri*, and their visualization was done with *ft_sourceplot*, in order to verify that they are correctly loaded.

¹ fil.ion.ucl.ac.uk/spm/

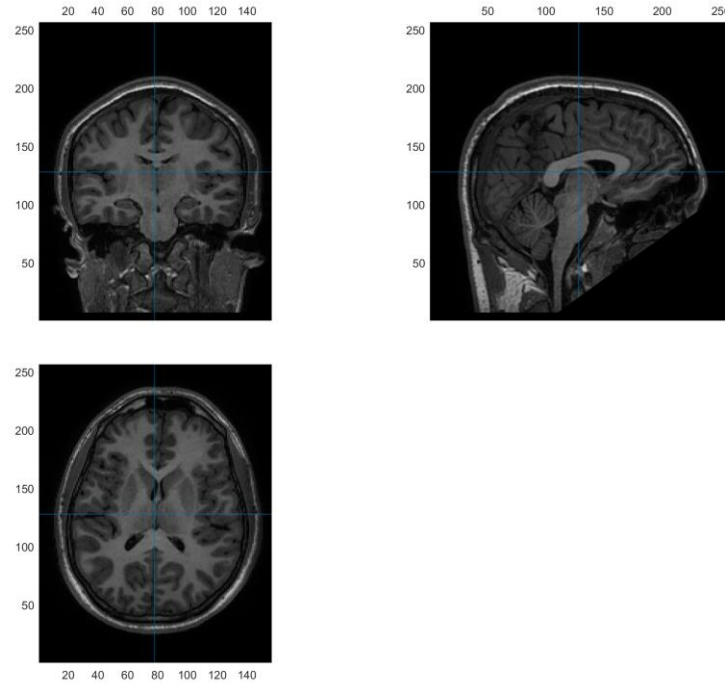


Figure 4. 5: The illustration of T1-weighted sequences with the FieldTrip function *ft_sourceplot*. To ensure subject anonymity, facial features were removed from the MRI.

The CAT12 takes T1w images and a default tissue probability map (TPM) as template input for initial spatial registration and segmentation. It is set to extract the segmented compartments of CSF, GM and WM and the anatomical brain regions with the Automated Anatomical Labelling 3 (AAL3) atlas (Rolls, et al., 2020). This study focusses on main brain tissue compartments and thus excludes the areas of Cerebellum, Vermis and deep brain areas such as Thalamus, resulting in the selection of the first 94 out of the 170 regions in AAL3 for further analysis.

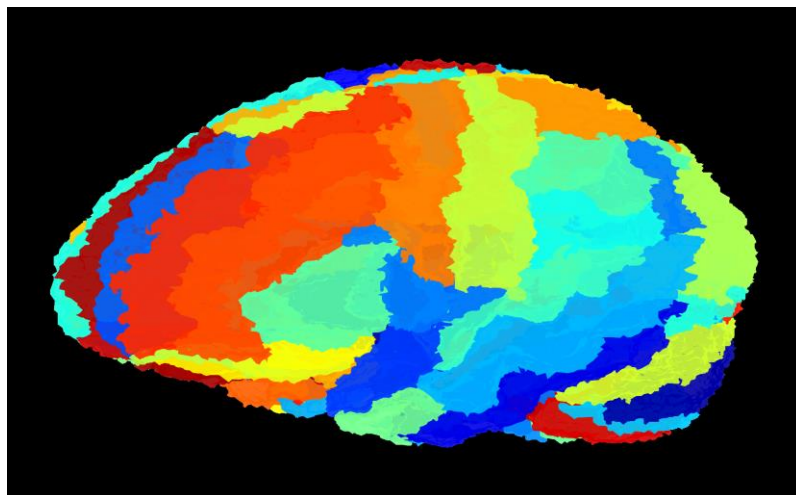


Figure 4. 6: Anatomical Brain Regions from AAL3 Atlas.

Returning to FieldTrip with SPM12, the function *ft_volumesegment* is called with the parameters *spmversion* set to *spm12*, *scalpsmooth* equal to 1, and *scalpthreshold* set to 0.05 in order to compute the scalp compartment. The *ft_volumesegment* function is then called again to extract the skull and brain compartments, where the brain consists of CSF, GM, and WM. The parameters used for *skullthreshold* are 0.10 and *skullsmooth* is equal to 3. Note that the values for the thresholds and smoothing parameters may vary from subject to subject. Afterwards, assessments are conducted on the segmented scalp for any unrealistic holes and on the brain region for any tiny unrealistic spots located in the central area. Appropriate measures are then taken to fill the identified holes and to remove the unrealistic spots. Then, each of the six compartments (scalp, skull, brain, CSF, WM, and GM) is converted into binary masks, and their combination is performed carefully to ensure there is no overlap between them. It is important to note that the brain mask is used exclusively for evaluation purposes and must encompass CSF, GM, and WM. Finally, a numerical label is assigned to each compartment, resulting in the creation of the final mask, as illustrated in the figure below.

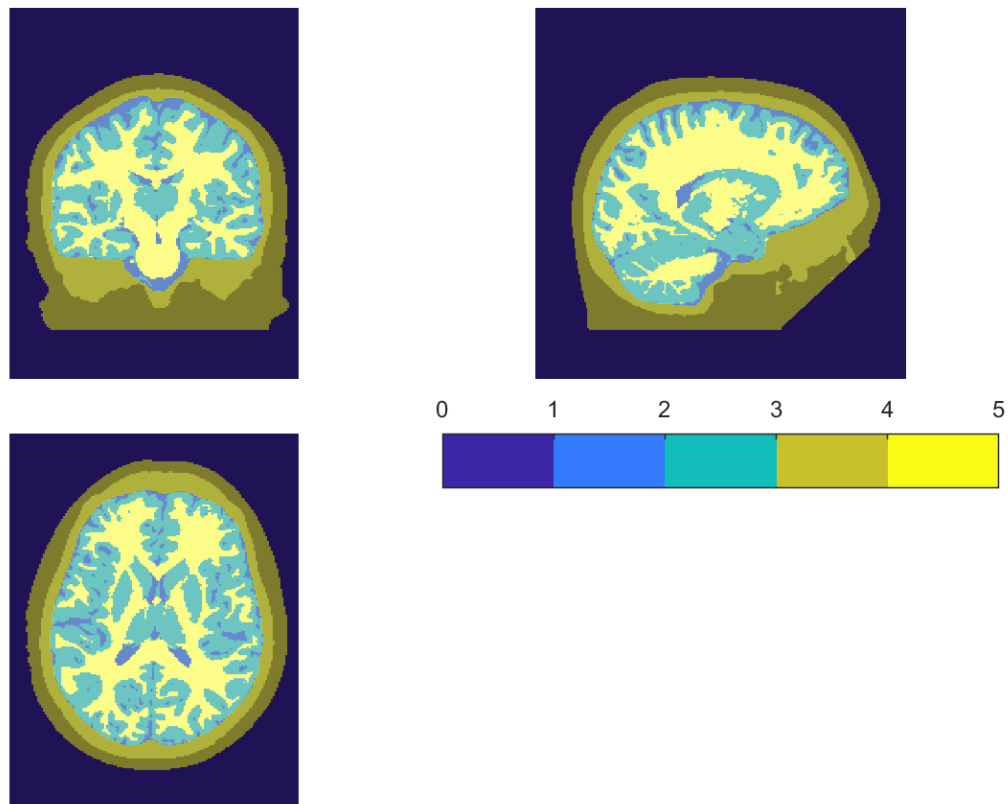


Figure 4. 7: The final mask with numerical labels: 5 for scalp (yellow), 4 for skull, 3 for CSF, 2 for GM, 1 for WM, and 0 for background (dark blue).

The *ft_prepare_mesh* function generates a mesh (Figure 4. 8) from the final mask, which is constructed using the FEM with hexahedral elements. The parameter *method* is set to *hexahedral*, the resolution is set to 1 mm and the shift is set to 0.3 mm. The final steps in preparing the mesh and the AAL3 atlas involve realignment and reslicing. For realignment, three fiducial points are required, which correspond to the anatomical landmarks nasion (NAS), left pre-auricular point (LPA) and right pre-auricular point (RPA) points. The function *ft_volumerealign* is used with the T1w images as input, setting the parameter *method* to *interactive* and *coordsys* to CTF. The fiducial points are then extracted interactively. Subsequently, the mesh and the atlas are realigned to these points in order to conform to the CTF coordinate system, where the sensor and the electrode positions are expressed. Finally, the data are resliced using *ft_volumereslice* to ensure homogeneous voxel sizes, meaning that the voxel dimensions are consistent in all directions. Realignment of the electrodes with the mesh is performed if they are not properly aligned, with the function *ft_electroderealign*. In our case, the MEG system is by default set at CTF coordinate system. The Figure 4. 9 points out the alignment of MEG sensor and electrodes with the anatomical structure of the mesh.

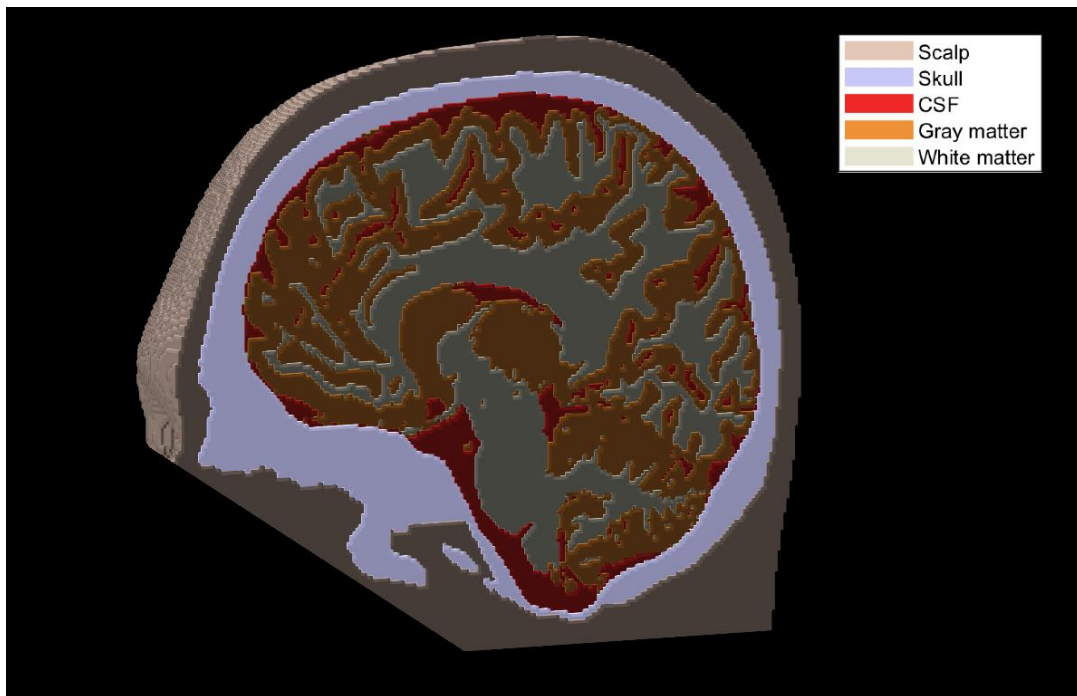


Figure 4. 8: The five compartments mesh (scalp, skull, CSF, white and gray matter)

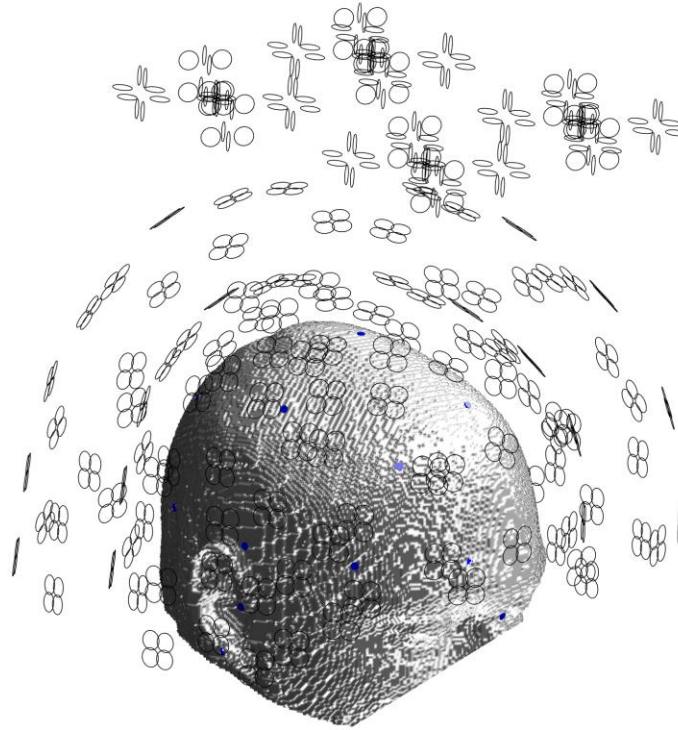


Figure 4. 9: Spatial visualization of the mesh with magnetometers (black circles) and electrodes (blue discs).

Then, in the Linux environment, the toolboxes FieldTrip (Oostenveld, et al., 2011) and SimBioInterface (Wolters, et al., 2007) were used to solve the EEG and MEG forward problem and compute the EEG and MEG lead-field matrices, for each subject. To compute the solution to the forward problem, three prerequisites are required: the source space (or source model), the positions of sensors or electrodes, and the head model. The lead-field matrix represents how each source, located at a point in source space, contributes to the observed measurement (i.e., at electrodes or sensors). These requirements must all be expressed in the same coordinate system and units, in our case, CTF and millimeters, respectively. The alignment of EEG electrodes, MEG sensors, and T1-weighted MRI sequences to the CTF coordinate system is explicitly described in the previous paragraph. If unit conversion for sensor or electrode positions is needed, it can be done using the *ft_convert_units* function. SimBioInterface requires the mesh (i.e. head model) in VISTA format, which can be converted from MAT format using the *ft_write_headshape* function. The source space is simulated by using the SimBioInterface with the Venant condition, meaning that each source node is appropriately situated within the gray matter compartment. For each subject, a 3 mm resolution source space in the center of the gray matter compartment was constructed. Finally, the realistic head model's conductivity values were set as follows: 0.41 S/m for the scalp, 0.048 S/m skull, 1.71 S/m for the CSF,

0.47 S/m for the grey matter and 0.22 S/m for white matter (McCann, et al., 2019). The MEG lead-fields were computed for the magnetometers. To convert it to the gradiometers, the transformation matrix in the sensor structure was used. In this study, the algebraic multigrid preconditioned conjugate gradient (AMG-CG) solver applied to robustly and efficiently resolve the large-scale sparse linear systems generated by the finite element discretization of the EEG/MEG forward problem. After the computation of the lead-fields, the pipeline continues in the Windows environment.

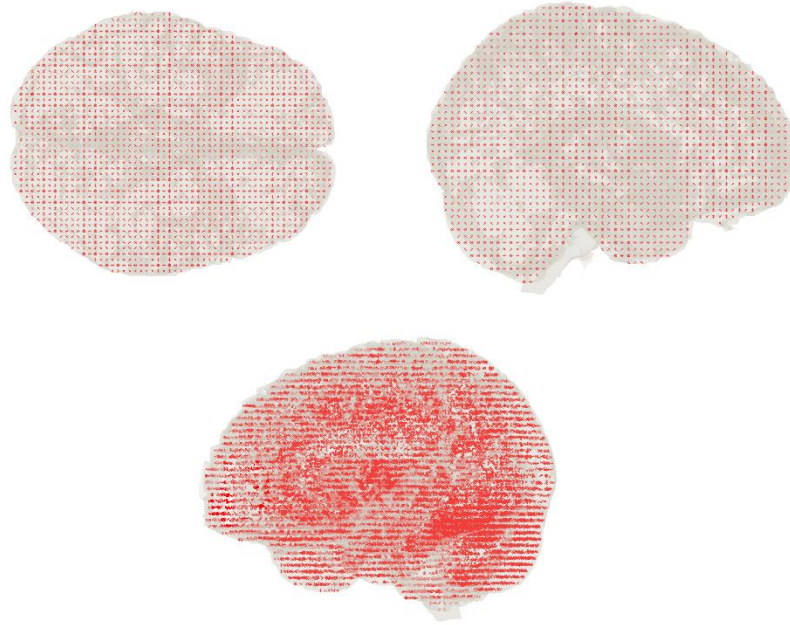


Figure 4. 10: The source model is represented by red dots located at the center of the gray matter.

4.3.2. INVERSE SOLUTION

In this study, the Linear Constraint Minimum Variance (LCMV) beamformer localization method is employed to reconstruct the resting-state source activity of EEG and MEG signals. To perform LCMV beamforming, *cfg.method* is set to 'lcmv' in the *ft_sourceanalysis* function, which takes as input the 3-min artifact free EEG or MEG data, the source model and the corresponding lead-field. With the option *cfg.lcmv.keepfilter* set to 'yes', the spatial filter is retained in the output source structure for further analysis and interpretation of MEG or EEG data within the FieldTrip framework. A small regularization parameter λ is set to 5 % in *cfg.lcmv.lambda* to regularize the covariance matrix used in the beamforming process. The information about the source space is entered into the function using the parameter *cfg.sourcemodel*, which includes the fields pos (the position of each source) and inside (a boolean value indicating whether a grid point is within the brain).

Additionally, the information from the lead-field is provided in *cfg.sourcemodel.leadfield*. If bad channels have been removed during the preprocessing steps, the same channels/rows must also be removed from the lead-fields. Since the realistic head model information is included in the lead-field, a single sphere head model is created using the *ft_prepare_headmodel* function to satisfy the function's check conditions. This model is then provided as input to *cfg.headmodel*. In order to run *ft_sourceanalysis*, the data must be converted into a FieldTrip structure using *ft_timelockanalysis*. Additionally, by setting *cfg.covariance* to 'yes', the covariance matrix is computed, which is essential for the LCMV beamformer.

4.4 DYNAMIC FUNCTIONAL CONNECTIVITY

After computing the source activity, the objective is to identify the source points corresponding to each region in the AAL3 atlas. For each region, the closest points in the source space that correspond to these anatomical regions are identified. The number of source points associated with each region varies based on the size of the region. Specifically, larger regions tend to encompass multiple points, while smaller regions may correspond to a minimum of one point. The *ft_prepare_mesh* function, with the method set to 'isosurface', creates a triangulated surface mesh for each region. For every triangle in the surface mesh, the center point is determined by calculating the k-means clustering on the positions of the three vertices. This step represents each region of AAL3 atlas in the space using the triangle centers. Subsequently, the corresponding source space for each region is computed by extracting the points from the k-nearest neighbors (kNN) searches between the triangle centers and the source space.

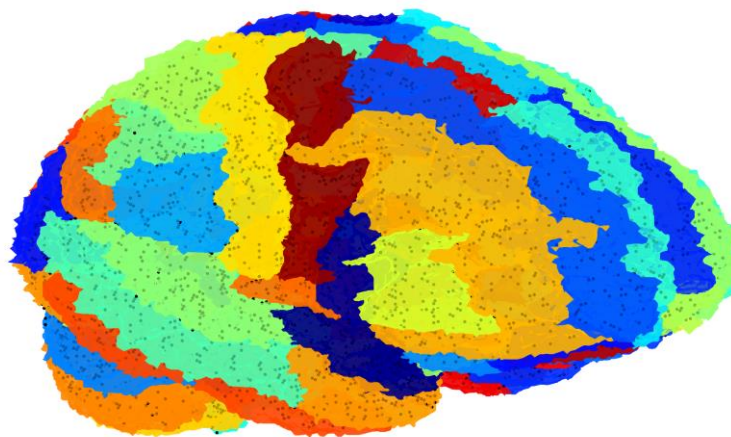


Figure 4. 11: AAL3 regions with their corresponding source spaces (black dots).

To summarize, each atlas region is characterized by a subset of the source space, where each point generates brain activity computed using LCMV beamforming. These subsets may consist of different numbers of source points. In order to preserve a more accurate representation of brain activity in each region, the representative virtual channel activity (Antonakakis, et al., 2020) is calculated by interpolating functional activity from the source space time series. For each atlas area, the distance correlation matrix is derived by calculating pairwise distances between source space activities using a correlation-based distance measure. The resulting weighted vector, obtained by summing the columns of the distance correlation matrix, is normalized so that its components sum to one. This weighted vector indicates how each source point's activity contributes to the virtual channel that records the brain activity of this region. Therefore, the representative time series is calculated as the sum of the element-wise multiplication between the weighted vector and the region's source space time series. The representative point among the source space points of the region is the one whose activity has the maximum power spectral density. In the rare case of a very small region with only one source point, the representative activity corresponds directly to the brain activity at that point.

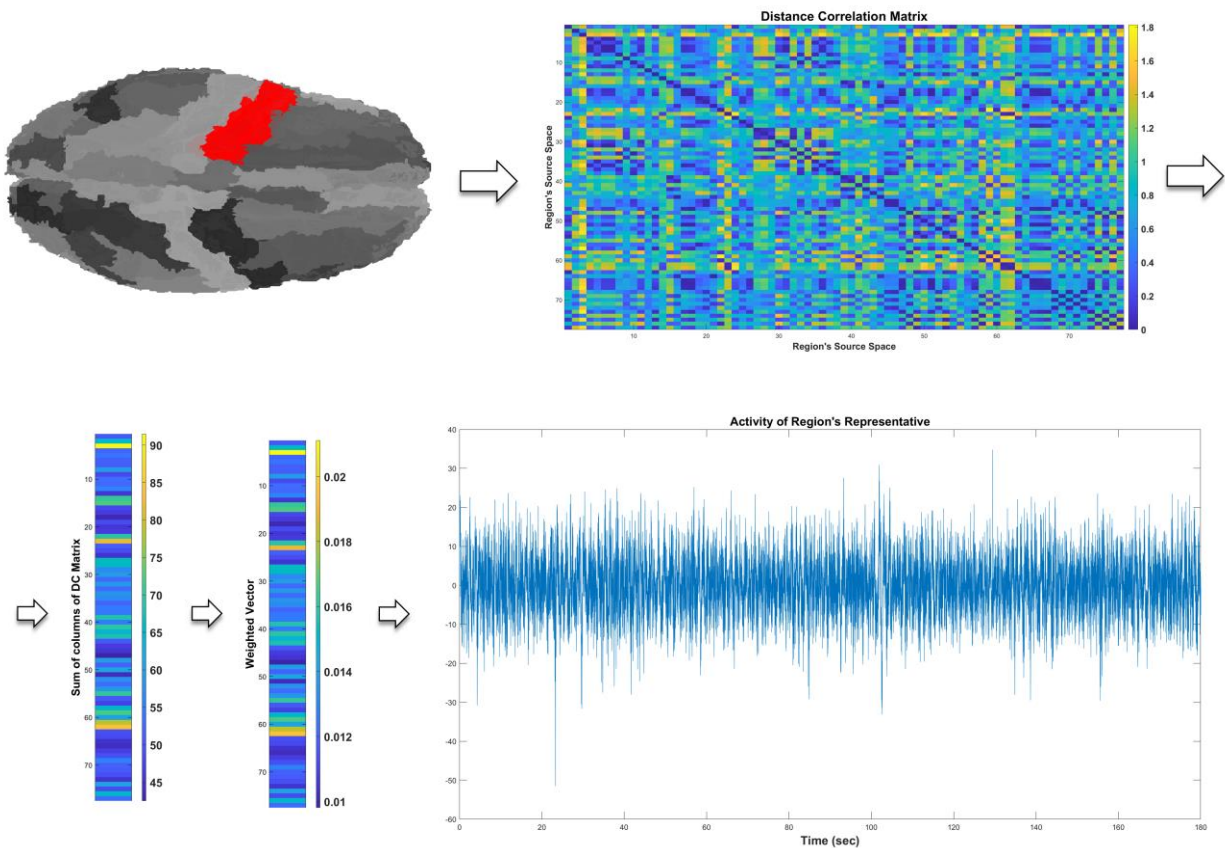


Figure 4. 12: The steps for calculating the representative virtual channel activity from the red atlas region.

The representative time series are then divided into three frequency bands. These investigated frequencies bands are δ (0.5–4 Hz), θ (4–8 Hz) and α (8–13Hz). This process is performed using the function *ft_preprocessing*, applying a 4th-order band-pass Butterworth filter. In the present study, Dynamic Functional Connectivity Graphs (DFCGs) were calculated separately for each frequency band. The dynamic aspect was achieved by dividing the three-minute data into a series of shifted, overlapping windows. The window length for each temporal segment (or timestamp) was set to 4 seconds, with a 30% overlap for each frequency band, resulting in 63 sliding windows (i.e. timestamps) for each band. As an estimator of functional connectivity, the correlation between pairs of Atlas Regions of Interest (ROIs) time series, extracted via the Hilbert transform, was computed for each timestamp. This procedure examines the time-varying changes in amplitude-to-amplitude interactions, capturing how the relationships between the amplitude envelopes of time series fluctuate over time, revealing dynamic shifts in functional connectivity across different brain regions. Topological filtering was applied to enhance the robustness and interpretability of the functional connectivity network by preserving meaningful connections while reducing noise and irrelevant information. Orthogonal Minimal Spanning Trees (OMST) were utilized to highlight the most dominant paths within each FCG. Subsequently, the degree of the graph for each ROI at each timestamp was calculated by summing the values in each row of the FCG. The image below provides a visual representation of the described procedure for a specific frequency band, detailing the sequential steps involved in calculating the degree for each timestamp and each Atlas ROIs.

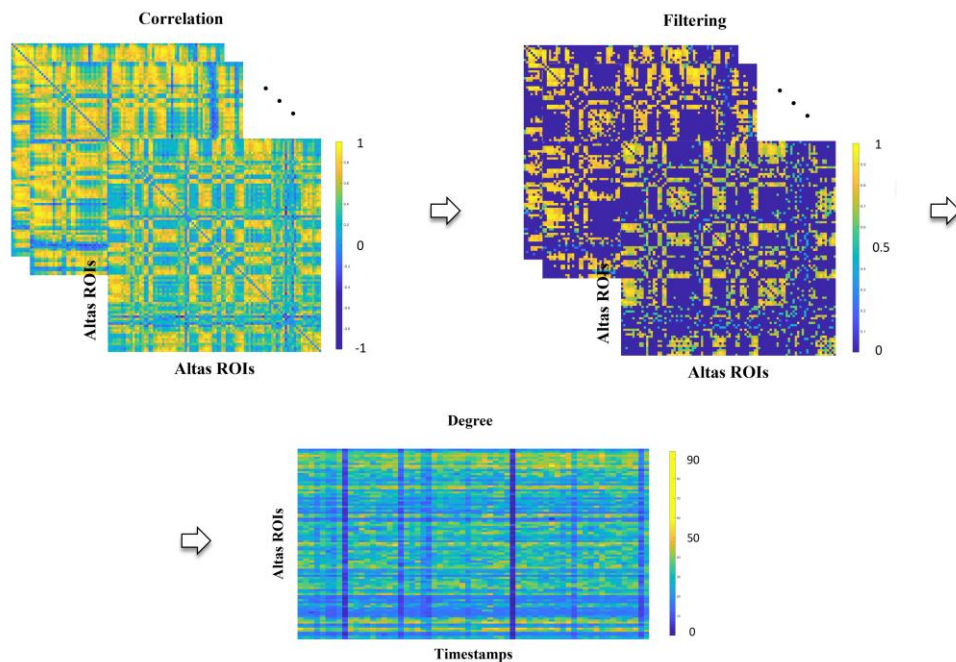


Figure 4. 13: A visual representation of the degree calculation process for a specific frequency band. From left to right, the sequential steps include calculating the Dynamic Functional Connectivity Graphs, applying topological filtering with OMST, and determining the degree of the graph for each ROI at each timestamp.

At this stage, for each subject and frequency band, the functional connectivity graph (FCG) degree is computed for each ROI at every timestamp, resulting in a degree matrix of dimensions [ROIs x TimeStamps]. In this study, the data are organized into six groups, three for each modality, with each group consisting of three subjects, as detailed in the table below.

Table II: The six distinct groups included in this study, each consisting of three subjects.

Groups	Modality	Subjects-Visits
1	EEG	mTBI 2nd week
2		mTBI 4th week
3		Orthopedic Control
4	MEG	mTBI 2nd week
5		mTBI 4th week
6		Orthopedic Control

For each group and frequency band, the Neural Gas (NG) algorithm is applied to a two-dimensional array formed by concatenating the degree matrices of all subjects in the group. This results in a concatenated matrix of dimensions [ROIs $\times$ (Timestamps $\times$ SubjectsInGroup)] = [94 x (63 x 3)] for each frequency band. The NG algorithm is applied to capture and compress dynamic connectivity patterns into symbolic forms. This is achieved by projecting the high-dimensional functional connectivity data onto a limited set of representative codebook vectors, enabling the construction of symbolic time series (STS). For each group and frequency band, the parameter k (the number of codebook vectors) is set to a predefined value, and the corresponding reconstruction error (distortion error, DE) derived from the NG algorithm is under 1% for all cases, as shown in Table III. For instance, the STS of EEG, group 1 and band δ consist of k different symbols (1,2,3 & 4).

Table III: For each group and frequency band, a predefined number of codebook vectors (k) is set, and the corresponding distortion error (DE) is computed using the NG algorithm.

Groups	Modality	Frequency Bands					
		δ		θ		α	
		k	DE (%)	k	DE (%)	k	DE (%)
1	EEG	4	0.46	3	0.53	2	0.78
2			0.51		0.47		0.73
3			0.36		0.45		0.54
4	MEG	8	0.61	8	0.75	8	0.75
5			0.64		0.67		0.67
6			0.73		0.68		0.63

Each STS generated by the NG algorithm represents the symbolic sequences of three subjects combined in a single array of size $[1 \times (\text{Timestamps} \times \text{SubjectsInGroup})]$. By segmenting this array, the individual symbolic sequence for each subject is extracted as a separate $[1 \times \text{Timestamps}]$ sequence. To assess the complexity and informational content of the symbolic sequences, the Complexity Index (CI) is computed separately for each subject. This index measures the variety of symbolic patterns in the STS by evaluating the number of unique sub-subwords of different lengths. To compute the CI, the maximum subword length is fixed at 5 for all cases. Normalization was not applied, as all symbolic sequences have identical lengths.

The current steps, which include concatenating the degree matrix, applying the Neural Gas algorithm, and computing the Complexity Index, are illustrated in Figure 4. 14. For each frequency band and subject group, the STS generated by the NG algorithm are illustrated for EEG data in Figure 4. 15 and for MEG data in Figure 4. 16. The corresponding CI values, reflecting the diversity of symbolic patterns, are summarized in Figure 4. 17 and Figure 4. 18.

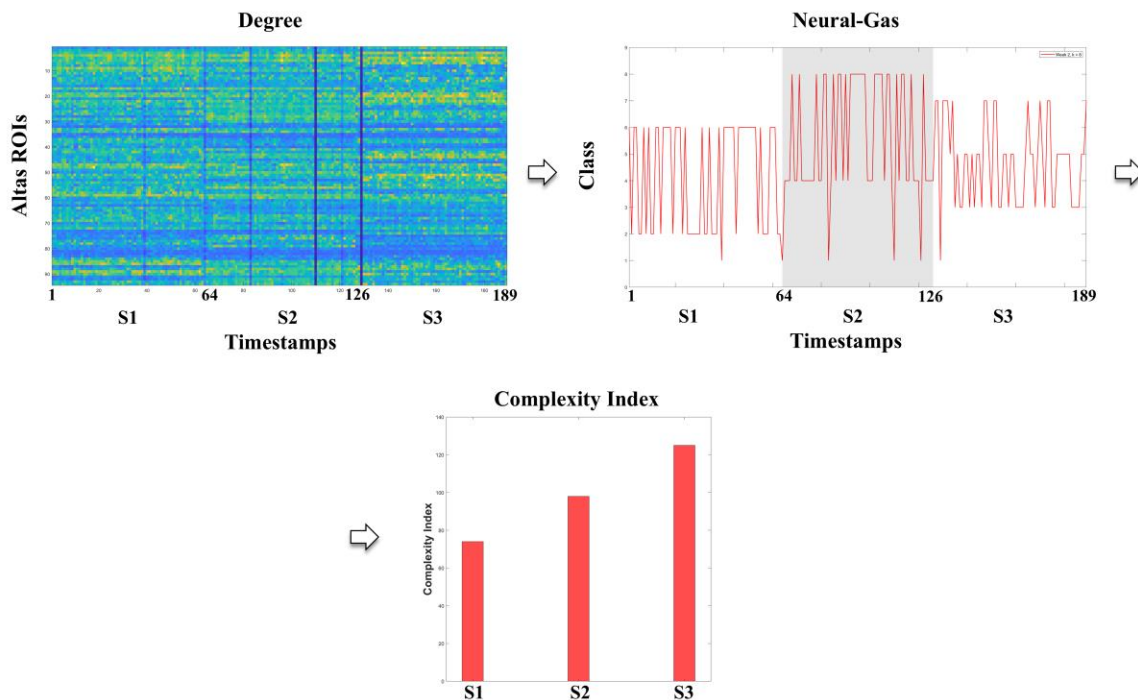


Figure 4. 14: illustrates the sequential steps involved: 1) concatenating the degree matrix, 2) applying the Neural Gas algorithm, and 3) computing the Complexity Index (CI) for a specific group, consisting of three subjects (S1, S2, and S3), and a selected frequency band.

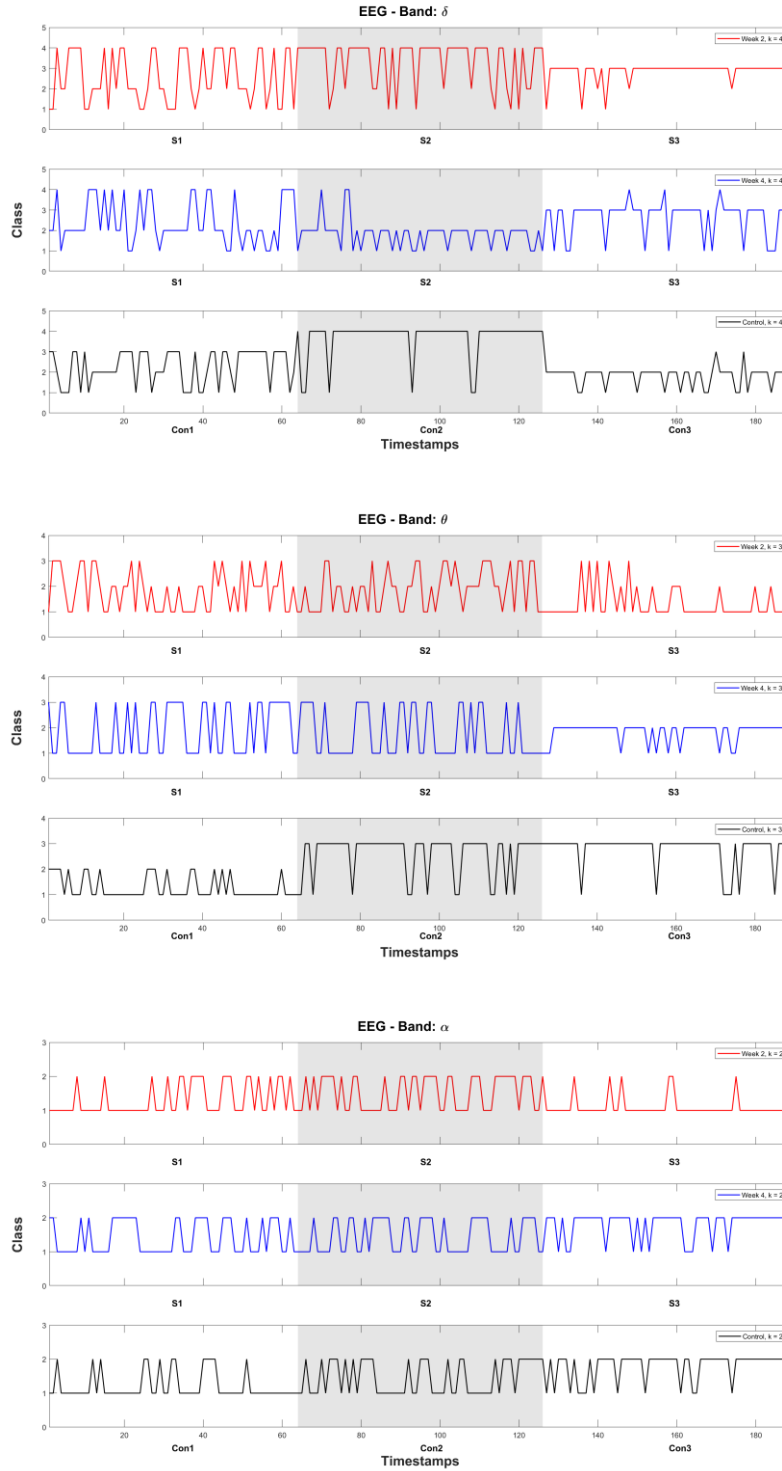


Figure 4. 15: For the EEG modality, this figure displays the symbolic time series generated by the Neural Gas algorithm for each of the three groups (red: mTBI 2nd week, blue: mTBI 4th week, black: Orthopedic Control) and for each of the three frequency bands (δ , θ , α).

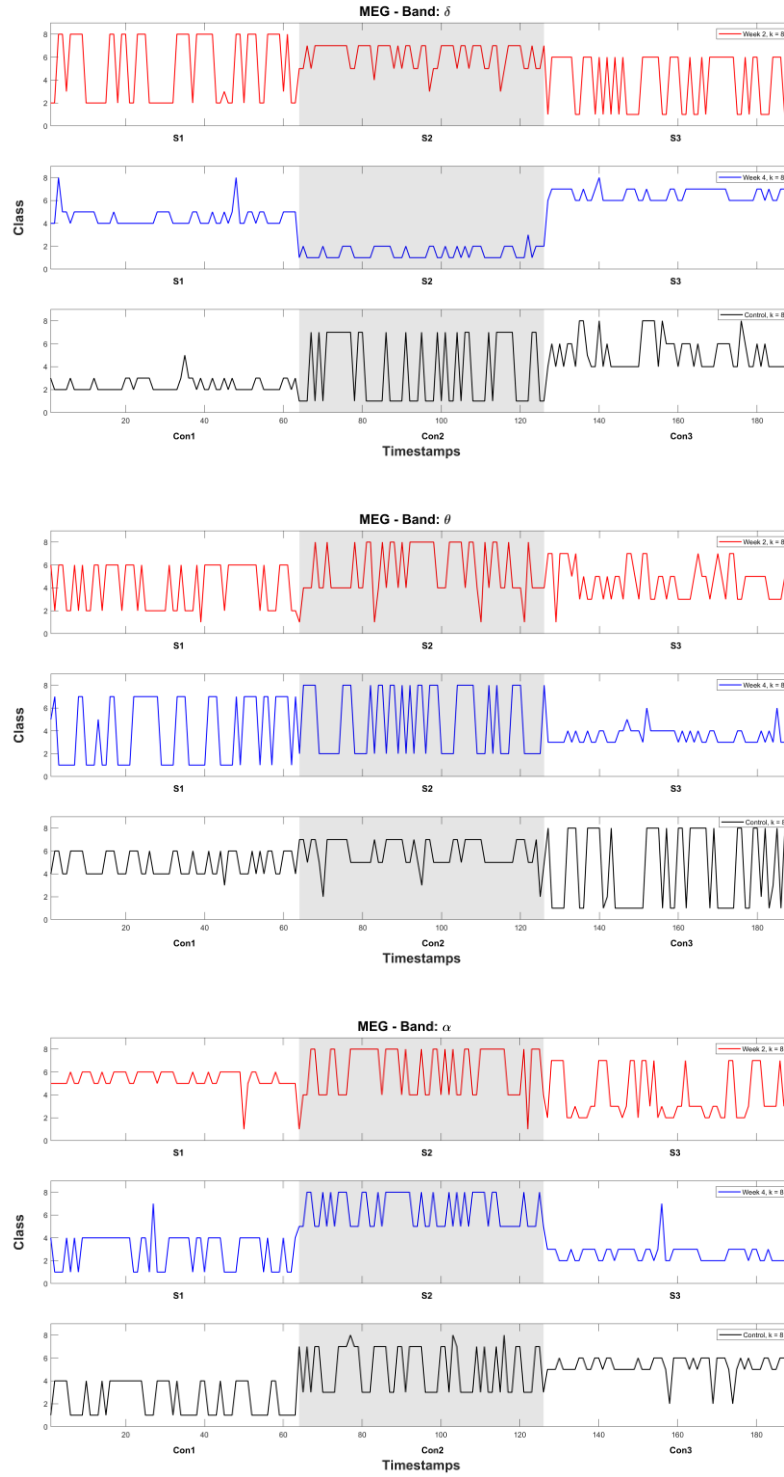


Figure 4. 16: For the MEG modality, this figure displays the symbolic time series generated by the Neural Gas algorithm for each of the three groups (red: mTBI 2nd week, blue: mTBI 4th week, black: Orthopedic Control) and for each of the three frequency bands (δ , θ , α).

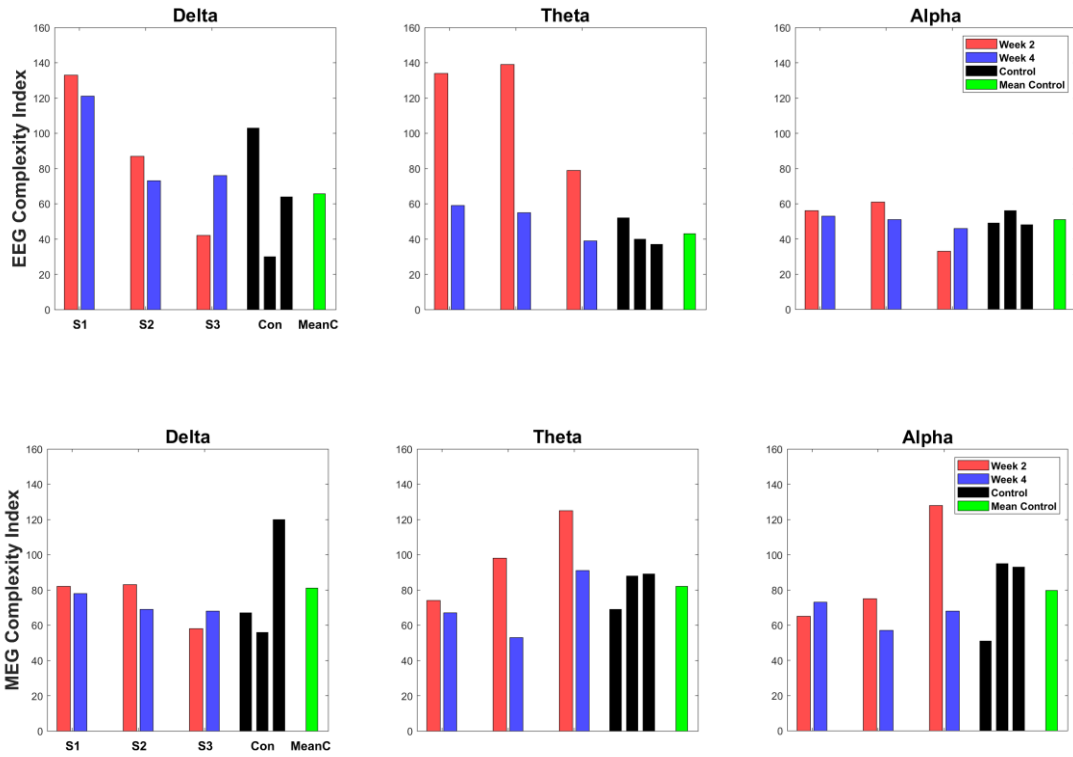


Figure 4. 17: For each frequency band (δ , θ , α), the Complexity Index (CI) is shown for three mTBI subjects (S1, S2, and S3), separated into week 2 (red) and week 4 (blue), and for three Orthopedic Control subjects (black), along with their average CI value (green). Results are presented for EEG data in the upper row and MEG data in the lower row.

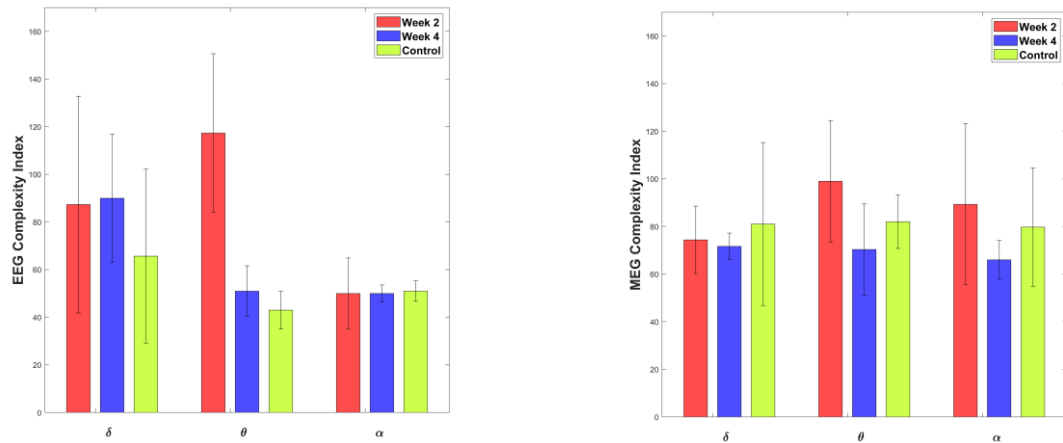


Figure 4. 18: For each frequency band (δ , θ , α), the mean Complexity Index (CI) is presented for mTBI subjects at week 2 (red) and week 4 (blue), as well as for Orthopedic Control subjects (green). Error bars indicate the corresponding variance. Results are shown for EEG data on the left and MEG data on the right.

CHAPTER 5: DISCUSSION AND CONCLUSION

5.1 DISCUSSION

This study developed and applied a personalized, multimodal pipeline to investigate functional brain dynamics during the subacute phase (2 - 4 weeks post-injury) of mTBI, a recovery window that remains relatively underexplored in the literature. The experimental cohort included three mTBI participants and three OC participants. The methodological framework integrated resting-state EEG or MEG data with anatomically realistic, subject-specific head models constructed using FEM. These head models comprised five tissue compartments (scalp, skull, CSF, WM, and GM) each assigned a predetermined conductivity value. This individualized modeling approach significantly improves the spatial accuracy of EEG source localization, enabling more precise analysis of neural dynamics at the source level. Brain activity was computed using an LCMV beamformer to enhance spatial accuracy. For each selected atlas' ROI, representative time series were extracted and filtered into three frequency bands (δ , θ and α), followed by DFC analysis. Functional connectivity was estimated by computing the amplitude envelope correlation between pairs of ROI time series to capture dynamic amplitude-to-amplitude interactions over time. To enhance interpretability, topological filtering was applied using the OMST algorithm. Graph degree was computed for each ROI over time, and the NG algorithm was employed to convert dynamic connectivity patterns into symbolic time series, for each group. Finally, brain activity was assessed using the CI, which quantifies the richness and variability of neural dynamics across frequency bands, enabling the detection of frequency-specific changes associated with injury and recovery. Concerning the thesis findings, three key aspects exist: 1) it examines longitudinal changes in neural complexity within the mTBI groups between weeks 2 and 4 post-injury to track recovery; 2) it compares mTBI at week 4 post-injury to OC participants to assess the extent of functional normalization, serving as an indicator of recovery status and 3) it investigates whether mTBI participants at week 2 post-injury can be distinguished from OC group, highlighting potential early biomarkers of injury.

Regarding the presented pipeline, this study introduces several novel advancements compared to (Antonakakis, et al., 2020). It employs a multimodal approach by utilizing both EEG and MEG data, whereas the previous work relied exclusively on MEG. The construction of realistic, subject-specific head models, which replace the previously used spherical head models, significantly improves the spatial accuracy of EEG source localization. Furthermore, in contrast to the realistic head model produced in (Politof, et al., 2021), the present dataset includes only T1-weighted MRI sequences, as opposed to

the combination of T1-, T2-, and diffusion-weighted imaging. This limitation prevented the segmentation of the skull into its two subcomponents, compacta and spongiosa, and excluded the modeling of anisotropic white matter conductivity. Despite these data constraints, an important methodological improvement lies in the compartment generation process. Specifically, SPM12 is used to segment the scalp and skull, while its extension, CAT12, is employed to generate the remaining compartments: CSF, GM, and WM, in conjunction with the AAL3 atlas, thereby enabling automated and standardized ROIs extraction. Compared to relying solely on SPM12, the integration of CAT12 enables more anatomically precise and computationally efficient segmentation, thereby enhancing both the accuracy and processing performance of the head model reconstruction (Gaser, et al., 2024; Tavares, et al., 2019).

Examining the results in detail, the dynamic changes in CI during the subacute phase of mTBI recovery provide important insights into neural reorganization and the potential for functional normalization over time. Figure 4.17 reveals a reduction in the CI among mTBI participants during the subacute recovery period, with both EEG and MEG data showing a consistent downward trend from week 2 (red) to week 4 (blue) post-injury. This observed decline, most pronounced in the theta band across all subjects and modalities, likely reflects neural plasticity and reorganization of brain networks as recovery progresses. Specifically, for EEG data, a decrease in the complexity index was observed in 2 out of 3 subjects (S1 & S2) in the delta band, all 3 subjects in the theta band, and 2 out of 3 subjects (S1 & S2) in the alpha band. Similarly, MEG data demonstrated reductions in 2 out of 3 subjects (S1 & S2) in the delta band, 3 out of 3 in the theta band, and 2 out of 3 (S2 & S3) in the alpha band. Figure 4.18 further compares mean CI values between mTBI at week 4 post-injury (blue) and OC participants (green) across EEG and MEG recordings. In the EEG data, the mTBI group shows a slightly higher mean CI in the delta band, while theta and alpha band values are comparable between groups. MEG data display a consistently lower mean CI across all three frequency bands in mTBI participants relative to controls; however, these differences remain modest and within a comparable range. Overall, these findings indicate that by week 4 post-injury, CI values across most frequency bands and modalities approach control levels, with minor variations potentially reflecting individual differences or modality-specific sensitivity, indicating a possible normalization of neural network function. These findings align with a prior study by Li et al. (2018), which analyzed MEG data derived from the same dataset using source-level connectivity measures and Granger causality. They observed more and stronger delta-band connections in mTBI patients compared to controls, with similar but less consistent findings in other bands. In contrast to their use of a directed connectivity approach, our use of undirected CI metrics revealed greater sensitivity in the theta band. Moreover, Li et al. reported a decline in group differences over time, and our analysis similarly captures a progressive normalization of brain activity to match the OC levels. This likely reflects a functional reorganization of

brain networks and supports the notion of neural plasticity during recovery, characterized by a general pattern of CI reduction over time, albeit with few exceptions. Together, these findings underscore the value of complexity-based metrics in capturing the evolving neural adaptations underlying recovery, complementing prior connectivity analyses and reinforcing the role of neural plasticity in mTBI rehabilitation.

The following findings explore the potential of theta-band complexity indices as early biomarkers for mTBI-related neural alterations. Our results indicate that the CI in the theta band may serve as a potential biomarker for distinguishing individuals with mTBI from OC participants at an early stage, specifically two weeks post-injury. As illustrated in Figure 4.18, the mean CI for the mTBI group (red) is higher than that of the OC group (green) within the theta band for both EEG and MEG data. Additionally, Figure 4.17 demonstrates consistent results at the individual level, with all three subjects showing this pattern in EEG data, and two out of three subjects (S2 and S3) exhibiting similar trends in MEG data. These observations support the utility of theta-band CI as an early indicator of neural changes following mTBI. Similarly, Antonakakis et al. (2020) reported elevated CI in theta and alpha bands and reduced CI in the delta band in mTBI MEG data shortly after injury, mirroring the patterns observed in our study and underscoring the robustness of CI as a biomarker across different datasets. Complementing these resting-state findings, Arakaki et al. (2018) analyzed task-related EEG data during a working memory paradigm, derived from the same dataset, and reported abnormal alpha-band activity associated with cognitive alterations in mTBI participants compared to controls. In contrast, our study emphasizes theta-band alterations observed in resting-state dynamics. This contrast highlights the complementary value of assessing multiple neural states and frequencies to fully characterize mTBI-related brain alterations. Furthermore, these findings reinforce the potential of EEG as a widely accessible, non-invasive tool for assessing functional brain changes in mTBI, particularly when used in conjunction with the more commonly applied MEG. Furthermore, the systematic review by Allen et al. (2021) reports that increased delta and theta band power and connectivity are frequently observed in individuals with mTBI compared to controls, while alpha band results were mixed. Although the review did not find sufficient evidence to support the clinical adoption of MEG for mTBI assessment due to methodological heterogeneity and limited reproducibility, it still emphasizes that resting-state low-frequency power and connectivity changes across all frequency bands as promising candidate biomarkers. Our study extends this literature by demonstrating that CI, particularly in the theta band, provide a sensitive and potentially more integrative measure of functional brain changes post-mTBI, offering a promising avenue for future biomarker development. Collectively, these results highlight the promise of theta-band CI as a sensitive and integrative metric for detecting early functional brain changes following mTBI, contributing to ongoing efforts in biomarker development.

The present findings suggest that the CI, particularly within the theta frequency band (4–8 Hz), may serve as a promising biomarker for characterizing functional brain alterations and monitoring recovery following mTBI. CI quantifies the richness and variability of neural signals over time, reflecting the underlying dynamical complexity of brain activity. A reduction in CI, consistently observed in the theta band across both EEG and MEG modalities in this study, reflects changes in neural complexity associated with mTBI recovery, indicating a potential neural signature of the healing process. The theta band holds particular relevance given its established role in working memory, attentional control, and cognitive integration (Tan, et al., 2024), cognitive domains frequently impaired in mTBI populations (Peitz, et al., 2021; Proskovec, et al., 2020; Huang, et al., 2017). The cross-modality consistency of CI reduction further supports its robustness and reliability as a neurophysiological marker. These results underscore the potential utility of theta-band CI as a sensitive and objective indicator of early-stage brain dysfunction, with important implications for both diagnosis and longitudinal monitoring of recovery in mTBI patients.

Future research will focus on expanding the sample size to include a larger and more diverse cohort across all groups, enhancing the statistical power and generalizability of the findings. A more extensive dataset will support robust subgroup analyses, enabling the investigation of individual variability, longitudinal effects, and clinically relevant correlations. Long-term follow-up beyond the subacute phase will be critical for characterizing chronic recovery trajectories and persistent alterations in brain function. The increased sample size will also facilitate the application of advanced machine learning techniques, such as classification and prediction, to identify potential biomarkers and categorize distinct recovery profiles. Moreover, incorporating additional imaging modalities (e.g., diffusion MRI or fMRI) and conducting large-scale evaluations of mTBI populations will provide a more comprehensive understanding of both structural and functional recovery mechanisms. Ultimately, these efforts aim to refine the proposed pipeline for broader clinical use and extend its applicability to other trauma-related or neurological conditions.

5.2 CONCLUSION

This study presents a personalized, multimodal analytic pipeline that advances the investigation of functional brain dynamics during the subacute phase of mTBI. By integrating EEG and MEG data with anatomically precise head models and applying dynamic functional connectivity and complexity measure, we identified frequency-specific neural alterations, particularly within the theta band, that differentiate mTBI participants from orthopedic controls and track recovery over time. Our findings align with and extend previous research, reinforcing the potential of source-level connectivity metrics as sensitive biomarkers for the diagnosis and prognosis of mTBI. However, several limitations must be acknowledged. The small sample size limits generalizability and statistical power, necessitating validation in larger cohorts. Additionally, the heterogeneity inherent to mTBI, combined with variability in data acquisition protocols across studies, challenges direct comparisons and clinical translation. While our individualized head modeling improves EEG source localization accuracy, further refinement and standardization of analytic pipelines are needed to enhance reproducibility. Finally, our focus on resting-state recordings complements but does not replace task-based assessments, which may capture distinct aspects of cognitive dysfunction.

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