

FACULDADE DE ENGENHARIA DA UNIVERSIDADE DO PORTO



Towards a Novel Neuroengineering Approach to Adaptive Neurostimulation in Epilepsy

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Mestrado em Bioengenharia

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Resumo

A epilepsia é uma doença neurológica caracterizada por convulsões recorrentes e imprevisíveis. Afeta mais de 65 milhões de pessoas no mundo, das quais cerca de 1/3 é resistente a medicamentos anticonvulsivos. Para estes casos, quando a cirurgia ressetiva não é viável ou falhou, a neuromodulação surge como uma terapia alternativa promissora. Ao longo dos últimos anos, a estimulação cerebral profunda do núcleo anterior do tálamo (ANT-DBS) tem-se vindo a estabelecer como uma opção terapêutica segura e eficaz. Está provado que o ANT desempenha um papel fundamental na propagação de crises epiléticas, no entanto, desvendar os mecanismos exatos subjacentes à ANT-DBS em epilepsia e prever desfechos clínicos permanece um desafio. A evidência atual sugere que a ANT-DBS em epilepsia induz alterações corticais, das quais a ativação de regiões da rede de modo padrão (DMN) deve ser destacada. Por sua vez, propõe-se a hipótese de que esta ativação desempenhe um papel no suporte aos efeitos anticonvulsivantes da ANT-DBS.

Esta dissertação avalia dinâmicas de conectividade funcional, não só entre o ANT e o córtex cerebral, mas também entre cada uma destas estruturas individualmente, em pacientes recetores do neuroestimulador Percept™ PC acordados. O foco assenta sobre a caracterização da impressão digital eletrofisiológica da rede tálamo-cortical em pacientes com epilepsia do lobo frontal (ELF) versus epilepsia do lobo temporal (ELT), e na contribuição para a definição de potenciais biomarcadores para diversas aplicações em DBS.

Sinais de eletroencefalografia (EEG) simultânea de superfície e do tálamo foram adquiridos de dois pacientes de epilepsia refratária recetores de ANT-DBS com um neuroestimulador Percept™ PC, um cujo foco está localizado no lobo frontal, e o outro no lobo temporal. Primeiro, segmentos de EEG acordado foram pré-processados em três principais passos: filtragem passa-banda (1-70 Hz) e *notch* (50 Hz), remoção de épocas ruidosas, e análise de componentes independentes. Este último passo não foi efetuado para os canais do tálamo. De seguida, a análise de conectividade funcional foi tripla: primeiro, entre o tálamo e o córtex; segundo, limitada às regiões da DMN após reconstrução de fontes elétricas cerebrais; e por último, exclusivamente para regiões do tálamo. Foram implementadas métricas matemáticas específicas, quer no domínio das frequências quer no do tempo, para quantificar tanto interações não-direcionadas como direcionadas.

De forma geral, as modulações são mais fortes quando ocorrem nos ritmos teta (4-8Hz) e alfa (8-13Hz), independentemente do subtipo de epilepsia. Em alfa, a informação flui de forma mais proeminente do tálamo para o córtex, especialmente para regiões associadas à DMN. Os valores de conectividade funcional revelaram-se mais elevados para o paciente de ELT, o que poderá explicar os melhores desfechos clínicos em ANT-DBS associados. O perfil de conectividade da DMN destaca-se entre outras regiões do cérebro no paciente de ELT. Adicionalmente, foi detetada ativação noutras regiões além da DMN, o que sugere uma possível associação de mais redes neuronais com a ANT-DBS em epilepsia, transcendendo a hipótese inicial. Por fim, não foi possível definir um padrão consistente de conectividade dentro do tálamo.

Para concluir, este trabalho elucidará acerca do potencial de estudar conectividade tálamo-cortical, assim como dos ritmos que a modulam em ANT-DBS, de modo a melhor compreender os fun-

damentos por trás da eficácia clínica da ANT-DBS. No entanto, uma maior amostra de pacientes é necessária para validar estas descobertas entre os diferentes tipos de epilepsia. Trabalho futuro assenta em verificar que os padrões tálamo-corticais característicos podem ser transpostos de EEG do tálamo para potenciais de campo local (LFP) do ANT, abrindo assim portas para a implementação de algoritmos de DBS adaptativa em tempo real.

Palavras-Chave: conectividade funcional, eletroencefalografia, eletroencefalografia estereotáxica, epilepsia focal, estimulação cerebral profunda, núcleo anterior do tálamo.

Abstract

Epilepsy is a neurological disease characterised by recurrent and unpredictable seizures. It affects over 65 million people worldwide, from which about 1/3 are resistant to antiseizure medication. For these cases, when resective surgery is not suitable or has failed, neuromodulation comes up as a promising alternative therapy. Over the last years, deep brain stimulation of the anterior nucleus of the thalamus (ANT-DBS) has been established as a safe and effective treatment option. The ANT has been proven to play a key role in epileptic seizure propagation, however, unravelling the exact mechanisms underlying ANT-DBS in epilepsy and predicting outcome remains a challenge. Current evidence suggests that ANT-DBS in epilepsy induces cortical alterations, from which the activation of regions associated with the default mode network (DMN) must be highlighted. In turn, this activation is hypothesised to play a role in supporting the antiseizure effects of ANT-DBS. This dissertation assesses functional connectivity dynamics, not only between the ANT and the brain cortex, but also within these structures solely, in awake Percept™ PC neurostimulator recipients. The focus lies on characterising the electrophysiological fingerprint of the thalamocortical network in frontal (FLE) versus temporal lobe epilepsy (TLE) patients, and to contribute to the definition of putative biomarkers for various applications in DBS.

Simultaneous scalp and thalamic electroencephalography (EEG) signals were collected from two refractory epilepsy patients receiving ANT-DBS with a Percept™ PC neurostimulator, one with focus located on the temporal lobe and the other on the frontal lobe. Awake EEG were firstly pre-processed in three main steps: bandpass (1-70Hz) and notch (50Hz) filtering, noisy epoch removal, and independent component analysis. The latter step was not performed for thalamic channels. Further, the conducted functional connectivity analysis was threefold: firstly, between the thalamus and cortex; secondly, limited to DMN regions post brain source reconstruction; and thirdly, exclusively for thalamic regions. Specific mathematical metrics, either in the time or in the frequency domain, quantifying both undirected and directed interactions, were employed.

Generally, modulations were stronger when in theta (4-8Hz) and alpha (8-13Hz) rhythms, regardless of the epilepsy subtype. In alpha, information flows more prominently from the thalamus to the cortex, particularly to regions associated with the DMN. Functional connectivity values were overall higher for the TLE patient, which may explain the associated better clinical outcomes in ANT-DBS reported in the literature. DMN's connectivity profile is highlighted among other brain regions in the TLE patient. In addition, activation was detected in brain regions beyond the DMN, which suggests a possible association of multiple networks with ANT-DBS in epilepsy, surpassing prior expectations. Finally, we were not able to define a consistent connectivity pattern within the thalamus.

To conclude, this work may shed light on the potential of studying thalamocortical connectivity and the brain rhythms modulating these in ANT-DBS, in order to better understand the electrophysiological fundamentals behind the clinical effectiveness of ANT-DBS. Nevertheless, a bigger cohort is needed to validate the findings across epilepsy subtypes. Future work stands on verifying that characteristic thalamocortical patterns can be transposed from thalamic EEG to ANT-local

field potentials (LFP), thus opening doors towards the implementation of online closed-loop DBS algorithms.

Keywords: anterior nucleus of the thalamus, deep brain stimulation, electroencephalography, focal epilepsy, functional connectivity, stereotactic electroencephalography.

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Assim se desvanecem 5 anos, que na minha memória se perpetuarão.

Ana Marta

*“To develop a complete mind:
Study the science of art;
Study the art of science.
Learn how to see.
Realise that everything connects to everything else.”*

Leonardo da Vinci

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Abbreviations

AAL	Automated Anatomical Labeling
AEDs	Anti-Epileptic Drugs
ANT	Anterior Nucleus of the Thalamus
BEM	Boundary Element Method
BOLD	Blood Oxygen Level Dependent
CE	<i>Conformité Européenne</i>
CMT	Centromedian Nucleus of the Thalamus
CNS	Central Nervous System
CT	Computed Tomography
DBS	Deep Brain Stimulation
DISTAL	DBS Intrinsic Template AtLas
DMN	Default Mode Network
DRE	Drug-Resistant Epilepsy
dwPLI	Debiased Weighted Phase Lag Index
ECG	Electrocardiogram
ECoG	Electrocorticogram
EEG	Electroencephalography
EOG	Electrooculogram
eLORETA	Exact Low-Resolution Electromagnetic Tomography
FDA	U.S. Food and Drug Administration
FEM	Finite Element Method
FLE	Frontal Lobe Epilepsy
fMRI	Functional Magnetic Resonance Imaging
HC	Hippocampus
HD-EEG	High-Density Electroencephalography
IBE	International Bureau for Epilepsy
ICs	Independent Components
ICA	Independent Component Analysis
IEDs	Interictal Discharges
iEEG	Intracranial Electroencephalography
IGE	Idiopathic Generalised Epilepsies
ILAE	International League for Epilepsy
IPG	Implanted Pulse Generator
lANG	Left Angular Gyrus
LFP	Local Field Potentials
LMICs	Low-Income and Middle-Income Countries
MEG	Magnetoencephalography
MNI	Montreal Neurological Institute

MORE	Medtronic Registry for Epilepsy
MPFC	Medial Prefrontal Cortex
MRI	Magnetic Resonance Imaging
PCA	Principal Component Analysis
PCC	Posterior Cingulate Cortex
PET	Positron Emission Tomography
PLI	Phase Lag Index
PSD	Power Spectral Density
rANG	Right Angular Gyrus
RNS	Responsive Neurostimulation
ROIs	Regions of Interest
RSNs	Resting State Networks
SANTE	Stimulation of the Anterior Nucleus of Thalamus for Epilepsy
SPM	Statistical Parameter Mapping
SOZ	Seizure Onset Zone
SNR	Signal-to-Noise Ratio
SUDEP	Sudden Unexpected Death in Epilepsy
tDCS	Transcranial Direct Current Stimulation
TLE	Temporal Lobe Epilepsy
TMS	Transcranial Magnetic Stimulation
TNS	Trigeminal Nerve Stimulation
tVNS	Transcutaneous Vagus Nerve Stimulation
VNS	Vagus Nerve Stimulation
VTa	Volume of Tissue Activation

Chapter 1

Introduction

1.1 Context and Motivation

Epilepsy is a neurological disease characterised by recurrent and unpredictable seizures, affecting over 65 million people worldwide [EL15, OAN⁺18]. From these people, about 1/3 have refractory epilepsy, which means they are unable to treat epilepsy with anti-seizure medication [EL15, XCB⁺22]. When resective surgery is not suitable or has failed, neuromodulation comes up as an alternative promising therapy [RRJW19]. Neuromodulation approaches can be classified either into open-loop or closed-loop. The former only delivers electrical stimulation, whilst the latter additionally employs a sensor to record a signal linked to symptoms, which adapts stimulation parameters according to the patient's disease state [PK17]. Neuro-electrophysiological signals known as biomarkers comprise, for instance, local field potentials (LFPs), electrocorticogram, action potentials, or electroencephalogram (EEG). Among the approved neuromodulation strategies, over the last years, deep brain stimulation of the anterior nucleus of the thalamus (ANT-DBS) has been established as a safe and effective treatment option [ZLS⁺19, SSG⁺21]. The ANT is a deep structure within the brain, occupying the superior region of the thalamus, which is thought to have a role in epileptic seizure propagation [CB13, JMG⁺22].

The mechanisms underlying the effect of ANT-DBS in epilepsy and the corresponding clinical outcomes remain, however, unclear. One putative explanation may be related to the role of the ANT within the Papez circuit, which gives a route of seizure propagation between the hippocampus and the thalamus [RRH⁺21, JMG⁺22]. Thus, targetting nodes within the Papez circuit, such as the ANT, may disrupt the maintenance and propagation of epileptic seizures [JMG⁺22, VGE⁺22]. Transposing this statement to a network neuroscience perspective, the ANT can be denoted as a key propagation point within the epileptogenic network, whose modulation is expected to have a therapeutic effect on epileptic patients [JMG⁺22].

In fact, epilepsy has been seen as a network disease over the last few decades, given that the propagation of abnormal brain activity alters networks at a broad range, regardless of the seizure onset zone (SOZ) [RBL⁺22, VGE⁺22]. Accordingly, both surgical and medical treatment modalities lead to neural network reorganisation in epilepsy. On one hand, resective surgery directly

pinpoints and destroys the putative SOZ, whilst neuromodulation targets specific points within the epileptogenic network, as an attempt to prevent onward seizure propagation [VGE⁺22, JMG⁺22]. This conceptual shift towards approaching epilepsy as a network disorder has been accompanied by advances in a broad range of neuroimaging techniques. Among these, EEG, recorded both invasively and non-invasively, and functional magnetic resonance imaging (fMRI) constitute the most widely used strategies to functionally map brain networks [JMG⁺22, RBL⁺22].

Considering that the ANT is characterised by mutual connectivity between both cortical and subcortical areas involved in seizure propagation, unravelling the therapeutic mechanism of ANT-DBS may imply determining not only the functional dynamics of the ANT, but also the associated cortical alterations [ALD⁺23]. Thalamocortical interactions can be assessed by simultaneously recording non-invasive and intracranial brain signals. Although other neuroimaging modalities may be employed, or even combined, this approach samples a whole range of brain regions with high temporal resolution, allowing one to easily and accurately assess oscillatory interactions between the scalp and the ANT, as an attempt to unriddle ANT-DBS mechanisms in epilepsy.

Furthermore, considering that epilepsy is a disease of brain networks, the next step to take in neuromodulation for epilepsy is to extract biomarkers from neural networks [JMG⁺22]. Apart from adapting DBS parameters, network biomarkers have been rising towards different utilities, for both research and clinical purposes. Key application areas of network biomarkers include screening cognitive impairments, surgical target identification, stimulation candidacy, target selection, and postoperative outcome prediction [LBBB21]. Non-invasive EEG represents the key tool to assess brain networks as DBS biomarkers, by being able to be recorded while delivering stimulation and, consequently, while collecting LFPs. To the acquired scalp EEG, source imaging algorithms may be applied, in order to guarantee that these signals are not influenced by current attenuation from the brain sources to the scalp, thus translating actual neuronal activity [MB19].

As a matter of fact, epilepsy-related networks go way beyond the epileptogenic network, considering that a global network reorganisation takes place [RBL⁺22]. Accordingly, epileptic patients present an altered level of activity and connectivity in canonical physiological networks established as part of the healthy connectome, most commonly in the default mode network (DMN) [VGE⁺22, RBL⁺22]. The DMN comprises the brain areas exhibiting the unique behaviour of decreasing their activity during goal-directed tasks [Rai15]. In epilepsy, when compared to a healthy state, the DMN alters its connectivity patterns. Indeed, interestingly, the network model associated with common epilepsy DBS targets was shown to overlap with several DMN regions [VGE⁺22]. Being the DMN a widely studied network, with generally consistent patterns across individuals with a similar clinical characterisation, assessing DMN's frequency-dependent functional connectivity as a network biomarker, using EEG source imaging, may be a promising, straightforward and futuristic approach for DBS in epilepsy [VGE⁺22].

Converging network neuroscience with neurostimulation, this work aims to characterise the electrophysiological fingerprint of the thalamocortical network, using functional connectivity, in adults receiving ANT-DBS for epilepsy. Moreover, the activation of regions associated with the DMN is highlighted along the analysis, considering that this network is a key player in brain func-

tion and, potentially, in ANT-DBS for epilepsy as well. Leaning towards personalised neuromodulation, connectivity patterns will be inspected in the two most common types of focal epileptic syndromes: frontal lobe (FLE) versus temporal lobe epilepsy (TLE). If coherent patterns differentiating FLE and TLE's connectivity profile are found, we expect to contribute to the definition of network-guided biomarkers. Further, from these biomarkers, specific features associated with the patient's state can be extracted and then fed into an algorithm to control the closed-loop DBS device. Nevertheless, considering the preliminary nature of this work, future validation is required prior to the real-life implementation of these biomarkers within online adaptive DBS approaches.

1.2 Dissertation Goals

Contributions to two main goals were set to be achieved within the scope of this dissertation, being these closely intertwined. Accordingly, these can be wrapped up into two research questions, formulated below.

1. Do connectivity patterns within the DMN change according to the epilepsy subtype?

One can answer this question by analysing waking state simultaneous surface and thalamic EEG, collected from ANT-DBS recipients with frontal and temporal lobe epilepsies. Firstly, cortical alterations deriving from the ANT will be assessed by computing functional connectivity between surface and thalamic electrodes, at the channel level. Complementary, the anatomical location within the thalamus that reflects best the DMN features can also be inferred. The EEG rhythms modulating these interactions will also be examined. Further, surface EEG will be solely analysed, in order to assess functional connectivity patterns within DMN regions. Whole brain regions will be estimated based on source imaging approaches, according to a predefined anatomical parcellation. For both cases, functional connectivity results will be compared between the FLE versus the TLE patients. If differences are found, the need for individualised neuromodulation therapies is highlighted.

2. Can these patterns contribute to the definition of potential biomarkers in ANT-DBS?

Prior to the analysis, the thalamic contacts precisely located in the ANT will be identified. Accordingly, functional connectivity patterns between the thalamic contacts will be computed. With this analysis, electrophysiological patterns characterising the thalamus and its substructures are expected to be found. Facing the case in which all the patterns of the threefold analysis are coherent for each epileptic syndrome solely, this work may represent a contribution towards the development of adaptive ANT-DBS approaches. Under the paradigm of epilepsy as a network disease, differences in functional connectivity may serve as potential biomarkers to differentiate FLE from TLE. The next step would be to apply the individual patient's brain networks, namely the DMN, to closed-loop DBS algorithms, thus maximising the delivered clinical impact to each patient.

1.3 Dissertation Structure

This dissertation contains six chapters, from which the present Chapter 1 briefly introduces the topic, motivation, and goals set for this research work.

In Chapter 2 – **Epilepsy and Neuromodulation** – a background on epilepsy and the corresponding neuromodulation therapies is provided, along with clinical studies proving the effectiveness of deep brain stimulation.

Chapter 3 – **Epilepsy as a Network Disorder** – approaches epilepsy as affecting whole brain networks, namely the default mode network, rather than just a certain epileptic foci. Core concepts on brain connectivity and state-of-the-art techniques to assess brain networks are presented as well.

Chapter 4 – **Methodology** – describes the whole experimental procedure associated with this work, from data collection to the corresponding analysis.

Chapter 5 – **Results and Discussion** – reports the observed results and their interpretation, comparing these with the current literature.

Lastly, Chapter 6 – **Conclusions and Further Work** – provides a conclusion and suggestions for future work on the topic.

Chapter 2

Epilepsy and Neuromodulation

2.1 Epilepsy and Epileptic Seizures

Epilepsy is a neurologic condition consisting of a lasting predisposition to generate spontaneous epileptic seizures, together with the associated neurobiological, cognitive, psychological and social consequences [OAN⁺18,RRJW19]. It is noteworthy that not all seizures fall into the definition of epilepsy, if provoked by a reversible, and not chronic, cause [EL15]. Thus, according to the International League for Epilepsy (ILAE) and to the International Bureau for Epilepsy (IBE), the term "epileptic seizure" stands for a transient clinical event due to abnormal excessive or synchronous neuronal activity in the brain [FBB⁺05].

2.1.1 Practical Clinical Definition of Epilepsy

In 2014, a Task Force of the ILAE revised and redefined the concept of epilepsy for clinical purposes [FAA⁺14]. Considering this redefinition, it can be stated that epilepsy exists in an individual if at least one of these conditions is taking place: (1) at least two unprovoked seizures occurring more than 24h apart; (2) one unprovoked seizure, but there is a high recurrence risk ($\geq 60\%$) over the following 10 years; (3) diagnosis of an epilepsy syndrome [FAA⁺14,OAN⁺18]. Moreover, epilepsy is considered to be resolved either if a patient is seizure-free for the past 10 years, with at least the last 5 years off antiseizure medication, or if a patient who had an age-dependent epilepsy syndrome has passed the applicable age [FAA⁺14].

2.1.2 Epidemiology and Mortality

Affecting approximately 65 million people, which represents about 1% of the population, epilepsy is the third highest contributor to the global neurological disease burden [EL15,OAN⁺18]. Up to a third of the epileptic patients have refractory, or drug-resistant, epilepsy (DRE), which means that their seizures were not controlled by at least two antiepileptic drugs (AEDs) [RRJW19,EL15]. Moreover, younger age groups and older age groups tend to have a higher incidence of epilepsy,

being that about 75% of epilepsy begins in childhood [OAN⁺18,EL15]. In contrary, prevalence is higher in early adulthood, and decreases in children and in the elderly [OAN⁺18].

Both prevalence and incidence vary according to the geographical region in analysis, being higher in low-income and middle-income countries (LMIC) [OAN⁺18]. About 80% of the people with epilepsy live in LMIC, which is thought to be a effect of a more frequent occurrence of birth injuries, traffic accidents, and neuroinfectious disorders, together with poor hygiene and basic sanitation conditions [RRJW19,OAN⁺18]. Regardless of the geographical location, structural, genetic, metabolic, immune or infectious aetologies may be the leading cause of epilepsy [OAN⁺18].

Epilepsy can be lethal due to the effect of seizures, either directly (sudden unexpected death in epilepsy, drowning, falls, burns, etc.), or indirectly (suicide, adverse events of AEDs such as obesity or cardiovascular events, etc.) [OAN⁺18]. The risk of premature mortality is reported to be higher in epilepsy patients, compared to individuals without epilepsy, thus posing a great public health problem [RRJW19, OAN⁺18]. Geographically speaking, mortality in LMIC is generally higher than in high income countries, specially due to external causes [RRJW19].

Sudden unexpected death in epilepsy (SUDEP) is one of the main causes of epilepsy-related deaths, occurring in approximately 1 per 1000 adults with a peak for those aged 20-40 years [OAN⁺18,RRJW19]. In most cases, SUDEP is unwitnessed and occurs during sleep, which explains the fact that individuals are frequently found in prone position [RRJW19]. There is neither a known cause for SUDEP, nor established preventive measures apart from nocturnal supervision and seizure reduction [RRJW19].

2.1.3 Classification

In 2017, the ILAE updated the scheme for the classification of the epilepsies, represented in Figure 2.1, being this the key tool nowadays for diagnosing individuals presenting seizures [SBC⁺17, OAN⁺18,RRJW19]. Classification is performed in a multilevel manner, starting from the seizure type (onset), then stepping into the epilepsy type, and, at the third level, the epilepsy syndrome [SBC⁺17]. At each stage of classification, causes and comorbidities should be considered, given that these may have associated therapeutic implications [SBC⁺17, RRJW19]. A range of six etiologic groups has been proposed: structural, genetic, infectious, metabolic, immune, or unknown [SBC⁺17].

Regarding their onset, seizures can be classified as focal, generalised or unknown [SBC⁺17]. Focal seizures are subdivided by the level of awareness and, further, according to the most prominent manifestation, which is either motor or non-motor [RRJW19]. For generalised seizures, these are divided into motor or non-motor seizures [RRJW19]. Sometimes, depending on the available resources in the clinical environment, this may be the maximum level of epilepsy classification [SBC⁺17]. Next, epilepsy types are divided into generalised, focal, combined generalised and focal, or unknown [SBC⁺17]. Diagnosing the epilepsy type requires clinical grounds, supported by electroencephalography (EEG) findings [SBC⁺17]. Finally, the highest level of precision is obtained if an epilepsy syndrome is identified [RRJW19]. "Epilepsy syndrome" refers to a cluster

of features that consistently occur together, such as age of onset, seizure types, comorbidity, EEG and imaging findings [EL15,RRJW19].

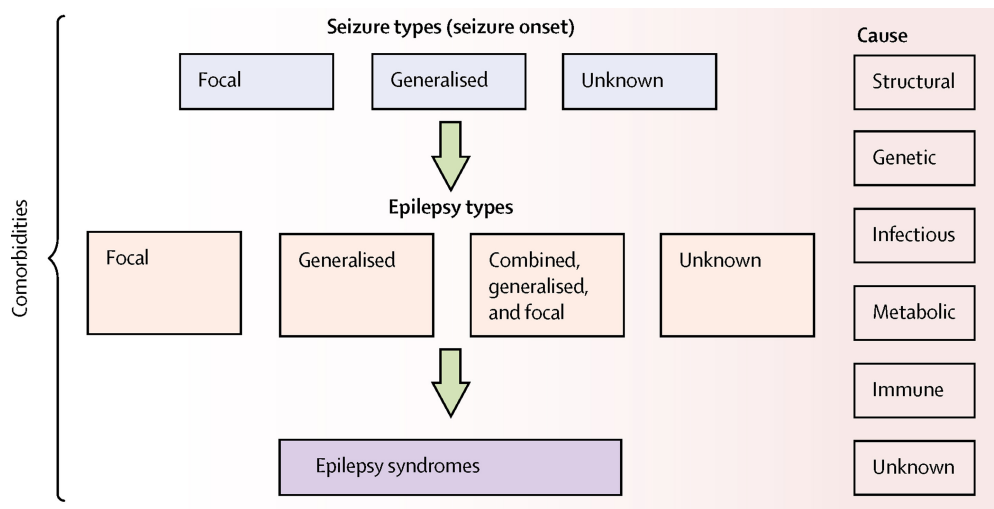


Figure 2.1: The ILAE Framework for Classifications of the Epilepsies. Source: [RRJW19].

2.1.4 Diagnosis

Up to date, there is no easy nor direct diagnosis for epilepsy, given the combined epidemiological and clinical basis on the definition of epilepsy, stated in Section 2.1.1 [OAN⁺18,RRJW19]. Since epilepsy is polymorphic and has no specific feature, epileptic seizures are often confused with other physiological or psychological conditions, for instance, migraine, breath-holding attacks, or daydreaming [OAN⁺18,RRJW19]. It is therefore necessary to make a cautious diagnosis of epilepsy by a specialist interested in epilepsy, based on a description of the events that occurred, as well as a review of the symptoms [RRJW19].

In order to confirm a certain epilepsy diagnostic, whenever the clinical history suggests it, EEG is widely useful, especially in differentiating epileptic from non-epileptic events and in classifying seizure types [RRJW19,EL15]. Moreover, simultaneous video-EEG long-term monitoring may yield a definitive diagnosis, if diagnostic uncertainty remains [EL15].

For patients with focal seizures, neuroimaging techniques are capable of detecting structural epileptogenic lesions within the central nervous system (CNS) [EL15]. Between the available neuroimaging techniques, magnetic resonance imaging (MRI) is generally preferred over computed tomography (CT), given its higher sensitivity [EL15].

2.1.5 Treatment

The main and first-line treatment for epilepsy is the administration of AEDs, which aim to decrease the electrical activity in the brain [EL15,RRJW19]. More than 20 AEDs, with different mechanisms of action, are already approved by the US Food and Drug Administration (FDA) and

by the European Medicines Agency [OAN⁺18,EL15]. However, about one third of the patients are not able to achieve seizure freedom, in spite of the wide variety of available AEDs [OAN⁺18].

After the failure of two adequate and appropriately chosen AEDs, it is assumed that the patient has DRE, as described in 2.1.2 [RRJW19]. In these cases, resective surgery is the first-line treatment, considering it has the highest chances to succeed in controlling seizures, since 50-80% of the patients reported to be seizure free afterwards [OAN⁺18,RRJW19]. Epilepsy surgery consists of removing or disconnecting the seizure onset zone (SOZ), a brain region or network responsible for the development of seizures, as a means to disrupt the epileptogenic network, i.e. the brain regions that interact to generate epileptic activity [RRJW19,JMG⁺22].

However, resective surgery is not always an appropriate option for DRE patients, given that nearly half of them are not eligible [ZLS⁺19,DG20]. Reasons for ineligibility include multifocal epilepsy, inaccessible seizure foci, or patients reluctant to receive operation [DG20,XCB⁺22]. Moreover, it is still possible that patients continue to have seizures after undergoing resective surgery, which is the case of about 50% of the people [MSR⁺21]. As such, despite being palliative, neuromodulation comes up a promising alternative therapy to reduce or prevent ictal events [XCB⁺22,RRH⁺21]. A more detailed description on neuromodulation approaches in epilepsy comes up in Section 2.2.

2.2 Neuromodulation in Epilepsy

The concept of electrical stimulation towards modulating the nervous system emerged back in ancient times (46 AD), when Scribonius Largus, physician of the Roman emperor Claudius, placed live torpedo fish, capable of producing electric discharges, on the cranial surface as a treatment for headache [Sir11]. Then, in the early nineteenth century, Giovanni Aldini discovered that electrical stimulation to the cortical surface could be applied to other contexts, from which the treatment of neuropsychiatric disorders must be highlighted [DG20, Sir11]. Ever since, neuromodulatory techniques have rapidly been becoming more sophisticated and widespread over the years [DG20]. Among the neurological diseases that neuromodulation may encompass, epilepsy, being characterised by abnormal electrical activity, has been widely studied by the scientific community. However, despite the promising outcomes reached so far, there are still challenges left to overcome, which are put in perspective along this section [DG20].

2.2.1 Techniques

Once neuromodulation has been the selected treatment for DRE, next, a neuromodulation technique has to be chosen [RRH⁺21]. The different techniques currently being employed are represented in Figure 2.2 and include: deep brain stimulation (DBS), responsive neurostimulation (RNS), vagus nerve stimulation (VNS), transcutaneous VNS (tVNS), transcranial direct current stimulation (tDCS), transcranial magnetic stimulation (TMS), and trigeminal nerve stimulation (TNS), being the first three invasive therapies, whilst the last four are non-invasive ones [XCB⁺22].

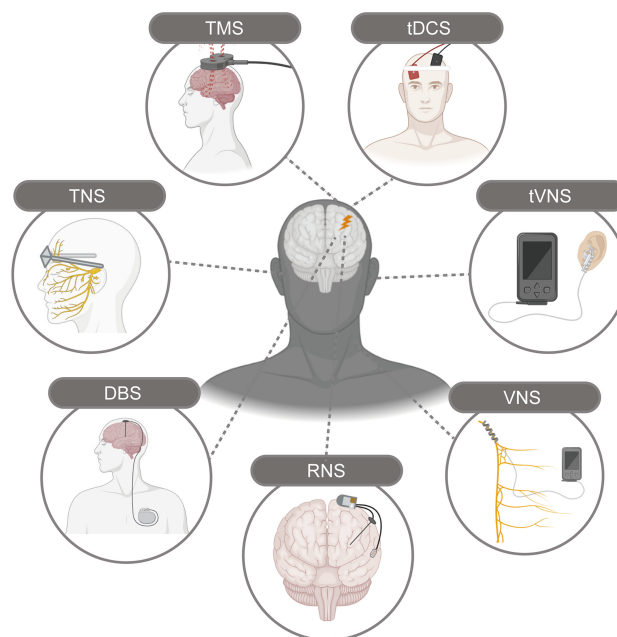


Figure 2.2: Types of Neurostimulation. Source: [XCB⁺22].

Neuromodulation strategies may be designed either under an open-loop or a closed-loop (also known as adaptive) paradigm [PK17]. For the former, stimulation parameters (amplitude, duration, pulse frequency) are predefined by the clinician and remain constant regardless of the patient's state, whilst for the latter the stimulation parameters are automatically adapted according to specific biomarkers¹ linked to the patient's symptoms [PK17, DG20].

Among the existing neuromodulation techniques, only VNS, RNS, and anterior nucleus of the thalamus-DBS (ANT-DBS) are currently FDA-approved for the treatment of focal DRE [XCB⁺22, RRH⁺21]. All these three strategies use surgically implanted devices and stimulation electrodes, but they work under different mechanisms [RRH⁺21].

VNS is based on a stimulating lead wire placed around the left vagus nerve, together with a pulse generator implanted in the subclavicular region [DG20, XCB⁺22, RRH⁺21]. As an alternative to the traditional open-loop VNS, recent closed-loop algorithms embedded in these generators, whose reliability has already been demonstrated, detect alterations in heart rate, given that most seizures are associated with tachycardia [RRH⁺21]. Then, without the need of a clinician, stimulation is triggered according to the patient's clinical state [RRH⁺21, DG20].

RNS, as the name suggests, responds to epileptiform activity in the SOZ, by sending high frequency electrical stimulation bursts, in order to abort any potential imminent seizure [JMG⁺22, RRH⁺21, XCB⁺22]. The RNS setup design works in a closed-loop manner, comprising a neurostimulator inserted in the skull together with a combination of electrocorticogram (ECoG) recording grid electrodes and stimulation electrodes, implanted into the SOZ [DG20, XCB⁺22].

DBS systems are composed by one or more leads implanted deep within the brain, connected subcutaneously to an implanted pulse generator (IPG) by extension wires [WLY⁺21, DG20]. The configuration of a standard DBS electrode, or lead, consists of an ≈ 1 mm cylinder with four electrode contacts. IPG devices, often compared to cardiac pacemakers, are primarily capable of sending stimulation signals, and, in recent IPGs, of recording brain activity as well [WLY⁺21]. Unlike RNS, DBS stimulation parameters are typically predefined by the clinician (open-loop), although closed-loop approaches are currently under development [DG20]. Furthermore, in opposition to VNS and RNS, DBS targets specific propagation points within the epileptogenic network, thus aiming to prevent further seizure initiation and propagation, either by inhibiting the target directly, or by disrupting a specific target, being it responsible for seizure spread [XCB⁺22, JMG⁺22]. Accordingly, DBS outcomes and side effects strongly vary based on different targets [XCB⁺22, WLY⁺21]. Given these variations, the ANT remains the only FDA-approved DBS target for the treatment of focal refractory epilepsy, although other potential stimulation targets are in increasing number and under investigation in multiple randomised trials [JMG⁺22, RRH⁺21, VFG⁺22, ZLS⁺19].

¹Biomarkers are defined by the National Institute of Health as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" [LBBB21].

2.2.2 DBS Targets

A wide range of brain targets have been investigated for DBS in epilepsy, these including the anterior nucleus of the thalamus (ANT), the centromedian nucleus of the thalamus (CMT) and the hippocampus (HC) [VGE⁺22]. Although this section will focus on the prior mentioned targets, which yielded better clinical outcomes so far, alternate targets have been proposed too, including the substantia nigra pars reticulata (SN), subthalamic nucleus (STN), caudal zona incerta (cZI), posterior hypothalamus (pHyp), fornix (Fx), nucleus accumbens (NA), caudate nucleus (CN), and dentate nucleus (DN), as labelled in Figure 2.3.

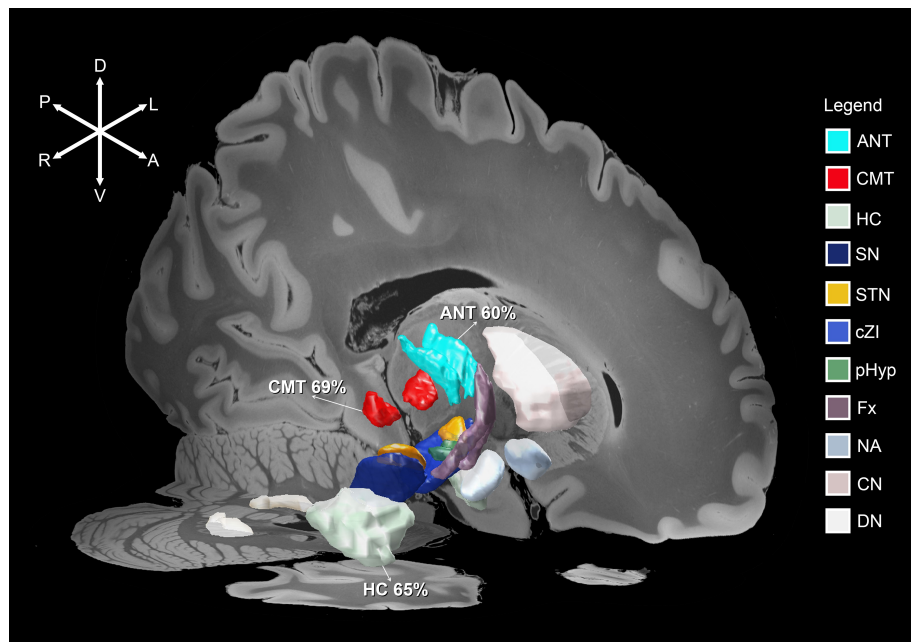


Figure 2.3: DBS targets in epilepsy. Percentage values stand for the corresponding target's mean seizure reduction. Source: [VGE⁺22].

Target selection can be thought based on three paradigms: (1) Stimulate the suspected SOZ directly, trying to inhibit it (e.g. hippocampus, hypothalamus, cortical zones); (2) Apply the stimulus on subcortical propagation points within the epileptogenic networks, thus disrupting it (e.g. thalamus, cerebellum); (3) Stimulate fiber bundles connected to distinct key structures in the brain, modulating the seizure circuit, which is located in different but connected brain structures (e.g. fornix, corpus callosum) [ZLS⁺19, JMG⁺22].

The choice of an appropriate target location is critical for DBS to be efficient and safe, being it dependent on the patient's symptoms, age and cognitive state [WLY⁺21]. Together with the target choice, other factors may impact clinical outcome after DBS, for instance, electrode location, type of epilepsy, time of stimulation, or stimulation parameters [VFG⁺22]. Performing further randomised trials, as well as studying which combination of factors suits best for each case, is expected to lead to improved outcomes after DBS in refractory epilepsy.

2.2.2.1 Anterior Nucleus of the Thalamus

The ANT occupies the superior region of the thalamus, a paired gray matter diencephalic structure located near the center of the brain [CB13, WYS⁺22]. The thalamus is divided into distinct nuclei, which each have different connectivity profiles and circuits [JMG⁺22, WYS⁺22]. However, these nuclei are highly interconnected and connected to the cerebral cortex via nerve fibers, thus allowing for the thalamus to represent an integrative hub for functional brain networks [JMG⁺22]. Functionally, thalamic nuclei can be divided into three basic types: (1) *Relay nuclei*, representing the majority of the thalamus, receives well-defined inputs, which are then projected to distinct zones of the cortex; (2) *Association nuclei* receive the input of information from the cortex and project back to it, more specifically, to the association areas regulating multimodal input onto the cerebral cortex-pulvinar nuclei; (3) *Nonspecific nuclei* project information to the cerebral cortex as well, but in a broader manner, being involved in general functions such as alerting [JM11]. Anatomically, as represented in Figure 2.4, each side of the thalamus contains three groups of thalamic nuclear masses: the lateral cell mass (in dots), the medial cell mass (in squares) and the anterior cell mass (in stripes), which get split by the the internal medullary laminae, a Y-shaped bundle of white matter [MF08, JM11]. More subdivisions within those three nuclei may be defined, based on structural and functional considerations [MF08].

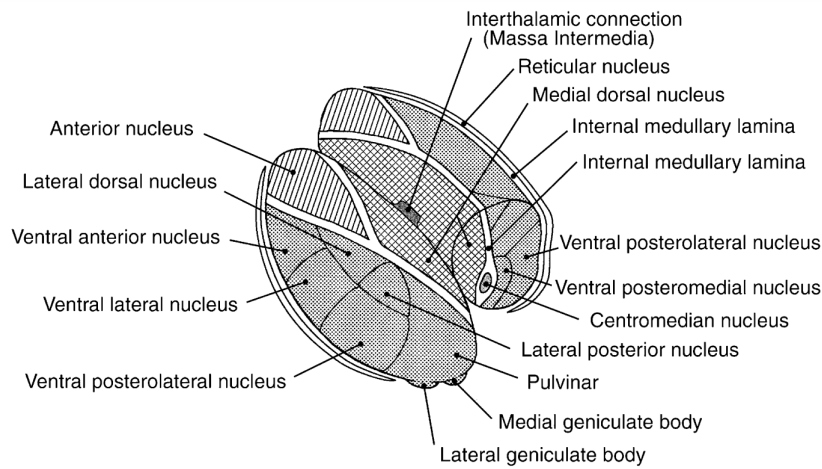


Figure 2.4: Relative location of various thalamic nuclei. Source: [MF08].

Given its structural and functional characteristics, the ANT is composed of three distinct sub-nuclei: anteroventral, anterodorsal, and anteromedial nuclei [WYS⁺22, CB13]. Although being often described as a single unit, each subnuclei has a different connectivity pattern, thus forming part of 3 different episodic memory circuits [CB13, WYS⁺22].

The ANT is a key component of the hippocampal system for episodic memory, since it receives inputs from the subicular cortex, retrosplenial cortex and mammillary bodies, while it outputs information to the medial prefrontal cortex [CB13, JMG⁺22]. All the referred structures are components of the well-known Papez circuit [JMG⁺22, NPV18]. The Papez circuit denotes a

closed-loop pathway comprising the limbic system, that is vital in episodic and recognition memory, and stated as the "anatomic basis of emotions" [NPV18]. Within this route, hippocampal projections are linked to the ANT through the fornix and mammillary nucleus [PMLG21]. Then, the ANT feeds back firstly to the cingulum, then to the parahippocampal gyrus and entorhinal cortex, until finally returning to the hippocampus [PMLG21, JMG⁺22]. The Papez circuit is described as a route for epileptic seizure propagation, since disruptions have been observed in various types of epilepsy [PMLG21, JMG⁺22]. Considering that high-frequency stimulation restores normal cortical network functioning, it makes sense to propose Papez circuit's nodes as DBS targets, for instance the ANT, as a means to desynchronise the corresponding network [JMG⁺22].

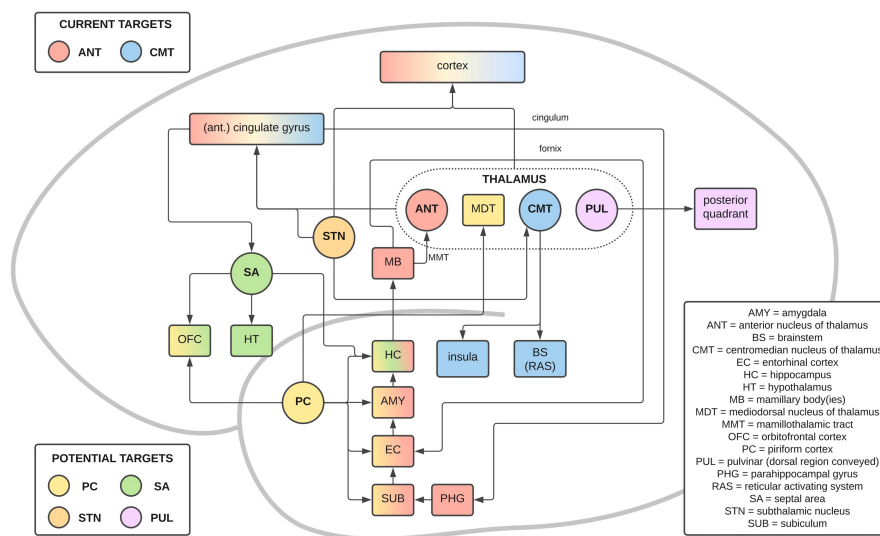


Figure 2.5: Schematic of the connections of the current and potential stimulation targets, including the circuit of Papez. Source: [JMG⁺22].

The ANT has been considered a suitable stimulation target for epilepsy for decades, being the DBS target with best scientific evidence so far [VFG⁺22, JMG⁺22]. After Kerrigan et al. [KLF⁺04] published an open-label pilot study of intermittent electrical stimulation of the ANT in five patients, interest in ANT-DBS has grown substantially [ZCF⁺18]. From 2008 to 2018, 20 studies on the topic were published, involving in total 220 epileptic patients, who presented responder rates ranging from 44% to 100% [ZCF⁺18]. The publication of the "Stimulation of the Anterior Nucleus of Thalamus for Epilepsy" (SANTE) trial's results in 2018 represented a turning point for ANT-DBS, since it allowed for this therapy to receive both FDA approval in the United States and a *conformité européenne* (CE) mark in Europe [ZLS⁺19, VFG⁺22, FSW⁺10]. Ever since, considering SANTE's follow-up studies' sustained efficacy, ANT-DBS became a well-established therapy for refractory epilepsy [ODWvW⁺23, ZCF⁺18].

The SANTE trial was a multicenter, double-blind, randomised controlled trial of bilateral stimulation of the ANT [FSW⁺10, SWW⁺15]. The initial cohort included 110 participants aged 18-65, with medically refractory partial seizures, including secondarily generalised seizures [FSW⁺10, SSG⁺21]. Patients had a baseline median seizure frequency of 19.5 per month and a disease

duration of 22.5 years, thus being guaranteed that the initial baseline demographics are similar [SSG⁺21]. From the 110 subjects who underwent bilateral ANT-DBS, 54 were randomly assigned to stimulated and 55 to control groups [FSW⁺10]. After a 3-month blinded treatment phase, all the participants received stimulation during 9 months in an unblinded phase [FSW⁺10, SSG⁺21]. In the unblinded phase, stimulation parameters were set to 5 V, 145 pulses per second, 90 μ s, 1 minute ON and 5 minutes OFF, for all the subjects [FSW⁺10]. Then, subjects continued to be assessed during the long-term follow-up phase, in which changes in AEDs and in stimulation parameters were allowed, so as to further characterise adverse events and the incidence of SUDEP [FSW⁺10, SSG⁺21]. Ten years of extended follow-up studies showed a 43% responder rate² at one year, 68% at five years, and 75% at 7 years [SWW⁺15, ODW⁺W⁺23]. On the other hand, reported adverse events of interest at 7 years include depression (37.3%), memory impairment (30%), and suicidality (10%) [SSG⁺21]. From implantation to 10 years after, most frequent side effects comprise paresthesias, implant site pain, implant site infection (12.7%) and leads not within target (8.2%) [FSW⁺10, SWW⁺15, SSG⁺21]. After year 7, adverse events were all related either to DBS or to epilepsy [SSG⁺21]. Eight deaths were reported in SANTE, from which four were classified as SUDEP, being that none of these deaths were directly attributed to the implant, device or therapy [SSG⁺21].

Although Salanova et al. [SSG⁺21] have proven with SANTE that the efficacy of ANT-DBS improves over time, some points still remain unclear [KS21]. These questions are expected to be unriddled by performing studies comparing, for instance, the efficacy of different thalamic targets based on the SOZ, the differences in responses in open-loop and in closed-loop paradigms, or even the optimum stimulation parameters [KS21]. Evaluations as such may shed light for the improvement of ANT-DBS outcomes [KS21]. Furthermore, a recent study tried to understand which patients could benefit the most from the therapy, by recruiting participants from multiple centers from different countries, instead of doing so in a single center [PCP⁺23]. To overcome these limitations and allow for results' generalisation, the Medtronic Registry for Epilepsy (MORE) came up to evaluate the safety and long-term effectiveness of ANT-DBS in routine clinical practice, which presents a wider diversity of patients [PCP⁺23]. Eligible candidates were at least 18 years old, with focal DRE, recruited from 25 centers across 13 countries [PCP⁺23]. Given the results described in [PCP⁺23], the safety and effectiveness of ANT-DBS in realistic settings, within a 2-year follow-up, is supported by this study. Future work onto clinical trials for ANT-DBS may include novel neurostimulator devices which record local field potentials (LFPs), thus allowing to understand the patient's state during the treatment and to optimise it [PCP⁺23].

2.2.2.2 Centromedian Nucleus of the Thalamus

The CMT is the most prominent intralaminar nucleus, a central oval mass found within the internal medullary lamina, as represented in Figure 2.4 [MF08, JM11]. Being posteriorly placed on coronal section, the CMT is located in the midthalamic region, between the medial and ventral posterior

²Reduction in seizure frequency greater or equal than 50%.

nuclei [JM11]. Furthermore, the CMT is thought to play a role in cortical arousal, particularly in response to external stimuli, given its extensive connections to somatosensory, reticular and diffuse cortical regions [MF08].

For more than 30 years, the CMT has been considered a suitable DBS target, especially for the control of generalised-onset seizures, namely Lennox-Gastaut syndrome³ [ZLS⁺19, JMG⁺22]. Considering CMT's anatomical patterns and connections, its role in the pathophysiology of generalised seizures is supported [ZLS⁺19]. Therefore, by electrically inhibiting and desynchronising CMT's circuits, CMT-DBS is expected to control seizures [XCB⁺22].

The first of two controlled CMT-DBS clinical trials was published by Fisher et al. [FUK⁺92] in 1992 [WYS⁺22]. A cohort of 7 patients with focal and generalised refractory epilepsy, from which 2 have Lennox-Gastaut syndrome, was bilaterally implanted [FUK⁺92, WYS⁺22]. A mean seizure reduction of 30% was achieved with stimulation, whilst there was a decrease of 8% when the stimulator was off [FUK⁺92]. Although these results did not reach significance, there were no side effects, which demonstrates the feasibility of CMT-DBS controlled trials and the need for further studies [FUK⁺92, WYS⁺22]. Then, in 2000, Velasco et al. [VVJ⁺00] evaluated the efficacy of chronic electrical stimulation of CMT in 13 patients with difficult-to-control seizures [VVJ⁺00, WYS⁺22]. Better results were obtained for Lennox-Gastaut syndrome, with an overall seizure reduction of 81.6%, compared to 57.3% for patients with primary focal epilepsies [VVJ⁺00, WYS⁺22]. Although these two studies represent important findings by supporting the CMT as a potentially efficacious stimulation target, additional large and controlled studies for CMT-DBS are still necessary [ZLS⁺19, JMG⁺22]. Prospective clinical trials supporting CMT-DBS and *in vivo* human studies towards the investigation of CMT's structural and functional networks are recently beginning to emerge [JMG⁺22].

2.2.2.3 Hippocampus

The hippocampus is a densely packed S-shaped structure, on the edge of the temporal lobe of the cerebral cortex [AD12]. It constitutes the posterior part of the limbic system, also known as "primitive brain", which is concerned with survival responses such as hunger, pain, pleasure, etc. [AD12]. Regarding function, the hippocampus is important in learning, memory, spatial navigation and emotional behaviour [AD12].

In several neuropsychiatric disorders, namely in epilepsy, the hippocampus is the earliest and most severely affected structure [AD12]. For instance, hippocampal atrophy in DRE is often associated with temporal lobe epilepsy (TLE), the most common form of focal epilepsy [AD12, ZLS⁺19]. The role of the hippocampus in seizure generation and propagation is evident due to its involvement in the circuit of Papez (Figure 2.5) [XCB⁺22]. Furthermore, it is stated that the hippocampus has an inhibitory effect on seizure threshold, thus keeping it high [AD12]. Thus, it makes sense to consider the HC as a potential DBS target as well, especially for refractory TLE cases [XCB⁺22, ZLS⁺19].

³Lennox-Gastaut syndrome is an epileptic encephalopathy characterised by seizures of multiple types. Patients' age of onset ranges between 1 and 6 years old [EL15].

Indeed, clinical studies support the antiseizure effect of electrically stimulating the hippocampus [ZLS⁺19]. Firstly, in 2006, Tellez-Zenteno et al. [TZMP⁺06] published a double blind, multiple cross-over, randomised controlled trial for unilateral HC-DBS. Four patients with refractory mesial temporal lobe epilepsy presented a 26% median seizure reduction with the stimulation ON, whilst for the OFF mode a 49% median increase in seizure frequency was observed, thus not representing statistical significance [TZMP⁺06, VFG⁺22]. Afterwards, in 2007, Velasco et al. conducted a randomised controlled trial including 9 patients which underwent bilateral hippocampal implantation [VVV⁺07]. Significant results were achieved since seizure frequency was roughly lower by the end of the 18-month follow-up for all the subjects [VVV⁺07]. Two more randomised clinical trials for HC-DBS showing statistically significant results were performed in 2010 and in 2017 [VFG⁺22]. However, the number of participants was not higher than 16 patients, which may limit clinical evidence on HC-DBS [VFG⁺22]. Future studies with large-scale cohorts and longer follow-up durations are still needed to validate clinical efficacy of HC-DBS [XCB⁺22].

2.2.2.4 Others

Alternate stimulation targets include cerebellum, caudate nucleus, pulvinar of the thalamus, piriform cortex, septal area, and others [XCB⁺22, JMG⁺22]. Further evidence is required to evaluate the efficacy of these potential targets against refractory epilepsy [XCB⁺22].

2.2.3 PerceptTM PC Neurostimulator

DBS systems from multiple manufacturers are currently available on the market for commercial use, with geographically variable specific indications between the United States, Europe and others [JS21, FCJ⁺22]. Up to date, companies involved in manufacturing DBS systems are Medtronic, Abbott, Boston Scientific, PINS Medical, and Scene Ray [FCJ⁺22, PLS⁺20]. Across this range of manufacturers, although each device has unique features, the basic stimulation principles remain the same: as a means to normalise neuronal patterns, apply an electrical field to specific nodes of the pathologic network [JS21]. Tools differentiating the existant devices rely on a broad range of advanced features such as electrode design, IPG size and rechargeability, MRI compatibility, stimulation parameters available, LFP sensing and visualisation software [JS21]. However, choosing the ideal DBS system may depend on the anatomical target, patient factors, and on surgeon or neurologist preferences [PLS⁺20]. Considering that Medtronic has dominated the market for the past decades, it is expected that practitioners are experienced with Medtronic systems, thus tending to choose it [PLS⁺20]. Currently commercially available Medtronic DBS systems encounter the ActivaTM RC and the PerceptTM PC, which can be coupled with the SenSightTM directional leads and with the SureTuneTM 4 Software [Med21]. PerceptTM PC received the CE Mark on 9 January 2020 in the European Union and FDA approval in the United States on 25 June 2020, thus being Medtronic's most recent and the first complete DBS system with sensing, directionality, and visual programming functionalities [Med20a, Med20b, Med21].

2.2.3.1 Device Specifications

Percept™ PC is the first and only EU commercially available DBS system capable of *in vivo* sensing brain signals while delivering active stimulation therapy to patients with neurologic disorders, mainly Parkinson’s disease, epilepsy, essential tremor and dystonia [Med20a, JS21]. All the other currently available DBS devices deliver electrical stimulation without recording brain signals, while Percept™ is able to simultaneously do both [JS21].

Ergonomically designed, Percept™ PC is 20% smaller and 20% thinner than Activa™ RC, Medtronic’s previous DBS system [Med22b]. Moreover, besides being conditionally compatible with 1.5T MRI systems like Activa™ RC, Percept™ PC is the first DBS system being also compatible with 3T MRI systems [Med22b, JS21]. Percept™ PC’s IPG is manufactured in a manner so that its battery life can be estimated in real-time, having a 5-year approximate longevity [Med22b, JS21]. Advanced visual programming capabilities embedded within Percept™ PC allow for an intuitive, optimised and data-driven usage of the system by clinicians, comprising functionalities such as assigning unique amplitude values to each electrode [Med22b].

Although impactful novelty was introduced, as described above, Percept™ PC has a structure similar to all the other DBS systems, comprising an IPG, an extension wire, and a DBS electrode [JS21]. Electrical current generated in the IPG according to the stimulation parameters travels through the extension wire to the DBS electrode, finally reaching the target tissue [JS21]. Besides, accompanying non-implanted hardware include a patient controller and a clinician programming tablet, as shown in Figure 2.6.



Figure 2.6: Percept™ PC Neurostimulator family: patient controller, dual-channel IPG, and clinician programming tablet (from left to right). ©2022 Medtronic. All rights reserved.

Percept™ PC’s IPG is compatible with different lead models, whose contacts differ in terms of length and spacing [JS21]. For epilepsy, Medtronic 3387 and 3389 are adequate and widely used

DBS lead models. As shown in Figure 2.7, four metal contacts lie at the end of each electrode. Both types of leads have 1.27 mm of diameter, whose contacts have a length of 1.5 mm. Their difference stands in the length between two adjacent contacts, which is equal to 0.5 mm in model 3389, and 1.5 mm in model 3387. Stimulation can be either monopolar, when it is induced between a contact and the IPG, or bipolar, if between two electrode contacts, thus causing current to flow into the target tissue [KPW⁺15]. Furthermore, considering the 6 electrode pairs per lead, bipolar montages can be split up into two types of combinations: the first pass, Pass1, which contains non-adjacent configurations (0-3, 1-3, 0-2); and the second pass, Pass2, comprising adjacent electrode pairs (0-1, 1-2, 2-3) [LRR⁺22].

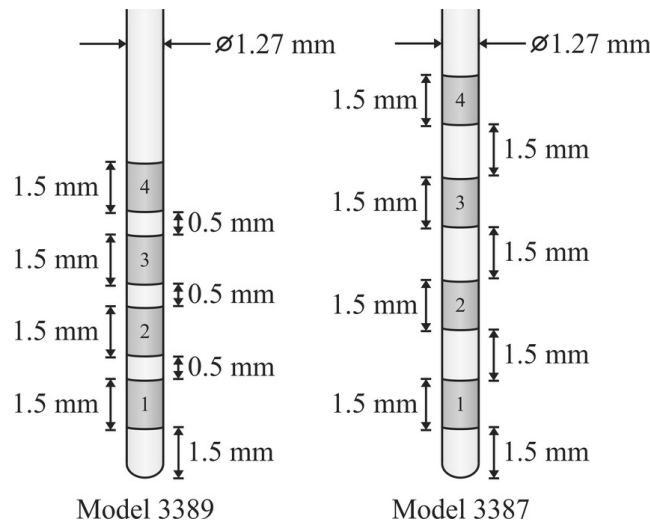


Figure 2.7: Medtronic 3389 and 3387 DBS Lead Models Scheme. Source: [JAKSN20].

PerceptTM PC's sensing ability is possible thanks to the BrainSenseTM technology, which allows physicians to track patients' brain signals (LFPs) and to correlate these with patient-related actions or experiences, such as symptoms, medication intake, or side effects [Med20a]. BrainSenseTM comprises several modes to record LFPs, which are described below and further summarised in Table 2.1.

Firstly, in order to use all the features of BrainSenseTM technology (except for BrainSenseTM Survey), the user must setup LFP sensing through BrainSenseTM Setup and select a frequency band of interest [Med22a]. This is the first and a crucial step to guarantee the correct tracking of the patient while outside-clinic, after checking for artefacts on their signal [Med22a]. After setup, BrainSenseTM Streaming, Timeline and Events can be used. In BrainSenseTM Streaming, one is allowed to view the quantitative impact of stimulation or other events on LFP power in a pre-selected frequency band, by real-time streaming data to the clinician's tablet [Med22a]. Furthermore, the user can collect time-domain LFP data from the selected channel to a JSON file for further offline analysis [Med22a]. For BrainSenseTM Timeline, this feature chronically records the power of a specific frequency band of interest in the LFP signal, in order to assess possible changes in LFP activity over the time spent out-of-office [Med22a,TPC⁺21]. On the other hand, when one wants to monitor patient events, such as medication intake or a seizure, the usage

of BrainSense™ Events is adequate [Med22a, JS21]. 30-seconds LFP Snapshots are captured whenever a patient marks an event that is predetermined by the clinician [JS21]. In the tablet, the magnitude of the LFP signal over a broad range of frequencies is visualised [Med22a]. Finally, BrainSense™ Survey is conducted with stimulation OFF and gives a broad spatial overview of the LFP signals, which can possibly aid into an objective contact selection [Med22a, TPC⁺21]. A graph of the differential in LFP between two contact pairs is generated, in the whole frequency spectrum (0-96.68 Hz), thus determining if the signal is detectable and in which pair of contacts [Med22a, JS21].

Table 2.1: Type of LFP data structures collected while using each BrainSense™ feature. Adapted from [LdCVBR⁺21, TPC⁺21].

BrainSense™ Feature	LFP Data	Description
BrainSense™ Survey	LfpMontageTimeDomain	Domain: Time Use: In-clinic Stimulation: OFF Duration: 20 seconds Channels: 6 in Pass1 and 6 in Pass2
	LfpMontageTimeDomain	Domain: Frequency Use: In-clinic Stimulation: OFF Duration: 20 seconds Channels: 6 in Pass1 and 6 in Pass2
	IndefiniteStreaming	Domain: Time Use: In-clinic Stimulation: OFF Duration: Up to 15 minutes Channels: 6 in Pass1
BrainSense™ Streaming	BrainSenseStreaming	Domain: Time Use: In-clinic Stimulation: ON or OFF Duration: Up to 15 minutes Channels: 2
BrainSense™ Timeline	BrainSenseTimeline	Domain: Power Use: Outside-clinic Stimulation: ON or OFF Duration: Indefinite Channels: 2
BrainSense™ Events	LfpFrequencySnapshotEvents	Domain: Frequency Use: Outside-clinic Stimulation: ON or OFF Duration: 15 minutes Channels: 2

2.2.3.2 Local Field Potentials

Local Field Potentials (LFP) are intracranially recorded biosignals that represent the activation of neuronal populations, by capturing local synaptic activity [MSM⁺23]. LFPs are a reflection of neuronal activity taking place around the region surrounding the electrode, in the extracellular space [PK17]. Besides high temporal resolution, LFPs have a considerable spatial resolution of around 1 mm [PK17]. LFPs' amplitude range may go up to 200 μ V, containing frequencies below 500 Hz [PK17]. Similarly to EEG, LFPs can be characterised into distinct frequency bands, although values may vary across the literature: delta (0-3 Hz), theta (4-7 Hz), alpha (8-12 Hz), beta (13-30 Hz), gamma (31-200 Hz), and high frequency (> 200 Hz) [Med22a].

Being LFPs stable direct recordings from the target tissue, dealing with these signals might seem easier at first sight, when compared to scalp recordings. However, like all other physiological signals, artefacts may show up. The main issue in LFP analysis is the artefact produced by the stimulation pulse, which saturates the recording system, preventing LFPs to be recorded while DBS is on [RMBP13]. Having this, many studies investigate LFP response right after DBS is turned off [RMBP13]. Furthermore, if any component of the DBS system moves in a way that it creates noise, movement artefacts may appear in the LFPs [Med22a]. Finally, fluid leakage along the sensing circuit may result in ECG artefacts, whose frequency range of 0-40 Hz might mask relevant information in the LFP [Med22a].

In spite of the abovementioned inherent artefacts, LFPs' suitability as the control variable in closed-loop DBS approaches has already been demonstrated [PK17]. The control variable must be a physiological biomarker easily measurable in patients undergoing DBS, without the need to implant more sensing devices, and able to reflect the patient's clinical condition [RMBP13, PK17]. Therefore, LFPs, by being measured directly through the DBS electrode and by being able to reflect patient's state in real-time, are the most used feedback signal in adaptive DBS [RMBP13, PK17].

Besides closed-loop approaches, LFPs have been useful for other applications. Although being invasive, when compared to non-invasive neuroimaging techniques such as EEG or MEG, LFPs' high temporal and spatial resolution has been a huge asset to understand neural mechanisms, brain connectivity patterns, or even to identify disease biomarkers [MSM⁺23]. Indeed, studies correlating LFP frequency bands to specific symptoms may be of high clinical relevance and have recently been emerging [Med22a]. For instance, recent reports correlate theta band with tremor, in Parkinson's Disease, and low frequency bands with dystonia [Med22a, MSM⁺23]. Regarding epilepsy, frequencies ranging from 4 to 11 Hz and peaks at around 26 Hz have been identified by PerceptTM PC as associated with seizures [Med22a]. Nevertheless, compared to other movement disorders such as Parkinson's disease, there are few studies associating LFPs oscillatory behaviour to disease state in epilepsy, thus opening room for future studies and enhancing the potential relevance of the present thesis [Med22a, MSM⁺23].

Chapter 3

Epilepsy as a Network Disorder

3.1 Connectomic Overlap in Epilepsy

The human brain can be described as a group structure in which ensembles of interconnected entities collectively give rise to macroscale function [RBL⁺22, JMG⁺22]. These ensembles are called brain networks: a functionally and anatomically connected set of cortical and subcortical structures or regions, in which activity in one part affects all the others at some extent [Spe02]. As such, neuroscience has increasingly been adopting the approach that brain regions should not be regarded as isolated modules [RBL⁺22]. Transposing this concept to epilepsy, in 2002, Spencer stated that seizure activity in a certain part of the brain network is influenced by activity elsewhere within the network [Spe02]. Ever since, advancements in brain connectivity research have driven epilepsy to be seen as a network disorder, characterised by an hypersynchronisation of ictogenic large-scale brain networks [JMG⁺22, ALD⁺23]. Indeed, changes in neural network organisation and dynamics are described both in the ictal and interictal state, and between one or both hemispheres [vMHFV19, VGE⁺22].

Likewise, epilepsy therapies must adopt a network neuroscience perspective [JMG⁺22]. Instead of focusing only on the local impact, network-guided neuromodulation approaches consider the remote impact on brain regions connected to the stimulation target, being thus applicable to both focal and generalised epilepsies [HF20]. On one hand, as an attempt to disrupt the epileptogenic network, resective surgery directly targets and destroys the putative SOZ, whilst DBS targets influential "propagation points" within the epileptogenic network [JMG⁺22]. Targets described in Section 2.2.2 constitute potential propagation points.

Thalamic hubness within the epileptogenic network has been a primary aim in current clinical practice [JMG⁺22]. Hubs are defined as brain regions with a large number of connections, supporting efficient and large-scale information flow across the network [RBL⁺22]. Within the thalamus, the ANT has shown high clinical efficacy as being a promising DBS target, supported by its connectivity profile. As a component of the Papez circuit, the ANT is characterised by mutual strong anatomical connectivity to cortical and subcortical regions involved in seizure generation and propagation [ALD⁺23]. However, it is not yet well known how ANT-DBS alters

cortical activity, nor their association with clinical responsiveness [ALD⁺23].

The next step in network-guided neuromodulation is to extract electrophysiological biomarkers from the epileptogenic network or hypothetical correlates, in order to determine stimulation candidacy, treatment efficacy, or even tailor targeting to the individual patient [JMG⁺22, ALD⁺23]. Towards this goal, recent studies are trying to understand how functional connectivity is altered in patients receiving DBS for epilepsy [VGE⁺22]. Many brain networks have been shown to vary in epileptic patients compared to healthy controls, but, among these, the default mode network (described in Section 3.3) has by far been the most extensively studied [MGS⁺18].

3.2 Assessing Brain Networks

A growing body of research approaches the human brain regions from a network perspective, and not as isolated modules. For a network disorder such as epilepsy, a network analysis must be performed. Analysing brain networks is made feasible thanks to recent progress in the acquisition and processing of neuroimaging and electrophysiological data [Spo13, RBL⁺22]. Some of the modern non-invasive imaging techniques applied to the human brain, namely for connectivity analysis, are below described.

3.2.1 Network Neuroscience Tools

Brain networks can be derived either from anatomical or physiological observations, resulting respectively in structural and functional networks [Spo13]. Although there is a clear distinction, both concepts are related and may coexist.

Structural connectivity denotes anatomical connections linking a set of neural elements [Spo13]. Typically, these links refer to white matter projections in the brain connecting cortical and subcortical regions [vMHFV19, Spo13]. Diffusion MRI and tractography are the most common techniques to create structural connectivity maps [RBL⁺22, Spo13]. The complete description of all the structural connections between neural elements is defined as the connectome [BS09]. Considering the plasticity of the human brain, connectomes are relatively stable over shorter periods of time, but may change at longer time scales [Spo13].

Functional connectivity describes the statistical relationship between two signals, thus implying that there are two brain regions communicating with each other, as translated by their statistical dependence [BS16, Spo13]. Generally, functional connectivity derives from time-series data, including electroencephalography (EEG), magnetoencephalography (MEG), and functional magnetic resonance imaging (fMRI) [Spo13]. Commonly used metrics to compute functional connectivity include, for instance, coherence, phase locking value, and cross-correlation [BS16]. Although structural network analysis allows one to understand the architecture of anatomical links within brain regions, a complete network analysis requires considering, through functional connectivity, how this architecture supports neurophysiological demands [BS09].

Effective connectivity comes up as a third mode of representing and analysing brain networks [Spo13]. In the ideal case, one seeks not only to have the idea that there is a relationship between

these two signals, but also to interpret the corresponding causality [BS16]. By wrapping up both these ideas, effective connectivity comes up as the union of structural and functional connectivity, [Spo13, BS09]. Models estimating the causal influence between neural elements include Granger causality and dynamic causal modelling [BS09]. Although effective connectivity analysis holds high potential, most of the network analysis studies are carried out computing either structural or functional connectivity [Spo13].

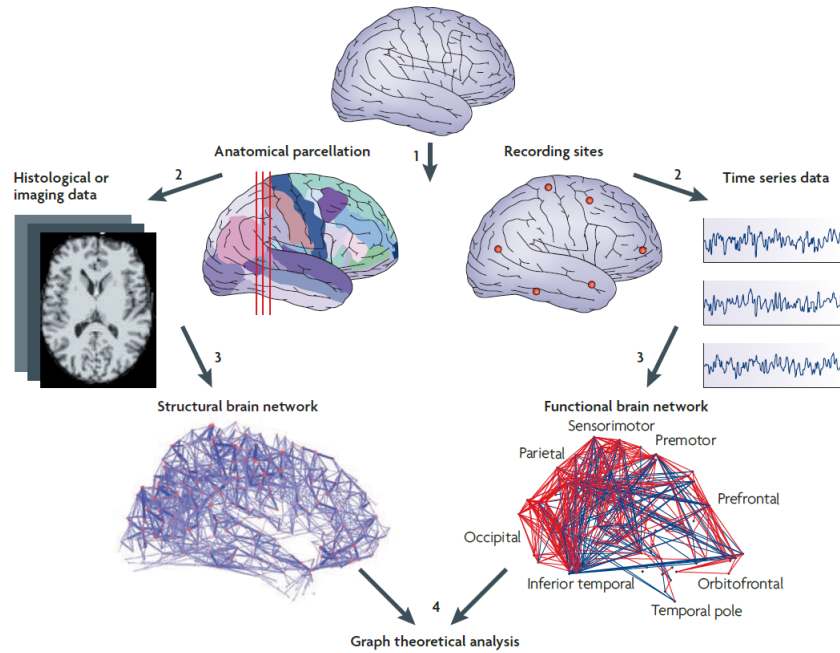


Figure 3.1: Structural and functional brain networks. Source: [BS09].

Structural and functional brain networks can be explored using *graph theory*, a powerful way of regarding the human brain as a set of nodes (neural elements) and edges (their mutual connections) [BS09, Spo13]. Graphs can be directed or undirected, depending if the edges have a specific direction or not. A graph theoretical analysis involves performing the following steps [BS09]:

1. Define the network nodes, which may be EEG electrodes or anatomically defined regions in structural data;
2. Compute a measure of association between the nodes (e.g. Granger causality);
3. Generate an adjacency matrix, which indicates the number of edges between each pair of nodes in a graph. Frequently, the adjacency matrix is specified as binary, with zeros indicating there is no edge between a given pair of nodes, and ones indicating there is an edge. For undirected graphs, the adjacency matrix is symmetrical;
4. Calculate network measures of interest to quantify graph topology (e.g. node degree).

Having this, accomplishing the established goal of understanding neural dynamics within pre-defined regions implies computing functional connectivity. Prior to obtaining a functional brain

network and the corresponding graph, time-series data must be extracted. Functional MRI, EEG, and MEG constitute the main techniques for obtaining time-series data from the brain, thus being below described in detail.

3.2.2 Functional Magnetic Resonance Imaging

Functional magnetic resonance imaging (fMRI) is an imaging technique which measures brain activity by detecting regional, time-varying alterations in metabolism [Glo11]. Metabolism changes measured through fMRI can be either a consequence of cognitive tasks (visual, auditory or other stimulus which induce neural state to change), or spontaneous modulation of neural metabolism [Glo11]. Increased neural activity can be detected by fMRI in two possible ways: through increased local cerebral blood flow, using an injected contrast agent and perfusion weighted MRI, or through BOLD contrast, which results from changes in the magnetic field surrounding the red blood cells, which in turn depends on the oxygen state of the hemoglobin [Glo11]

fMRI is the most widely used technique to measure functional connectivity [LFP⁺17,RBL⁺22]. Its high spatial resolution at the order of millimeters allows one to build accurate maps of functional networks across the brain [LFP⁺17]. Although most of the fMRI studies evaluate the neural response to specific stimulus, in recent years, functional connectivity has been increasingly studied in task-free (i.e. resting-state) paradigms [Glo11,RBL⁺22]. Indeed, fMRI allowed to establish RSNs as a phenomenon. However, a significant drawback is fMRI's low temporal resolution, limited by a slow hemodynamic response time [Glo11,LFP⁺17]. Given their high temporal resolution, EEG and MEG may show up as an alternative to accurately capture the dynamic of evoked responses.

3.2.3 Electroencephalography

Electroencephalography (EEG) is a technique used to measure the electric potential recorded from the human scalp [SN12]. EEG shows up as an important tool to investigate the temporal dynamics of the brain's large scale neuronal circuits [MML⁺04]. The related technology, MEG, measures the magnetic field generated by brain current sources [SN12]. Both EEG and MEG have a high temporal resolution, being capable of measuring the electrical activity of neuronal cell assemblies at a resolution lower than one millisecond [SN12,MML⁺04]. Conversely, EEG and MEG's spatial resolution is poor, when compared to other modern imaging techniques [SN12].

3.2.3.1 EEG Rhythms

EEG is typically differentiated into five different frequency bands: delta (δ), theta (θ), alpha (α), beta (β), and gamma (γ). All the information described below is further summarised in Table 3.1.

Delta rhythm includes all the waves between 1 and 4 Hz, representing the lowest frequency component in the EEG but with the highest amplitude values. Delta waves are usually seen during deep sleep states [dS10]. However, in waking adults, intermittent delta activity with frontal emphasis may represent abnormalities [TS13].

Theta ranges from 4 Hz to 8 Hz. In healthy and alert adults, theta is generally absent, appearing in stages of light sleep, drowsiness, daydreaming, or during situations of emotional stress (disappointment or frustration) [TS13].

Alpha waves occur at a frequency between 8 Hz and 13 Hz. Alpha rhythms are usually seen in an awake but relaxed person, with their eyes closed. If one is either sleeping or attentive, these waves tend to disappear [TS13, dS10].

Beta activity goes from 13 Hz to 30 Hz. These are closely associated to motor tasks, cognitive processes, active thinking, concentration, or even stress and anxiety.

Gamma rhythms represent all brain waves from 30 Hz to 80 Hz. Above 80 Hz, high-frequency oscillations are observed [BP22]. Due to gamma's low amplitudes, sometimes they are difficult to record with common scalp EEG systems. Gamma is thought to be modulated by sensory input and internal processes such as cognitive thinking, working memory and attention [TS13].

Table 3.1: EEG Rhythms. Based on [TS13, BP22]

Type	Frequency (Hz)	Behavioural State
Delta	1-4	Deep sleep
Theta	4-8	Light sleep, emotional stress
Alpha	8-13	Awake but relaxed adult
Beta	13-30	Motor tasks, active thinking, concentration
Gamma	30-80	Attention, working memory, cognitive processes

3.2.3.2 Standardised EEG Electrode Systems

EEG systems have their scalp electrode arrays with standardised positions and nomenclature. In standard systems, electrode positions are based on percentages of the circumferential measurements from fiducial landmarks of the skull. EEG fiducial landmarks are: nasion (depression at the intersection of the frontal bone and the two nasal bones), inion (most prominent projection of the external occipital protuberance), and the left and right preauricular points (depressions at the posterior root of the zygomatic arch) [SKB⁺17]. Electrode nomenclature consists of letters and numbers, each with a specific meaning. The letters F, P, T and O indicate the underlying brain lobe (frontal, parietal, temporal and occipital, respectively), whilst the letter C indicates the central region and Fp stands for fronto-polar electrodes [SKB⁺17]. Regarding the numbers, odd numbers are on the left side, and even numbers are on the right side. Finally, electrodes in the midline are annotated with a "z" (standing for zero), instead of a number.

The 10-20 system, represented in Figure 3.2, was the first suggested electrode configuration and constitutes the basic EEG electrode array. The name "10-20" comes from the distances between the electrodes. For instance, considering the midline (from the nasion to the inion) as a distance of 100%, then, in the anterior-posterior direction, the distance between each of the electrodes in the midline is given by 10%, from the nasion to Fpz, then by 20% from Fpz to Fz, from Fz to Cz, from Cz to Pz, and from Pz to Oz, and finally by 10%, from Oz to the inion [SKB⁺17]. Therefore, the official standard 10-20 system consists of 21 scalp electrodes.

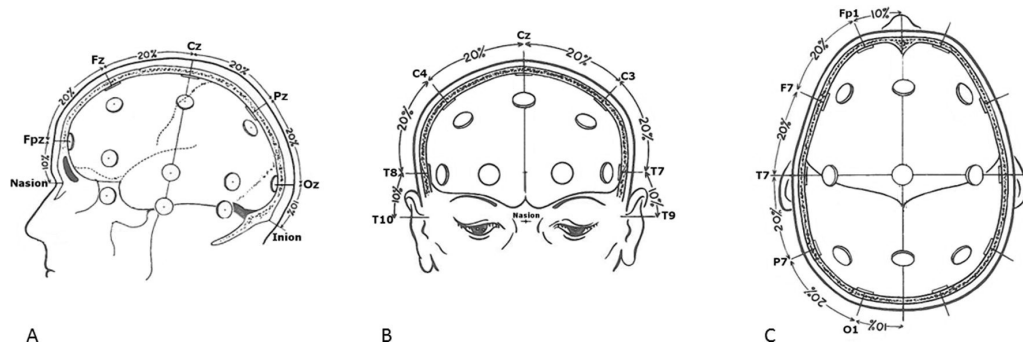


Figure 3.2: Placement of the standard electrodes of the 10-20 system. A: lateral view, B: frontal view, C: top view. Source: [SKB⁺17].

Although 21 electrodes are still considered enough for most clinical applications, some research areas required higher electrode density. Having this, extensions to the original 10-20 system were suggested. When additional electrode sites are added to the scalp in the first place, these have to be located at the points halfway between the 10-20 electrode system's sites [NCE⁺98]. Therefore, the extended 10-20, 10-10, or 10% electrode system, as the name suggests, places electrodes at every 10%. Previously unlabelled EEG electrodes kept the nomenclature explained above consistent, by using combinations of letters together with numbers [SKB⁺17]. For example, "FT" electrodes are placed between the frontal and temporal rows. The only exception lies on the new coronal row "AF" that is located halfway between frontal (F) and frontopolar (Fp) rows, indicating anterior frontal placement [NCE⁺98, SKB⁺17].

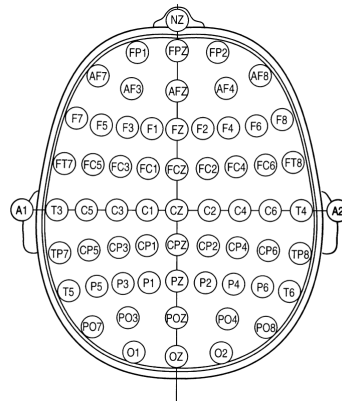


Figure 3.3: Placement of the standard electrodes of the 10-10 system. Source: [NCE⁺98].

Further on, within the scope of source imaging, high-density EEG (HD-EEG) arrays were created. HD-EEG systems use a minimum of 64 electrodes, being it typically 128 or 256 [SKB⁺17, LFP⁺17]. The higher number of electrodes allows for a dense and even sampling of the whole scalp, neck, and cheeks, whose brain activity could not be detected otherwise [SKB⁺17, MML⁺04]. However, HD-EEG is not yet widespread across the scientific community, since the majority of the researchers still make use of systems with 32 or 64 electrodes [LFP⁺17].

3.2.3.3 EEG Functional Connectivity in the Source Space

Electrical source imaging, or source localisation, algorithms have been developed in order to estimate the brain sources that originate certain scalp distributions [SKB⁺17, MML⁺04]. Indeed, signals measured on the scalp do not allow to accurately assess the location of the active brain sources due to the static electromagnetic inverse problem, which states that one given distribution of potentials can be generated by multiple source configurations [MML⁺04]. Solving the so-called inverse problem implies introducing reasonable *a priori* constraints on the generation of EEG signals, being it either functional, anatomical, biophysical or mathematical [MML⁺04]. For instance, integrating EEG with a structural MRI allows for the localisation of EEG sources in anatomically defined head models, which in turn incorporate both the exact positions of the EEG sensors and the properties of head and brain anatomy [MML⁺04, LFP⁺17]. Source estimates allow, therefore, for brain signals to be approximated from both cortical and deeper regions, when compared to scalp recordings. Considering source imaging's purpose, it is understandable that the reliability of the inverse solution is only guaranteed if there is a high spatial sampling density and a large head coverage, which can be achieved by means of HD-EEG [LFP⁺17].

Functional connectivity estimates can be obtained from EEG or MEG too, as stated above in Subsection 3.2.1. When interpreting neuronal interactions from non-invasive recordings such as EEG or MEG, one must take into account the volume conduction problem [BS16]. Volume conduction corresponds to the currents around active neuronal sources, due to electromagnetic field spreading [BS16, MML⁺04]. Thus, due to this phenomenon, a recording channel picks up not only the activity of the underlying neurons, but also of other multiple neuronal sources, which may be reflected in further functional connectivity estimates [BS16]. Consequently, for a realistic interpretation, neuronal interactions must be studied at the source level, and not at the scalp level.

Comparing fMRI with EEG/MEG for functional connectivity estimates, it can be stated that the former has a high spatial resolution but a poor temporal resolution, whilst the opposite characterises the latter. Particularly for network analysis, a higher temporal resolution is crucial in order to accurately assess network dynamics, directionality and time-varying functional organisation [RBL⁺22]. Using EEG/MEG source imaging, by combining *a priori* constraints and assumptions with the time-series data, one may actually achieve a spatial resolution similar to that of standard fMRI [MML⁺04]. Finally, comparing EEG and MEG, given that MEG is an expensive and non-portable technique, EEG stands out for being a cheap and efficient solution [LFP⁺17].

3.2.4 Multimodal Imaging

In order to overcome the disadvantages of each of the described techniques, some researchers implement multimodal imaging approaches [SLM⁺19, SMP⁺20]. For instance, by combining fMRI with EEG, the former's high spatial resolution is combined with the latter's high temporal resolution, allowing for a better comprehension of dynamic functional connectivity.

3.2.5 Neuroimaging Software Tools

Neuroimaging toolboxes play a pivotal role in contemporary neuroscience, enabling researchers to process, interpret, and visualise complex brain data with precision and depth. These packages provide a comprehensive suite of tools and methodologies, comprising either command-line toolboxes in popular programming languages, or standalone graphical user interface software. Below, a selection of prominent neuroimaging toolboxes will be described.

SPM is a widely used and highly respected free and open-source software toolbox in the field of neuroimaging [SPM]. SPM stands for Statistical Parameter Mapping, which in turn involves modelling the data using statistical parameters, conducting hypothesis testing, and creating maps that depict the strength and location of the brain's response to the experimental manipulations. Brain imaging data currently able to be analysed with SPM comprises fMRI, PET, single photon emission CT, EEG and MEG.

Brain Connectivity Toolbox is an open-source MATLAB toolbox for complex-network graph analysis of structural and functional brain connectivity datasets [RS10]. This toolbox includes many recently developed network measures which are not widely available, functions for network manipulation, and datasets for large-scale neuroanatomical networks.

FieldTrip is an open-source MATLAB toolbox for the analysis of EEG, MEG, and other electrophysiological data [OFMS11]. FieldTrip comprises a set of high-level functions with well-defined, sequential, and consistent function calls, but without a Graphical User Interface. Worth mentioning functionalities include data preprocessing, event-related response analysis, spectral analysis, forward and inverse source modelling, connectivity analysis, real-time data processing, and statistical inference.

MNE-Python is an open-source software package for exploring, visualising and analysing neurophysiological data, such as EEG or MEG [GLL⁺13]. MNE-Python provides state-of-the-art algorithms and utilities implemented in Python, in a consistent manner with well-documented interfaces. Being tightly integrated with core Python libraries such as NumPy [Num] or matplotlib [Mat], users can perform high-level neurophysiological data analysis by writing simple Python scripts.

Brainstorm is an open-source, collaborative, and user-friendly software platform designed for the analysis of brain imaging data, driven by an interactive graphical user interface [TBM⁺11]. Brainstorm is primarily designed to process and analyse MEG and EEG data, which, ideally, is further coupled with the anatomy of the subject and the 3D location of the sensors, for cortical source estimation.

Diving into more specific functionalities, **Lead-DBS** is a novel open-source MATLAB toolbox designed for DBS electrode localisation and visualisation [HK15]. Lead-DBS is designed with a user-friendly interface, making it accessible and easy to use for both researchers and clinicians. Indeed, clinical outcomes and adverse effects associated with DBS in epilepsy may depend on the placement of DBS electrode contacts. Thus, post-operative knowledge about the DBS electrode positions and trajectories can assist clinicians in pinpointing optimal stimulation contacts based on

specific anatomical targets, potentially reducing the duration of test stimulation protocols [HK15]. For functional connectivity analysis involving subcortical structures, Lead-DBS can represent a huge asset by providing the exact coordinates of lead electrode contacts.

More toolboxes are available for use in the field of neuroimaging, namely for assessing brain functional connectivity. Each of these holds unique strengths, whether in versatility, specialisation, or widespread adoption. Collectively, these toolboxes empower researchers to delve into the intricacies of brain function.

3.3 Default Mode Network

The resting human brain is functionally organised in large-scale brain networks, called resting-state¹ networks (RSNs) [SMP⁺20, Rai15]. Observing spatially coherent patterns in the brain during resting-state led the scientific community to name these as RSNs, in analogy to brain networks that are modulated during task performance [SMP⁺20, Rai15]. Typically reported RSNs in resting-state neuroimaging studies include, for instance, the default mode, the dorsal and ventral attention, the sensorimotor, the salience, the language, and the visual networks [SMP⁺20, Rai15]. Among these, the DMN is the most prominent RSN, playing a key role on the brain's intrinsic activity in health and disease [Rai15].

3.3.1 Topology and Function

The DMN is characterised by reducing its activity while performing goal-directed tasks, thus being preferentially active during rest [MGS⁺18, Rai15]. This network comprises several core brain regions, in which the posterior cingulate cortex (PCC), medial prefrontal cortex (MPFC), precuneus, and left (lANG) and right angular gyrus (rANG) play a key role [MGS⁺18, SLM⁺19]. Subcortical structures such as thalamic nuclei, cerebellum and hippocampus have also been shown to be connected to the DMN [MGS⁺18, GKO⁺20].

Despite each DMN node may serve distinct functions, the overall network lies on a continuum [DGB11]. Exact functions of the DMN are still a matter of debate, however, data suggests that the DMN instantiates processes supporting emotional processing, self-referential mental activity, and recollection of prior experiences [Rai15]. Furthermore, it makes perfect sense to associate the DMN with spontaneous cognition, namely daydreaming or mind-wandering, this being a common mental state during rest [Rai15].

Spectral and connectional properties of the DMN have been extensively analysed in resting-state neuroimaging studies. DMN's activity is modulated by a specific electrophysiological signature, in which the α and β rhythms play an important role [SLM⁺19]. Furthermore, the frequency-dependent connectivity profile between pairs of DMN nodes show peaks at 9-11 Hz [SLM⁺19]. Depending on the connection, peaks at higher frequencies may be observed as well, thus supporting the existence of sub-networks within the DMN [SLM⁺19]. These findings go according to the

¹An individual is considered to be in resting-state if quietly awake and alert, but not engaging to any specific cognitive task or behaviour [BS09].

principle that higher frequencies support short-range communications in the brain, whilst lower frequencies modulate long-range communications in the brain.

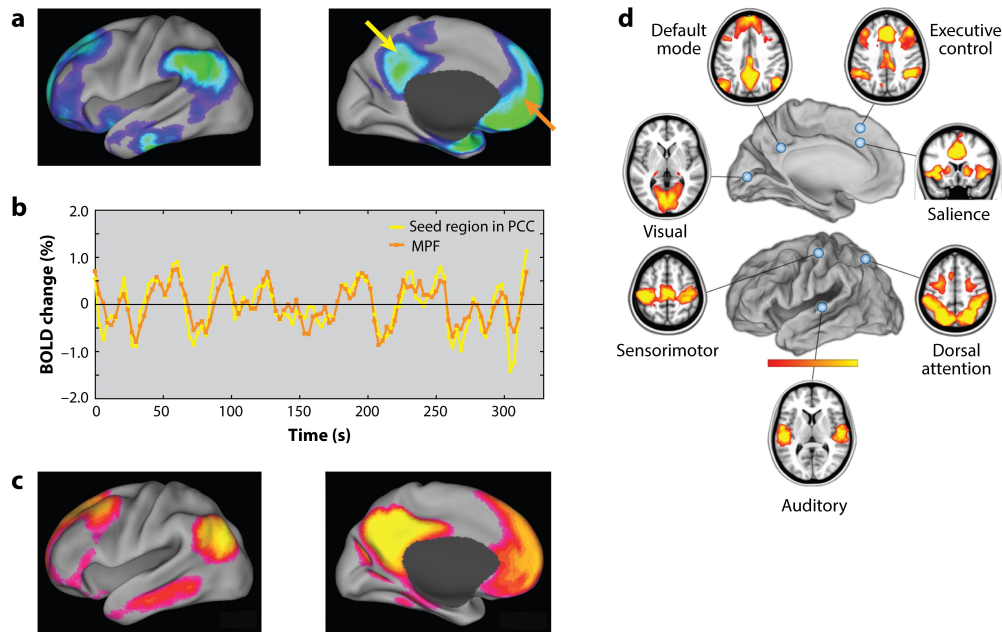


Figure 3.4: Views of the DMN: (a) activity decreases during task performance; (b and c) resting-state functional connectivity; (d) in relation to other RSNs. The yellow and orange arrows in panel a denote the source of the BOLD time-activity curves shown in panel b. Abbreviations: BOLD, blood-oxygen-level-dependent; MPF, medial prefrontal cortex; PCC, precuneus and posterior cingulate cortex. Source: [Rai15].

3.3.2 Alterations to the Default Mode Network in Epilepsy

Brain networks are susceptible to pathology-related structural and functional alterations. In fact, disruption of DMN's activity has been associated with many conditions characterised by cognitive function decline [FZT⁺13]. As it will be further described, this is not an exception for epilepsy.

3.3.2.1 In Ictal Periods

Clinical manifestations of epileptic seizures typically include loss of consciousness, whose degree may vary across patients and across seizure types [DGB11]. Associated to loss of consciousness in patients with different types of seizures (focal, generalised and absence), Danielson et al. [DGB11] observed a decrease in DMN's activity, with strong involvement of the thalamus. These results not only suggest that the DMN plays a central role in seizure activity, but also that focal epilepsies implicate a wider network than previously considered.

3.3.2.2 In Interictal Periods

Given DMN's deactivation at the time of epileptic activity, the hypothesis that DMN regions are altered in interictal periods as well was proposed. Indeed, Fahoum et al. [FZT⁺13], demonstrated, by means of functional MRI (fMRI), that, during interictal discharges² (IED), DMN regions decreased their metabolic demand. Additionally, a relationship between DMN deactivation, decreased higher frequencies (50-150 Hz), and increased lower frequencies (<30 Hz) in the EEG was observed [FZT⁺13]. Ever since, baseline decreased connectivity in the DMN has been a common feature of epilepsy, whose reduction is correlated with seizure frequency [MGS⁺18].

3.3.2.3 In DBS Patients

As previously described in Subsection 2.2.1, the therapeutic effect of DBS is centered on the modulation of epileptogenic networks, with variable clinical efficacy according to the target. Thus, alterations in resting-state functional connectivity are expected to take place in epileptic patients receiving DBS. Within this scope, several recent studies focused on examining resting-state fMRI changes in these patients, namely in those receiving ANT-DBS [VGE⁺22]. In 2018, from electrode volume of tissue activation (VTA) analysis in three ANT-DBS responders, Middlebrooks et al. [MGS⁺18] reported increased functional connectivity in the DMN. Later, using resting-state blood-oxygen-level-dependent (BOLD) fMRI, Middlebrooks et al. [MLO⁺20], in a study involving two patients undergoing ANT-DBS for epilepsy, concluded that active ANT stimulation produced activation in regions including the thalamus, PCC, precuneus, MPFC, rANG, hippocampus, amygdala and striatum. These results suggest that these nodes, belonging to the limbic network and to the DMN, may modulate the effect of seizure control with ANT-DBS. Further on, Sarica et al. [SYL⁺21] confirmed the association of ANT-DBS with the DMN in patients with long-term ANT stimulation.

3.3.2.4 According to the Epilepsy Subtype

DBS therapy is advancing towards being tailored to individual patients, whose differences in functional connectivity may show up as potential biomarkers in patient candidacy, stimulation parameters, or even neuromodulation target selection [VGE⁺22]. Tailoring the treatment to each individual may start by understanding if these correlates remain significant in patients with different epilepsy types and focus.

Concerning focal epilepsies, the idea of establishing a correlation between epileptic foci and resting-state activity comes from older days. Way back in 1995, not only specific patterns in basal activity were found, but also the so-called "scars of focus" in patients that are considered as almost recovered from epilepsy [Cun95]. These scars show that, as seizures are fading, brain electrogenesis reorganises along time, highlighting the importance of studying basal activity in

²Interictal discharges are transient bursts of activity that occur between seizures, resulting in distinct waveform patterns observed in electroencephalographic recordings.

epilepsy. Therefore, a DMN change may be pinpointed in the resting-state EEG activity of focal epilepsy patients.

Among focal epilepsy subtypes, temporal lobe epilepsy (TLE) is the most common, being divided into mesial temporal epilepsy, which involves the medial structures of the temporal lobe, and neocortical TLE [GKO⁺20]. Being the most frequent type of epilepsy, specially mesial temporal epilepsy, it has been extensively analysed. For instance, Liao et al. [LZP⁺10] demonstrated a decreased functional connectivity in DMN areas, in patients with mesial TLE. Moreover, an increase in functional connectivity within the medial temporal lobe, the frontal lobe, and between the parietal and the frontal lobes was observed.

In addition, frontal lobe epilepsy (FLE) represents the second most common type of focal epilepsy syndrome [CQX⁺14]. However, compared to TLE, FLE is generally less studied, which may open room to new studies. Seizures characteristic of FLE patients comprise variable clinical manifestations, from motor symptoms to other abnormalities [CQX⁺14, LXY⁺20]. Regarding network alterations of the DMN in FLE, Cao et al. split the DMN into its anterior and posterior areas, allowing them to observe increased functional connectivity in both areas separately [CQX⁺14]. In FLE patients, this increase in functional connectivity of posterior DMN areas is hypothesised to play a compensatory role as a response to the cognitive impairment led by decreased functional connectivity of overall DMN. Moreover, in Leng et al., which assessed DMN functional connectivity in patients with cingulate gyrus epilepsy, significantly higher functional connectivity was observed in all the EEG frequency spectrum [LXY⁺20].

Regarding generalised epilepsies, idiopathic generalised epilepsy (IGE) is thought to be of genetic origin and accounts for 20 to 30% of the people with epilepsy [PBVD20]. Various studies consistently reported a functional connectivity reduction on DMN regions, being this the most affected network, irrespective of the IGE subtype [PBVD20, GKO⁺20]. Behaviour of the DMN in other types of epilepsies has been analysed as well, although at a much smaller extent [GKO⁺20]. As a side note, curiously, a study in Lennox-Gastaut syndrome by Warren et al. observed abnormally enhanced functional connectivity between the mediodorsal and ventrolateral thalamus, and between default mode and executive-control networks, which goes against the deactivation pattern previously stated [WAJA17].

Therefore, and most importantly, this review allows one to conclude that different types of epilepsy have distinct effects of the DMN. In a general perspective, a lot of studies demonstrate DMN alterations in epilepsy, namely comparing the effect of laterality, prior surgery, disease duration or even hippocampal sclerosis, in these alterations [GKO⁺20]. These parameters were shown to induce alterations in specific nodes of the DMN and at different extents, however, an overall DMN deactivation is denoted across this range of studies [GKO⁺20].

3.3.2.5 According to the EEG Rhythm

Identifying more specific and accurate biomarkers of the DMN in epilepsy for DBS applications may imply understanding if the rhythms modulating the DMN change according to the epilepsy type. For TLE patients, Chiosa et al. [CGC⁺17] found significant temporo-thalamic connectivity

in the theta band, as well as fronto-thalamic connectivity in the alpha band, from which the medial temporal and frontal lobes constitute a part of the DMN. In IGE patients, Qing et al. [QZC⁺21] observed hyperconnectivity patterns in the thalamus-default mode circuit, modulated by an increased alpha power. However, in FLE, the scenario seems to change. Leng et al. [LXY⁺20] assessed functional connectivity changes in the DMN in patients with cingulate gyrus epilepsy, a type of FLE. Functional reorganisation and plasticity was observed in specific nodes of the DMN. Interestingly, gamma band was found to play an important role in the DMN in cingulate gyrus epilepsy, although a higher connectivity in the alpha and beta bands was also observed, when compared to healthy controls.

3.3.2.6 Further Work

This being said, the effect of DBS neither has been compared between distinct epileptic foci, nor analysed across different EEG rhythms yet. Considering that the DMN behaviour changes if the patient is undergoing DBS, that the active DMN nodes may change according to the epilepsy type (without DBS), and that different EEG rhythms modulate the DMN in different conditions, it is legit to suppose that alterations may occur if we put all these parameters into consideration. Doors are open towards a deeper analysis on the impact of the foci and of the frequency bands that modulate DMN's behaviour in epilepsy while receiving DBS.

3.3.3 Subcortical Control of the Default Mode Network

The efficacy of the ANT as a suitable DBS target has already been proven with the SANTE trial [SSG⁺21]. Thalamic involvement in seizure generation and maintenance, particularly of the ANT, has been discussed as well. However, cortical alterations deriving from ANT-DBS remain mostly uncovered [ALD⁺23]. Recent studies trying to unravel this are below described.

In 2022, Vetkas et al. [VGE⁺22] proposed that ANT, CMT and HC, as the most common targets for DBS in epilepsy, would exhibit connectomic overlap, thus explaining their antiseizure effect. Moreover, it was proposed that their corresponding functional networks would overlap with epileptic circuits and with the DMN. Through graph network analysis, results showed that the various DBS targets for epilepsy share a common cortico-subcortical network, which in turn shares hubs with epileptic networks and brain regions involved in seizure propagation. Anterior and posterior cingulate, MPFC, bilateral insulae (cortical), cerebellum and basal ganglia (subcortical) were some of the identified nodes within this network. This demonstrates a partial overlap of the normative network model associated with common DBS targets in epilepsy with the DMN and with the salience network. Interestingly, the ANT was identified as a central hub in the network, which may explain its best clinical outcomes as a DBS target in epilepsy so far.

In a study released this year (2023), Aiello et al. [ALD⁺23] characterised how the ANT interacts with the cortex, attempting to extract neural biomarkers of responsiveness to DBS. Main findings state that ANT-scalp connectivity was highly modulated by θ rhythm, specially between the ANT and ipsilateral centro-frontal regions, which correspond to DMN regions. Moreover,

ANT-DBS responders were characterised by higher θ power both in the EEG and in the ANT. Specifically, patients whose lead contacts were placed in the anterosuperior region of the ANT showed better outcomes. Having this, the region of the ANT with stronger θ oscillations may be the one with a higher probability of successful clinical response. Both the feasibility and the clinical significance of the proposed biomarkers could be denoted through the study, considering that scalp EEG is easily acquired and monitored along time, and that the dynamics between ANT and the cortex could be characterised. However, it is worth noting that the presence of anesthesia during data collection in the Aiello et al. study may introduce limitations and potential biases in the results, especially concerning the observed neural oscillations [ALD⁺23]. Further work suggested by the authors included recruiting patients with follow-ups longer than 6 months, studying a cohort bigger than 15 subjects, and validating these results in awake and sleep states [ALD⁺23]. Additionally, the subjects are only described as DRE patients, without any specification on the epilepsy type, which may open room for new comparisons based on the described analysis.

Chapter 4

Methodology

4.1 Participants

Participants included in this study comprised two patients at the Epilepsy Center of the Ludwig-Maximilians-Universität München (Munich, Germany) receiving ANT-DBS with a Percept™ PC IPG, one with epileptic focus located in the frontal lobe, and the other one with epileptic focus located in the temporal lobe. Given the analysis purpose, these patients were chosen considering they had both scalp and thalamic EEG available. Further, it is worth mentioning that the entire dataset is unique among the scientific community, thus representing a huge asset for brain connectivity studies in ANT-DBS for epilepsy.

Inclusion criteria for a patient to receive ANT-DBS comprised being aged over 18 years old, having epilepsy with focal onset seizures (with or without secondary generalization), and no candidacy, failed, or unwillingness to undergo epilepsy surgery. Conversely, exclusion criteria included having a lesion within the DBS target region, contraindication for surgery, and severe depression or any history of suicidal ideation.

The clinical description of the patients included in this analysis is in Table 4.1, below. Apart from this description, it is noteworthy that all patients received antiseizure medication, although of different compositions and administered in different doses. Thus, one is unaware to what extent this factor may influence brain dynamics. To prevent disclosure of any patient-related personally identifiable information, data was anonymised.

Table 4.1: Clinical description of the patients.

ID	Sex	Age	Disease Onset	Disease Duration	Syndrome	Hemisphere	Follow-up
ANT-18	F	28	8	20	FLE	Bilateral	77 months
ANT-25	F	33	4	29	TLE	Bilateral	37 months

4.2 Data Acquisition

All the data included in this analysis was recorded at the Epilepsy Center, Department of Neurology, Ludwig-Maximilians-Universität München. Furthermore, the recording procedure below described is reported in the literature, in Schreiner et al. [SKN⁺22].

Simultaneous intracranial and scalp EEG signals were collected from patients with depth electrodes bilaterally implanted in the thalamus for ANT-DBS therapy of refractory epilepsy. Although technically and logistically demanding, recording non-invasive and intracranial brain signals simultaneously may provide a more complete perspective to interpret complex clinical questions [MDT⁺22]. Accounting for the study's purpose, subjects were awake and in a resting-state paradigm during data acquisition, considering that the DMN is active in passive rest. Moreover, recording duration was different for each participant, being it equal to 80 minutes for ANT-18, and to 240 minutes for ANT-25.

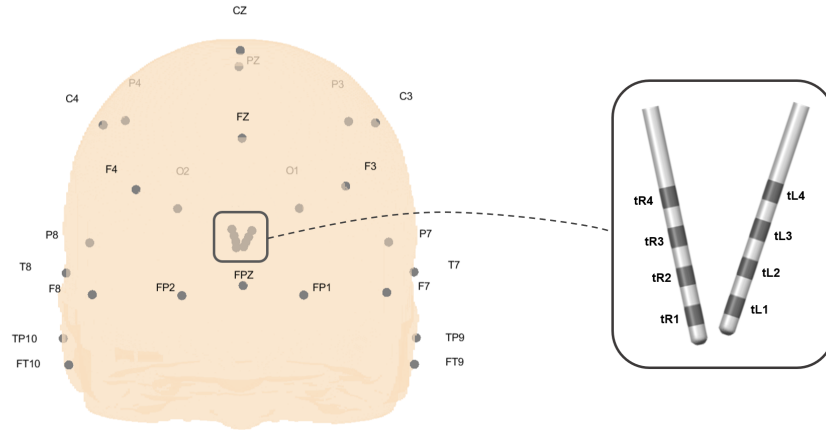
Lead implantation followed the transventricular approach, which consists in two main steps. Firstly, patients were under general anesthesia for the stereotactical implantation of stimulation electrodes. Afterwards, DBS leads were externalised post-surgery, allowing for simultaneous scalp and thalamic EEG recording. In the second place, the extension wire was implanted, tunneled, and connected to the IPG [SKN⁺22].

In the next two paragraphs, the setup of each EEG data type included in the simultaneous acquisition is further described. Intracranial EEG (iEEG) data were recorded with bilateral depth electrodes, containing 4 contacts each, implanted in the thalamus for DBS therapy. Given the clinical relevance of the ANT in DBS for epilepsy, ideally, all the 8 electrode contacts would be located in both hemispheres of the ANT. However, due to the small size and high variability across subjects of this structure, some contacts may end up outside the ANT, but within the thalamus [SKN⁺22]. The XLTEK Neuroworks software (Natus Medical, San Carlos, CA, USA), together with a XLTEK EMU128FS amplifier, were used to acquire recordings, at a sampling frequency of 256 Hz per channel, being the voltages online referenced to electrode CPz.

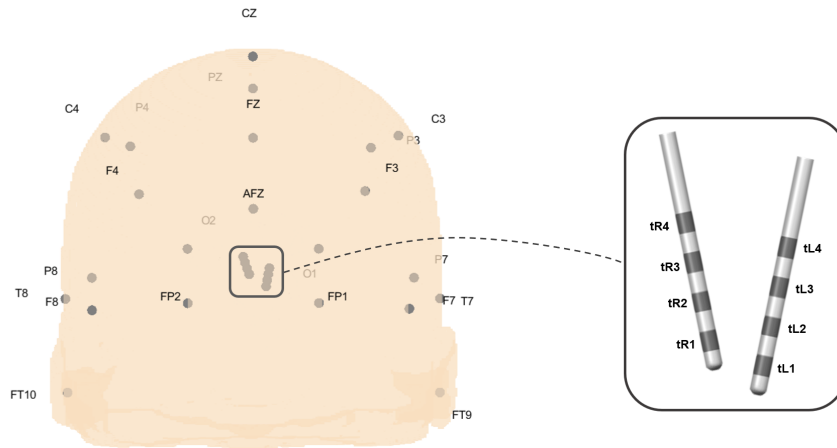
Simultaneously with iEEG, scalp EEG was acquired at a sampling rate of 256 Hz as well, via a common amplifier, and online referenced to the CPz electrode. Being this, synchronisation between both signals is guaranteed. Single gold-plated electrodes were placed on the scalp according to the international 10-20 system. Channels exhibiting significant epileptic activity were discarded. Moreover, some regions in the scalp were wounded, making the access to the scalp difficult. Thus, electrode montages were not exactly identical across patients. Furthermore, additional channels were placed in order to monitor physiological parameters, or even for other experiments. For instance, electrocardiogram (ECG) and electrooculogram (EOG) channels were included in the system, allowing to monitor and then remove these types of non-neural activity from the EEG.

For each subject, the electrode montage of the simultaneous scalp and thalamic EEG acquisition setup is represented in Figure 4.1, below. As abovementioned, although according to the standard 10-20 system, the scalp electrode montages were different between the two subjects. In

addition to the 22 electrodes considered for ANT-25, TP9 and TP10 were also included in ANT-18's montage. Regarding the intracranial electrodes, leads were of Medtronic's model 3387, as represented in Figure 2.7. Electrode contacts were labelled according to the hemisphere, R standing for the right hemisphere and L for the left hemisphere, and to its depth, with 1 corresponding to the deepest contact and 4 to the most superficial one.



(a) ANT-18



(b) ANT-25

Figure 4.1: Simultaneous scalp and thalamic EEG electrode montages.

In addition, a pre-operative T1-weighted MRI and a post-operative CT image were acquired, in order to reconstruct the exact locations of the electrode contacts within the thalamus. The corresponding procedure is described in Subsection 4.3.2. The T1-weighted MRI was used to generate an individual head model as well, in order to reconstruct brain sources from scalp EEG, as explained in Subsection 4.4.3.

4.3 Preprocessing

EEG, like all the other types of electrophysiological recording, may include noise and artefacts mixed within the data, which must be removed for a correct analysis. The preprocessing pipeline was developed under the basis of MNE-Python (Version 1.5.1), a powerful and popular toolbox for this purpose, which offers a rich set of features and a strong community of users and developers. A wide range of functions and tools is provided, covering data import, filtering, artefact removal, re-referencing, epoching, automated rejection of bad epochs, baseline correction, and others. For supporting several standard EEG file formats, for providing efficient data visualization tools, and for allowing extensive customisation, MNE-Python stands out.

In order to avoid inconsistency across the analysis, an issue one must priorly correct is removing data segments in which the subject is asleep. Considering that the DMN is a brain network which is active during passive rest, as abovementioned in Subsection 3.3.1, it only makes sense to perform any related evaluation in awake states. Thus, in Ludwig-Maximilians-Universität München, the EEG signals were visually inspected to differentiate the sleep and the awake segments. In the end, only the awake segments of the signals were kept for further analysis.

4.3.1 Scalp EEG

Below, Figure 4.2 schematically sums up the preprocessing workflow for scalp EEG signals.

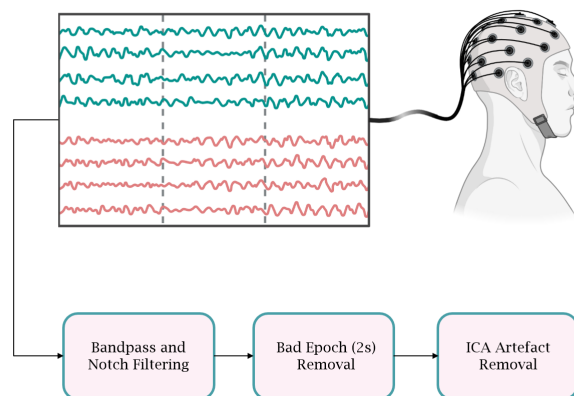


Figure 4.2: Pipeline for scalp EEG preprocessing.

Considering the priorly computed power spectral density (PSD) of the EEG signals, these were band-pass filtered in the frequency range 1-70 Hz, which is typically recommended by epileptologists. Moreover, a notch filter with cutoff frequency equal to 50 Hz was computed, in order to remove powerline interference. Default settings were kept when computing both filters using the `mne.filter.filter_data` function, meaning that these are linear phase FIR with length automatically defined according to the data, using a Hamming window [mne].

Then, for further computations, data was split into 2-second epochs. Typically, the duration of EEG epochs is chosen according to specific events that can be visualised in the signal, such as IEDs

or ictal events. However, since we are working with resting-state data, epoch duration was not chosen based on events. Instead, considering that the next step consists on removing noisy epochs, a smaller duration should be selected, otherwise, quality data could be being removed together with the shorter noisy segment. Criteria for removing bad epochs were automatically set using the *autoreject* Python package, which seamlessly integrates with MNE-Python workflows [JEB⁺17]. In an automated fashion, *autoreject* estimates the optimal peak-to-peak threshold for identifying bad epochs in M/EEG. To tackle this challenge, cross-validation is employed in combination with Bayesian optimisation [JEB⁺17]. Once the threshold is determined, separately for each sensor, it becomes possible to reject noisy epochs from the signal and retain the clean ones.

Besides environmental artefacts, which are expected to be removed through the abovementioned steps, EEG signals may also contain biological artefacts. Biological artefacts are originated from sources in the body, comprising eye movements or blinks, cardiac artefacts, or even muscular activity [MB19]. Indeed, considering that EEG recordings measure electrical activity from the scalp, these are a cumulative sum of neural and non-neural (i.e. artefactual) sources [DNL⁺16]. A commonly used technique for the removal of such artefacts is independent component analysis (ICA). ICA is a statistical method that separates a complex signal into mathematically independent components (ICs) [DNL⁺16]. To compute ICA, the FastICA algorithm [Uni13], embedded in MNE-Python, was chosen, given its good performance and fast execution [DNL⁺16]. Furthermore, an explained variance of 99% was selected, meaning that components explaining 99% of the total variance were kept. It is worth noting that since large amplitudes mean higher variance, the bad epoch removal step is crucial for a good ICA fitting to the data. Having fitted ICA to data, one must inspect the obtained ICs, in order to manually classify them as artefactual or not. ICs can be visualised either as time-series data or as scalp topography maps, which show how the potential is spatially distributed along the head, averaged over time. Ocular, cardiac, and muscular ICs present characteristic patterns that can be easily identified. For instance, ICs corresponding to blink artefacts present scalp topographies most heavily weighted at right and left anterior scalp locations, whilst for muscle artefacts the IC scalp topography is characterised by a strong peripheral focus. Analysing the corresponding time-series data is also important, since electrophysiological signals have specific waveforms that can aid in identifying artefactual components, such as the QRS peaks in cardiac signals. Automatic methods to detect biological artefacts are implemented within MNE-Python, being, for *find_bads_eog* and *find_bads_ecg* functions, based on the correlation between each IC and channels that the user has designated as EOG or ECG channels, respectively, according to the type of artefact one seeks to find [mneb]. For example, to detect ocular artefacts, if no EOG channels are included in the system, it makes sense to select Fp1 and F8 as EOG channels, in order to detect both vertical and horizontal eye movements, respectively. In the case of muscular artefacts, using *find_bads_muscle* function, their detection is not based on the correlation of the IC with other channels, but instead based on predefined spectrally-related criteria [mneb]. However, since automated algorithms are not always perfect, a subjective judgement call by the user must be made as well. Thus, after validating the automated selection of the artefactual ICs with visual inspection, these were removed from the signal.

4.3.2 Intracranial EEG

A similar procedure to the one applied to the scalp EEG signals was applied to the iEEG signals. Indeed, many aspects of iEEG signal processing do not differ much from non-invasive recordings, depending on the research question. The corresponding workflow is illustrated in Figure 4.3.

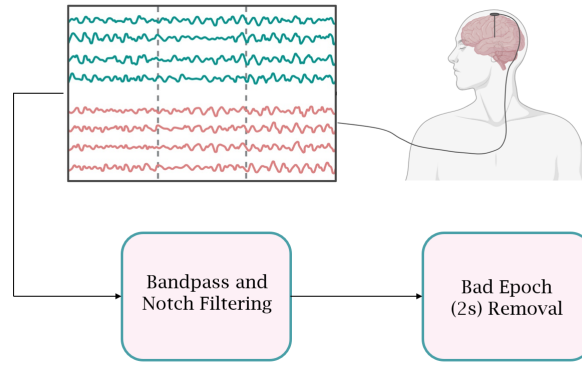


Figure 4.3: Pipeline for iEEG preprocessing.

Therefore, iEEG signals were firstly bandpass filtered within the frequency range 1-70 Hz and notch filtered at 50 Hz. Then, for consistency purposes, the epochs classified as noisy in the scalp recordings were removed from the iEEG as well, thus allowing for the same data segments in time to be analysed. By directly recording activity from populations of neurons in the vicinity of the electrode, iEEG has a high signal-to-noise ratio (SNR) and a high spatial specificity, in contrary to scalp EEG. Thus, the presence of biological artefacts is less evident, opposing to non-invasive recordings, in which these are a major source of contamination [MDT⁺22]. Considering this, and after inspecting the obtained signals, ICA was not computed in iEEG recordings.

In addition, the thalamic electrodes' positions are necessary for further steps. DBS electrode contacts coordinates can be obtained in a semi-automated fashion using Lead-DBS. By co-registering the post-operative CT scan to the pre-operative T1-weighted MRI, and then by normalising the scans to the Montreal Neurological Institute (MNI) space (based on the MRI), the trajectories of the electrodes and the coordinates of the contacts (based on the CT) can be reconstructed [SKN⁺22, HK15]. This particular processing step was performed in Ludwig-Maximilians Universität München, and not by the author.

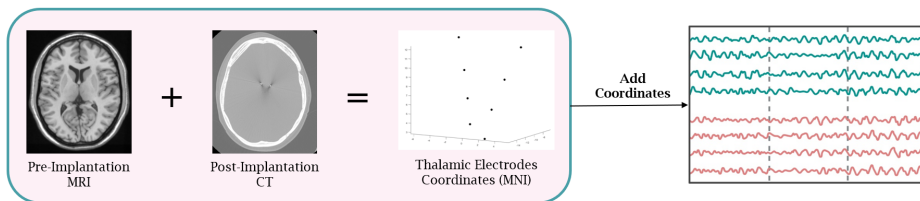


Figure 4.4: Pipeline for obtaining the locations of the thalamic electrode contacts.

4.4 Functional Connectivity Analysis

Being the signals pre-processed, one is able to go forward in the procedure. Prior to roughly explaining the methodology itself, a theoretical background on the employed functional connectivity metrics, common among the neuroscience community, is provided in Section 4.4.1. Considering the diverse aims of this work, three main parts can be distinguished from the whole functional connectivity analysis:

1. **Thalamocortical Connectivity**, in Section 4.4.2, attempts to unravel the cortical alterations deriving from ANT-DBS. This is performed by evaluating functional connectivity between pairs composed by a scalp electrode and a thalamic one, across the whole typical EEG band. It is noteworthy that the electrodes closer to DMN regions will receive special attention.
2. **DMN Connectivity**, in Section 4.4.3, whose goal is to evaluate connectivity between pairs of regions of interest (ROIs) within the DMN. These ROIs are obtained based on a parcellation of reconstructed source activities, which in turn are estimated by putting EEG data and a realistic head model together.
3. **Thalamic Connectivity**, in Section 4.4.4, in which functional connectivity is computed between pairs of thalamic electrode contacts, considering both hemispheres, directly from the iEEG signal. This step will allow one to observe if connectivity patterns vary within the thalamus, with a special focus on the ANT.

All the pipeline below described was based on FieldTrip¹ (v.22/05/2023), considering the research purpose and the type of data to be analysed. As a matter of fact, FieldTrip supports various types of neuroimaging data (including EEG and iEEG) and offers a wide array of capabilities, including preprocessing, source localisation, time-frequency analysis, and connectivity analysis, being particularly strong in the latter. Besides, while being powerful and versatile, this toolbox is designed with an intuitive workflow structure comprising typical function calls, consistent integration of a configuration structure, and well-defined data structures. FieldTrip is widely used and cited in the neuroscience community, indicating its credibility and reliability for conducting rigorous research.

MNE-Python and FieldTrip share a lot of functionalities towards analysing electrophysiological data, being easily integrated. After the preprocessing step conducted in MNE-Python, the final output is an *Epochs* object, which corresponds to multiple epochs of data (in our case, EEG). In FieldTrip, *Epochs* objects are interpreted as *ft_datatype_raw* structures containing multiple epochs. Importing *Epochs* objects into FieldTrip is thus straightforward, done by saving it as a *.fif* file, and then reading this file in MATLAB using *ft_preprocessing*.

¹ All the functions are publicly available in <https://github.com/fieldtrip/fieldtrip/tree/master>

4.4.1 Background on Commonly Used Metrics

Complementary to what is described in Section 3.2.1, taxonomy of functional connectivity metrics typically includes various types of subdivisions. Similar to graphs, functional connectivity metrics may quantify or not the direction of the neural interaction. Likewise, **non-directed** metrics capture statistical dependence between two signals, without any reference to the direction of influence. In practice, non-directed functional connectivity metrics apply if there is a consistent time lag and a predominantly unidirectional interaction, denigrating most of the real-life cases. Conversely, **directed** metrics, based on the principle that causes precede effects, statistically quantify bidirectional interactions, providing two estimates of connectivity for a given signal pair [BS16].

One other distinction is to define whether the metric is **model-based** or **data-driven**. Like the names suggest, for the former, a certain *a priori* generative model for connectivity is selected and validated according to evidence within the data, while for the latter a black-box algorithm with an embedded functional connectivity metric is applied and adapted to the data [BS16].

Another obvious division is whether the functional connectivity metric is defined in the **time** or in the **frequency domain** representation of the signals. For time domain metrics, computation is direct, whilst for frequency domain metrics, one must transform the signal from the time to the frequency domain prior to computing the functional connectivity metric. However, studying typical neuronal oscillations implies representing the signals in the frequency domain [BS16].

Pearson correlation, ρ , represents the simplest measure for non-directed data-driven interactions, estimating the statistical relationship between two random variables [BS16]. Although computed in the time domain, ρ ignores the temporal structure in the data, by treating the time series as random variables [BS16]. The Pearson correlation coefficient is given by Equation 4.1, in which X_k and X_l represent two time series, N is the length of the time series, μ_{X_k} is the mean value of the time series X_k , and σ_{X_k} is its standard deviation [OHKD19]. It is bounded between -1 and 1, in which 1 indicates a perfect positive linear relationship, -1 a perfect negative linear relationship, and 0 no linear relationship between the time series.

$$\rho(X_k, X_l) = \frac{1}{N-1} \frac{\sum_{i=1}^N (X_{k,i} - \mu_{X_k})(X_{l,i} - \mu_{X_l})}{\sigma_{X_k} \sigma_{X_l}} \quad (4.1)$$

Nevertheless, given the aim of assessing the neural oscillations that modulate epilepsy's brain networks, it is convenient to represent the signals in the frequency domain. Applying, for instance, Fourier decomposition, the transformation to the frequency domain can be achieved, allowing one to further compute frequency-domain functional connectivity metrics. Although each of these measures has its own advantages and disadvantages, many of them end up looking at the phase synchrony between the oscillatory components in the signals. Therefore, if the two signals, standing for brain regions, are tuned at the same frequency with a specific phase relationship, this means that information is efficiently transferred across these brain regions.

Oscillations per se can be defined using three main parameters: the period (which translates to a frequency), the amplitude, and the phase. For convenience, these parameters are often mathematically represented as complex-valued numbers, $Ae^{i\varphi}$, or, equivalently, $x + yi$. Within connec-

tivity's scope, the goal is to compare a pair of brain oscillations, being this often performed by taking the phase difference between the two signals. Accordingly, the departure point of most of the frequency-domain measures computing synchrony is to combine the Fourier estimates of the two signals into a single number, called the cross-spectral density. This combination, given by $x_1 x_2^* = A_1 A_2 e^{i(\phi_1 - \phi_2)}$, is performed by multiplying the first signal, x_1 , with the conjugate of the second one, x_2 , whose imaginary part ends up estimating the phase difference [BS16].

Coherence is a widely used functional connectivity measure quantifying phase synchrony between a pair of signals, accounting for signal amplitude as well. In simpler terms, coherence is actually equivalent to the frequency domain representation of the Pearson correlation coefficient, being it computed from the cross-spectral density. Equation 4.2 represents the coherence coefficient between signal x and y at frequency ω , across n epochs, in which A_x and A_y stand for the amplitude of signal x and y , while ϕ_x and ϕ_y correspond to the phase of signal x and y , respectively. The coherence coefficient is a normalised quantity bounded between 0 and 1, in which 0 means no synchrony at all and 1 means perfect synchrony [BS16].

$$coh_{xy}(\omega) = \frac{\left| \frac{1}{n} \sum_{k=1}^n A_x(\omega, k) A_y(\omega, k) e^{i(\phi_x(\omega, k) - \phi_y(\omega, k))} \right|}{\sqrt{\left(\frac{1}{n} \sum_{k=1}^n A_x^2(\omega, k) \right) \left(\frac{1}{n} \sum_{k=1}^n A_y^2(\omega, k) \right)}} \quad (4.2)$$

Debiased Weighted Phase Lag Index (dwPLI) was proposed as an improvement to the phase lag index (PLI), in order to increase its robustness. In turn, the PLI is an index that evaluates, for a particular frequency, the asymmetry in the distribution of phase differences between two signals across epochs, regardless of their amplitude [SND07, VOv⁺11]. PLI values range from 0 to 1 ($0 \leq \text{PLI} \leq 1$), from which a PLI of 0 indicates either no coupling or coupling with a phase difference around 0 mod π . Conversely, a PLI equal to 1 indicates perfect phase coupling and, thus, synchronisation between the two brain regions. This goes according to Equation 4.3, describing how to obtain the PLI from a time series of phase differences, $\Delta\phi(t_k), k = 1 \dots N$ [SND07].

$$PLI = |\langle \text{sign}(\Delta\phi(t_k)) \rangle| \quad (4.3)$$

However, the PLI is highly sensitive to noise and volume conduction, as small perturbations may turn phase lags into leads and vice-versa. Facing this, the weighted PLI, a related index, was introduced as a novel measure of phase synchronisation. Then, as an attempt to diminish the sample-size bias, Vinck et al. defined a debiased estimator of the weighted PLI, simply called debiased weighted PLI [VOv⁺11]. Below, Equation 4.4 describes the dwPLI, where $\Im\{X\}$ is the imaginary component of the cross-spectral density, and $E\{\cdot\}$ is the expected value operator.

$$dwPLI = \frac{|E\{\Im\{X\}\}|}{E\{|\Im\{X\}|\}} \quad (4.4)$$

So far, the described connectivity metrics inferred directionality, at best, based on the sign of the phase difference between two signals, which is quite limiting in terms of interpretation and applicability. Conversely, **Granger Causality**, as a directed connectivity metric, determines the direction of information flow [BS16, ALD⁺23]. By quantifying bidirectional interactions,

two estimates of directed connectivity for a given signal pair (e.g., X and Y) are provided, thus separately assessing the directed influence of X on Y , and of Y on X [BS16].

In the first place, the concept of Granger causality was formulated in the time domain by Granger in 1969 [Gra69]. Further on, extensions of this metric to the frequency domain were proposed, being these particularly relevant for neuroscience applications. Taking a step back into the time domain, signals can be described based on autoregressive models as a weighted sum of past values of X at time t , with τ referring to the time lag, considering some noise η too, $X(t) = \sum \beta_\tau X(t - \tau) + \eta$. There is no connectivity with only one signal, therefore, bivariate autoregressive models are employed as $X(t) = \sum \beta_{\tau 11} X(t - \tau) + \sum \beta_{\tau 21} Y(t - \tau) + \varepsilon_1$, in which the values of time series X are predicted based on past values of both X and Y , plus residuals given by ε_1 . Then, Granger causality is defined in Equation 4.5 as being the natural logarithm of a ratio of residual variances.

$$F_{Y \rightarrow X} = \ln \left(\frac{\text{var}(\eta)}{\text{var}(\varepsilon_1)} \right) \quad (4.5)$$

Based on Equation 4.5, one can extract the meaning of the Granger causality value [Gra69]. Comparing the univariate with the bivariate model predictions of signal X , if ε_1 is lower than η , it means that including information about the past of signal Y substantially improves the prediction of X [BS16]. In these cases, the variance ratio is higher than 1, and, therefore, the natural logarithm of this ratio be higher than 0, which allows one to state that signal Y Granger-causes signal X . The same logic is inversely applied to estimate Granger causality from signal X to Y [Gra69, BS16].

Computing Granger causality in the frequency domain priorly requires estimating two quantities: the spectral transfer matrix, and the covariance of the autoregressive model's residuals. Applying the Fourier transform to the bivariate autoregressive model equation, one is able to obtain $\begin{bmatrix} E_X(\omega) \\ E_Y(\omega) \end{bmatrix} = A(\omega) \begin{bmatrix} X(\omega) \\ Y(\omega) \end{bmatrix}$, with $A(\omega)$ being the coefficient matrix at frequency ω . In turn, the latter expression can be manipulated by multiplying each side of the equation by the inverse of $A(\omega)$, in order to obtain Equation 4.6, where $H(\omega)$ (defined as $A^{-1}(\omega)$) denotes the spectral transfer matrix [BS16].

$$H(\omega) \begin{bmatrix} E_X(\omega) \\ E_Y(\omega) \end{bmatrix} = \begin{bmatrix} X(\omega) \\ Y(\omega) \end{bmatrix} \quad (4.6)$$

Then, multiplying each side of Equation 4.6 with its conjugate transpose, the following fundamental identity holds $H(\omega)\Sigma H(\omega)^* = S(\omega)$, with $S(\omega)$ being the cross-spectral density matrix for a given signal pair (X, Y) at frequency ω , and Σ being the covariance matrix of the residuals of the autoregressive model. Having this, the frequency-dependent Granger causality can be computed as follows in Equation 4.7, below.

$$\text{GC}_{x \rightarrow y}(\omega) = \ln \left(\frac{S_{yy}(\omega)}{S_{yy}(\omega) - \left(\Sigma_{xx} - \frac{\Sigma_{yx}^2}{\Sigma_{yy}} \right) |H_{yx}(\omega)|^2} \right) \quad (4.7)$$

4.4.2 Thalamocortical Connectivity

Functional interactions between the cerebral cortex and the thalamus, including the ANT, were characterised by means of functional connectivity analysis. Intracranial signals, being measured directly from brain sources, are not as impacted by volume conduction as signals measured in the scalp. Nevertheless, sources located at distances further from the electrode's vicinity can still affect recordings through volume conduction [HSH18]. Some previous studies have applied source imaging to iEEG recordings, although this possibility is not yet fully exploited [HSH18]. For this purpose, functional connectivity between scalp and thalamic electrodes was computed at the channel level. Functional connectivity metrics that are less or more sensitive to volume conduction will further be taken into account when evaluating the reliability of the results.

Firstly, scalp and intracranial EEG data pre-processed in MNE-Python were similarly loaded to FieldTrip using *ft_preprocessing* function. Then, for further analysis, these data were appended into the same structure using *ft_appenddata* function. Now, functional connectivity can be directly computed from the EEG data, between the scalp and thalamic electrodes. For this analysis, all the metrics above described in Section 4.4.1: Pearson correlation, coherence, dwPLI, and Granger causality, were employed. In FieldTrip, this calculation is straightforward, by simply calling the function *ft_connectivityanalysis* with the option *cfg.method* set for the desired metric, being all these four metrics already embedded within the toolbox.

For connectivity metrics operating in the frequency domain, the input data structure must firstly be converted to the frequency domain through the function *ft_freqanalysis*. Configurations for the frequency analysis were set based on Xie et al. and on the input requirements of the connectivity metrics [XTN22]. Thus, a frequency range of interest from 1 to 70 Hz (*cfg.foi = 1:70*), a Hanning taper (*cfg.taper = 'hanning'*), method set to analyse the entire spectrum for the entire data length (*cfg.method = 'mtmfft'*), and output parameter set for both power and cross-spectra (*cfg.output = 'powandcsd'*), were selected. For an easier visualisation and interpretation, next, the functional connectivity values were averaged across each EEG typical frequency band: δ , from 1 to 4 Hz, θ , from 4 to 8 Hz, α , from 8 to 13 Hz, β , from 13 to 30 Hz, and γ , from 30 to 70 Hz. This step is performed directly through the FieldTrip function *ft_selectdata*, with *cfg.frequency* equal to a 2-element array containing the limits for the desired frequency range, and *cfg.avgoverfreq = 'yes'* set.

Finally, depending on the EEG scalp montage, 30×30 or 32×32 connectivity matrices were obtained. From these, only the values standing for interactions between the scalp and the thalamus, discarding the repeated values resultant of the connectivity metric being non-directed (for coherence and dwPLI), were plotted, resulting in matrices of size 20×8 or 22×8 . Regarding Pearson correlation and Granger causality, given the different nature of these metrics (the former is in the time-domain, while the latter is a directed metric), all the electrodes were considered for plotting.

So far, the described workflow defined functional connectivity metrics for pairwise interactions. However, understanding brain dynamics at a bigger scale may imply evaluating the pattern of multiple of these interactions. For this, graph theoretical approaches can be employed,

in order to quantify network topology. In graph theory, a network is defined as a set of nodes linked to each other by edges [BS09]. Based on the delivered insights, a wide range of graph measures is available to quantify, for instance, the importance of a node or edge to a network, how densely connected a node is to its neighbours, or even the ability of a network as a whole to be interconnected [BS09, Spo13]. The simplest, but correlated with other more complex, graph theory measure is the **node degree**, which corresponds to the number of edges attached to a given node [BS09]. In FieldTrip, node degree can be easily computed by means of the *ft_networkanalysis* function. Considering a connectivity matrix, in which each element corresponds to the functional connectivity value between a pair of regions, this function will apply a threshold to each of these values. This will generate a binary matrix, in which, for a given node, a value of 1 indicates that the connectivity value is higher than the predefined threshold, whilst 0 stands for a connectivity value lower than the threshold. Finally, counting the number of values equal to 1 for each region, the node degree value is obtained. Configurations set according to the desired requirements comprise *cfg.method = 'degrees'*, and *cfg.threshold* equal to the threshold considered to generate the binary adjacency matrix. The threshold was set to 0.1 when computing functional connectivity, except for Pearson correlation and for coherence, which was set to 0.3, since the obtained values are generally higher than with the other implemented metrics.

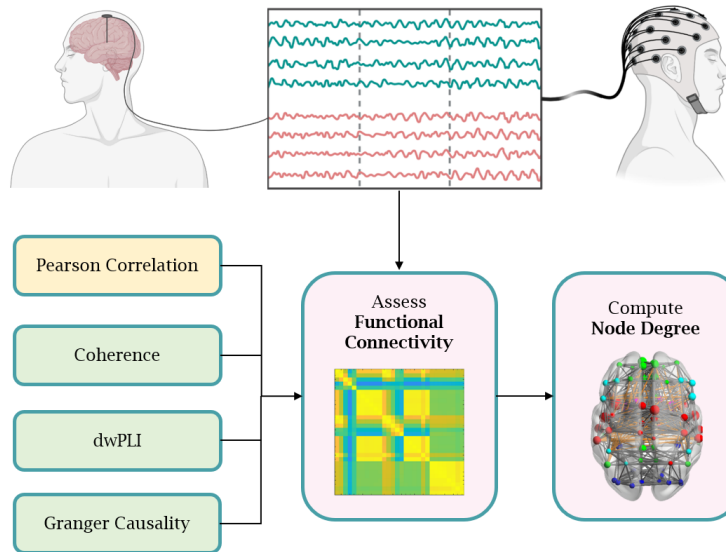


Figure 4.5: Pipeline to assess functional connectivity between the ANT and the cortex. Yellow boxes contain time-domain metrics, whilst green boxes contain frequency domain metrics.

4.4.3 DMN Connectivity

As introduced in Subsection 3.2.3.3, functional connectivity from EEG is typically computed in the source space, in order to reduce the effects of volume conduction at the scalp level. The electrical source imaging step is, therefore, critical to guarantee that the content on the data is actually translating brain activity, allowing for a correct interpretation of the results. Then, reconstructed

source activity is parcellated into brain ROIs, for further network estimation. Finally, connectivity can be computed and evaluated between each pair of ROIs.

4.4.3.1 Forward Solution

Prior to determining the inverse solution, one must firstly solve the forward problem. Based on the reciprocity principle, the Equation 4.8 expresses the forward solution, which aims to determine the potential at the scalp electrodes generated by a known source in the brain [LFP⁺17]. Thus, the scalp electric potentials, $\Phi \in \Re^{N_E \times 1}$ [V], are obtained by multiplying the leadfield matrix, $L \in \Re^{N_E \times (3N_V)}$ [V/(A·m)], with the current density at the source, $J \in \Re^{3N_V \times 1}$ [A·m], considering N_E the number of electrodes, and N_V the number of dipolar sources in the gray matter (i.e. voxels) [SY23].

$$\Phi = L \cdot J \quad (4.8)$$

Conversely, the inverse solution, as the name suggests, determines the intracranial sources that generate a given potential on the scalp [MML⁺04, MB19]. Solving the equation and, thus, the inverse problem, implies obtaining a leadfield matrix. The leadfield matrix determines how the electric activity at a given scalp electrode is related to the activity of different sources in the brain [MB19]. This relationship and, therefore, the values of the matrix, depend on the electromagnetic (permeability and conductivity) and geometrical (head shape) properties of the individual head model [MML⁺04].

A realistic head model is built from an individual MRI and from the exact positions of the scalp electrodes. Considering that, from the source to the scalp, currents are attenuated by different tissues, specially by the skull, each with different electromagnetic properties, one must consider these. Moreover, human heads are not spherical, thus, the distance from the scalp to the center of the head is variable across individuals. Therefore, it makes sense to introduce the exact electrode positions into the head model. Then, the head model's properties are mathematically incorporated in the leadfield matrix, allowing one to reconstruct the brain sources [MML⁺04, MB19].

Accurately building a realistic head model is crucial for a correct EEG source analysis. Stepping into FieldTrip, the steps involved in this task were based on Vorwerk et al. [VOP⁺18]. Firstly, the software reads the MRI image using *ft_read_mri*, creating an anatomical data structure. In order to build the individual headmodel, to facilitate further calculations, the next step must be the normalisation of the MRI to the MNI space. To do so, *ft_volumenormalise* was called, which registers the input MRI to a template MRI embedded in the toolbox, which in turn is already in the MNI space. Then, to ensure that the image structure is aligned into the cartesian axis and that all the voxels have the same size, one must call the *ft_volumereslice* function, in this case, according to 1 mm of resolution. Next, since a realistic headmodel requires the definition of multiple tissue classes of the head, each characterised by the different electromagnetic properties, the MRI image must be priorly segmented. Using *ft_volumesegment*, probabilistic tissue maps of each of 5 tissue classes (gray matter, white matter, cerebrospinal fluid, skull, and scalp) were created. In these

probabilistic maps, if a certain voxel did not belong to the corresponding tissue, the value of that voxel in the map would be 0; otherwise, the voxel would have a value between 0 and 1. Based on this segmentation, a hexahedral mesh is directly generated through *ft_prepare_mesh*. To avoid staircase effects, mesh nodes at tissue boundaries were shifted 0.3 mm, thus allowing to obtain a more smooth representation of the boundaries [VOP⁺18].

Following the mesh generation, one is able to compute the finite element method (FEM) to solve the forward problem. Despite having a higher computational load, boundary element method (BEM) and FEM are the most popular techniques for realistic head modelling, being superior to spherical head models [MML⁺04, MB19]. Furthermore, compared to BEM, FEM allows to model more complex geometries, taking anisotropies and skull-breaches into account, with only weak influence on the computational load [MML⁺04, LFP⁺17, VOP⁺18]. Specifically, the SimBio software was used for FEM, being it already integrated in FieldTrip [Gue22]. Having this, adding the conductivity values of the 5 brain tissues, *ft_prepare_headmodel* is able to compute the associated stiffness matrix. The conductivity value associated with each tissue class was defined based on McCann et al., being equal to 0.47 S/m for the gray matter, 0.22 S/m for the white matter, 1.71 S/m for the cerebrospinal fluid, 0.02 S/m for the skull, and 0.41 S/m for the scalp [MPB19].

Then, to consider the geometric properties within the head volume conductor, the exact electrode positions must be considered. However, in our case, since we were not able to obtain the individual electrodes' positions, a template 10-20 electrode montage file available on FieldTrip (*standard_1020.elc*) was considered for all the subjects. These electrode positions are represented in the MNI coordinate system, thus being in the same space as the individual MRI. Nevertheless, to guarantee that the electrodes are correctly aligned with the surface of the head, through *ft_electroderealign*, the positions of the electrodes were co-registered to the head contour, by projecting it to the nearest point on the head surface mesh. Being the electrodes positions available to introduce into the pipeline, together with the stiffness matrix and the mesh geometry, *ft_prepare_vol_sens* computes the transfer matrix. The transfer matrix is obtained from the scalar product of the electric field that results at a dipole location with the dipole moment [HVG⁺07]. Thus, further calculations are instead performed for each electrode position, rather than for each dipole position. Next, a 3D grid of voxels containing the positions where the brain sources will be defined, i.e. the solution space, was computed using *ft_prepare_sourcemodel*, considering a resolution of 6 mm. Finally, putting together the co-registered electrode positions, the source model, and the head model, the leadfield matrix is able to be computed, using *ft_prepare_leadfield*. As above described, the leadfield matrix mathematically defines the individual geometric and electromagnetic properties [MML⁺04].

4.4.3.2 Inverse Solution

In these conditions, one is able to reconstruct brain source activity. To this end, the exact low-resolution electromagnetic tomography (eLORETA) was used [PMLK⁺11]. eLORETA came up as an attempt to improve the mislocalisation of deep sources, outperforming other weighted linear solutions for brain source localisation. Under ideal (no-noise) conditions, the particular weights

used in eLORETA allow the corresponding solution to yield zero localisation error when tested with point sources anywhere in the brain. Thus, eLORETA estimates the matrix of source activity in the brain J according to the Equation 4.9, below, where $\alpha \geq 0$ is the Tikhonov regularisation parameter, $W \in \mathbb{R}^{N_V \times N_V}$ is a symmetric positive definite weight matrix, and $H \in \mathbb{R}^{N_E \times N_E}$ is a matrix that depends on the EEG reference. The superscript "+" denotes the Moore-Penrose pseudoinverse [PMLK⁺11].

$$J = W^{-1} L^T (LW^{-1} L^T + \alpha H)^+ \Phi \quad (4.9)$$

In FieldTrip, by means of the *ft_sourceanalysis* function, the inverse solution can be calculated, using the eLORETA method. Firstly, since the regularisation parameter α is based on the noise covariance matrix, *ft_timelockanalysis* outputs it together with the timelocked EEG data, keeping the information of the EEG epochs. Then, the timelock structure (containing the functional data and the covariance matrix), the forward solution (output of *ft_prepare_leadfield*), and the head model (output of *ft_prepare_headmodel*) must be provided as inputs to *ft_sourceanalysis*. One first run of this function is computed in order to priorly output eLORETA's spatial filter. Then, a rerun is performed accounting for the corresponding filter, to further obtain the source estimation. Due to computational issues, coupled to recordings with durations of hours, EEG epochs were averaged prior to performing source analysis.

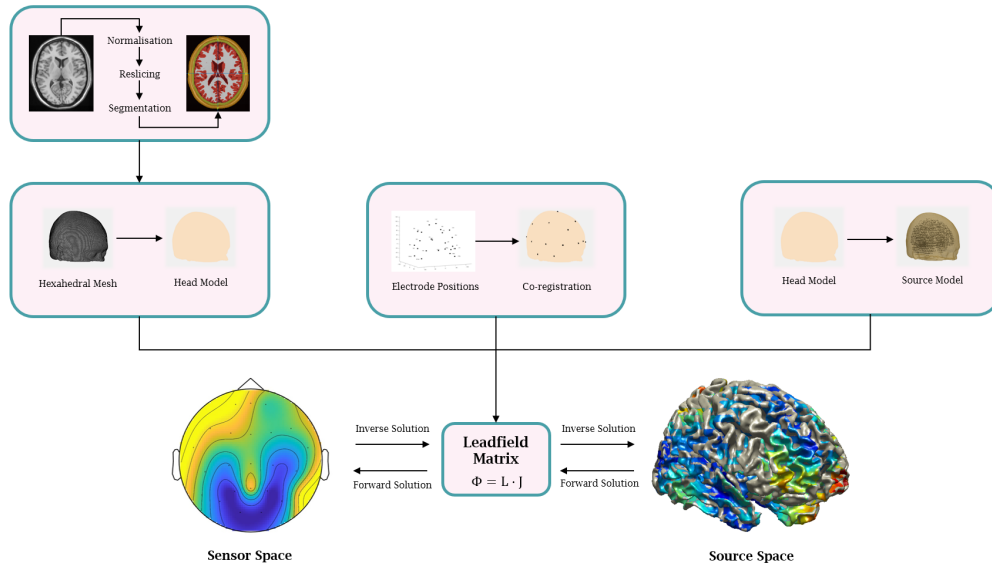


Figure 4.6: Pipeline to reconstruct brain sources from EEG.

Time-series at the voxel level are 3-dimensional, standing for the dipole moments in x , y and z directions. To make further calculations easier, *ft_sourcedescriptives* with *cfg.projectmom = 'yes'* projects the dipole orientation of each voxel along the first axis of principal component analysis (PCA), thus, into the direction that explains most of the source variance.

Finally, in order to visualise the source reconstruction results, *ft_sourceplot* was computed in three different manners: on a template brain surface embedded in FieldTrip, on 2D slices and on three orthogonal slices of the individual T1-weighted MRI (after interpolating source activity into the MRI space, using *ft_sourceinterpolate*). Although the *'mom'* field contains the actual time courses of the dipole moment at the source level, for convenience, the *'pow'* field of the structure is selected instead as the functional data parameter to plot. Being a scalar per dipole position (voxel), it reflects the source variance over a time window of interest.

4.4.3.3 Source Parcellation into Regions of Interest

From source imaging, neuronal activity can be estimated over time in specific ROIs within the brain. ROIs are defined based on a cortical parcellation, which in turn may be based on an atlas or designed by the researchers for a specific study [vMHFV19]. In this work, the ROIs were defined based on the Automated Anatomical Labelling (AAL) atlas, included with FieldTrip. The AAL atlas consists of an anatomical labeling of activations detected with PET or fMRI studies, based on the high-resolution single-subject T1-weighted MRI provided by the MNI [TMLP⁺02]. Excluding the cerebellum, the AAL atlas partitions the cerebral cortex into 90 distinct regions.

In FieldTrip, when reading the AAL atlas using *ft_read_atlas*, the brain is defined as a 3D matrix of size $91 \times 109 \times 91$, segmented into 116 distinct regions (including the cerebellum). On the other hand, the source space is defined as a 3D matrix of size $24 \times 30 \times 24$, given the chosen resolution of 6 mm when preparing the source model, which is not consistent with the atlas. Therefore, one must interpolate AAL's tissue parcellation into the source space dimensions, which is feasible given that both volumes are in the MNI space. This step is performed by the function *ft_sourceinterpolate*, using the nearest neighbour interpolation method (*cfg.method = 'nearest'*). The obtained volume is a 3D matrix equal in size to the source space ($24 \times 30 \times 24$), anatomically labelled with the AAL atlas' 116 classes of tissues.

Then, considering that the goal is to estimate source activity in specific ROIs, the source reconstruction parameters must be combined over the parcels of the AAL atlas. To do so, the source values were averaged along the voxels belonging to each ROI, using *ft_sourceparcellate*. Thus, the output is a channel-based representation of the source reconstruction parameters per ROI, meaning that each ROI is interpreted by the software as if it were an EEG channel.

Finally, aiming to estimate functional connectivity in the DMN, the corresponding regions were selected from the 90 (excluding the cerebellum) available in the AAL atlas, being these the *Frontal Superior Medial R*, *Frontal Superior Medial L*, *Cingulum Anterior R*, *Cingulum Anterior L*, *Cingulum Posterior R*, *Cingulum Posterior L*, *Angular R*, *Angular L*, *Precuneus R*, and *Precuneus L*, in which *R* and *L* respectively stand for right and left hemisphere [OHKD19]. From the obtained parcellation, these 10 ROIs were selected for further connectivity analysis. Besides, to evaluate how the DMN may be highlighted among other brain regions, functional connectivity between the 90 AAL ROIs was also computed. Below, Figure 4.7 (a) represents the whole brain parcellation according to the AAL atlas' regions in the predefined source space, whilst Figure 4.7 (b) only shows the corresponding DMN regions.

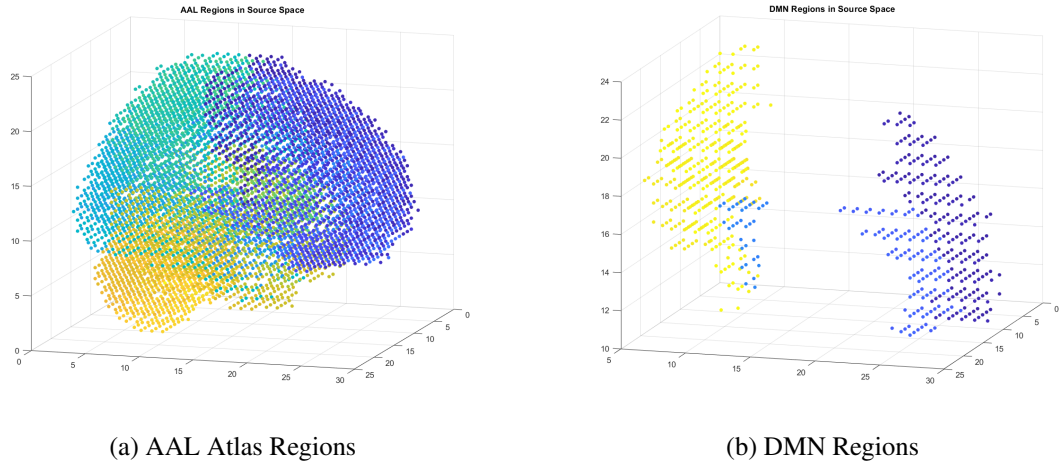


Figure 4.7: Plot of brain parcellation points in the source space dimensions.

4.4.3.4 Connectivity Computation

Having obtained the parcellation of reconstructed source activities, functional connectivity can be calculated between pairs of ROIs, either belonging to the DMN or not (resulting connectivity matrices are sized 10×10 or 90×90 , respectively). Given the nature of the four above described connectivity metrics, considering that one ended up obtaining a single trial of source data, it makes no sense to compute metrics estimating synchrony, such as coherence or dwPLI, since these operate across epochs. Neither does it make sense to compute Granger causality, since without past trial values, there is no autoregressive model, and thus no valid result. Therefore, only the Pearson correlation was computed between the estimated activity at each brain ROI.

Finally, in order to understand DMN's dynamics at a bigger scale, a graph theoretical approach was employed. Similarly to what is described in Section 4.4.2, node degree was separately estimated across both the 10 DMN ROIs and all the 90 brain ROIs of the AAL atlas. In FieldTrip, the `ft_networkanalysis` function was called with `cfg.method = 'degrees'` and `cfg.threshold = 0.3` parameters set.

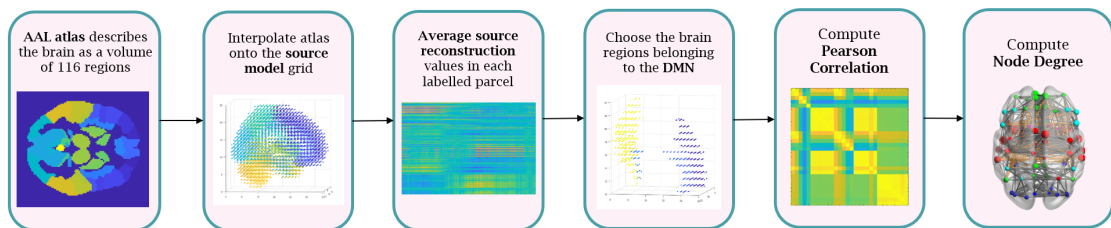


Figure 4.8: Pipeline to assess functional connectivity within the DMN, from brain sources.

4.4.4 Thalamic Connectivity

Having obtained the electrode contacts coordinates using Lead-DBS, one can understand which of these are located in the ANT. To do so, a visual inspection was performed based on the DBS Intrinsic Template AtLAS (DISTAL) atlas. DISTAL is a 3D atlas of subcortical brain structures of reference in neuroscience and neurology [EPL⁺18]. The DISTAL atlas is preinstalled in Lead-DBS, thus, this was the software chosen for an easier visualisation. Firstly, the electrode contact coordinates, the pre-operative T1-w MRI, and the post-operative CT were provided to the Lead-DBS software. Then, considering that the Region 28 in DISTAL, corresponding to the *nucleus anterior principalis* according to the Hassler/Schaltenbrand-Wahren nomenclature, covers most areas of the ANT, it was selected for plotting [GKK⁺21].

Knowing which contacts of the DBS electrodes are within the ANT and which are not, one is able to analyse at which extent connectional properties vary according to the location in the thalamus. Similarly to what is above described, frequency-dependent functional connectivity is computed between pairs of thalamic electrodes, for both the right and left hemispheres. Considering that iEEG signals are directly recorded from the brain sources, thus not being highly impacted by volume conduction, connectivity was computed at the channel level [HSH18]. In order to understand connectomic patterns within the thalamus, with special focus for the ANT, *ft_connectivityanalysis* was computed in FieldTrip. All the metrics described in Section 4.4.1 were employed: Pearson correlation, coherence, dwPLI, and Granger causality. For metrics operating in the frequency domain, *ft_freqanalysis* was applied to the iEEG data prior to computing functional connectivity, considering the same parameters as in Section 4.4.2. Equally, results were visualised by averaging the connectivity values across the EEG rhythms: δ , θ , α , β , and γ . Regarding graph theory measures, these were not evaluated in this case, considering that the thalamus, although connected within itself, does not constitute a whole brain network.

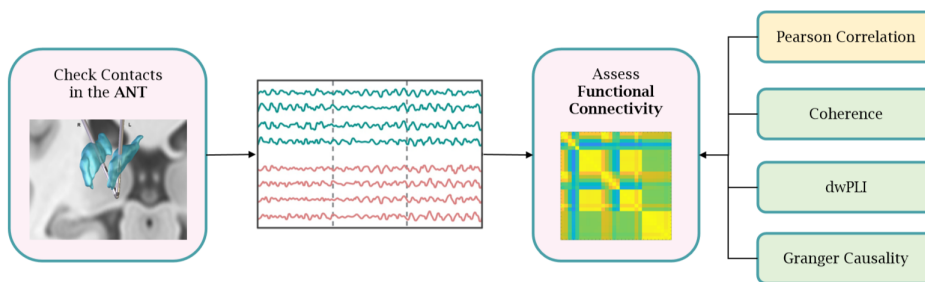


Figure 4.9: Pipeline to assess functional connectivity within the thalamus. Yellow boxes contain time-domain metrics, whilst green boxes contain frequency domain metrics.

Chapter 5

Results and Discussion

This chapter describes the obtained results for each phase of this work, together with a discussion of these. Accordingly, sections are organised in a similar manner to the one presented in Chapter 4, thus splitting the connectivity analysis into three main parts.

For a convenient visualisation of the connectivity matrices, these are displayed as images with scaled colours, from 0 to the maximum connectivity value per subject and per metric. Finally, given that only two subjects were analysed, it makes no sense to perform a statistical analysis.

5.1 Thalamocortical Connectivity

5.1.1 Results

5.1.1.1 Pearson Correlation

Functional connectivity results obtained with Pearson correlation were plotted across all the 30 (or 32) channels under analysis. Below, Figure 5.1 shows the corresponding connectivity matrices. At first sight, clear differences can be observed between Figure 5.1 (a) and (b), reminiscing that the former stands for a FLE subject, and the latter for a TLE one.

For **ANT-18** patient, considering the scalp electrodes, higher correlation coefficient values are observed among some physically close electrodes, namely between FT9 and TP9, Fz and Cz with Fpz and Pz, or even within F7, T7, and P7. Regarding thalamo-cortical functional connectivity patterns, higher values can be denoted for the F4, FPz, Pz, Fz and Cz scalp electrodes, being these slightly higher for the left thalamic electrode (tL1, tL2, tL3, and tL4).

For **ANT-25** patient, three clusters of a high correlation coefficient close to 1 (discarding the cluster composed by the thalamic electrodes) stand out from the rest of the matrix. Being comprised by F3, C3, P3, FT9, Fz, and Cz on the left hemisphere, and by F4, C4, P4, FT10, AFz, and Pz on the right hemisphere, these clusters are located mostly on the upper frontal and central regions of the brain. Regarding interactions between the thalamus and the cortex, stronger values are achieved in the Fp1, Fp2, F7, F8, and AFz scalp electrodes, which cover most of the frontal

lobe. Across the thalamus, values are similar except for the tR3 electrode, in which the correlation coefficient is generally lower.

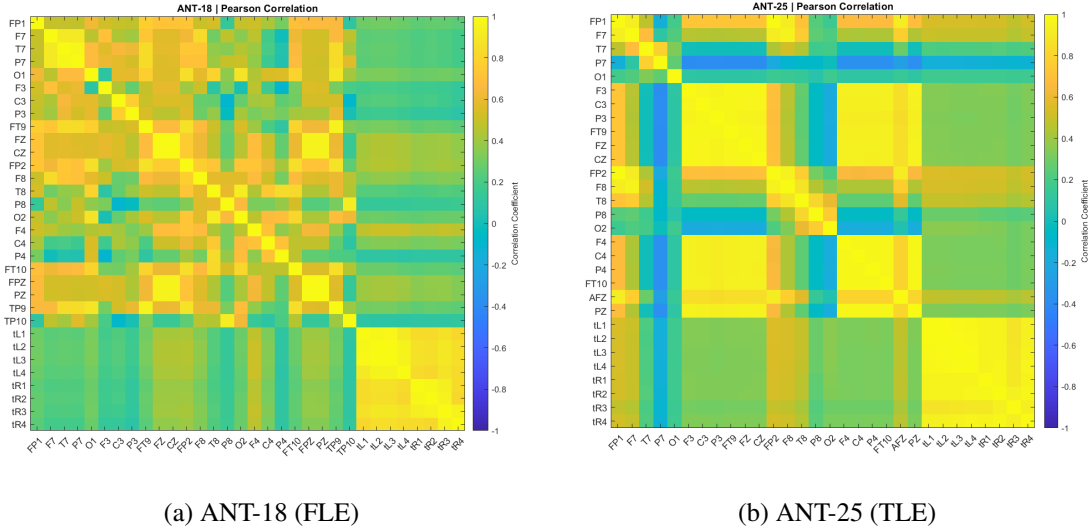


Figure 5.1: Thalamocortical functional connectivity matrices obtained with Pearson correlation.

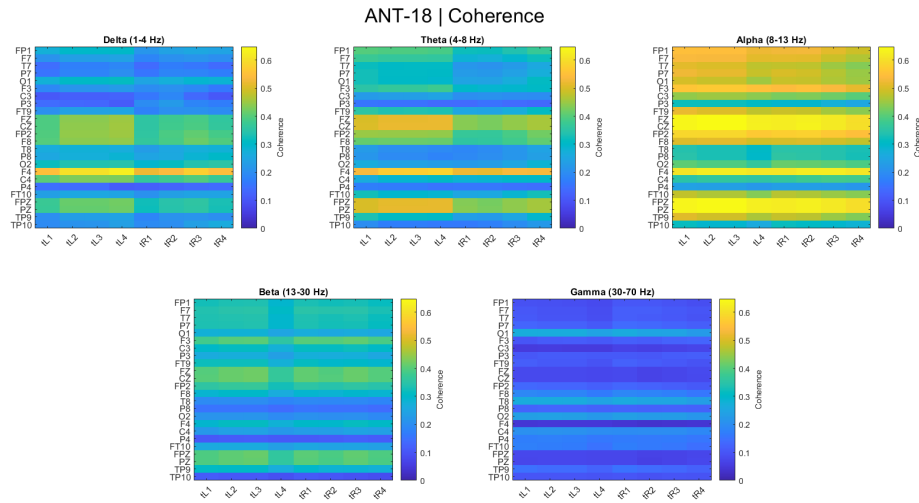
For the **node degree** analysis, the highest values obtained were equal to 31 in Fp2 and F4 (right frontal electrodes), for ANT-18, and to 28 in F8 (right frontotemporal electrode), for ANT-25. On the other hand, the lowest values were equal to 12 in P4 and TP10, for ANT-18, and to 2 in P7 and in O1, for ANT-25.

5.1.1.2 Coherence

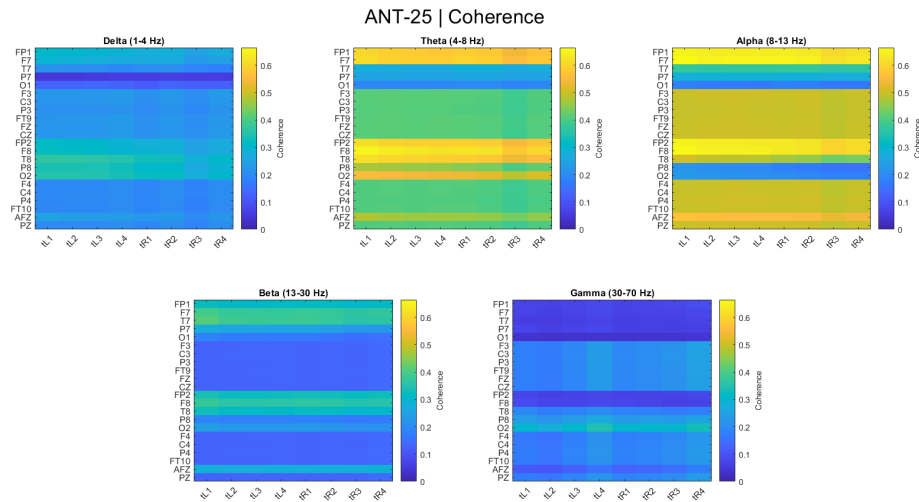
Regarding the results obtained with coherence, in Figure 5.2, being this a functional connectivity metric computed in the frequency domain, for a more consistent interpretation and visualisation, values were averaged per EEG rhythm, δ : 1-4 Hz, θ : 4-8 Hz, α : 8-13 Hz, β : 13-30 Hz, and γ : 30-70 Hz. Furthermore, only the interactions of interest were plotted, considering that coherence is undirected, and that the main focus is assessing thalamocortical interactions.

For **ANT-18**, the FLE patient, coherence values are generally higher in the alpha band, particularly for the Fz, Cz, FPz, and Pz electrodes, being these located in the midline. Interestingly, these same electrodes also show high values in the theta band. When compared to the other scalp electrodes, F4 (right frontal electrode) shows too high coherence values for interactions with all the thalamic electrodes, especially in the delta and theta bands, which allows one to pose the hypothesis of being in the presence of an outlier. Moreover, when analysing the coherence values across thalamic electrodes, stronger values are clear for the left hemisphere, in particular tL4, especially in lower bands such as delta and theta. Concerning higher frequency bands (beta and gamma), although some activity in the frontotemporal region appears to be modulated by beta, coherence values are relatively low to be relevant for further analysis.

For **ANT-25**, the TLE patient, the frequency bands strongly modulating brain activity can be identified at a glance: theta and alpha. Curiously, clusters of similar functional connectivity values among pairs of scalp electrodes in opposite hemispheres (F3/C3/P3/FT9/Fz/Cz and F4/C4/P4/FT10/Pz) are obtained, from which some are physically close, showing consistency along a given brain region. For theta, Fp1, F7, Fp2, F8, and T8 show higher coherence values. Similarly, for alpha, higher connectivity is denoted in Fp1, F7, Fp2, and F8. Across the thalamic electrodes, coherence values are approximately equal, although slightly lower for tR3.



(a) ANT-18 (FLE)



(b) ANT-25 (TLE)

Figure 5.2: Thalamocortical functional connectivity matrices obtained with coherence.

Regarding the **node degree** analysis, values were obtained per electrode and per frequency value, thus resulting in a matrix sized 32×70 , for ANT-18 (FLE), or 30×70 , for ANT-25 (TLE).

For convenience and consistency, values for each node were averaged per EEG rhythm, however, only the maximum and minimum node degree values will be analysed in this section. These are represented in Table 5.1, together with the node (i.e. electrode) in which this value occurs.

Table 5.1: Maximum and minimum node degree values obtained with coherence.

(a) ANT-18 (FLE)

EEG Rhythm	Maximum		Minimum	
	Electrode(s)	Value	Electrode(s)	Value
δ	Fp2/F4	28.8	P4	9.5
θ	F8	29.5	P4	10.8
α	F8/FT10/O1	30.8	P4	13.4
β	Fp2	25.2	TP10	7.7
γ	Fp2	17.8	P4	4.6

(b) ANT-25 (TLE)

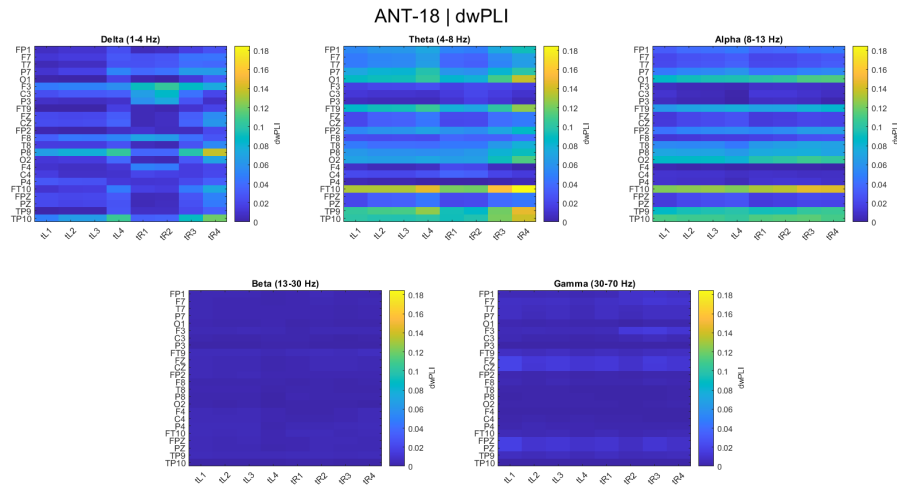
EEG Rhythm	Maximum		Minimum	
	Electrode(s)	Value	Electrode(s)	Value
δ	F8	21.0	O1	1.5
θ	Fp2	27.0	O1	2.0
α	F8	26.0	O1	2.0
β	Fp2	22.3	O1	2.1
γ	O2	17.5	O1	1.5

5.1.1.3 Debiased Weighted Phase Lag Index

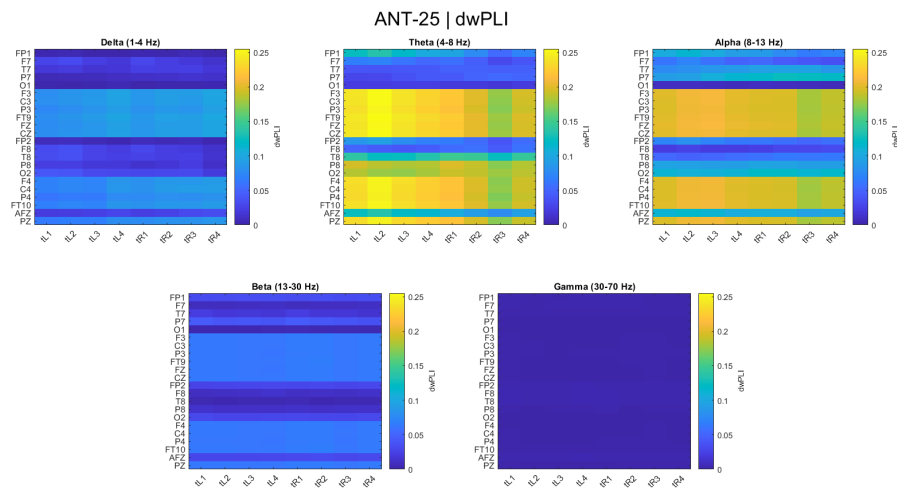
Concerning dwPLI results, in Figure 5.3, these are presented in a manner similar to coherence, given the nature of both metrics. In general, functional connectivity is dominantly modulated by theta and alpha frequency bands, whose dominance is stronger in ANT-25 (TLE), given the higher dwPLI values when compared to ANT-18 (FLE).

For **ANT-18**, the FLE patient, functional connectivity results are quite different to the ones obtained with coherence. Nevertheless, theta and alpha remain the bands that strongly modulate functional connectivity, with the addition of delta in some specific electrodes. Indeed, in delta, variable patterns across the thalamic electrodes can be observed, with higher values occurring both in the right and left hemisphere, depending on the scalp electrode. Regardless of the thalamic electrode, higher dwPLI values are obtained in P8, TP10, and F3 scalp electrodes. For theta, the highest dwPLI values are observed in the O1, FT9, FT10, TP9, and TP10 scalp electrodes. For all these cases, when comparing the connectivity values along the thalamus, higher values can be consistently denoted for the tL4, tR3, and tR4. In alpha, higher dwPLI is observed in O1, FT10, TP9, and TP10, with approximate values along all the thalamic electrodes. In addition, F4 shows lower dwPLI values for all the frequency bands, when compared to the other scalp electrodes, which reinforces the idea that it may be an outlier, as it was hypothesised with coherence.

For **ANT-25**, the TLE patient, dwPLI values are overall higher than the ones obtained with ANT-18. Regarding the rhythms modulating connectivity, theta and alpha stand out. Particularly for theta, dwPLI values are slightly higher compared to alpha. Furthermore, similar clusters of scalp electrodes are noticeable in dwPLI as observed in coherence, for both theta and alpha, being these composed by F3/C3/P3/FT9/Fz/Cz and F4/C4/P4/FT10/Pz. Concerning the distribution of these values across the thalamus in both theta and alpha, the maximum is seen in tL2 and the minimum in tR3. Interestingly, values tend to be higher in the left hemisphere compared to the right hemisphere, irrespective of the scalp electrode. Besides, some interactions may also be modulated by delta and beta, being relatively higher in the abovementioned scalp electrode clusters.



(a) ANT-18 (FLE)



(b) ANT-25 (TLE)

Figure 5.3: Thalamocortical functional connectivity matrices obtained with dwPLI.

Concerning **node degree** analysis, similarly to what was done with coherence, maximum and minimum values per frequency band are represented in Table 5.2, below.

Table 5.2: Maximum and minimum node degree values obtained with dwPLI.

(a) ANT-18 (FLE)

EEG Rhythm	Maximum		Minimum	
	Electrode(s)	Value	Electrode(s)	Value
δ	TP10	7.5	Fpz/Pz	0.0
θ	tR4/tL4	8.8	C3/P3/C4	0.0
α	O1	3.8	F3/C3/P3/P4	0.0
β	tR1	0.3	All the scalp electrodes	0.0
γ	Pz	0.8	F7/T7/P7/P3/F8/T8/P8/O2/F4/P4/FT10/TP9/TP10	0.0

(b) ANT-25 (TLE)

EEG Rhythm	Maximum		Minimum	
	Electrode(s)	Value	Electrode(s)	Value
δ	tR3	8.3	All the scalp electrodes	0.0
θ	tR1/tR2/tR4//tL4	17.0	Fp1	0.0
α	tL4	15.0	Fp1/O1/P8/O2	0.0
β	tL4	2.6	Fp1/O1/T8/P8	0.0
γ	F4/C4/P4/FT10/Pz	0.5	Remaining electrodes	0

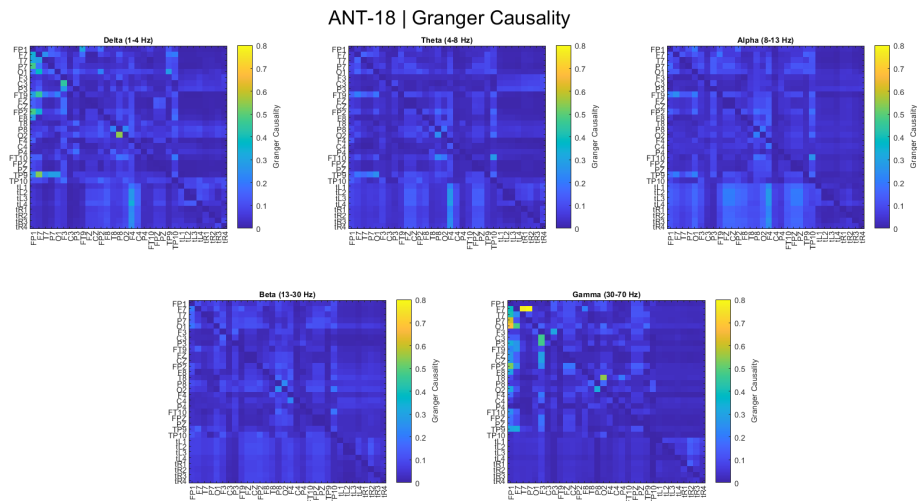
5.1.1.4 Granger Causality

For Granger causality results, in Figure 5.4, all the electrodes were selected for plotting, in order to infer directionality of information transfer. For interpretation, the vertical axis represents where the information comes from, while the horizontal axis stands for where the information goes to.

For **ANT-18**, the FLE patient, starting with thalamocortical functional connectivity, it appears to be strongly modulated by delta, theta and alpha. In beta and gamma, Granger causality values are too low to be relevant for the analysis, especially in gamma. Looking at the connectivity matrices, from delta to alpha, one can observe that interactions from the thalamus to the cortex become stronger, when compared to the opposite direction. In delta, Granger causality values from the thalamic to the scalp electrodes and from the scalp to the thalamic electrodes are similar, with the exception of the F4 scalp electrode, which was already proposed above as being an outlier. On the other hand, in alpha, clear differences are observed below and above the identity line of the matrix, given that interactions from the thalamic to the scalp electrodes appear to be way stronger than in the opposite direction. Furthermore, both in theta and in alpha, the scalp electrodes corresponding to the cortex regions that are shown to receive more information from the thalamus are Fz, Cz,

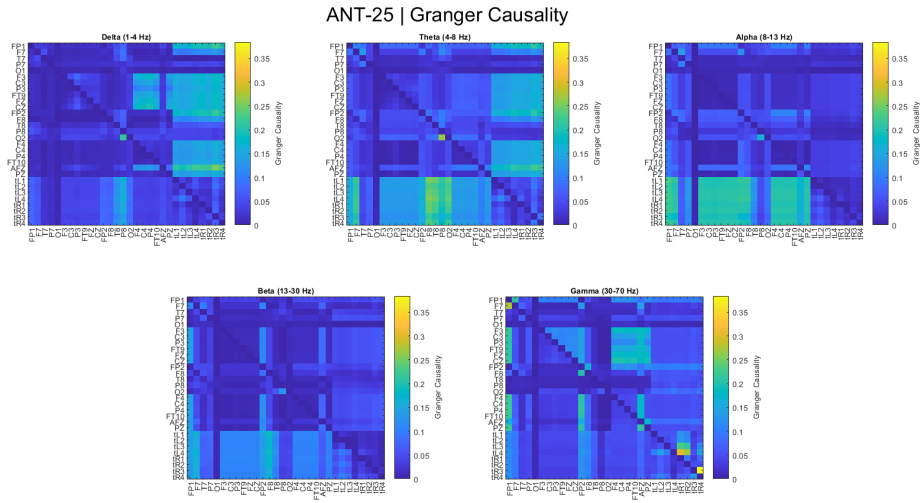
Fp2, F8, Fpz, Pz, and F4. Regarding the thalamic electrodes, for the left hemisphere, tL2, tL3, and tL4 are observed to establish ascendingly stronger interactions. For the right hemisphere, tR3 has stronger Granger causality values, although these are smaller than in the left hemisphere. Within the scalp electrodes, there is a consistent pattern across delta, theta and gamma noteworthy. Looking closer, from FT9 and from TP9, a "line" of stronger interactions is observed, which means that information may flow from these two electrodes to Fp1, F7, T7, P7, and O1, which are physically close. Single values of high Granger causality observed across all the bands are not relevant for the whole analysis and may represent outliers.

For **ANT-25**, the TLE patient, interestingly, for thalamo-cortical interactions, from delta to alpha, a transition of the direction of information flow can be observed. On one hand, in delta, Granger causality values are overall higher for interactions taking place from scalp to thalamic electrodes. In theta, values are similar for both directions, although slightly higher from the thalamus to the cortex when considering the F8, T8, F7, and O2 electrodes. Conversely, it is clear that interactions flowing from the thalamus to the cortex are strongly modulated by alpha, whilst this does not occur for the opposite direction. In delta, regarding the scalp electrodes presenting higher Granger causality values when information flows from the cortex to the thalamus, these comprise Fp1, F7, F3, C3, P3, FT9, Fz, Cz, Fp2, F8, F4, C4, P4, FT10, and Pz, covering most of the cortical surface. In alpha, higher Granger causality values are observed from the thalamus to these same electrodes. For beta and gamma, Granger causality values standing for thalamo-cortical interactions are overall lower when compared to the other frequency bands. Irrespective of the rhythm and the scalp electrode, values are approximately consistent across thalamic electrodes, except for tR3, which presents slightly higher Granger causality. Concerning interactions among scalp electrodes, high values of Granger causality are observed from F3/C3/P3/FT9/Fz/Cz to F4/C4/P4/FT10/Pz, forming a cluster on the matrix in the delta and gamma bands.



(a) ANT-18 (FLE)

Figure 5.4: Thalamocortical functional connectivity matrices obtained with Granger causality.



(b) ANT-25 (TLE)

Figure 5.4: Thalamocortical functional connectivity matrices obtained with Granger causality (Continued).

Regarding **node degree** analysis, results are represented in a similar manner to what was above performed, in Table 5.3.

Table 5.3: Maximum and minimum node degree values obtained with Granger causality.

(a) ANT-18 (FLE)

EEG Rhythm	Maximum		Minimum	
	Electrode(s)	Value	Electrode(s)	Value
δ	O2	18.8	C3	3.5
θ	F4	16.3	P4	0.5
α	O1	23.0	C3	0.8
β	O1	16.6	C3	1.3
γ	Fp1	19.2	tL4	1.1

(b) ANT-25 (TLE)

EEG Rhythm	Maximum		Minimum	
	Electrode(s)	Value	Electrode(s)	Value
δ	tR3	21.0	P7/O1	0.0
θ	tR3	31.8	O1	0.0
α	tR3	19.2	O1	0.0
β	Fp1	13.7	O1	0.0
γ	Fp1	22.3	O1/P8	0.0

5.1.2 Discussion

Along this discussion, regardless of the functional connectivity metric, both the connectivity matrices and the corresponding node degree will be analysed. On one hand, local connectivity patterns can be inspected with the matrices. Complementary, node degree will allow one to understand how these regions interact within a brain network. Further, these results are compared with the current associated literature and reasons for potential spurious estimates are put into perspective.

5.1.2.1 Limitations and Potential Pitfalls of the Employed Metrics

Assessing EEG-based functional connectivity is a valuable endeavour in the field of neuroscience, offering insights into the dynamic interactions between distinct regions of the human brain. However, this is not an easy nor straightforward task. When facing functional connectivity results, one must be able to understand if the estimates reflect a realistic effect with regard to neuronal interactions. Spurious connectivity estimates may lie on noisy EEG signals, or even when interpreting the obtained connectivity patterns [BS16]. Accordingly, a certain functional connectivity metric may be more or less sensitive to common practical issues.

For instance, the volume conduction, or field spread, problem is one of the greatest issues when quantifying neuronal interactions, especially when the estimates are based on non-invasive recordings. One can easily realise that, despite being commonly employed, Pearson correlation, by directly measuring the linear relationship between two signals (which in turn contain noise), can provide spurious estimates. Furthermore, since volume conduction spuriously inflates phase synchronisation estimates, which are directly quantified by coherence, alternatives to this metric were proposed afterwards. The debiased weighted PLI was introduced as a measure of phase synchronisation which, besides being insensitive to volume conduction, also reduces the influence of common noise sources [VOv⁺11, BS16]. Field spread also affects directed functional connectivity estimates, such as Granger causality [ALD⁺23]. Another issue commonly associated with Granger causality is the problem of a different SNR across channels, which may lead one to misinterpret the directionality of interactions [BS16]. No data nor metric is perfect, thus, false positives estimates can still be obtained, meaning that unexistent neuronal interactions may end up being quantified. Results will be consciously interpreted, taking putative issues into account.

5.1.2.2 Cortical Regions Influenced by the Thalamus

As mentioned in Subsection 3.3.2.3, ANT-DBS has already been shown to be associated with increased functional connectivity and activity in DMN regions. Therefore, the obtained functional connectivity patterns will be explored according to this association. When considering EEG electrode positions as seeds, one must consider that the activity of multiple networks may coexist in a single seed. However, within a standard 10-20 EEG montage, Fp1, Fp2, Fpz, F3, F4, F7, Fz, T3, T4, P3, P4 were shown to highly correlate with the DMN [RAM⁺18]. Therefore, higher functional connectivity values are expected to be found between these seeds and the thalamic electrodes. For

both subjects, the obtained results were largely diverse across the four connectivity metrics under analysis. Nevertheless, given the distinct nature of these metrics and associated pitfalls, this was already expected to occur.

In order to correlate a certain electrode to the underlying brain region, we recommend the readers to accompany the analysis of this subsection with Figure 4.1, thus allowing for an easier interpretation of the results. Starting with **ANT-18**, the FLE patient, results partially correspond to the literature. As a matter of fact, node degree maximum values were obtained for Fp2, F4, F8, FT10, TP10. As a reference, considering that the network under analysis contains 32 nodes (i.e. electrodes), this means that the maximum value possible for the node degree would be equal to 31. Although F8, FT10, and TP10 were not found as highly correlated with the DMN by Rojas et al., these are positioned above frontotemporal regions, thus being of interest to this analysis as well [RAM⁺18]. In addition, unexpected nodes such as O1 and O2 were observed to present higher node degree values. Given that the corresponding values were obtained with coherence and Granger causality, highly susceptible to noise, one can propose that, considering that both occipital electrodes are closely located to target regions of the DMN, this activity was wrongly picked up. However, in Aiello et al., both these electrodes revealed strong connectivity patterns to the ANT, which may indicate either the influence of noise or that other networks apart from the DMN communicate with the ANT [ALD⁺23]. Interestingly, by means of dwPLI, node degree values were higher in the theta band for the tR4 and tL4 thalamic electrodes. In turn, these are located in the ANT (see Figure 5.11), which may indicate the key role of the ANT onto modulating cortical activity in stimulation paradigms, particularly in θ . Since, in contrary to the other three metrics, dwPLI is insensitive to volume conduction, it is probable that thalamic signals do not get uncovered by the noise coming from scalp signals in this case, thus outputting different estimates. Minimum node degree values occurred in P4, TP10, C3 and tL4. Apart from C3, these results do not make much sense, which may be due to noise and volume conduction effects in the estimates. However, tL4 was obtained for the gamma band, which is not thought to modulate interactions in resting state paradigms. Moreover, with dwPLI, all the scalp electrodes ended up presenting a node degree equal to 0 across the whole EEG band. This is not expected at all, and is probably a result of having set a too high value for the threshold to generate the adjacency matrix.

For **ANT-25**, the TLE patient, a similar scenario of partial correspondence to the literature occurs. Regarding maximum node degree values, these occurred for the F8, Fp2, O2, and Fp1 scalp electrodes. Except for O2, all these electrodes are expected to catch DMN's main activity. Having been obtained with coherence, O2 may have wrongly caught up significant brain activity to account such high node degree value. Again, with dwPLI, maximum node degree values were obtained for thalamic electrodes, namely tR1, tR2, tR3, tR4, and tL4. Only tR3 and tR4 are located in the ANT (Figure 5.11), which leads one to pose the hypothesis that the whole thalamus may modulate interactions with the cortex. In addition, with Granger causality, maximum node degree values were obtained in delta, theta, and alpha for tR3. In spite of the putative interference of noise in these estimates, this result may indicate an important role of the ANT in modulating cortical interactions, which take place in lower bands. Conversely, minimum node degree values

were obtained for the P7, P8, and O1 scalp electrodes, from which none is part of those electrodes highly correlated with the DMN. Node degrees equal to 0 were again obtained for all the scalp electrodes by means of dwPLI, probably due to the same abovementioned reason.

Node degree values were generally consistent with the connectivity matrices. One must keep in mind that these node degree values were computed based, not only on thalamocortical interactions, but also on cortical and thalamic, which brings up the volume conduction effect at a stronger extent. Since thalamic recordings are less subjected to volume conduction, thalamocortical connectivity estimates are more reliable than the ones between two scalp electrodes. However, by visually inspecting the obtained connectivity matrices, one can infer the scalp electrodes associated to higher functional connectivity values. Electrodes with consistently high connectivity values across all the metrics comprise, for instance, Fp2, F8, F4, and FT10, which were previously found to be highly correlated with the DMN [RAM⁺18]. Therefore, overall results reinforce the association of ANT-DBS with the DMN.

Wrapping up all the topics discussed along this section, one can infer that the thalamus, and the ANT in particular, strongly interacts with the cortex. Within the cortex, DMN may play a key role, as detected by surface electrodes located near these regions. However, one important question has not yet been posed: do these interactions take place from the thalamus to the cortex, or from the cortex to the thalamus? Within this scope, by means of Granger causality, Aiello et al. found that interactions from the ANT to the scalp were focused on temporal channels, whilst interactions from the scalp to the ANT were the highest in frontal channels [ALD⁺23]. Nevertheless, patients in Aiello et al. were under anesthesia, which may influence brain dynamics, thus preventing our results from being directly comparable. As a matter of fact, neither for ANT-18 nor for ANT-25 this channel distinction could be performed. Instead, a strong dependence of the directionality of the interactions on the EEG rhythms is observed and will be analysed in more detail further on. Interestingly, although dependent on the frequency band, the strongest thalamocortical Granger causality values, regardless of the direction, are observed in scalp electrodes highly correlated with the DMN, mainly F4, Fz, Fpz, and F8.

5.1.2.3 Rhythmic Modulation of Thalamocortical Interactions

Brain oscillations are characterised by well-known specific frequency bands: delta, theta, alpha, beta, and gamma. Accordingly, interactions between the thalamus and the cortex involve the rhythmic modulation of neural activity between these two brain regions. Understanding how EEG frequency bands modulate these interactions was possible by computing functional connectivity metrics operating in the frequency domain, such as coherence, dwPLI, and Granger causality.

Generically, Aiello et al. observed that frequency bands had a significant effect on connectivity [ALD⁺23]. More in specific, connectivity in higher frequency bands (β , γ) was generally reduced when compared to lower bands (δ , θ , α). In addition, the strongest connectivity was observed to be modulated by theta oscillations. However, results from this study are not directly comparable to ours, since their patients were under anesthesia (*sevoflurane*) during data collection, which may affect neuronal oscillations and does not accomplish DMN studies' requirement to be awake for

signal acquisition [Rai15]. Accordingly, other previous studies verified increased theta power during *sevoflurane* administration. On the other hand, for our study, only awake segments of data were considered. As a matter of fact, lower oscillations such as theta are associated with sleep stages, whilst alpha oscillations are characteristic of awake state adults [TS13]. Thus, we may hypothesise expecting to find stronger alpha oscillations modulating thalamocortical interactions, by transposing Aiello et al.'s finding to awake state subjects. Interestingly, the alpha rhythm is strongly modulated during resting-state in the DMN, although no association with thalamocortical interaction is guaranteed [SLM⁺19].

Looking at the results at a glance, one can easily notice that connectivity values are widely variable across frequency bands. Further, it is also possible to observe that modulations are generally stronger in delta, theta, and alpha (in ascending order), which goes in accordance to the expected. More in detail, when computed with coherence, functional connectivity is highly modulated by alpha, both for ANT-18 and for ANT-25. On the other hand, with dwPLI, values are slightly higher in the theta band for both subjects. Considering dwPLI's insensitivity to volume conduction, it can be proposed that the EEG included noise between the scalp and the actual brain source in the alpha band, thus affecting the results obtained with coherence. However, there is no guarantee that the effect of volume conduction was completely discarded, nor that other sources of noise are corrupting the estimate.

In addition, by means of Granger causality, one is able to infer the directionality of information transfer. Within this scope, Aiello et al. observed that the information in theta band mostly flows from the ANT to the cortex [ALD⁺23]. Nevertheless, they did not discuss this for other frequency bands, which may also be important in modulating thalamocortical interactions. Concerning our study, the obtained results indicate that the strongest direction of information flow may change across EEG rhythms. In delta, information appears to strongly flow from the cortex to the thalamus, whilst in alpha the opposite takes place. For theta, no dominant direction of information transfer can be inferred, since both take place at similar extents. This highlights, on one hand, the importance of the ANT in modulating alpha oscillations at the cortical level, in awake state. Conversely, lower bands modulate information transfer from the cortex, mainly frontocentral regions, to the thalamus. By proving there's a network involving the ANT and the cortex, these findings may support a putative theory explaining the effectiveness of ANT-DBS. Accordingly, by targetting the ANT, epileptic activity on the cortex will be influenced. Moreover, assuming the reliability of both Aiello et al.'s and our study, it can be inferred that thalamocortical interactions take place in both sleep and awake states, although modulated by a different rhythmic fingerprint.

These patterns of directionality are strongly enhanced in ANT-25 (TLE), when compared to ANT-18 (FLE). Additionally, functional connectivity values are overall higher for ANT-25 than for ANT-18, across all the metrics. In fact, given the reported patient outcomes, patients with refractory TLE are among the best candidates for ANT-DBS [KBB⁺20]. Therefore, this reinforces the hypothesis that thalamocortical interactions may explain the effectiveness of ANT-DBS.

5.1.2.4 Towards Putative Outliers

As abovementioned, various reasons can lead one to obtain spurious connectivity estimates. Apart from the nature of each functional connectivity, a noisy signal is enough for the analysis to be corrupted, although preprocessing has been performed. In this section, possible outliers will be discussed and compared to the original signal, in order to try to understand if it's actually an outlier.

In Figure 5.2 (a), when compared to the other electrodes, F4 presents much higher coherence values for delta, theta, and alpha. Although F4 is associated with DMN regions, such high values are not expected to be observed in delta. By inspecting the segment in Figure 5.5, patterns that are not typically observed in EEG appear in the F4 channel, which may explain a possible spurious estimate obtained with coherence.

In addition, one may have noticed that the mentioned patterns observed in Granger causality were not enough highlighted given the low contrast in the matrices. The scales for each matrix were set from 0 to the maximum value of functional connectivity among the 5 bands for one metric. However, too high values of Granger causality are observed in gamma from F7 to T7 and to P7. Thus, this influenced the scale of matrices of bands of interest, such as theta and alpha. Although we are not focused on cortical connectivity in this section, it is not expected to observe such high value in the gamma band, corrupting the observation of results that actually matter. Being this problem observed in ANT-18 as well, Figure 5.5 can be analysed. By inspecting the F7, T7 and P7 channels in Figure 5.5, no apparent noise can be seen. One may infer that either this interaction actually takes place, or that other issues inherent to Granger causality may have led this value to occur.

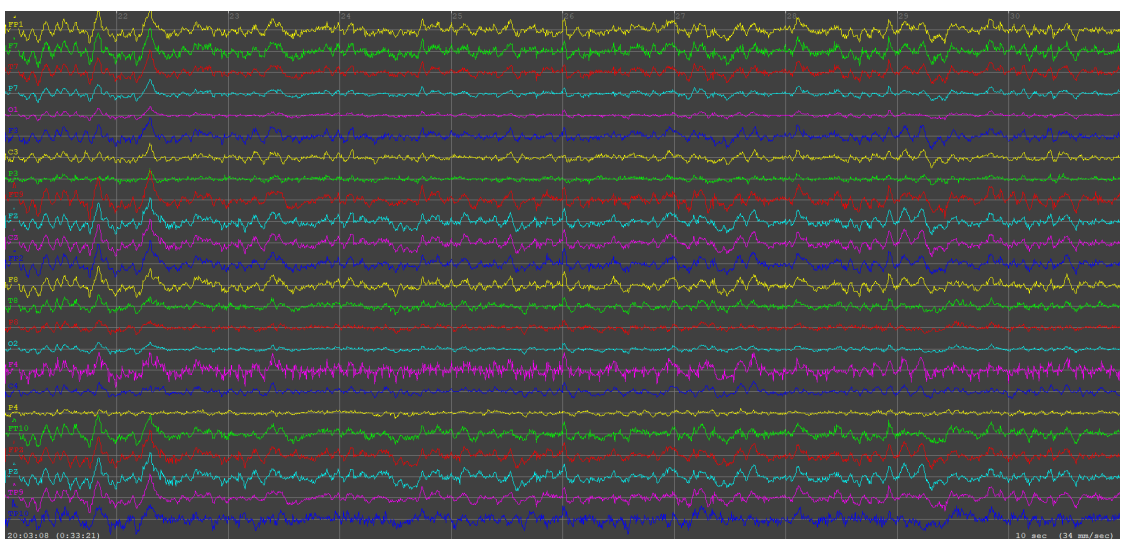


Figure 5.5: Segment of Preprocessed Scalp EEG for ANT-18. Image obtained with EDFbrowser.

5.1.2.5 Exploring the Thalamus

The role of the thalamus within the epileptogenic network has been a recent study focus, particularly in TLE patients [JMG⁺22]. However, the thalamus is structurally and functionally divided in subnuclei, with different connectivity patterns [CB13]. One can thus pose that each subnuclei may have distinct roles in controlling the epileptogenic network. Indeed, results reported diverse patterns of functional connectivity across the thalamus.

In ANT-18, which stands for a FLE patient, thalamic electrodes associated to higher connectivity values vary according to the metric. On one hand, with coherence, particularly in theta, values in the left hemisphere are higher than in the right hemisphere. However, when looking at one hemisphere at once, connectivity values raise as we get closer to the ANT (1 $\rightarrow$ 4). Conversely, with dwPLI, tL4, tR3, and tR4 present higher functional connectivity values, being this enhanced in theta. Both with Pearson correlation and with Granger causality, these patterns are widely variable, although functional connectivity is generally higher for the left hemisphere and, more in specific, in tL3 and tL4. This may indicate not only the dominance of regions closer to the ANT in modulating cortical interactions, but also a possible bias on the lateralisation, tending to the left hemisphere. Although one must be cautious when analysing the metrics, either higher connectivity in the left hemisphere or in electrodes closer to the ANT were consistently observed.

In ANT-25, standing for a TLE patient, across all the metrics, functional connectivity values are overall lower for tR3. In contrary to the other metrics, in which the connectivity values for all the other thalamic electrodes are approximately similar, one can observe higher dwPLI values standing out for the left hemisphere, particularly in tL2. For this case, electrodes located in the ANT comprise tR3 and tR4 (see Figure 5.11 (b)), which are the ones presenting consistently lower connectivity values. This may lead one to infer that other structures within the thalamus may be modulating interactions with the cortex in TLE. However, we were expecting to observe higher connectivity values in electrodes located in the ANT, in order to try to explain the clinical outcomes proving the effectiveness of ANT-DBS in TLE patients.

Finally, one of the goals would be to assess the anatomical location within the thalamus that reflects best the DMN features. Accordingly, this implies checking which contacts present stronger connectivity with the scalp sensors closer to DMN regions. On one hand, ANT-18 revealed higher functional connectivity patterns in contacts located in the ANT. Conversely, for ANT-25, no specific electrode showed to markedly reflect DMN properties, since only electrodes in the ANT showed lower functional connectivity values when compared to the other thalamic contacts. Therefore, DMN properties may be reflected by different electrodes within the thalamus, and not only by the ones located in the ANT, whose differences may be associated to each epilepsy subtype. However, a bigger cohort is necessary in order to deeply understand this topic and take clearer conclusions.

5.2 DMN Connectivity

5.2.1 Results

5.2.1.1 Head Model Generation and Electrode Co-registration

Generating an accurate head model is crucial for a reliable brain source estimation. Looking at Equation 4.8, it is straightforward to understand that forward modelling errors are known to have a significant effect on the accuracy of source analysis. Therefore, guaranteeing the reliability of source reconstruction implies checking if the electrode co-registration went as expected.

Figure 5.6 represents the electrodes plotted together with the head surface, in the MNI space. By visual inspection, one can check that the electrodes' positions are aligned with the head surface. In Appendix A.1, co-registration results for ANT-25 are shown as well.

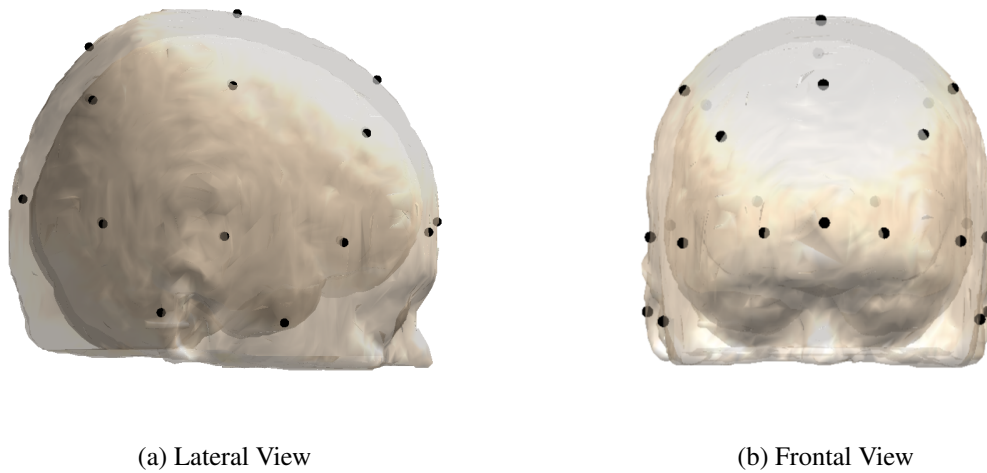
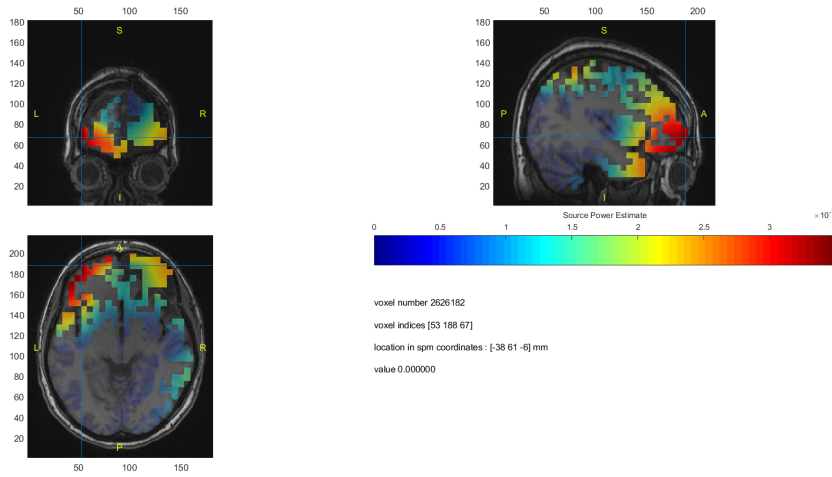


Figure 5.6: Co-registration of EEG electrodes with realistic head model (ANT-18).

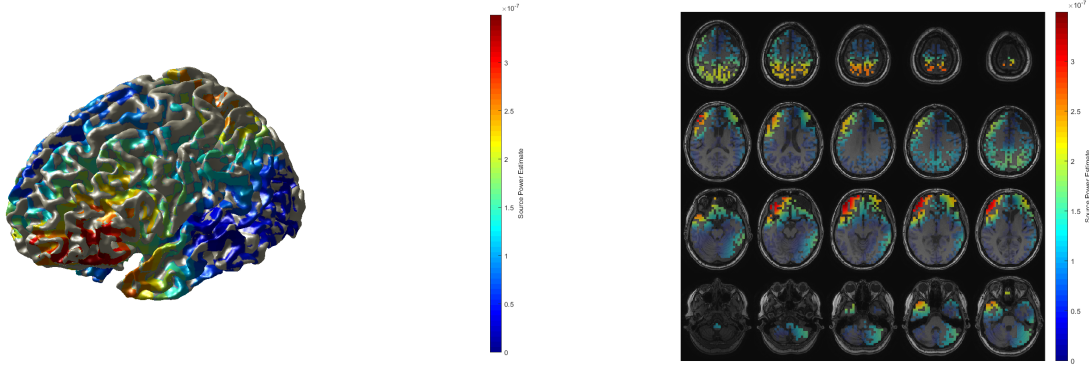
5.2.1.2 Source Reconstruction

Being the electrodes' positions correctly aligned with the head model surface, one can proceed onto source reconstruction. For ANT-18, Figure 5.7 shows three types of plots that allowed to visualise source localisation results, both in a template 3D brain surface and in the individual MRI. Similar plots standing for ANT-25 are shown in Appendix A.2. Higher values of activity can be observed mostly in regions near the frontal, parietal and temporal lobe, which seems reasonable.

As a side note, evaluating source reconstruction implies verifying if the source estimates accurately recreate the underlying brain dynamics [TOSZ21]. In addition, it could have been interesting to compare the output of different source reconstruction algorithms, which may lead to different solutions. However, these kind of calculations go out of the scope of this work, which is focused on assessing brain functional connectivity, thus not being computed.



(a) Plot on Three Orthogonal Slices of the MRI



(b) Plot on a Template 3D Brain Surface

(c) Plot on Slices of the MRI (Axial Plane)

Figure 5.7: Functional source reconstruction power estimates (ANT-18).

5.2.1.3 Functional Connectivity Assessment

Figure 5.8 shows the connectivity matrices obtained with Pearson correlation, calculated between DMN ROIs. Regarding the short names on the axis labels, *Prec* stands for the precuneus, *Ang* for the angular, *PCC* for the posterior cingulate, *ACC* for the anterior cingulate, and *FSMed* for the Frontal Superior Medial [OHKD19]. *L* and *R* correspond to left and right, respectively.

At a glance, comparing ANT-18 and ANT-25, patterns that present interspersed correlated (1) and anticorrelated (-1) connectivity values show up in different locations of the matrices. Moreover, the pairs of nodes showing higher connectivity values are variable between the two subjects.

For **ANT-18**, the FLE patient, the following node pairs must be highlighted: AngR/PrecR, ACCR/PCCR, FSMedR/PCCR, ACCL/PCCL, FSMedL/PCCL, FSMedR/ACCR, FSMedL/ACCL. Among opposite hemispheres, only interactions between PrecR/PrecL and PrecL/AngR show sufficiently high correlation values. Oddly, some values of connectivity close to 0 can be observed as well. Looking at the node degree values, in Table 5.4, except for the anterior cingulate, all the values standing for the right hemisphere are higher than for the corresponding node in the

left hemisphere. Accordingly, FSMedR presents the maximum node degree value of 6, while the anterior cingulate presents the minimum value equal to 2.

For **ANT-25**, the TLE patient, higher Pearson correlation coefficient values are observed in the pairs AngR/PrecR, AngL/PrecL, FSMedR/PCCR, and FSMedL/FSMedR. Overall, values are lower and most of them are close to 0, when compared to ANT-18. Regarding node degree, in Table 5.4, in this case, values are more consistent, being either 2 or 3. Considering that connectivity values are overall lower when compared to ANT-18, the node degree threshold set to 0.3 led this to occur. In this case, no hemisphere seems to dominate the other by having more nodes with higher node degree values.

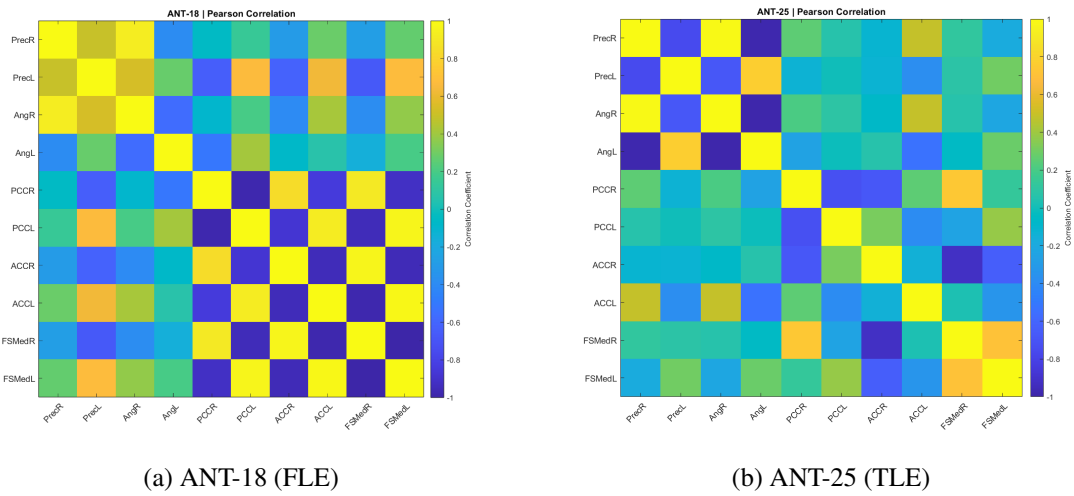


Figure 5.8: DMN functional connectivity matrices obtained with Pearson correlation (*Prec*: precuneus; *Ang*: angular; *ACC*: anterior cingulate; *PCC*: posterior cingulate; *FSMed*: frontal superior medial, with *R* as right and *L* as left).

Table 5.4: Node degree values for DMN ROIs obtained with Pearson correlation.

Label	Node Degree	
	ANT-18 (FLE)	ANT-25 (TLE)
Frontal Sup Medial L	3	3
Frontal Sup Medial R	6	2
Cingulum Ant L	5	3
Cingulum Ant R	2	2
Cingulum Post L	3	2
Cingulum Post R	5	3
Angular L	3	2
Angular R	5	3
Precuneus L	3	3
Precuneus R	5	3

Figure 5.9 represents the connectivity matrix containing all the ROIs described in the AAL atlas, excluding cerebellar regions, for **ANT-18 (FLE)**. DMN ROIs are pinpointed with a blue dot at the left of each corresponding label on the vertical axis. One can observe that various regions of the brain present high values of connectivity. However, interactions presenting higher correlation coefficient do not include most of DMN nodes. For DMN ROIs, only Angular R/L and Precuneus R/L show values close to 1, when interacting with parietal and central regions within the same hemisphere. Clusters of high values outside of the DMN comprise limbic and temporal regions.

Table 5.5 shows the node degree values obtained for ANT-18, considering all the ROIs in AAL atlas. The maximum value of 57 was obtained for the right hippocampus, whilst the minimum value equal to 16 stands for the left supplementary motor area. Regarding DMN nodes, the right angular (55) and the right precuneus (54) must be highlighted as having high node degree values.

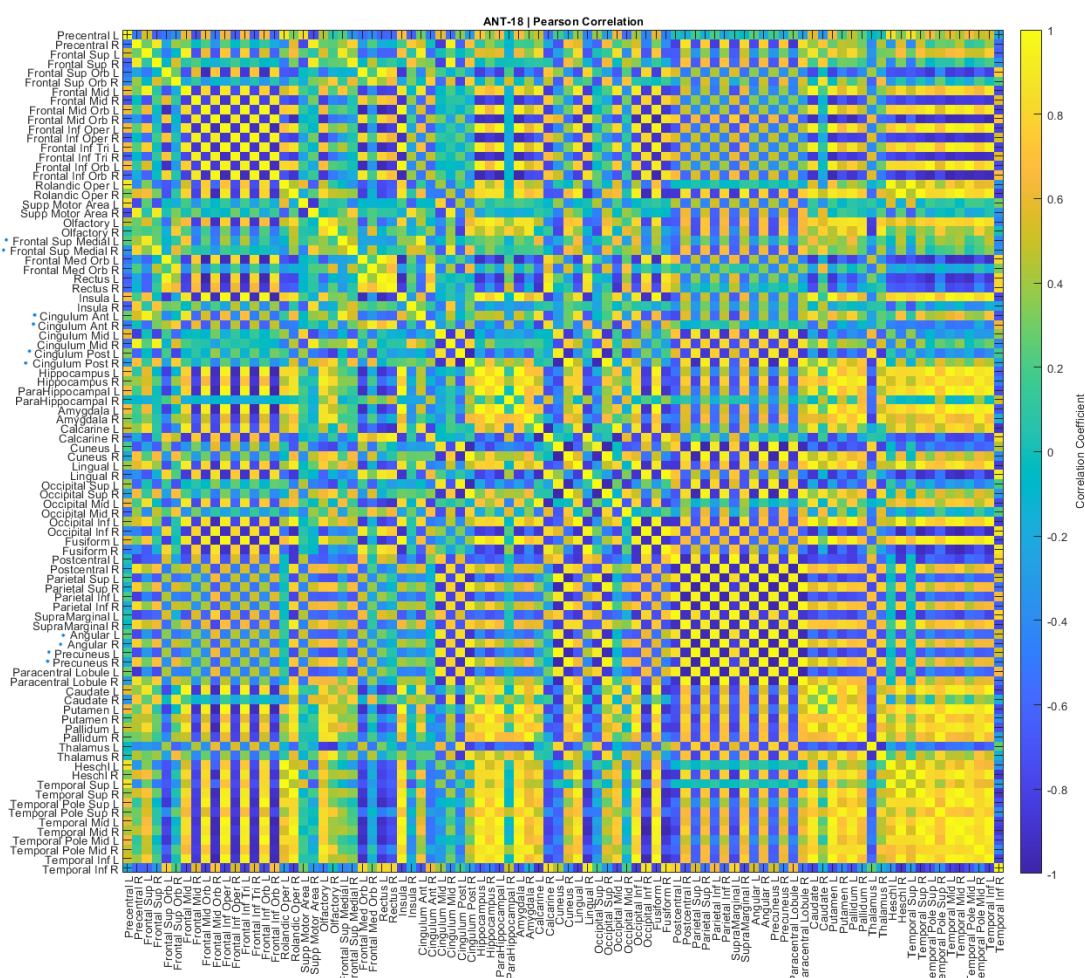


Figure 5.9: Whole Brain ROIs functional connectivity matrices obtained with Pearson correlation (ANT-18).

Table 5.5: Node degree values for whole brain ROIs obtained with Pearson correlation (ANT-18).

Label	Node Degree	Label	Node Degree
Precentral L	39	Cuneus R	49
Precentral R	36	Lingual L	56
Frontal Sup L	45	Lingual R	27
Frontal Sup R	28	Occipital Sup L	16
Frontal Sup Orb L	24	Occipital Sup R	47
Frontal Sup Orb R	32	Occipital Mid L	38
Frontal Mid L	48	Occipital Mid R	31
Frontal Mid R	28	Occipital Inf L	56
Frontal Mid Orb L	45	Occipital Inf R	27
Frontal Mid Orb R	27	Fusiform L	52
Frontal Inf Oper L	50	Fusiform R	25
Frontal Inf Oper R	26	Postcentral L	28
Frontal Inf Tri L	48	Postcentral R	56
Frontal Inf Tri R	25	Parietal Sup L	25
Frontal Inf Orb L	45	Parietal Sup R	55
Frontal Inf Orb R	25	Parietal Inf L	26
Rolandic Oper L	38	Parietal Inf R	56
Rolandic Oper R	56	SupraMarginal L	28
Supp Motor Area L	16	SupraMarginal R	56
Supp Motor Area R	22	Angular L	25
Olfactory L	55	Angular R	55
Olfactory R	46	Precuneus L	25
Frontal Sup Medial L	36	Precuneus R	54
Frontal Sup Medial R	37	Paracentral Lobule L	25
Frontal Med Orb L	24	Paracentral Lobule R	56
Frontal Med Orb R	25	Caudate L	55
Rectus L	26	Caudate R	42
Rectus R	21	Putamen L	51
Insula L	49	Putamen R	55
Insula R	21	Pallidum L	55
Cingulum Ant L	48	Pallidum R	52
Cingulum Ant R	26	Thalamus L	23
Cingulum Mid L	20	Thalamus R	49
Cingulum Mid R	36	Heschl L	39
Cingulum Post L	16	Heschl R	56
Cingulum Post R	45	Temporal Sup L	37
Hippocampus L	49	Temporal Sup R	55
Hippocampus R	57	Temporal Pole Sup L	48
ParaHippocampal L	50	Temporal Pole Sup R	53
ParaHippocampal R	24	Temporal Mid L	51
Amygdala L	51	Temporal Mid R	55
Amygdala R	51	Temporal Pole Mid L	49
Calcarine L	44	Temporal Pole Mid R	52
Calcarine R	22	Temporal Inf L	55
Cuneus L	24	Temporal Inf R	26

For **ANT-25** (TLE), one can observe in Figure 5.10 that some of the "clusters" of high correlation coefficient values involve DMN nodes. Therefore, in this case, comparing to other regions of the brain, DMN regions stand out with higher connectivity values. In addition, of course, other regions exhibit patterns of high connectivity as well, for instance frontal regions, hippocampus, and amygdala. Although it is not relevant for the analysis, Pallidum L shows coefficients of 0 across all its connections, which may be an error occurred along connectivity computation.

Regarding node degree analysis, results are represented in Table 5.6. In general, compared to ANT-18, the values are more consistent among themselves, which means that brain regions are approximately equally interconnected. The maximum value equal to 41 stands for the left insula, while the minimum value of 0 was obtained for the left pallidum. The left anterior cingulate and the left frontal superior medial present the highest node degree value among DMN nodes, equal to 32. Nevertheless, comparing with the remaining brain regions, all the DMN nodes present high node degree values.

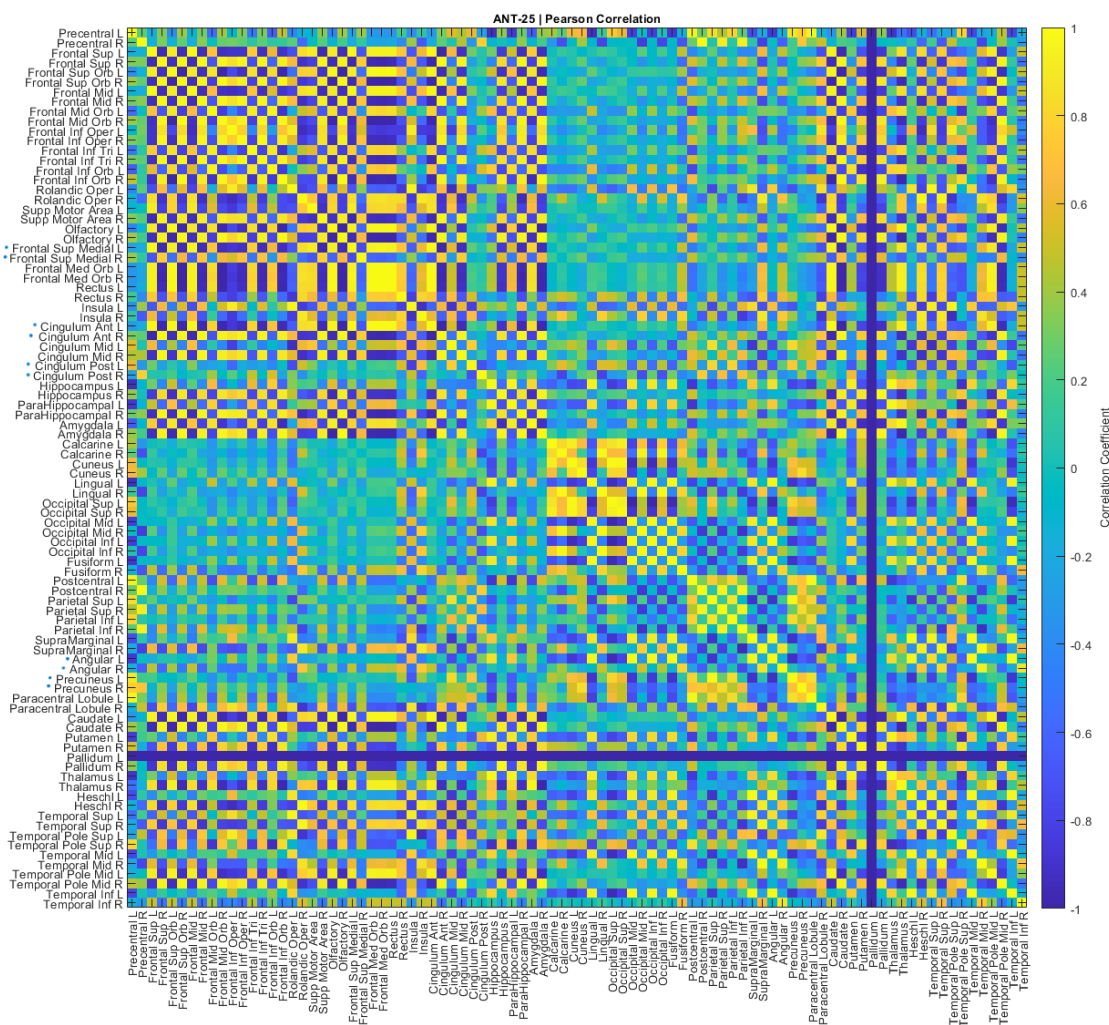


Figure 5.10: Whole Brain ROIs functional connectivity matrices obtained with Pearson correlation (ANT-25).

Table 5.6: Node degree values for whole brain ROIs obtained with Pearson correlation (ANT-25).

Label	Node Degree	Label	Node Degree
Precentral L	33	Cuneus R	19
Precentral R	17	Lingual L	25
Frontal Sup L	31	Lingual R	20
Frontal Sup R	34	Occipital Sup L	23
Frontal Sup Orb L	32	Occipital Sup R	21
Frontal Sup Orb R	32	Occipital Mid L	24
Frontal Mid L	31	Occipital Mid R	18
Frontal Mid R	34	Occipital Inf L	24
Frontal Mid Orb L	34	Occipital Inf R	19
Frontal Mid Orb R	32	Fusiform L	23
Frontal Inf Oper L	37	Fusiform R	31
Frontal Inf Oper R	32	Postcentral L	37
Frontal Inf Tri L	30	Postcentral R	18
Frontal Inf Tri R	31	Parietal Sup L	23
Frontal Inf Orb L	33	Parietal Sup R	29
Frontal Inf Orb R	31	Parietal Inf L	12
Rolandic Oper L	38	Parietal Inf R	31
Rolandic Oper R	35	SupraMarginal L	23
Supp Motor Area L	31	SupraMarginal R	31
Supp Motor Area R	31	Angular L	23
Olfactory L	33	Angular R	27
Olfactory R	32	Precuneus L	18
Frontal Sup Medial L	32	Precuneus R	29
Frontal Sup Medial R	30	Paracentral Lobule L	37
Frontal Med Orb L	32	Paracentral Lobule R	38
Frontal Med Orb R	32	Caudate L	32
Rectus L	32	Caudate R	32
Rectus R	38	Putamen L	32
Insula L	41	Putamen R	32
Insula R	34	Pallidum L	0
Cingulum Ant L	32	Pallidum R	29
Cingulum Ant R	31	Thalamus L	32
Cingulum Mid L	33	Thalamus R	35
Cingulum Mid R	35	Heschl L	22
Cingulum Post L	26	Heschl R	35
Cingulum Post R	25	Temporal Sup L	37
Hippocampus L	32	Temporal Sup R	33
Hippocampus R	30	Temporal Pole Sup L	39
ParaHippocampal L	34	Temporal Pole Sup R	34
ParaHippocampal R	35	Temporal Mid L	21
Amygdala L	35	Temporal Mid R	31
Amygdala R	31	Temporal Pole Mid L	32
Calcarine L	20	Temporal Pole Mid R	35
Calcarine R	23	Temporal Inf L	22
Cuneus L	22	Temporal Inf R	26

5.2.2 Discussion

Potential pitfalls may arise along the source imaging procedure. For instance, the number and distribution of the electrodes along the scalp is an important issue to discuss. There is no established minimum number of electrodes in order to get a reliable source estimation [MB19]. As a reference, several studies have demonstrated that using montages with less than 32 electrodes may lead to a blurred solution, given the associated low spatial sampling [MML⁺04, MB19]. Nevertheless, this does not detract the use of these EEG systems for source reconstruction purposes, since one can still gain valuable insights about the underlying sources [MB19]. Furthermore, a prerequisite to correctly define the inverse solution within the head surface of the patient's T1-w MRI is the co-registration between the EEG and the MRI space. This step requires that the electrode positions are matched to the scalp surface [MML⁺04]. In Figure 5.6, which shows the co-registration result, it is possible to observe that the electrodes are correctly aligned with the head surface. Although some electrodes are located slightly deeper than others, this represents a satisfactory result for an electrode co-registration, given the difficulty of the task. Still, the electrodes' positions used for co-registration were based on a template 10-20 montage, and not on the exact individual positions, which may limit the solution's accuracy.

No prior study has yet compared DMN patterns between FLE versus TLE patients undergoing ANT-DBS. As a reference, although the patient's epileptic syndrome is not specified, Middlebrooks et al. observed, for ANT-DBS responders, increased connectivity in the precuneus, PCC, MPFC, and inferior parietal lobule [MGS⁺18]. Accordingly, these nodes showed high node degree values in both ANT-18 and ANT-25, which may indicate the importance of the DMN in both FLE and TLE. Furthermore, both subjects presented interspersed functional connectivity values of either approximately 1 or -1 (Figure 5.8). Adapting the interpretation of these values to the context, $\rho = 1$ indicates that, when one brain region is highly activated, the corresponding pair is highly activated as well. For $\rho = -1$, the opposite takes place, meaning that, if one brain region is highly active, the other brain region is highly inactive. Being interspersed refers to the fact that if, for a certain node, the ρ value with a node in the right hemisphere is equal to 1, then, for the corresponding node in the left hemisphere, $\rho = -1$. This pattern strengthens the statement that the DMN has sub-networks, along the same hemisphere, which in turn may be interconnected among themselves [SLM⁺19]. Besides, observing that the interspersed patterns occur in different nodes for both subjects may indicate that these sub-networks vary across epilepsy subtypes.

Having inferred that the DMN is activated in both FLE and TLE patients undergoing ANT-DBS, then, one must understand whether or not these effects are stronger in one of these syndromes. On one hand, DMN nodes appear to be more interconnected in ANT-18, considering that higher node degree values are achieved than in ANT-25 (see Table 5.4). However, looking at the bigger picture, in ANT-25, regions belonging to the DMN highlight among the rest of the brain. Therefore, this may mean that temporal lobe epilepsy syndromes reflect best DMN properties, when compared to frontal lobe.

In addition, by analysing connectivity among all the brain regions defined in the AAL atlas, more nodes apart from those belonging to the DMN were highlighted. For instance, the hippocampus, superior temporal lobe, temporal pole, middle frontal gyrus, postcentral gyrus, and amygdala presented high connectivity values. On one hand, deeper structures (amygdala, hippocampus, thalamus, putamen) belonging to the circuit of Papez show activation, which is expected, considering the overlap with the epileptogenic network. Conversely, besides the DMN, other canonical resting state networks have also been shown to be activated in patients receiving DBS in epilepsy, for instance the salience and the limbic networks [VGE⁺22]. Therefore, it is expected that other regions apart from the DMN ones would be activated in this paradigm. Nevertheless, one must be cautious when analysing deeper structures in this context, considering that the corresponding source reconstruction results are not very precise, thus highlighting the relevance of using intracranial electrodes in connectivity studies.

Nevertheless, one must be cautious when generalising conclusions as such. Firstly, evidence is only taken from one subject per epilepsy subtype. Although indicative, these results do not reach significance to state any eventual difference in the DMN between epileptic syndromes. Expanding this analysis to a bigger cohort is urgent, in order to be able to perform statistics, to analyse the reliability of the observations. Secondly, errors in the connectivity estimate may have occurred and led to potentially wrong conclusions. As explained above, both the low number of electrodes and not using the individual electrode positions may have limited the accuracy of the inverse solution. Additionally, having averaged the epochs before computing source reconstruction removes a lot of information about the signal, and may have compromised the final connectivity estimate.

5.3 Thalamic Connectivity

Although the thalamic regions do not constitute a network itself, different connectivity patterns exist along the thalamus [CB13]. In epilepsy and, particularly, when undergoing ANT-DBS, these connectivity patterns within the thalamus may be altered. Therefore, this part of the work does not intend to assess a brain network, but instead, patterns of thalamic connectivity. More specifically, we expect to find a specific fingerprint characterising the ANT in FLE versus TLE, given its established role across epilepsy subtypes. For further analysis, all the functional connectivity matrices were plotted in a similar manner than in the previous parts of this work.

5.3.1 Results

5.3.1.1 Lead Reconstruction

In Lead-DBS, the priorly provided lead contact coordinates were plotted together with the *nucleus anterior principalis* structure in DISTAL atlas, which covers most of the ANT. By visually inspecting Figure 5.11, one can infer if the lead contacts are located in the ANT or not. Thus, for **ANT-18**, lead contacts within the ANT are tR4, tL3, and tL4. Conversely, for **ANT-25**, only tR3 and tR4 are located in the ANT.

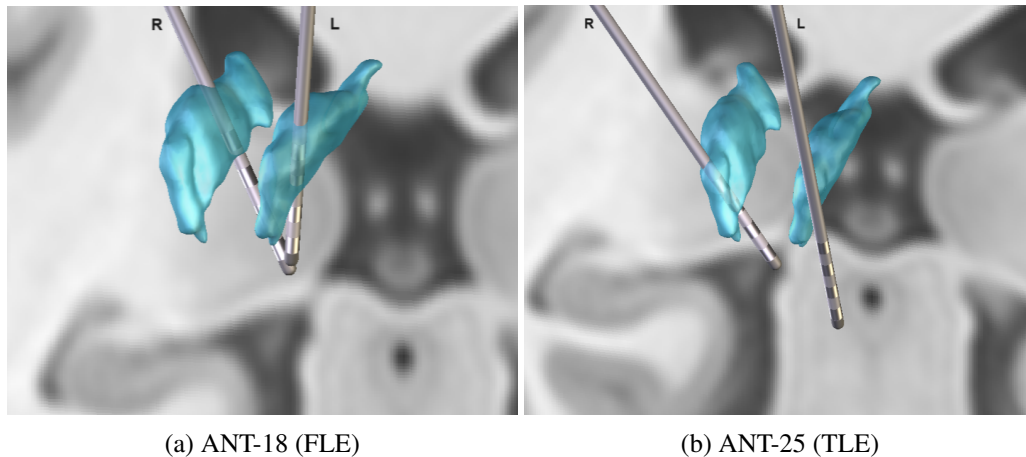


Figure 5.11: Lead reconstruction in DISTAL atlas.

5.3.1.2 Pearson Correlation

Functional connectivity matrices obtained with Pearson correlation are in Figure 5.12. At first sight, one can observe that all the connectivity values are close to 1, both for ANT-18 and for ANT-25. However, for **ANT-18** (FLE), values are slightly higher when interactions take place within the same hemisphere, being higher between tL2 and tL3. On the other hand, for **ANT-25** (TLE), values are a bit lower for all the electrode pairs involving tR3.

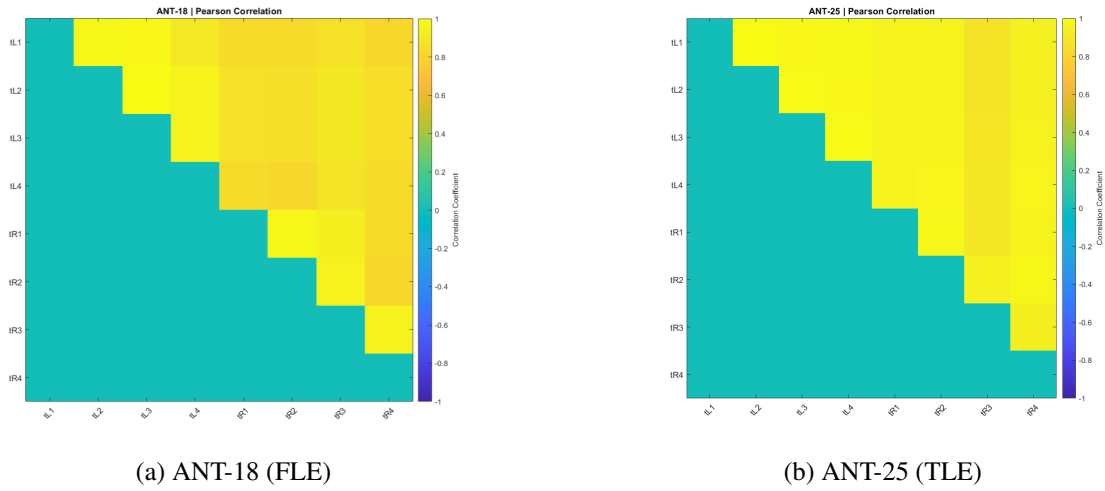


Figure 5.12: Thalamic functional connectivity matrices obtained with Pearson correlation.

5.3.1.3 Coherence

Figure 5.13 shows the results concerning functional connectivity obtained with coherence. Overall, connectivity values were also relatively high, mostly for theta and alpha bands. However, in **ANT-18**, the FLE patient, values are reduced for all the interactions involving tL4, in a consistent manner from theta to gamma. Moreover, mostly in theta, lower connectivity values are observed for interactions with tR4. Compared to the other rhythms, alpha presents higher coherence values in general. For **ANT-25**, the TLE patient, values are overall higher for theta and alpha bands. From delta to alpha, a reduction in connectivity for interactions involving tR3 is observed, although this pattern is stronger in delta. Additionally, in gamma, a cluster of lower values standing for connectivity values between electrodes of opposite hemispheres can be denoted.

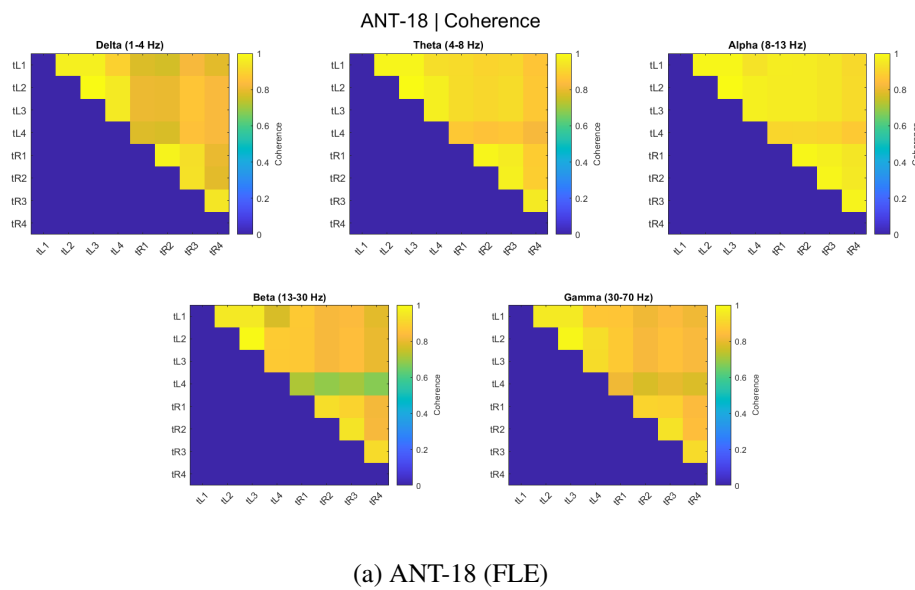
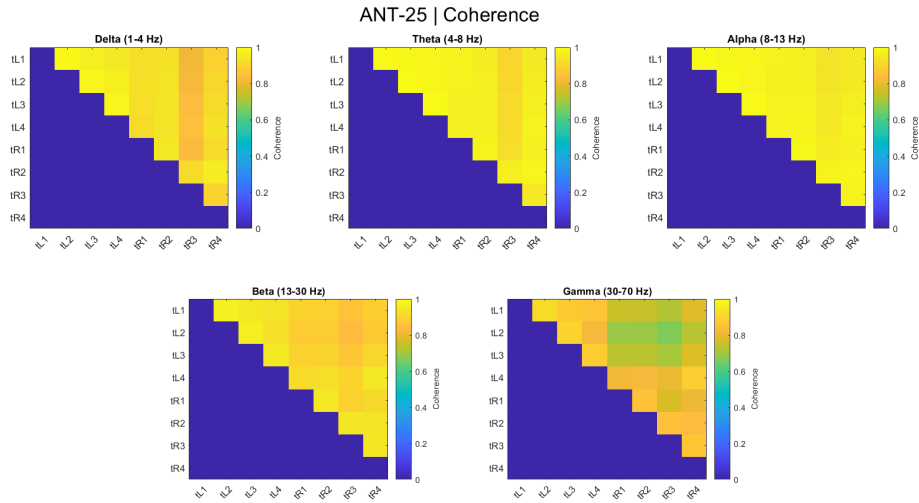


Figure 5.13: Thalamic functional connectivity matrices obtained with coherence.



(b) ANT-25 (TLE)

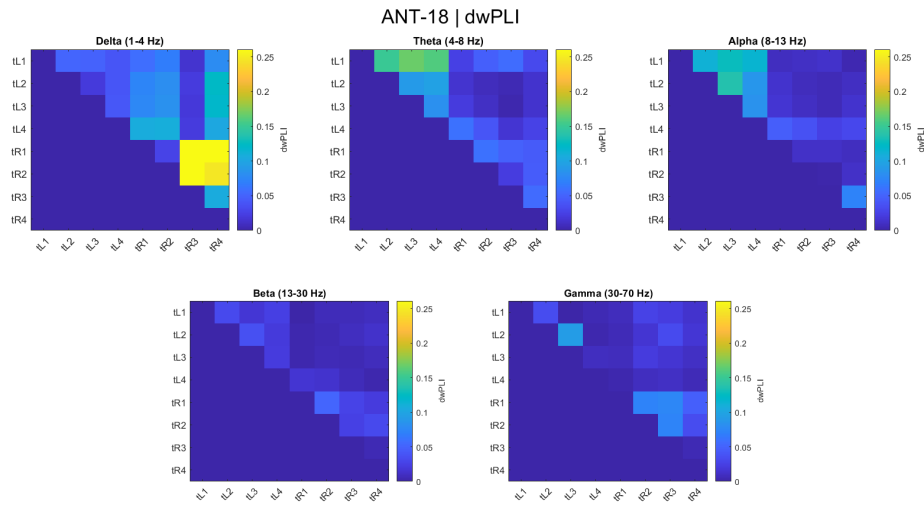
Figure 5.13: Thalamic functional connectivity matrices obtained with coherence (Continued).

5.3.1.4 Debiased Weighted Phase Lag Index

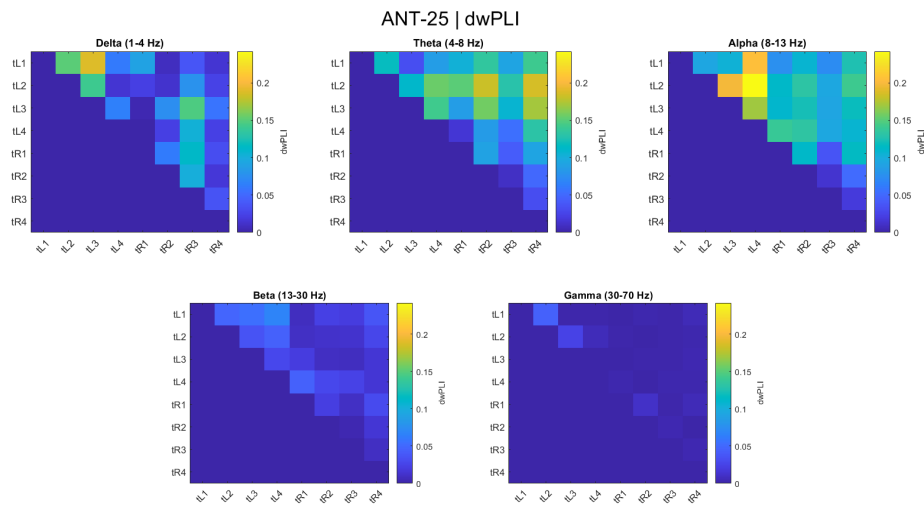
Results referring to functional connectivity obtained with dwPLI are represented in Figure 5.14. At a glance, regardless of the subject, connectivity values are widely variable among themselves and much lower than the ones obtained with Pearson correlation and with coherence.

For **ANT-18**, the FLE patient, a cluster of higher dwPLI values is observed in delta, between tR1/tR2 and tR3/tR4. Nevertheless, all the interactions that tR3 establishes with the left thalamus present very low values. In theta, it is worth mentioning the higher values of connectivity that tL1 shows when interacting with the other left thalamic electrodes. For alpha, higher functional connectivity values can be observed for interactions involving electrodes in the left thalamus. However, no rhythm in particular can notoriously be highlighted as the one that mostly modulates thalamic connectivity. Given the observed low connectivity values, beta and gamma bands are not relevant for further analysis.

For **ANT-25**, the TLE patient, across all the bands, the highest functional connectivity value is observed between tL2 and tL4 in alpha. For this rhythm, stronger interactions take place among the left hemisphere. From the remaining bands, the highest values are observed in delta and theta. For the former, the highest values are observed between tL1 and tL3, tL1 and tL2, and tL2 and tL3 in ascending order. In addition, one can observe a "vertical line" of higher values, representing interactions involving tR3. For theta, interestingly, highest dwPLI values are observed in interactions between different hemispheres, being particularly higher between tL2 and tR2, and tL2 and tR4. Neither beta nor gamma rhythms are pertinent for further discussion, considering the associated low dwPLI values.



(a) ANT-18 (FLE)



(b) ANT-25 (TLE)

Figure 5.14: Thalamic functional connectivity matrices obtained with dwPLI.

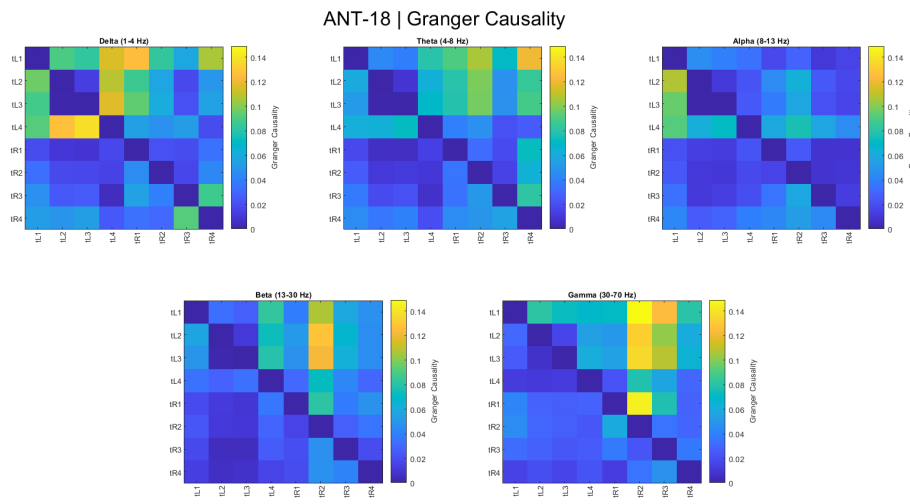
5.3.1.5 Granger causality

In Figure 5.15, functional connectivity results obtained with Granger causality are represented.

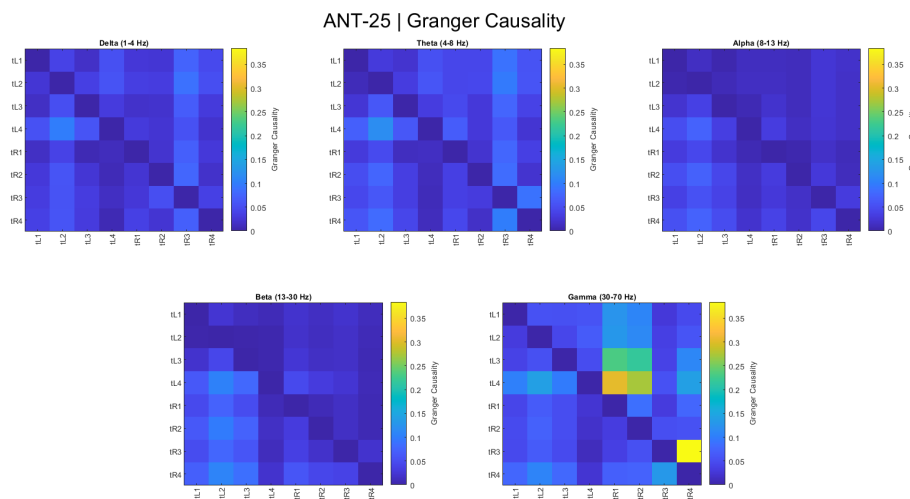
For **ANT-18**, the FLE patient, different patterns can be observed for distinct EEG rhythms. In delta, stronger interactions take place from and to tL4, as well as from and to tL1. A high Granger causality value is also observed from tL1 to rR1. Nevertheless, interactions involving the left thalamus appear to be strongly modulated by delta. On the other hand, in theta, the highest connectivity values are for interactions from tL1 to tR2 and to tR4. In alpha, interactions tend to be stronger within the left hemisphere, especially from tL2, tL3, and tL4 to tL1. In higher bands (beta and gamma), the situation changes, considering that higher connectivity values are achieved

from thalamic electrodes in the left hemisphere to the right hemisphere. Moreover, gamma reaches its maximum Granger causality value from tR1 to tR2.

In **ANT-25**, the TLE patient, there's a peak in gamma, from tR3 to tR4, that seems to influence the scale of all the other matrices, thus corrupting its visualisation and analysis. Nevertheless, some patterns can still be observed. For instance, in delta and theta, a "vertical line", standing for interaction from tL1 to all the other thalamic electrodes, can be observed. High Granger causality values can be achieved as well for all the interactions directed to tL2, reaching a peak when from tL4. In alpha and beta, interactions from tL3, tL4, tR1, tR2, tR3, and tR4 to tL1, tL2, and tL3 reach higher functional connectivity. Finally, in gamma, besides the peak from tR3 to tR4, high Granger causality values can be observed from tL3 and tL4 to tR1 and tR2.



(a) ANT-18 (FLE)



(b) ANT-25 (TLE)

Figure 5.15: Thalamic functional connectivity matrices obtained with Granger causality.

5.3.2 Discussion

Regarding the reconstruction of the lead contact positions, no reference can be taken into account to infer accuracy. However, it would be expected that, for ANT-25, at least one contact of the left thalamic electrode was located in the ANT. It is common that either 1 or 2 contacts per lead are located in the ANT, considering the size of this structure and the lack of guidance during lead implantation.

Going onto the functional connectivity estimates, although the same above described four metrics are being analysed, there's one difference in this case. Since these estimates were computed with intracranial signals, the volume conduction effect is reduced, when compared to non-invasive EEG. Therefore, although results must still be handled with care, more reliable estimates can be obtained, especially in metrics sensitive to field spread.

With **Pearson correlation**, all the obtained values were equal or close to 1, which stands for maximum correlation. Indeed, thalamic signals have similar amplitudes and waveform across these channels. Thus, considering the nature of the metric, this was expected to take place. Considering the simplicity of Pearson correlation, turns out that it might not be the best connectivity metric to compute for this specific task. Nevertheless, the fact that connectivity values are higher among the same hemisphere was expected, considering that these signals present even more similarities. Discussing the lower connectivity values associated with tR3 in ANT-25, these are involving an electrode located in the ANT. However, we may be facing a spurious estimate, since tR4 is also located in the ANT and does not present any reduction in connectivity.

For **coherence**, functional connectivity values close to 1 can also be observed. However, with **dwPLI**, tables turn. Compared with coherence, although both vary between 0 and 1, connectivity estimates obtained with dwPLI are far from being close to 1. These differences may be attributed to the underlying mathematical principles and assumptions of the two measures. On one hand, with coherence, the cross-spectral densities of consecutive epochs across time are summed and normalised, which means that we are quantifying the linear relationship between two signals in terms of both amplitude and phase. Conversely, dwPLI focuses primarily on phase differences, being insensitive to volume conduction and common sources. Therefore, the lower values obtained with dwPLI compared to coherence may indicate that dwPLI is providing a more conservative and potentially more accurate estimate of functional connectivity, based on phase. Although volume conduction is expected to be reduced in these kind of recordings, it can still exist and affect the final estimate, especially for the case of coherence.

For **Granger causality**, the highest functional connectivity estimates are observed in gamma, with special highlight to ANT-25. Considering the principle that higher frequencies support short-range communications in the brain, this represents an interesting observation. However, by being too high when compared to the other rhythms, it is also possible that these values represent outliers. For ANT-18, considerably high values are also observed in delta, from all the left thalamic electrodes to tL4, and vice-versa. This represents a countersense to the mentioned principle, which may allow one to doubt the reliability of this observation.

Overall, wrapping up all the metrics' results, it can be observed that the highest functional connectivity values are often observed for interactions involving the left hemisphere. As a matter of fact, high functional connectivity profiles are expected to be observed in the thalamus ipsilateral to the epileptogenic zone [PTS⁺21]. However, both subjects have bilateral epilepsies, as seen in Table 4.1. One can thus propose that their bilaterality may be biased to the left hemisphere. Indeed, comparing with the results presented in Section 5.1, especially for ANT-25, the TLE patient, the highest functional connectivity values often stand for interactions involving the left thalamus over the right thalamus. Considering the role of the thalamus in modulating cortical interactions, these observations reinforce the potential bias in the epilepsy's laterality.

At last, delta, theta and alpha represent the stronger rhythms modulating interactions within the thalamus. However, across metrics, no concise conclusion can be taken, given the different results outputted. Interesting peaks of connectivity observed in gamma may be either outliers or punctual short-range interactions characterised by higher bands. Finally, interactions between the two opposite hemispheres show that the two thalamus communicate and transfer information between themselves.

Chapter 6

Conclusions and Further Work

6.1 Conclusion

In this dissertation, three methodological perspectives intertwined towards two main goals. Leveraging functional connectivity, a robust tool in neuroscience for comprehending brain function, we successfully characterised the electrophysiological fingerprint of the thalamocortical network in patients with FLE compared to those with TLE. This characterisation stands as a significant contribution towards the future establishment of potential biomarkers with diverse applications in DBS. Going from preprocessed simultaneous scalp and thalamic EEG, the conducted functional connectivity analysis was threefold: firstly, between the thalamus and cortex; secondly, limited to DMN regions post brain source reconstruction; and thirdly, exclusively for thalamic regions.

Firstly, results indicate that the thalamus strongly interacts with the cortex, particularly in scalp electrodes highly correlated with the DMN. Modulations are stronger when in theta and in alpha bands. For these same rhythms, especially for alpha, information mostly flows from the thalamus to the cortex. Moreover, in some of the interactions, especially for the FLE patient, electrodes located in the ANT stand out as presenting higher functional thalamocortical connectivity values. Overall, the TLE patient presents a higher connectivity profile, which reinforces the hypothesis that thalamocortical interactions may underlie the effectiveness of ANT-DBS, considering the associated clinical outcomes.

Concerning the second analysis, results indicate high connectivity profiles within well-known DMN regions. DMN-related patterns are highlighted among other brain regions in the TLE patient over the FLE one. In addition, activations are observed in brain regions beyond the DMN, suggesting a potential association of more networks with ANT-DBS in epilepsy than previously hypothesised.

At last, no concise conclusion can be taken regarding connectivity patterns within the thalamus, since results are widely variable across metrics. Nevertheless, delta, theta and alpha rhythms appear to strongly modulate these interactions. Interestingly, some peaks of high functional connectivity in gamma are also observed.

Reflecting on these exciting findings, through continued research on this topic, we aspire to bridge the gap between theoretical insights and transformative clinical applications towards personalised network-guided approaches in ANT-DBS for epilepsy.

6.2 Limitations and Future Work

Some limitations of this study are noteworthy. Firstly, the small cohort limits the robustness of the findings and reflects the pilot nature of this work. Indeed, it is naïve to generalise a certain finding to the associated epilepsy subtype, when only one subject per subtype was analysed. Spanning the analysis to a bigger cohort is urgent for the findings to reach significance. All the conditions are set for this to occur, since the whole dataset contains 26 subjects with available and ready-to-use data, thus representing an unique asset in the scientific area. However, circumstances and time constraints did not allow the entire cohort to be included in this study. Within this dataset, several features can be distinguished as an attempt to develop individualised biomarkers in the future. For instance, novelty starts as we have access to EEG data from patients with more than 2 years of follow-up. Therefore, DMN long-term alterations can be pinpointed between these same epilepsy subtypes, whose distinction has never been conducted before.

Furthermore, computing frequency domain functional connectivity metrics among DMN ROIs would allow one to understand, not only the nodes, but also the rhythms modulating these interactions. However, considering that data epochs were averaged prior to source imaging into a single time segment, neither quantifying phase synchrony nor designing an autoregressive model would make sense. Having this, implementing other source localisation algorithm rather than eLORETA is proposed to avoid this limitation. Another suggestion may lie on computing connectivity from stereo-EEG signals covering the whole head, which is available on the referred dataset. Instead of computing source reconstruction, which represents a difficult and time consuming task that is not feasible to perform online, estimating connectivity from intracranial recordings also reduces the effect of volume conduction.

Finally, validating that DMN features can be transposed from thalamic EEG to ANT-LFPs would be crucial to further develop closed-loop DBS approaches. Comparing the obtained thalamocortical connectivity biomarkers with LFPs from the ANT would be the way to get this conclusion. Even if those biomarkers were found applicable in the first place using other techniques rather than LFPs, for logistical purposes, applying these in-clinic would be easier by means of LFPs, using the same electrode as the stimulation one instead of an extra intracranial electrode. Therefore, verifying that the same characteristic properties determined using simultaneous scalp and thalamic EEG can also be extracted using LFPs is urgent for the development of advanced closed-loop DBS approaches based on brain networks.

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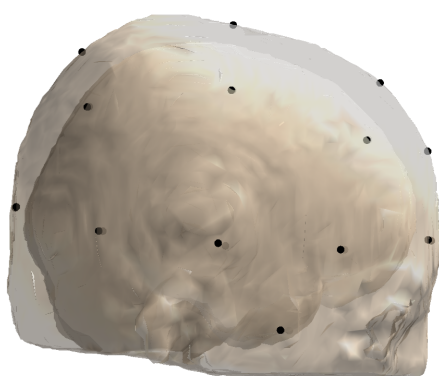
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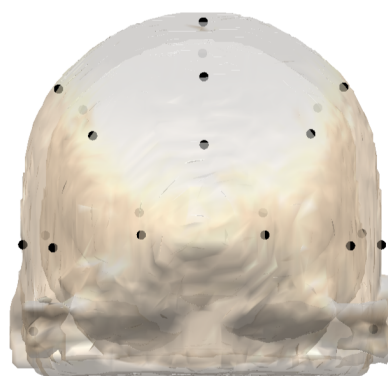
Appendix A

Supplementary Results

A.1 Head Model Generation for ANT-25



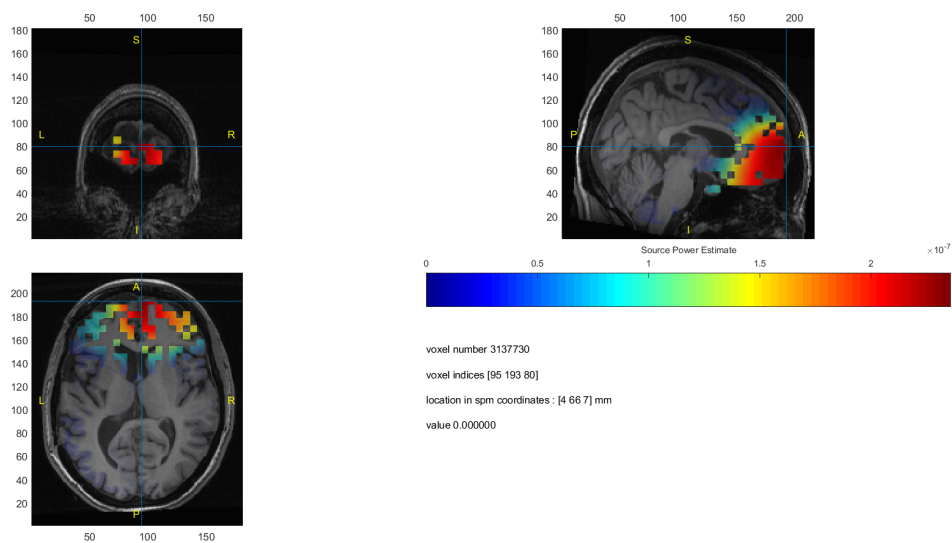
(a) Lateral View



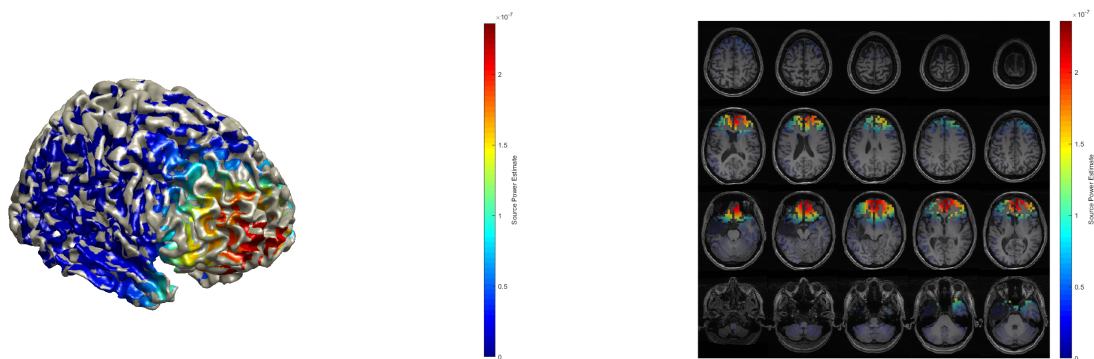
(b) Frontal View

Figure A.1: Co-registration of EEG electrodes with realistic head model (ANT-25).

A.2 Source Reconstruction for ANT-25



(a) Plot on Three Orthogonal Slices of the MRI



(b) Plot on a Template 3D Brain Surface

(c) Plot on Slices of the MRI (Axial Plane)

Figure A.2: Functional source reconstruction power estimates (ANT-25).