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Doctoral Program of
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Doctoral Thesis

From local activation to global synchronisation: Methodological challenges of M/EEG analysis for biomedical applications

Thesis presented by **D. Víctor Rodríguez González**
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from the *University of Valladolid*

Directed by:
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Sigue nadando, nadando, nadando...

Defense

Título	From local activation to global synchronisation: Methodological challenges of M/EEG analysis for biomedical applications
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Escuela Técnica Superior de Ingenieros de Telecomunicación
Departamento de Teoría de la Señal y Comunicaciones e Ingeniería Telemática

Research Stay for the International Mention

City:	Obihiro (Japan)
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Unit:	Institute of Mental Health Research
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Abstract

Neuroscience has dedicated centuries to the study of the human brain and its functions, leading to significant strides in comprehending the neural underpinnings of complex cognitive processes such as perception, memory, integration of information, and learning. Since their invention in the 20th century, neurophysiological recordings have emerged as a pivotal tool that has greatly enhanced our insights into the intricacies of the brain. Despite the increasing knowledge gained in this field in the last decades, the human brain remains the most profound mystery in our anatomy, with numerous challenges and opportunities for further exploration and understanding.

There are a wide variety of metrics that have been used to characterise M/EEG signals and the alterations that the neurological and psychiatric disorders elicit on them. Nevertheless, most of them can be grouped into one of these two categories: (i) local activation analyses, which assess the signals recorded by the sensors individually (that is, they are used to analyse the signals recorded by each sensor independently); and (ii) global synchronisation analyses, that consider the brain operation as an integrated network, and thus evaluate the interactions between the recorded signals. In this regard, this Doctoral Thesis is focused on delving into the existing literature about the analysis of MEG and EEG signals, identifying potential methodological challenges and, subsequently, proposing effective solutions to address them. Specifically, we have gone through these two ways of evaluating M/EEG signals assessing aspects that still lack a consensus, or in which the implications (and potential caveats) of all their analysis steps have not yet been explored. Moreover, these advancements have opened new avenues for innovative clinical applications of MEG and EEG (M/EEG) signals in the context of mild cognitive impairment (MCI) and dementia associated with Alzheimer's disease (AD). In brief, this Doctoral Thesis is aimed at addressing unresolved methodological challenges existing in the field of M/EEG signal analysis, proposing solutions and

potential clinical applications for the new methods.

Throughout the studies included in this Doctoral Thesis, we have employed five different databases of MEG and EEG recordings. Two of the MEG databases were acquired with a 160 axial gradiometer MEG system: the first one was composed by 122 healthy participants; whereas the second one was formed by 39 healthy elderly participants, 44 MCI patients, and 50 AD patients. This latter database also included longitudinal recordings from 19 of the patients with AD that underwent a non-pharmacological therapy (NPT). The first EEG database was composed by 252 recordings, acquired with a 19-channel EEG system. Also, the second EEG database was formed by 45 healthy elderly controls, recorded with a 19-channel EEG acquisition device. Finally, the third EEG dataset included 27 healthy women, and was acquired with a 32-channel EEG system.

The main contributions of this Thesis were organised based on the two aforementioned levels of analysis, with a methodological advance followed by a clinical application within each level. First, **(i)** it was observed a substantial consistency in the local activation parameters between sensor- and source-level signals, which suggests that, for these metrics, the source inversion process becomes necessary only when the spatial dimension significantly influences the results. Also, **(ii)** it was demonstrated the validity of local activation metrics to predict the outcome of a NPT against AD, with the spatial dimension emerging as a crucial factor in this predictive capability. Moreover, **(iii)** it was developed a subject-specific data-driven algorithm for frequency band segmentation that overcomes the limitations of the current approaches: the Connectivity-based Meta-Bands (CMB) algorithm. Finally, **(iv)** the potential of CMB to detect alterations that MCI and AD provoke in the frequency structure of the neural network was assessed.

These contributions have successfully addressed the long-standing question of whether to conduct local-activation analyses at the sensor or source level, a dilemma that persisted for years. The findings revealed a high consistency in metrics at both levels, albeit with some spatial dimension information missing at the sensor level. This broadened knowledge about this type of metrics led to consider them as potential predictors of the outcome of a NPT against AD, demonstrating their predictive potential. Additionally, the introduction of the CMB algorithm marked a significant advancement by providing a data-driven, subject-specific frequency band segmentation. This algorithm unveiled the true frequency-dependent structure of neural networks, presenting an intriguing alternative to canonical frequency bands that may not fully capture this intricate structure. Lastly, applying this novel methodology facilitated the characterisation of pathological alterations

induced by MCI and AD in the frequency-dependent structure of the neural network. In conclusion, the present Doctoral Thesis has addressed two methodological open challenges, proposing relevant solutions to them, and assessing potential clinical applications that opened up new possibilities for future research in the field.

Acronyms

AB	Amyloid-Beta
AD	Alzheimer's Disease
AEC	Amplitude Envelope Correlation
ApoE	Apolipoprotein E
AS	Attraction Strength
B_{LZC}	Band Complexity
CMB	Connectivity-based Meta-Bands
Coh	Coherence
CTM	Central Tendency Measure
DBD-13	Dementia Behaviour Disturbance Scale
DMN	Default-Mode Network
DoD	Degree of Divergence
DoI	Degree of Invasiveness
dSPM	dynamical Statistical Parametric Mapping
EC	Effective Connectivity
ECoG	ElectroCorticoGraphy
EEG	ElectroEncephaloGraphy
FC	Functional Connectivity
fMRI	functional Magnetic Resonance Imaging
fNIRS	functional Near-Infrared Spectroscopy
GABA	Gamma-AminoButyric Acid
GS	Global Synchronisation
HC	Healthy Control subject
Hz	Hertz
JCR	Journal Citation Reports
LA	Local Activation

LCMV	Linear Constrained Minimum Variance
LZC	Lempel-Ziv Complexity
M/EEG	Electroencephalography and Magnetoencephalography
MB	Meta-Band
MCI	Mild Cognitive Impairment
MEG	MagnetoEncephaloGraphy
MMSE	Mini-Mental State Examination
MRI	Magnetic Resonance Imaging
NIA-AA	National Institute on Aging - Alzheimer's Association
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
NPT	Non-Pharmacological Therapy
PET	Positron Emission Tomography
PLI	Phase Lag Index
PSD	Power Spectral Density
ROI	Region Of Interest
RP	Relative Power
SampEn	Sample Entropy
SE	Spectral Entropy
sEEG	stereo-ElectroEncephaloGraphy
sLORETA	standardised LOw-Resolution brain Elecromagnetic TomogrAphy
SR	Switching Rate
SSE	Spatial Shannon Entropy
TA	Topological Adaptation
wMNE	weighted Minimum Norm Estimate

Contents

List of Figures

Chapter 1

Introduction

This Doctoral Thesis is intended to explore the literature about the analysis of magnetoencephalographic (MEG) and electroencephalographic (EEG) signals, looking for potential methodological caveats, and proposing solutions to them. Furthermore, this has paved the way for novel clinical applications of MEG and EEG (M/EEG) to characterise the physiopathological signature of mild cognitive impairment (MCI) and dementia due to Alzheimer's disease (AD). To this end, we employed four different datasets composed by resting-state M/EEG recordings of healthy controls (HC), MCI patients, and AD patients. During the course of the thesis research, four papers were published in scientific journals indexed in the Journal Citation Reports (JCR) from the Web of Science between October 2020 and January 2024. The scientific production demonstrates thematic consistency and a coherent nature, resulting in the Doctoral Thesis being presented as a compendium of publications, according to the normative of the University of Valladolid.

Section 1.1 describes the thematic consistency between the manuscripts. Section 1.2 provides an overview of the general context of the Doctoral Thesis, on the scientific field of Biomedical Engineering. Next, Section 1.3 is devoted to describe MCI and dementia due to AD. Furthermore, Section 1.4 provides an overview of different neuroimaging techniques, with special emphasis on M/EEG. Finally, the methods used for analysing M/EEG signals and the novel approach introduced to define user-specific frequency segmentations of the neural activity are explained in Section 1.5.

It noteworthy that, while each of the published papers is a complete study in its own right, they also form a cohesive research unit with the common goal of

assessing methodological challenges in the field of the M/EEG signals analysis, and opening up the way for novel clinical applications to MCI and dementia due to AD. Consequently, this document provides a concluding summary that encompasses the outcomes of all the papers highlighting their collective contributions.

1.1 Compendium of publications: thematic consistency

Human brain is continuously processing vast amounts of information. This process relies on the transmission of action potentials, which are electrical waves generated by the exchange of neurotransmitters between neurons (Standring, 2021). When a neuron receives enough excitatory inputs, action potentials trigger electrochemical pulses, which initiate further action potentials that enable the transmission of signals to other neurons (Standring, 2021). Despite being a relatively new field, neuroscience has made significant advances in our understanding of brain, with a large amount of literature published. In this regard, M/EEG play a pivotal role in the progress of this field (van Diessen et al., 2015; Schomer and da Silva, 2017; Supek and Aine, 2019). From analysing the temporal dynamics of individual brain regions, to evaluating their operation as an integrated network of interconnected neurons, the analysis of M/EEG signals have allowed to achieve significant progress on describing how brain operates, how it processes the information and stimuli, and how different neurological and psychiatric diseases alter neural activity (Bassett and Sporns, 2017; Coppola et al., 2019; Engels et al., 2017; Maran et al., 2016; Schomer and da Silva, 2017; Supek and Aine, 2019).

Notwithstanding this flourishing progress, there are still unresolved methodological challenges regarding the analysis of M/EEG signals that require attention. This Doctoral Thesis has extensively examined the literature, identifying and assessing methodological pitfalls, and proposing solutions that eliminate potential bias factors that they may be provoking. Moreover, addressing these open issues has opened up new opportunities for potential clinical applications of M/EEG. In this regard, this Doctoral Thesis has focused on MCI and dementia due to AD because of their high prevalence and relevance, specially for the elderly (Alzheimer's Association, 2022). Nonetheless, the novel clinical developments presented in this Thesis can be extended to other disorders or conditions that affect the central nervous system, such as schizophrenia or migraine. Figure 1.1 depicts a graphical summary of the thematic consistency of this Doctoral Thesis, along with the

relationships between the four papers included in the compendium of publications.

These papers explore the two main level of analysis of the studies focused on assessing neural activity: (i) **local activation**, which independently analyses the signals generated by individual neuronal pools; and (ii) **global synchronisation**, which evaluates the pairwise interactions between sensors (or brain regions), and the properties of the resulting network. Of note, this two-level approach reflects the chronological publication sequence of the papers, making it easier to interpret the Doctoral Thesis in a continuous manner. The Doctoral Thesis begins with a novel methodological contribution, followed by a clinical application for MCI and AD dementia. The first two publications focus on the first level of analysis of M/EEG signals (*i.e.*, local activation). The first one, Rodríguez-González et al. (2020), presents a comprehensive assessment on how local activation parameters extracted from M/EEG activity are altered as the neural signals travel from the cortex, where they are generated, to the scalp level, where they are recorded by M/EEG systems. These alterations, known as volume conduction and source mixing effects, have been previously assessed (Asadzadeh et al., 2020; Bonaiuto et al., 2018; Michel and Brunet, 2019; Song et al., 2015), including a study that evaluated how they modify global synchronisation metrics (Lai et al., 2018). However, no studies have investigated the impact of volume conduction and source mixing effects on local activation metrics. Before conducting the study presented in Rodríguez-González et al. (2020) there were no clear guidelines of whether it was better to evaluate the local activation metrics at sensor-level (*i.e.*, directly working with the signals provided by the M/EEG sensors), or at source-level (*i.e.*, estimating the signals in the neural generators). As a result, authors made that decision without a complete comprehension of the problem. Our results evidenced for the first time that local activation metrics are robust against volume conduction and source mixing effects, thereby the source inversion process was not a always necessary. However, results also suggested that the studies in which the spatial dimension plays an important role require source-level parameters to avoid loss of relevant information.

Based on the main findings of the first study, the second paper, Rodríguez-González et al. (2021a), assessed whether it is possible to predict the outcome of a non-pharmacological treatment (NPT) against dementia using local activation parameters. To this end, association networks were employed, as they provide an intuitive framework to explore the complex interactions between the outcome of the therapy (measured by means of neuropsychological tests evaluating cognition and behaviour) and the neurophysiological patterns (quantified using MEG-derived local activation metrics at source-level). This publication takes over a preliminary

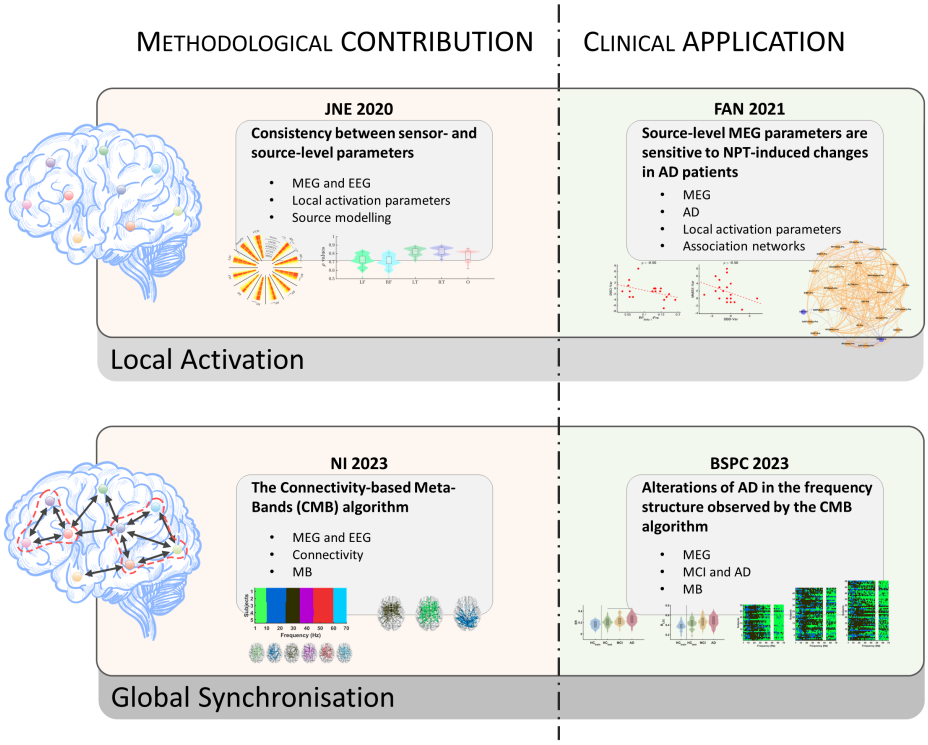

Figure 1.1: Schema summarising the thematic consistency of the Thesis, as well as the relationships between the papers included in the compendium of publications. Of note, all the studies were conducted analysing resting-state neural activity. AD: Alzheimer's disease; BSPC: Biomedical Signal Processing and Control; EEG: Electroencephalography; FAN: Frontiers in Aging Neuroscience; JNE: Journal of Neural Engineering; MB: Meta-bands; MCI: Mild cognitive impairment; MEG: Magnetoencephalography; NI: NeuroImage; NPT: Non-pharmacological Treatment.

study of our research group (not included in the compendium of publications), where it was suggested that certain brain oscillatory patterns are related with the outcome of a NPT against dementia (Shigihara et al., 2020a). Of note, the first publication of the compendium Rodríguez-González et al. (2020) provided relevant knowledge to continue the study initiated in Shigihara et al. (2020a) in a twofold manner. First, the deeper insights on the local activation parameters thoroughly assessed in Rodríguez-González et al. (2020) led us to apply them in Rodríguez-González et al. (2021a), as we observed that they are: i) explainable, which is of paramount importance for the clinicians; and ii) robust, which is also relevant to use them in different clinical settings consistently. Second, in Rodríguez-González et al. (2020) it was observed that when the spatial patterns are relevant for the

analyses, it is necessary to employ source-level signals; as in Shigihara et al. (2020a) we observed that the spatial dimension played a pivotal role in the neural changes induced by NPT, we performed the subsequent analyses on source-level MEG signals. In line with that, in Rodríguez-González et al. (2021a) it was introduced a new metric, the spatial Shannon entropy (SSE), which summarises the spatial distribution of a local activation parameter, and was demonstrated to be able to predict the outcome of the NPT. The results also highlighted the relevance of association networks, as they are useful to intuitively detect changes elicited by going through a NPT in the complex relationships between the variables at hand. Besides, this study suggested that the outcome of the NPT can be effectively predicted by the neurophysiological status of the patients, providing further evidence on the potential of MEG activity to quantify the NPT-related cognitive and behavioural changes.

The third and fourth publications included in the compendium explored the second level of analysis (*i.e.*, global synchronisation). The third paper, Rodríguez-González et al. (2023), challenges the canonical definition of frequency bands that are usually employed in M/EEG analyses, highlighting potential caveats associated with their use: (i) they were defined almost a century ago, with acquisition techniques that have changed enormously since then; (ii) the analysis methods have greatly evolved; (iii) there is no consensus on their specific frequency limits; and (iv) they are fixed, disregarding the between-subject variability (Rodríguez-González et al., 2024, 2023). To overcome these issues, we proposed the first unsupervised, user-specific, data-driven frequency band segmentation method based on functional connectivity (FC) patterns: the Connectivity-based Meta-Bands (CMB) algorithm. Our results revealed, for the first time, an underlying FC frequency structure with three network topologies recurrently repeating across frequencies; they were considered as "attractors" of the frequency-dependent FC patterns. These recurrent network topologies were called "meta-bands". Crucially, we found evidence that the sensitivity of EEG signals is not sufficient to unveil that meta-band structure. It was also observed that, although canonical frequency bands adequately reflect the group-level neural patterns in MEG signals, they are missing relevant individual idiosyncrasies that can be an important bias factor. Our findings paved the way for a new level of personalisation in MEG analyses that would improve the accuracy and reliability of the identification of alterations associated with neural disorders. The algorithm developed in this paper is partially inspired on a prior line of investigation by our research group that developed a methodology to identify network topologies recurrent over time, known

as meta-states (Núñez et al., 2021).

In the fourth publication included in the compendium, Rodríguez-González et al. (2024), we assessed whether the FC frequency structure revealed by the CMB algorithm is altered by MCI and dementia due to AD. We extended the CMB algorithm proposing novel metrics sensitive to the alterations in the frequency-dependent FC patterns. Our results showed that MCI and AD dementia modify the underlying FC structure eliciting more heterogeneous and widespread network patterns, *i.e.*, they are less "attracted" by the meta-band topologies. Furthermore, we reported for the first time a progressive dilution of the FC frequency structure provoked by these pathologies. This paper can be considered as the frequency counterpart of the findings in Núñez et al. (2021), where authors reported a dilution of the FC temporal structure. Considering both studies together, we can conclude that MCI and AD dementia dilute the FC network structure in a twofold manner: in frequency and time.

The format of this Doctoral Thesis is a compendium of publications. As acceding to all the papers comprising the compendium is crucial for a complete understanding of the manuscript, all the publications have been included in the Chapter **??**. The most important details of the papers included in the compendium of publications are listed below, including their titles, authors, abstracts, and the journals in which they were published, including their corresponding ranks and impact factors.

Consistency of local activation parameters at sensor- and source-level in neural signals (Rodríguez-González et al., 2020).

Víctor Rodríguez-González, Carlos Gómez, Yoshihito Shigihara, Hideyuki Hoshi, Marcos Revilla-Vallejo, Roberto Hornero, and Jesús Poza. *Journal of Neural Engineering*, vol. 14(5), p. 056020, 2020, DOI: 10.1088/1741-2552/abb582. Impact factor in 2020: 5.379, Q1 (20/89) in "ENGINEERING, BIOMEDICAL" and Q1 (66/273) in "NEUROSCIENCES" (Journal Citation Reports - Web of Science, JCR-WOS).

Objective: Although magnetoencephalography and electroencephalography (M/EEG) signals at sensor level are robust and reliable, they suffer from different degrees of distortion due to changes in brain tissue conductivities, known as field spread and volume conduction effects. To estimate original neural generators from M/EEG activity acquired at sensor level, diverse source localisation algorithms have been proposed; however, they are not exempt from limitations and usually

involve time-consuming procedures. Connectivity and network-based M/EEG analyses have been found to be affected by field spread and volume conduction effects; nevertheless, the influence of the aforementioned effects on widely used local activation parameters has not been assessed yet. The goal of this study is to evaluate the consistency of various local activation parameters when they are computed at sensor- and source-level. *Approach:* Six spectral (relative power, median frequency, and individual alpha frequency) and non-linear parameters (Lempel-Ziv complexity, sample entropy, and central tendency measure) are computed from M/EEG signals at sensor- and source-level using four source inversion methods: weighted Minimum Norm Estimate (wMNE), standardised LOw-Resolution brain Electromagnetic TomogrAphy (sLORETA), Linear Constrained Minimum Variance (LCMV), and dynamical Statistical Parametric Mapping (dSPM). *Main results:* Our results show that the spectral and nonlinear parameters yield similar results at sensor- and source-level, showing high correlation values between them for all the source inversion methods evaluated and both modalities of signal, M/EEG. Furthermore, the correlation values remain high when performing coarse-grained spatial analyses. *Significance:* To the best of our knowledge, this is the first study analysing how field spread and volume conduction effects impact on local activation parameters computed from resting-state neural activity. Our findings evidence that local activation parameters are robust against field spread and volume conduction effects and provide equivalent information at sensor- and source-level even when performing regional analyses.

Exploring the Interactions Between Neurophysiology and Cognitive and Behavioral Changes Induced by a Non-pharmacological Treatment: A Network Approach (Rodríguez-González et al., 2021a).

Víctor Rodríguez-González, Carlos Gómez, Hideyuki Hoshi, Yoshihito Shigihara, Roberto Hornero, and Jesús Poza. *Frontiers in Aging Neuroscience*, vol. 13(696174), p. 1-15, 2021, DOI: 10.3389/fnagi.2021.696174. Impact factor in 2021: 5.702, Q1 (67/275) in "NEUROSCIENCES" and Q2 (16/54) in "GERIATRICS & GERONTOLOGY" (Journal Citation Reports - Web of Science, JCR-WOS).

Dementia due to Alzheimer's disease (AD) is a neurological disorder that has an increasing impact in our society, provoking behavioural, cognitive, and functional disorders. AD lacks an effective pharmacological treatment; thereby, non-pharmacological treatments (NPTs) play a role of utmost importance in its treatment, as they have been proven to ameliorate AD symptoms. Nevertheless,

results associated with NPTs are patient-dependent, and new tools are needed to predict their outcome and to improve their effectiveness. In this study, 19 patients with AD underwent an NPT. Magnetoencephalographic activity was recorded at the beginning and at the end of the NPT to evaluate the neurophysiological state of each patient. Additionally, their cognitive (quantified by means of the Mini-Mental State Examination, MMSE) and behavioural (measured in terms of the Dementia Behavior Disturbance Scale, DBD-13) statuses were collected before and after the NPT. We analysed the interactions between cognitive, behavioural, and neurophysiological states by generating diverse association networks, able to intuitively characterise the relationships between variables from different nature. Our results suggest that the NPT remarkably changed the structure of the association network, reinforcing the interactions between the DBD-13 and the neurophysiological parameters. We also found that the changes in cognition and behaviour are related with the changes in spectral-based neurophysiological parameters. Furthermore, our results support the idea that neurophysiological parameters can predict NPT outcome; specifically, a less degree of AD neurophysiological alterations (i.e., neural oscillatory slowing, decreased variety of spectral components, and increased signal regularity) predicts a better prognosis of the NPT. This study provides deeper insights into the relationships between neurophysiology and, both, cognitive and behavioural statuses, proving the potential of network-based methodologies to further understand the complex interactions elicited by NPTs.

Connectivity-based Meta-Bands: A new approach for automatic frequency band identification in connectivity analyses (Rodríguez-González et al., 2023).

Víctor Rodríguez-González, Pablo Núñez, Carlos Gómez, Yoshihito Shigihara, Hideyuki Hoshi, Miguel Ángel Tola-Arribas, Mónica Cano, Ángel Guerrero, David García-Azorín, Roberto Hornero, and Jesús Poza. *NeuroImage*, vol. 280, p. 120332, 2023, DOI: 10.1016/j.neuroimage.2023.120332. Impact factor in 2022: 5.700, D1 (1/14) in "NEUROIMAGING", Q1 (50/272) in "NEUROSCIENCES", and Q1 (17/135) in "RADIOLOGY, NUCLEAR MEDICINE & MEDICAL IMAGING" (Journal Citation Reports - Web of Science, JCR-WOS).

The majority of electroencephalographic (EEG) and magnetoencephalographic (MEG) studies filter and analyse neural signals in specific frequency ranges, known as canonical frequency bands. However, this segmentation, is not exempt

from limitations, mainly due to the lack of adaptation to the neural idiosyncrasies of each individual. In this study, we introduce a new data-driven method to automatically identify frequency ranges based on the topological similarity of the frequency-dependent functional neural network. The resting-state neural activity of 195 cognitively healthy subjects from three different databases (MEG: 123 subjects; EEG_1: 27 subjects; EEG_2: 45 subjects) was analysed. In a first step, M/EEG signals were filtered with a narrow-band filter bank (1 Hz bandwidth) from 1 to 70 Hz with a 0.5 Hz step. Next, the connectivity in each of these filtered signals was estimated using the orthogonalised version of the amplitude envelope correlation to obtain the frequency-dependent functional neural network. Finally, a community detection algorithm was used to identify communities in the frequency domain showing a similar network topology. We have called this approach the "Connectivity-based Meta-Bands" (CMB) algorithm. Additionally, two types of synthetic signals were used to configure the hyper-parameters of the CMB algorithm. We observed that the classical approaches to band segmentation reflect the underlying network topologies at group level for the MEG signals, but they fail to adapt to the individual differentiating patterns revealed by our methodology. On the other hand, the sensitivity of EEG signals to reflect this underlying frequency-dependent network structure is limited. To the best of our knowledge, this is the first study that proposes an unsupervised band segmentation method based on the topological similarity of functional neural network across frequencies. This methodology fully accounts for subject-specific patterns, providing more robust and personalised analyses, and paving the way for new studies focused on exploring the frequency-dependent structure of brain connectivity.

Alterations in the frequency-dependent connectivity structure in MCI and AD (Rodríguez-González et al., 2024).

Víctor Rodríguez-González, Pablo Núñez, Carlos Gómez, Hideyuki Hoshi, Yoshihito Shigihara, Roberto Hornero, and Jesús Poza. *Biomedical Signal Processing and Control*, vol. 87, p. 105512, 2024, DOI: 10.1016/j.bspc.2023.105512. Impact factor in 2022: 5.100, Q2 (26/96) in "ENGINEERING, BIOMEDICAL" (Journal Citation Reports - Web of Science, JCR-WOS).

Mild cognitive impairment (MCI) and dementia due to Alzheimer's disease (AD) are neurological disorders that affect cognition, brain function, and memory. Magnetoencephalography (MEG) is a neuroimaging technique used to study changes

in brain oscillations caused by neural pathologies. However, MEG studies often use fixed frequency bands, assuming a common frequency structure and overlooking both subject-specific variations and the potential influence of pathologies on frequency distribution. To address this issue, a novel methodology called Connectivity-based Meta-Bands (CMB) was applied to obtain a subject-specific functional connectivity-based frequency bands segmentation. Resting-state MEG activity was acquired from 161 participants: 67 healthy controls, 44 MCI patients, and 50 AD patients. The CMB algorithm was used to identify "meta-bands" (*i.e.*, recurrent network topologies across frequencies). The meta-bands were used to extract an individualised frequency band segmentation. The network topology of the meta-bands and their sequencing were analysed to identify alterations associated with MCI and AD in the underlying frequency-dependent connectivity structure. We found that MCI and AD alter the neural network topology, leading to connectivity patterns both more widespread in the frequency spectrum and heterogeneous. Furthermore, the meta-band frequency sequencing was modified, with MCI and AD patients exhibiting sequences with increased complexity, suggesting a progressive dilution of the frequency structure. The study highlights the relevance of considering the impact of neural pathologies on the frequency-dependent connectivity structure and the potential bias introduced by using fixed frequency bands in MEG studies.

1.2 Neuroengineering

Neuroengineering encompasses the interdisciplinary integration of engineering and computational methodologies to address challenges within both fundamental and clinical neuroscience domains (Coyle and Sosnik, 2015). Education and research in neuroengineering span across the disciplines of engineering, mathematics, and computer science, intertwining with molecular, cellular, and systems neurosciences (Coyle and Sosnik, 2015). Key objectives within this field include the restoration and enhancement of human capabilities through direct interactions between the nervous system and artificial devices. This involves deciphering the encoding and processing of information in sensory and motor systems, quantifying the alterations elicited by pathological conditions, and exploring methods to manipulate it via interactions with artificial devices (Coyle and Sosnik, 2015). This Thesis falls in the this field, and more specifically, in the area of neural signal processing. Of note, very different signal processing techniques are applied to neural signals in order to extract information that cannot be appreciated by visual inspection. This unveiled

information can help us to understand, for example, how different brain regions interact, and how different pathologies modify those interactions (Bassett and Sporns, 2017; Stam and van Straaten, 2012). Early in the last century, engineering has been used in order to get deeper insights on the neural mechanisms involved in different brain processes. Since then, and specially in the last few years, the neural signal processing field has experienced a fast growing thanks to both, the increase in size and quality of the neural data available, and the computational power of current processing systems (Bassett and Sporns, 2017). However, there are still many open questions regarding the neural dynamics underlying brain organisation and function (Bassett and Sporns, 2017).

In this Doctoral Thesis, different signal processing techniques were applied to M/EEG neural signals. All the neurophysiological recordings analysed in the studies included in the compendium of publications were acquired in a resting-state condition to characterise the spontaneous brain dynamics. On the one hand, we used recordings from healthy controls to develop novel methodologies that propose solutions to methodological pitfalls encountered in the field. On the other hand, recordings from patients with MCI and dementia due to AD were employed to devise potential clinical applications for the characterisation and treatment of these alterations. Furthermore, it is noteworthy that synthetic signals were also used to thoroughly evaluate the capabilities of the developed methods.

1.3 Dementia due to Alzheimer's disease

Dementia due to Alzheimer's disease (AD) is a neurodegenerative pathology that provokes progressive cognitive, behavioural, and functional alterations (Knopman et al., 2021). AD is the most common type of dementia, provoking between 60% and 80% of all dementia cases (Alzheimer's Association, 2022). This pathology is associated with deterioration in neurons, and abnormal deposition of hyper-phosphorylated tau tangles and amyloid-beta plaques (Alzheimer's Disease International, 2022). It is thought that the first alterations in the brain elicited by AD appear about 20 years before the symptoms start (and, thus, also before the diagnosis is issued) (Alzheimer's Association, 2022; Bateman et al., 2012).

According to the World Health Organization figures, in 2019, 55 million people lived with dementia, and this number is expected to reach 139 million in 2050. This increase is due to the ageing population, as the age is the main risk factor for AD (Alzheimer's Disease International, 2022). About a 11% of the people aged 65 or older suffer from AD, with the prevalence increasing with age: 5% in people aged

from 65 to 74, 13% in people aged from 75 to 84, and 33% in people aged 85 years and over (Alzheimer's Association, 2022). In Europe, these values are similar: 3% in people aged from 65 to 74, 14% in people aged from 75 to 84, and 36% in people aged 85 years and over (Niu et al., 2017). Moreover, AD is considered to be the fifth cause of death in people aged 65 and older, with an average life expectancy between 4 and 8 years after the diagnosis (Alzheimer's Association, 2022). Besides, the economic impact of AD is estimated in US$1.3 trillion worldwide, with an average annual cost of US$26.300 per patient (Alzheimer's Association, 2022). All these factors make AD a medical, social, and economical problem of the utmost concern.

Stages of Alzheimer's disease

As the symptoms evolve from mild to severe, three different stages of AD are defined (Alzheimer's Association, 2022):

1. *Mild dementia due to Alzheimer's disease.* Subjects with mild AD still have a functional independence in their daily life. Nevertheless, they may require assistance with some activities.
2. *Moderate dementia due to Alzheimer's disease.* This is considered the longest stage. Individuals experience behavioural, functional, memory, and cognitive problems: language problems, agitation, incontinence, personality changes, and issues recognising the loved ones. At this point, the independence of the individuals decay, as they may experience problems performing some activities of their daily life such as bathing or dressing.
3. *Severe dementia due to Alzheimer's disease.* Patients with severe AD experience majors problems to communicate, move, or even eat or drink. Complications such as blood clots, sepsis, or aspiration pneumonia emerge. Hence, they require full-time assistance. This is the last stage of AD, which ultimately leads to death.

1.3.1 Mild cognitive impairment

Mild cognitive impairment (MCI) was considered to be a prodromal stage of AD; however, now it is defined as an heterogeneous construct of symptoms characterised by minor changes in cognition, function, and memory (Wolk and Vaishnavi, 2016). These changes are not sufficient to interfere with the daily life of the patient, but severe enough not to be considered part of the normal ageing process (Alzheimer's Association, 2022). Accumulating evidence suggests that these symptoms emerge

when the brain is not able to compensate the neuronal damage provoked by the dementia (Alzheimer's Association, 2022). There are two main types of MCI: amnesic and non-amnesic. In patients with amnesic MCI the memory-related issues predominate; while in non-amnesic MCI other cognitive abilities (*i.e.*, reasoning, language, or executive functions) are more affected than memory (Jongsiriyanyong and Limpawattana, 2018; Petersen et al., 2018).

Due to the heterogeneous characteristics of MCI, many different factors, such as medication, depression, or sleep disorders, can be involved in its onset (Jongsiriyanyong and Limpawattana, 2018). This makes MCI diagnosis very troublesome for physicians (Jongsiriyanyong and Limpawattana, 2018). This diagnosis is usually performed by analysing patient's history and conducting some cognitive and memory tests (Petersen et al., 2018). Besides, it is also important to discard other pathologies with similar symptoms such as cerebrovascular diseases or cancer (Petersen et al., 2018).

The prevalence of MCI is estimated to be between 12% and 18% for people 60 years old and over (Alzheimer's Association, 2022). Additionally, this clinical state is associated with a higher risk of developing dementia, with between 10% and 15% of the MCI patients developing dementia each year (Alzheimer's Association, 2022). Around 50% of the individuals with MCI have also AD-related biomarkers, thus being considered MCI due to AD (Alzheimer's Association, 2022). This type of MCI is considered as a precursor stage before AD criteria are met, with patients of the amnesic type of MCI being more likely to develop AD (Liss et al., 2021).

1.3.2 Risk factors of Alzheimer's disease

It is thought that AD onset is not provoked by a single cause, but as a consequence of the interactions between several risk factors (Alzheimer's Association, 2022).

Age

Ageing is the most relevant risk factor for AD, with a prevalence of 5% on people aged 65 and over that badly increases to 33% for people aged 85% or above (Alzheimer's Association, 2022). Nonetheless, ageing is not sufficient to provoke the onset of AD (Alzheimer's Association, 2022).

Genetics

Genetic factors also play a relevant role in the onset of AD. The amyloid precursor proteins, Presenilin-1, Presenilin-2, and apolipoprotein E (ApoE) are related with

AD, specially the allele $\epsilon 4$ of ApoE (Breijyeh and Karaman, 2020).

Family history

Family history also influences AD onset. It has been reported that having a first-degree relative with AD doubles the risk of developing this pathology (Loy et al., 2014).

Environmental factors

There are some environmental factors that have been associated with AD. Having a physically active and a heart-healthy diet may reduce the risk of developing dementia (Alzheimer's Association, 2022). Air pollution may also provoke cognitive impairment as well as an increased amyloid-beta deposition (Moulton and Yang, 2012).

Cognitive reserve

Having had a very active life from a cognitive point of view, that is, having a high cognitive reserve is also associated with a lower risk of AD (Alzheimer's Association, 2022).

Medical factors

Some medical conditions, such as diabetes, obesity, cardiovascular diseases, or traumatic brain injury, have been linked with an increased risk of developing AD (Alzheimer's Association, 2022; Breijyeh and Karaman, 2020).

1.3.3 Causes of Alzheimer's disease

Although AD has been broadly studied, its pathological causes are still not clear (Alzheimer's Association, 2022). Many hypotheses trying to explain the onset of AD have been posed, though two of them are more widely accepted: the cholinergic hypothesis, and the amyloid hypothesis (Breijyeh and Karaman, 2020).

The cholinergic hypothesis argues that AD is due to a dysfunction in the cholinergic neurotransmitter system. It is based on three principles: i) cholinergic deficits related with acetylcholine, which plays an important role in cognitive processes; ii) neuronal loss in the nucleus basalis of Meynert, which is the source of cholinergic

diffusion to the cortex; and iii) the role of cholinergic antagonists, which are related with memory deficits, while agonists have an opposite effect (Hampel et al., 2018).

On the other hand, the amyloid hypothesis states that the deposition of amyloid-beta (AB) plaques are the cause of AD. Ageing or pathological reasons provoke dysfunctions in AB degradation, which lead to its abnormal deposition in the brain and, thus, to an increase in neurotoxicity and tau-phosphorylated tangles deposition (Breijyeh and Karaman, 2020). Finally, this causes neurodegeneration and neuronal death (Breijyeh and Karaman, 2020).

1.3.4 Diagnosis of Alzheimer's disease

The diagnosis of Alzheimer's disease is not simple. In the daily clinical routine it is commonly done by combining approaches in which different professionals, as physicians, neurologists, or psychologists are involved (Alzheimer's Association, 2021). These approaches, among others, include:

- Information from family or caregivers about changes in cognition, memory, or behaviour of the patient.
- Analysis of the family history of the patient looking for previous cases of psychiatric or neurological disorders.
- Neuropsychological tests to assess the cognitive status of the patient.
- Physical and neurologic evaluations.
- Blood tests or brain imaging to discard other potential factors provoking dementia-related symptoms.
- A differential diagnosis between AD and other types of dementia.

The diagnosis of dementia is reliable; nonetheless, AD diagnosis is more challenging. In 1984, the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) established the diagnosis criteria for AD. These criteria were updated in 2021 by the National Institute on Aging - Alzheimer's Association (NIA-AA) to increase their sensitivity and specificity (Alzheimer's Association, 2021). In this update, the definite diagnosis of AD was defined based on the presence of three types of biomarkers: amyloid-related, tau-related, and signs of neurodegeneration and neural injury (Jack et al., 2018, 2016). However, obtaining evidence of the presence of all these biomarkers is invasive, dangerous for the patient, and costly. Consequently, they are barely used in clinical settings, and the

previously mentioned criteria are commonly applied. To address this issue, new biomarkers, less invasive and expensive, are already being explored (Cheng et al., 2022; Gunes et al., 2022; Klyucherev et al., 2022). It is estimated that about 15%-30% of AD cases are misdiagnosed, being actually other types of dementia (Alzheimer's Association, 2021). Despite this, AD is still an underdiagnosed pathology (Amjad et al., 2018; Lang et al., 2017).

1.3.5 Treatments of Alzheimer's disease

Pharmacological treatments

Although AD is a concerning health issue, only seven drugs for AD treatment have been approved by the U.S. Food and Drug Administration: donepezil, rivastigmine, galantamine, memantine (combined or not with donepezil), aducanumab, and lecanemab (Alzheimer's Association, 2022). These drugs, apart from aducanumab, treat the AD symptoms, but have not effect on the development of the disease (Alzheimer's Association, 2022). On the one hand, memantine protects brain from glutamate, as it can damage neurons (Alzheimer's Association, 2022). On the other hand, the other drugs stimulate the generation of other neurotransmitters (Alzheimer's Association, 2022). Additionally, aducanumab uses a different approach, as it addresses AD neuropathology by removing AB plaques (Cummings et al., 2021). Finally, lecanemab is the last drug for AD to be approved. Although it has been proven that this drug slow the cognitive decline in dementia due to AD patients in early stage, it also has remarkable side effects such as brain swelling or bleeding (Cummings et al., 2023).

The pharmaceutical industry is making huge efforts to develop an effective drug for AD; however, it is still a long way to go. Some factors such as the difficulty in recruiting patients, the long time required to observe the outcome of the treatments, and the lack of knowledge in certain aspects of the disease are hindering the development of effective treatments (Alzheimer's Association, 2021).

Non-pharmacological treatments

These treatments do not modify the underlying AD biology, but try to maintain or improve the cognitive, behavioural, and functional status of the patients (Alzheimer's Association, 2022). The final objective of these therapeutic interventions is to increase the patient's independence, thus providing a better quality of life. This type of treatments are based on different approaches (Zucchella et al., 2018): cognitive intervention, music therapy, psychological therapy, or physical

exercise. These therapies are also used to address behavioural problems such as depression, apathy, or sleep disturbances in AD patients (Alzheimer's Association, 2022). Additionally, they have been proven to be more effective than drugs to address aggression and agitation in AD patients (Watt et al., 2019). A report published in 2020 by The Lancet Commission supported these therapeutic approaches, as they proposed multicomponent interventions to address neuropsychiatric symptoms of dementia (Livingston et al., 2020).

1.4 Brain imaging

The brain is the most complex system of the human body. In consequence, it employs 25% of body oxygen expenditure and demands around 15% of the blood pumped by the cardiovascular system (Standring, 2021). The brain is in charge of processing both external and internal stimuli, generating responses to them, and maintaining the basal activity during rest (Wolpaw and Wolpaw, 2012), which is possible thanks to the interconnection of billions of neurons that interact behaving like an integrated synergic network (Standring, 2021). This activity can be altered by different neurological pathologies. Thus, measuring neural activity can help us to not only to understand how brain works, but also to unveil the pathological fingerprints of different brain diseases (Bronzino and Peterson, 2014). This activity has a chemical basis, as it is generated by a neurotransmitter exchange in the neuron, which can yield (or not) to the transmission of an action potential that will propagate through the neurons, enable the communication between them, and generate the so-called brain activity (Bronzino and Peterson, 2014). Many different methods to record brain organisation and functional activity have been developed, trying to deepen its knowledge about brain. In Figure 1.2, different brain imaging techniques, as well as diverse properties, are depicted (Wolpaw and Wolpaw, 2012). Based on the physical principle on which they are based, these acquisition techniques can be divided in two main categories:

- *Electrophysiological.* Recording the electromagnetic activity of the brain may be the most intuitive way of measuring neural activity. Electroencephalography (EEG), magnetoencephalography (MEG), electrocorticography (ECoG), stereo-electroencephalography (sEEG), and microarrays belong to this category. Although their temporal resolution is high, the spatial resolution depends on their degree of Invasiveness (DoI), typically with more invasive techniques providing higher spatial resolution (Wolpaw and Wolpaw, 2012).

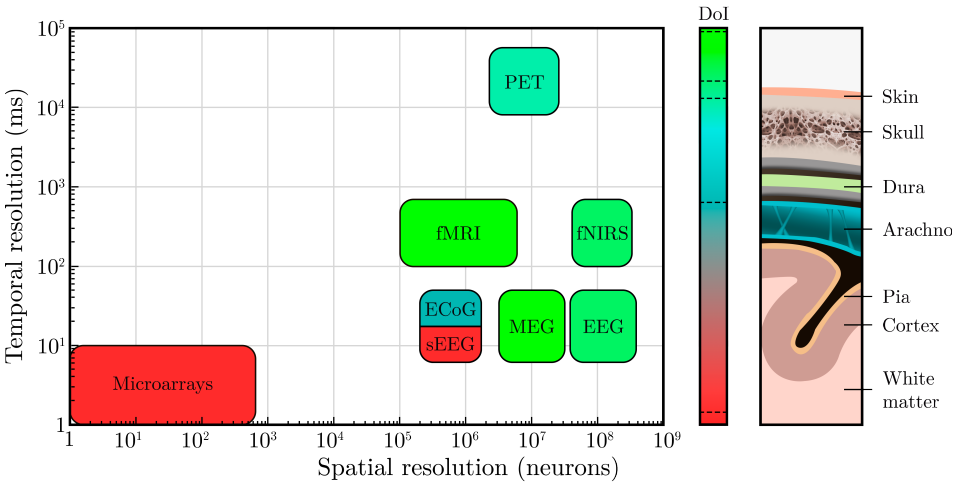

Figure 1.2: Different neuroimaging techniques ordered by their spatial and temporal resolution. Additionally, the degree of invasiveness (DoI) is indicated by the colour of the rectangles. In the right part of the image, the brain layers corresponding with the different levels of invasivity are summarised. PET: positron emission tomography, fMRI: functional magnetic resonance imaging, fNIRS: functional near-infrared spectroscopy, ECoG: electrocorticography, sEEG: stereo-electroencephalography, MEG: magnetoencephalography, EEG: electroencephalography. Based on Wolpaw and Wolpaw (2012)

In addition, the magnetic activity of the brain can be measured by means of MEG. Magnetic activity has an increased robustness against volume conduction effects compared to electric activity, and its signal-to-noise ratio is higher (Bronzino and Peterson, 2014; Illman et al., 2020)

- *Metabolic.* Techniques belonging to this category provide a indirect measure of brain activity. When neurons transmit action potentials, they require more energy, thus demanding more glucose and oxygen. This provokes an increase of the blood flow through these neurons (Wolpaw and Wolpaw, 2012). Hence, several techniques use the blood flow to measure brain activity. On the one hand, positron emission tomography (PET) detects the blood flow using a radiotracer (Wolpaw and Wolpaw, 2012). On the other hand, functional magnetic resonance imaging (fMRI) and functional near-infrared spectroscopy (fNIRS) record brain activity by measuring oxygen consumption; while the former is based on magnetic fields, the latter uses infrared light (Wolpaw and Wolpaw, 2012).

In the present Doctoral Thesis, we have focused on two of these techniques, EEG and MEG (M/EEG), as they are non-invasive, measure brain activity in a

direct way, and provide a high temporal resolution. Besides, MEG also has a high spatial resolution, and EEG has low cost. In the following sections, we will get deeper insights on them.

1.4.1 Electroencephalography

Although the development of EEG systems was possible thanks to the contribution of many scientists, as Dr. Luigi Galvani, Dr. Edouard Hitzig, or Vladimir Pravdich-Neminsky, Dr. Hans Berger is considered to be "the father of EEG" (Schomer and da Silva, 2017). He performed the first human EEG recording in 1924 (Berger, 1929). Although his findings were first seen with scepticism, they were confirmed in later 1930s, opening a new field of study: a new way of assessing brain activity had been established (Stone and Hughes, 2013; Supek and Aine, 2019).

When a neuron is activated due to the stimulation of its dendrites, it generates a small electric field (Singh, 2014). EEG has its origin in the pyramidal neurons of the cortex, as they are placed in parallel and generate the electric activity synchronously, which makes the associated electromagnetic field strong enough to be recorded by EEG sensors (Singh, 2014). In addition, it is noteworthy that EEG is not generated by action potentials, as their duration in time is not sufficient, but by the extracellular currents of the postsynaptic potentials associated with them (Biasiucci et al., 2019; Singh, 2014).

EEG systems are usually portable, so there are almost no restrictions with the recording place (Biasiucci et al., 2019). To acquire the signals, an elastic cap with sensors is placed in the scalp of the patients. The sensors are commonly located according a specific layout, being the most used the International 10/20, 10/10, or 10/5 Systems (Jurcak et al., 2007). There are some types of sensors that require using conductive gel to reduce the electric impedance of the scalp (Mathewson et al., 2017). It is worth noting that many EEG devices have been recently developed to acquire high-quality recordings without using conductive gel, thus reducing the inconveniences for the patient associated with the application and cleaning of it (Damalerio et al., 2023; Hinrichs et al., 2020; Yang et al., 2022).

1.4.2 Magnetoencephalography

Dr. David Cohen, with the contributions of Dr. James Edward Zimmerman, conducted the first MEG recording (Cohen, 1968, 1972; Zimmerman et al., 1970). This acquisition was achieved in a magnetically-shielded room, and provided a

clear signal, similar to that recorded by EEG. This attracted the interest of scientific community, leading to the flourish of the MEG field. The bases of modern MEG were established when whole-head MEG systems were developed in 1990s (Supek and Aine, 2019).

The physiological basis of MEG is similar to that of EEG: the postsynaptic potentials of the pyramidal neurons of the cortex (Biasiucci et al., 2019; Supek and Aine, 2019). Nonetheless, although the sources of M/EEG are similar, they are not exactly the same: EEG is mainly generated by extracellular currents, whereas MEG is more sensitive to intracellular ones (Lopes da Silva, 2013; Singh, 2014; Supek and Aine, 2019). Besides, EEG is sensitive to tangential and radial neuronal oscillations, but MEG is only sensitive to tangential activity (Cohen and Cuffin, 1987; Singh, 2014; Supek and Aine, 2019).

MEG acquisition is usually performed in a magnetically shielded room, as the magnetic fields of the brain are very small compared with the external noise (Singh, 2014). The subject has to place the head in a fixed system located into that room (Supek and Aine, 2019). Additionally, super-conductor materials are required to acquire these tiny magnetic fields (that are in the order of femtoTesla) (Singh, 2014). These materials operate at extremely low temperatures and, thus, a cooling system with liquid helium (which is about 3° Kelvin) is normally employed (Singh, 2014). Furthermore, the head position regarding the acquisition sensors is usually recorded by means of coil markers placed in fixed positions to ease the localisation of neural sources. This is required as the subjects have some freedom to place the head in the helmet (Supek and Aine, 2019).

The current restriction of MEG systems of having to be in fixed and dedicated locations is trying to be overcome by a new paradigm of MEG sensors: Optically Pumped Magnetometers (Brookes et al., 2022; Zhang et al., 2022; Zhao et al., 2023).MEG systems based on this technology are much smaller, as they are able to obtain high-quality neural activity recordings without requiring cryogenic temperatures (Zhang et al., 2022).

1.4.3 Comparison between EEG and MEG

Apart from the aforementioned differences in their origin, EEG presents some advantages compared with MEG. First, EEG systems are portable, as they have a very small size compared with MEG ones (Ilmoniemi and Sarvas, 2019). This is useful to record brain signals from patients that cannot move or suffer from claustrophobia in an easier way. Additionally, the cost of EEG systems is significantly

lower than that of MEG, thanks to what they are more widespread in both clinical and research environments (Ilmoniemi and Sarvas, 2019; Supek and Aine, 2019).

On the other hand, MEG has also some upsides compared with EEG. Firstly, the spatial resolution of MEG systems is normally greater than that of EEG systems (Wolpaw and Wolpaw, 2012). Besides, as the MEG sensors do not require the usage of conductor gel, the preparation time is usually lower. Also, MEG has an increased signal-to-noise ratio (Illman et al., 2020). Finally, as the magnetic permeability of the head tissues is almost homogeneous, MEG signals are barely influenced by volume conduction and field spread effects (Singh, 2014; Supek and Aine, 2019).

Although M/EEG are generated by similar neural sources, they have different properties, and do not provide exactly the same information (Illman et al., 2020; Ilmoniemi and Sarvas, 2019; Singh, 2014). This makes these techniques complementary among them (Malmivuo, 2012; Rampp and Stefan, 2007).

1.5 Analysis of M/EEG signals

M/EEG signals have been widely analysed to get deeper insights on brain operation, and how different pathologies alter the neural function. Although there are many different experimental settings for acquiring and analysing M/EEG recordings, it can be established a "common" analysis pipeline. In Figure 1.3 it is depicted the main analysis stages for analysing M/EEG signals followed during this Doctoral Thesis, which are aligned with these "common" steps. Notably, in Figure 1.3, it is also indicated the relationship between the papers included in the compendium of publications and the corresponding analysis steps.

For acquiring M/EEG recordings, different experimental settings have been employed. On the one hand, task-related paradigms have been employed to evaluate the brain organisation during some tasks involving different brain functions, such as cognition, memory, or inhibition (Schomer and da Silva, 2017). These kind of settings have allowed to understand which neural mechanisms enable these processes, and how psychiatric disorders such as psychosis (Martin et al., 2018) or bipolar disorder (Wada et al., 2019) alter these mechanisms. Furthermore, these type of experiments have yielded to the development of brain-computer interfaces, which allow to establish direct communication between the brain and an external device, such as a computer, a prosthetic limb, or a domotic system, and can be operated by subjects with disabilities (Abiri et al., 2019). On the other hand, resting-state paradigms record neural activity during rest, thus characteris-

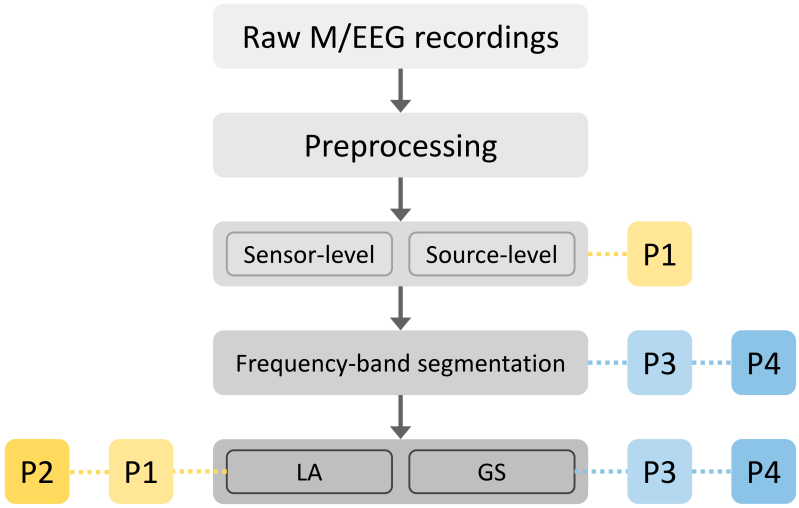

Figure 1.3: Schema of the analysis pipeline of M/EEG signals followed during this Thesis. First, M/EEG raw recordings are preprocessed (typically, filtering and artefact rejection), and the source-level signals are estimated (when required). Then, both sensor- and source-level signals are segmented in frequency bands. Finally different local activation and global synchronisation methods are applied. Furthermore, the relationships between the publications of the compendium and the corresponding analysis steps are indicated. LA: local activation; GS: global synchronisation; P1: first publication of the compendium (Rodríguez-González et al., 2020); P2: second publication of the compendium (Rodríguez-González et al., 2021a); P3: third publication of the compendium (Rodríguez-González et al., 2023); P4: fourth publication of the compendium (Rodríguez-González et al., 2024).

ing the intrinsic brain dynamics. This Doctoral Thesis has focused in resting-state paradigm, therefore, they are described in the next section.

1.6 Resting-state paradigms

The first recording of neural activity was conducted in 1929 by Hans Berger in a resting-state condition (Berger, 1929). There, it was observed that the alpha waves (oscillations of about 10 Hz) dominated this activity, specially over the occipital areas (Berger, 1929; Supek and Aine, 2019). Since then, a vast amount of literature have studied this activity, from a local activation perspective, but also from a global synchronisation point of view. This paved the way to deepen our understanding on how brain operates during rest, and how different pathologies alter this intrinsic activity (Deco et al., 2013; van Diessen et al., 2015; Engels et al., 2017; Perrottelli et al., 2021; Tewarie et al., 2016).

This paradigm acquires neural activity with the subject seated or in supine position. It can be conducted with the eyes open or closed, being the latter more widespread in clinical and research environment. During resting-state recordings, the participants are asked to remain awake and still, and the neural activity is normally monitored in real time by experts to avoid participants falling asleep. These settings acquire spontaneous brain activity, which holds significance for the underlying brain state (Bai et al., 2017). As these settings are cost-effective and convenient, they are very widespread in clinical and research settings (Bai et al., 2017). Furthermore, resting-state recordings are specially relevant for some patients that, because of their disabilities, may be unable to follow the instructions of task-related paradigms, such as dementia patients or subjects with a low level of consciousness.

1.7 Frequency bands of neural activity

One of the most important features of the neural activity elicited during brain function is its oscillatory nature. To perform more exhaustive evaluations of these oscillations, they are normally analysed depending on their frequency (Cohen, 2014). Hence, different frequency ranges have been associated with different brain functions (Cohen, 2014). Moreover, it has been observed that neural pathologies have varying impacts on neural activity depending on the frequency ranges (Ilmoniemi and Sarvas, 2019; Supek and Aine, 2019). It is imperative to interpret cautiously spectral components, as they may be attributed to rhythmic oscillations or non-synchronous waveforms (Schomer and da Silva, 2017). The M/EEG literature has conventionally segmented neural signals in five ranges, with logarithmically-increasing centre frequency and width (Cohen, 2014). These canonical frequency bands are illustrated in Figure 1.4:

- *Delta (δ, 1-4 Hz).* Slow waves are predominantly associated with sleep and anesthesia. Research suggests that these oscillations mainly arise from the thalamus and cortex (Schomer and da Silva, 2017). Their excessive presence can indicate subcortical lesions, such as heightened intracranial pressure (Tatum, 2021).
- *Theta (θ, 4-8 Hz).* Primarily, theta activity originates in the hippocampal region, although it can also appear in other regions (Tatum, 2021; Uhlhaas et al., 2008). Theta waves have been linked to recall and memory-related processes (Uhlhaas et al., 2008).

- *Alpha (α, 8-13 Hz).* Alpha rhythms are often described as the 'idling' state of the brain, and their discovery by Hans Berger marked the beginning of EEG research (Schomer and da Silva, 2017; Trajkovic et al., 2021; Uhlhaas et al., 2008). These oscillations are prominent in the occipital cortex of adult humans during periods of relaxation, especially when the eyes are closed (Schomer and da Silva, 2017). Additionally, the act of opening the eyes causes alpha blocking (*i.e.*, reduction of this activity), which has been associated with active stimulus processing (Uhlhaas et al., 2008). Nonetheless, studies on mental imagery have also demonstrated the involvement of alpha rhythms in information processing (Uhlhaas et al., 2008).
- *Beta (β, 13-30 Hz).* Beta rhythms, which are indicative of wakefulness and alertness, are found in all cortical areas (Schomer and da Silva, 2017). They have been associated with cognitive tasks, including stimulus salience and long-range synchronisation (Uhlhaas et al., 2008). The beta band is typically divided into two sub-bands: beta-1 (β_1, 13-19 Hz) and beta-2 (β_2, 19-30 Hz).
- *Gamma (γ, 30-70 Hz).* Gamma activity is primarily associated with states of high alertness (Schomer and da Silva, 2017), as well as higher sensory and cognitive processing (Uhlhaas et al., 2008). Additionally, studies have provided evidence of their role in long-term and working memory (Uhlhaas et al., 2008).

Of note, there is a significant disparity in the specific definition of frequency bands across studies, as there are variations in band boundaries, and even in the number of bands (*e.g.*, while certain studies recognise beta as a distinct band, others divide it into beta-1 and beta-2) (Newson and Thiagarajan, 2019). Moreover, it has also been proposed subject-specific definitions of the frequency bands, with different degrees of personalisation: from simply adapting them to the alpha peak of each subject, to more sophisticated fully-individualised definitions (Babiloni et al., 2010; Borghini et al., 2019; Cohen, 2021; Pascarelli et al., 2020; Puxeddu et al., 2021; Vecchiato et al., 2011).

1.7.1 Estimation of source-level signals

The signals extracted from M/EEG systems are "sensor-level" signals, which means that they have been recorded on the scalp surface. Typically, we are not interested in assessing the activity observed in the sensors, but in that generated by the different brain regions. However, we cannot consider that the activity of a sensor has been generated by the sources directly below that sensor (Michel and

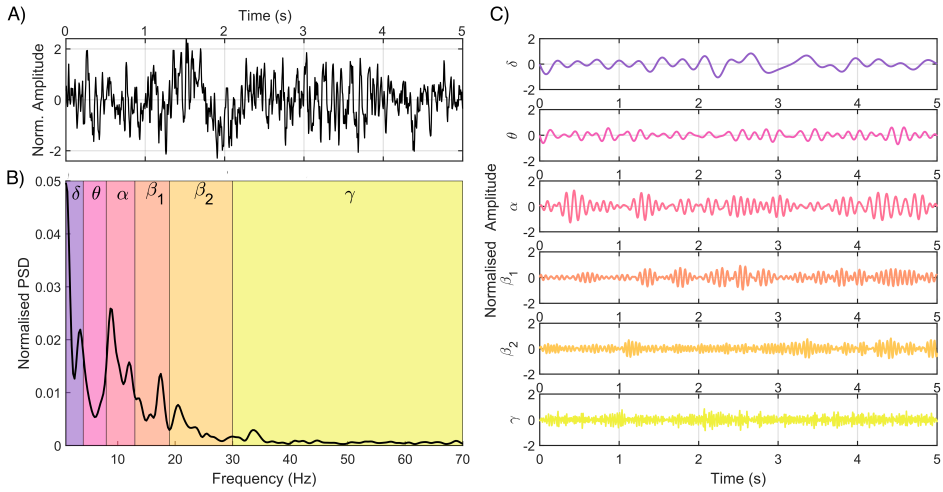

Figure 1.4: EEG activity acquired during rest from a cognitively healthy elderly control. A) 5-second EEG activity from channel Pz. B) Power spectral density (PSD) of the previous EEG segment. C) EEG segment decomposed into the canonical frequency bands: delta (δ, 1-4 Hz), theta (θ, 4-8 Hz), alpha (α , 8-13 Hz), beta-1 (β_1, 13-19 Hz), beta-2 (β_2, 19-30 Hz), and gamma (γ, 30-50 Hz). Based on Martínez-Cagigal (2020).

Brunet, 2019). The process of reconstructing the activity of neural sources from the activity observed in the sensors (*i.e.*, obtaining the "source-level" signals) is known as "the inverse problem" (Michel and Brunet, 2019).

Solving this problem is not straightforward, as the neural signals are distorted and mixed when travelling across the different brain tissues; they suffer from the so-called volume conduction and source mixing effects (Michel and Brunet, 2019). These effects are depicted in Figure 1.5. Of note, although MEG signals are more robust against these effects than EEG recordings, due to the homogeneity of the magnetic permeability of head tissues, they are still affected by them (Rampp and Stefan, 2007; Supek and Aine, 2019). Furthermore, the localisation of the neural sources is an ill-posed problem that requires making assumptions to restrict the solutions. There are different source localisation algorithms that limit the solutions making different types of assumptions: maximising correlation between neighbouring sources, minimising the energy of the solution, or considering spatial discriminators (Jatoi et al., 2014). In addition, this process requires *a-priori* knowledge about head tissues, and their physiology and conductivity (Michel and Brunet, 2019).

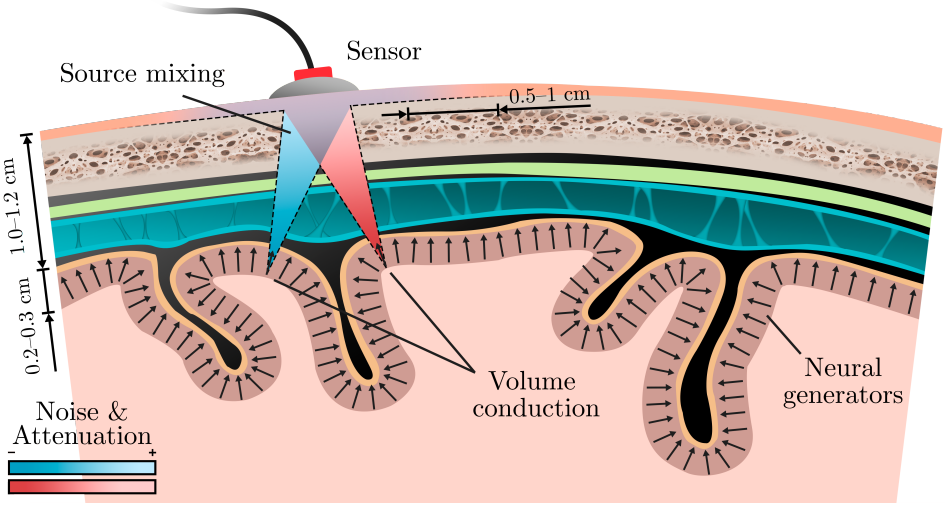

Figure 1.5: Illustration of the volume conduction and source mixing effects that M/EEG signals suffer when travelling across the different head tissues. The black arrows represent the different cortical sources. It has been represented how two of them (in red and blue) travel through the different tissues of the head, thus being distorted (this distortion is known as "volume conduction effects"); this effect has been represented here with a colour dilution and a progressive widening of the source. Also, during its travel the sources are mixed (which is known as "source mixing effects"), this effect appears in the figure in the greyish-blue area. This activity, distorted and mixed, is finally recorded by the acquisition sensor at the scalp. Based on Martínez-Cagigal (2020).

1.7.2 Traditional levels of analysis of M/EEG signals

The traditional analyses performed with M/EEG signals are typically grouped into two main categories:

- *Local activation analyses.* The objective of these studies is to evaluate the level of arousal of individual functional units, which can range from neurons to relatively large brain areas (Schomer and da Silva, 2017; Supek and Aine, 2019). Various metrics are used to achieve this goal, that can be mainly divided in two categories. On the one hand, the spectral parameters, which quantify the properties of the M/EEG signals in the frequency domain. These metrics evaluate the different oscillatory rhythms composing the signal (*e.g.*, relative power, RP), the diversity of frequency components of the power spectrum (*e.g.*, spectral entropy, SE), or specific properties of its shape (*e.g.*, skewness) (Ruiz-Gómez et al., 2018a; Sanei and Chambers, 2021; Schomer and da Silva, 2017; Supek and Aine, 2019). On the other

hand, the brain also exhibit a non-linear behaviour that can be studied in terms of the non-linear dynamics of brain activity (Guevara Erra et al., 2017). Hence, non-linear metrics measure the complexity (*e.g.*, Lempel-Ziv complexity, LZC), the variability (*e.g.*, Central Tendency Measure, CTM), or the irregularity (*e.g.*, Sample Entropy , SampEn) of neural activity (Gómez et al., 2009; Ren et al., 2023; Ruiz-Gómez et al., 2018a; Salankar et al., 2021).

- *Global synchronisation analyses.* These analyses assess the statistical dependency (*i.e.*, connectivity) between the time courses of the activity of individual neuronal pools (Engels et al., 2017). Connectivity measures estimate the neural coupling based on the amplitude (*e.g.*, amplitude envelope correlation, AEC), phase (*e.g.*, phase lag index, PLI), or time-frequency content (*e.g.*, coherence, Coh) of the signals (Bastos and Schoffelen, 2016; Cao et al., 2022; Colclough et al., 2016; Friston, 2011). For M/EEG time series, two different categories of connectivity can be found: i) functional connectivity, which evaluates the undirected association between pairs of sensors or sources; and ii) effective connectivity (EC), which also assesses causality (*i.e.*, the direction of these associations) (Friston, 2011). In this Doctoral Thesis we have focused on FC, as it is more widespread and is normally model-free, which reduces the requirement of making strict assumptions on the data (Cao et al., 2022). This level of analysis also encompasses the evaluation of the brain as a graph, with sensors (or brain areas) being the nodes, and the FC between them the links (Stam et al., 2009). To this end, network metrics based on graph theory are employed. These parameters offer valuable insights into the structure and properties of the brain network, such as integration, segregation, centrality, and complexity (Engels et al., 2017; Gomez-Pilar et al., 2018). Derived from connectivity studies, a new research field has emerged to analyse the dynamics of time-varying networks: chronnectomics. This new research area is focused on the identification of recurrent network topologies ("meta-states") and their fluctuation across time (Deco et al., 2013; Núñez et al., 2022, 2021).

1.7.3 Association networks

In this Doctoral Thesis we have also employed the so-called "association networks". They constitute a useful tool to quantify the complex relationships between heterogeneous variables by building a network whose nodes are the variables under study and the edges (or weights) are the links between them (Rodríguez-González

et al., 2021a). The association networks can be applied to variables of any nature, although their use in neuroscience research is a hot topic. In this regard, they have been employed to depict the complex interactions between symptoms in psychiatric disorders (Borsboom, 2017; Borsboom and Cramer, 2013; Jimeno et al., 2020), genes (Gutiérrez-Díez et al., 2021), or EEG-derived parameters and clinical variables (Gutiérrez-Tobal et al., 2021).

1.7.4 The Connectivity-based Meta-Bands algorithm

One of the main methodological contributions of this Doctoral Thesis that deserves further attention is the development of the Connectivity-based Meta-Bands (CMB) algorithm. As we have previously mentioned, most of the M/EEG literature considers the "conventional" frequency ranges. These bands have been extensively studied and validated physiologically, with abundant literature supporting the notion that they reflect specific brain patterns (Sanei and Chambers, 2021; Uhlhaas et al., 2008). Furthermore, they are widespread, which eases the replication across studies, as they provide a common framework. Nonetheless, their definition presents a series of limitations that should be considered:

- They were identified approximately 80 years ago, at a time when neural activity acquisition techniques were significantly different from those currently available (Berger, 1934; Jasper and Andrews, 1936, 1938; Walter, 1936; Walter and Dovey, 1944).

- The specific boundaries of the frequency bands present severe inconsistencies across studies (Newson and Thiagarajan, 2019). Besides, the number of frequency bands also varies (*e.g.*, some studies consider beta as a single band, while in others it is divided in beta-1, beta-2, and even, beta-3 and beta-4) (Hasanzadeh et al., 2020; Newson and Thiagarajan, 2019).

- The canonical frequency bands were introduced before the development of many of the current analysis methods, including connectivity and network analyses. Consequently, they were defined based on local activation patterns and may lose relevant features of global neural dynamics.

- They dismiss the individual idiosyncrasies of each person. To overcome this limitation, alternative approaches to frequency band segmentation have been proposed (Babiloni et al., 2010; Borghini et al., 2019; Cohen, 2021; Pascarelli et al., 2020; Puxeddu et al., 2021; Vecchiato et al., 2011). However, they use

fixed parameters, such as the number of bands or their bandwidth, which limits their ability to capture individual variability.

All these reasons conducted us to propose an automatic, and subject-specific frequency band segmentation algorithm, that we called the CMB algorithm. We based our algorithm in FC patters as it has been proposed that these dynamics reflect not only the long-range interactions, but also, to some extent, local activation patterns, thus providing a complete perspective of neural activity (Rodríguez-González et al., 2021b; Tewarie et al., 2019). The CMB algorithms enables, for the first time, to obtain a data-driven unsupervised frequency band segmentation based on the topology of the frequency-dependent connectivity structure.

This methodology starts by extracting a complete description of the connectivity patterns of the M/EEG recordings with a high frequency resolution. Then, the Louvain GJA community detection algorithm is applied to detect communities based on their connectivity topologies and obtain the meta-bands, *i.e.*, the individualised frequency band segmentation. This methodology allows to deepen the understanding of brain activity, by extracting the underlying frequency structure of neural dynamics. In addition, the CMB algorithm can also be employed to characterise the influence of neurological disorders in brain activity, by assessing how this structure is affected. In Rodríguez-González et al. (2023) the CMB algorithm was defined, and in Rodríguez-González et al. (2024) it was extended and its potential clinical use was evaluated to characterise MCI and AD dementia.

1.8 Doctoral Thesis overview

This Doctoral Thesis is presented as a compendium of four publications and, consequently, it is organised by chapters according to the following schema, following the normative of the University of Valladolid:

- **Chapter 1: Introduction**. This chapter provides the theoretical background required to understand the following chapters. Also, the thematic consistency is described to understand the publications, not as different contributions, but as a single scientific advance.
- **Chapter 2: Hypothesis and objectives**. This chapter sets forth the hypothesis and objective statement of this Doctoral Thesis..
- **Chapter 3: Papers included in this Doctoral Thesis**. This chapter encompasses all the papers included in the compendium of publications.

- **Chapter 4: Discussion**. This chapter presents the main findings of the research as well as their interpretation. Moreover, the main limitations of the conducted studies are described.

- **Chapter 5: Conclusions**. This section emphasises the primary contributions of the Doctoral Thesis and the key findings that we believe will be valuable for future researchers in the field. Additionally, the most interesting lines for future research are highlighted.

Chapter 2

Hypotheses and objectives

Human brain is considered as one of the most complex systems known by the human being. This complexity is likely why there are still unresolved methodological questions despite the extensive research on neuroscience, and more specifically in the analysis of M/EEG signals. In this Thesis we assessed two critical methodological open issues, employing a two-level approach: i) local activation analysis, thoroughly analysing these kind of metrics, with the focus in exploring their robustness against volume conduction and field spread effects; and ii) global synchronisation analysis, developing an individualised frequency band segmentation approach based on the FC network topologies. Within each level, innovative methodological solutions were proposed to address these challenges. Besides, these solutions paved the way for novel clinical applications of M/EEG signal analysis for patients with MCI and AD. Thereby, Section 2.1 details the hypotheses that have driven each of the studies included in the compendium of publications of this Doctoral Thesis, along with the overarching hypothesis that justifies the entire body of work. In addition, Section 2.2 outlines the main and specific objectives formulated to substantiate these hypotheses.

2.1 Hypotheses

Since their inception, M/EEG have undergone extensive research, resulting in significant advancements in our comprehension of brain function and organisation. Additionally, these techniques have expanded our knowledge of various disorders affecting the central nervous system and the changes they elicit in neural activity. Notably, MCI and dementia due to AD are particularly interesting due to their

high prevalence and the severity of their symptoms, making them a pressing social, medical, and economic concern, specially for most developed societies. However, this scientific field is still relatively young, leaving many open questions. Consequently the main hypothesis of this Doctoral Thesis is: *there are many methodological open questions that require attention, as they can be biasing many of the studies in the literature; addressing these questions is of utmost importance to solidify the already-established knowledge while unlocking new research prospects to enhance our understanding of neural activity; moreover, these newfound insights can facilitate the development of clinical applications of M/EEG signals.*

The neural signals recorded by M/EEG systems at the scalp undergo distortion as they travel through different head tissues, suffering what is known as volume conduction and field spread effects. Estimating the signals generated in the cortex (*i.e.*, source-level signals) from the M/EEG recordings acquired at the scalp (*i.e.*, sensor-level signals) is a hot research topic (Asadzadeh et al., 2020; Bonaiuto et al., 2018; Michel and Brunet, 2019; Song et al., 2015). Notwithstanding, the influence of volume conduction and field spread effects in the local activation parameters (those extracted from the time course of individual sensors) remains unexplored. Consequently, we hypothesise that: *the spectral and non-linear properties of M/EEG signals estimated at source-level are similar to those acquired at sensor-level; because of that, the studies evaluating these metrics should not generally require to solve the inverse problem to work with source-level signals; however, if the analyses involve a detailed evaluation of the spatial dimension, relevant information may be overlooked if conducted solely with sensor-level signals.* In Shigihara et al. (2020a) it was observed that local activation parameters are able to reflect the changes elicited by a non-pharmacological treatment against AD in neural signals. Considering the apparent relevance of the spatial dimension in these changes, we further hypothesise that: *the local activation parameters extracted from MEG activity are modulated by the NPT against AD, with the spatial patterns playing a pivotal role in reflecting such changes; as a consequence, these type of metrics can be able to predict the outcome of the NPT.*

One of the most commonly employed processes in the analysis of M/EEG signals is to filter them in the canonical frequency bands. However, these bands were defined at group-level, disregarding all the subject-specific neural idiosyncrasies. While this approach is supported by a large body of literature (Uhlhaas et al., 2008), modern tools and analysis techniques allow now more adaptive and personalised approaches (Goetz and Schork, 2018; Keizer, 2021). Although some adaptive band segmentation procedures have been proposed (Babiloni et al., 2010;

Cohen, 2021; Pascarelli et al., 2020; Puxeddu et al., 2021; Vecchiato et al., 2011), they are based on the activation of individual sensors, thus not accounting for the global synchronisation patterns, which are crucial in cognition and brain operation (Miljevic et al., 2022; Pessoa, 2014). Thus, we hypothesise that: *the frequency-dependent functional neural network structure has a remarkable between-subject variability that is not reflected by the canonical frequency bands.* In Núñez et al. (2021) it was observed a progressive blurring of the temporal structure of dynamic FC in patients with MCI and dementia due to AD. Therefore, we pose the hypothesis that: *MCI and dementia due to AD elicit alterations in the frequency-dependent functional neural network structure.*

2.2 Objectives

The leading objective of this Doctoral Thesis is *to propose novel methodological solutions to address two crucial methodological caveats in the field of the analysis of M/EEG signals. These solutions can be used as a foundation to develop potential clinical applications of M/EEG to patients with MCI and AD.* The Thesis follows a bottom-up approach: starting from the local activation level, where the neural activity at individual sensors (or sources) is analysed, and progressing to the global synchronisation level, where the whole brain is evaluated as an integrated system. Within each level, a methodological development is presented, and after that, its potential application for patients with MCI and AD is proposed. To this end, the following specific objectives are put forward:

SO1. To build a comprehensive dataset, composed by M/EEG recordings from three groups: healthy controls, patients with MCI, and patients with dementia due to AD. This dataset will also include sociodemographic data, clinical variables, and longitudinal follow-up information to provide a thorough characterisation of the subjects involved.

SO2. To asses the robustness of local activation parameters against volume conduction and field spread effects, that is, to assess the alterations that these parameters suffer when M/EEG signals travel across the different tissues of the head.

SO3. To explore whether local-activation source-level metrics derived from neural activity can predict the outcome of a NPT against dementia due to AD.

SO4. To develop an unattended, subject-specific, FC-based frequency band segmentation methodology useful to quantify the frequency-dependent connectivity structure of neural activity.

SO5. To explore and quantify the alterations that MCI and dementia due to AD elicit in the frequency-dependent FC structure of neural activity.

SO6. To critically assess and discuss the results to extract appropriate conclusions, by comparing our findings with those obtained in previous M/EEG studies.

SO7. To disseminate the main findings and conclusions of the studies in scientific journals indexed in the Journal Citation Reports (JCR), national and international conferences, scientific divulgation magazines, as well as media platforms and outreach activities for the communication of scientific knowledge to the general public.

Chapter 3

Papers included in this Doctoral Thesis

3.1 Consistency of local activation parameters at sensor- and source-level in neural signals

Consistency of local activation parameters at sensor- and source-level in neural signals (Rodríguez-González et al., 2020).

Víctor Rodríguez-González, Carlos Gómez, Yoshihito Shigihara, Hideyuki Hoshi, Marcos Revilla-Vallejo, Roberto Hornero, and Jesús Poza. *Journal of Neural Engineering*, vol. 14(5), p. 056020, 2020, DOI: 10.1088/1741-2552/abb582. Impact factor in 2020: 5.379, Q1 (20/89) in "ENGINEERING, BIOMEDICAL" and Q1 (66/273) in "NEUROSCIENCES" (Journal Citation Reports - Web of Science, JCR-WOS).

Objective: Although magnetoencephalography and electroencephalography (M/EEG) signals at sensor level are robust and reliable, they suffer from different degrees of distortion due to changes in brain tissue conductivities, known as field spread and volume conduction effects. To estimate original neural generators from M/EEG activity acquired at sensor level, diverse source localisation algorithms have been proposed; however, they are not exempt from limitations and usually involve time-consuming procedures. Connectivity and network-based M/EEG analyses have been found to be affected by field spread and volume conduction effects; nevertheless, the influence of the aforementioned effects on widely used local activation parameters has not been assessed yet. The goal of this study is to evaluate the consistency of various local activation parameters when they are computed at sensor- and source-level. *Approach:* Six spectral (relative power, median frequency, and individual alpha frequency) and non-linear parameters (Lempel-Ziv complexity, sample entropy, and central tendency measure) are computed from M/EEG signals at sensor- and source-level using four source inversion methods: weighted Minimum Norm Estimate (wMNE), standardised LOw-Resolution brain Electromagnetic TomograAphy (sLORETA), Linear Constrained Minimum Variance (LCMV), and dynamical Statistical Parametric Mapping (dSPM). *Main results:* Our results show that the spectral and nonlinear parameters yield similar results at sensor- and source-level, showing high correlation values between them for all the source inversion methods evaluated and both modalities of signal, M/EEG. Furthermore, the correlation values remain high when performing coarse-grained spatial analyses. *Significance:* To the best of our knowledge, this is the first study analysing how field spread and volume conduction effects impact on local activation parameters computed from resting-state neural activity. Our

findings evidence that local activation parameters are robust against field spread and volume conduction effects and provide equivalent information at sensor- and source-level even when performing regional analyses.

3.2 Exploring the interactions between neurophysiology and cognitive and behavioral changes induced by a non-pharmacological treatment: a network approach

Exploring the Interactions Between Neurophysiology and Cognitive and Behavioral Changes Induced by a Non-pharmacological Treatment: A Network Approach (Rodríguez-González et al., 2021a).

Víctor Rodríguez-González, Carlos Gómez, Hideyuki Hoshi, Yoshihito Shigihara, Roberto Hornero, and Jesús Poza. *Frontiers in Aging Neuroscience*, vol. 13(696174), p. 1-15, 2021, DOI: 10.3389/fnagi.2021.696174. Impact factor in 2021: 5.702, Q1 (67/275) in "NEUROSCIENCES" and Q2 (16/54) in "GERIATRICS & GERONTOLOGY" (Journal Citation Reports - Web of Science, JCR-WOS).

Dementia due to Alzheimer's disease (AD) is a neurological disorder that has an increasing impact in our society, provoking behavioural, cognitive, and functional disorders. AD lacks an effective pharmacological treatment; thereby, non-pharmacological treatments (NPTs) play a role of utmost importance in its treatment, as they have been proven to ameliorate AD symptoms. Nevertheless, results associated with NPTs are patient-dependent, and new tools are needed to predict their outcome and to improve their effectiveness. In this study, 19 patients with AD underwent an NPT. Magnetoencephalographic activity was recorded at the beginning and at the end of the NPT to evaluate the neurophysiological state of each patient. Additionally, their cognitive (quantified by means of the Mini-Mental State Examination, MMSE) and behavioural (measured in terms of the Dementia Behavior Disturbance Scale, DBD-13) statuses were collected before and after the NPT. We analysed the interactions between cognitive, behavioural, and neurophysiological states by generating diverse association networks, able to intuitively characterise the relationships between variables from different nature. Our results suggest that the NPT remarkably changed the structure of the association network, reinforcing the interactions between the DBD-13 and the neurophysiological parameters. We also found that the changes in cognition and behaviour are related with the changes in spectral-based neurophysiological parameters. Furthermore, our results support the idea that neurophysiological parameters can predict NPT outcome; specifically, a less degree of AD neurophysiological alterations (*i.e.*, neural oscillatory slowing, decreased variety of spectral components, and increased

signal regularity) predicts a better prognosis of the NPT. This study provides deeper insights into the relationships between neurophysiology and, both, cognitive and behavioural statuses, proving the potential of network-based methodologies to further understand the complex interactions elicited by NPTs.

3.3 Connectivity-based Meta-Bands: A new approach for automatic frequency band identification in connectivity analyses

Connectivity-based Meta-Bands: A new approach for automatic frequency band identification in connectivity analyses (Rodríguez-González et al., 2023).

Víctor Rodríguez-González, Pablo Núñez, Carlos Gómez, Yoshihito Shigihara, Hideyuki Hoshi, Miguel Ángel Tola-Arribas, Mónica Cano, Ángel Guerrero, David García-Azorín, Roberto Hornero, and Jesús Poza. *NeuroImage*, vol. 280, p. 120332, 2023, DOI: 10.1016/j.neuroimage.2023.120332. Impact factor in 2022: 5.700, D1 (1/14) in "NEUROIMAGING", Q1 (50/272) in "NEUROSCIENCES", and Q1 (17/135) in "RADIOLOGY, NUCLEAR MEDICINE & MEDICAL IMAGING" (Journal Citation Reports - Web of Science, JCR-WOS).

The majority of electroencephalographic (EEG) and magnetoencephalographic (MEG) studies filter and analyse neural signals in specific frequency ranges, known as canonical frequency bands. However, this segmentation, is not exempt from limitations, mainly due to the lack of adaptation to the neural idiosyncrasies of each individual. In this study, we introduce a new data-driven method to automatically identify frequency ranges based on the topological similarity of the frequency-dependent functional neural network. The resting-state neural activity of 195 cognitively healthy subjects from three different databases (MEG: 123 subjects; EEG_1: 27 subjects; EEG_2: 45 subjects) was analysed. In a first step, M/EEG signals were filtered with a narrow-band filter bank (1 Hz bandwidth) from 1 to 70 Hz with a 0.5 Hz step. Next, the connectivity in each of these filtered signals was estimated using the orthogonalised version of the amplitude envelope correlation to obtain the frequency-dependent functional neural network. Finally, a community detection algorithm was used to identify communities in the frequency domain showing a similar network topology. We have called this approach the "Connectivity-based Meta-Bands" (CMB) algorithm. Additionally, two types of synthetic signals were used to configure the hyper-parameters of the CMB algorithm. We observed that the classical approaches to band segmentation reflect the underlying network topologies at group level for the MEG signals, but they fail to adapt to the individual differentiating patterns revealed by our methodology. On the other hand, the sensitivity of EEG signals to reflect this underlying

frequency-dependent network structure is limited. To the best of our knowledge, this is the first study that proposes an unsupervised band segmentation method based on the topological similarity of functional neural network across frequencies. This methodology fully accounts for subject-specific patterns, providing more robust and personalised analyses, and paving the way for new studies focused on exploring the frequency-dependent structure of brain connectivity.

3.4 Unveiling the alterations in the frequency-dependent connectivity structure of MEG signals in mild cognitive impairment and Alzheimer's disease

Alterations in the frequency-dependent connectivity structure in MCI and AD (Rodríguez-González et al., 2024).

Víctor Rodríguez-González, Pablo Núñez, Carlos Gómez, Hideyuki Hoshi, Yoshihito Shigihara, Roberto Hornero, and Jesús Poza. *Biomedical Signal Processing and Control*, vol. 87, p. 105512, 2024, DOI: 10.1016/j.bspc.2023.105512. Impact factor in 2022: 5.100, Q2 (26/96) in "ENGINEERING, BIOMEDICAL" (Journal Citation Reports - Web of Science, JCR-WOS).

Mild cognitive impairment (MCI) and dementia due to Alzheimer's disease (AD) are neurological disorders that affect cognition, brain function, and memory. Magnetoencephalography (MEG) is a neuroimaging technique used to study changes in brain oscillations caused by neural pathologies. However, MEG studies often use fixed frequency bands, assuming a common frequency structure and overlooking both subject-specific variations and the potential influence of pathologies on frequency distribution. To address this issue, a novel methodology called Connectivity-based Meta-Bands (CMB) was applied to obtain a subject-specific functional connectivity-based frequency bands segmentation. Resting-state MEG activity was acquired from 161 participants: 67 healthy controls, 44 MCI patients, and 50 AD patients. The CMB algorithm was used to identify "meta-bands" (*i.e.*, recurrent network topologies across frequencies). The meta-bands were used to extract an individualised frequency band segmentation. The network topology of the meta-bands and their sequencing were analysed to identify alterations associated with MCI and AD in the underlying frequency-dependent connectivity structure. We found that MCI and AD alter the neural network topology, leading to connectivity patterns both more widespread in the frequency spectrum and heterogeneous. Furthermore, the meta-band frequency sequencing was modified, with MCI and AD patients exhibiting sequences with increased complexity, suggesting a progressive dilution of the frequency structure. The study highlights the relevance of considering the impact of neural pathologies on the frequency-dependent connectivity structure and the potential bias introduced by using fixed frequency bands in MEG studies.

Chapter 4

Discussion

In this Doctoral Thesis, relevant methodological caveats that have been biasing past and current studies in the field of M/EEG signal analysis were explored. In this process a two-level analysis was conducted. First, from a local activation point of view, the resilience of the local activation parameters against volume conduction and field spread effects was assessed. Next, the potential of these parameters to detect the neurophysiological changes elicited by a NPT for AD was evaluated by means of association networks. Second, in the global synchronisation level, *i.e.* considering the brain as an integrated system, it was assessed the frequency structure underlying the network brain dynamics. Derived from this study, a novel, unattended, subject-specific band segmentation algorithm was proposed. Also, it was assessed how the underlying frequency-dependent connectivity structure was altered by MCI and dementia due to AD.

This chapter will further discuss the key findings obtained through this two-level analysis. Additionally, in the last section, the main limitations of the Thesis will be presented.

4.1 Robustness of local activation metrics against volume conduction and field spread effects

In the study developed in Rodríguez-González et al. (2020) two main findings were extracted: *i) the local activation parameters consistently estimate various spectral and non-linear characteristics of neural oscillations, regardless of whether they are computed at the sensor- or source-level from EEG or MEG activity; ii)*

the regional patterns of the local activation parameters exhibit a strong correlation between both levels, however, fine spatial patterns may be lost if sensor-level signals are considered.

4.1.1 Consistency of local activation metrics between sensor- and source-level in neural signals

The volume conduction and field spread effects have been thoroughly studied (Asadzadeh et al., 2020; Bonaiuto et al., 2018; Lai et al., 2018; Michel and Brunet, 2019; Song et al., 2015). In this regard, in Lai et al. (2018) the alterations that these effects provoke in global synchronisation parameters were evaluated. Nonetheless, no previous works have considered how these effects influence the local activation parameters. In Rodríguez-González et al. (2020) this issue was addressed. To this end, several local activation parameters (3 spectral and 3 non-linear metrics) were calculated at sensor- and source-level (estimated by means of four different source inversion techniques: weighted Minimum-Norm Estimation, wMNE, standardised LOw-Resolution brain Electromagnetic TomogrAphy, sLORETA, Linearly Constrained Minimum Variance, LCMV, and dynamic Statistical Parametric Mapping, dSPM), and the consistency between them was evaluated. It was observed that these metrics are barely altered when the signals travel across the different structures of the head. Thus, scalp-level recordings reflect the overall neural fluctuations, albeit with subtle alterations in their spatio-temporal properties due to field spread and volume conduction effects. The different assumptions and restrictions made to calculate the local activation parameters at sensor- and source-level are likely eliciting these differences. However, as hypothesised, the parameters calculated at both levels exhibit strong relationships, and their distributions share similar shapes. These findings suggest that both sensor- and source-levels M/EEG recordings can capture the global properties of synchronous firing of neural populations in a similar way.

More specifically, it was observed that the only parameters that significantly differ between these levels are the non-linear ones; specifically, this issue was only observed for the LCMV source inversion method, with scalp-level recordings depicting more complex patterns. These results are in line with the literature, where studies analysing scalp-level signals report higher complexity values than those employing source-level recordings (Fernández et al., 2018, 2011; Ruiz-Gómez et al., 2018a; Shumbayawonda et al., 2020; Zhao et al., 2017; Zhu et al., 2017). In this regard, the results obtained by Echegoyen et al. (2020) are specially relevant, as they

found that the complexity and irregularity of MEG activity, measured by means of statistical complexity and permutation entropy, were slightly lower for the source-level time courses (estimated with LCMV) than for the sensor-level data. The LCMV source localisation algorithm is a beamforming technique, which involves applying spatial filters to the signal (van Veen et al., 1997). Thus, it is reasonable to hypothesise that this process could potentially lead to the attenuation of higher frequencies or a reduction in noise bandwidth, both of which are known to be associated with a loss of complexity (Aboy et al., 2006; Hornero et al., 2005). The influence of sampling frequency and epoch length on the consistency of local activation parameters between sensor- and source-level was also considered in Rodríguez-González et al. (2020). Interestingly, it was observed that both parameters exert an influence on this property, with higher values (of sampling frequency and epoch length) associated with a higher consistency between sensor and source levels, until the stability is reached and no further increases are obtained. This suggests that a minimum epoch length and sampling frequency are required to obtain robust estimations of the source-level recordings. Short epoch lengths may prevent the registration of slow neural activity, as the limited number of available oscillations hampers accurate estimation of the power spectral density, thereby introducing bias into the computation of spectral parameters (Roach and Mathalon, 2008). On the other hand, while the inversion process is less impacted by sampling frequency, lower values of this parameter may lead to distortion capturing the neural activity at higher frequencies (Rodríguez-González et al., 2020).

4.1.2 Influence of volume conduction and field spread effects in the spatial patterns of neural activity

The influence of volume conduction effects in local activation parameters was also evaluated in five different regions of interest (ROIs). Although the correlation values of the parameters between sensor- and source-level decrease when considering specific spatial regions, they are still very high; so it can be concluded that regional analyses yield highly comparable results when conducted at both levels. It is noteworthy that MEG signals showed increased consistency compared with EEG, which can be explained by different factors: i) the increased spatial resolution of the MEG recordings, as it has been proven that this parameter positively affects the accuracy of the source localisation (Lai et al., 2018; Lantz et al., 2003); ii) the anatomic atlas (Desikan-Killiany) implies artificially upsampling the spatial resolution of the EEG recordings, and this could potentially hamper

an accurate reconstruction of the neural sources; iii) the reference electrode of the EEG recordings has a noticeable impact in the analyses (Yao et al., 2005), thus it was hypothesised that it may also be influencing the source estimation results, although the selection was carefully performed based on previous studies (Rodríguez-González et al., 2020); iv) the intrinsic differences between EEG and MEG, as EEG is sensitive to radial and tangential sources, whereas MEG is only sensitive to the latter ones (Ahlfors et al., 2010; Cohen and Cuffin, 1987; Singh, 2014; Supek and Aine, 2019); and v) magnetic permeability remains relatively constant across all head tissues and free space, and thus MEG signals are more robust against volume conduction and field spread effects (Hämäläinen et al., 1993; Lai et al., 2018). Finally, it is important to indicate that in Rodríguez-González et al. (2020) a "coarse-grain" spatial segmentation approach was employed, so it is likely that using a "fine-grain" segmentation would reveal significant differences in activation patterns between sensor- and source-levels.

4.2 Local activation parameters to evaluate the changes in the interplay between electrophysiology, cognition, and behaviour elicited by a NPT for dementia due to AD

The efforts carried out during the work in Rodríguez-González et al. (2020) allowed to get deep insights into the local activation parameters. First of all, the expertise acquired during the development and analyses of the set of parameters employed there planted the seed of considering their potential to be used in a real clinical scenario, such as the prediction of the outcome of therapies. Crucially, the conclusions extracted in Rodríguez-González et al. (2020) led to the analyses of Rodríguez-González et al. (2021a) at source-level, as we wanted to capture all the information contained in the spatial dimension of neural patterns by means of a novel metric, the Shannon Spatial Entropy (SSE).

Consequently, in Rodríguez-González et al. (2021a) the impact of a NPT on the neurophysiology of AD patients was examined. The NPT demonstrated significant improvements in both cognition (measured by the Mini-Mental State Examination, MMSE), and behaviour (assessed by the Dementia Behavior Disturbance Scale, DBD-13). This is in line with other NPTs against dementia, that have been proven to reduce the symptoms (Shigihara et al., 2020b; Zucchella et al., 2018). Interest-

ingly, it was also assessed whether local activation MEG parameters could predict the effectiveness of the NPT. To this end, association networks were employed, as they provide an intuitive framework to assess complex interactions between variables of different nature. Three main findings were observed in this study: *i) the NPT alters the complex interplay between neurophysiological metrics and the neuropsychological variables; ii) the observed changes elicited by the NPT are connected to those observed in the behavioural status of the patients, supporting the idea that the NPT modulates their behavioural symptoms; and iii) the values of the local activation parameters extracted from resting-state MEG activity before conducting the NPT are related with the outcome of the therapy, suggesting their potential predictive power.*

4.2.1 Changes in the complex interactions between local activation metrics and neuropsychological variables induced by the NPT

Before conducting the NPT, the local activation parameters showed association with the cognition (measured by means of the MMSE), but not with the behavioural disturbances (measured by means of the DBD-13). Despite both tests measure alterations provoked by dementia, they are sensitive to different cognitive domains. MMSE assesses cognitive impairment from a broader perspective, encompassing various cognitive dimensions including attention, orientation, language, perception, calculation, and the ability to follow simple instructions (Folstein et al., 1975). On the other hand, DBD-13 is strictly sensitive to behavioural alterations, considered as "*the outward manifestation of some underlying cognitive, psychological, or physiological deficit—regardless of etiology—likely to cause stress to those caring for the patient*" (Baumgarten et al., 1990). This indicates that, while the broad cognitive alterations are directly related with the neurophysiological state, the behavioural disturbances may be mediated by external factors such as the environment or daily habits that can be controlled during the NPT. Interestingly, conducting the NPT unlinked the associations between RP_{Gamma} and $S(RP_{Gamma})$ (*i.e.*, the SSE of the RP_{Gamma} values). This finding can be interpreted as the NPT modulating the alterations in the neural oscillatory components at the gamma band caused by AD. Gamma activity is linked to gamma-aminobutyric acid (GABA), which is the primary inhibitory neurotransmitter (Bartos et al., 2007; Porges et al., 2017). As higher levels of GABA are associated with improved cognitive performance, it can be hypothesised a connec-

tion between gamma activity and cognitive function (Bartos et al., 2007; Mably and Colgin, 2018; Porges et al., 2017). Furthermore, GABA system has been previously associated with behavioural and psychological symptoms of dementia (Lanctôt et al., 2004). Moreover, an increase in gamma band activity in the angular gyrus has been observed after conducting a NPT for AD (Shigihara et al., 2020b). This increase is believed to be associated with the NPT triggering compensatory mechanisms to counteract the functional deficits caused by dementia (Shigihara et al., 2020b). Conducting the NPT revealed new correlations between MMSE and RP_{Delta}, RP_{Beta1}, RP_{Beta2}, and $S(RP_{Beta2})$. These frequency bands are linked to the widely documented slowing in oscillatory neural activity provoked by AD (Dauwels et al., 2011; Jeong, 2004), so it is reasonable to hypothesise that the NPT affect the neuronal pools firing at these frequency ranges.

Behavioural symptoms are very prevalent in dementia, and have a significant impact in health and quality of life of the patients (Dyer et al., 2018). Importantly, results revealed that most of the associations that exhibited the greatest changes after undergoing the NPT involve the DBD-13 (which is the test employed to measure the behavioural alterations). This observation can be attributed to the controlled environment and regulated habits during the NPT; that is, the therapeutic intervention is controlling external factors that could obscuring the associations between DBD-13 and the neurophysiological parameters. In this regard, it was demonstrated that the NPT not only reduced the behavioural symptoms of the patients, but also revealed their correlation with neurophysiological oscillatory activity (Rodríguez-González et al., 2021a). These findings are aligned with previous studies that demonstrated NPTs to be more effective against behavioural symptoms compared to cognitive symptoms (Zucchella et al., 2018). Notably, more than half of these most-significant associations involving DBD-13 are SSEs of the neurophysiological parameters. This suggests that the spatial dimension of neurophysiology plays a substantial role in the changes induced by the NPT; hence, different brain regions are affected by the NPT in a distinctive manner and, consequently, the SSE of local activation metrics can quantify such changes. This is supported by prior research where NPT effects were observed in specific brain regions (Shigihara et al., 2020a,b; Zucchella et al., 2018).

4.2.2 Relationships between the changes in neurophysiology, cognition, and behaviour

In Rodríguez-González et al. (2021a), it was observed an association between the changes in beta activity (and the associated SSE), and the outcome of the treatment (*i.e.*, the changes in cognition and behaviour). This is supported by previous studies that have reported associations between RP_{Beta} and cognitive changes induced by an NPT in dementia patients (Shigihara et al., 2020a,b). The beta activity has been related with AD in the literature, with a widely reported decreased beta intensity in MCI and AD patients (Dauwels et al., 2011; Fernández et al., 2006; Jeong, 2004; Poza et al., 2007; Roh et al., 2011), which suggests its use as a clinical tool for aiding in AD diagnosis and assessing neural disruption processes (Poil et al., 2013). This frequency band is associated with emotional processes, somatosensory functions, and GABA activity (Jensen et al., 2005; Poil et al., 2013); with the latter also being linked to neuroplasticity (Griffen and Maffei, 2014), and behavioural and psychological symptoms of dementia (Lanctôt et al., 2004).

The presence of relationships between the changes in SSEs of neurophysiological parameters and the outcome of the NPT supports the previous idea that the NPT affects diverse brain regions differently. In other words, the changes induced by the NPT follow a specific spatial pattern. This is in line with previous studies that reported a differential effect of the NPT in different brain areas (Shigihara et al., 2020a,b; Zucchella et al., 2018). This may be attributed to the ability of the NPT to rehabilitate specific cognitive domains (Zucchella et al., 2018), which are associated with particular brain regions (Augustine, 2007). Interestingly, the changes of non-linear parameter are not associated with the outcome of the NPT, which may be explained by the non-linear metrics affecting specific cognitive domains not (or only barely) reflected by the MMSE or DBD-13. This also can be attributed to the limited sensitivity of non-linear metrics to AD disruptions, which is supported by previous studies that reported lower efficiency of non-linear metrics to detect AD using MEG recordings compared with the spectral ones (Escudero et al., 2009; Hornero et al., 2008; Poza et al., 2012).

4.2.3 Potential of neurophysiological parameters to predict the outcome of the NPT

Remarkable between-subject differences in the success of the NPT have been previously reported, with some subjects showing big improvements, while others remaining unresponsive (Shigihara et al., 2020a). Hence, being able to predict the

outcome of the therapy is of paramount interest in clinical settings, as it allows to adjust the treatment or find alternative clinical pathways, increasing the efficiency of the healthcare systems when dealing with dementia.

It can be observed that the spectral metrics show stronger correlations with the NPT outcome than the non-linear ones, which can be related with the increased alterations elicited by AD in the spectral properties of neural oscillations regarding the non-linear ones (Escudero et al., 2009; Hornero et al., 2008; Poza et al., 2012). Looking at the spectral components, the delta and beta frequencies seem to be more relevant for the prediction of the NPT outcome. As previously discussed, beta band is closely related with cognition and AD. Nonetheless, delta range has been also associated with the progression of AD, the cognitive status, neurodegeneration, and the cholinergic level (which has been suggested to be involved in the onset of AD) (Fernández et al., 2013; Nakamura et al., 2018; Shigihara et al., 2020a). Interestingly, the delta-beta ratio has been widely employed to measure the disruptions provoked by AD (Babiloni et al., 2004; Knyazeva et al., 2010; Poza et al., 2008; Wang et al., 2017). Also, the results showed that a less degree of AD-related disruptions (*i.e.*, slowing and loss of complexity of neural oscillations (Dauwels et al., 2011; Escudero et al., 2009; Jeong, 2004)) is associated with a better prognosis.

Lastly, it is noteworthy that many of the metrics related with the outcome of the NPT are SSEs and, notably, they show a positive correlation with it. This finding is aligned with previous studies that highlighted the relevance of the spatial dimension in the changes that NPTs produce in neural oscillations (Shigihara et al., 2020a,b). In addition, this issue suggests that a more uniform distribution of the corresponding local activation parameters across the brain predicts a better prognosis for the NPT. As AD progresses through the different brain regions gradually (Raji et al., 2009), a decreased SSE indicates neural damage concentrated in specific areas. Consequently, the NPT may be unable to restore the functionality of these regions, yielding to a decreased performance of the therapy.

4.3 Connectivity-based Meta-Bands: an unattended, subject-based band segmentation approach

The two first papers included in the compendium of publications (*i.e.*, Rodríguez-González et al. (2021a, 2020)) covered one of the broad categories of M/EEG

analysis: the local activation patterns. These metrics evaluate the activity of individual neuronal pools, and have yielded the neuroscience field to achieve enormous advances during the last decades (Babiloni et al., 2021; Cohen, 2014; Supek and Aine, 2019). However, this type of metrics disregards a relevant aspect of brain functioning: the interactions between different brain regions enable their operation as an integrated system (Cohen, 2014). Hence, connectivity analyses provide a more comprehensive evaluation of neural function, as they capture the statistical dependencies between the neural activity from different brain regions (Cohen, 2014). The next two papers included in the compendium of publications assess one issue of utmost importance in this level of analysis: the segmentation of neural activity into fixed frequency bands. Although they are supported by a large number of papers, they are subject to a variety of pitfalls that yielded us to challenge their usage.

The study presented in Rodríguez-González et al. (2023) introduces the "Connectivity-based Meta-Bands" (CMB) algorithm, a novel data-driven method for identifying subject-specific frequency ranges in M/EEG signals. The research considered synthetic neural signals, as well as resting-state EEG and MEG recordings from 195 cognitively healthy subjects. Three main findings were extracted from this study: *i) the CMB algorithm is able to decipher the underlying frequency structure of functional connectivity; ii) this algorithm revealed that classical approaches for band segmentation align only partially with the true frequency structure in MEG signals at group-level, but they are missing relevant individual idiosyncrasies that should be considered; and iii) the EEG signals displayed a simpler frequency parcellation that did not fit the canonical bands.* This innovative methodology, the first of its kind, provides a more personalised and robust approach to assess brain connectivity, opening new avenues for research in neuroscience.

4.3.1 Revisiting canonical frequency bands

The well-known canonical frequency bands have garnered substantial support from an extensive body of research. It is evident that these bands reflect fundamental physiological mechanisms (Buzsáki and Draguhn, 2004; Sanei and Chambers, 2021). However, several challenges associated with them prompt us to seek an alternative: i) they were defined about eight decades ago, when the neural activity acquisition techniques offered remarkably lower quality than those currently available (Berger, 1934; Jasper and Andrews, 1936, 1938; Walter, 1936; Walter and Dovey, 1944); ii) their specific definition is remarkably inconsistent, with different

band boundaries across studies (Newson and Thiagarajan, 2019); iii) they were defined by visually inspecting the recordings, focusing on the amplitude and dominant frequency of the signals, whereas now we have advanced analysis methods that enable a more comprehensive signal characterisation; and iv) the canonical frequency bands disregard all the subject-specific neural dynamics. Other algorithms for frequency band segmentation proposed adaptive frequency bands, but they are also based on the amplitude or dominant frequency of the signals, and make some *a-priori* assumptions about the frequency ranges to be considered for the bands (Borghini et al., 2019; Pascarelli et al., 2020). Nevertheless, the growing interest in personalised analyses has encouraged us to the development of the CMB algorithm, enabling the definition of frequency bands tailored to the individual neural idiosyncrasies, with a novel data-driven method that allows an increased level of personalisation compared with the currently available adaptive approaches. Hence, in Rodríguez-González et al. (2023) we proposed the CMB algorithm, which defines a new, user-specific frequency band segmentation based in the concept of "meta-bands". Meta-bands are network topologies recurrent across frequencies, that can be considered as "attractors" of the connectivity topology at each frequency bin.

A direct comparison between the frequency segmentation provided by the CMB algorithm and the canonical bands is not straightforward, since the CMB algorithm discards any assumption made by the canonical bands: the frequency ranges do not match, the number of meta-bands is different, and the meta-bands span through non-adjacent frequency ranges. In the case of resting-state activity, the only reasonable comparison could be made with canonical alpha band (*i.e.*, 8-13 Hz), as we have identified a meta-band consistently active around alpha frequencies. This makes sense, considering that it has been proved that alpha activity governs brain dynamics during rest-state eyes-closed condition (Millett, 2001; Trajkovic et al., 2021). Notably, this meta-band exhibits occipital connectivity traits, akin that observed in the canonical alpha band during rest (Goldstein et al., 2015; de Vries et al., 2013). However, the coincidence of this meta-band with the fixed alpha band is just 60%, and with adaptive alpha band 67%. This points out that, although the well-established band segmentation methods offer a good initial approach about the underlying topological structure of functional connectivity at group-level, they fail to capture the individual neural idiosyncrasies. In this context, the CMB algorithm can flexibly adapt to the specific neural patterns of each individual, devoid of any prior assumptions, in contrast to the canonical and adaptive methods.

Taking into account these ideas, we formulated some insights about the us-

age of the canonical frequency bands. On the one hand, we considered that their usage with EEG signals should be executed with caution, as our findings showed that they do not accurately capture the underlying frequency structure of functional connectivity. On the other hand, for MEG signals, the canonical frequency bands offer a convenient framework that facilitates cross-study comparisons, but overlooking relevant subject-specific neural specificities. In this regard, if computational capabilities allow it, the CMB algorithm should be employed in resting-state connectivity analyses, as it fully adapts to the individual frequency-dependent connectivity patterns, removing the bias associated to employing the canonical frequency bands.

4.3.2 Unveiling the fundamental functional network configurations

For MEG signals, three well-defined meta-bands can be observed in resting-state neural activity, whereas in the EEG databases, only two dominant meta-bands are identified. It is important to emphasise that these findings do not imply that our resting-state neural activity is characterised by only two or three specific network topologies; rather, they point out to the recurring presence of three network topologies across different frequencies during the resting-state condition.

This is the first time that the neural meta-bands were identified, so it is not possible to make direct associations with previous works. However, if we consider the meta-bands as the frequential counterpart of the meta-states detected in the time domain (Núñez et al., 2021), we can extract some interesting insights. Although the number of time meta-states identified varies across studies, their repertoire is typically constrained, often following a heavy-tail distribution where a small set of meta-states are frequently activated (von Schwanenflug et al., 2023). This configuration provides an efficient approach to process neural information (Ramirez-Mahaluf et al., 2020; von Schwanenflug et al., 2023). Hence, it is reasonable to hypothesise that the limited number of meta-band topologies that we have identified may also arise from the optimisation of neural information processing, which has been suggested to be one of the primary factors shaping brain organisation (Bullmore and Sporns, 2012).

It is noteworthy that the meta-bands expand across disjoint frequency ranges. Three factors may be explaining this finding: i) a blending effect provoked by averaging different trials of resting-state activity, which has been proved to exhibit a highly dynamic evolution of network topologies (Núñez et al., 2021); ii)

cross-frequency couplings, as these interactions are known to be pivotal in the processing and transmission of neural information (Cho et al., 2015; Händel and Haarmeier, 2009; Riddle et al., 2021); and iii) an optimisation of neural resources, with a reduced number of topologies serving different functions depending on the frequency range in which they operate (Bullmore and Sporns, 2012; Uhlhaas et al., 2008), which is supported by previous studies that revealed the preservation of certain graph characteristics of neural networks across different frequencies (Bassett et al., 2006; Bullmore and Sporns, 2009). Of note, from a mathematical perspective, the canonical frequency bands also show similar network topologies for distant frequency ranges (Rodríguez-González et al., 2023).

The meta-band identified across the canonical alpha frequencies shows an occipital topology, similar to what has been observed in other studies investigating resting-state M/EEG signals within the alpha band (Colclough et al., 2016; Hillebrand et al., 2012; Miraglia et al., 2017). This topology resembles the posterior areas of the default-mode network (DMN), which is believed to dominate brain activity during periods of rest (Fauchon et al., 2022; Raichle et al., 2001; Raichle and Snyder, 2007; Vidaurre et al., 2018). This association with the posterior DMN is supported by previous research, which observed increased alpha activity (Fauchon et al., 2022; Vidaurre et al., 2018) and connectivity (Vidaurre et al., 2018) in these regions during rest. Notably, the posterior areas of the DMN have been linked to higher cognitive functions, including information integration, attention, empathy, self-reflection, and the occurrence of mental thoughts during periods of rest (Culham and Kanwisher, 2001; Fauchon et al., 2022; Raichle and Snyder, 2007).

There is another meta-band consistently activated in theta and beta frequencies that shows a fronto-central topology. This topology resembles that observed in a previous work with resting-state MEG signals in the beta band (Hillebrand et al., 2012). This meta-band could be associated with the anterior DMN (Fauchon et al., 2022; Vidaurre et al., 2018), which is highly active in theta frequencies (Fauchon et al., 2022; Vidaurre et al., 2018). The anterior DMN is known to play a role in higher cognitive functions such as semantic integration, emotional processing, and decision-making (Fellows and Farah, 2007; Tsapkini et al., 2011). Moreover, the activity around beta frequencies of this meta-band may be associated with the sensorimotor network, which is highly active and connected in the beta frequencies (Fauchon et al., 2022), and shares some overlapping areas with this meta-band (Fauchon et al., 2022). The sensorimotor network is also involved in neural processes related to perception, proprioception, and motor functions (Caspers et al., 2021; Chenji et al., 2016; Feher, 2012). Additionally, the beta

band plays crucial role in forming canonical resting-state networks (Hipp et al., 2012), implying a significant contribution to information processing within and across cortical circuits (Little et al., 2019), which may explain, at least partially, the role of this meta-band in brain function.

4.4 Unveiling the alterations in the frequency-dependent connectivity structure of MEG signals in mild cognitive impairment and Alzheimer's disease

The conclusions extracted in Rodríguez-González et al. (2023) led to develop a potential clinical application to the CMB algorithm. As this methodology was able to characterise the subject-specific frequency-dependent connectivity structure, we hypothesised whether MCI and AD elicit alterations in this structure. This is particularly relevant, as may pose an explanation to the inconsistencies found across connectivity studies involving dementia patients (Fide et al., 2022; Jalili, 2016; Kaminski and Blinowska, 2018).

In Rodríguez-González et al. (2024), the CMB algorithm was used to evaluate the alterations that MCI and AD elicit in the frequency-based structure of brain connectivity. To this end, resting-state MEG data from 161 participants, including healthy controls, MCI patients, and patients with dementia due to AD were analysed. Two key findings were derived from this study: *i) MCI and AD alter the brain's network frequency structure provoking more widespread and heterogeneous connectivity patterns; ii) MCI and AD also modify this structure provoking alterations in the "meta-band" sequencing, eliciting a progressive dilution of the frequency structure.* This research provides a fresh perspective that paves the way for future research in this domain. In this regard, this study underscores the importance of considering pathology-induced alterations in frequency-dependent connectivity when studying cognitive disorders and highlights the potential bias introduced by fixed frequency bands in MEG studies.

4.4.1 The frequency-dependent functional connectivity patterns

The HC_{train} and HC_{test} frequency band sequencing depicted three dominating meta-bands, with a sequencing aligned with the findings in Rodríguez-González

et al. (2023). Interestingly, the sample included there was larger (123 subjects) and included also healthy young participants. The most noticeable difference between these two contributions is in the meta-band activated around alpha frequencies: while in Rodríguez-González et al. (2023) it dominates in alpha and in high beta frequencies, here it is mainly centred in alpha. The two previously-mentioned differences in the cohorts of subjects included in the studies may be explaining this divergence. On the one hand, the sample size has been proven to influence the resulting meta-band sequencing, although its influence is not huge (Rodríguez-González et al., 2023). On the other hand, the age may also be contributing to this difference, as previous studies proved that the functional connectivity patterns are altered during the lifespan (Schäfer et al., 2014; Smit et al., 2012; Wen et al., 2020).

4.4.2 Beyond the disconnection syndrome: blurring of the meta-band structure

This study analysed for the first time how MCI and dementia due to AD progressively affect the meta-band topology and its sequencing. To quantify the alterations in the frequency-dependent connectivity structure, novel metrics were introduced in this study for the first time. Previous studies already identified alterations in the functional connectivity elicited by MCI and dementia due to AD, leading to their consideration as "disconnection syndromes" (Badhwar et al., 2017; Delbeuck et al., 2007; Engels et al., 2015; Ishii et al., 2017; Koelewijn et al., 2017; Sheline and Raichle, 2013); however they often yielded contradictory conclusions (Fide et al., 2022; Jalili, 2016; Kaminski and Blinowska, 2018), which may be provoked by the bias associated to the segmentation of the neural signals in the canonical frequency bands (Rodríguez-González et al., 2023). Moreover, a recent study has proposed a novel approach that takes advantage of deep learning and explainable artificial intelligence techniques to investigate these frequency-dependent connectivity alterations linked to MCI and dementia due to AD, with a specific emphasis on understanding the dynamics underlying the transition from MCI to AD dementia (Morabito et al., 2023). However, the work developed in Rodríguez-González et al. (2024) provides a unique perspective on these alterations. Instead of considering them solely as disconnections, it provides a complete description of the specific alterations that occurs in each frequency. In this regard, this innovative approach sheds new light on the complex changes in neural activity associated with dementia, and offers a fresh angle for understanding the progression of this

condition.

The Topological Adaptation (TA) showed statistically significant differences between HC and AD groups, suggesting that the dementia influences the frequency-dependent topological structure of functional connectivity. These results are in line with previous research conducted by Knyazeva et al. (2013, 2010), who also identified global functional connectivity alterations in AD when analysing the broadband. Moreover, the connectivity matrices associated with the meta-band activated around delta and gamma bands (MB1) exhibited significant differences between HC individuals and patients with MCI in all comparisons. These findings may suggest that early cognitive alterations manifest within these frequencies. This finding is consistent with prior studies that reported changes in functional connectivity in individuals with MCI and early dementia due to AD within delta (Handayani et al., 2018; Musaeus et al., 2019; Tóth et al., 2014) and gamma frequencies (Gómez et al., 2009). Notably, the functional connectivity of delta and theta bands has been linked to the MCI-to-AD dementia progression (Musaeus et al., 2019). Besides, Musaeus et al. (2019) observed that the pathological alterations associated with that progression occur in a widespread fashion, which agrees with the topology of MB1.

The analysis of the Attraction Strength (AS) metric reveals statistically significant differences only in the comparison between HC and AD patients. This suggests that the topological similarity between the connectivity matrices and their corresponding meta-band mainly occurs in advanced stages of the dementia. On the other hand, the mean of the Degree of Divergence (DoD) displays statistically significant differences between HC and AD, and the standard deviation of the DoD for all the comparisons (HC-AD, HC-MCI, and MCI-AD). This may suggest that the pathological disruptions are also reducing the similarity balance between the dominant meta-band and the other ones. In essence, these results indicate that the progression of dementia gradually elicits a dilution of the network topologies, which is evident as: i) the similarity of the connectivity matrices with their corresponding meta-bands is decreased; ii) the difference in similarity between the connectivity matrices and both the dominant meta-band and the non-dominant meta-bands is reduced; and iii) the standard deviation of the DoD, which measures the variety of this balance, is also reduced. This finding suggests a shift toward more homogeneous topologies, supporting the loss of specialised and integrated networks, with their functions potentially assumed by other brain regions. This is supported by previous contributions, which observed decreased clustering coefficient and modularity for AD patients, indicative of more homogeneous and

widespread network topologies (Brier et al., 2014; de Haan et al., 2009; Stam et al., 2009).

The data distributions of the Switching Rate (SR) and the Band Complexity (B_{LZC}) show similar tendencies: progressively higher values with the onset of the pathology, and statistically significant differences between HC and AD dementia patients. However, it is important to note that, although both metrics parametrise the meta-band sequence, they are sensitive to different properties. The SR values indicates that the pathological states (MCI and AD dementia) have less stable meta-bands, with more transitions between the active meta-band through the broadband. This metric is conceptually similar to the dwell time parameter used by Núñez et al. (2022, 2021), which characterised the stability of time-dependent meta-states. They concluded that the stability of the meta-states decreased for MCI and dementia due to AD patients, which is in line with our observations in the frequency dimension (Núñez et al., 2021). Notably, a prior study reported narrower alpha bands for AD patients (as indicated by the decreased transition frequency) (Moretti et al., 2004), which might be associated with neural compensatory mechanisms (Moretti et al., 2004). Moreover, the progressive increase in B_{LZC} for MCI and dementia due to AD patients indicates that the mechanisms governing meta-band transitions are also affected by the disease. In this regard, Núñez et al. (2021) reported an increase in the complexity in the sequence of time-dependent EEG meta-states for MCI and AD patients. These results support the idea of a progressive loss of time-frequency structure of the neural networks with the development of dementia. Previous studies demonstrated that more stable temporal meta-states are associated with increased network efficiency (Ramirez-Mahaluf et al., 2020; Zalesky et al., 2014). Moreover, efficient transitions between meta-states are related with higher-level cognitive processes (Ramirez-Mahaluf et al., 2020). Thus, it is reasonable to consider that the increased B_{LZC} observed in patients may be attributed to a loss of optimisation in neural mechanisms.

These findings hold great significance, as they provide insights into the underlying mechanisms driving the progression of dementia. They also offer a potential explanation about the lack of consensus observed regarding the network alterations associated with MCI and dementia due to AD, where different studies have yielded very different (and often contradictory) results (Briels et al., 2020; Fide et al., 2022; Franciotti et al., 2019; Jalili, 2016; Kaminski and Blinowska, 2018). The framework applied in our study opens up new avenues for understanding and characterising the neural alterations associated with MCI and AD, enabling new research lines in this domain.

4.5 Limitations of the thesis

The results of this Doctoral Thesis are novel, significant, and relevant; nevertheless, it is important to acknowledge and address some limitations that deserve further consideration. First of all, across all the studies we have employed five different databases, that accumulate more than 500 subjects. Although this number is enough for obtaining meaningful and robust conclusions, and larger than many of the M/EEG studies in the literature, it is clear that all the employed databases would benefit from the incorporation of new recordings. Increasing the sample size would allow to obtain a more comprehensive characterisation of neural dynamics, allowing a more robust estimation of the frequency-dependent functional connectivity structure of HC and dementia patients, as described in Rodríguez-González et al. (2024, 2023). Regarding the EEG datasets, it is worth mentioning that the time courses of 68 ROIs were reconstructed from 19 or 32 electrodes (depending on the database). That is, the spatial resolution of the results is artificially upsampled. Hence, the results, in terms of the spatial dimension, should be carefully evaluated, analysing broad brain areas (*e.g.*, right prefrontal regions) instead of focusing in specific ROIs (*e.g.*, right frontal pole).

In Rodríguez-González et al. (2024, 2023) we presented and assessed the CMB algorithm, which is based on the Louvain GJA algorithm for the automatic community detection process. Although this method exhibits advantageous properties, providing good performance in scenarios with weakly-defined communities (Gates et al., 2016), there are a wide array of community detection methods in the literature that could be explored and compared with the Louvain GJA.

Also, in Rodríguez-González et al. (2024, 2023), due to the high computational burden associated to the CMB algorithm, the functional connectivity was considered to remain static across time. However, as observed in Núñez et al. (2022, 2021) neural networks exhibit a highly dynamic behaviour, that is modified due to dementia-related pathological alterations (Núñez et al., 2021). Therefore, disregarding the intrinsic time-varying patterns in functional neural networks may be influencing the information extracted about the frequency-dependent neural networks.

Finally, the CMB algorithm employed the orthogonalised version of the AEC to estimate the connectivity. This metric was employed as it is replicable, consistent, and robust against volume conduction effects (Colclough et al., 2016; Schoonhoven et al., 2022); however, it has been reported that different connectivity metrics are sensitive to diverse neural patterns (He et al., 2019; Schoonhoven et al., 2022).

Moreover, the employed orthogonalisation procedure is not able to totally remove the signal leakage, as it assumes that the data follows a Gaussian distribution and has a constant signal-to-noise ratio in time and frequency domains (Brookes et al., 2012).

Chapter 5

Conclusions

This Doctoral Thesis has gone through two broad categories of analyses of neural activity, addressing open issues that could be biasing the studies conducted using M/EEG signals. In this regard, methodological solutions to these open questions were proposed; expanding our knowledge about well-established methodological processes, and potentially improving the validity of the corresponding results by reducing bias factors.

Moreover, the solutions proposed for these open issues paved the way for the clinical applications on MCI and dementia due to AD, which were also developed in this Thesis. It is intended for these two clinical studies to be the stepping stone towards a: i) development of a computerised tool that helps the doctors to predict the outcome of NPT against dementia; and ii) deepen our understanding of the neural alterations associated with MCI and AD dementia, getting deeper insights on the pathological pathways of these disorders.

During the development of this Doctoral Thesis, it was revealed the implications of conducting the local-activation analyses at sensor- or source-level, which remained an open issue for the last years. It was observed that these metrics present high consistency at both levels, although some information about the spatial dimension of the data is missing at sensor-level. This broadened knowledge about this type of metrics led to consider them as potential predictors of the outcome of a NPT against AD, observing their promising capabilities in this predictive role.

Furthermore, a new algorithm for providing a data-driven subject-specific frequency band segmentation for M/EEG signals was developed: the CMB algorithm. This allowed to unveil the true frequency-dependent structure of neural networks,

posing a interesting alternative to the canonical frequency bands that are not able to fully reflect this underlying structure of the hierarchical organisation of brain activity. Finally, this novel methodology was used to characterise the pathological alterations that MCI and dementia due to AD elicit in the frequency-dependent connectivity structure.

In this chapter, the original contributions achieved in this Doctoral Thesis are highlighted (section 5.1), and the main conclusions extracted from the papers composing the compendium of publications are listed (section 5.2). Finally, the future research lines that were established during the studies that encompass the compendium of publications are described (section 5.3).

5.1 Contributions

The main contributions achieved during the development of this Doctoral Thesis are listed below:

i) Comparison of the neural patterns that a representative set of local activation metrics show between sensor- and source-level. Different local activation metrics were calculated at sensor- and source-level using different source inversion techniques (sLORETA, wMNE, LCMV, and dSPM), and a thorough comparison between them was made. Results showed high consistency between both levels, suggesting that, for these types of analyses, the source inversion process is only necessary when the spatial dimension plays a significant role (Rodríguez-González et al., 2020).

ii) Characterisation of the ability of local activation metrics extracted from resting-state MEG activity to predict the outcome of a NPT against AD. Results demonstrated that the application of a NPT modifies the complex relationships between the different local activation metrics studied and the neuropsychological status of the patients (Rodríguez-González et al., 2021a).

iii) Demonstration of the potential of association networks as intuitive tools to ease the interpretation of the complex interactions between the heterogeneous variables involved in assessing the outcome of a NPT (Rodríguez-González et al., 2021a).

iv) Development of a new metric, the Shannon Spatial Entropy (SSE), that is sensitive to spatially-limited alterations in neural activity (Rodríguez-González et al., 2021a).

v) Development of a subject-specific data-driven algorithm for automatic frequency band segmentation that overcomes the limitations of the current approaches: the CMB algorithm. Results revealed a frequency-dependent connectivity structure only partially overlapped with canonical frequency bands, with many individual particularities that can now be accounted for. The CMB algorithm introduces a new framework to explore and quantify the frequency-dependent structure of functional connectivity in M/EEG signals (Rodríguez-González et al., 2023).

vi) Assessment of the different sensitivity of EEG and MEG to the frequency-dependent neural network structure. Results showed an increased sensitivity of MEG recordings to the underlying organisation of connectivity patterns in the frequency domain (Rodríguez-González et al., 2023).

vii) Characterisation of the alterations that MCI and dementia due to AD elicit in the frequency-based structure of connectivity identified by the CMB algorithm. Our findings revealed that both pathologies elicit a progressive dilution of the frequency structure of the connectivity patterns and less defined network topologies (Rodríguez-González et al., 2024).

5.2 Main conclusions

The exhaustive examination of the findings obtained in this Doctoral Thesis, as well as their discussion in Chapter 4, allowed deriving the following global conclusions:

i) Local activation metrics are robust against volume conduction and field spread effects. The global data distribution of spectral and non-linear parameters show great similarity between sensor- and source-level, independently of the source localisation algorithm. If the spatial dimension of the results is considered, the correlation between levels is reduced; hence, studies where spatial information is specially relevant should be conducted at source-level (Rodríguez-González et al., 2020).

ii) Undergoing a NPT against AD not only modifies the values of the local activation metrics calculated from resting-state MEG signals, but also the statistical dependencies between them (Rodríguez-González et al., 2021a).

iii) Local activation metrics extracted from resting-state MEG activity have the potential to predict the outcome of a NPT against AD. A higher neurophysiological decline (indicated by slower and less complex resting-state activity) is associated with a worse prognosis of the therapy (Rodríguez-González et al., 2021a).

iv) The CMB algorithm arises as a promising alternative to the current methodologies for frequency band segmentation of M/EEG signals, overcoming their limitations and fully adapting to the specific idiosyncrasies of the individuals and to the neural activity recording modality (Rodríguez-González et al., 2023).

v) The CMB algorithm revealed, for the first time, a frequency-dependent connectivity structure composed by three dominating meta-bands for resting-state MEG signals. In the case of resting-state EEG recordings, only two dominant meta-bands were appreciated (Rodríguez-González et al., 2023). These meta-bands are network topologies that can be considered as "attractors" of the functional connectivity during rest (Rodríguez-González et al., 2023).

vi) The canonical frequency bands partially reflect the underlying frequency-dependent connectivity structure for resting-state MEG signals. The structure that they provide reflects the group-level frequency structure of functional connectivity; however, there are several subject-specific idiosyncrasies that they are not considering and could be biasing many studies (Rodríguez-González et al., 2023).

vii) The canonical frequency bands do not match the frequential network structure for resting-state EEG recordings. In this regard, their usage should be carefully considered in connectivity studies (Rodríguez-González et al., 2023).

viii) EEG recordings are not as sensitive as MEG signals to detect the underlying frequency-dependent structure of brain connectivity (Rodríguez-González et al., 2023).

ix) MCI and dementia due to AD elicit alterations in the frequency structure of functional neural networks identified by the CMB algorithm that can be grouped in two different categories. On the one hand, the topologies observed across frequencies are more heterogeneous, which may be related with the

loss of specialised neural networks. On the other hand, these pathologies also blur the meta-band sequencing, with less stable meta-band activations, possibly associated with a loss of neural optimisation processes (Rodríguez-González et al., 2024).

x) The CMB algorithm opens new research avenues by allowing the individual study of the alterations that different neurological and psychiatric pathologies produce in the frequential structure of the brain connectivity (Rodríguez-González et al., 2024, 2023).

The main objective of this Doctoral Thesis was achieved, as two relevant open issues for the scientific community focused on analysing M/EEG signals were effectively addressed. Also, the studies dedicated to solve these pitfalls paved the way for the development of novel clinical applications of the analysis of M/EEG recordings and for increasing our comprehension of MCI and dementia due to AD. All the specific objectives established to accomplish the main one were also successfully achieved, concretely:

SO1. A complete dataset, composed by recordings of different signal modalities (EEG and MEG) from HC, patients with MCI, and patients with AD was built. Crucially, this dataset was continuously expanded during the course of the Doctoral Thesis

SO2. The robustness of local activation parameters against volume conduction and field spread effects was thoroughly assessed, revealing a high stability of these metrics against them.

SO3. The potential of local-activation metrics to predict the outcome of a NPT against AD was successfully demonstrated.

SO4. An innovative, subject-specific, automatic, FC-based frequency band segmentation approach was developed: the CMB algorithm.

SO5. The alterations that MCI and dementia due to AD elicit in the frequency-dependent connectivity structure were characterised, contributing to our understanding of these neurodegenerative diseases.

SO6. All the results were critically assessed, drawing appropriate conclusions by comparing our findings with previous M/EEG studies, and adding depth to the existing body of knowledge in the field.

SO7. The main findings and conclusions of the studies conducted in this Doctoral Thesis were disseminated in scientific journals indexed in the JCR index, in national and international conferences, and in scientific divulgation magazines, as demonstrated by the Appendix A: Scientific achievements of this document. Besides, they were also effectively communicated to the general public through media platforms and outreach activities, fostering broader awareness and understanding of this novel knowledge.

5.3 Future research lines

The research carried out throughout the Doctoral Thesis has provided solutions to methodological pitfalls in the field of M/EEG analysis, while simultaneously unveiling additional questions. The following avenues of research remain captivating and should be explored in forthcoming research endeavours; however, they were not included in this Thesis as they are out of scope.

First, the sample size is high, but it could be expanded, not only to increase the statistical power of the results, but also to include recordings of different nature. Adding high-density EEG recordings would enable more fair comparisons with the MEG signals, as their original spatial resolution (*i.e.*, the number of sensors) would be more alike. This is particularly interesting to assess, by means of the CMB algorithm, whether high-density EEG recordings provide a similar sensitivity to the underlying frequency-dependent functional connectivity structure as MEG signals (Rodríguez-González et al., 2023). Also, incorporating additional medical imaging techniques such as fNIRS, MRI, or PET scans would allow to make more thorough analyses of brain function and obtain a more comprehensive understanding of the pathological pathways of MCI and AD dementia. Moreover, task-related recordings would also help us to increase our understanding of brain operation not only in an instrinsic state, but also when it is involved in different tasks. Additionally, longitudinal recordings and evaluations of the participants should be incorporated to the databases to explore the MCI-AD continuum. This would enable the differentiation between patients with MCI who later progress to dementia due to AD and those who do not. Such a distinction opens up numerous research avenues, including the exploration of neurological differences in the brains of these two groups. In this regard, the detection of neural networks associated with mechanisms that prevent the development of AD in individuals affected by MCI could be facilitated. This line of research could significantly advance our understanding of the factors that influence disease progression and may lead to

more targeted therapies for those individuals at risk of developing AD. Finally, increasing the sample size of the database employed in (Rodríguez-González et al., 2021a) will allow to perform more thorough evaluations of the impact of the NPT in AD patients, thus being able to do subject-specific adaptations to increase its effectiveness.

Connected with the issue above, larger sample sizes would enable to conduct reliable machine-learning, or even deep-learning classification studies that will possibly lead to the development of potential early biomarkers of AD. This is specially relevant, as new promising AD treatments are emerging (Alzheimer's Disease International, 2022), and it has been observed that some of them (both pharmacological and non-pharmacological) are more effective in the initial phases of the disease (Cummings et al., 2023; Rodríguez-González et al., 2021a). In the near future, developing a reliable and effective computerised diagnostic support tool would be of utmost importance for healthcare systems.

The CMB algorithm was developed employing the Louvain GJA community detection algorithm, which is unattended and has good performance with poorly defined communities (Blondel et al., 2008; Gates et al., 2016; Núñez et al., 2022, 2021); nevertheless, the CMB algorithm was specially designed to be able to operate with any community detection approach. In this regard, exploring other community detection algorithms may uncover community structures that the current detection procedure may not be able to capture effectively. Moreover, expanding the database would allow to evaluate its performance with task-related recordings. Also, the CMB algorithm was developed employing only the AEC as connectivity metric. It has been observed that different connectivity metrics are sensitive to different features of brain operation (He et al., 2019; Schoonhoven et al., 2022). Thus, it would be interesting to assess the performance of the CMB algorithm with different connectivity metrics. In this line, considering effective connectivity methods may also be an interesting future research line.

Additionally, the CMB algorithm employs a static functional connectivity approach, mainly due to the high computational cost. By optimising its operation, it may be possible to employ a dFC approach, which would allow to capture the highly dynamic behaviour associated to brain functional networks (Núñez et al., 2022, 2021). It would be interesting to merge the CMB algorithm with the "meta-state" identification pipeline developed in Núñez et al. (2021) in order to develop an algorithm able to identify dynamically evolving meta-bands (*i.e.*, neural states that dynamically evolve in both time and frequency).

Furthermore, it is intriguing to explore the precise roles of meta-bands by de-

signing specific experiments known to be linked to particular functional networks. This approach would not only serve to further validate the meta-band identification algorithm, but also to facilitate the examination and discussion of the results obtained with the CMB algorithm.

Lastly, it would be of utmost importance to replicate the results obtained in the studies conducted in this Doctoral Thesis with public independent databases from different centres (clinical and research ones). This will contribute to address the problem of the "replication crisis" that neuroscience is suffering (Miłkowski et al., 2018).

In summary, in this Doctoral Thesis we have designed synthetic signals to demonstrate the validity of the methodological contributions, and analysed resting-state EEG and MEG data from HC, patients with MCI, and patients with AD. The efforts carried out in the studies composing the Doctoral Thesis addressed two relevant open issues for the two main levels of analysis of M/EEG signals. The solutions proposed for these pitfalls paved the way to clinical applications for MCI and dementia due to AD. Crucially, a novel algorithm was proposed to overcome the limitations of the canonical frequency bands. This innovation has paved the way for exploring novel research directions, offering valuable insights into the complexities of brain functioning, the mechanisms behind higher cognitive functions, the neuropathological pathways of different neurological and psychiatric pathologies, and, in short, enhancing our comprehension of the intricate system governing our behaviour: the brain.

Appendix A

Scientific achievements

A.1 Publications

A.1.1 Papers indexed in the JCR

1. Pablo Núñez, Jesús Poza, Carlos Gómez, **Víctor Rodríguez-González**, Arjan Hillebrand, Miguel A. Tola-Arribas, Mónica Cano, Roberto Hornero, Characterizing the fluctuations of dynamic resting-state electrophysiological functional connectivity: Reduced neuronal coupling variability in mild cognitive impairment and dementia due to Alzheimer's disease, Journal of Neural Engineering, vol. 16 (5), pp. 056030, September, 2019, DOI: 10.1088/1741-2552/ab234b.

2. **Víctor Rodríguez-González**, Carlos Gómez, Yoshihito Shigihara, Hideyuki Hoshi, Roberto Hornero, Marcos Revilla-Vallejo, Jesús Poza, Consistency of local activation parameters at sensor- and source-level in neural signals, Journal of Neural Engineering, vol. 17 (5), pp. 1-14, October, 2020, DOI: 10.1088/1741-2552/abb582.

3. Yoshihito Shigihara, Hideyuki Hoshi, Jesús Poza, **Víctor Rodríguez-González**, Carlos Gómez, Predicting the outcome of non-pharmacological treatment for patients with dementia-related mild cognitive impairment, Aging-Us, vol. 12 (23), pp. 24101-24116, December, 2020, DOI: 10.18632/aging.202270.

4. Saúl J. Ruiz-Gómez, Roberto Hornero, Jesús Poza, Eduardo Santamaría-Vázquez, **Víctor Rodríguez-González**, Aarón Maturana-Candelas, Carlos

Gómez, A new method to build multiplex networks using Canonical Correlation Analysis for the characterization of the Alzheimer's disease continuum, Journal of Neural Engineering, vol. 18 (2), pp. 026002, February, 2021, DOI: 10.1088/1741-2552/abd82c.

5. Pablo Núñez, Jesús Poza, Carlos Gómez, **Víctor Rodríguez-González**, Arjan Hillebrand, Prejaas Tewarie, Miguel A. Tola-Arribas, Mónica Cano, Roberto Hornero, Abnormal meta-state activation of dynamic brain networks across the Alzheimer spectrum, Neuroimage, vol. 232, pp. 117898, May, 2021, DOI: 10.1016/j.neuroimage.2021.117898.

6. Rika Haraguchi, Hideyuki Hoshi, Sayuri Ichikawa, Mayuko Hanyu, Kohei Nakamura, Keisuke Fukasawa, Jesús Poza, **Víctor Rodríguez-González**, Carlos Gómez, Yoshihito Shigihara, The menstrual cycle alters resting-state cortical activity: A magnetoencephalography study, Frontiers in Human Neuroscience, vol. 15, pp. 652789, July, 2021, DOI: 10.3389/fnhum.2021.652789

7. Takahiro Matsumoto, Hideyuki Hoshi, Yoko Hirata, Sayuri Ichikawa, Keisuke Fukasawa, Tomoyuki Gonda, Jesús Poza, **Víctor Rodríguez-González**, Carlos Gómez, Yoshihito Shigihara, The association between carotid blood flow and resting-state brain activity in patients with cerebrovascular diseases, Scientific Reports, vol. 11, pp. 15225, July, 2021, DOI: 10.1038/s41598-021-94717-0.

8. **Víctor Rodríguez-González**, Carlos Gómez, Hideyuki Hoshi, Yoshihito Shigihara, Roberto Hornero, Jesús Poza, Exploring the interactions between neurophysiology and cognitive and behavioral changes induced by a non-pharmacological treatment: a network approach, Frontiers in Aging Neuroscience, vol. 13, pp. 696174, July, 2021, DOI: 10.3389/fnagi.2021.696174.

9. Aarón Maturana-Candelas, Carlos Gómez, Jesús Poza, **Víctor Rodríguez-González**, Víctor Gutiérrez-de Pablo, Alexandra M. Lopes, Nádia Pinto, Roberto Hornero, Influence of PICALM and CLU risk variants on beta EEG activity in Alzheimer's disease patients, Scientific Reports, vol. 11, pp. 20465, October, 2021, DOI:10.1038/s41598-021-99589-y.

10. Pablo Núñez, Carlos Gómez, **Víctor Rodríguez-González**, Arjan Hillebrand, Prejaas Tewarie, Javier Gomez-Pilar, Vicente Molina, Roberto Hornero, Jesús Poza, Schizophrenia induces abnormal frequency-dependent

patterns of dynamic brain network reconfiguration during an auditory oddball task, Journal of Neural Engineering, vol. 19 (1), pp. 016033, February, 2022, DOI: 10.1088/1741-2552/ac514e.

11. Hideyuki Hoshi, Yoko Hirata, Momoko Kobayashi, Yuki Sakamoto, Keisuke Fukasawa, Sayuri Ichikawa, Jesús Poza, **Víctor Rodríguez-González**, Carlos Gómez, Yoshihito Shigihara, Distinctive effects of executive dysfunction and loss of learning/memory abilities on resting- state brain activity, Scientific Reports, vol. 12, pp. 3459, March, 2022, DOI: 10.1038/s41598-022-07202-7.

12. Eduardo Santamaría-Vázquez, Víctor Martínez-Cagigal, Diego Marcos-Martínez, **Víctor Rodríguez-González**, Sergio Pérez-Velasco, Selene Moreno-Calderón, Roberto Hornero, MEDUSA©: A novel Python-based software ecosystem to accelerate brain-computer interface and cognitive neuroscience research, Computer Methods and Programs in Biomedicine, vol. 230, pp. 107357, March, 2023, DOI: 10.1016/j.cmpb.2023.107357.

13. Diego Marcos-Martínez, Eduardo Santamaría-Vázquez, Víctor Martínez-Cagigal, Sergio Pérez-Velasco, **Víctor Rodríguez-González**, Ana Martín-Fernández, Selene Moreno-Calderón, Roberto Hornero, ITACA: An open-source framework for Neurofeedback based on Brain-Computer Interfaces, Computers in Biology and Medicine, vol. 160, June, 2023, DOI: 10.1016/j.compbiomed.2023.107011.

14. **Víctor Rodríguez-González**, Pablo Núñez, Carlos Gómez, Yoshihito Shigihara, Hideyuki Hoshi, Miguel A. Tola-Arribas, Mónica Cano, Ángel Luis Guerrero, David García Azorín, Roberto Hornero, Jesús Poza, Connectivity-based Meta-Bands: A new approach for automatic frequency band identification in connectivity analyses, Neuroimage, vol. 280, pp. 120332, October, 2023, DOI: 10.1016/j.neuroimage.2023.120332.

15. **Víctor Rodríguez-González**, Pablo Núñez, Carlos Gómez, Hideyuki Hoshi, Yoshihito Shigihara, Roberto Hornero, Jesús Poza, Unveiling the alterations in the frequency-dependent connectivity structure of MEG signals in mild cognitive impairment and Alzheimer's disease, Biomedical Signal Processing and Control, vol. 87, pp. 105512, January, 2024, DOI: 10.1016/j.bspc.2023.105512.

16. Inés Fernández-Linsenbarth, Gema Mijancos, Alejandro Bachiller, Pablo Núñez, **Víctor Rodríguez-González**, Rosa M. Beño-Ruiz-de-la-Sierra, Alejandro Roig-Herrero, Antonio Arjona-Valladares, Jesús Poza, Miguel A. Mañanas, Vicente Molina, Relation between task-related activity modulation and cortical inhibitory function in schizophrenia and healthy controls: A TMS-EEG study, European Archives of Psychiatry and Clinical Neuroscience, January, 2024, DOI: 10.1007/s00406-023-01745-0.

17. Natalia Kopiś-Posiej, Andrzej Cudo, Pawel Krukow, Mark D. Griffiths, Jesús Poza, Carlos Gómez, Víctor Rodríguez-González, The relationship of problematic Facebook use and Facebook context on empathy for pain processing: A functional near-infrared spectroscopy study, Computers in Human Behavior, vol. 114 (108196), pp. 1-7, June, 2024, DOI: 10.1016/j.chb.2024.108196.

18. Víctor Gutiérrez-de Pablo, Jesús Poza, Aarón Maturana-Candelas, **Víctor Rodríguez-González**, Miguel A. Tola-Arribas, Mónica Cano, Hideyuki Hoshi, Yoshihito Shigihara, Roberto Hornero, Carlos Gómez, Exploring the disruptions of the neurophysiological organization in Alzheimer's disease: An integrative approach, Computer Methods and Programs in Biomedicine, vol. 250, pp. 108197, June, 2024, DOI: 10.1016/j.cmpb.2024.108197.

A.1.2 Non-indexed papers

1. **Víctor Rodríguez-González**, El reto de 'fotografiar' la huella eléctrica que deja el alzhéimer para encontrar sus puntos débiles, The Conversation, 2022

2. Francisco Salto Alemany, Carmen Requena Hernández, Paula Álvarez Merino, **Víctor Rodríguez-González**, Jesús Poza, Roberto Hornero, Electrical analysis of logical complexity: An exploratory EEG study of logically valid/invalid deductive inference, Brain Informatics, vol. 10 (13), pp. 1-15, June, 2023, DOI: 10.1186/s40708-023-00194-8.

A.1.3 International conferences

1. Pablo Núñez, Jesús Poza, Carlos Gómez, Saúl J. Ruiz-Gómez, **Víctor Rodríguez-González**, Miguel A. Tola-Arribas, Mónica Cano, Roberto Hornero, Analysis of Electroencephalographic Dynamic Functional Connectivity in Alzheimer's Disease, World Congress on Medical Physics & Biomed-

ical Engineering (IUPESM 2018), pp. 165-168, Prague (Czech Republic), 3 June - 8 June, 2018.

2. Pablo Núñez, Jesús Poza, Carlos Gómez, **Víctor Rodríguez-González**, Saúl J. Ruiz-Gómez, Aarón Maturana-Candelas, Roberto Hornero, Characterizing Non-stationarity in Alzheimer's Disease and Mild Cognitive Impairment by Means of Kullback-Leibler Divergence, International Conference on NeuroRehabilitation (ICNR 2018), ISBN: 978-3-030-01844-3, pp. 574-578, Pisa (Italy), 16 October - 20 October, 2018.

3. Saúl J. Ruiz-Gómez, Carlos Gómez, Jesús Poza, Pablo Núñez, **Víctor Rodríguez-González**, Aarón Maturana-Candelas, Roberto Hornero, Analysis of Information Flux in Alzheimer's Disease and Mild Cognitive Impairment by Means of Graph-Theory Parameters, International Conference on NeuroRehabilitation (ICNR 2018), ISBN: 978-3-030-01844-3, pp. 569-573, Pisa (Italy), 16 October - 20 October, 2018

4. **Víctor Rodríguez-González**, Jesús Poza, Pablo Núñez, Carlos Gómez, María García, Yoshihito Shigihara, Hideyuki Hoshi, Eduardo Santamaría-Vázquez, Roberto Hornero, Towards Automatic Artifact Rejection in Resting-State MEG Recordings: Evaluating the Performance of the SOUND Algorithm, 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society, ISBN: 978-1-5386-1311-5, pp. 4807-4810, Berlin (Germany), 23 July - 27 July, 2019.

5. Saúl J. Ruiz-Gómez, Carlos Gómez, Jesús Poza, Aarón Maturana-Candelas, **Víctor Rodríguez-González**, María García, Miguel A. Tola-Arribas, Mónica Cano, Roberto Hornero, Analysis of Volume Conduction Effects on Different Functional Connectivity Metrics: Application to Alzheimer's Disease EEG Signals, 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society, ISBN: 978-1-5386-1311-5, pp. 6434-6437, Berlin (Germany), 23 July - 27 July, 2019.

6. Saúl J. Ruiz-Gómez, Carlos Gómez, Jesús Poza, Marcos Revilla-Vallejo, Víctor Gutiérrez-de Pablo, **Víctor Rodríguez-González**, Aarón Maturana-Candelas, Roberto Hornero, Volume Conduction Effects on Connectivity Metrics: Application of Network Parameters to Characterize Alzheimer's Disease Continuum, 42nd Annual International Conference of the IEEE Engineering in Medicine and Biology Society, ISBN: 978-1-7281-1990-8, Montreal (Canada), 20 July - 24 July, 2020.

7. Marcos Revilla-Vallejo, Saúl J. Ruiz-Gómez, **Víctor Rodríguez-González**, Víctor Gutiérrez-de Pablo, Roberto Hornero, Carlos Gómez, Jesús Poza, Functional connectivity metrics and volume conduction effects in Alzheimer's disease, Basic and Clinical Multimodal Imaging International Conference, pp. 14-15, Online (Italy), 14 October - 17 October, 2021.

8. Pablo Núñez, **Víctor Rodríguez-González**, Víctor Gutiérrez-de Pablo, Carlos Gómez, Yoshihito Shigihara, Hideyuki Hoshi, Roberto Hornero, Jesús Poza, Effect of segment length, sampling frequency, and imaging modality on the estimation of measures of brain meta-state activation: an MEG/EEG study, 43rd Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC 2021), ISBN: 978-1-7281-1179-7, pp. 315-318, Online (Mexico), 1 November - 5 November, 2021.

9. **Víctor Rodríguez-González**, Víctor Gutiérrez-de Pablo, Carlos Gómez, Yoshihito Shigihara, Hideyuki Hoshi, Roberto Hornero, Miguel A. Tola-Arribas, Mónica Cano, Jesús Poza, High Frequential Resolution Networks: Considerations on a New Functional Brain Connectivity Framework, 43rd Annual International Conference of Mexico), 1 November - 5 November, 2021.

10. **Víctor Rodríguez-González**, Carlos Gómez, Hideyuki Hoshi, Yoshihito Shigihara, Roberto Hornero, Jesús Poza, Assessing The Influence of Power Line Interference In Connectivity Analyses, IUPESM World Congress on Medical Physics and Biomedical Engineering 2022, pp. 125, Singapur (Singapur), 12 June - 17 June, 2022.

11. Eduardo Santamaría-Vázquez, Víctor Martínez-Cagigal, **Víctor Rodríguez-González**, Sergio Pérez-Velasco, Diego Marcos-Martínez, Roberto Hornero, MEDUSA: A Novel Platform for Modern Non-invasive Brain-computer Interfaces, IUPESM World Congress on Medical Physics and Biomedical Engineering 2022, Singapur (Singapur), 12 June - 17 June, 2022.

12. Marcos Revilla-Vallejo, Carlos Gómez, Javier Gomez-Pilar, Pablo Núñez, **Víctor Rodríguez-González**, Hideyuki Hoshi, Yoshihito Shigihara, Roberto Hornero, Jesús Poza, Exploring the robustness of the MEG functional neural network in patients with dementia due to Alzheimer's disease, The 22nd International Conference on Biomagnetism (BIOMAG 2022), Birmingham (United Kingdom), 28 August - 1 September, 2022.

A.1.4 National conferences

1. Saúl J. Ruiz-Gómez, Carlos Gómez, Jesús Poza, Pablo Núñez, **Víctor Rodríguez-González**, Miguel A. Tola-Arribas, Mónica Cano, Roberto Hornero, Caracterización de los Patrones de Flujo de Información en el EEG de Pacientes con Deterioro Cognitivo Leve, XXXV Congreso Anual de la Sociedad Española de Ingeniería Biomédica (CASEIB 2017), ISBN: 978-84-9082-797-0, pp. 217-220, Bilbao (Spain), 29 November - 1 December, 2017.

2. **Víctor Rodríguez-González**, Jesús Poza, Carlos Gómez, Pablo Núñez, Saúl J. Ruiz-Gómez, Aarón Maturana-Candelas, Roberto Hornero, Localización de fuentes cerebrales para la caracterización de la demencia debida a enfermedad de Alzheimer, XXXVI Congreso Anual de la Sociedad Española de Ingeniería Biomédica (CASEIB 2018), ISBN: 978-84-09-06253-9, pp. 195-198, Ciudad Real (Spain), 21 November - 23November, 2018.

3. Saúl J. Ruiz-Gómez, Carlos Gómez, Jesús Poza, Pablo Núñez, **Víctor Rodríguez-González**, Adrián Martín-Montero, Aarón Maturana-Candelas, Roberto Hornero, Estudio del efecto de la conducción de volumen en medidas de conectividad funcional derivadas de la coherencia, XXXVI Congreso Anual de la Sociedad Española de Ingeniería Biomédica (CASEIB 2018), ISBN: 978-84-09-06253-9, pp. 241-244, Ciudad Real (Spain), 21 November - 23 November, 2018.

4. **Víctor Rodríguez-González**, Jesús Poza, Carlos Gómez, Miguel A. Tola-Arribas, Mónica Cano, Roberto Hornero, Assessing the influence of cognitive reserve in EEG signals through Alzheimer's Disease progression, XXXIV Simposium Nacional de la Unión Científica Internacional de Radio (URSI 2019), ISBN: 978-84-09-12961-4, pp. 1-4, Seville (Spain), 4 September - 6 September, 2019.

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6. **Víctor Rodríguez-González**, Carlos Gómez, Marcos Revilla-Vallejo,

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8. Javier Gomez-Pilar, Víctor Gutiérrez-de Pablo, **Víctor Rodríguez-González**, Carlos Gómez, Ángel Luis Guerrero, Miguel Alves-Ferreira, Nádia Pinto, Roberto Hornero, Análisis espectral de la electroencefalográfica basal a nivel de fuente para la diferenciación de subtipos de migraña, XL Congreso Anual de la Sociedad Española de Ingeniería Biomédica (CASEIB 2022), ISBN: 978-84-09-45972-8, pp. 287-290, Valladolid (Spain), 23 November - 25 November, 2022.

9. Víctor Gutiérrez-de Pablo, Javier Gomez-Pilar, **Víctor Rodríguez-González**, Jesús Poza, Ángel Luis Guerrero, Miguel Alves-Ferreira, Nádia Pinto, Roberto Hornero, Carlos Gómez, Alteraciones patológicas de la estructura neurofisiológica en los diferentes subtipos de migraña en mujeres, XL Congreso Anual de la Sociedad Española de Ingeniería Biomédica (CASEIB 2022), ISBN: 978-84-09-45972-8, pp. 402-405, Valladolid (Spain), 23 November - 25 November, 2022.

10. Laura Gutiérrez-de Pablo, Sergio Pérez-Velasco, **Víctor Rodríguez-González**, Víctor Gutiérrez-de Pablo, Carlos Gómez, Jesús Poza, Aplicación de Deep Learning para el procesado automático de componentes ICA de registros de magnetoencefalografía, XL Congreso Anual de la Sociedad Española de Ingeniería Biomédica (CASEIB 2022), ISBN: 978-84-09-45972-8, pp. 316-319, Valladolid (Spain), 23 November - 25 November, 2022.

11. Pablo Núñez, Jitka Annen, Prejaas Tewarie, **Víctor Rodríguez-González**, Naji Alnagger, Glenn Van der Lande, Marie Vitello, Paolo Cardone, Aurore Thibaut, Emilie Szymkowicz, Charlotte Martial, Steven Laureys, Olivia

Gosseries, Characterization of dynamic electrophysiological functional connectivity fluctuations: application to disorders of consciousness, GIGA Day 2023, pp. 66, Liége (Belgium), 4 September, 2023.

12. Diego Marcos-Martínez, **Víctor Rodríguez-González**, Sergio Pérez-Velasco, Eduardo Santamaría-Vázquez, Víctor Martínez-Cagigal, Roberto Hornero, Influencia de los sistemas Brain-Computer Interface basados en Neurofeedback en las características de la red cerebral, XLI Congreso Anual de la Sociedad Española de Ingeniería Biomédica (CASEIB 2023), ISBN: 978-84-17853-76-1, pp. 500-503, Cartagena (Spain), 22 November - 24 November, 2023.

13. Amalia Gil-Correa, Sergio Pérez-Velasco, **Víctor Rodríguez-González**, Hideyuki Hoshi, Yoshihito Shigihara, Carlos Gómez, Jesús Poza, Detector automático de artefactos en señales neuronales basado en técnicas de Inteligencia Artificial, XLI Congreso Anual de la Sociedad Española de Ingeniería Biomédica (CASEIB 2023), ISBN: 978-84-17853-76-1, pp. 500-503, Cartagena (Spain), 22 November - 24 November, 2023.

A.2 International internship

Three-month research internship at Hokuto Hospital (Obihiro, Japan) and Kumagaya General Hospital (Kumagaya, Japan).

i. **Purpose of the internship**
The internship took place with Dr. Yoshihito Shigihara, at the "Precision Medicine Centre" (Japan) where magnetoencephalographic (MEG) studies are conducted on patients with different neurological pathologies as part of research projects and clinical routine in two different hospitals. Therefore, the main objective was to develop advanced MEG signal processing algorithms that can help characterise dementia and assist in its diagnosis. Another important objective was to strengthen the collaboration with Hokuto and Kumagaya General hospitals. This collaboration provided valuable clinical and applied insights into the research results and foster future collaborations in international projects. Additionally, the research stay enabled the doctoral candidate to pursue a Thesis with International Doctorate mention.

ii. **Internship summary**
During the internship, the methodology presented in Rodríguez-González

et al. (2023) was developed and improved, known as the CMB algorithm. The methodology, known as the CMB algorithm, was presented to the research team of the receiving institution. By following their comments and suggestions, the validation strategies, the statistics behind the methodology, and the discussion of the physiological significance of the results were improved.

Also, the CMB algorithm was applied to patients with MCI and dementia due to AD in order to characterise the alterations that these disorders elicit in the frequency-based network structure of resting-state MEG activity. These analyses were published in Rodríguez-González et al. (2024). In this regard the researchers with a more developed clinical profile were of utmost importance to analyse, interpret, and discuss the results. In addition, the meetings conducted with them highlighted the potential clinical relevance of the methodology, and established a future line to further explore its potential applications to different pathologies that affect central nervous system.

Apart from the above mention achievements, during the internship different talks were given to the scientific and clinical staff of the receiving institution, as well as to some of their research and engineering collaborators. Furthermore, an oral presentation was given at the conference "9th MEG education and training program: utility of magnetoencephalography for epilepsy and Alzheimer's disease diagnosis"; it focused on defending the potential of MEG to predict the outcome of NPT against neural disorders based on the results obtained in (Rodríguez-González et al., 2021a).

iii. Quality indicators of the institution

The research stay took place in Hokuto and Kumagaya General Hospitals. These hospitals are equipped with several brain imaging devices: MRI scanners, PET scanners, and a two MEG systems (one at each hospital). These equipment have high costs, both in terms of acquisition and operation, which makes accessing signals and medical images from these devices challenging and valuable. Among them, the MEG systems are of particular interest to the doctoral candidate, as his Doctoral Thesis focuses on the analysis of these signals. Since their installation, the MEG systems have been used both in clinical practice (dementia, epilepsy, rehabilitation, etc.) and in research projects.

The supervisor of the internship was Dr. Yoshihito Shigihara, who has extensive experience in both clinical practice and research. Dr. Shigihara

possesses a dual educational background as both a medical doctor and an engineer, which provides him with broad and extensive knowledge in the field of biomedical engineering, as it encompasses both areas of his education. In addition to his extensive clinical career, Dr. Shigihara also has a distinguished scientific career, supported by the publication of 42 indexed scientific articles in JCR (h-index=14, Scopus).

A.3 Research Projects

1. Automatic fundus image analysis as an implementation of diabetic retinopathy screening systems (A2IFO), from 02/12/2015 to 30/11/2018. Funded by Ministerio de Economía y Competitividad, and FEDER funds. Principal Investigator: Roberto Hornero Sánchez.

2. New non-hospital paradigms for simplifying the diagnosis of sleep apnea. Design and development of an automatic screening test using the oximetry signal (ScreenOX), from 02/12/2015 to 31/03/2019. Funded by Ministerio de Economía y Competitividad, and FEDER funds. Principal Investigator: Roberto Hornero Sánchez.

3. Simplification of infant sleep apnea diagnosis using new cardiorespiratory signal processing techniques (SIMPLICITY), from 01/01/2018 to 31/07/2021. Funded by Ministerio de Economía y Competitividad, and FEDER funds. Principal Investigator: Roberto Hornero Sánchez.

4. Computational simulation of neurodegenerative mechanisms in Alzheimer's disease: deciphering neural network alterations (SIMULATIO), from 01/01/2019 to 31/12/2022. Funded by Agencia Estatal de Investigación, Ministerio de Ciencia e Innovación, and FEDER funds. Principal Investigator: Jesús Poza Crespo

5. Design of interpretable automatic predictive models in pediatric sleep apnea. Application of deep learning and explainable artificial intelligence techniques (DeepXleep), from 01/09/2021 to 31/08/2024. Funded by Agencia Estatal de Investigación, and Ministerio de Ciencia e Innovación. Principal Investigators: Roberto Hornero Sánchez and Félix del Campo Matía

6. Towards the digitization of cognitive training through brain-computer interface systems, physical exercise and neuropsychological self-assessment

(BrainGYM), from 01/12/2022 to 30/11/2024. Funded by Agencia Estatal de Investigación, Unión Europea – Next Generation UE: Plan de Recuperación, Transformación y Resiliencia, and Ministerio de Ciencia e Innovación. Principal Investigator: Roberto Hornero Sánchez

7. Deep learning and explainable artificial intelligence techniques in age-related macular degeneration screening (DeepScreenAMD), from 01/12/2022 to 30/11/2024. Funded by Agencia Estatal de Investigación, Unión Europea – Next Generation UE: Plan de Recuperación, Transformación y Resiliencia, and Ministerio de Ciencia e Innovación. Principal Investigators: María Isabel López Gálvez and María García Gadañón

8. Correlation of biometric data with cognitive and emotional states in in-vehicle interior scenarios and investigation of corrective stimuli and advanced control functions (GENIUS), from 01/12/2022 to 31/12/2024. Funded by Grupo Antolín Ingeniería S.A.U. Principal Investigator: Roberto Hornero Sánchez

A.4 Organisation of conferences

2020: Member of the Organising Committee of the "XXXVIII Congreso Anual de la Sociedad Española de Ingeniería Biomédica (CASEIB 2020)", held online by the "Spanish Society of Biomedical Engineering" (Spain) from 25 November 2020 to 27 November 2020.

2022: Member of the Organising Committee of the "XL Congreso Anual de la Sociedad Española de Ingeniería Biomédica (CASEIB 2022)", held by the "Spanish Society of Biomedical Engineering" in Valladolid (Spain) from 23 November 2022 to 25 November 2022.

A.5 Teaching experience

2019: Mentoring of Master's Thesis entitled "Estudio de nuevas aproximaciones metodológicas para identificar de forma precisa la activación de fuentes cerebrales mediante LORETA" by Daniel Bueno Pacheco. Master in Telecomunication Engineering. Supervisors: Jesús Poza Crespo and **Víctor Rodríguez González**.

2022: Teaching of the course "Radiodetermination" in the Bachelor's Degree in Telecommunications Engineering (University of Valladolid).

2022: Invited talk in the course "Analysis of Biomedical Signals" in the Master in Mathematics (University of Valladolid).

2022: Teaching of the course "Biomedical Signals" in the Bachelor's Degree in Biomedical Engineering (University of Valladolid).

2023: Mentoring of Bachelor's Thesis entitled "Detector automático de artefactos en señales neuronales basado en técnicas de inteligencia artificial" by Amalia Gil Correa. Bachelor's Degree in Telecomunication Engineering. Supervisors: Jesús Poza Crespo, Sergio Perez Velasco, and **Víctor Rodríguez González**.

2023: Teaching of the course "Clinical Simulation Devices" in the Bachelor's Degree in Biomedical Engineering (University of Valladolid).

2024: Teaching of the course "High Fidelity Clinical Simulation" in the Master in Biomedical Engineering (University of Valladolid).

A.6 Attendance to scientific events

04/2018: Attendance to the "I Jornada de Investigación en Bioingeniería y Medicina", held by the Doctoral School of the University of Valladolid in Valladolid (Spain), 2018.

05/2018: Attendance to the "V Encuentro Internacional sobre Esquizofrenia: Heterogeneidad de la Esquizofrenia", held by the "Instituto de Estudios de Ciencias de la Salud de Castilla y León" in Valladolid (Spain), 2018.

09/2019: Attendance to the "XXXIV Simposium Nacional de la Unión Científica Internacional de Radio (URSI 2019)", held by the International Scientific Radio Union in Seville (Spain), from 04/09/2019 to 06/09/2019.

11/2019: Attendance to the "Jornada de demostración e instalación Teórico-Práctica del Sistema de Electroencefalografía actiCHAMPS-PLUS", held by Brain Products GmbH in Valladolid (Spain), 2019.

11/2019: Attendance to the "XXXVII Congreso Anual de la Sociedad Española de Ingeniería Biomédica (CASEIB 2019)", held by the Spanish Society

of Biomedical Engineering in Santander (Spain), from 27/11/2019 to 29/11/2019.

11/2020: Attendance to the "XXXVIII Congreso Anual de la Sociedad Española de Ingeniería Biomédica (CASEIB 2020)", held online by the Spanish Society of Biomedical Engineering in Valladolid (Spain), from 25/11/2020 to 27/11/2020.

03/2021: Attendance to the "Jornada de Investigación en Tecnologías de la Información y de las Telecomunicaciones", held online by the Doctoral School of the University of Valladolid in Valladolid (Spain), 2021.

11/2021: Attendance to the "XV Jornadas Anuales del CIBER-BBN", held online by the "Centro de Investigación Biomédica en Red (CIBER) in the subject area of Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN)", 2021.

06/2022: Attendance to the "IUPESM World Congress on Medical Physics and Biomedical Engineering 2022 (IUPESM WC 2022)", held by the International Union for Physical and Engineering Sciences in Medicine in Singapore (Singapore), from 12/06/2022 to 17/06/2022.

11/2022: Attendance to the "XL Congreso Anual de la Sociedad Española de Ingeniería Biomédica (CASEIB 2022)", held by the Spanish Society of Biomedical Engineering in Valladolid (Spain), from 23/11/2022 to 25/11/2022.

05/2023: Attendance to the "Jornadas de Doctorado en Tecnologías de la Información y las Telecomunicaciones", held by the Doctoral School of the University of Valladolid in Valladolid (Spain), 2023.

A.7 Awards and honours

06/2018: **Coauthor of the paper finalist in the Young Investigator Competition award of the IUPESM World Congress on Medical Physics and Biomedical Engineering 2018 (IUPESM 2018)**, for the study entitled "Analysis of Electroencephalographic Dynamic Functional Connectivity in Alzheimer's Disease", conducted by P. Núñez, J. Poza, C. Gómez, S. J. Ruiz-Gómez, **V. Rodríguez-González**, M. A. Tola-Arribas, M. Cano, R. Hornero.

07/2019: **Finalist in the 3-Minute Thesis research communication competition of the University of Valladolid in 2019**, for the presentation entitled "Cuánto antes, mejor", conducted by **V. Rodríguez-González**.

11/2019: **Winner of the José María Ferrero Corral award of the XXXVII Congreso Anual de la Sociedad Española de Ingeniería Biomédica (CASEIB 2019)**, for the study entitled "Influencia de la reserva cognitiva en los patrones neurofisiológicos asociados a la evolución de la enfermedad de Alzheimer", conducted by **V. Rodríguez-González**, V. Gutiérrez-de Pablo, J. Poza, C. Gómez, M.A. Tola-Arribas, M. Cano del Pozo, R. Hornero.

10/2022: **Coauthor of the paper awarded with the Best Bioengineering Papers Published in 2021 by Young Researchers award of the CIBER-BBN**, for the study entitled "Abnormal meta-state activation of dynamic brain networks across the Alzheimer spectrum", conducted by P. Núñez, J. Poza, C. Gómez, **V. Rodríguez-González**, A. Hillebrand, P. Tewarie, M. A. Tola-Arribas, M. Cano, R. Hornero.

11/2022: **Coauthor of the paper awarded with the José María Ferrero Corral award of the XL Congreso Anual de la Sociedad Española de Ingeniería Biomédica (CASEIB 2022)**, for the study entitled "Alteraciones patológicas de la estructura neurofisiológica en los diferentes subtipos de migraña en mujeres", conducted by V. Gutiérrez-de Pablo, J. Gómez-Pilar, **V. Rodríguez-González**, J. Poza, A. L. Guerrero, M. Alves-Ferreira, N. Pinto, R. Hornero.

12/2023: **Winner the Mutual Medica Award for the Best Paper in Bioengineering of the "Real Academia de Medicina y Cirugía"**, for the study entitled "Connectivity based meta bands (CMB): Un nuevo algoritmo para la identificación automática para bandas de frecuencias personalizadas en la actividad neuronal para la detección de enfermedades neurológicas", conducted by **V. Rodríguez-González**, M. A. Tola-Arribas, M. Cano, A. Guerrero, D. García-Azorín, Y. Shigihara, H. Hoshi, R. Hornero, C. Gómez, J. Poza.

A.8 Scientific outreach

10/2019: Participation in the "3-Minute Thesis" research communication competition, intended to explain the topic of a Doctoral Thesis to the general public in less than 3 minutes.

07/2021: Participation in the program "Capaciénciate", aimed at disseminating scientific knowledge to individuals with intellectual disability in the institution "Salud Mental Segovia".

11/2021: Participation in the program "Semana de la Ciencia", with the talk "Las ondas cerebrales. De la teoría a la práctica" intended to disseminate scientific knowledge to academic community of the University of Valladolid.

03/2022: Participation in the program "Mes de la Salud", intended to disseminate research in healthcare to the students of the Faculty of Medicine (University of Valladolid).

03/2022: Participation in the program "#ElFuturoDeLaUva", aimed at disseminating research done in the University of Valladolid in social networks (University of Valladolid).

10/2022: Invited talk in the program "XIII Um Dia da Biometria" presenting a work entitled "Chronnectomics: Unravelling the temporal structure of neural activity" (Universidade Estadual Paulista "Júlio de Mesquita Filho").

A.9 Intellectual property

11/2023: Intellectual property registration: MEDUSA-Kernel: An independent python toolbox for brain-computer interfaces to process neural biosignals. ID: 00/2023/4682. Authors: Santamaría Vázquez, Eduardo; Martínez Cagigal, Víctor; Hornero Sánchez, Roberto; **Rodríguez González, Víctor**; and Marcos Martínez, Diego.

11/2023: Intellectual property registration: CMB: Connectivity-based Meta-Bands. A MATLAB-based toolbox to extract the underlying frequency structure of electro- and magnetoencephalographic signals. ID: 00/2023/4684. Authors: Hornero Sánchez, Roberto; Poza Crespo, Jesús; Gómez Peña, Carlos and **Rodríguez González, Víctor**.

Apéndice B

Resumen en castellano

B.1 Introducción

El cerebro humano es capaz de procesar ingentes cantidades de información de manera continua. Esto es posible gracias a la transmisión de potenciales de acción, que son ondas eléctricas generadas mediante el intercambio de neurotransmisores entre neuronas (Standring, 2021). Cuando una neurona recibe suficientes estímulos excitatorios en forma de potenciales de acción, se desencadenan intercambios electro-químicos que inician nuevos potenciales de acción en las siguientes neuronas, posibilitando la propagación de estas ondas por todo el cerebro (Standring, 2021). A pesar de ser un campo relativamente nuevo, la neurociencia ha conseguido importantes avances que han permitido lograr notables avances en el conocimiento de nuestro cerebro. Todos estos avances han llevado a un florecimiento de este campo científico, con una creciente cantidad de artículos publicados en los últimos años. Cabe mencionar que las señales magnetoencefalográficas (MEG) y electroencefalográficas (EEG) están desempeñando un papel fundamental en el desarrollo de este campo (van Diessen et al., 2015; Schomer and da Silva, 2017; Supek and Aine, 2019). Desde analizar las propiedades tiempo-frecuencia y no-lineales de regiones cerebrales específicas, hasta evaluar el funcionamiento del cerebro como una red integrada de neuronas interconectadas, analizar la actividad cerebral mediante señales MEG y EEG (M/EEG) ha permitido lograr una mayor comprensión de cómo funciona nuestro cerebro. Esto ha permitido profundizar nuestros conocimientos acerca de los sustratos biológicos de distintas funciones cognitivas superiores como la memoria, el razonamiento o la integración de información, y de cómo distintas patologías neurológicas y psiquiátricas alteran el normal fun-

cionamiento del cerebro (Bassett and Sporns, 2017; Coppola et al., 2019; Engels et al., 2017; Maran et al., 2016; Schomer and da Silva, 2017; Supek and Aine, 2019). Esta Tesis Doctoral pretende revisar la literatura publicada en el campo del análisis de señales M/EEG, buscando cuestiones y retos metodológicos que aún no hayan sido abordados y que puedan estar suponiendo un factor de confusión en estudios actuales y futuros. A raíz de ello, se proponen soluciones novedosas a estas cuestiones y aplicaciones clínicas derivadas de ellas, con especial énfasis en el deterioro cognitivo leve (DCL) y la demencia por enfermedad de Alzheimer (EA), debido a su especial relevancia clínica, económica y social (Alzheimer's Disease International, 2022).

La demencia debida a la EA es una enfermedad neurodegenerativa que provoca una alteración progresiva en la función cerebral, la cognición y la conducta (Knopman et al., 2021). La EA es el tipo más común de demencia, siendo responsable de entre el 60 % y el 80 % de los casos de demencia (Alzheimer's Association, 2022). Esta patología está asociada a una deposición anormal de ovillos de tau hiperfosforilada y placas de proteína beta-amiloide (Alzheimer's Disease International, 2022). De acuerdo con las cifras de la Organización Mundial de la Salud, en 2019 55 millones de personas vivían con demencia; y se espera que este número alcance los 139 millones en 2050 (Alzheimer's Disease International, 2022). Además, el coste económico asociado a la EA también es notable, con un impacto estimado de 1.3 miles de millones de dólares estadounidenses (Alzheimer's Association, 2022). Todos estos factores convierten a la EA en un problema médico, social y económico de primer nivel. Por otro lado, el DCL es un constructo heterogéneo de síntomas caracterizado por cambios menores en la cognición, la función y la memoria (Wolk and Vaishnavi, 2016). Estos cambios son lo suficientemente severos como para no ser considerados parte de un envejecimiento normal, pero no lo suficientemente graves como para ser considerados demencia (Alzheimer's Association, 2022). Cabe destacar que este estado clínico se asocia con un mayor riesgo de desarrollar demencia, con entre el 10 % y el 15 % de los pacientes con DCL desarrollando demencia cada año (Alzheimer's Association, 2022). Además, alrededor del 50 % de las personas con DCL también tienen biomarcadores relacionados con la EA, considerándose, por tanto, una subclase de DCL conocida como DCL debida a la EA (Alzheimer's Association, 2022). Este tipo de DCL se considera una etapa prodrómica de la EA, donde aún no se han cumplido los criterios diagnósticos de esta (Liss et al., 2021).

Registrar la actividad electromagnética del cerebro es, posiblemente, la forma más intuitiva de medir la actividad neuronal, y evaluar como distintas patologías

como el DCL y la EA la modifican. En esta Tesis Doctoral vamos a emplear dos de las técnicas más usadas para adquirir esta actividad electromagnética: el EEG y la MEG. Nos centramos en estas dos técnicas por su no invasividad y su alta resolución temporal, que las permite registrar de una manera sencilla incluso las oscilaciones neuronales más rápidas. El EEG y la MEG tiene su origen en las neuronas piramidales de la corteza cerebral, ya que están dispuestas en paralelo y generan actividad eléctrica de manera sincrónica, lo que hace que el campo electromagnético asociado sea lo suficientemente fuerte como para ser registrado por los sensores de M/EEG a nivel del cuero cabelludo (Singh, 2014; Supek and Aine, 2019). Además, cabe destacar que la actividad M/EEG no se genera por potenciales de acción, ya que son demasiado rápidos, sino por los potenciales postsinápticos asociados a ellos, de menor amplitud pero mayor duración temporal (Biasiucci et al., 2019; Singh, 2014; Supek and Aine, 2019). A pesar de que el EEG y la MEG tengan un sustrato biológico muy similar, presentan algunas diferencias que vale la pena mencionar. En primer lugar, la resolución espacial de los sistemas MEG suele ser mayor que la de los EEG (Wolpaw and Wolpaw, 2012). Además, como los sensores de MEG no requieren el uso de gel conductor, el tiempo de preparación suele ser menor. Adicionalmente, la MEG tiene una mayor relación señal-ruido (Illman et al., 2020). Finalmente, como la permeabilidad magnética de los tejidos cerebrales es casi homogénea, estas señales apenas se ven influenciadas por efectos de conducción de volumen y dispersión de campo (Singh, 2014; Supek and Aine, 2019). Por otro lado, el EEG también presenta ventajas respecto a la MEG. Los sistemas EEG son portátiles, gracias a su reducido tamaño y a que, a diferencia de la MEG, no necesitan una sala aislada magnéticamente (Ilmoniemi and Sarvas, 2019). Esto es útil para registrar de una manera sencilla señales cerebrales de pacientes que no pueden moverse o sufren de claustrofobia. Además, el costo de los sistemas EEG es significativamente menor que el de la MEG, lo que hace que estén más extendido tanto en entornos clínicos como de investigación (Ilmoniemi and Sarvas, 2019; Supek and Aine, 2019). Aunque existen muchos entornos experimentales para adquirir y analizar señales M/EEG, en esta Tesis Doctoral hemos empleado registros realizados en estado de reposo, pues nos permite caracterizar la actividad cerebral intrínseca, sin tener que considerar la influencia de ninguna tarea en particular.

Los análisis que se realizan sobre señales M/EEG se pueden agrupar, de forma general, en dos grandes categorías:

- **Análisis de activación local**. Este tipo de análisis evalúa las propiedades

de la actividad electromagnética de unidades funcionales individuales, que pueden variar desde neuronas hasta áreas cerebrales relativamente grandes, de manera independiente (Schomer and da Silva, 2017; Supek and Aine, 2019). Para ello, se utilizan diversas métricas, que a su vez se pueden dividir en dos clases: (i) parámetros espectrales, que cuantifican las propiedades tiempo-frecuencia de las señales de M/EEG (Rodríguez-González et al., 2020; Schomer and da Silva, 2017; Supek and Aine, 2019); y (ii) parámetros no-lineales, que evalúan propiedades como la complejidad, la irregularidad o la variablidad de los distintos grupos neuronales.

- **Análisis de sincronización global**. Este tipo de análisis evalúa la dependencia estadística (*i.e.*, conectividad) entre la actividad electromagnética generada por cada par de sensores (o fuentes cerebrales) (Engels et al., 2017). Se consideran dos tipos diferentes de conectividad: i) conectividad funcional, que analiza la asociación entre pares de sensores o fuentes; y ii) conectividad efectiva (EC), que también evalúa la causalidad (es decir, la dirección) de estas asociaciones (Friston, 2011). En esta Tesis Doctoral, nos hemos centrado en la conectividad funcional, ya que este tipo de análisis está más extendido, y normalmente no requiere un modelo *a-priori*, lo que reduce la necesidad de hacer suposiciones estrictas sobre los datos (Cao et al., 2022). En este nivel de análisis también se incluyen las métricas derivadas de la teoría de grafos, que permiten analizar el comportamiento del cerebro como una red integrada, donde los sensores (o las áreas cerebrales) son los nodos y la conectividad funcional entre ellos los enlaces (Stam et al., 2009). Este tipo de parámetros ofrecen información muy interesante sobre la estructura y propiedades de la red cerebral, tales como la integración, la segregación, la centralidad y la complejidad (Engels et al., 2017). Derivado de este tipo de análisis, ha surgido un campo de estudio que ha adquirido una notable relevancia en los últimos años, y que se basa en identificar topologías de red consistentes a lo largo del tiempo ("meta-estados") y la frecuencia ("meta-bandas"), y analizar sus fluctuaciones dinámicas (Deco et al., 2013; Núñez et al., 2022, 2021; Rodríguez-González et al., 2024, 2023).

Los estudios incluidos en el compendio de publicaciones de esta Tesis Doctoral recorren los dos niveles de análisis descritos, abordando cuestiones abiertas que necesitaban ser estudiadas en profundidad para evitar sesgos. Para cada nivel de análisis, esta Tesis Doctoral presenta una contribución metodológica novedosa, seguida de una aplicación clínica para el DCL y la EA derivada de dicha contri-

bución. Las dos primeras publicaciones se centran en el primero de los nivel de análisis de las señales de M/EEG. En Rodríguez-González et al. (2020), se presenta una evaluación integral de cómo los parámetros de activación local se alteran a medida que las señales neuronales viajan desde la corteza cerebral, donde se generan, hasta el cuero cabelludo, donde son registradas por los sistemas M/EEG. El segundo artículo, Rodríguez-González et al. (2021a), evaluó si es posible predecir el resultado de un tratamiento no farmacológico (NPT) contra la enfermedad de Alzheimer utilizando parámetros de activación local. Cabe destacar que la primera publicación del compendio proporcionó la base teórico-práctica necesaria para llevar a cabo este estudio en dos aspectos: (i) los conocimientos adquiridos sobre los parámetros de activación local considerados en Rodríguez-González et al. (2020) posibilitaron su aplicación en Rodríguez-González et al. (2021a); y (ii) en Rodríguez-González et al. (2020) se observó que cuando los patrones espaciales son relevantes para los análisis, es necesario emplear señales a nivel de fuente. En este sentido, al observarse en Shigihara et al. (2020a) que la dimensión espacial desempeñaba un papel fundamental en los cambios neuronales inducidos por un NPT, todos los análisis de (Rodríguez-González et al., 2021a) se llevaron a cabo a nivel de fuente. Las tercera y cuarta publicaciones incluidas en el compendio exploraron el segundo nivel de análisis, es decir, los análisis de sincronización global. El tercer artículo, Rodríguez-González et al. (2023), desafía la definición canónica de bandas de frecuencia que se utilizan habitualmente en análisis de señales M/EEG, proponiendo el primer método de segmentación en bandas de frecuencia no supervisado, individualizado, *data-driven*, y basado en los patrones de conectividad funcional: el algoritmo *Connectivity-based Meta-Bands* (CMB). Finalmente, la cuarta publicación del compendio, Rodríguez-González et al. (2024), evaluó si la estructura de frecuencia de la conectividad funcional identificada por el algoritmo CMB se ve alterada por el DCL y la demencia por EA.

B.2 Hipótesis y objetivos

El cerebro humano es uno de los sistemas más complejos conocidos por el ser humano. Esta complejidad es probablemente la razón por la cual aún persisten cuestiones metodológicas abiertas en neurociencia, y más concretamente en el análisis de señales M/EEG, a pesar de la extensa investigación llevada a cabo en este ámbito. Por lo tanto, en esta Tesis Doctoral se plantea la hipótesis principal de que *existen cuestiones metodológicas abiertas en el campo del análisis de señales M/EEG que requieren atención, ya que podrían ser un importante factor de ses-*

go; abordar estas preguntas es de suma relevancia para consolidar el conocimiento ya establecido y abrir nuevas perspectivas de investigación que mejoren nuestra comprensión del cerebro; además, estos nuevos conocimientos pueden facilitar el desarrollo de aplicaciones clínicas de las señales M/EEG.

Las señales registradas por equipos M/EEG al nivel del cuero cabelludo se distorsionan al atravesar los diferentes tejidos de la cabeza, experimentando lo que se conoce como efectos de conducción de volumen y dispersión de campo. Aunque estos efectos han sido muy estudiados, su influencia en los parámetros de activación local aún es desconocida. Por lo tanto, se formula la hipótesis de que: *las propiedades espectrales y no lineales de las señales M/EEG a nivel de fuente son similares a las que presentan a nivel de sensor*. Gracias a la experiencia adquirida al trabajar con estos parámetros, se planteó la hipótesis adicional de que: *los parámetros de activación local son modulados por la intervención no-farmacológica contra EA, desempeñando los patrones espaciales un papel fundamental a la hora de reflejar dichos cambios.*Una de las etapas más comunes al analizar señales M/EEG consiste en filtrarlas en las bandas de frecuencia canónicas. Sin embargo, estas bandas fueron definidas sin tener en cuenta los patrones neurales específicos de cada sujeto. Aunque este enfoque está respaldado por una amplia cantidad de literatura (Uhlhaas et al., 2008), las herramientas y técnicas de análisis modernas permiten emplear enfoques más sofisticados (Goetz and Schork, 2018; Keizer, 2021). Por lo tanto, formulamos la hipótesis de que: *la estructura en frecuencia de la red neural tiene una notable variabilidad entre sujetos que no se refleja en las bandas de frecuencia canónicas, y se puede diseñar un nuevo método adaptativo capaz de reflejar esta variabilidad.* Asimismo, como en Núñez et al. (2021) se observó una pérdida progresiva de la estructura temporal de la red cerebral en pacientes con DCL y EA, planteamos la hipótesis de que: *el DCL y la demencia por EA provocan alteraciones en la estructura en frecuencia de la red neuronal, provocando una pérdida progresiva de esta.*

Por tanto, el objetivo principal de esta Tesis Doctoral es *proponer soluciones novedosas para abordar dos problemas metodológicos pertenecientes al campo del análisis de las señales M/EEG. Estas soluciones servirán como base para desarrollar aplicaciones clínicas de las señales M/EEG en pacientes con DCL y EA*. Para llevar a cabo esto, se plantean los siguientes objetivos específicos:

OE1. Construir una base de datos de registros M/EEG de tres grupos de población: controles sanos, pacientes con DCL y pacientes con demencia por EA. Esta base de datos también incluirá información sociodemográfica, variables

clínicas y un seguimiento longitudinal para proporcionar una caracterización exhaustiva de los sujetos involucrados.

OE2. Evaluar la robustez de los parámetros de activación local frente a los efectos de conducción de volumen y la dispersión de campo.

OE3. Explorar si las métricas de activación local a nivel de fuente extraídas de registros MEG pueden predecir el éxito de una terapia no farmacológica contra la EA.

OE4. Desarrollar una metodología de segmentación en bandas de frecuencia individualizada, no supervisada y basada en la conectividad funcional, que sea capaz de cuantificar la estructura en frecuencia de red neuronal.

OE5. Analizar y cuantificar las alteraciones que el DCL y la demencia debida a EA provocan en la estructura en frecuencia de la red cerebral.

OE6. Evaluar críticamente y discutir los resultados obtenidos para extraer conclusiones apropiadas, comparando nuestros hallazgos con los obtenidos en estudios previos.

OE7. Diseminar los principales hallazgos y conclusiones de los estudios realizados en revistas científicas indexadas en el *Journal Citation Reports* (JCR), conferencias nacionales e internacionales, así como en medios de comunicación y plataformas de divulgación para la difusión del conocimiento científico al público en general.

B.3 Materiales

Para poder llevar a canbo esta Tesis Doctoral, se contó con cinco bases de datos diferentes de registros MEG y EEG. Las dos bases de datos MEG fueron registradas con un sistema MEG de gradiómetros axiales de 160 canales. Mientras que la primera estaba formada por 122 sujetos de control sanos, la segunda se componía de 39 controles sanos de edad avanzada, 44 pacientes con DCL y 50 pacientes con EA. Esta última base de datos también incluía registros longitudinales para 19 de los pacientes con EA, los cuales fueron sometidos a una terapia no farmacológica para paliar la sintomatología de la EA. Por otro lado, la primera base de datos de EEG estaba compuesta por 252 registros, adquiridos con un sistema EEG de 19 canales; la segunda base de datos de EEG estaba formada por 45 controles ancianos sanos, también registrados con un dispositivo de 19 canales; mientras

que la tercera base de datos de EEG estaba compuesta por 27 mujeres sanas, y fue registrada con un sistema EEG de 32 canales.

B.4 Métodos

En la Figura B.1 se puede apreciar un esquema común del procedimiento de análisis llevado a cabo en los estudios llevados a cabo en el marco de esta Tesis Doctoral. Cada uno de estos estudios tiene una metodología diferente, aplicándose procedimientos analíticos distintos dentro de cada una de las categoría indicadas en la Figura B.1. Sin embargo, esta Figura nos proporciona esquema común de los métodos empleados, por lo que nos basaremos en ella para describir la metodología empleada en esta Tesis Doctoral.

B.4.1 Preprocesado

Los registros en bruto que se obtienen directamente de los equipos de registro M/EEG están contaminadas por ruido y artefactos que influyen en la calidad de la señal y pueden comprometer las conclusiones extraídas del análisis de datos (Cohen, 2014; Supek and Aine, 2019; Wolpaw and Wolpaw, 2012). Por ello, es necesario aplicar algún procedimientos de eliminación de ruido, de manera que se minimice la presencia de señales de origen no neural.

En esta Tesis Doctoral se ha aplicado un algoritmo de preprocesado consistente en 4 pasos, que ya había sido empleado previamente de manera exitosa (Núñez et al., 2019; Ruiz-Gómez et al., 2018a,b, 2019): (i) Filtrado *Finite Impulse Response* (FIR) paso banda para limitar el ancho de banda del ruido (entre 1 y 70 Hz); (ii) filtrado FIR elimina-banda para reducir la influencia del ruido asociado a la red eléctrica; (iii) eliminación de artefactos mediante *Independent Component Analysis* (ICA); (iv) selección visual de épocas de 5 segundos libres de ruido. Gracias a su elevada resolución espacial, para las bases de datos MEG se pudo aplicar un método de eliminación de artefactos adicional: el algoritmo *SOurce-estimate-Utilizing Noise-Discarding* (SOUND) (Mutanen et al., 2018; Rodríguez-González et al., 2019).

B.4.2 Localización de fuentes

Tanto las señales EEG como las MEG se registran en el cuero cabelludo (nivel de sensor). Estas señales, desde se generan en el cortex cerebral (nivel de fuente) hasta que se registran en los sensores M/EEG sufren lo que se conoce cómo efectos

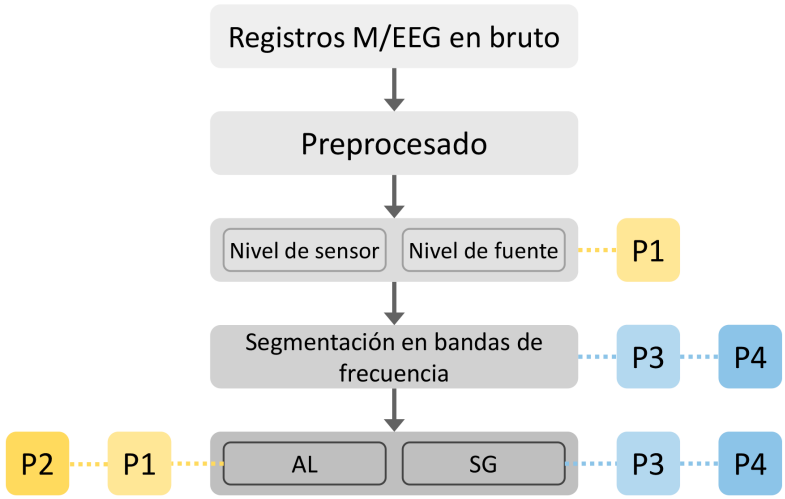

Figura B.1: Esquema del proceso de análisis de señales M/EEG llevado a cabo en esta Tesis Doctoral. En primer lugar, los registros M/EEG en bruto se preprocesan (normalmente, filtrando y eliminando los artefactos) y se estiman las señales a nivel de fuente (cuando es necesario). A continuación, tanto las señales a nivel de sensor como las señales a nivel de fuente se segmentan en bandas de frecuencia. Por último, se aplican distintas metodologías de análisis de activación local y sincronización global. En la figura también se indican las relaciones entre las distintas publicaciones del compendio y las etapas del proceso de análisis que abarcan cada una de ellas. AL: activación local; SG: sincronización global; P1: primera publicación del compendio (Rodríguez-González et al., 2020); P2: segunda publicación del compendio (Rodríguez-González et al., 2021a); P3: tercera publicación del compendio (Rodríguez-González et al., 2023); P4: cuarta publicación del compendio (Rodríguez-González et al., 2024).

de conducción de volumen y dispersión de campo; que provocan efectos ruidosos en ellas. Por tanto, en muchos estudios se opta por estimar las señales a nivel de fuente, de forma que se eliminan los efectos de conducción de volumen y dispersión de campo.

Para llevar a cabo la reconstrucción de fuentes se empleo un *head model* basado en la plantilla anatómica ICBM152 con 15000 fuentes, creado mediante *Boundary Elements Method* (Douw et al., 2018; Fonov et al., 2009). El volumen de la cabeza se segmentó en tres tejidos: cerebro, cráneo y cuero cabelludo (Mahjoory et al., 2017). El espacio donde se podían ubicar las fuentes se limitó al córtex cerebral; Además, la orientación de estas restringió para que fuera normal al córtex (Lai et al., 2018). Cómo no se disponía de registros de ruido, se empleó una matriz identidad cómo covarianza de ruido (Lai et al., 2018). La alta dimensionalidad de las señales a nivel de fuente se limitó proyectando las 15000 fuentes en las 68

regiones de interés (ROIs) definidas en el atlas Desikan-Killiany (Lai et al., 2018). Esta proyección se realizó promediando las señales de las fuentes pertenecientes a cada una de las ROIs, tras rotar las fuentes de dirección opuesta para evitar que se cancelen (Lai et al., 2018).

En esta Tesis Doctoral se ha trabajado con cuatro algoritmos de localización de fuentes diferentes, empleando uno u otro en función de las características del estudio y de la modalidad de registro (EEG o MEG) con la que se trabajaba: weighted Minimum Norm Estimate (wMNE) (Lin et al., 2004), standardised LOw-Resolution brain Electromagnetic TomogrAphy (sLORETA) (Pascual-Marqui, 2002), Linear Constrained Minimum Variance (LCMV) (van Veen et al., 1997), y dynamical Statistical Parametric Mapping (dSPM) (Dale et al., 2000).

B.4.3 Segmentación en bandas de frecuencia

Al estudiar la actividad neuronal, es muy común realizar análisis en función de su frecuencia (Cohen, 2014). De esta forma, se han asociado distintas funciones cerebrales a diferentes rangos de frecuencias, y se ha observado efectos de enfermedades neurológicas y psiquiátricas diferentes según la frecuencia (Ilmoniemi and Sarvas, 2019; Supek and Aine, 2019; Uhlhaas et al., 2008). En la literatura, las señales M/EEG se han segmentado en cinco rangos, con una frecuencia central y una anchura que aumentan logarítmicamente (Cohen, 2014): delta (δ, 1-4 Hz), zeta (θ, 4-8 Hz), alfa (α, 8-13 Hz), beta (β, 13-30 Hz), y gamma (γ, 30-70 Hz).

Aunque estas bandas están respaldadas por una gran cantidad de literatura, tienen una serie de desventajas que vale mencionar: no hay un consenso claro en cuanto a sus límites específicos (Newson and Thiagarajan, 2019); están basadas únicamente en patrones tiempo-frecuencia, sin tener en cuenta el comportamiento del cerebro como una red integrada; no tienen en cuenta las idiosincrasias individuales de la actividad neural... Estas desventajas llevaron a plantear en Rodríguez-González et al. (2023) un nuevo algoritmo de segmentación en bandas de frecuencia individualizado, automático y basado en la conectividad funcional que superara las desventajas asociadas a las bandas de frecuencia canónicas.

B.4.4 Niveles de análisis: activación local y sincronización global

Finalmente, se aplicarán diferentes metodologías y se calcularán distintas métricas sobre las señales. Los análisis realizados en esta Tesis Doctoral se pueden agrupar en dos categorías:

- *Análisis de activación local.* Este tipo de análisis caracterizan la actividad de unidades funcionales individuales, que pueden ser desde neuronas hasta áreas relativamente grandes del cerebro (Schomer and da Silva, 2017; Supek and Aine, 2019). Este tipo de métricas se pueden dividir en dos categorías: (i) espectrales, que cuantifican las propiedades tiempo-frecuencia de las señales M/EEG (Ruiz-Gómez et al., 2018a; Sanei and Chambers, 2021; Schomer and da Silva, 2017; Supek and Aine, 2019); y (ii) no-lineales, que estudian la dinámica no lineal de la actividad cerebral en términos como la complejidad, la variabilidad o la irregularidad (Gómez et al., 2009; Jie et al., 2014; Ren et al., 2023; Ruiz-Gómez et al., 2018a; Salankar et al., 2021).
- *Análisis de sincronización global.* Este tipo de análisis evalúan la dependencia estadística (*i.e.*, conectividad funcional) entre la actividad de distintos sensores (o fuentes neuronales) (Engels et al., 2017). Este nivel de análisis también abarca la caracterización del cerebro como un grafo, empleando métricas de red basadas en la teoría de grafos. Estas ofrecen información valiosa sobre la estructura y propiedades de la red cerebral, como la integración, segregación, centralidad y complejidad (Engels et al., 2017; Gomez-Pilar et al., 2018).

B.5 Resultados y discusión

En esta Tesis Doctoral se exploraron cuestiones metodológicas abiertas que representan posibles factores de confusión en el campo del análisis de señales M/EEG. Durante este proceso se llevó a cabo un análisis en dos niveles. En primer lugar, desde la perspectiva de la activación local, se evaluó la robustez de este tipo de parámetros a los efectos de conducción de volumen y la dispersión de campo. Seguidamente, como extensión clínica de esta contribución, se evaluó el potencial de estos mismos parámetros para detectar los cambios neurofisiológicos provocados por una NPT contra la EA empleando redes de asociación. En segundo lugar, a nivel de sincronización global, se evaluó la estructura de frecuencia subyacente de la red cerebral. A partir de este estudio, se propuso un algoritmo de segmentación de bandas automático y específico para cada sujeto. Como contribución clínica, se evaluó cómo esta estructura en frecuencia se ve alterada por el DCL y la EA.

B.5.1 Robustez de las métricas de activación local ante los efectos de conducción de volumen y la dispersión de campo

El trabajo llevado a cabo en Rodríguez-González et al. (2020) permitió extraer dos conclusiones relevantes: i) los parámetros de activación local ofrecen una caracterización de las señales muy similar a nivel de sensor y de fuente para señales M/EEG; ii) los patrones espaciales de los parámetros de activación local también muestran una fuerte correlación entre los niveles de sensor y fuente, sin embargo existen ciertos detalles acerca estos que pueden perderse si no se emplean señales a nivel de fuente.

Los efectos de conducción de volumen y de dispersión de campo han sido muy estudiados (Asadzadeh et al., 2020; Bonaiuto et al., 2018; Lai et al., 2018; Michel and Brunet, 2019; Song et al., 2015). Sin embargo, aún no se ha evaluado cómo estos efectos influyen en los parámetros de activación local. En Rodríguez-González et al. (2020) se abordó este problema calculando parámetros de activación local a nivel de sensor y a nivel de fuente, y examinando la consistencia entre ambos niveles. Se observó que estas métricas apenas se ven alteradas por estos efectos, es decir, los parámetros de activación local registros M/EEG a nivel de sensor y de fuente caracterizan la actividad sincrónica de poblaciones neuronales de manera similar. Específicamente, se observó los parámetros no-lineales del algoritmo de localización de fuentes LCMV son menos consistentes que el resto, con valores menos complejos a nivel de sensor. Este algoritmo implica la aplicación de filtros espaciales a la señal (van Veen et al., 1997). Por lo tanto, es razonable hipotetizar que este proceso podría atenuar las frecuencias más altas, o reducir el ancho de banda del ruido, lo cual está relacionado con una pérdida de complejidad (Aboy et al., 2006; Hornero et al., 2005). Además, también se consideró la influencia de la frecuencia de muestreo y la longitud de época en la robustez de los parámetros de activación local entre los niveles de sensor y de fuente. Curiosamente, se observó que ambos parámetros la afectan, con valores más altos asociados a una mayor consistencia entre los niveles de sensor y fuente, hasta que se alcanza la estabilidad y no se obtienen mejoras de consistencia adicionales. Esto sugiere que se requiere una longitud de época y una frecuencia de muestreo mínimas para obtener estimaciones robustas de las señales a nivel de fuente.

Al considerar regiones espaciales específicas, los valores de consistencia entre los niveles de sensor y fuente disminuyen, sin embargo, estos valores aún son muy elevados, por lo que se puede concluir que los análisis regionales arrojan resultados

altamente comparables cuando se llevan a cabo en ambos niveles. Cabe destacar que las señales de MEG mostraron una consistencia mayor que las EEG, lo cual puede explicarse por su mayor resolución espacial (Lai et al., 2018; Lantz et al., 2003) o el hecho de que la permeabilidad magnética permanece relativamente constante en todos los tejidos de la cabeza (Hämäläinen et al., 1993; Lai et al., 2018). Finalmente, cabe destacar que en Rodríguez-González et al. (2020) se empleó una segmentación espacial de los parámetros poco detallada (es decir, de baja resolución). Por tanto, es probable que al emplear una segmentación espacial más fina se revelen diferencias más notorias en los patrones de activación local entre los niveles de sensor y fuente.

B.5.2 Los parámetros de activación local son sensibles a los cambios en la interacción entre electrofisiología, cognición y comportamiento provocados por una terapia no farmacológica contra la EA

Los conocimientos adquiridos durante el estudio anterior permitieron considerar su uso en un escenario clínico real, como la predicción de los resultados de una terapia no-farmacológica. Cabe destacar que las conclusiones extraídas en Rodríguez-González et al. (2020) llevaron a analizar registros de actividad MEG en estado de reposo en Rodríguez-González et al. (2021a) a nivel de fuente, con el objetivo de explorar la dimensión espacial de una forma minuciosa empleando una métrica novedosa: la Entropía Espacial de Shannon (SSE). Por lo tanto, en Rodríguez-González et al. (2021a) se examinó el impacto de una NPT en la neurofisiología de pacientes con EA, caracterizada mediante parámetros de activación local de señales MEG en estado de reposo. Además, también se evaluó si estos parámetros podían predecir su eficacia. Para ello, se emplearon redes de asociación, ya que proporcionan un marco intuitivo para evaluar la compleja interacción entre variables de diferente naturaleza. En este estudio se obtuvieron tres hallazgos principales: i) la NPT altera la compleja interacción entre los patrones neurofisiológicos y las variables neuropsicológicas; ii) los cambios provocados por la NPT en la neurofisiología y en el estado conductual están asociados; y iii) los valores de los parámetros de activación local extraídos de la actividad MEG en estado de reposo antes de realizar la NPT están relacionados con el resultado de la terapia, lo cual sugiere una potencial capacidad predictiva de los mismos.

Se observó, gracias a las redes de asociación, que la NPT modificaba la estructura de relaciones entre los patrones neurofisiológicos y los estados cognitivo y

conductual. Por un lado, se perdían relaciones entre el estado neuropsicológico y la actividad en la banda gamma, lo que sugiere que la NPT modula la alteración de las poblaciones neuronales en esta banda de frecuencia debido a la EA. Cabe mencionar que la actividad gamma está relacionada con el rendimiento cognitivo, a través del neurotransmisor GABA (Bartos et al., 2007; Mably and Colgin, 2018; Porges et al., 2017). Por otro lado, se observaron nuevas asociaciones con la potencia relativa en distintas bandas de frecuencia, lo que podría estar vinculado con la ralentización de la actividad neuronal provocada por la EA (Dauwels et al., 2011; Jeong, 2004). En el presente estudio también se observó una asociación entre los cambios en la actividad beta (y su SSE) y el resultado del tratamiento (es decir, los cambios en la cognición y el comportamiento), lo que está en línea con lo observado por estudios previos (Shigihara et al., 2020a,b). La actividad beta ha sido relacionada con el DCL y la EA (Dauwels et al., 2011; Fernández et al., 2006; Jeong, 2004; Poza et al., 2007; Roh et al., 2011), y se ha sugerido su potencial para ayudar en el diagnóstico de estas patologías y para evaluar procesos de disrupción neural (Poil et al., 2013). La importancia de la SSE en estas relaciones respalda la idea de que la NPT afecta a diferentes regiones cerebrales de manera diferente. Esta idea está respaldada por estudios anteriores que han sugerido un papel importante de la dimensión espacial en las modificaciones neuronales causadas por una NPT (Shigihara et al., 2020a,b; Zucchella et al., 2018). Finalmente, los resultados mostraron que un menor grado de alteraciones relacionadas con la EA (es decir, la ralentización del espectro y pérdida de complejidad de las oscilaciones neuronales (Dauwels et al., 2011; Escudero et al., 2009; Jeong, 2004)) se asocia con un mejor pronóstico de la terapia. Es decir, se observó que señales con un mayor predominio de frecuencias altas, y oscilaciones más complejas e irregulares, predicen un mejor resultado de la NPT. Cabe destacar que las métricas espectrales muestran correlaciones más altas con el resultado de la NPT que las métricas no-lineales, lo cual puede estar relacionado con una mayor sensibilidad de los parámetros espectrales para reflejar las alteraciones provocadas por la EA (Escudero et al., 2009; Hornero et al., 2008; Poza et al., 2012). Por último, se aprecia que muchas de las métricas relacionadas con el resultado de la NPT se basan en la SSE, mostrando una correlación positiva. Estos hallazgos están alineados con estudios previos que destacaron la importancia de los patrones espaciales de las oscilaciones neuronales para caracterizar una NPT (Shigihara et al., 2020a,b).

B.5.3 *Connectivity-based Meta-Bands* (CMB): un algoritmo automático, individualizado y basado en la conectividad funcional de segmentación en bandas de frecuencia

Como se ha mencionado previamente, los dos primeros artículos incluidos en el compendio de publicaciones abarcan los análisis realizados para el nivel de activación local. Este tipo de análisis ha permitido lograr importantes avances en el campo de la neurociencia (Babiloni et al., 2021; Cohen, 2014; Supek and Aine, 2019). Sin embargo, pasan por alto aspectos muy relevantes del funcionamiento cerebral: las interacciones entre regiones cerebrales, que recogen el funcionamiento del cerebro como una red integrada (Cohen, 2014). Por ello, los dos siguientes artículos del compendio de publicaciones abordan el nivel de análisis de sincronización global.

Aunque la segmentación en bandas de frecuencia usada actualmente está respaldada por mucha literatura científica, está sujeta a una serie de problemas que nos llevaron a cuestionar su uso. En Rodríguez-González et al. (2023) se introduce el algoritmo "Connectivity-based Meta-Bands"(CMB), un novedoso método para identificar bandas de frecuencia individualizadas de manera automática basado en los patrones de conectividad funcional, por lo que recoge información más completa de la actividad cerebral (Tewarie et al., 2019). Gracias al algoritmo CMB se extrajeron dos conclusiones importantes: i) los enfoques clásicos para la segmentación de bandas de frecuencia se alinean parcialmente con la estructura en frecuencia de la red neuronal al emplear señales MEG en estado de reposo, pero no capturan idiosincrasias individuales relevantes; y ii) las señales de EEG no tienen sensibilidad suficiente para extraer la estructura en frecuencia de la red neural similar a la que asumen las bandas canónicas.

Las bandas de frecuencia canónicas reflejan mecanismos fisiológicos fundamentales y están respaldadas por una gran cantidad de literatura científica (Buzsáki and Draguhn, 2004; Sanei and Chambers, 2021; Uhlhaas et al., 2008). Sin embargo, presentan varios problemas: i) fueron definidas usando técnicas de neuroimagen muy rudimentarias (Berger, 1934; Jasper and Andrews, 1936, 1938; Walter, 1936; Walter and Dovey, 1944); ii) su definición es inconsistente (Newson and Thiagarajan, 2019); iii) fueron definidas en base a patrones (amplitud y frecuencia dominante) muy simples; y iv) no tienen en cuenta los patrones neurales específicos de cada sujeto. Aunque existen algoritmos para la definición de bandas adaptativas, estos también se basan en patrones relativamente simples de las señales y asumen

características *a-priori* de las bandas a obtener (Borghini et al., 2019; Pascarelli et al., 2020). En este sentido, el algoritmo CMB supera estos problemas pues proporciona una segmentación individualizada, automática, y basada en los patrones de conectividad funcional, los cuales proporcionan una caracterización completa de los patrones neuronales (Tewarie et al., 2019).

En el caso de las señales de MEG, los resultados mostraron tres meta-bandas claramente definidas; mientras que en las bases de datos de EEG se obtuvo una segmentación mucho menos detallada, con solo dos meta-bandas dominantes. Un repertorio limitado de estados cerebrales se ha vinculado con un mecanismo de optimización del procesado de la información neural (Ramirez-Mahaluf et al., 2020; von Schwanenflug et al., 2023). Por lo tanto, es razonable plantear la hipótesis de que el número limitado de meta-bandas identificadas también puede deberse a una optimización del procesamiento de información neural, el cual podría ser uno de los principales factores que configuran la organización cerebral (Bullmore and Sporns, 2012).

La meta-banda identificada para las señales MEG en frecuencias cercanas a la banda alfa presenta una topología de red occipital, similar a lo que se ha observado en otros estudios que han analizado conectividad funcional en la banda alfa en estado de reposo con señales M/EEG (Colclough et al., 2016; Hillebrand et al., 2012; Miraglia et al., 2017). Esta topología se asemeja a la observada en las áreas posteriores de la red de modo por defecto (DMN, por sus siglas en inglés) (Fauchon et al., 2022; Raichle et al., 2001; Raichle and Snyder, 2007; Vidaurre et al., 2018). Las áreas posteriores de la DMN se han vinculado a funciones cognitivas superiores, como la integración de información, la atención, la empatía y la autorreflexión (Culham and Kanwisher, 2001; Fauchon et al., 2022; Raichle and Snyder, 2007). Si se compara nuestra meta-banda presente en las frecuencias de la banda alfa con dos definiciones distintas de esta banda (canónica y adaptativa), se puede ver que la definición adaptativa se ajusta mejor que la canónica (67 % y 60 % de coincidencia, respectivamente). Esto subraya el hecho de que existe una cantidad no desdeñable de patrones neurales individuales que no se están considerando al emplear los enfoques actuales de segmentación en bandas de frecuencia.

La otra meta-banda destacable en la atividad MEG en estado de reposo es la presente en las frecuencias zeta y beta, que presenta una topología fronto-central. Esta meta-banda podría asociarse con la DMN anterior (Fauchon et al., 2022; Vidaurre et al., 2018), que está altamente activa para frecuencias zeta (Fauchon et al., 2022; Vidaurre et al., 2018). Se sabe que la DMN anterior está implicada en funciones cognitivas superiores como la integración semántica, el procesamiento de

emociones y la toma de decisiones (Fellows and Farah, 2007; Tsapkini et al., 2011). Esta meta-banda también podría estar relacionada con la red sensoriomotora, que está altamente activa y conectada en frecuencias de la banda beta (Fauchon et al., 2022) y comparte algunas áreas cerebrales con esta meta-banda (Fauchon et al., 2022). La red sensoriomotora también está involucrada en procesos neurales relacionados con la percepción, la propiocepción y las funciones motoras (Caspers et al., 2021; Chenji et al., 2016; Feher, 2012). Además, la banda beta desempeña un papel crucial en la formación de redes durante el estado de reposo (Hipp et al., 2012), contribuyendo al procesamiento de información dentro y entre los circuitos corticales (Little et al., 2019), lo que podría explicar el papel de esta meta-banda.

Estos hallazgos sugieren que el uso de las bandas canónicas con señales de EEG en análisis de conectividad debería realizarse con precaución, pues estas señales no capturan con precisión la estructura en frecuencia de la red. Por otro lado, para señales de MEG, las bandas de frecuencia canónicas ofrecen un marco conveniente que facilita las comparaciones entre estudios, si bien no consideran especificidades individuales relevantes. En este sentido, se debería emplear el algoritmo CMB en análisis de conectividad en estado de reposo, ya que se adapta completamente a los patrones en frecuencia de conectividad de cada individuo, eliminando el sesgo asociado al uso de las bandas de frecuencia canónicas.

B.5.4 Desvelando las alteraciones en la estructura en frecuencia de la red neuronal provocadas por el deterioro cognitivo leve y la enfermedad de Alzheimer empleando señales MEG

Dada la capacidad del algoritmo CMB para caracterizar de manera individualizada la estructura en frecuencia de la conectividad, planteamos la hipótesis de si el DCL y la EA provocan alteraciones en dicha estructura. Esto es particularmente relevante, ya que podría explicar las inconsistencias observadas en estudios que analizan cómo estas patologías afectan a la conectividad neuronal (Fide et al., 2022; Jalili, 2016; Kaminski and Blinowska, 2018).

En Rodríguez-González et al. (2024), se empleó el algoritmo CMB para evaluar las alteraciones que el DCL y la EA provocan en la organización en frecuencia de la red cerebral. En este estudio se observó que: i) el DCL y la EA influyen en la estructura topológica de la de la red cerebral, provocando patrones de conectividad más heterogéneos, y ii) estas patologías también alteran la secuencia de "meta-bandas", provocando una pérdida progresiva de la estructura en frecuencia.

El DCL y la EA han sido considerados por numerosos trabajos como "síndromes de desconexión"(Badhwar et al., 2017; Delbeuck et al., 2007; Engels et al., 2015; Ishii et al., 2017; Koelewijn et al., 2017; Sheline and Raichle, 2013). Sin embargo, estos estudios a menudo han llegado a conclusiones contradictorias (Fide et al., 2022; Jalili, 2016; Kaminski and Blinowska, 2018). El trabajo desarrollado en Rodríguez-González et al. (2024) pretende abordar este problema, proporcionando una nueva perspectiva sobre las alteraciones que provocan estas patologías que permita caracterizarlas de una manera más profunda.

En línea con investigaciones previas, se ha observado que el DCL y la EA afectan a la estructura topológica de la red cerebral (Knyazeva et al., 2013, 2010). Concretamente, se han encontrado diferencias importantes entre sujetos de control y pacientes con DCL en la topología de las matrices de conectividad asociadas con la meta-banda activa alrededor de las bandas delta y gamma. Esto sugiere que las alteraciones tempranas asociadas a la demencia se manifiestan en estas frecuencias, lo que es consistente con otros estudios (Gómez et al., 2009; Handayani et al., 2018; Musaeus et al., 2019; Tóth et al., 2014). Además, la conectividad funcional de las bandas delta y zeta se ha vinculado anteriormente con la progresión desde la etapa de DCL a la de demencia por EA (Musaeus et al., 2019). Tras un análisis más profundo de la similitud entre las matrices de conectividad asociadas a una meta-banda y la topología de esta, se puede concluir que la demencia provoca que las topologías de red se desdibujen progresivamente. Este hallazgo sugiere que la progresión de la demencia está asociada a la aparición de topologías cada vez más homogéneas, lo que sugiere la pérdida de redes especializadas e integradas, con sus funciones potencialmente asumidas por otras regiones cerebrales. Esto es respaldado por contribuciones previas, que observaron una disminución del coeficiente de agrupamiento y la modularidad en pacientes con EA, lo que produciría topologías de red más uniformes (Brier et al., 2014; de Haan et al., 2009; Stam et al., 2009).

También se observó que el DCL y la demencia por EA conllevan meta-bandas menos estables, con más transiciones entre ellas. En estudios previos llevados a cabo por Núñez et al. (2022, 2021), se presentó el *DWell time*, utilizado para caracterizar la estabilidad de estados cerebrales en tiempo. Concluyeron, en línea con nuestros resultados, que la estabilidad de los meta-estados disminuía para pacientes con DCL y EA (Núñez et al., 2021). También hemos observado un aumento de la complejidad en la secuencia de meta-bandas en pacientes con DCL y EA, similar al observado por Núñez *et al.* en la secuencia de meta-estados cerebrales en tiempo durante el estado de reposo (Núñez et al., 2021). Estos resultados respaldan la idea de una pérdida progresiva de la estructura tiempo-frecuencia de las

redes neuronales con la progresión la demencia. Estudios previos demostraron que estados cerebrales más estables en tiempo están asociados con un aumento en la eficiencia de la red (Ramirez-Mahaluf et al., 2020; Zalesky et al., 2014). Además, las transiciones eficientes entre estados se relacionan con procesos cognitivos de alto nivel (Ramirez-Mahaluf et al., 2020). Por lo tanto, es razonable considerar que el aumento de la complejidad en la secuencia de meta-bandas en pacientes puede atribuirse a una pérdida de optimización en los mecanismos neuronales.

Estos hallazgos son de una gran relevancia, pues ofrecen una posible explicación a la falta de consenso observada al caracterizar las alteraciones que el DCL y la EA provocan en la red cerebral (Briels et al., 2020; Fide et al., 2022; Franciotti et al., 2019; Jalili, 2016; Kaminski and Blinowska, 2018). Este estudio abre nuevas vías para comprender y caracterizar de una manera más profunda las alteraciones que distintas patologías neurológicas y psiquiátricas provocan en la red cerebral, abriendo nuevas líneas de investigación en este ámbito.

B.6 Conclusiones

El análisis exhaustivo de los hallazgos obtenidos durante esta Tesis Doctoral, así como su posterior discusión, permitió extraer las siguientes conclusiones:

- Las métricas de activación local extraídas de la actividad M/EEG en estado de reposo son robustas frente a los efectos de conducción de volumen y dispersión del campo. Sin embargo, si se considera la dimensión espacial, estos efectos se hacen más notorios (Rodríguez-González et al., 2020).

- Someterse a una NPT contra la EA no solo modifica la neurofisiología cerebral y el estado cognitivo y conductual de los pacientes, sino que también modifica la estructura de dependencias estadísticas entre estos dominios (Rodríguez-González et al., 2021a).

- Las métricas de activación local extraídas de actividad MEG en estado de reposo tienen el potencial de predecir el resultado de una NPT contra la EA, con un mayor nivel de deterioro neurofisiológico (indicado por señales MEG con mayor potencia a frecuencias bajas y menor complejidad) asociado a un peor pronóstico de la terapia (Rodríguez-González et al., 2021a).

- El algoritmo CMB reveló, una estructura en frecuencia de la red cerebral funcional compuesta por: tres meta-bandas para señales de MEG y dos para señales EEG (Rodríguez-González et al., 2023).

- Las bandas de frecuencia canónicas solo reflejan parcialmente la estructura en frecuencia de la conectividad para las señales de MEG en estado de reposo. Al emplearlas no se están considerando una cantidad importante de características individuales de cada sujeto, lo cual podría estar sesgando los estudios llevados a cabo en este ámbito (Rodríguez-González et al., 2023).

- En el caso de las señales EEG, las bandas de frecuencia canónicas no coinciden con la estructura en frecuencia de la red cerebral. Por lo tanto, su uso debería ser reconsiderado (Rodríguez-González et al., 2023).

- Las señales EEG no son tan sensibles como las MEG a la estructura en frecuencia de la conectividad cerebral (Rodríguez-González et al., 2023).

- El algoritmo CMB es una alternativa prometedora a las metodologías actuales de segmentación en bandas de frecuencia, superando sus limitaciones y adaptándose a las idiosincrasias específicas de los individuos y la modalidad de registro empleada (Rodríguez-González et al., 2023).

- El algoritmo CMB permite identificar alteraciones provocadas por el DCL y la demencia por EA en la estructura en frecuencia de las redes cerebrales. Estas alteraciones se pueden dividir en dos tipos: (i) topológicas, provocando redes más heterogéneas, lo que puede estar relacionado con una pérdida de redes neuronales especializadas; y (ii) en la secuenciación de meta-bandas, provocando activaciones menos estables y, por tanto, más cambios entre ellas, posiblemente debido a alteraciones en los mecanismos de optimización neuronal (Rodríguez-González et al., 2024).

- El algoritmo CMB abre la puerta a un nuevo tipo de análisis, al poder estudiar de manera individual las alteraciones que distintas patologías neurológicas y psiquiátricas producen en la estructura en frecuencia de la red cerebral.

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Index