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UNIVERSITY OF CALIFORNIA

Los Angeles

Learning Pathological Brain Dynamics: EEG Foundation Models and Epilepsy

A dissertation submitted in partial satisfaction

of the requirements for the degree

Doctor of Philosophy in Medical Informatics

by

Saarang Panchavati

ABSTRACT OF THE DISSERTATION

Learning Pathological Brain Dynamics: EEG Foundation Models and Epilepsy

by

Saarang Panchavati

Doctor of Philosophy in Medical Informatics

University of California, Los Angeles, 2026

Professor William Speier, Chair

Epilepsy affects approximately 50 million people worldwide, and roughly one-third of patients are drug-resistant. For these patients, closed-loop neurostimulation offers an alternative to surgical resection, but current devices close the loop on detection rather than on outcome: stimulation parameters are set at periodic clinic visits and are not informed by what the brain is currently doing or about to do. Progress depends on two open problems: how to track brain state in real time from EEG, and how seizure activity evolves through thalamocortical networks. This dissertation studies both problems and connects them through a learned model of seizure dynamics for closed-loop intervention planning.

The first thread develops scalable self-supervised methods for EEG representation learning, progressing from a pretrained transformer-CNN for seizure detection from wearable behind-the-ear EEG, to Mentality, a Mamba-based foundation model that learns from reconstruction, to Laya, the first LeJEPa-based EEG foundation model. Predicting in latent space rather than signal space produces more transferable representations of brain state across downstream tasks, suggesting that the choice of pretext task shapes what is clinically useful.

The second thread characterizes thalamocortical network dynamics across focal seizures using intracranial EEG. At ictal onset, the anterior and centromedian thalamic nuclei are recruited bidirectionally, with broadband inflow from the seizure onset zone to the thala-

mus and slow-frequency outflow from the thalamus to cortex; the centromedian nucleus is preferentially recruited in frontal seizures and the anterior nucleus in limbic seizures. Slow- and beta-band thalamocortical coupling builds through the late ictal phase and disengages at termination. Thalamic spectral and thalamocortical connectivity features classify seizure state, supporting their evaluation as candidate biomarkers for adaptive thalamic stimulation.

These two threads are brought together conceptually and architecturally in Alap, an action-conditioned world model of seizure dynamics. Alap connects learned EEG representations with mechanistic network measurements. Empirical validation against the thalamocortical signatures identified here remains future work. Together these contributions move toward a mechanistic, predictive account of pathological brain dynamics and a foundation for personalized neurostimulation.

The dissertation of Saarang Panchavati is approved.

Corey Arnold

Hiroki Nariai

William Hsu

Jonathan Kao

William Speier, Committee Chair

University of California, Los Angeles

2026

Dedicated to my friends and family, for their sunshine.

Special thanks to Becky and Snowy for their unconditional love.

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Selected Publications

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CHAPTER 1

Introduction

This dissertation develops general-purpose foundation models for EEG and characterizes the thalamocortical network dynamics that underlie focal seizures, using drug-resistant epilepsy as the primary application domain. These threads meet in a seizure world model that represents seizures as trajectories through a learned state space. The model forecasts those trajectories and evaluates stimulation effects to support future closed-loop intervention planning. I introduce Laya, the first LeJEPa-based EEG foundation model. I find that latent prediction learns more transferable brain-state representations than reconstruction-based approaches, and that thalamocortical networks exhibit structured, frequency-specific dynamics at seizure onset and termination that are relevant to adaptive neurostimulation.

1.1 Motivation

Epilepsy affects ~ 50 million people worldwide [1]. Epilepsy causes seizures which impair employment, driving, and independence, and carry elevated risk of sudden unexpected death [2]. Roughly one-third of patients are drug-resistant, meaning seizures persist despite medication [3, 4]. For these patients, surgical resection can sometimes be curative, but many are not candidates for surgery. One alternative is responsive neurostimulation (RNS), a closed-loop system that detects ictal activity at a cortical focus and delivers stimulation in response [5, 6]. RNS is effective but rarely curative: roughly 18–21% of patients achieve at least one year of seizure freedom on long-term follow-up [7]. Thalamic neurostimulation offers an

alternative target, particularly at the anterior nucleus (ANT) and the centromedian nucleus (CM), and has shown promise in clinical trials [8, 9]. Further progress in either modality depends on two open questions: how to track brain state in real time to support closed-loop intervention, and how seizures evolve through cortical and thalamic networks.

Scalp EEG is the primary tool for measuring brain state in epilepsy: standard of care for seizure classification and surgical planning, the substrate for continuous monitoring in epilepsy monitoring units, and a dominant modality for non-invasive brain-computer interfaces [10, 11]. Its accessibility has also produced the largest publicly available corpora of brain recordings, which makes it a natural target for large-scale self-supervised learning. Intracranial EEG (SEEG) complements scalp EEG by recording simultaneously from cortical foci and the thalamic nuclei targeted by stimulation therapies, tracking the evolution of seizure activity across cortical and subcortical sites in real time. Scalp EEG supports population-scale questions about brain state; SEEG supports patient-specific questions about seizure network dynamics.

Both modalities have their own challenges. EEG analysis is challenging due to low signal-to-noise ratio and significant inter-subject variability, which hinder generalization and limit the discovery of robust biomarkers. Supervised deep learning approaches have achieved strong performance on task-specific EEG datasets but still fail to generalize to new subjects or recording setups [12]. Addressing this gap requires developing self-supervised foundation models that can learn general representations of brain state from unlabeled EEG data [13]. Existing approaches have focused on raw signal reconstruction as the pretraining objective; while they achieve reasonable benchmark performance, they may not be capturing useful, interpretable brain-state structure [12, 13], and to date have yet to reveal new insights into the brain. No prior work has systematically compared reconstruction-based and latent-prediction-based pretraining for EEG at scale. On the SEEG side, network neuroscience has produced detailed mechanistic accounts of thalamocortical connectivity at seizure onset and termination, but these analyses remain patient-specific and lack predictive power [14].

These two threads (learning representations of brain state from EEG and characterizing thalamocortical network dynamics from SEEG) have proceeded largely independently. Neither alone provides what a complete understanding of the pathological brain requires.

Together, these lines of work motivate Alap. Learned representations define the state space, and action-conditioned dynamics model how that state changes under stimulation.

1.2 Contributions

The main contributions of this dissertation fall into three threads:

1. Scalable self-supervised methods for EEG representation learning, from task-specific pretraining to general-purpose latent prediction.
 - a. A pretrained transformer-CNN for seizure detection from wearable behind-the-ear EEG, showing that transfer learning improves performance in low-data settings.
 - b. Mentality, a Mamba-based EEG foundation model demonstrating reconstruction-based self-supervised pretraining for long-context seizure detection.
 - c. Laya, a latent-prediction approach to EEG representation learning, showing that predicting in latent space captures brain-state structure more effectively than reconstruction.
2. Characterization of thalamocortical network dynamics across focal seizures using intracranial EEG.
 - a. Identification of thalamocortical connectivity patterns at ictal onset involving the anterior and centromedian thalamic nuclei.
 - b. A frequency-specific map of directed connectivity across seizure evolution and termination.

3. A seizure world model for forecasting seizure dynamics and evaluating stimulation effects.
 - a. A seizure world model extending Laya with a JEPA-based dynamics predictor that learns seizure-state trajectories from SEEG.
 - b. Evaluation showing that simulations with and without stimulation track held-out recordings.
 - c. A counterfactual ictal-shift measure that predicts whether stimulation induces a seizure and outperforms baselines using the same pre-stimulation recording.

1.3 Outline of the Dissertation

The remaining chapters of this dissertation are organized as follows:

Chapter 2 reviews background material on epilepsy and drug-resistant epilepsy, EEG and SEEG as measurements of brain state, thalamocortical networks, connectivity measures for seizure networks, and self-supervised learning for EEG.

Chapter 3 presents the first step toward learned EEG representations: a pretrained transformer-CNN for seizure detection from wearable behind-the-ear EEG. This chapter establishes that transformer architectures can extract seizure-relevant features from consumer-grade EEG, and motivates the shift to self-supervised pretraining by exposing the generalization gap of supervised, task-specific training.

Chapter 4 introduces Mentality, a Mamba-based EEG foundation model that addresses the long-context temporal structure of neural recordings through reconstruction-based self-supervised pretraining on the Temple University Hospital EEG Seizure Corpus.

Chapter 5 introduces Laya, a latent-prediction approach to EEG representation learning. Building on the limitations of reconstruction-based pretraining, Laya predicts in latent space rather than signal space, and demonstrates more transferable representations of brain state across downstream tasks.

Chapter 6 shifts from learned representations to mechanistic network analysis, characterizing thalamocortical connectivity at ictal onset using SEEG. This chapter identifies early recruitment patterns involving the anterior and centromedian thalamic nuclei and establishes frequency-specific signatures of thalamocortical coupling at seizure onset.

Chapter 7 extends this analysis across the full ictal trajectory, mapping frequency-specific directed connectivity from onset through termination. This chapter characterizes how thalamocortical networks disengage at seizure termination and identifies connectivity patterns relevant to closed-loop neuromodulation.

Chapter 8 synthesizes both threads of the dissertation in Alap, a latent dynamics model that predicts seizure-state trajectories under stimulation. Counterfactual rollouts predict whether a stimulation induces a seizure and provide a foundation for future closed-loop neurostimulation planning.

Chapter 9 summarizes the contributions of the dissertation, discusses limitations, and outlines directions for future work.

CHAPTER 2

Background

2.1 EEG and SEEG as Windows into Brain State

Electroencephalography (EEG) records electrical potentials generated by synchronized post-synaptic currents across populations of cortical neurons [15, 16]. Measured at the scalp via an array of electrodes, EEG offers temporal resolution on the order of milliseconds, making it uniquely suited to tracking the rapid dynamics of neural oscillations, seizure onset, and state transitions. This combination of temporal resolution and clinical accessibility (EEG is noninvasive, relatively inexpensive, and widely available) has made it the primary tool for seizure monitoring in both research and clinical settings [17]. Beyond epilepsy, EEG is the dominant modality for brain-computer interfaces (BCIs) — systems that decode neural signals to enable communication or device control for people with motor impairments [18]. The same properties that make EEG useful for seizure detection — high temporal resolution and wearability — make it attractive for real-time decoding of motor intent, imagined speech, and other cognitive states.

Despite these advantages, scalp EEG has limitations. The signal recorded at any electrode reflects a weighted superposition of activity from many cortical sources, attenuated and smeared by volume conduction through the brain, the skull and everything in between. Deep structures, including mesial temporal lobe, insula, and subcortical nuclei, contribute negligibly to scalp recordings [15, 17]. Muscular activity, eye movements, cardiac signals, and environmental interference further degrade signal quality. The resulting recordings are

noisy, spatially ambiguous, and exhibit substantial patient-to-patient variability in electrode impedance, scalp anatomy, and underlying neural dynamics. A useful analogy is to imagine trying to listen to a conversation inside a sports stadium from the outside: perhaps one might be able to understand which parts of the stadium are louder than others, or which parts are celebrating a goal, but picking out a conversation is impossible. Further, interpreting long EEG recordings requires expert neurologists, and even in carefully studied settings (such as the ICU), inter-rater agreement on rhythmic and periodic patterns is only moderate [19].

Stereoelectroencephalography (SEEG) addresses some of these limitations by placing recording contacts directly within brain tissue via stereotactically implanted depth electrodes [20]. SEEG is used clinically in the presurgical evaluation of patients with drug-resistant focal epilepsy whose seizure onset zone cannot be adequately characterized by noninvasive means. Electrodes sample activity from dozens to hundreds of cortical and subcortical sites simultaneously, offering high spatial resolution, high signal-to-noise ratio, and direct access to structures including the hippocampus, amygdala, insula, and thalamus. Because SEEG is recorded continuously over days to weeks during a patient’s typical seizure period, it captures a rich sample of both interictal and ictal dynamics. Beyond clinical evaluation, SEEG has become a valuable tool for human neuroscience research more broadly: the rare access it provides to deep structures has been used to study memory, language, emotion, and sensorimotor processing in ways that are simply not possible with noninvasive recordings [21]. Both EEG and SEEG are best understood not as static diagnostic tests, but as ongoing measurements of an evolving brain state — a framing that motivates the modeling approaches developed throughout this dissertation.

2.2 Epilepsy and Drug-Resistant Epilepsy

Epilepsy is one of the most common serious neurological disorders, affecting approximately 50 million people worldwide [1]. It is defined by recurrent, unprovoked seizures — transient

episodes of abnormal, hypersynchronous neuronal activity that disrupt normal brain function [22]. Seizures are broadly classified as focal, arising from a localized cortical network, or generalized, engaging bilateral networks from the outset. Focal seizures may remain confined to their site of origin or may secondarily generalize, and they range widely in their clinical manifestation depending on the cortical regions involved. This heterogeneity — across patients, across seizure types, and even within a single patient’s seizure history — makes epilepsy a challenging target for both clinical management and computational modeling.

First-line epilepsy treatment is pharmacological, and the majority of patients achieve adequate seizure control with antiseizure medication [3]. However, approximately one-third of patients continue to experience seizures despite trials of multiple appropriate medications, meeting the clinical definition of drug-resistant epilepsy (DRE), also termed medically refractory epilepsy (MRE) [4]. For these patients, the impact on quality of life is severe: persistent seizures impair employment, driving, independence, and cognitive function, and carry elevated risk of sudden unexpected death in epilepsy (SUDEP) [2]. Identifying and characterizing the seizure onset zone (SOZ) — the cortical territory necessary and sufficient for seizure generation — is the central goal of presurgical evaluation, because surgical resection or ablation of the SOZ can be curative in carefully selected patients [23].

Not all patients with DRE are surgical candidates. In some cases the SOZ overlaps with eloquent cortex; in others, seizures arise from multiple foci or from networks that cannot be cleanly resected. For this population, neuromodulation offers an alternative treatment strategy. Responsive neurostimulation (RNS) delivers closed-loop electrical stimulation triggered by detected ictal activity, and received FDA approval based on a pivotal trial [5]. Deep brain stimulation (DBS) applies continuous or scheduled open-loop stimulation to subcortical targets, most commonly the anterior nucleus of the thalamus (AN) and the centromedian nucleus (CM) [24, 9]. AN DBS received regulatory approval based on the SANTE trial [24, 8]; CM stimulation is supported by more recent controlled evidence in Lennox-Gastaut syndrome [25] but has not received the same broad regulatory indication. Across these

therapies, response is variable and the mechanisms of action remain incompletely understood. Understanding thalamocortical network dynamics during seizures, as studied in the later chapters of this dissertation, is directly relevant to improving and individualizing these therapies.

The thalamus is a paired subcortical structure that serves as the primary relay and integration hub between subcortical inputs and the cortex [16, 26]. Rather than a passive relay, the thalamus actively participates in shaping cortical dynamics through dense, reciprocal thalamocortical loops: cortical regions project back to the same thalamic nuclei that drive them, creating circuits capable of sustaining and modulating oscillatory activity [26]. Different thalamic nuclei have distinct cortical targets and functional roles. The anterior nucleus (AN) connects primarily to limbic and cingulate regions and is thought to play a role in memory and spatial processing; the centromedian nucleus (CM) projects broadly to frontal and motor cortex and is implicated in arousal and attentional gating [27, 26]. Both are clinically exploited as stimulation targets in drug-resistant epilepsy. Because thalamocortical loops can both generate and propagate rhythmic activity, the thalamus occupies a central position in theories of seizure dynamics — it is not merely a bystander but a participant whose connectivity patterns shape how ictal activity spreads and terminates.

2.3 EEG Signal Analysis

Neural activity captured by EEG spans a wide range of oscillatory frequencies, each associated with different behavioral states, cognitive processes, and pathological conditions. Conventional frequency bands include delta (<4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz), low gamma (30–70 Hz), and high-frequency oscillations (HFOs) above 80 Hz [15, 17].

Decomposing EEG into its frequency components is useful because different rhythms reflect distinct neural computations and circuit mechanisms. Alpha oscillations, for instance,

are prominent during wakeful rest and are suppressed by visual or cognitive engagement; delta power increases during slow-wave sleep; theta rhythms are associated with memory encoding and spatial navigation [15, 17]. This frequency specificity means that the power spectrum — or its time-resolved analog, the spectrogram — serves as a compact summary of brain state. Clinically, EEG spectral analysis is used for sleep staging, anesthesia monitoring, and seizure detection, among other applications [17].

Beyond power, the phase relationships between signals at specific frequencies carry information about how brain regions coordinate. Because different frequency bands can reflect different underlying network states, connectivity analyses are typically performed in a frequency-resolved manner rather than on broadband signals. This frequency-domain perspective runs throughout the dissertation: the signal-processing methods in the connectivity chapters characterize inter-regional coupling at specific frequencies, while the machine-learning chapters implicitly leverage spectral structure through the temporal patterns that pretrained models learn to represent.

2.4 Connectivity Measures for Seizure Networks

Characterizing how brain regions interact during seizures requires measures that capture both the frequency content and the directionality of inter-regional coupling. Several complementary connectivity measures are used throughout this dissertation, each with distinct assumptions and sensitivities.

Coherence is an undirected, frequency-specific measure of linear coupling between two signals[28]. Defined as the squared magnitude of the normalized cross-spectrum, coherence ranges from 0 (no coupling) to 1 (perfect linear phase relationship at a given frequency). It is intuitive and widely used, but shares a key vulnerability with many EEG connectivity measures: it is sensitive to volume conduction, in which a single neural source projects to multiple electrodes, producing apparent coherence that reflects shared anatomy rather than

true network interaction.

Imaginary coherence was introduced to address this problem[29]. By discarding the real part of the cross-spectrum and retaining only the imaginary component, it eliminates contributions from zero-lag coupling — the signature of volume conduction, which cannot produce a phase lag. The imaginary coherence is therefore insensitive to instantaneous common sources and provides a more conservative, spatially specific estimate of true inter-regional coupling. Its cost is reduced sensitivity: genuinely coupled regions that happen to interact at very small phase lags may be missed.

Spectral Granger causality extends the coherence framework to directed interactions [30]. Based on the principle that a cause should improve prediction of its effect, Granger causality in the spectral domain asks whether the past of signal X reduces the prediction error for signal Y at a given frequency, over and above what Y 's own past provides. This yields an asymmetric, frequency-resolved measure of directed influence that can distinguish whether, for example, thalamic activity drives cortical dynamics or vice versa during a seizure. Together, these three measures provide a toolkit for characterizing undirected coupling, artifact-robust coupling, and directed influence within seizure networks.

2.5 Machine Learning for EEG

The scale and complexity of clinical EEG data create both a need and an opportunity for machine learning. Continuous EEG monitoring generates gigabytes of data per patient; SEEG implantations can span weeks of recordings across dozens of channels. Manual review by expert neurologists is time-consuming, variable, and impractical at scale [19]. Automated seizure detection, artifact rejection, sleep staging, and BCI decoding have therefore been active research areas for decades, evolving from rule-based systems to modern deep-learning approaches [31, 32].

Early automated EEG analysis relied on hand-engineered features derived from domain

knowledge: spectral power in specific frequency bands, line-length (a measure of signal amplitude and rate of change), wavelet decompositions, and statistical moments [31]. These features were fed to classical classifiers such as support vector machines, LDA, and random forests. While effective for constrained settings, hand-engineered pipelines require significant expert effort to design, are brittle to recording condition changes, and may miss complex multi-channel patterns that are not anticipated in advance.

Deep learning methods, particularly convolutional and recurrent neural networks, replaced much of the feature engineering with learned representations [32, 33]. A *representation* is the internal activation pattern that a neural network assigns to an input — a vector of numbers in a high-dimensional space that encodes the input in a compressed, abstract form. Good representations capture structure that is relevant to the task (for example, whether a segment of EEG contains a seizure) while discarding irrelevant variation (for example, differences in electrode impedance or patient-specific baseline amplitude). Rather than specifying this structure by hand, deep networks learn it from data by optimizing a task objective end-to-end. These models can discover hierarchical temporal and spectral structure directly from raw or lightly preprocessed EEG, and have achieved strong performance on benchmark seizure detection tasks. However, EEG poses several challenges that limit the naive application of methods developed for other domains. Signal-to-noise ratios are low and artifacts are diverse, including muscle contamination, loss of electrode contact, and shifting of electrodes. Electrode configurations differ across centers and recording systems. Most critically, labeled EEG data is scarce: clinical annotations are expensive to obtain, subject to inter-rater disagreement, and rarely standardized across institutions. These factors drive interest in self-supervised and transfer-learning approaches that can leverage unlabeled EEG at scale.

2.6 Foundation Models and Self-Supervised Learning

Foundation models are large neural networks pretrained on broad, diverse datasets and subsequently adapted to downstream tasks with modest amounts of labeled data [34]. Pioneered in natural language processing, where models such as BERT and GPT demonstrated that large-scale pretraining on unlabeled text yields powerful general-purpose representations [35, 36], the foundation model paradigm has since expanded to computer vision, speech, and biomedical time series [34]. The key insight is that pretraining on large unlabeled corpora encourages the model to learn rich, transferable features of the data distribution, reducing the dependence on large corpora of task-specific labeled examples for fine-tuning.

The *transformer* architecture underlies most modern foundation models [37]. Its core mechanism is *self-attention*: given a sequence of input tokens, the model computes for each token a weighted average of all other tokens, where the weights are learned and reflect the relevance of each position to the current one. Self-attention allows the model to capture dependencies across arbitrary distances in the sequence without the locality bias of convolutional networks or the sequential bottleneck of recurrent networks. In practice, self-attention is applied in parallel across multiple *heads* — each head learns a different attention pattern — and the outputs are combined, giving the model flexibility to simultaneously represent different types of relationships within the input. Transformers are therefore well suited to EEG, where relevant structure spans multiple timescales and channels simultaneously.

Self-supervised learning (SSL) provides the mechanism for pretraining transformers without manual annotation. Rather than relying on labeled examples, SSL defines a pretext task whose supervision signal comes from the structure of the data itself. The model is trained on this task at scale, and the learned representations are then transferred to downstream tasks with relatively little labeled data. For sequential data, the most widely used SSL strategy is *masked prediction*: segments of the input are masked, and the model is trained to reconstruct or predict the missing content from the surrounding context — analogous to the “fill in the blank” intuition behind BERT [35]. Applied to EEG, this encourages the model

to internalize temporal dependencies and spectral patterns across channels. Several recent EEG foundation models adopt this approach, pretraining on large multi-center datasets and demonstrating improved performance on seizure detection, pathology classification, and brain-computer interface tasks [38, 39].

Reconstruction-based pretraining has a structural limitation, however. When the target is the raw input signal, the model is rewarded for accurately recovering the exact waveform, including high-variance, low-information components such as artifacts and electrode noise. This can cause the model to allocate representational capacity toward signal details that are not semantically meaningful, motivating alternatives that operate in representation space rather than signal space. One such family of approaches, joint-embedding predictive architectures (JEPA), instead predicts masked content in a learned representation space, so that the objective rewards capturing the abstract structure of the signal rather than its exact waveform [40]. Because the prediction target is itself a learned embedding, the model can suppress noise and artifact contributions that reconstruction is forced to model, at the cost of introducing a target that evolves jointly with the encoder and must be stabilized during training.

CHAPTER 3

Pretrained Transformers for Seizure Detection

The background established why learned EEG representations are attractive for clinical neuroscience: hand-designed biomarkers are brittle, labeling is expensive, and the signal is high-dimensional and heterogeneous. This chapter presents the first step toward learned representations in this dissertation: a pretrained transformer-CNN for automated seizure detection from wearable behind-the-ear EEG, developed for the 2023 ICASSP Seizure Detection Challenge. While task-specific and supervised, this work establishes that transformer architectures can extract seizure-relevant features from consumer-grade EEG. The generalization gap it reveals motivates the self-supervised pretraining strategies developed in the chapters that follow.

3.1 Introduction

Epilepsy is the second most common neurological disorder behind stroke, impacting nearly 60 million patients worldwide[1]. Epilepsy is characterized by abnormal discharges of electrical activity in the brain due to genetics, environment, injury, and pathophysiology. Seizures can cause involuntary muscle contractions, altered consciousness, loss of consciousness, and can lead to suffocation, injury, or even death.

Clinicians use electroencephalography (EEG) to detect, diagnose, and treat epilepsy. However, EEG requires specialized equipment and is not often accessible outside of a clinical context. Advances in wireless communication, computing power, and miniaturization of

electronic devices have allowed for the development of a wearable behind-the-ear EEG device (bhe-EEG) [41]. This device was developed to provide patients the freedom and flexibility to monitor neural activity outside of a hospital or lab environment, without the need to rely on bulky EEG systems.

Manual detection of seizures from EEG recordings remains time-consuming and requires examination by a trained physician. This process also suffers from a lack of inter-scorer consistency [19]. These limitations pose a significant challenge in providing patients with a timely and accurate diagnosis that is essential to initiate antiepileptic drug therapies or surgeries. Automated, reader-invariant methods are required to improve the accuracy and speed of seizure diagnosis. Machine learning (ML) is a promising approach to aid in the development of a computer-assisted automatic seizure detection method. Previous ML studies have shown high accuracy and sensitivity in identifying and diagnosing seizures from EEG recordings [42].

In this work, we developed a transformer-based deep neural network for the 2023 ICASSP Signals and Processing Seizure Detection Challenge to augment the ability of the bhe-EEG system to detect seizures. The challenge consists of two tasks: (1) to develop an ML model for detecting seizures in the wearable bhe-EEG data in conjunction with annotated EEG data and to apply a data manipulation technique to optimize the performance (robustness and generalizability) of a provided model for wearable seizure detection.

3.2 Methods

3.2.1 Data

The development set (SeizeIT1[43]) provided by the organizers includes vEEG (scalp EEG with video monitoring), bhe-EEG, and ECG (electrocardiogram) data. Seizures were annotated by a trained clinician using gold-standard techniques on vEEG. Data was originally recorded from 82 patients, 54 of whom wore bhe-EEG devices. Of the 54 patients who wore a

bhe-EEG device, 42 patients had a confirmed seizure. The validation datasets (SeizeIT2[44]) provided by the organizers include bhe-EEG and ECG data from an international multicenter dataset that was recorded from more than 350 patients suffering from epilepsy. For the challenge, the bhe-EEG recordings from patients diagnosed with focal seizures recorded at UZ Leuven were used for validation.

We also used a subset of the Temple University Hospital (TUH) Seizure Corpus [45] to pretrain the seizure detection model. The TUH evaluation dataset consists of both background and 469 seizure events across 43 patients. In contrast to the main dataset, the TUH dataset has full 10-20 scalp EEG recordings. To ensure robust pretraining, and avoid overfitting to the TUH dataset, we randomly select channels pairwise to match the two-channel configuration of the challenge data. We also filter and resample the data to 200 Hz, 2-second trials. Any trials that contain partial seizure were not used in this analysis.

3.2.2 Seizure Detection

We employed a mixed Transformer and Convolutional Neural Network (CNN) architecture[37]. The model consisted of several transformer blocks followed by average pooling and a few fully connected layers before a final classification softmax fully connected layer. Each transformer block consisted of a normalization layer, a multi-headed attention layer, and a feed-forward network with a residual connection. The output of the transformer blocks was then passed through a 1D convolutional layer that learned higher-level features from the outputs of the multi-headed attention layer. In our implementation, we used eight self-attention heads and two dense fully connected layers. We also used dropout to reduce overfitting.

To improve the robustness of the model and ameliorate issues with a smaller dataset, we first pretrained the model on the TUH EEG Seizure Corpus. The model was then fine-tuned on the challenge dataset and evaluated on a hold-out test set. During training, we generated a dataset that contains a 5:1 imbalance of non-seizure to seizure samples. We also used class

weighting to increase the penalty for missed seizures. We also employed an early stopping scheme to prevent overfitting to the training data.

3.2.3 Data-centric seizure detection

We also aimed to improve the ChronoNet [33] which is an RNN-based model for abnormal EEG identification. The ChronoNet model uses mixed CNN and RNN architecture to extract meaningful features from EEG timeseries. To improve the baseline performance of the ChronoNet model we focused on ways to boost the signal-to-noise ratio of the EEG data while preserving the temporal structure, thereby facilitating the seizure classification task for the model. Studies have shown that gamma power in the frequency range of 30-80Hz increases before and after a seizure event [46]. We hypothesized that enhancing the gamma signal-to-noise ratio would improve classification accuracy. We accomplished this by applying a high pass filter of order 4 with a cutoff frequency of 30 Hz to the data. We also performed a randomized grid-search across various training parameters to optimize the training of the ChronoNet model. We identified an optimal training set class imbalance of 10:1 to overrepresent the negative class, a class weighting factor of 50, and a learning rate of 0.001. We also augmented the data by using a quarter-second stride to increase the number of seizure events artificially.

3.3 Results

Quantification and evaluation of seizure detection models is difficult due to the sparsity of seizure events. For this reason, we evaluate the models using Epoch False Alarm rate per hour (FAH) and Any-Overlap Sensitivity[47]. The final score is calculated by subtracting 40% of the FAH from the sensitivity. We evaluate results on a hold-out test set (from SeizeT1 or SeizeT2), as well as 3 patients from the competition validation dataset. The total points, FAH, and Sensitivity score are given in Table 1 for both our hold-out sets and

Task	Dataset	Sensitivity	FAH	Final Score
1	Hold Out Test Set	100%	1.78	99.29
1	Validation Subset	45.0%	23.64	35.54
2	Hold Out Test Set	100%	17.47	93.01
2	Validation Subset	31.57%	42.877	14.42
Baseline	Validation Set	58.22%	117.12	11.37

Table 3.1: Summary of Results.

the challenge validation subset. The metrics for the baseline model[48] are evaluated on the entire competition validation dataset. While the transformer model performed nearly perfectly on the hold-out test set, the score dropped (35.54) on the external validation subset. In task 2, our approach demonstrates a slight increase over the baseline model. By comparing the results of Task 1 and Task 2, it is clear that modifying the model could provide greater improvements in seizure detection performance, as opposed to solely enhancing preprocessing techniques. Figure 1 shows the ground truth (T) against the predicted condition (P) given the EEG signals.

3.4 Discussion & Conclusion

As part of the IEEE ICASSP Seizure Detection Challenge, we present our methods for improving seizure detection using behind-the-ear EEG and a data-centric approach to augment the performance of an existing model. We demonstrate the efficacy of a pre-trained transformer model on bhe-EEG for seizure classification with high sensitivity and low false alarm rate. We also note that the primary model was trained on regular pairwise scalp EEG, but still generalizes well to a novel data source. This may indicate the ability and expressiveness of transformer-based models for EEG analysis and seizure detection. In conjunction with optimizing training routine hyperparameters, we also demonstrate that a simple frequency filter to isolate relevant frequencies significantly improves the performance of the ChronoNet model on the seizure detection task.

CHAPTER 4

Mentality: A Mamba-based Approach towards Foundation Models for EEG

The preceding chapter demonstrated that transformers can learn seizure-relevant EEG features, but the sharp drop from held-out to external validation exposed the limits of supervised, single-task training: the model learns representations tied to the training distribution rather than to the underlying structure of brain activity. The natural next step is self-supervised pretraining, learning from large quantities of unlabeled EEG without requiring seizure annotations. This chapter introduces Mentality, a Mamba-based EEG foundation model that addresses this through reconstruction-based pretraining, while also tackling the long-context temporal structure of neural recordings that standard transformers handle poorly.

4.1 Introduction

Scalp EEG is noisy and exhibits substantial inter-patient variability, and current clinical practice still relies on time-consuming manual review (Section 2.1). Deep learning and, more recently, foundation models offer a route toward automated EEG analysis at scale (Section 2.6), but work developing such models in a clinical context remains limited.

Recent advances in sequence modeling, specifically with selective state space modeling offer a unique opportunity for novel approaches to foundation models applied to biomedical data such as EEG. In particular, Mamba [49] has emerged as a powerful selective state space model with comparable performance to transformer-based approaches on language modeling,

genomics, and audio.

In this work, we aim to build a foundation model for EEG, first by relaxing the problem to a more focused context. We train a Mamba-based model on a large public dataset that contains both seizure and non-seizure EEG recordings, first on a self-supervised reconstruction task, and then a downstream seizure detection task.

4.2 Methods

4.2.1 Data

We train and test our data on the Temple University Hospital EEG Seizure Corpus (TUSZ) v2.0.1 [50], which is one of the largest annotated seizure corpora to date. The training data subset contains 579 patients, with 2,138 seizure events. The testing subset contains a disjoint set of 43 patients, with 469 seizure events. We included 19 channels from the standard 10-20 EEG montage, all referenced to a reference electrode. All signals are resampled to 200 Hz, and we remove 60 and 120 Hz interference via a notch filter. Data are segmented into 10s non-overlapping windows. Windows are classified as “seizure” or “not seizure” if there is a seizure event in a window.

4.2.2 Model Architecture and Training

Mamba is a deep selective state space model proposed by Gu and Dao [49], capable of analyzing long-range dependencies in sequences. Mamba has been shown to outperform many state-of-the-art tasks in long-context modeling including audio and language. In this work we utilize Mamba “blocks”; which include a Mamba layer followed by layer normalization and a residual connection, which can be stacked together similarly to transformer blocks. In this work, we take inspiration from EEGNet [32], and SaShiMi [51] for a full encoder/decoder architecture with Mamba blocks. EEGNet is a lightweight CNN-based model for processing EEG data. SaShiMi is a U-Net [52] like architecture interspersed with S4 blocks (a precursor

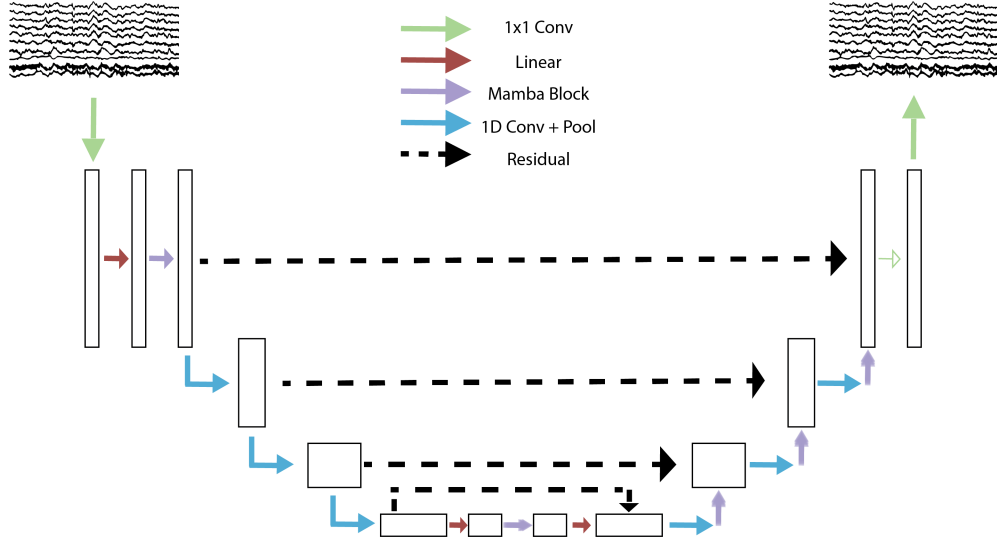


Figure 4.1: Proposed Model Architecture. Inspired by SaShiMi, U-Net, and EEGNet, the model learns a state space representation of frequency-based filters, before downsampling to a smaller representation. The model upsamples back to reconstruct the signal, learning state space representations at each level of sampling till a final output.

to Mamba), where downsampling and upsampling are done by reshaping rather than repeated convolution and pooling.

Our model begins with a 1D CNN layer of kernel size 100 (half the sampling rate of the signal) to learn “frequency-based” filters up to 50 Hz from each channel. Subsequently, a “channel mixing” linear layer is applied to try to learn the relationships between the channels. This is followed by several Mamba blocks to learn a state space representation of the data, emphasizing the temporal dynamics.

The output is then downsampled through the traditional U-Net block, composed of a double convolution and mean pooling. We then pass the downsampled input through another set of Mamba blocks, to obtain a downsampled hidden representation of the data. During reconstruction, this is then upsampled through repeated Mamba-transpose convolution - - double convolution blocks. Following the strategy of the U-Net, we concatenate the output of the corresponding downsampling layer to form residual connections with each upsampling layer output to preserve features. We also add a final convolutional layer initialized with

zeros to improve sparsity in the final output.

In the downstream task, the downsampled hidden representation is max-pooled along the temporal dimension and then passed through linear layers to obtain a classification probability.

To improve the reconstruction, we employ a combination of mean-squared-error (MSE) loss with a spectral loss, which computes the loss in the Fourier domain.

4.3 Results

4.3.1 Pretraining

Our best model achieves a MSE of 0.0063. Removing the spectral loss resulted in a four-fold increase in MSE (0.025). Figure 2 demonstrates an example of the reconstruction on an example in the test data.

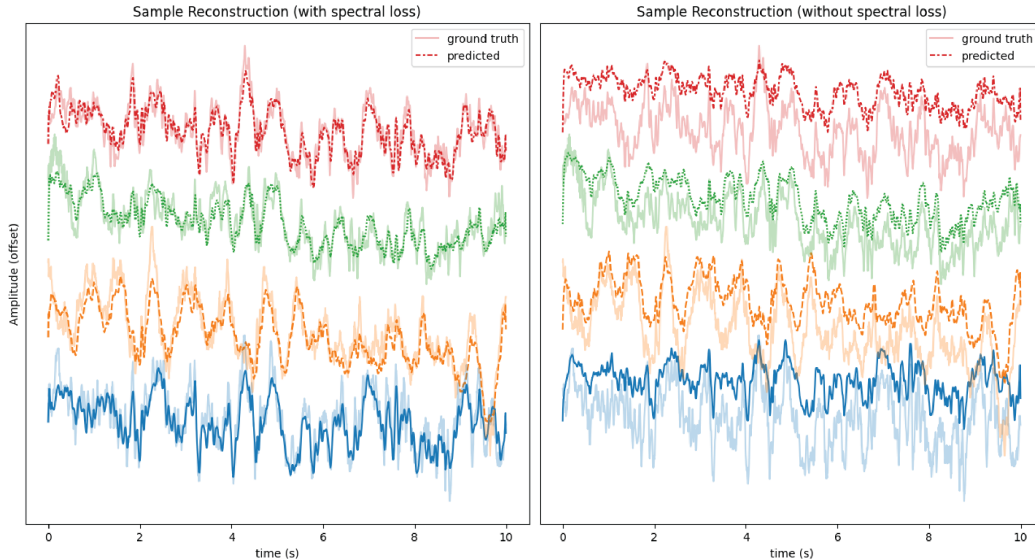


Figure 4.2: Example reconstruction of input sequence on a test sample. Predicted time series are dashed, while ground truth are solid lines. The model captures the general patterns in the time series very well but sometimes fails to completely capture higher frequency components of the signals. The model with spectral loss reconstructs the signal much better than that without.

4.3.2 Seizure Detection

We find that using a pretrained model followed by two linear layers, we can achieve a detection AUROC of 0.72. When we use a model trained from scratch, the detection AUROC drops to 0.64.

4.3.3 Model Interpretability

A limitation of Mamba blocks is that they do not have a way to analyze the interpretability of their representations. In this work, we rely on analyzing model weights and saliency maps for interpretability. To identify channel importance we compute channel-wise saliency based on particular inputs. Figure 3 demonstrates a manner of highlighting channel importance for a seizure sample. We can also look at the weights of the initial convolutional layer (similar to the EEGNet approach) to identify what types of patterns or frequencies are activated based on the input.

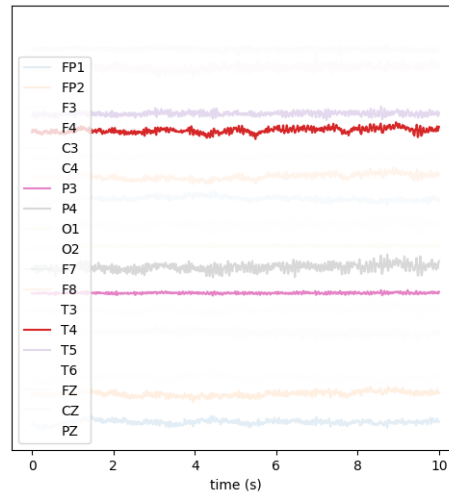


Figure 4.3: Sample seizure window with channel-wise saliency. Channel opacity is a function of its importance to the output. Here, channels T4 and P4 are highlighted as being particularly important to classify the sample as a seizure. We note that these channels exhibit the high-frequency signals characteristic of many seizures.

4.4 Discussion

This work presents a first step towards developing foundation models for EEG and neural data. Our preliminary results demonstrate the promise that Mamba-based models have for analyzing neural data. We find that the inclusion of a spectral loss significantly improves the performance of the pretrained model. We also find that pretraining boosts the downstream AUROC significantly, pointing to the importance of this self-supervised pretraining approach.

One continued drawback of most deep learning approaches to EEG is that while the temporal dynamics of the signal are captured well, the spatial relationships between channels are not meaningfully incorporated into the model. State space models like Mamba process each channel independently. In the approach presented here, we learn a “mixing” of the channels, but this does not necessarily capture the more rigid geometric and functional connections between channels. For example, future works will incorporate a graph-based approach to learning spatio-temporal dynamics at different time windows, similar to Tang et al. [53]. Graphs can be constructed both functionally (based on connectivity metrics such as coherence or Granger causality) and/or geometrically, based on spatial distance between electrodes. Exploring these representations will enable the model to extend to various EEG setups and geometries.

Another significant challenge in EEG analysis is the variability in channel configurations across subjects and datasets. Many previous studies address this issue by standardizing the number of channels or interpolating missing channels. These approaches are not geared towards using data from different applications, hardware, and institutions, which contain greater variability and valuable within-patient patterns. In lieu of this, we propose a masked training approach where channels are randomly excluded during model training. This approach will force the model to learn a robust representation based on the available channels. This approach to training along with a structured graph-based architecture can help enhance this model’s usefulness across different setups and in real-world settings such as wearable EEGs.

4.4.1 Future Directions

To expand this model’s applicability, we plan to extend the pretraining stage to a variety of neurological conditions beyond seizure detection. This will include datasets from larger EEG corpora such as the larger TUH EEG Corpus [54] and the UNM Predict+CT [55], which cover a range of disorders like Parkinson’s Disease, along with healthy control subjects. This will enhance the range of downstream tasks that this foundation model is capable of, as well as improve the model’s ability to learn neural signatures characteristic of these conditions.

In this approach, we do not explicitly use the learned state-space dynamics in our model (we just use the final hidden representation output of the Mamba blocks). Incorporating these dynamics more explicitly may offer further insights into the temporal dynamics of the EEG signals. These dynamics, combined with the graph approach could greatly improve the interpretability of this model. Clinicians may be able to better understand how channel interactions at a particular time point may contribute to a certain neurological phenomenon.

As an extension of detection and prediction, this approach may also be extended to help learn relationships between behavioral and neural data, similar to CEBRA [56], which learns a joint latent representation between neural data and behavioral data. Mamba’s ability to learn state space representations between sequences offers a similar opportunity to learn related dynamics, perhaps in an even more expressive manner. Broader future directions building on this work are discussed in Chapter 9.

4.4.2 Conclusions

The development of a foundation model for EEG data has several practical implications. Such a model would enable researchers and clinicians to more robustly elucidate information from noisy EEG data by adapting to various EEG configurations and formats. This work is an initial step towards that end. Expanding the training data to better cover a range of neurological conditions along with more advanced models will further enhance this ability to analyze neural activity. Such a model could make tangible differences in diagnosis and

developing treatments, making an impactful improvement to the understanding and care of neurological disorders.

Acknowledgments

The authors would like to acknowledge Dhruva Karkada and Ekaterina Redekop for their valuable insights in developing this work.

CHAPTER 5

Laya: A LeJEPa Approach to EEG via Latent Prediction over Reconstruction

Reconstruction-based pretraining optimizes the model to reproduce the observed signal. This is a useful self-supervised objective, but one that may overemphasize high-variance waveform details rather than the structure of the underlying brain states being measured. This chapter introduces Laya,¹ which replaces reconstruction with latent prediction: rather than predicting what the next EEG epoch looks like, the model predicts what the next brain state is in an abstract latent space. This shift in objective has substantial consequences for the quality of learned representations, and Laya demonstrates it at the scale of a large multi-dataset EEG benchmark.

5.1 Introduction

EEG analysis is challenged by low signal-to-noise ratio and substantial inter-subject variability, which limit the discovery of robust biomarkers and the generalization of supervised models across subjects or recording setups (see Section 2.1). Deep learning has emerged as an alternative to hand-crafted pipelines [11, 10], motivating large-scale self-supervised pretraining (Section 2.6) to learn EEG representations without requiring task-specific labels.

Recent years have seen growing interest in EEG foundation models — large neural networks pretrained on large EEG corpora to learn transferable representations across tasks and datasets [13].

¹In Hindustani classical music, *laya* refers to musical time, especially tempo and rhythm.

Models such as LaBraM [38], LUNA [57], CBraMod [58], and REVE [59] have demonstrated state-of-the-art capabilities in both clinical applications and BCI tasks like motor imagery decoding. By leveraging large, cross-subject EEG corpora, these approaches highlight the potential of EEG foundation models to learn reusable neural representations that generalize across both long-duration, state-level clinical tasks, and short-horizon, event-driven BCI tasks.

Despite these successes, however, recent benchmarking studies such as EEG-Bench [60] indicate that EEG foundation models do not consistently outperform simpler baselines. Reported gains are often modest and highly task-dependent. Frozen linear probing often yields near-chance performance, indicating weak intrinsic representations that require extensive adaptation and finetuning to be competitive. This raises questions about the usefulness of these models in the real world, particularly given the substantial computational cost of pretraining [12, 60, 61].

Several recurring limitations help explain these mixed results. Generalization across tasks and datasets remains limited, with pretrained representations often failing to transfer beyond the pretraining distribution. Moreover, scaling laws in EEG are not yet well-established; larger models do not consistently yield better transfer performance, especially under frozen evaluation protocols [12, 13]. Almost all existing approaches rely on reconstruction-based pretraining objectives applied directly to raw EEG signals. Because EEG is inherently noisy and dominated by non-task-relevant variability, optimizing for signal-space reconstruction may encourage models to learn nuisance variables rather than semantic structure [62], resulting in weak linear-probe performance and heavy reliance on downstream fine-tuning.

These observations suggest that while EEG foundation models are a promising direction, current approaches leave significant room for improvement. In particular, there is a need for representation learning objectives that better align with downstream discriminative tasks, improve data efficiency, and generalize across heterogeneous EEG domains without extensive task-specific adaptation.

5.1.1 JEPA and LeJEPA

Joint Embedding Predictive Architectures (JEPAs) [63] learn representations by predicting latent embeddings rather than reconstructing raw inputs, encouraging semantically rich features while discarding unpredictable variation [64, 65, 62]. A key challenge is preventing representation collapse; LeJEPA [66] addresses this through explicit geometric regularization (SIGReg), removing reliance on momentum-updated target encoders.

This is particularly relevant for EEG, where high-variance artifacts often dominate the signal. We hypothesize that latent prediction objectives naturally filter irrelevant noise, yielding better EEG representations. While emerging works have explored JEPA-style objectives for EEG [67, 68], they rely on standard heuristics to prevent collapse and have not demonstrated broad generalization at foundation model scale. We adapt LeJEPA to a masked temporal prediction setting, eliminating asymmetric encoders and learning by predicting temporally masked representations [69, 70]. Our results suggest that latent prediction objectives are a promising direction for large-scale EEG representation learning, with the clearest benefits in noisy clinical tasks where meaningful state-dependent structure can be subtle.

5.1.2 Our Contributions

- We introduce **Laya**, the first LeJEPA-based EEG foundation model, designed for clinically realistic settings with scarce labels, heterogeneous montages, and substantial noise.
- We show that **Laya** learns semantically organized representations: embeddings track seizure onset and distinguish imagined left- from right-hand movements as spatially distinct structures, in both cases more clearly than reconstruction-based baselines—indicating that latent prediction induces brain-state-aligned organization across clinical and BCI domains.

- We demonstrate that this representational structure transfers to noisy clinical EEG tasks: latent prediction achieves the strongest clinical mean accuracy under frozen linear probing.
- We show that **Laya** learns representations that are resilient to noise—maintaining performance at SNR levels where reconstruction-based models degrade substantially.
- We confirm via controlled MAE ablations that the pretraining objective — not architecture or data — is the primary driver of these clinical gains.
- We extend EEG-Bench with noise robustness evaluation, linear probing protocols, and additional baselines including LUNA, CBraMod, and REVE.

5.2 Related Works

5.2.1 JEPAs

Joint Embedding Predictive Architectures (JEPAs) learn by predicting latent representations rather than reconstructing pixels or raw inputs. I-JEPA and V-JEPA demonstrate this principle for images and video using masked latent prediction with target encoders [40, 69]. LeJEPA augments the latent-prediction objective with Sketched Isotropic Gaussian Regularization (SIGReg), removing reliance on momentum-updated EMA teachers while maintaining stable, collapse-free pretraining [66].

5.2.2 EEG Foundation Models

Recent EEG foundation models adapt masked modeling and transformer architectures to large-scale EEG pretraining. LaBraM tokenizes EEG patches for masked reconstruction, CBraMod separates spatial and temporal dependencies with criss-cross attention, REVE uses coordinate-based spatio-temporal encodings for flexible electrode layouts, and LUNA

compresses variable-channel EEG into learned latent queries [38, 58, 59, 57]. These models establish strong baselines for transfer, but rely primarily on reconstruction objectives; our work instead evaluates latent prediction as the central pretraining signal.

5.2.3 JEPA-inspired EEG Foundation models

Recent work has explored JEPA-style training at scale and across modalities, including spatial block masking over EEG channels, latent prediction over fMRI regions, and video-inspired spatiotemporal masking for EEG [68, 71, 67]. EEG-DINO instead uses hierarchical self-distillation rather than masking-based prediction, but is evaluated on a narrower downstream suite [72]. Laya differs by pairing a LeJEPA objective with topology-agnostic EEG modeling and evaluating frozen representations across a broader clinical and BCI benchmark.

5.3 Methods

5.3.1 LeJEPA

Joint-Embedding Predictive Architectures (JEPA) learn representations by predicting latent embeddings of masked or augmented views rather than reconstructing raw inputs. Formally, let x be an input split into a context x_C and a target x_T . Let $f_\theta : \mathcal{X} \rightarrow \mathbb{R}^d$ be an encoder and $g_\phi : \mathbb{R}^d \rightarrow \mathbb{R}^d$ a latent predictor. The JEPA objective minimizes:

$$\mathcal{L}_{\text{JEPA}} = \mathbb{E}_x \|g_\phi(f_\theta(x_C)) - f_\theta(x_T)\|_2^2. \quad (5.1)$$

A key challenge is preventing representation collapse; prior approaches address this with momentum-updated target encoders, which complicate optimization. LeJEPA [66] introduces *Sketched Isotropic Gaussian Regularization* (SIGReg), which stabilizes latent prediction by encouraging batch-level embeddings to be diverse and approximately isotropic, re-

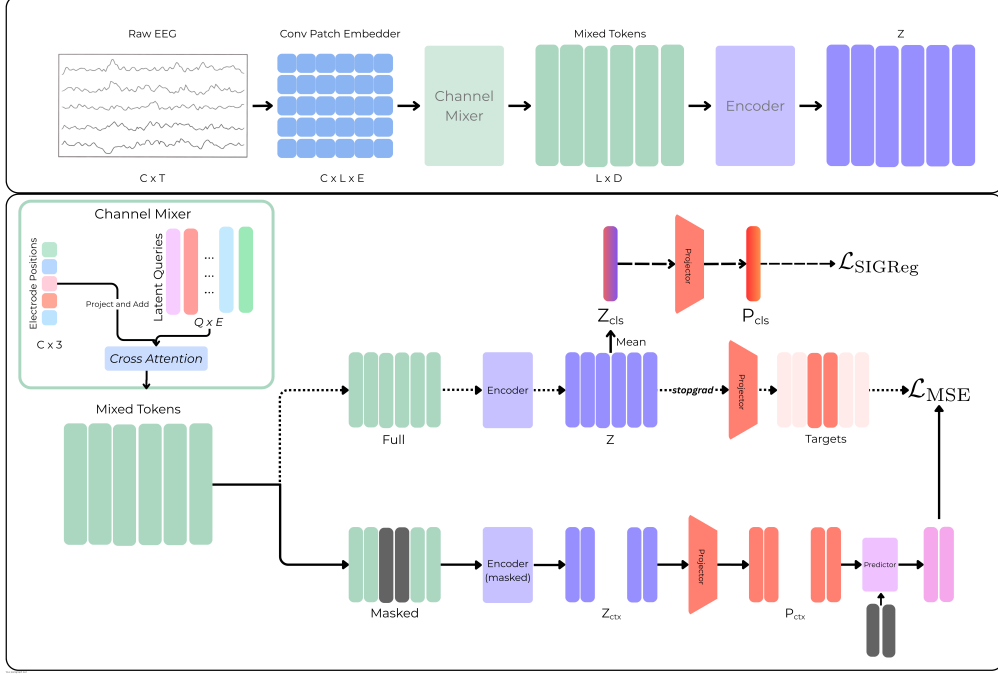


Figure 5.1: **Laya architecture overview.** Raw EEG is embedded into temporal patches, compressed across channels by a learned channel mixer, and encoded into latent brain-state representations. During pretraining, the model predicts masked latent targets from visible context while SIGReg regularizes the embedding geometry.

moving reliance on EMA teachers. The combined objective is:

$$\mathcal{L}_{\text{LeJEPa}} = \mathcal{L}_{\text{JEPa}} + \lambda \mathcal{L}_{\text{SIGReg}}, \quad (5.2)$$

where $\mathcal{L}_{\text{SIGReg}}$ operates directly on batches of latent representations to prevent collapse and enable stable representation learning that translates directly to downstream performance.

5.3.2 Laya

Pretraining Objective

We adopt two components from LeJEPa: the JEPa latent prediction objective (Eq. 1) and SIGReg for collapse prevention. We depart from the original formulation in two ways. First,

rather than using augmented views as context and target, we instantiate x_C and x_T as observed and masked temporal segments of the same EEG sequence—a masked prediction paradigm analogous to V-JEPA [69] and S-JEPA [68]. Second, we do not employ a cross-view invariance loss; SIGReg is applied solely as a geometric regularizer on the global embedding of the masked sequence. Given EEG input $\mathbf{x} \in \mathbb{R}^{B \times C \times T}$, we extract and embed non-overlapping temporal patches to obtain $\tilde{\mathbf{x}} \in \mathbb{R}^{B \times C \times N \times E}$, where N is the number of patches, and E is the latent dimension of the patch embedder. We then apply a learned channel mixer to produce a sequence $\mathbf{S} \in \mathbb{R}^{B \times N \times D}$ of latent brain states which we interpret as mixed-channel representations at each temporal position. We mask contiguous blocks of time and task the model with predicting these masked regions in latent space. The full pretraining step is provided in Appendix Section 5.6.1.

Patch Embedder

We use a 1D convolution to convert raw EEG time series $\mathbf{x} \in \mathbb{R}^{B \times C \times T}$ into patch-level embeddings $\tilde{\mathbf{x}} \in \mathbb{R}^{B \times C \times N \times E}$. A depthwise 1D convolution is applied independently to each channel, with kernel size and stride equal to the patch length P , producing non-overlapping temporal patches. Each convolutional kernel maps P contiguous time samples directly to an E -dimensional embedding. By treating channels independently at this stage, the patch embedder avoids imposing inductive biases tied to specific electrode montages.

Dynamic Channel Mixer

To aggregate information across EEG channels, we adopt the channel-mixing mechanism introduced in LUNA [57], which uses learned queries and cross-attention to compress multi-channel EEG into a compact latent representation. At each temporal position, learned query vectors attend across channels, enabling the model to summarize spatially distributed activity into a fixed-dimensional embedding. To make this operation spatially aware yet montage-agnostic, electrode coordinates are encoded and incorporated into the channel rep-

representations prior to attention, allowing the mixer to exploit spatial relationships without assuming a fixed electrode layout.

Given patch embeddings $\tilde{\mathbf{x}} \in \mathbb{R}^{B \times C \times N \times E}$ and electrode coordinates $\mathbf{E} \in \mathbb{R}^{C \times 3}$, we incorporate spatial information by encoding electrode coordinates with fixed Fourier features and adding the resulting embeddings to the channel representations. Learned query vectors then attend over these spatially augmented channel embeddings at each temporal patch, producing

$$\mathbf{A} \in \mathbb{R}^{B \times N \times N_q \times E},$$

where N_q is the number of queries. We flatten the final two dimensions of $\mathbf{A}$ and apply a linear projection to obtain a channel-mixed latent brain-state sequence

$$\mathbf{S} \in \mathbb{R}^{B \times N \times D}.$$

By explicitly encoding spatial information and using multiple learned query outputs per patch, the channel mixer produces a rich, montage-agnostic representation that decouples spatial aggregation from temporal modeling.

Query Specialization Loss. Following LUNA, we regularize the query–channel affinity induced by the channel mixer to encourage specialization across learned queries. Let $\mathbf{W} \in \mathbb{R}^{B \times N_q \times C}$ denote the query–channel affinity matrix obtained by averaging attention weights across heads. We penalize pairwise similarity between different query affinity vectors by minimizing the off-diagonal entries of $\mathbf{W}\mathbf{W}^T$. This loss discourages redundant queries while preserving soft spatial aggregation.

Pretraining

Hyperparameters and implementation details are provided in Appendix 5.6.

Masking Strategy. Consistent with previous EEG foundation model approaches, and other video modeling [38, 73], we employ a block masking strategy that masks contiguous spans of time rather than random patch masking. Block masking forces the model to bridge longer temporal gaps, learning structural dependencies rather than autocorrelation. We mask 60% of the sequence using randomly sampled blocks spanning 500ms to 1s.

Encoder. The encoder is a standard transformer encoder implemented using the `x-transformers` library. We use rotary positional embeddings (RoPE) [74] and do not introduce additional absolute positional embeddings to avoid overfitting to fixed temporal locations under masking.

The encoder is applied in two passes: first over the full sequence to produce embeddings $\mathbf{Z}$ and global summary $\mathbf{z}_{\text{cls}}$ (with *StopGrad* applied to $\mathbf{Z}$), then over the context-only sequence with target positions masked to produce context embeddings $\mathbf{Z}_{\text{ctx}}$.

Projector. Following [66], the projector is a 3-layer MLP with batch normalization that expands the representation dimension ($D_{\text{up}} \gg D$) before compressing them down to the projector dimension $D_{\text{proj}} < D$. The projector is applied to $\mathbf{Z}$, $\mathbf{z}_{\text{cls}}$, and $\mathbf{Z}_{\text{ctx}}$.

Predictor. Following MAE and V-JEPA design principles, the predictor is a lightweight Transformer encoder operating at dimension D_{proj} . Given the bottlenecked context embeddings $\mathbf{P}_{\text{ctx}}$, it predicts latent representations $\hat{\mathbf{T}}$ at masked temporal positions. Learnable mask tokens are inserted at masked positions before being passed to the predictor. As in the encoder, RoPE is used to encode relative temporal structure.

Objective. The full Laya training objective extends LeJEPA with the query specialization loss from the channel mixer:

$$\mathcal{L}_{\text{Laya}} = \mathcal{L}_{\text{LeJEPA}} + \gamma \mathcal{L}_{\text{query}}, \quad (5.3)$$

where $\mathcal{L}_{\text{LeJEPA}}$ minimizes MSE between predicted masked embeddings $\hat{\mathbf{T}}$ and stopped-gradient targets $\mathbf{T}$ at masked positions while applying SIGReg to $\mathbf{p}_{\text{cls}}$, and $\mathcal{L}_{\text{query}}$ encourages

specialization across channel mixer queries. In our experiments, $\gamma = 1$.

5.4 Experiments

Pretraining datasets. Laya is pretrained on a diverse corpus of EEG recordings drawn from multiple large-scale and task-specific sources: the Temple University Hospital EEG Corpus [75], NMT [76], **EEGDash** (a filtered aggregation of OpenNeuro EEG datasets), the Healthy Brain Network (HBN) [77], and several MOABB BCI datasets [78]. All datasets are converted into fixed-length chunks using a consistent preprocessing pipeline. After filtering and quality control, the final pretraining corpus contains 913,314 samples totaling 29,109 hours of EEG, spanning 20,940 subjects and 17 distinct channel topologies. This mixture spans a wide range of tasks, montages, and acquisition settings. To prevent leakage into downstream evaluation, we exclude datasets used in EEG-Bench evaluation and remove TUH subjects appearing in downstream validation or test sets; further details are provided in Appendix Section 5.8.

Implementation Details. Both variants use an effective sample batch size of 512, distributed across two NVIDIA L40S GPUs. Input sequences are generated by random sampling 16-second crops from the available 120-second recording segments. Comprehensive hyperparameters and optimization details are provided in Section 5.6. We present two variants of Laya: Laya-S, and Laya-B. Laya-S was trained on 10% (3K hours) of the total training dataset for 10K steps (sampled equally from all datasets in the mix). Laya-B was trained on all 30K hours for 20K steps.

5.4.1 Downstream Evaluation with EEG-Bench

Benchmark Framework and Baselines. We evaluate downstream performance using EEG-Bench [60], a standardized benchmarking framework spanning 14 diverse brain-computer interface (BCI) and clinical EEG tasks. We compare Laya against established

EEG foundation models: LaBraM [38], LUNA [57], CBraMod [58], and REVE [59]. For all baselines, we use publicly released pretrained checkpoints. Dataset details are provided in Section 5.9.1.

Fine-tuning protocols. We primarily assess representation quality under a linear probing protocol. The pretrained encoder parameters are frozen, and a task-specific linear classification head is trained on the embeddings. We focus on frozen linear probing because our goal is to evaluate the intrinsic quality of the pretrained representations while minimizing confounds from model-specific downstream architectures and hyperparameter tuning.

Metrics. We report Balanced Accuracy from linear probing as the primary task-level metric to account for the significant class imbalance common in clinical EEG datasets. For multi-label tasks, metrics are computed on flattened predictions across temporal segments.

5.4.2 Laya learns semantically organized representations

Before evaluating downstream accuracy, we first ask whether latent prediction changes the structure of the learned EEG representations. If **Laya** is learning clinically meaningful state information rather than reconstructing high-variance signal detail, its embeddings should vary coherently with changes in brain state.

To assess learned representations, we visualize patch embeddings from a seizure recording using PCA, following Oquab et al. [79]. We project patch embeddings to three principal components and map them to RGB channels, overlaying the result on the raw EEG (Figure 5.2).

Laya’s embeddings show clear temporal structure aligned with seizure onset and termination: at a state change, the colors shift distinctly. In contrast, LaBraM’s embeddings fluctuate throughout the recording without clear correspondence to the clinical event. This representational structure generalizes beyond seizures: Figure 5.2 (right) shows that **Laya** also produces distinct embeddings for imagined left- versus right-hand movements, with visually separable color regions across motor states. LaBraM shows no such structure in either

setting. This suggests **Laya** learns features organized around semantically meaningful brain states rather than surface-level signal statistics—a property that holds across both clinical and BCI domains. Further examples can be found in Appendix 5.10.3.

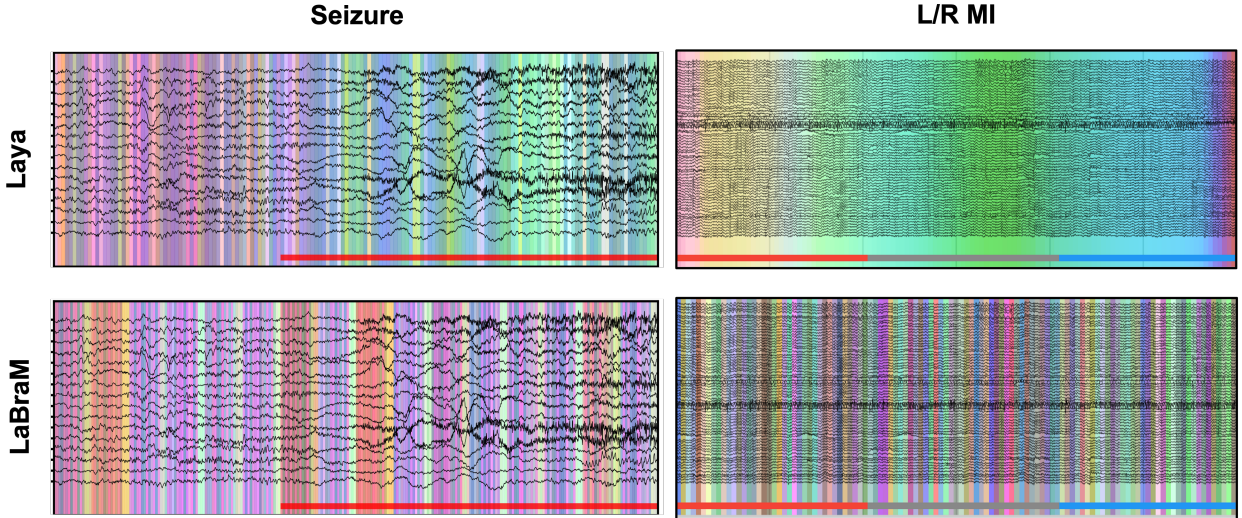


Figure 5.2: PCA visualization of patch embeddings (three principal components mapped to RGB) on a seizure recording (left) and an L/R motor imagery recording (right). Top row: **Laya-B**; bottom row: **LaBraM**. On the seizure recording, the red bar marks seizure onset. On the motor imagery recording, color bars indicate motor state: red = right hand, blue = left hand, grey = rest. **Laya-B** shows a clear representational shift at seizure onset and distinct spatial structure across motor states; **LaBraM** does not.

5.4.3 Downstream Results on EEG-Bench

We next evaluate whether this representational structure translates into downstream transfer under frozen linear probing, particularly on noisy clinical EEG tasks where relevant state-dependent patterns can be subtle.

On motor imagery tasks, performance is mixed across models. **Laya** achieves the highest mean BCI accuracy (0.395) but does not consistently outperform across individual tasks.

On clinical tasks, **Laya-S** achieves the highest mean accuracy (0.603) despite using only 10% of pretraining data, outperforming **LaBraM** (0.578), **REVE** (0.547), **LUNA** (0.540), and **CBraMod** (0.511). Gains are most pronounced on tasks where relevant neural patterns are

Table 5.1: Linear probe performance on motor imagery tasks (balanced accuracy, mean $\pm$ std over 5 seeds). **Bold**: best, underline: second best.

Task	LaBraM	LUNA	CBraMod	REVE	Laya-S	Laya-B
5-Finger MI	0.208 $\pm$ 0.005	0.202 $\pm$ 0.005	0.204 $\pm$ 0.005	0.234 $\pm$ 0.004	<u>0.210</u> $\pm$ 0.007	0.205 $\pm$ 0.005
LH vs RH MI	0.471 $\pm$ 0.019	0.493 $\pm$ 0.007	0.491 $\pm$ 0.015	0.513 $\pm$ 0.017	<u>0.510</u> $\pm$ 0.003	0.507 $\pm$ 0.004
4-Class MI	0.289 $\pm$ 0.005	0.259 $\pm$ 0.009	0.271 $\pm$ 0.017	0.280 $\pm$ 0.007	0.273 $\pm$ 0.005	<u>0.288</u> $\pm$ 0.007
RH vs Feet MI	0.524 $\pm$ 0.017	0.501 $\pm$ 0.002	0.515 $\pm$ 0.011	0.508 $\pm$ 0.009	0.586 $\pm$ 0.002	<u>0.578</u> $\pm$ 0.002
Mean	0.373	0.364	0.370	0.384	0.395	<u>0.394</u>

Table 5.2: Linear probe performance on clinical tasks (balanced accuracy, mean $\pm$ std over 5 seeds). **Bold**: best, underline: second best.

Task	LaBraM	LUNA	CBraMod	REVE	Laya-S	Laya-B
Abnormal	<u>0.781</u> $\pm$ 0.013	0.733 $\pm$ 0.018	0.605 $\pm$ 0.011	0.500 $\pm$ 0.000	0.798 $\pm$ 0.007	0.778 $\pm$ 0.006
Artifact (Binary)	<u>0.725</u> $\pm$ 0.003	0.707 $\pm$ 0.023	0.690 $\pm$ 0.001	0.720 $\pm$ 0.003	0.716 $\pm$ 0.001	0.737 $\pm$ 0.001
Epilepsy	0.696 $\pm$ 0.019	0.647 $\pm$ 0.128	0.557 $\pm$ 0.017	<u>0.667</u> $\pm$ 0.018	0.657 $\pm$ 0.023	0.596 $\pm$ 0.012
mTBI	0.549 $\pm$ 0.133	0.613 $\pm$ 0.052	0.499 $\pm$ 0.002	0.682 $\pm$ 0.053	<u>0.699</u> $\pm$ 0.030	0.815 $\pm$ 0.048
Artifact (Multiclass)	0.374 $\pm$ 0.006	0.288 $\pm$ 0.019	0.298 $\pm$ 0.004	0.431 $\pm$ 0.058	0.375 $\pm$ 0.002	<u>0.382</u> $\pm$ 0.008
OCD	0.697 $\pm$ 0.175	0.546 $\pm$ 0.063	0.600 $\pm$ 0.173	<u>0.633</u> $\pm$ 0.000	0.627 $\pm$ 0.144	0.567 $\pm$ 0.037
Parkinson’s	0.537 $\pm$ 0.139	0.500 $\pm$ 0.000	0.508 $\pm$ 0.039	0.562 $\pm$ 0.031	0.708 $\pm$ 0.012	<u>0.683</u> $\pm$ 0.012
Schizophrenia	0.562 $\pm$ 0.080	0.423 $\pm$ 0.085	0.481 $\pm$ 0.043	0.444 $\pm$ 0.100	0.479 $\pm$ 0.060	<u>0.502</u> $\pm$ 0.042
Seizure	0.678 $\pm$ 0.002	<u>0.759</u> $\pm$ 0.008	0.699 $\pm$ 0.002	0.561 $\pm$ 0.023	0.786 $\pm$ 0.014	0.723 $\pm$ 0.005
Sleep Stages	0.184 $\pm$ 0.000	<u>0.182</u> $\pm$ 0.002	0.173 $\pm$ 0.000	0.267 $\pm$ 0.004	<u>0.185</u> $\pm$ 0.000	0.183 $\pm$ 0.001
Mean	0.578	0.540	0.511	0.547	0.603	<u>0.597</u>

subtle and easily obscured by high-variance artifacts. Notably, **Laya-S** achieves this with only 10% of pretraining data, highlighting the sample efficiency of latent prediction-based pretraining.

Laya-B leads on binary artifact detection (0.737). On multiclass artifact classification, REVE achieves the highest score (0.431), with **Laya-B** close behind (0.382), while LaBraM, LUNA, and CBraMod trail substantially (0.374, 0.288, 0.298).

5.4.4 Laya learns robust representations

We evaluated robustness by injecting noise (Gaussian, 1/f, EMG, channel dropout) at varying SNR levels with frozen probes. **Laya** retains 91% of its clean accuracy at 10 dB SNR on abnormal detection while LaBraM drops to 78%, consistent with our hypothesis that reconstruction-based models learn features correlated with high-variance input components,

Table 5.3: Controlled MAE ablation. All variants use identical architecture, data, and training configuration. Clinical Mean is averaged over clinical tasks in EEG-Bench. **Bold**: best.

Variant	Objective	BCI Mean	Clinical Mean
Laya-MAE-Decoder	Raw signal reconstruction	0.390	0.529
Laya-MAE	Channel-mixed token prediction	0.389	0.567
Laya-S	Latent prediction	0.395	0.603
Laya-B	Latent prediction	0.394	0.597

making them vulnerable when noise is introduced. Full degradation curves across clinical tasks are shown in Appendix Section 5.10.2.

5.4.5 Ablations

SIGReg is essential to prevent collapse. We found that SIGReg regularization is essential for stable training. With $\lambda < 0.02$ the model collapses to a constant embedding across the batch, resulting in chance-level downstream performance. Similarly, removing the projector severely degraded downstream performance, yielding a mean accuracy of 0.476.

Latent prediction outperforms reconstruction on clinical tasks. To directly test whether the pretraining objective drives clinical gains, we trained two MAE variants using identical architecture, data, and training configuration as Laya-S. Laya-MAE-Decoder adds a lightweight decoder to reconstruct raw EEG signals; Laya-MAE predicts the channel-mixed token sequence (**S**, the output of the channel mixer) rather than the encoder’s contextualized representations (**Z**), isolating the prediction target while keeping all other components fixed.

Across both BCI and clinical tasks, both MAE variants underperform Laya-S and Laya-B. Laya-MAE-Decoder trails Laya-S by 7.4 points on clinical mean and also underperforms on BCI. These results directly isolate the pretraining objective as the primary driver of Laya’s advantage.

StopGrad stabilizes longer training. In Laya, StopGrad serves a narrower role than in I-JEPA or V-JEPA: we use a single shared encoder with no separate teacher network,

so StopGrad only decouples target representations from the predictor gradient path while SIGReg prevents dimensional collapse. Removing StopGrad has a small effect at the **Laya-S** scale but substantially degrades clinical performance at 20K steps, indicating that StopGrad becomes increasingly important for preserving representation quality during longer training (Appendix Section 5.7).

5.5 Discussion

We introduce **Laya**, the first application of LeJEPa to EEG representation learning, and show that stable latent prediction enabled by LeJEPa and SIGReg provides a strong alternative to reconstruction-based pretraining for noisy clinical EEG tasks with subtle state-dependent structure. By predicting in latent space, **Laya** achieves greater sample efficiency, robustness, and semantic organization in these settings.

Across downstream benchmarks, **Laya** matches or exceeds reconstruction-based baselines. On BCI motor imagery tasks, **Laya** performs comparably to reconstruction-based baselines in aggregate; however, PCA visualizations reveal that **Laya** does learn qualitatively distinct representations across left- and right-hand motor states, while LaBraM shows no such structure, suggesting that quantitative parity may reflect task-specific confounds (e.g., subject variability, trial-level decoding) rather than a failure to encode motor-relevant information. In contrast, **Laya** achieves substantial gains on clinical tasks. **Laya-S** trained on only 10% of the pretraining data attains the highest mean balanced accuracy. Notably, **Laya** exhibits strong sample efficiency and learns noise-resilient representations.

Ablation results show that removing SIGReg makes training unstable, underscoring the necessity of explicit geometric regularization. Controlled MAE ablations further confirm that the latent predictive objective — not architecture or data — is the primary driver of **Laya**’s clinical gains.

While the pretraining objective plays a central role, these results also emphasize the

importance of architectural inductive biases for EEG, particularly channel mixing. Structured channel interactions are critical for enabling JEPA-style objectives to learn stable and transferable representations, suggesting that objective and architecture must be designed jointly.

Conclusion. These results indicate that reconstruction is not a necessary (and may be a suboptimal) objective for noisy clinical EEG representation learning. Controlled MAE ablations confirm that this clinical advantage stems directly from the latent predictive objective, rather than architectural or data-driven factors. Latent prediction therefore offers a strong alternative to signal reconstruction for scalable and clinically relevant EEG representation learning, especially when useful features are subtle, noisy, and expensive to annotate at scale.

5.5.1 Limitations

Laya-S was only trained on 10% of the overall curated data, and while this yielded strong results, Laya-B did not consistently outperform Laya-S on clinical tasks despite $10\times$ more pretraining data and $2\times$ more training steps. We reduced the SIGReg weight from $\lambda = 0.05$ to $\lambda = 0.02$ for Laya-B to maintain stability over longer training, but a systematic sweep over schedule length, λ , and data mixture was not feasible with our available compute (2 GPUs); we leave a careful study of scaling dynamics for latent-prediction EEG models to future work. Despite this, Laya-B matches or exceeds all reconstruction-based baselines on clinical mean (0.597), suggesting that the latent predictive objective provides a strong performance floor even without optimal scaling.

EEG-Bench focuses on classification tasks and does not extend to retrieval-style tasks like cognitive decoding, emotion recognition, or forecasting (e.g., seizure prediction rather than detection). Evaluating on other benchmarks like AdaBrain-Bench [61] or EEG-FM-Bench [80] is necessary to fully characterize representation quality. Additionally, linear probing may underestimate the utility of learned representations for tasks requiring nonlinear adaptation or subject-specific calibration. BCI performance remains limited across all

self-supervised methods, consistent with recent benchmarks showing that EEG foundation models often struggle to outperform simpler or task-specific decoders on fine-grained motor decoding tasks [12, 60]. This suggests that frozen population-level EEG representations may be insufficient for granular task-related changes, and that future approaches may need to model neural activity and behavior jointly, or incorporate subject-level adaptation, to capture the structure required for BCI.

5.5.2 Future Work

Our work suggests that latent prediction can yield semantically meaningful EEG representations, but it also raises several open questions. A key direction is developing a clearer understanding of what structure these representations encode. Further analysis is needed to characterize how temporal, spectral, and spatial information are organized in LeJEPA embeddings, and how this organization differs from that induced by reconstruction-based objectives. Laya’s quantitative and qualitative results on seizure-related tasks, together with qualitative evidence of structured motor-state representations, suggest promising applications of JEPA-style architectures for seizure forecasting, interpretable clinical decision support, and BCI systems requiring robust population-level representations, where robustness and semantic organization are critical.

More broadly, our findings suggest that future work on EEG SSL should prioritize principled regularization and objective design over architectural complexity alone.

From a practical perspective, a more systematic search over pretraining recipe hyperparameters — schedule length, SIGReg strength, and data mixture — remains an important next step. Related questions around context length and long-range temporal modeling also remain open.

Progress in EEG foundation models also depends on more extensive and standardized benchmarks, alongside improved data curation and shared pretraining pipelines. Greater agreement on task definitions, evaluation protocols, and preprocessing would enable more

meaningful comparisons and faster iteration across the field. Broader future directions building on this work are discussed in Chapter 9.

5.6 Pretraining Details

Table 5.4: Pretraining details for Laya-S (10% data) and Laya-B (full data).

	Laya-S	Laya-B
Data		
Training data fraction	10%	100%
Max input duration	16 s (160 timesteps)	16 s (160 timesteps)
Batch size	256	256
Model		
Encoder dim	384	384
Encoder depth / heads	12 / 6	12 / 6
Predictor depth / heads	4 / 4	4 / 4
Projection/Predictor dim	128	128
Patch size	25 samples	25 samples
Channel Queries	16	16
Channel Mixer Dim	32	32
Masking and Objective		
Mask ratio	0.6	0.6
Mask block sizes	5–10 patches	5–10 patches
Global crops	1×16 s	1×16 s
Regularization		
SigReg weight	0.05	0.02
Query loss weight	1.0	1.0
Optimization		
Learning rate	1×10^{-4}	1×10^{-4}
Weight decay	0.05	0.05
LR schedule	Warmup + cosine	Warmup + cosine
Warmup	1K steps	1k steps
Min LR	1×10^{-6}	1×10^{-6}
Training		
Max steps	10k	20k
Precision	bf16-mixed	bf16-mixed

5.6.1 Pretraining Algorithm

Algorithm 1 Laya Pretraining Step

Require: Latent brain states $\mathbf{S} \in \mathbb{R}^{B \times N \times D}$ and channel-mixer affinity weights $\mathbf{W}$

- 1: Sample contiguous temporal mask $\mathbf{m} \subset \{1, \dots, N\}$
 - 2: $\mathbf{Z} \leftarrow \text{Encoder}(\mathbf{S})$
 - 3: $\mathbf{z}_{\text{cls}} \leftarrow \text{Mean}(\mathbf{Z}, \text{dim} = 1)$
 - 4: $\mathbf{T} \leftarrow \text{Projector}(\text{StopGrad}(\mathbf{Z}))$
 - 5: $\mathbf{p}_{\text{cls}} \leftarrow \text{Projector}(\mathbf{z}_{\text{cls}})$
 - 6: $\mathbf{Z}_{\text{ctx}} \leftarrow \text{Encoder}(\mathbf{S}, \mathbf{m})$
 - 7: $\mathbf{P}_{\text{ctx}} \leftarrow \text{Projector}(\mathbf{Z}_{\text{ctx}})$
 - 8: $\hat{\mathbf{T}} \leftarrow \text{Predictor}(\mathbf{P}_{\text{ctx}}, \mathbf{m})$
 - 9: $\mathcal{L}_{\text{query}} \leftarrow \text{QueryLoss}(\mathbf{W})$
 - 10: $\mathcal{L} \leftarrow \text{MSE}(\hat{\mathbf{T}}, \mathbf{T}[\mathbf{m}]) + \lambda \cdot \text{SIGReg}(\mathbf{p}_{\text{cls}}) + \gamma \cdot \mathcal{L}_{\text{query}}$
-

5.7 StopGrad Ablation

In Laya, StopGrad serves a narrower role than in I-JEPA or V-JEPA, where it is coupled with a momentum-updated EMA target encoder. Here, we use a single shared encoder with no separate teacher network; StopGrad only decouples the target representations from the predictor gradient path, while SIGReg prevents dimensional collapse.

Table 5.5: StopGrad ablation under frozen linear probing. Removing StopGrad while keeping SIGReg fixed.

Configuration	StopGrad	BCI Mean	Clinical Mean
Laya-S	✓	0.395	0.603
Laya-S	×	0.391	0.559
Laya-B (20K)	✓	0.394	0.597
Laya-B (20K)	×	0.353	0.466

At the Laya-S scale (10K steps), removing StopGrad leaves BCI performance nearly

unchanged (-0.4pp) but reduces clinical accuracy by 4.4pp . At 20K steps, the effect is substantially larger, with a 13.1pp clinical drop, indicating that StopGrad plays an increasingly important stabilizing role over longer training. Overall, SIGReg is the primary mechanism preventing collapse; StopGrad plays a complementary role in preserving representation quality during extended training.

5.8 Pretraining Datasets

TUH EEG. We use the Temple University Hospital EEG corpus, a large-scale clinical dataset consisting of long-duration, multi-channel EEG recordings with substantial inter-subject and inter-session variability. We ensured that no subjects appearing in the TUH-based downstream validation or test sets were included during pretraining. [75]

HBN EEG. We use EEG recordings from the Healthy Brain Network (HBN), a large-scale pediatric neurodevelopmental dataset comprising multimodal data collected from typically developing children and individuals with psychiatric or learning disorders under standardized experimental protocols [77].

NMT. We use the NMT Scalp EEG Dataset, a large-scale open-source corpus of clinically acquired EEG recordings labeled as normal or abnormal. The dataset comprises long-duration, multi-channel scalp EEG. [76]

MOABB. We use the following MOABB datasets for downstream evaluation: Shin2017A [81], BNCI2014_002 [82], Ofner2017 [83], GrosseWentrup2009 [84], Stieger2021 [85], and Lee2019_MI [86].

EEGDash. We query EEGDash and use a diverse selection of available datasets [ds003474](#) [ds003478](#) [ds003506](#) [ds003518](#) [ds003522](#) [ds003523](#) [ds003638](#) [ds003655](#) [ds003690](#) [ds003838](#) [ds004256](#) [ds004279](#) [ds004448](#) [ds004504](#) [ds004515](#) [ds004532](#) [ds004572](#) [ds004579](#) [ds004580](#)

ds004584 ds004595 ds004602 ds004626 ds004718 ds004771 ds004883 ds004902 ds004942
ds005131 ds005305 ds005385 ds005410 ds005540 ds005863.

Preprocessing. All recordings are resampled to a sampling rate of 250 Hz, band-pass filtered between 0.5–100 Hz, and notch filtered at both 50 Hz and 60 Hz. Channel layouts are preserved in their native montages (10–20, BioSemi128, or 10–05), with reference channels removed where applicable. To exclude non-informative segments, we apply leading-edge trimming based on signal statistics, discarding windows with near-zero variance or excessive clipping. Signals are robust scaled as in Défossez and others [117]. Preprocessed recordings are then segmented into non-overlapping 120-second chunks and stored as WebDataset shards containing both signals and metadata.

5.9 Benchmark Details

To ensure comparability, each model follows a preprocessing pipeline aligned with its original design, as implemented in EEG-Bench. Across models, channels are harmonized to standard 10–20 montages where required; missing channels are handled via zero-padding or interpolation according to the model implementation. Signals are segmented into fixed-length windows, with window duration determined by each model architecture and task configuration.

5.9.1 Downstream Datasets

BCI Tasks.

BCI tasks operate on short, trial-based recordings (typically 2–10 s) collected under controlled experimental paradigms, primarily motor imagery and event-related potential decoding.

Left Hand vs Right Hand Motor Imagery (LH/RH MI). Binary classification of

imagined left- versus right-hand movements. Evaluated on BCI Competition IV-2a and IV-2b [118], PhysioNet Motor Imagery [119, 120], and multiple motor imagery datasets including Weibo2014 [121], Cho2017 [122], Liu2022[123], Schirrmeister2017[124], Zhou2016[125], and Kaya2018 [126].

Right Hand vs Feet Motor Imagery (RH/Feet MI). Right-hand vs feet motor imagery (RH/Feet MI) is evaluated on Weibo2014 [121], PhysioNet Motor Movement/Imagery [120], BCI Competition IV-2a [118], Barachant2012 [127], Faller2012 [128], Scherer2015 [129], Schirrmeister2017 [124], Zhou2016 [125], and Kaya2018 [126].

Four-Class Motor Imagery (4-Class MI). Multi-class motor imagery classification across left hand, right hand, feet, and tongue. Evaluated on BCI Competition IV-2a and Kaya2018.

Five Fingers Motor Imagery. Fine-grained motor imagery classification of individual finger movements, evaluated on Kaya2018 [126].

Clinical Tasks.

Clinical tasks operate on long-duration EEG recordings (minutes to hours) collected in diagnostic or monitoring settings. Tasks include both recording-level classification and segment-level event detection.

Abnormal EEG Detection. Binary classification of EEG recordings as normal or abnormal. Evaluated on the Temple University Hospital Abnormal EEG Corpus (TUAB) [75].

Epilepsy Detection. Binary classification of epileptic versus non-epileptic recordings. Evaluated on the Temple University Hospital Epilepsy Corpus (TUEP) [75].

Seizure Detection. Per-segment seizure event detection in continuous EEG recordings. Evaluated on the CHB-MIT dataset [31].

Sleep Staging. Per-epoch sleep stage classification (W, N1, N2, N3/4, REM). Evaluated on Sleep-Telemetry (Sleep-EDF) [130].

Artifact Detection. Binary and multi-class artifact classification tasks identifying EEG

contamination (e.g., eye movement, muscle, electrode artifacts). Evaluated on the Temple University Artifact Corpus (TUAR) [131].

Neurological and Psychiatric Disorder Classification. Recording-level classification tasks distinguishing patients from healthy controls, including Parkinson’s disease [132, 133, 134, 135, 136], schizophrenia [137], mild traumatic brain injury [138], and obsessive-compulsive disorder [139]. These tasks are evaluated on EEG datasets released via OpenNeuro and related repositories.

Segment-Based and Multi-Label Tasks. For seizure detection, sleep staging, and artifact detection, recordings are divided into 16-second windows. For each window, models predict 16 class labels (one per second), and F1 score is computed across all per-second predictions.

5.10 Additional Analyses

5.10.1 Laya Dynamic Channel Mixer

As in LUNA, Laya learns to attend to different channels, each query attending to, and learning a rich latent brain state at each time step. In Figure 5.4 we show 8 queries and the channel weights they learn for one sample in the TUH dataset. In Figure 5.3 we show 8 queries and channel weights they learn for one sample in the HBN dataset during a movie watching task.

5.10.2 Detailed Noise Robustness Results

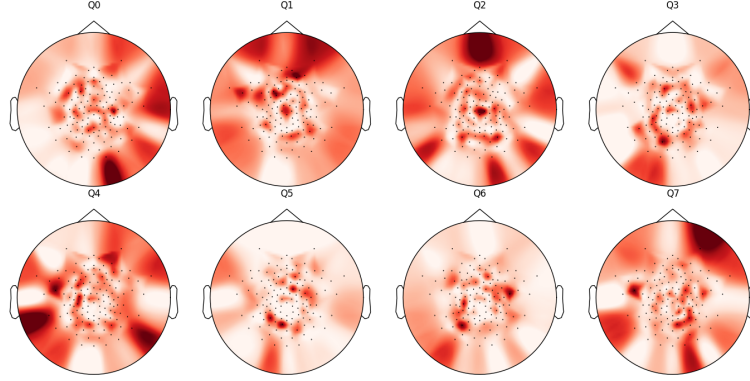


Figure 5.3: Topoplot of the channel weights for eight queries on the HBN dataset during movie watching task (DiaryOfAWimpyKid).

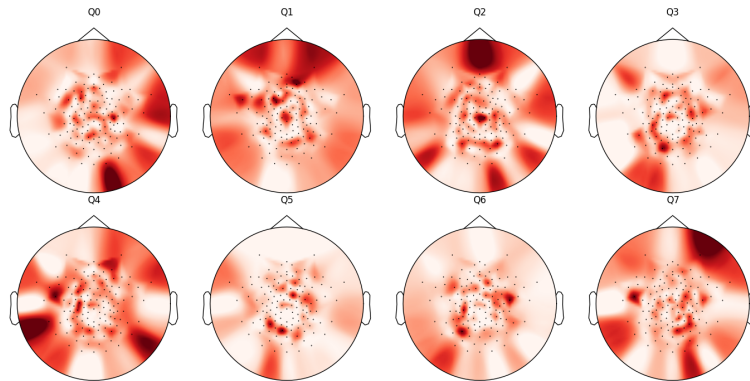


Figure 5.4: Topoplot of the channel weights for eight queries on the TUH dataset.

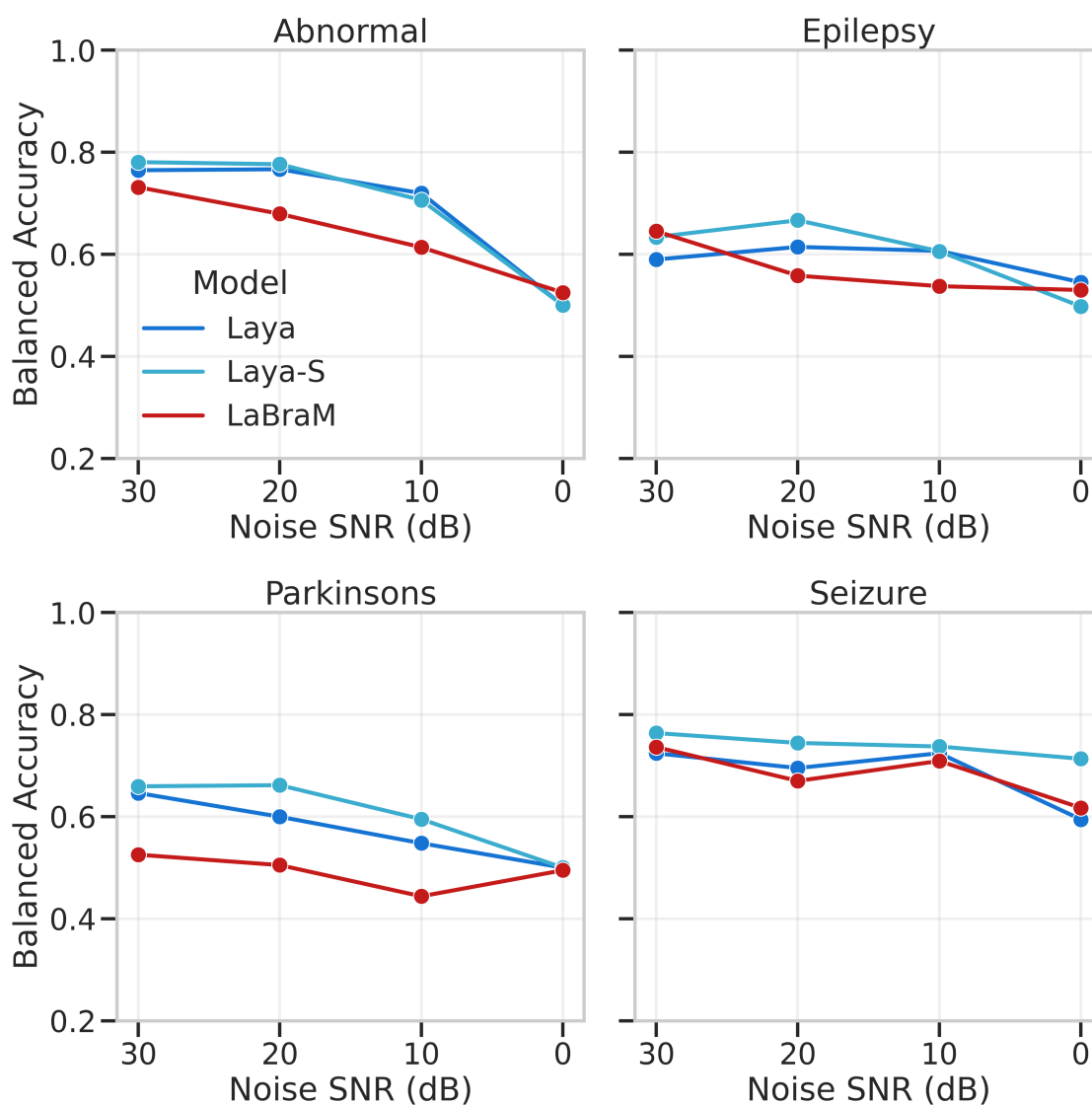


Figure 5.5: Laya is resilient to noise across clinical tasks. Performance shown under combined noise (Gaussian, 1/f, EMG, channel dropout) at varying SNR levels.

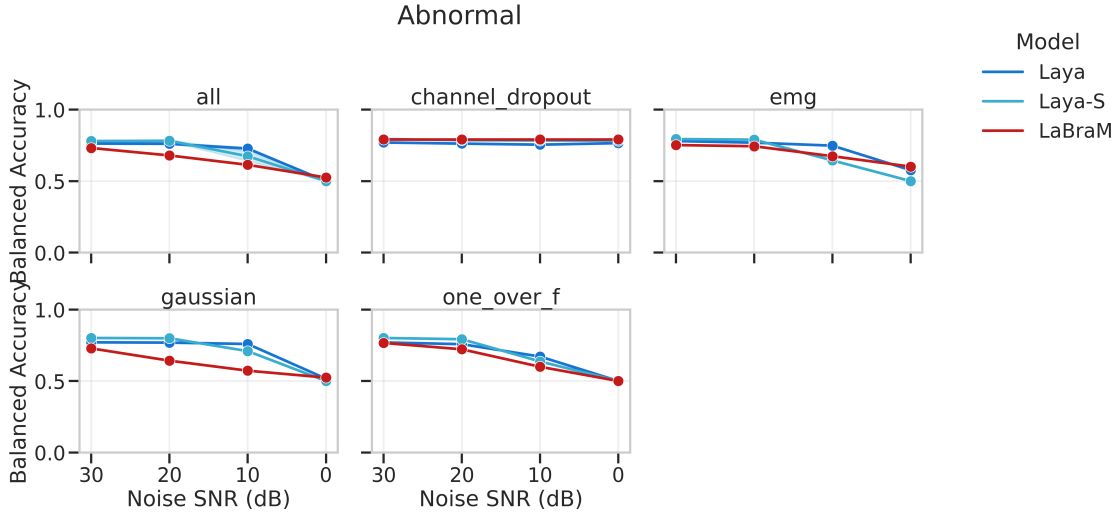


Figure 5.6: Noise robustness on Abnormal EEG detection.

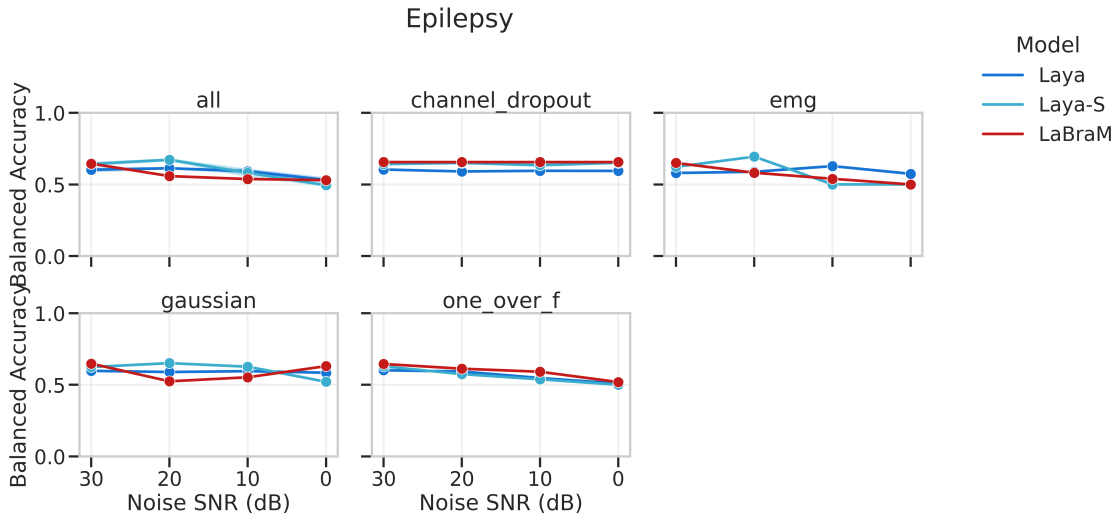


Figure 5.7: Noise robustness on Epilepsy detection.

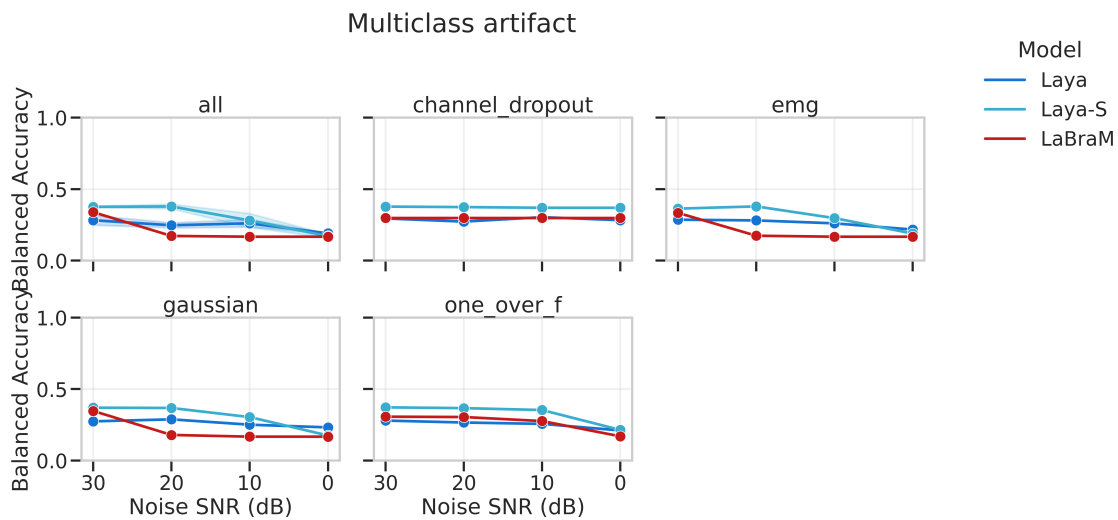


Figure 5.8: Noise robustness on Multiclass Artifact classification.

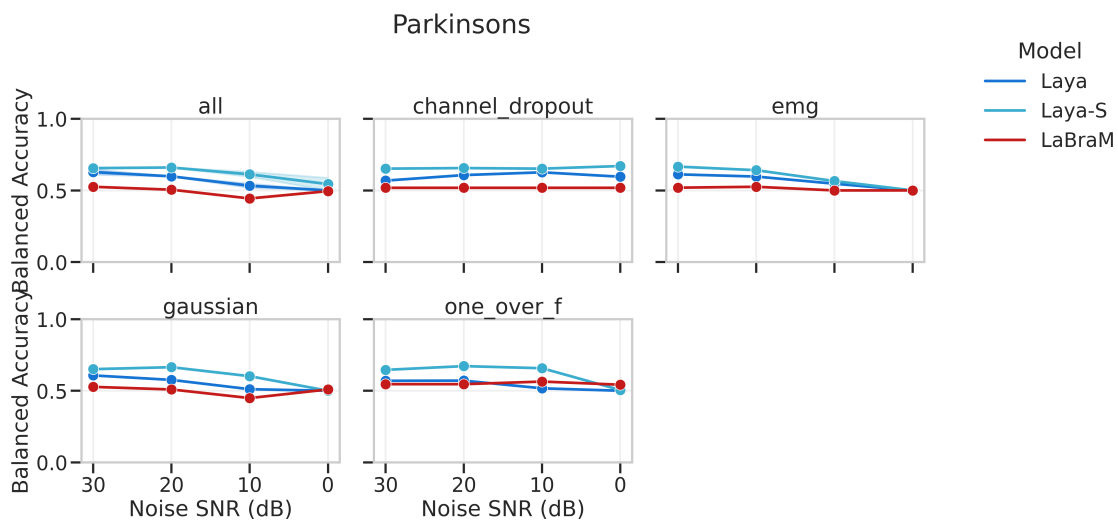


Figure 5.9: Noise robustness on Parkinson's disease detection.

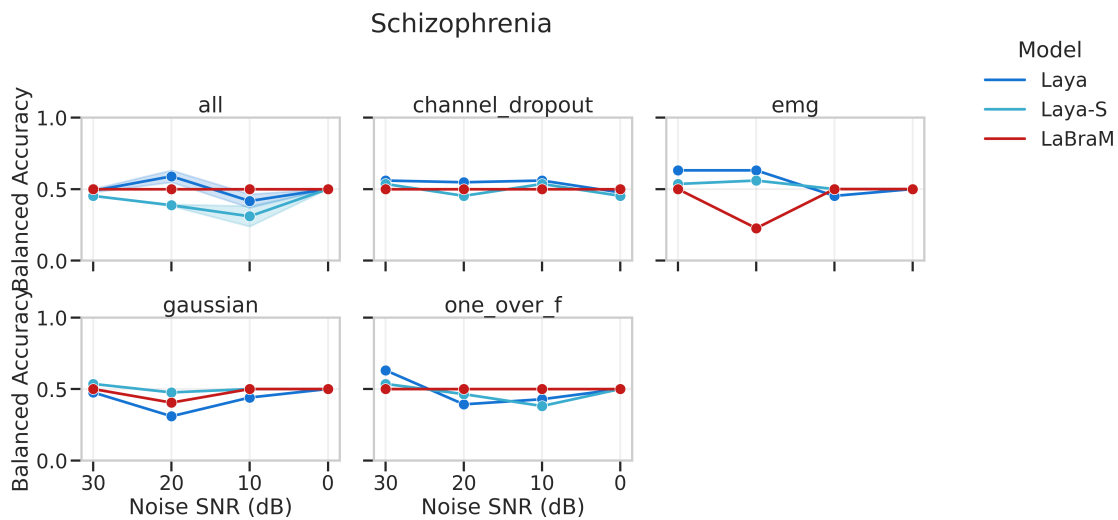


Figure 5.10: Noise robustness on Schizophrenia detection.

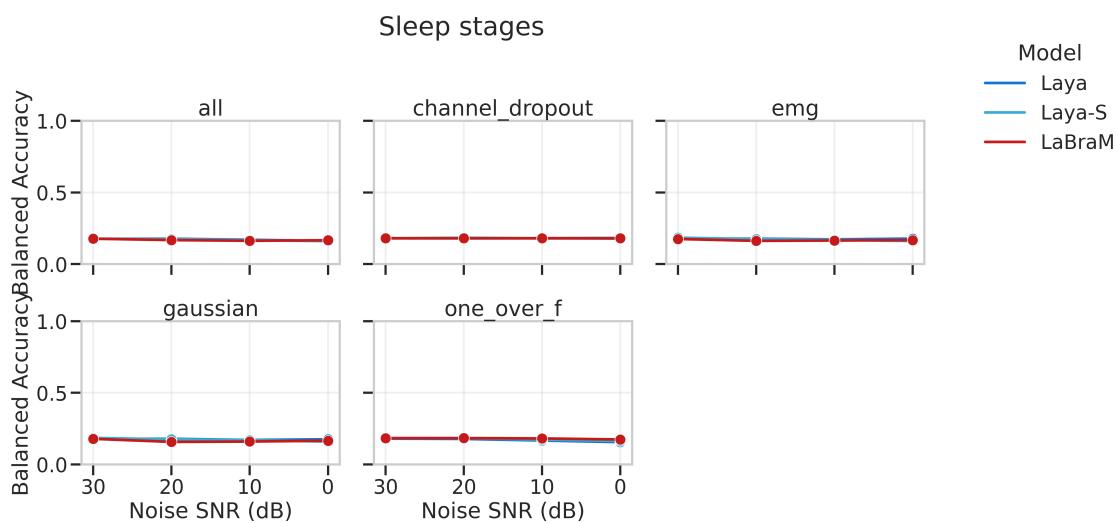


Figure 5.11: Noise robustness on Sleep Staging.

5.10.3 Further Examples of Laya Rich Temporal Embeddings on Seizure Recordings

Further examples of Laya ability to distinguish semantic meaning from noisy EEG signals can be found in Figure 5.12.

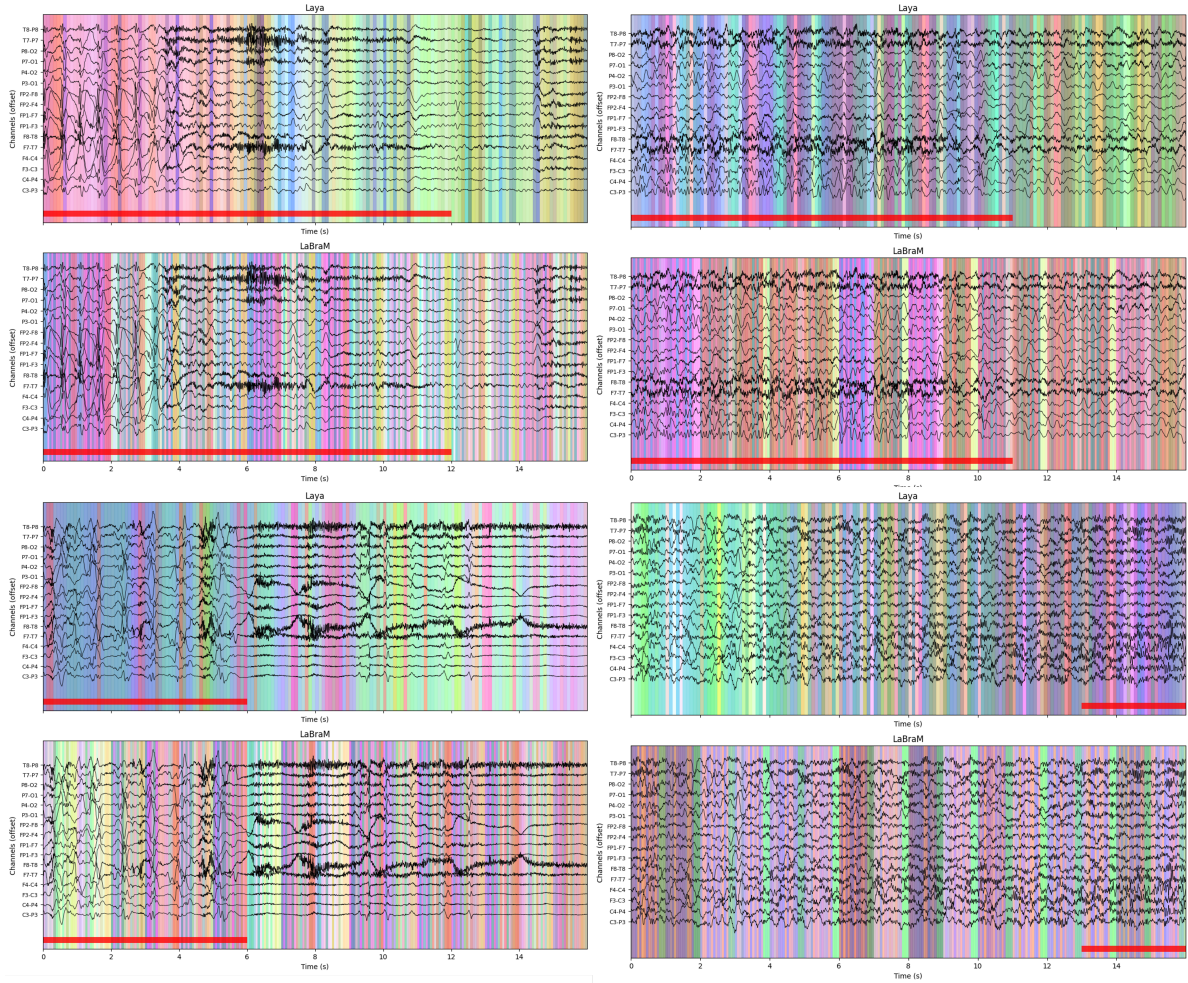


Figure 5.12: PCA visualization of patch embeddings on several seizure recordings. We map three principal components to RGB. Top: Laya-B. Bottom: LaBraM. Red bar indicates seizure.

5.11 Additional Related Work

I-JEPA. I-JEPA applies the JEPA architecture to images by training a predictor to infer the latent embeddings of masked image blocks from a visible context block using an encoder–predictor architecture with an EMA target network, enabling semantic prediction without pixel-level reconstruction [40].

V-JEPA. V-JEPA extends JEPA to video by tokenizing clips into spatiotemporal blocks and training a predictor to infer masked block embeddings from visible ones using an encoder–predictor with an EMA target, operating entirely in representation space rather than reconstructing pixels [69].

LeJEPA. LeJEPA augments the JEPA latent-prediction objective with Sketched Isotropic Gaussian Regularization (SIGReg), which encourages encoder embeddings to match an isotropic Gaussian, a distribution shown to minimize expected downstream risk. SIGReg uses random 1D projections to enforce this distribution with linear complexity, removing reliance on momentum-updated EMA teachers. The combined objective yields stable, collapse-free pretraining with a single trade-off hyperparameter and robust performance across architectures and domains [66].

LaBraM. LaBraM was among the first large-scale EEG foundation models, pretraining a transformer on over 2,500 hours of data using masked token prediction. The model discretizes EEG patches via a neural tokenizer trained to reconstruct Fourier spectra, then predicts masked tokens over a flattened channel–time sequence [38].

CBraMod. CBraMod introduces a criss-cross transformer that models spatial and temporal dependencies separately using parallel attention mechanisms, rather than jointly attending over all channel–time tokens. The model employs patch-based masked EEG reconstruction with an asymmetric conditional positional encoding that dynamically encodes spatial

and temporal relationships, improving adaptability across datasets with varying formats and reference schemes [58].

REVE. REVE adopts a masked autoencoding objective with structured spatio-temporal block masking and introduces a 4D positional encoding derived directly from electrode 3D coordinates and temporal indices. REVE supports arbitrary electrode layouts and sequence lengths without fine-tuning positional priors [59].

LUNA. LUNA introduces an efficient, topology-agnostic EEG foundation model that handles variable electrode configurations by compressing channel-wise patch features into a fixed-size latent space via learned queries and cross-attention, enabling linear scaling with channel count. Pretrained on over 21,000 hours of EEG using masked patch reconstruction, LUNA achieves strong transfer performance while reducing computational cost by orders of magnitude [57].

S-JEPA. S-JEPA employs spatial block masking over EEG channels, masking contiguous scalp regions to encourage learning of spatial dependencies and dynamic channel attention. Experiments across multiple BCI paradigms demonstrate improved cross-dataset transfer relative to reconstruction-based SSL [68].

Brain-JEPA. Brain-JEPA is an fMRI foundation model that predicts latent representations of masked spatiotemporal regions. The model introduces functional gradient-based positional encodings and structured spatiotemporal masking to address the lack of a natural spatial ordering in brain data [71].

EEG-VJEPa. EEG-VJEPa adapts Video-JEPA to EEG by treating multichannel recordings as video-like spatiotemporal sequences and performing large contiguous spatiotemporal block masking with latent-space prediction. The model employs a ViT backbone with EMA-stabilized target encoders to learn long-range temporal and cross-channel dependencies [67].

EEG-DINO. EEG-DINO is a large-scale EEG foundation model based on hierarchical self-distillation rather than masking-based prediction. EEG-DINO is pretrained on approximately 9,000 hours of EEG but is evaluated on only three downstream tasks, two of which overlap with its pretraining corpus, limiting conclusions about representation generality. The method aligns representations across multiple channel- and time-augmented views using a teacher–student framework with decoupled spatial and temporal positional embeddings [72].

5.12 Broader Impacts

This work studies self-supervised EEG representation learning. Potential benefits include more reusable EEG representations for clinical neuroscience and more sample-efficient downstream modeling when labeled data are limited.

The model is not a clinical diagnostic system and should not be used for medical decision making without task-specific validation, prospective testing, and appropriate regulatory review. Because EEG data vary across populations, devices, montages, and sites, downstream use should account for distribution shift, privacy, and subgroup performance where metadata are available.

CHAPTER 6

Uncovering Spatiotemporal Dynamics of the Corticothalamic Network at Ictal Onset

The preceding three chapters asked how much clinically useful structure can be extracted from scalp EEG using learned representations. The next two chapters take a complementary approach, using stereoelectroencephalography (SEEG) to ask what seizure networks actually look like at a mechanistic level. This chapter examines thalamocortical dynamics at ictal onset, asking whether the thalamus is differentially recruited in the first moments of a focal seizure and what frequency-specific structure that recruitment carries.

6.1 Introduction

Approximately one-third of patients with epilepsy develop drug-resistant epilepsy (DRE), and those who are not surgical candidates are typically offered neuromodulation (see Chapter 2). Among these options, thalamic stimulation has shown promise due to the thalamus' role as a central hub in the cortical network. Animal and human studies using neuroimaging[140, 141] and neurophysiology[142, 143, 144] have provided evidence supporting the critical involvement of the thalamus in the generation, maintenance, and termination of neocortical seizures. The clinical efficacy of DBS targeting the anterior nucleus (AN) of the thalamus has been extensively studied, and studies have shown efficacy in reducing temporal and limbic seizures,[6, 8] presumably due to the strong connection between AN and the temporal lobe/limbic system.

However, it has been found that the efficacy of AN stimulation is suboptimal in seizures

other than temporal or limbic onset.[6] As a result, some researchers have investigated the stimulation of the centromedian nucleus (CM) in the context of Lennox-Gastaut syndrome (LGS),[9] generalized,[145] and focal neocortical epilepsy.[146, 147] Recent studies, including a randomized controlled trial, have demonstrated promising results for CM stimulation in patients with LGS.[25] This suggests that the CM may exhibit stronger connections to frontal and other brain areas, thereby further supporting its potential as an effective target for neuromodulation in non-temporal/limbic epilepsy. It has also been shown that ictal EEG changes, especially in the fast frequency band, are observed at various thalamic nuclei during various seizure onsets.[148, 149] The presence of ictal EEG changes at the thalamus may justify closed-loop neuromodulation by RNS.[150]

Despite the promise, few studies have investigated changes in corticothalamic connectivity between thalamic nuclei and different seizure foci during seizures. Neuroimaging techniques, such as functional MRI, offer good spatial resolution but lack temporal resolution, making them inadequate for elucidating dynamic temporal changes in seizure networks. On the other hand, EEG provides excellent temporal resolution, but sampling signals from the thalamus is challenging unless clinically indicated. However, several recent studies using SEEG (see Section 2.1) demonstrated that in temporal lobe seizures, active involvement of the pulvinar nucleus,[144, 151] and CM,[152] along with AN was demonstrated. To enable personalized neuromodulation treatment, it is crucial to understand the distinct roles of each thalamic nucleus during seizures, taking into account their anatomically specific seizure onsets. Particularly, understanding the dynamic changes of the corticothalamic network at ictal onset will help in optimizing the detection of seizures through thalamic sampling with RNS.

To address this knowledge gap, we aimed to investigate the dynamic connectivity changes within the corticothalamic network at ictal onset by employing undirected and directional connectivity analysis. We analyzed a unique cohort of patients with thalamic sampling during SEEG evaluation for thalamic neuromodulation. Considering the distinct anatomical

regions, we explored the intricate interactions between the seizure onset zones and thalamic nuclei (AN and CM) across various seizure foci.

6.2 Materials and Methods

Patient Cohort

This was a retrospective study. Patients with pediatric-onset epilepsy admitted to the UCLA Mattel Children's Hospital and underwent a chronic SEEG implantation with electrodes inserted into the thalamus (AN and/or CM) from November 2020 to February 2023 were identified. Those patients were suspected of having DRE with focal onset and were possible candidates for thalamic neuromodulation. There were no exclusion criteria.

Standard protocol approvals, registrations, and patient consent

The institutional review board at UCLA approved the use of human subjects and waived the need for written informed consent. All testing was deemed clinically relevant for patient care, and all retrospective EEG data used for this study were de-identified before data extraction and analysis. This study was not a clinical trial, and it was not registered in any public registry.

Patient and seizure evaluation

The plan for SEEG placement was discussed at our multidisciplinary epilepsy surgery conference (consisting of epileptologists, neurosurgeons, radiologists, and neuropsychologists) and was based on the combination of data from seizure semiology, neurological examination, neuroimaging findings (MRI, PET, and magnetoencephalography), neuropsychological evaluation, and scalp EEG with emphasis primarily on seizure onset zones. Ipsilateral (to the presumed site of the presumed seizure onset) AN and CM thalamic SEEG electrodes were

placed to determine whether an ictal pattern can be detected in the thalamus and provide a potential target for neuromodulation. Seizures captured during SEEG monitoring were classified based on the recent classification and terminology defined by the International League Against Epilepsy.[153] We considered seizure types to be distinct if their electrographic patterns differed, regardless of whether their clinical manifestations were identical, thereby taking into account variations in the seizure onset zones. We determined the seizure onset zone as regions initially exhibiting sustained rhythmic waveforms prior to the onset of habitual seizures. If the patient had bilateral seizure onsets during the phase 1 monitoring, thalamic SEEG electrodes were placed on the side of the most significant seizure burden, or if unclear, bilateral thalamic electrodes were placed. To enable a group analysis, for each patient, we identified up to three seizures in each seizure type, which had no preceding seizures within 30 minutes. For example, if a patient had two different clinical seizure semiologies or two seizures with similar clinical semiology but clearly different electrographic onsets, these were considered different seizure types, and six seizures were reviewed (see details in Appendix Section A.1).

SEEG placement and confirmation

BrainLab Elements software was used for planning the electrodes to the intended targets using T1-weighted sequences, and the trajectories were guided by a gadolinium-enhanced T1-weighted MRI. Target subcortical structures (including AN and CM) were identified and outlined by an experienced neuroradiologist (NS) on a case-by-case basis prior to the trajectory planning. The targets and trajectories that were planned using the MRI MPRAGE2 sequence were then co-registered to a volumetric computed tomography (CT) scan acquired after placing the patient's head into the Leksell frame. Each electrode was placed using the Leksell coordinates obtained from the BrainLab elements software. Four contact Spencer Depth Electrodes with 2.5 mm spacing were used exclusively for thalamic targets. The chosen entry point for the procedure was typically positioned 4 to 6 centimeters away from the

midline at the level where the coronal suture lies, aiming towards either AN or CM of the thalamus. Procedures targeting AN always involved an intraventricular path, whereas those targeting CM were strictly extraventricular. An intraoperative or immediate postoperative CT scan was used to rule out intracranial hemorrhage and confirm the final position and trajectory of each electrode placed. The location of electrode placement was verified postoperatively with CT co-registered with the pre-op T1-weighted MRI using the BrainLab Elements software. Outlines for target subcortical nuclei were identified and overlaid onto the postoperative CT scan. Electrode contact placement in relation to the target nuclei was then determined. For contacts placed outside of the desired nucleus, distance-to-target measurements were then recorded from the edge of the respective contact to the edge of the nucleus of interest. Our prior study showed that more than 90% of our cases had active contact in or within 1 mm of the nucleus it was intended for.[149] For those leads with no electrode in the intended nucleus, the mean distance from the edge of the electrode to the edge of the thalamic nucleus was 0.4 mm for CM and 1.6 mm for AN. There were no complications, and specifically no intracranial hemorrhage, as a result of placing SEEG electrodes, including thalamic SEEG electrodes.

EEG data acquisition

Intracranial EEG (iEEG) recording was obtained using Nihon Kohden (Irvine, California, USA) with a digital sampling frequency of 200 Hz or 2000 Hz and a proprietary band-pass frequency of 0.08-300 Hz. All iEEGs were part of the clinical EEG recording. The iEEG data were preprocessed using a notch filter at 60 Hz intervals to remove power-line noise. All data were downsampled to 200 Hz to ensure the same sampling rate across EEG recordings and improve computational tractability. We time-locked each seizure recording to the seizure onset and used 20 minutes of data before and after the seizure.

EEG channel coregistration and channel selection for analysis

We obtained preoperative high-resolution 3D magnetization-prepared rapid acquisition with gradient echo (MPRAGE) T1-weighted image of the entire head. Anatomical segmentation was conducted by using preoperative MRI scans to generate a patient-specific reconstruction with FreeSurfer.[154] Subsequently, this reconstruction facilitated the co-registration process in Brainstorm using post-implant CT images, allowing for the precise localization of each depth electrode's contacts (Figure 6.1)[155, 156] The positions of these contacts were classified according to the Desikan-Killiany-Tourville atlas.[157] The location of thalamic contacts was visually verified against the pre-defined targets on the axial, coronal, and sagittal slides on the co-registered T1 MRI. We restricted our analysis to electrodes located only in relevant regions and removed any electrodes primarily located in white matter, within abnormal structural lesions (such as tubers), outside the brain, or exhibited significant recording artifacts. A maximum of three seizure onset electrodes were defined as those immediately surrounding the clinically labeled seizure onset electrodes based on visual analysis by two board-certified clinical neurophysiologists.[149] The analyses included all the thalamic channels (AN and CM). The subsequent quantitative analyses used the bipolar montage. For further subgroup analysis, all electrodes were categorized into seizure onset, AN, CM, frontal, temporal, parietal, occipital, basal ganglia, and limbic system based on the reconstruction using FreeSurfer-based Desikan-Killiany atlas. The limbic system electrodes included those from the hippocampus, parahippocampus, amygdala, cingulate, and insula. Then all the seizures from each category were collected and analyzed.

Connectivity analysis

Using a bipolar montage, we segmented the SEEG data into four-second non-overlapping windows and calculated measures of connectivity on each window. This study employed coherence and spectral Granger causality to explore connectivity at the baseline (20-10 mins before the seizure) and ictal segment (0-20s after visually marked EEG seizure onset). Such

connectivity values were contrasted between the baseline and the ictal segment to determine the connectivity change. We quantified connectivity between the seizure onset zones and AN and CM. We also explored connections between different brain lobes for different seizure foci. We also investigated the connectivity changes across various frequency bands: delta (1.5-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), beta (12-30 Hz), and gamma (30-100 Hz) (a case example presented in Figure 6.1). The MNE-Python package[158] was used for all preprocessing of the data.

Coherence: Coherence is an undirected measure of synchronization and correlation between two-time series signals at different frequencies. Values of coherence range between 0 and 1, where 1 represents the highest degree of synchrony between two signals. Coherence has widely been used in EEG data analysis to understand functional connectivity between different brain regions.[159] We calculated pairwise coherence between electrodes using the MNE-connectivity open-source Python package.[158] We averaged coherence values within each of the frequency bands of interest. Subsequently, these values were averaged across the different electrode interactions. For example, coherence between electrodes in the thalamus and at seizure onset was averaged to obtain a coherence value for thalamic-onset interactions at a particular time window and frequency band.

Granger Causality: In the time domain, Granger causality analysis (GCA) is a statistical measure of how one time series influences another based on two autoregressive models. If the inclusion of the history of time series A with the history of time series B reduces the prediction error for B compared to just the history of B, then A is said to Granger cause time series B. While this is a directed measure, causality can be bidirectional, where two signals can influence each other. Like coherence, Granger causality has been used in prior studies for neural signal analysis, including EEG research to capture directed functional connectivity.[30, 160] In this study, we used spectral GCA, which is a variation of the traditional time series GCA. Spectral GCA measures the fraction of the total power of a signal at a frequency contributed by another signal.[161] We calculated spectral GCA in a similar manner to

coherence, in which our final result was a value between 0 and 1 for a directed interaction (thalamus Granger causes seizure onset region or vice versa) at a particular time window and frequency band. Spectral GCA was calculated using the open-source spectral-connectivity Python package (https://github.com/Eden-Kramer-Lab/spectral_connectivity/).

Phase amplitude coupling (PAC)

To investigate the interaction between slow and fast frequency bands in the context of brain connectivity, we calculate the delta phase and gamma amplitude coupling at AN, CM, and the seizure onset zone.[162] PAC values were calculated using a 40-second window at baseline, 20 minutes before seizure onset, and another 40-second window starting at the seizure onset. The delta phase was aggregated using a sliding window from 1-4 Hz of width 0.2 Hz. Gamma amplitude was aggregated using a sliding window of 30-100 Hz of width 10 Hz to account for computational constraints. PAC was calculated using the Modulation Index (MI) method.[163] To eliminate the marginal distribution and ensure it was sensitive to the joint distribution, we computed 200 random surrogates with various time lags.[164] The final PAC values were normalized by the z-score of the surrogates. We computed the statistical significance of change at each phase/amplitude value using a Wilcoxon signed rank test. We also compute the mean z-score change across all seizures.

Statistical Analysis

The Mann-Whitney U test was used to characterize ictal and post-ictal changes in connectivity quantitatively. We used a one-sided test to determine if there was a statistically significant increase in connectivity. The baseline was set to the connectivity (coherence values or spectral GCA values) 20 to 10 minutes before seizure onset. We then calculated the statistical significance between a 32-second sliding window with a 4-second step size and the baseline. Bonferroni correction was used to correct for multiple comparisons by adjusting the statistical significance threshold alpha (0.05) by the number of comparisons. The total

number of comparisons was defined as the product of the number of windows, frequency bands, and interactions. We defined the latency of interaction as the first time at which a statistically significant increase from baseline was observed, while the duration refers to the length of time during which the increase remained statistically significant. We also conducted two-sided Mann-Whitney U tests to identify statistically significant differences between frequency bands or thalamic nuclei. In the post-hoc analysis, we used a paired Wilcoxon signed-rank test to obtain paired differences in coherence connectivity between the thalamic nuclei. For subject-wise analysis, connectivity measurements were averaged across all seizures in each subject to determine a statistically significant increase from baseline. We used a one-sided Mann-Whitney U Test to assess the significance between the baseline and a sliding window. Since the number of tests increased by an order of magnitude, we applied the Benjamin-Hochberg procedure to control the false discovery rate (FDR).

Data Sharing and Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

6.3 Results

Cohort and seizure characteristics

Ten patients (four females) were identified for this study. The median age at thalamic recording was 18.4 years (range 2.7–28.1 years). A total of 870 contacts were placed: 80 in the thalamus and 790 in non-thalamus regions (Figure 6.1B). Each patient had a median of 83 contacts (range: 38–148). Nine patients had unilateral SEEG sampling in the AN/CM implant, and one had bilateral AN coverage. Epilepsy etiology included tuberous sclerosis complex, Rasmussen's encephalitis, focal cortical dysplasia (FCD), encephalocele, and unknown. Seizure types included focal motor, focal impaired awareness, focal motor to

bilateral tonic-clonic, myoclonic, epileptic spasms, and startle-induced. There were no patients excluded. A total of 36 seizures were analyzed for further group analysis (the median number was 4, with a range of 2-5 per patient). (see details in Appendix Section A.1).

Undirected connectivity changes based on coherence analysis

With the group analysis for the coherence analysis (36 seizures across ten patients), we demonstrated that there was a significant increase in the undirected connectivity during seizures in all frequency bands (delta, theta, alpha, beta, and gamma) at the group level, except beta band in AN (Figure 6.2A and Table 6.1). The increase in coherence change (% change) was greater in the delta band compared to the gamma band, with values of 16.2% vs. 4.8% (AN) and 14.9% vs. 5.4% (CM), respectively ($p < 0.001$ and $p < 0.005$). Also, the increase in coherence change (% change) was greater in the ipsilateral AN compared to the contralateral AN (16.2% vs. 5.9%; $p = 0.03$). With the limited number of seizures contralateral to CM sampling ($n = 4$), we were unable to compare the coherence changes between the ipsilateral and contralateral CM. In the subject-wise analysis, most subjects demonstrated a statistically significant coherence increase between the onset and ipsilateral AN (60-100%) as well as the ipsilateral CM (80-90%) across five frequency bands: delta, theta, alpha, beta, and gamma (see Table 6.2).

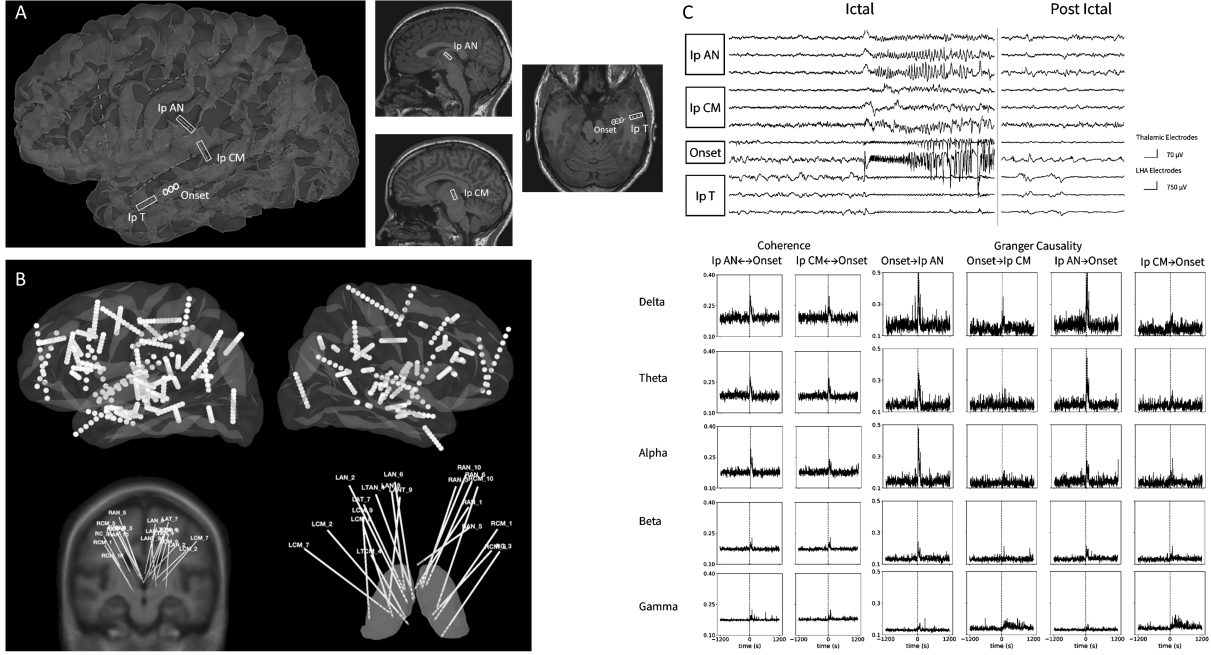


Figure 6.1: SEEG placement, ictal iEEG signature, Coherence, and spectral Granger Causality. (A) A lateral view of a 3D reconstruction of the SEEG implantation, and the trajectory of the electrodes superimposed on the sagittal view for thalamic channels and the axial view for temporal cortical and onset channels were shown. (B) A total of 870 intracranial contacts were placed. There were 80 contacts in the thalamus and 790 in the non-thalamus regions. Thalamic contacts were visualized on the coronal MRI slice of the standardized brain and within the 3D reconstruction of the thalamus using Brainstorm. Each patient had a median of 83 contacts (range: 38–148). Nine patients had unilateral SEEG sampling in the AN/CM implant, and one had bilateral AN coverage. (C) An example of a patient with limbic seizures (subject #6). The seizure onset in the iEEG tracing is clearly observed in both thalamic and non-thalamic channels as low-voltage fast patterns at the top panel. The time courses for coherence and spectral Granger causality are presented from 20 minutes before the seizure to 20 minutes after at the bottom panels. There was a significant increase in bidirectional connectivity at the time of seizure onset for both seizures. Notably, the changes in Granger causality were inversely proportional to the frequency band, with the delta band exhibiting a more significant increase compared to the beta/gamma bands. Ip: ipsilateral; AN: anterior nucleus; CM: centromedian; T: temporal; SEEG: stereotactic EEG

Table 6.1: Summary of coherence and Granger causality analysis

Coherence Analysis										Granger Causality Analysis																			
Onset <->					Ip_ AN Onset <->					Ip_ CM Onset <->					Co_ AN Onset <->					Inflow					Outflow				
Delta	Raw Ictal Coherence	0.23	0.20	0.22	0.19	0.20	0.20	0.19	0.20	Raw Ictal GCA	0.28	0.23	0.23	0.18	0.27	Raw Baseline GCA	0.19	0.16	0.18	0.16	64.59%								
	Raw Baseline Coherence	0.20	0.20	0.19	0.19	0.19	0.19	0.19	0.19	%Change	54.49%	0.19	0.17	0.18	78.25%	Duration (s)	40	92	80	40	40								
	Latency (s)	104	3	7	64	7	NA	NA	NA	Latency (s)	7	7	7	7	7	Raw Ictal GCA	0.25	0.22	0.26	0.25	25								
	Raw Ictal Coherence	0.22	0.20	0.21	0.19	0.20	0.20	0.19	0.19	Raw Baseline GCA	0.17	0.16	0.16	0.16	0.16	%Change	49.81%	42.18%	63.01%	55.82%	24								
	Raw Baseline Coherence	0.19	0.19	0.19	0.19	0.19	0.19	0.19	0.19	Duration (s)	108	116	116	40	24	Latency (s)	3	-5	3	15	15								
Theta	Raw Ictal Coherence	0.21	0.21	0.21	0.18	0.20	0.20	0.20	0.20	Raw Ictal GCA	0.23	0.23	0.22	0.23	0.22	Raw Baseline GCA	0.17	0.16	0.16	0.16	0.16								
	Raw Baseline Coherence	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18	%Change	35.50%	35.50%	42.02%	47.85%	47.76%	Duration (s)	96	108	108	4	4								
	Latency (s)	48	7	-1	NA	NA	NA	NA	NA	Latency (s)	7	3	7	7	31	Raw Ictal GCA	0.23	0.21	0.19	0.19	0.19								
	Raw Ictal Coherence	0.19	0.19	0.19	0.18	0.20	0.20	0.19	0.19	Raw Baseline GCA	0.16	0.16	0.15	0.15	0.14	%Change	45.49%	41.28%	30.16%	31.80%	14								
	Raw Baseline Coherence	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18	Duration (s)	20	4	4	4	48	Latency (s)	7	15	NA	51	51								
Alpha	Raw Ictal Coherence	0.19	0.19	0.19	0.18	0.18	0.18	0.18	0.18	Raw Ictal GCA	0.26	0.26	0.21	0.18	0.17	Raw Baseline GCA	0.16	0.15	0.16	0.16	0.16								
	Raw Baseline Coherence	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18	%Change	58.13%	58.13%	44.48%	12.32%	10.81%	Duration (s)	55	40	8	8	92								
	Latency (s)	124	15	35	NA	NA	NA	NA	NA	Latency (s)	40	23	23	87	51	Raw Ictal GCA	0.23	0.21	0.19	0.19	0.19								
	Raw Ictal Coherence	0.23	0.20	0.22	0.19	0.20	0.20	0.19	0.20	Raw Baseline GCA	0.16	0.16	0.15	0.15	0.14	%Change	45.49%	41.28%	30.16%	31.80%	14								
	Raw Baseline Coherence	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18	Duration (s)	20	4	4	4	48	Latency (s)	7	15	NA	51	51								
Beta	Raw Ictal Coherence	0.23	0.20	0.22	0.19	0.20	0.20	0.19	0.20	Raw Ictal GCA	0.28	0.23	0.23	0.18	0.27	Raw Baseline GCA	0.19	0.16	0.18	0.16	0.16								
	Raw Baseline Coherence	0.20	0.20	0.19	0.19	0.19	0.19	0.19	0.19	%Change	54.49%	0.19	0.17	0.18	78.25%	Duration (s)	40	92	80	40	40								
	Latency (s)	104	3	7	64	7	NA	NA	NA	Latency (s)	7	7	7	7	7	Raw Ictal GCA	0.25	0.22	0.26	0.25	25								
	Raw Ictal Coherence	0.22	0.20	0.21	0.19	0.20	0.20	0.19	0.19	Raw Baseline GCA	0.17	0.16	0.16	0.16	0.16	%Change	49.81%	42.18%	63.01%	55.82%	24								
	Raw Baseline Coherence	0.19	0.19	0.19	0.19	0.19	0.19	0.19	0.19	Duration (s)	108	116	116	40	24	Latency (s)	3	-5	3	15	15								
Gamma	Raw Ictal Coherence	0.21	0.21	0.21	0.18	0.20	0.20	0.20	0.20	Raw Ictal GCA	0.23	0.23	0.22	0.23	0.22	Raw Baseline GCA	0.17	0.16	0.16	0.16	0.16								
	Raw Baseline Coherence	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18	%Change	35.50%	35.50%	42.02%	47.85%	47.76%	Duration (s)	96	108	108	4	4								
	Latency (s)	48	7	-1	NA	NA	NA	NA	NA	Latency (s)	7	3	7	7	31	Raw Ictal GCA	0.23	0.21	0.19	0.19	0.19								
	Raw Ictal Coherence	0.19	0.19	0.19	0.18	0.20	0.20	0.19	0.19	Raw Baseline GCA	0.16	0.16	0.15	0.15	0.14	%Change	45.49%	41.28%	30.16%	31.80%	14								
	Raw Baseline Coherence	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18	Duration (s)	20	4	4	4	48	Latency (s)	7	15	NA	51	51								
Delta	Raw Ictal Coherence	0.23	0.20	0.22	0.19	0.20	0.20	0.19	0.20	Raw Ictal GCA	0.28	0.23	0.23	0.18	0.27	Raw Baseline GCA	0.19	0.16	0.18	0.16	0.16								
	Raw Baseline Coherence	0.20	0.20	0.19	0.19	0.19	0.19	0.19	0.19	%Change	54.49%	0.19	0.17	0.18	78.25%	Duration (s)	40	92	80	40	40								
	Latency (s)	104	3	7	64	7	NA	NA	NA	Latency (s)	7	7	7	7	7	Raw Ictal GCA	0.25	0.22	0.26	0.25	25								
	Raw Ictal Coherence	0.22	0.20	0.21	0.19	0.20	0.20	0.19	0.19	Raw Baseline GCA	0.17	0.16	0.16	0.16	0.16	%Change	49.81%	42.18%	63.01%	55.82%	24								
	Raw Baseline Coherence	0.19	0.19	0.19	0.19	0.19	0.19	0.19	0.19	Duration (s)	108	116	116	40	24	Latency (s)	3	-5	3	15	15								
Alpha	Raw Ictal Coherence	0.21	0.21	0.21	0.18	0.20	0.20	0.20	0.20	Raw Ictal GCA	0.23	0.23	0.22	0.23	0.22	Raw Baseline GCA	0.17	0.16	0.16	0.16	0.16								
	Raw Baseline Coherence	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18	%Change	35.50%	35.50%	42.02%	47.85%	47.76%	Duration (s)	96	108	108	4	4								
	Latency (s)	48	7	-1	NA	NA	NA	NA	NA	Latency (s)	7	3	7	7	31	Raw Ictal GCA	0.23	0.21	0.19	0.19	0.19								
	Raw Ictal Coherence	0.19	0.19	0.19	0.18	0.20	0.20	0.19	0.19	Raw Baseline GCA	0.16	0.16	0.15	0.15	0.14	%Change	45.49%	41.28%	30.16%	31.80%	14								
	Raw Baseline Coherence	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18	Duration (s)	20	4	4	4	48	Latency (s)	7	15	NA	51	51								
Beta	Raw Ictal Coherence	0.23	0.20	0.22	0.19	0.20	0.20	0.19	0.20	Raw Ictal GCA	0.28	0.23	0.23	0.18	0.27	Raw Baseline GCA	0.19	0.16	0.18	0.16	0.16								
	Raw Baseline Coherence	0.20	0.20	0.19	0.19	0.19	0.19	0.19	0.19	%Change	54.49%	0.19	0.17	0.18	78.25%	Duration (s)	40	92	80	40	40								
	Latency (s)	104	3	7	64	7	NA	NA	NA	Latency (s)	7	7	7	7	7	Raw Ictal GCA	0.25	0.22	0.26	0.25	25								
	Raw Ictal Coherence	0.22	0.20	0.21	0.19	0.20	0.20	0.19	0.19	Raw Baseline GCA	0.17	0.16	0.16	0.16	0.16	%Change	49.81%	42.18%	63.01%	55.82%	24								
	Raw Baseline Coherence	0.19	0.19	0.19	0.19	0.19	0.19	0.19	0.19	Duration (s)	108	116	116	40	24	Latency (s)	3	-5	3	15	15								
Gamma	Raw Ictal Coherence	0.21	0.21	0.21	0.18	0.20	0.20	0.20	0.20	Raw Ictal GCA	0.23	0.23	0.22	0.23	0.22	Raw Baseline GCA	0.17	0.16	0.16	0.16	0.16								
	Raw Baseline Coherence	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18	%Change	35.50%	35.50%	42.02%	47.85%	47.76%	Duration (s)	96	108	108	4	4								
	Latency (s)	48	7	-1	NA	NA	NA	NA	NA	Latency (s)	7	3	7	7	31	Raw Ictal GCA	0.23	0.21	0.19	0.19	0.19								
	Raw Ictal Coherence	0.19	0.19	0.19	0.18	0.20	0.20	0.19	0.19	Raw Baseline GCA	0.16	0.16	0.15	0.15	0.14	%Change	45.49%	41.28%	30.16%	31.80%	14								
	Raw Baseline Coherence	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18	Duration (s)	20	4	4	4	48	Latency (s)	7	15	NA	51	51								
Delta	Raw Ictal Coherence	0.23	0.20	0.22	0.19	0.20	0.20	0.19	0.20	Raw Ictal GCA	0.28	0.23	0.23	0.18	0.27	Raw Baseline GCA	0.19	0.16	0.18	0.16	0.16								
	Raw Baseline Coherence	0.20	0.20	0.19	0.19	0.19	0.19	0.19	0.19	%Change	54.49%	0.19	0.17	0.18	78.25%	Duration (s)	40	92	80	40	40								
	Latency (s)	104	3	7	64	7	NA	NA	NA	Latency (s)	7	7	7	7	7	Raw Ictal GCA	0.25	0.22	0.26	0.25	25								
	Raw Ictal Coherence	0.22	0.20	0.21	0.19	0.20	0.20	0.19	0.19	Raw Baseline GCA	0.17	0.16	0.16	0.16	0.16	%Change	49.81%	42.18%	63.01%	55.82%	24								
	Raw Baseline Coherence	0.19	0.19	0.19	0.19	0.19	0.19	0.19	0.19	Duration (s)	108	116	116	40	24	Latency (s)	3	-5	3	15	15								
Alpha	Raw Ictal Coherence	0.21	0.21	0.21	0.18	0.20	0.20	0.20	0.20	Raw Ictal GCA	0.23	0.23	0.22	0.23	0.22	Raw Baseline GCA	0.17	0.16	0.16	0.16	0.16								
	Raw Baseline Coherence	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18	%Change	35.50%	35.50%	42.02%	47.85%	47.76%	Duration (s)	96	108	108	4	4								
	Latency (s)	48	7	-1	NA	NA	NA	NA	NA	Latency (s)	7	3	7	7	31	Raw Ictal GCA	0.23	0.21	0.19	0.19	0.19								
	Raw Ictal Coherence	0.19	0.19	0.19	0.18	0.20	0.20	0.19	0.19	Raw Baseline GCA	0.16	0.16	0.15	0.15	0.14	%Change	45.49%	41.28%	30.16%	31.80%	14								
	Raw Baseline Coherence	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18	Duration (s)	20	4	4	4	48	Latency (s)	7	15	NA	51	51								
Beta	Raw Ictal Coherence	0.23	0.20	0.22	0.19	0.20	0.20	0.19	0.20	Raw Ictal GCA	0.28	0.23	0.23	0.18	0.27	Raw Baseline GCA	0.19	0.16	0.18	0.16	0.16								
	Raw Baseline Coherence	0.20	0.20	0.19	0.19	0.19	0.19	0.19	0.19	%Change	54.49%	0.19	0.17	0.18	78.25%	Duration (s)	40	92	80	40	40								
	Latency (s)	104	3	7	64	7	NA	NA	NA	Latency (s)	7	7	7	7	7	Raw Ictal GCA	0.25	0.22	0.26	0.25	25								
	Raw Ictal Coherence	0.22	0.20	0.21	0.19	0.20	0.20	0.19	0.19	Raw Baseline GCA	0.17	0.16	0.16	0.16	0.16	%Change	49.81%	42.18%	63.01%	55.82%	24								
	Raw Baseline Coherence	0.19	0.19	0.19	0.19	0.19	0.19	0.19	0.19	Duration (s)	108	116	116	40	24	Latency (s)	3	-5	3	15	15								
Gamma	Raw Ictal Coherence	0.21	0.21	0.21	0.18	0.20	0.20	0.20	0.20	Raw Ictal GCA	0.23	0.23	0.22	0.23	0.22	Raw Baseline GCA	0.17	0.16	0.16	0.16	0.16								
	Raw Baseline Coherence	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18	%Change	35.50%	35.50%	42.02%	47.85%	47.76%	Duration (s)	96	108	108	4	4								
	Latency (s)	48	7	-1	NA	NA	NA	NA	NA	Latency (s)	7	3	7	7	31	Raw Ictal GCA	0.23	0.21	0.19	0.19	0.19								
	Raw Ictal Coherence	0.19	0.19	0.19	0.18	0.20	0.20	0.19	0.19	Raw Baseline GCA	0.16	0.16	0.15	0.15	0.14	%Change	45.49%	41.28%	30.16%	31.80%	14								
	Raw Baseline Coherence	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18	Duration (s)	20	4	4	4	48	Latency (s)	7	15	NA	51	51								
Delta	Raw Ictal Coherence	0.23	0.20	0.22	0.19	0.20	0.20	0.19	0.20	Raw Ictal GCA	0.28	0.23	0.23	0.18	0.27	Raw Baseline GCA	0.19	0.16	0.18	0.16	0.16								
	Raw Baseline Coherence	0.20	0.20	0.19	0.19	0.19	0.19	0.19	0.19	%Change	54.49%	0.19	0.17	0.18	78.25%	Duration (s)	40	92	80	40	40								
	Latency (s)	104	3	7	64	7</																							

Directional connectivity changes based on GCA

With the group analysis for GCA (36 seizures across ten patients), we demonstrated a significant increase in the bidirectional connectivity during seizures, except outflow (to the onset from the thalamus) in the alpha and beta bands (Figure 6.2B). While the inflow of information increased during seizures across the frequency bands, the outflow of information was most prominently observed in the delta band. Also, the onset latency of the increase in functional connectivity in both directions during seizures was earlier in the slow frequencies (delta and theta) than in the fast frequencies (beta and gamma) (Figure 6.3 and Table 6.1). In the subject-wise analysis, the majority of subjects exhibited a statistically significant increase in GCA inflow from the onset to both the ipsilateral AN (70-80%) and CM (70-80%) across the five frequency bands. Similarly, there was a significant rise in GCA outflow to the onset from the ipsilateral AN (60-80%) and CM (70-80%) in these bands (refer to Table 6.2).

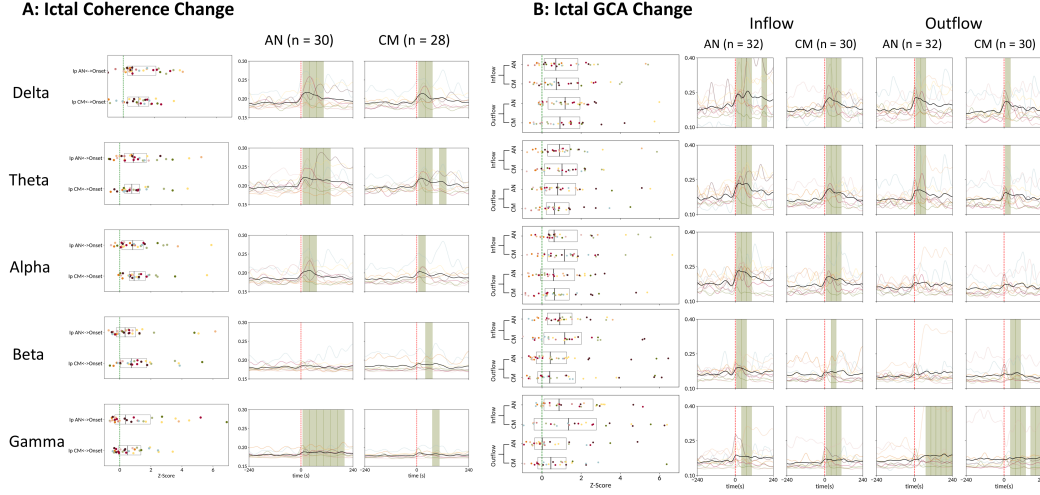


Figure 6.2: **Summary of a group analysis of ictal coherence and GCA changes.**

(A) The ictal coherence changes across seizures. The left panels illustrate the z-score difference between ipsilateral AN and onset, as well as ipsilateral CM and onset, during the 0-20s interval after the seizure compared to the baseline (20-10 mins before the seizure) for five frequency bands. Each colored dot represents an individual subject. Overall, coherence demonstrates an increase in all frequency bands during seizures. The right panels display a group analysis of coherence time courses from 4 minutes before seizure to 4 minutes after seizure for different frequency bands and interactions between AN and onset and CM and onset. The shaded green region indicates a statistically significant (Mann-Whitney U Test) increase in coherence relative to the aforementioned baseline. The calculations were performed using a sliding window of size 32s and a 4s step. The colored lines represent the average coherence across seizures for each patient, while the bolded black line represents the mean time course across all patients and seizures. There is a notable increase in connectivity between both thalamic nuclei and the seizure onset at all frequency bands except for the Beta band at AN. (B) The ictal GCA changes across seizures. The left panels illustrate the z-scored change in spectral Granger causality from the baseline period (20-10 mins before seizure) to the seizure window (0-10s after seizure), while the right panels depict the group analysis of the time course of spectral Granger causality from 4 minutes before seizure to 4 minutes after seizure for different electrode interactions. Inflow refers to the directed spectral Granger causality from the onset to AN or CM, while outflow refers to the directed causality from AN or CM to the onset. The shaded green regions indicate if a window exhibits a statistically significant increase in spectral Granger causality. The differently colored lines represent the mean values of all seizures for a specific patient, and the bolded black line represents the mean across all seizures. Overall, there is a clear and significant increase in bidirectional spectral Granger causality between the thalamus and cortical onset in the Delta, Theta, Beta, and Gamma frequency bands. In the Alpha band, there are only statistically significant increases in the inflow to the thalamus. GCA: Granger causality analysis; AN: anterior nucleus; CM: centromedian

Table 6.2: Subject-wise connectivity analysis

	Coherence (n=10)			Granger causality analysis (n=10)					
	Ip_AN	AN <-> Onset	Ip_CM <-> Onset	Delta	Onset -> Ip_AN	Onset -> Ip_CM	Ip_AN -> Onset	Ip_CM -> Onset	Onset
Delta	8		9		6	7	9	7	7
Theta	9		8	Theta	8	7	6	7	7
Alpha	9		8	Alpha	8	8	8	8	8
Beta	6		8	Beta	8	7	7	8	8
Gamma	10		8	Gamma	7	8	8	8	8

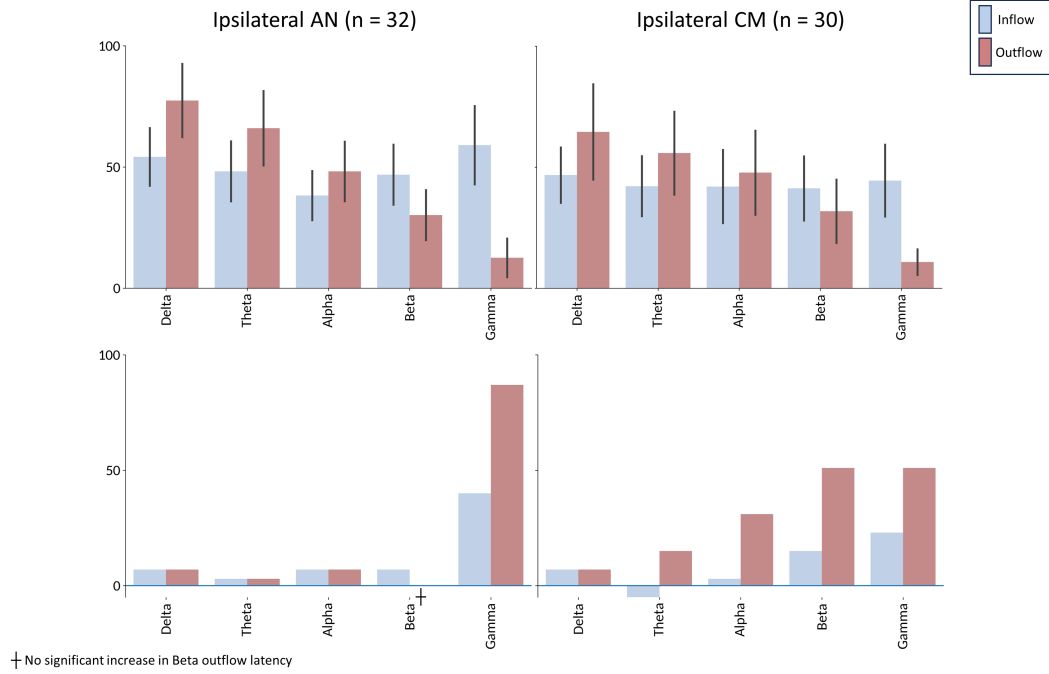


Figure 6.3: **Summary of percent change and latency in Granger causality.** The top panel provides a summary of the percentage change in inflow and outflow to the ipsilateral AN and CM. There was a statistically significant difference (Mann-Whitney U Test) between Delta outflow and Beta/Gamma outflow in the AN and between Delta and Gamma outflow in the CM. The bottom panel summarizes the latency, which indicates how soon after seizure onset, a significant increase occurs for ipsilateral AN and CM inflow and outflow. We observed that the latency increased as the frequency bands became faster. Of note, there was no statistically significant increase in outflow from the AN in the beta band. AN: anterior nucleus; CM: centromedian

PAC at the baseline and seizure onset: We demonstrated evidence of PAC between delta and gamma bands in both interictal and ictal periods at seizure onset zones, AN, and CM. While there was a moderate increase in the normalized PAC in the regions of interest, this increase was mostly not statistically significant. In AN, there was a significant increase in PAC during the ictal period compared to the baseline (Figure 6.4).

Connectivity changes based on seizure onset focus

We investigated undirected and directional connectivity changes based on different seizure onsets as the post-hoc analysis (Figure 6.5). The delta coherence showed a more pronounced

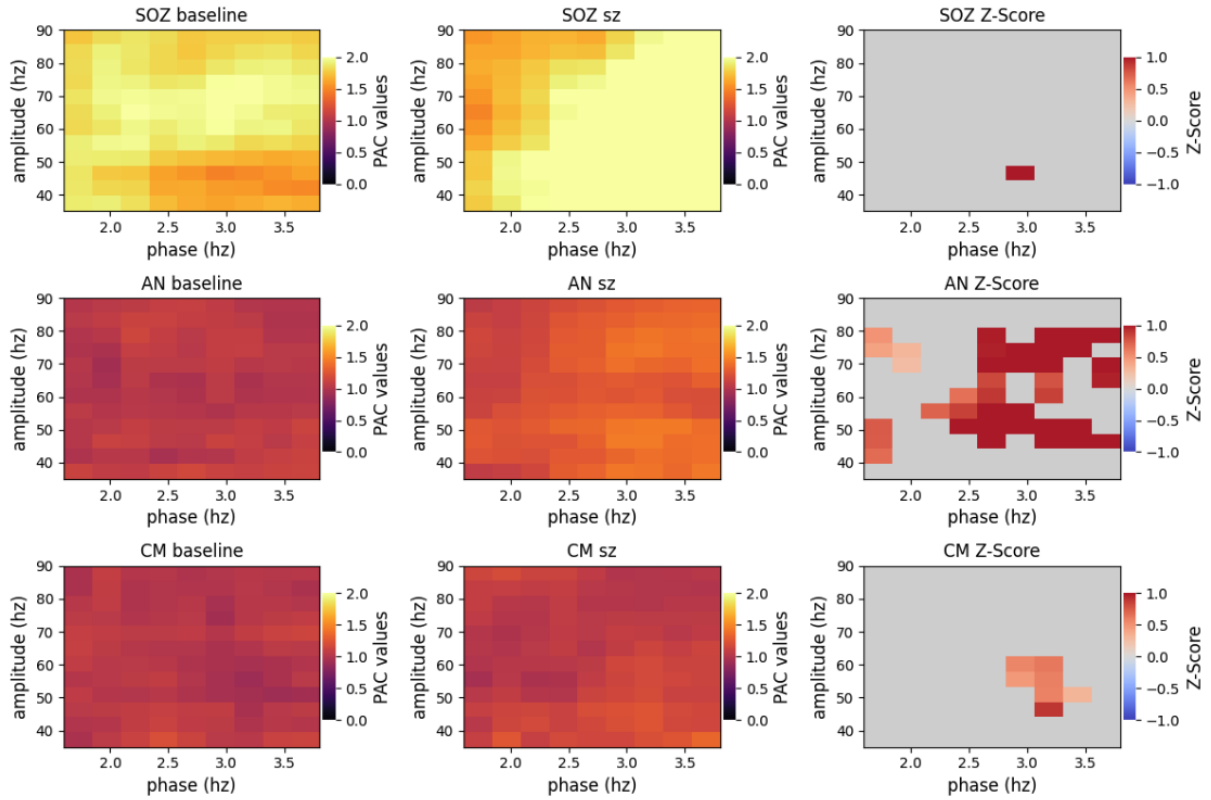


Figure 6.4: **Phase amplitude coupling (PAC) between the delta band phase and gamma band amplitude.** PAC at baseline (left column), during seizure (middle column), and z-score change from baseline to during seizure (right column). PAC was calculated using a 40-second window for baseline and seizure onset, starting from 20 minutes before seizure onset, and the seizure onset, respectively. The rows indicate PAC calculated in SOZ, anterior nucleus of the thalamus (AN), and centromedian nucleus of the thalamus (CM). In the Z score comparison, only significant values are shown, while the remaining are colored in grey.

increase at CM than at AN during frontal lobe seizures ($n=13$) (14.7% vs. 8.3%; $p < 0.01$). Conversely, in limbic seizures ($n=12$), the increase was greater at AN compared to CM (14.7% vs. 7.1%; $p = 0.02$). In the case of parietal lobe seizures ($n=12$), no difference was noted between CM vs. AN (28.8% vs. 23.1%; $p = 0.84$). We did not make any comparisons in the temporal neocortical seizures since the number was limited ($n = 4$). With the directional connectivity analysis, we demonstrated that the inflow to the thalamus from the onsets increased mostly ipsilaterally during seizures across the frequency bands but more prominently in slower frequencies (delta, theta, and alpha). Similarly, each brain region's outflow from the thalamus was relatively limited to ipsilateral and slower frequency bands (delta, theta, and alpha) (Figures 6.6 and 6.7).

6.4 Discussion

This study investigated a unique cohort of ten patients with DRE who had thalamic iEEG sampling within AN and CM. Using undirected and directed connectivity analysis, we elucidated the dynamic changes in corticothalamic connectivity between thalamic nuclei and different seizure foci during seizures. We found that coherence between seizure onset and thalamic nuclei significantly increased across all frequency bands, especially in slower frequencies (delta, theta, and alpha) compared to faster frequencies (beta and gamma). In the spectral GCA, we observed an increased information flow from seizure onset regions to the thalamus in all frequency bands. However, the outflows from the thalamus to other brain regions were primarily in slower frequency bands, particularly in the delta band. In the delta frequency range, rather than faster frequencies, the increase in directed connectivity occurred simultaneously in both inflows and outflows at the start of the ictal EEG. Typically, we observe fast frequencies at the seizure onset, and it slows down as the seizure evolves on EEG. However, slow frequencies, such as ictal direct current (DC) shift, can also emerge at the onset of seizures.[165] Such ictal DC shift can precede faster frequencies, such as high-frequency os-

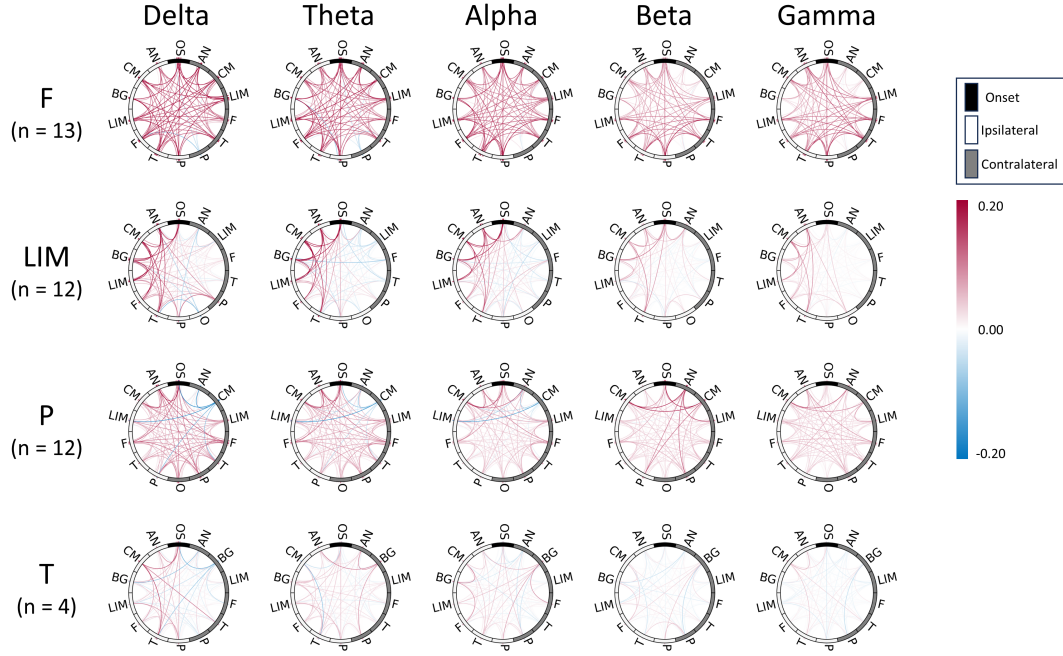


Figure 6.5: **Coherence changes across different seizure foci and frequency bands.**

Each node on the circles represents a collection of electrodes within a specific brain region. Nodes colored white indicate ipsilateral locations to the seizure, while grey-colored nodes represent contralateral regions. A line connecting two nodes signifies a non-zero change in coherence, and the hue of the line denotes the percentage change in coherence between the aforementioned baseline and the 0-20s interval after the seizure. Seizures are categorized based on their onset brain regions. In frontal lobe seizures, there is a pronounced bilateral increase in coherence between the cortical onset and other brain regions. In limbic seizures, coherence increases are predominantly observed ipsilateral to the seizure onset. Parietal lobe seizures exhibit similar coherence patterns as frontal onset seizures but with fewer coherence increases following seizure onset. It is important to note that this figure includes the post-hoc analysis (all seizures were analyzed for limbic seizures). F: Frontal; LIM: Limbic; P: Parietal; T: Temporal; AN:Anterior Nucleus; CM: Centromedian; BG: Basal Ganglia; O: Occipital; OS: Onset; Ip: ipsilateral; Co: contralateral

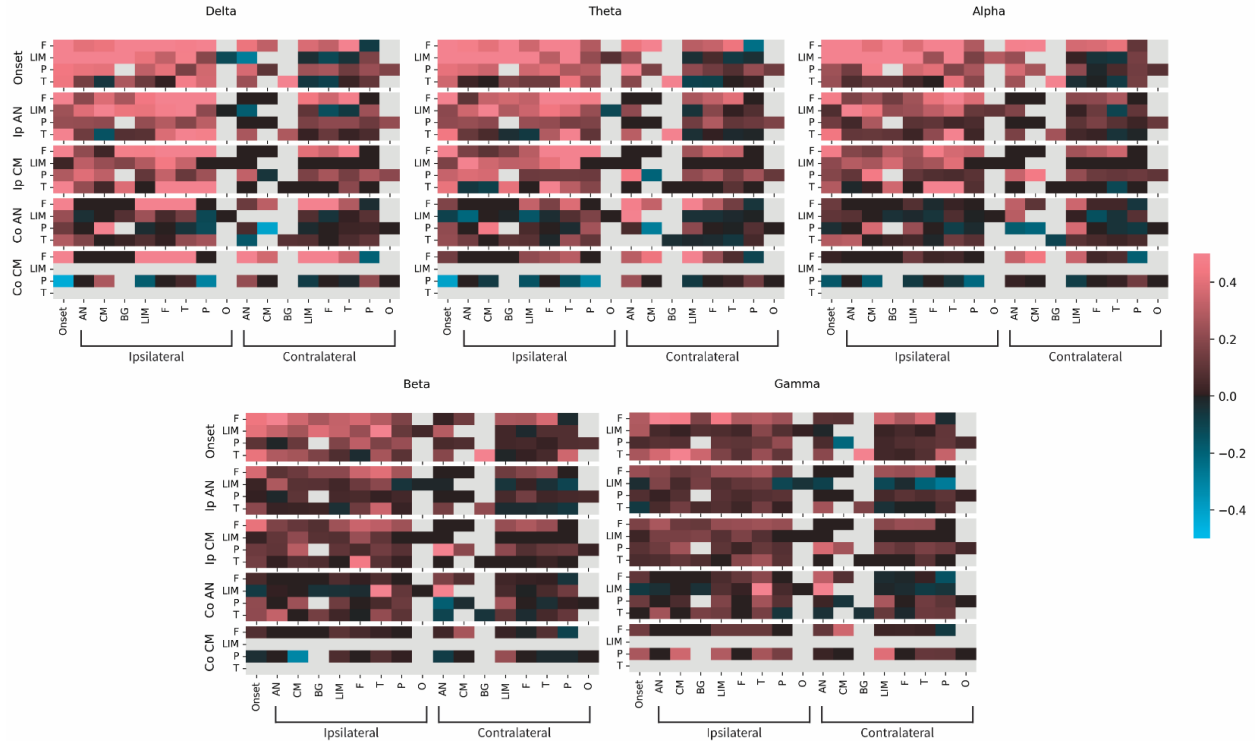


Figure 6.6: **Percent change in spectral Granger causality inflow across lobes and frequency bands.** Each heatmap demonstrates the percent change in spectral Granger causality from baseline (20-10 mins before seizure) to 0-10s after seizure for a particular frequency band. The rows in each heatmap represent the mean of seizures for a particular seizure onset lobe, and every grouping of 4 rows represents the inflow of causality from a particular set of electrodes (cortical onset and thalamus). Each column represents the electrode to which information is flowing. (F = Frontal, LIM = Limbic, P = Parietal, T = Temporal, AN = Anterior Nucleus of the Thalamus, CM = Centromedian Nucleus of the thalamus, BG = Basal Ganglia, O = Occipital, Ip = ipsilateral, Co = contralateral).

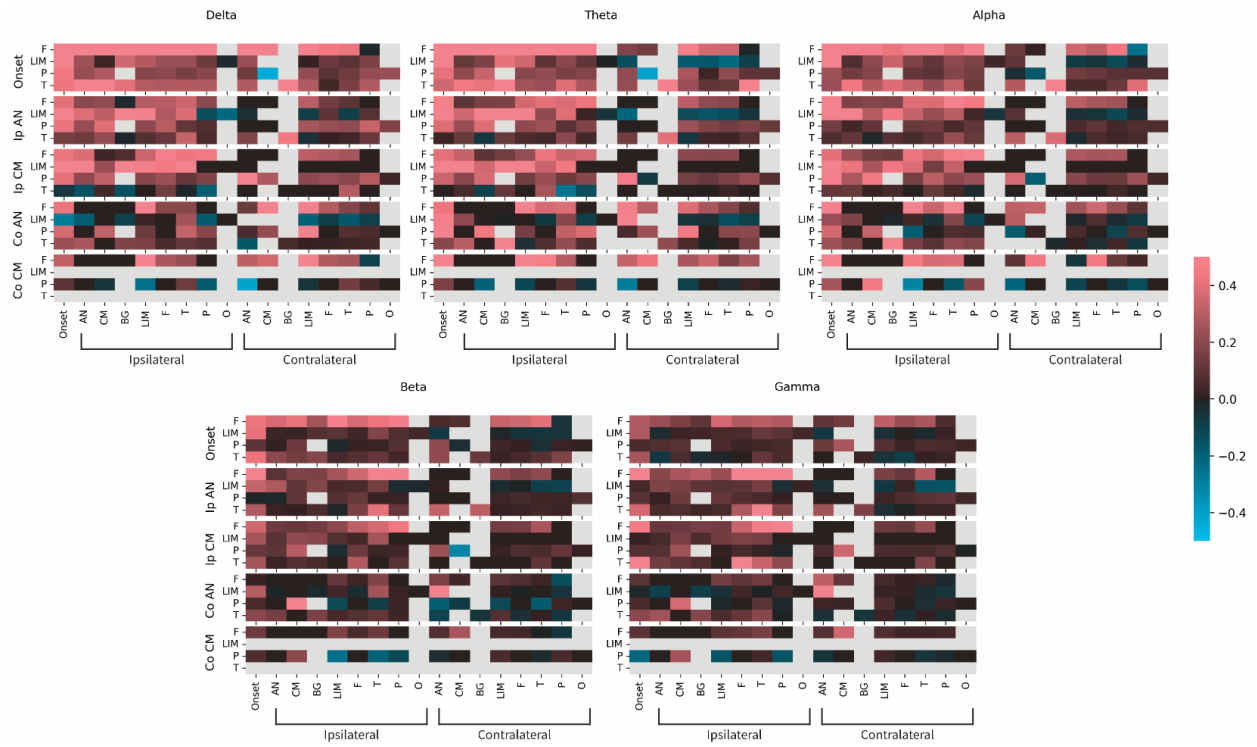


Figure 6.7: **Percent change in spectral Granger causality outflow across lobes and frequency bands.** This figure is similar to Suppl. Fig. 1, except each grouping of 4 rows represents the outflow of causality from the same set of electrodes.

cillations during seizures.[166] Slow frequencies, due to inhibitory long-range corticothalamic network, may emerge early and sustain during seizures, as prior studies suggested.[26, 167] In a study using an animal model, bidirectional cortical and thalamic interactions during absence seizures were demonstrated.[142] Another study showed hippocampal seizures suppressed the intralaminar thalamic and brainstem arousal system, inhibiting the cortical function (network inhibition hypothesis).[168] Our results provide compelling evidence that bidirectional delta frequency serves as a distinct marker of increased thalamocortical activity, which contains inhibitory outflow from the thalamus to the seizure onset zone. This finding strongly aligns with the traditional theory proposing that the delta component observed in the 3 Hz spike-wave discharges during absence seizures originate from the inhibitory corticothalamic input.[26] Ictal delta frequencies are known to couple with faster frequencies at the seizure onset.[169] We demonstrated that ictal delta-gamma PAC can also occur in the thalamus, suggesting a cross-frequency, long-range network involving both the seizure onset zones and the thalamus during seizures.

Our results underscore the significance of comprehending the spatiotemporal dynamics of the corticothalamic network during seizures. We observed that during frontal lobe seizures, the increase in delta coherence was more prominent in CM compared to AN. Conversely, in limbic seizures, the delta coherence increase was greater in AN than in CM. This finding aligns with previous studies utilizing noninvasive structural and functional imaging techniques, which have consistently demonstrated strong physiological thalamocortical connections between the frontal lobe and CM, as well as between the limbic area and AN.[27] Our findings are in line with the results of a recent SEEG study that investigated changes in ictal connectivity during temporal seizures. The study reported increased connectivity between the temporal lobe and AN.[151] However, using the spectral GCA, we further clarified that delta frequency was the main outflow information from the thalamus to the seizure onset. To our knowledge, this study is the first to provide evidence demonstrating the selective involvement of the CM over the AN in frontal lobe seizures.

Successful treatment of epilepsy can be achieved by accurately stimulating the relevant thalamic nucleus involved in the seizure network. A human study showed that by stimulating the central lateral nucleus of the intralaminar thalamus during limbic seizures, cortical EEG signals were effectively restored, leading to improved arousal in individuals with limbic epilepsy.[170] Another study further demonstrated that high-frequency stimulation (> 45 Hz) of the AN resulted in the desynchronization of ipsilateral hippocampal activity, successfully reducing seizure generation and propagation.[171] Using the ESTEL trial cohort, a study identified the parvocellular CM border as the optimal target for DBS in the LGS population using probabilistic stimulation mapping and structural connectivity analysis.[172] Regarding pulvinar stimulation, a study demonstrated that stimulation during seizures modified connectivity values by lowering the level of synchrony to improve awareness level.[173] Future studies will likely optimize stimulation parameters and elucidate the mechanisms underlying seizure modulation via CM or pulvinar stimulation.

This study has several limitations. The GCA typically requires signals to be stationary and linear,[174] and it is worth noting that the EEG signals utilized in this study may not strictly adhere to these assumptions. We employed various strategies to mitigate the deviation from stationarity assumptions. These strategies included filtering techniques to eliminate power line noise[175] and adopting windowing approaches to analyze shorter intervals, thereby enhancing the approximation to stationarity.[176] Our primary objective in this study was to establish a connection between cortical seizure foci and the thalamus. However, we will consider using other sophisticated measures of causality[177, 178] or non-linear regression approaches proposed in prior SEEG connectivity studies[151, 179] to further verify our results. In terms of the study cohort, the sample size was small ($n=10$) and included individuals with heterogeneous epilepsy etiologies. Such pathological variability might have introduced variability in the network underlying seizures. Notably, occipital lobe epilepsy was not included in this study. Additionally, our investigation solely focused on the AN and CM thalamic nuclei. As previous studies have emphasized the significance of the pul-

vinar nucleus in limbic and temporal lobe epilepsy, it would be of interest to extend the network analysis to incorporate the pulvinar nucleus. Furthermore, exploring connectivity changes at the end of seizure segments, as other research teams conducted,[143, 151] would also be valuable. Technical limitations, including the challenge of accurately delineating thalamic nuclei and subnuclei—particularly in pediatric cases—should be recognized. Each case requires meticulous verification by an experienced radiologist. Furthermore, to facilitate fully automated segmentation[180] and electrode co-registration, the compilation of a large dataset, especially from pediatric population is essential. Lastly, we acknowledge a fundamental limitation of using SEEG: the inability to ascertain whether we accurately or sufficiently sampled from the true epileptogenic zones or seizure onset.

In future studies, we plan to include more individuals with comprehensive thalamic sampling, as clinically indicated, including bithalamic or sampling of the pulvinar nucleus (in cases such as temporal, parietal, and occipital epilepsy). Furthermore, we are keen to explore the analysis of various seizure types (including epileptic spasms, focal seizures with or without alteration of awareness, or focal motor seizures evolving to bilateral tonic-clonic activities) originating from the same anatomical seizure onset. Studying a larger number of subjects with various epilepsy etiologies will likely provide more generalizable ictal corticothalamic network information. Exact dynamic sequences of how each frequency band changes and interacts with each other would be an important area of research, and we plan to investigate them in more detail in future studies. With the continuous progress in technology and increased awareness of neuromodulatory treatment options, it is anticipated that there will be a larger pool of candidates eligible for thalamic stimulation.[6, 25] Broader future directions building on this work are discussed in Chapter 9.

CHAPTER 7

Frequency-Specific Thalamocortical Network Dynamics During Focal Seizures in Humans

The previous chapter showed that thalamocortical networks exhibit structured recruitment at focal seizure onset, with distinct frequency-specific signatures visible across cortical and thalamic sites. A natural sequel is to ask how this recruitment evolves across the full seizure and, ultimately, how it disengages at termination. From a neuromodulation perspective, termination is the moment the system must both detect and eventually accelerate. This chapter characterizes frequency-specific thalamocortical network dynamics across the full ictal trajectory, from onset through termination, using directed connectivity and spectral Granger causality.

7.1 Introduction

Approximately one-third of patients with epilepsy develop drug-resistant disease (Chapter 2), and for individuals who are not candidates for curative resection, neuromodulation has emerged as an increasingly important therapeutic strategy. In particular, stimulation of thalamic nuclei, including the anterior and centromedian nuclei (AN and CM), is now widely used in both deep brain stimulation (DBS) and responsive neurostimulation (RNS) paradigms.[6, 5, 25, 181, 182] Despite growing clinical adoption of thalamic neuromodulation, the role of the thalamus in human focal seizure evolution remains incompletely understood, particularly at seizure onset and termination.

Prior stereo-electroencephalography (SEEG) studies have demonstrated thalamic involve-

ment in both focal and generalized epilepsies.[143, 148, 144, 149, 183, 184, 185, 186] Visual analyses and spectral measures have shown that thalamic activity often emerges early during seizures and persists through their evolution.[143, 148] Ictal connectivity studies have revealed increased thalamocortical connectivity that initiates at ictal onset.[143, 183] In terms of frequency band, slow and beta frequency rhythms are well suited to long-range synchronization and are known to be modulated by thalamocortical circuitry during physiological brain states and epilepsy.[187, 188, 189] Determining whether such frequency-specific and directional thalamocortical interactions are engaged during seizures is therefore critical, not only for clarifying seizure network organization but also for informing the design of adaptive or closed-loop neuromodulation strategies.

In parallel to the thalamocortical network, cortico-cortical interactions are well-established contributors to seizure propagation, with increased synchronization observed across cortical networks from seizure onset to termination.[190, 191, 192, 193] However, these two lines of investigation have largely progressed independently. Consequently, it remains unclear how thalamocortical and cortico-cortical networks interact dynamically during focal seizures, and whether thalamocortical engagement reflects a core component of seizure organization rather than only a downstream consequence of cortical spread.

In this study, we used human SEEG recordings with simultaneous cortical and thalamic sampling to characterize frequency-specific and directional thalamocortical network dynamics across seizure evolution and to compare them with cortico-cortical networks. We also evaluated whether thalamic spectral and connectivity features carry seizure-state information, relevant to thalamic biomarker development for closed-loop or adaptive neuromodulation.

7.2 Methods

7.2.1 Patient Cohort

Patients with pediatric-onset (age at onset ≤ 18 years) drug-resistant epilepsy admitted to UCLA Mattel Children’s Hospital were retrospectively studied. All underwent chronic SEEG implantation between November 2020 and July 2024, sampling an anticipated epileptic network that included the thalamus. Thalamic electrodes targeted AN and CM. All had suspected focal seizure onset and were considered candidates for thalamic neuromodulation. Thalamic sampling was clinically justified, and no electrodes were placed solely for research. Patients were excluded if their seizures consisted exclusively of brief (< 10 s) or intermittent events (e.g., myoclonic seizures or epileptic spasms), which preclude analysis of temporal network dynamics.

7.2.2 Standard Protocol Approvals

The research protocol was approved by the Institutional Review Board at the University of California, Los Angeles. Written informed consent was obtained for surgical procedures, including SEEG implantation involving thalamic targets, and for research use of SEEG data.

7.2.3 Surgical Evaluation and Electrode Localization

SEEG implantation plans were determined at a multidisciplinary epilepsy surgery conference including epileptologists, neurosurgeons, neuroradiologists, and neuropsychologists. Implantation strategies were guided by seizure semiology, neurological examination, neuroimaging (MRI, PET, SPECT, magnetoencephalography), neuropsychological testing, and scalp EEG, with emphasis on localizing the seizure onset zone (SOZ). Unilateral thalamic sampling was selected based on the suspected SOZ and its anatomical connectivity, whereas bilateral thalamic sampling was considered in cases with diffuse or poorly localized seizure onset.

Electrode trajectories were planned using BrainLab Elements software (Brainlab AG,

Munich, Germany) based on gadolinium-enhanced and non-enhanced T1-weighted MRI sequences. Target thalamic nuclei were manually outlined by an experienced neuroradiologist (NS).[149, 183] MP2RAGE-based trajectories were coregistered to volumetric computed tomography for surgical guidance. Four-contact Spencer depth electrodes with 1.1 mm diameter and 2.5 mm intercontact spacing were used for thalamic targets, while six- to twelve-contact electrodes with 5 mm spacing were used for cortical regions. Postoperative computed tomography confirmed electrode placement and excluded intracranial hemorrhage.

Cortical surfaces were reconstructed using preoperative MRI with FreeSurfer or Infant FreeSurfer for patients aged ≥ 2 or < 2 years, respectively.[154, 194] Electrode contact locations were verified using Brainstorm software,[155] and thalamic electrode positions were confirmed using automated thalamic segmentation with subsequent visual inspection.[180]

7.2.4 EEG Acquisition and Preprocessing

SEEG recordings were obtained using a Nihon Kohden JE-120A amplifier (Irvine, CA) at sampling rates of 200 or 2,000 Hz with a high-pass filter of 0.01 Hz and stored in European Data Format. Data were processed using MNE-Python.[158] SEEG signals were notch-filtered at 60 Hz and its harmonics up to half the sampling frequency to remove line noise. Recordings were downsampled to 200 Hz to standardize sampling across seizures. A bipolar montage was applied to minimize the effects of volume conduction. Channels in white matter, outside the brain, or containing artifacts were excluded. Canonical frequency bands were defined as slow (1–12 Hz), beta (13–30 Hz), and gamma (30–70 Hz). Slow frequencies were pooled to capture long-range synchronization while maintaining stable estimates across short analysis windows; supplementary analyses evaluated conventional sub-bands separately. Periods of interest were defined as follows: preictal (15 seconds before seizure onset), ictal (the first 15 seconds after seizure onset), end-of-seizure (ES; the final 15 seconds before seizure termination), and postictal (15 seconds after seizure termination). For seizures shorter than 30 seconds, ictal and ES periods were divided at the seizure midpoint. Interictal baseline

was defined as a 1-minute segment occurring 20 to 19 minutes before seizure onset.

7.2.5 Identification of Ictal Patterns

All seizures were reviewed to determine seizure onset and termination. Seizure onset was defined as the emergence of sustained rhythmic EEG patterns distinct from the interictal baseline,[149, 183] as identified by visual review by experienced clinical investigators (AD, SO, and HN). Seizure termination was defined as the disappearance of these sustained rhythmic EEG patterns and a return toward interictal activity. A maximum of three bipolar channels demonstrating the earliest and most prominent ictal involvement were designated as SOZ channels. Channels showing ictal changes within 10 seconds of onset were labeled propagation channels; remaining channels were classified as other.

Thalamic ictal patterns were independently assessed by two board-certified epileptologists (AD and SK). For each seizure, the reviewers annotated (i) involvement of the thalamus at seizure onset, (ii) thalamic onset EEG pattern, (iii) involvement of the thalamus at seizure offset, and (iv) thalamic offset EEG pattern. Early or peri-termination thalamic involvement was determined as ictal changes in the thalamus within 10 seconds from seizure onset, or within 10 seconds before seizure termination. Thalamic EEG patterns were categorized based on previously established classifications[148] into the following categories: none, low-voltage fast activity (LVFA), rhythmic spike, spike-and-wave or rhythmic slow-wave activity (RS/RSw), and slow wave without rhythmicity. Multiple ictal EEG patterns could be present simultaneously within the thalamus during a given seizure. When LVFA co-occurred with any other ictal EEG pattern, LVFA was designated as the primary pattern. RS/RSw was annotated when spike-and-wave or rhythmic slow-wave activity was the dominant pattern in the absence of clear fast activity. The slow-wave category was selected when an increase in slow-frequency power without rhythmicity was observed and neither LVFA nor RS/RSw criteria were met. In cases of disagreement, final classification was determined by consensus with a third reviewer (HN). Interrater reliability was assessed using Cohen κ for thalamic

involvement and ictal pattern classification at seizure onset and offset.

For post hoc analyses, each seizure was further classified according to seizure focus, ictal onset pattern, and presence of diffuse involvement at onset. Seizure focus was defined by lobar localization of the SOZ, including frontal, parietal, temporal, occipital, and limbic regions, with limbic regions comprising the hippocampus, parahippocampal gyrus, amygdala, cingulate gyrus, and insula. Diffuse involvement at seizure onset was defined as early ictal involvement (SOZ and propagation channels) spanning bilateral hemispheres or three ipsilateral systems (e.g., left frontal, temporal, and limbic regions).

7.2.6 EEG Analysis

For each seizure, we computed spectral power, imaginary coherence, and spectral Granger causality during the predefined periods of interest and interictal baseline periods. To characterize temporal evolution, each metric was calculated in non-overlapping two-second windows across the baseline, preictal, ictal, ES, and postictal time windows. To mitigate intersubject variability, spectral power and connectivity measures were expressed as either percent change or log-ratio relative to the interictal baseline, as appropriate. Analyses focused on the AN and CM ipsilateral to the SOZ (Ip AN and Ip CM). Metrics were first computed at the level of individual SEEG channels and subsequently averaged within anatomically defined regions to yield a single measure per region per time window.

Spectral Analysis

Power spectral density (PSD) was computed for each period of interest, time window, channel, and frequency band. Canonical frequency bands were defined a priori as slow (1–12 Hz), beta (13–30 Hz), and gamma (30–70 Hz). Spectral power values were averaged across time windows corresponding to each seizure phase (interictal, preictal, ictal, ES, and postictal).

Imaginary Coherence (iCoh)

Coherence quantifies undirected synchronization between two time-series signals across frequencies.[159] Values of coherence range between 0 and 1, where 1 represents the highest degree of synchrony between two signals. Coherence has widely been used in EEG data analysis to understand functional connectivity between different brain regions.[183, 159] Traditional coherence measures are susceptible to volume conduction effects, which can artificially inflate connectivity estimates. The iCoh isolates the imaginary component of the cross-spectrum and thus captures non-zero phase-lagged interactions between signals. Imaginary coherence was computed using the MNE-connectivity Python package.[158] For each seizure, iCoh was calculated between all channel pairs and subsequently grouped according to anatomical location, including SOZ, Ip AN, Ip CM, propagation channels, and other channels. iCoh values were then averaged within each interaction type to yield robust region-to-region connectivity measures across time and frequency bands.

Spectral Granger Causality (GCA)

While imaginary coherence provides an undirected measure of functional connectivity, it does not capture directionality. Granger causality analysis (GCA) quantifies whether past values of one signal improve prediction of another, and it has been widely applied in neuroscience to characterize directed measures of connectivity, including epilepsy research.[183, 184, 195, 196] The spectral extension enables frequency-domain estimation of directional interactions. Spectral GCA was computed using the spectral-connectivity Python package.[197] Directed connectivity was defined as thalamic inflow ($\text{SOZ} \rightarrow \text{thalamic nucleus}$) and thalamic outflow ($\text{thalamic nucleus} \rightarrow \text{SOZ}$), allowing assessment of bidirectional thalamocortical influence across seizure evolution and frequency bands. Unlike imaginary coherence, spectral Granger causality does not inherently correct for volume conduction. While bipolar montaging and anatomical distance between the thalamus and gray matter minimize such effects, residual mixing cannot be fully excluded; therefore, directional estimates should be interpreted as

putative directed functional interactions.

Random Forest Classification of Seizure State

To evaluate the translational utility of thalamic signals for real-time seizure detection, we used random forest classifiers to distinguish ictal from non-ictal states. Random forests were selected because they can accommodate nonlinear feature interactions and correlated predictors in moderate-sized datasets.[198] EEG data were epoched from seizure onset to termination, with an additional one-minute preictal and postictal window. Each seizure was segmented into non-overlapping two-second windows. Very short (< 10 s) and very long (> 300 s) seizures were excluded because they yield imbalanced numbers of ictal and non-ictal windows, potentially biasing performance estimates. Separate random forest classifiers were trained for AN and CM features. Feature sets included thalamic spectral power, iCoh, and spectral GCA between the thalamus and SOZ. Each model classified whether a given time window corresponded to an ictal or non-ictal state.

Model performance was evaluated using leave-one-patient-out cross-validation, and performance was quantified using the area under the receiver operating characteristic curve (AUROC) for held-out seizures. To improve interpretability, SHAP (SHapley Additive exPlanations)[199] were computed across all cross-validation folds and averaged to estimate the magnitude and direction of feature importance. Ablation analyses were performed by systematically removing feature categories (e.g., spectral power only, connectivity only, or specific frequency bands) to assess their relative contributions to classification performance.

7.2.7 Statistical Analysis

Effect sizes were reported as rank-biserial correlations (r_{rb}), with positive values indicating increases relative to interictal baseline. For group-level comparisons, two-tailed Wilcoxon signed-rank tests were used to assess whether spectral power, iCoh, or spectral GCA values differed significantly from the interictal baseline. For comparisons between non-overlapping

network groups (e.g., thalamocortical vs cortico-cortical interactions), Mann–Whitney U tests were applied. The seizure was treated as the unit of analysis, with values averaged within seizure before group-level testing. All p values were corrected for multiple comparisons using Bonferroni adjustment, accounting for the number of frequency bands, interaction types, and time windows tested.

7.3 Results

7.3.1 Patient characteristics

Twenty-one patients were initially identified. Two were excluded because recorded events consisted exclusively of epileptic spasms or focal seizures followed by epileptic spasms lasting <5 seconds, precluding analysis of seizure dynamics. Consequently, 19 patients (6 females) were included in the final cohort (Appendix Section A.2). The median age at thalamic recording was 16.9 years (range, 1.0–28.1 years). In total, 1,599 SEEG contacts were implanted, including 101 thalamic contacts (51 in AN and 50 in CM) (Figure 7.1). Each patient had a median of 83 contacts implanted (range, 38–148). Unilateral thalamic sampling was performed in 18 patients, while one patient underwent bilateral thalamic sampling. A total of 66 focal seizures were analyzed, with a median of 3 seizures per patient (range, 1–8).

7.3.2 Visual analysis

Visual analysis showed early thalamic recruitment in most sampled contacts, which became nearly universal by seizure termination. Within the AN ($n = 51$), ictal activity was observed at seizure onset in 39 contacts (76.4%), comprising LVFA in 21 (41.2%), RS/RSw in 15 (29.4%), and slow-wave activity in 3 (5.9%). At seizure termination, ictal changes were present in 48 AN contacts (94.1%), with LVFA in 2 (3.9%), RS/RSw in 39 (76.5%), and slow-wave activity in 7 (13.7%). Within the CM ($n = 50$), ictal changes at seizure onset were observed in 43 contacts (86.0%), consisting of LVFA in 25 (50.0%) and RS/RSw in 18

(36.0%). At seizure termination, ictal activity was present in 47 CM contacts (94.0%), with LVFA in 3 (6.0%), RS/RSw in 40 (80.0%), and slow-wave activity in 4 (8.0%) (Figure 7.1).

Overall, thalamic ictal patterns evolved from LVFA at seizure onset toward RS/RSw patterns at seizure termination across both nuclei. Cohen’s kappa demonstrated substantial interrater agreement for ictal onset involvement ($\kappa = 0.78$) and onset pattern classification ($\kappa = 0.82$), and moderate agreement for ictal offset involvement ($\kappa = 0.63$) and ictal offset pattern classification ($\kappa = 0.57$).

7.3.3 Frequency-Specific Thalamic and SOZ Spectral Power Changes Across Seizure Periods

Spectral power changes in the AN, CM, and SOZ were compared with the interictal baseline across predefined seizure periods. Broadband power increased during seizures (ictal and ES periods) and rapidly decreased after termination in both the thalamus and SOZ (Figure 7.2A,B). Within the thalamus, slow- and beta-band activity predominated toward seizure termination in both nuclei (Figure 7.2C). Significant slow-band power increases were observed in thalamic channels during the ES period, and in the AN during the ictal period, with the largest effects at ES (Figure 7.2D; AN: $p = 1.83 \times 10^{-6}$; CM: $p = 5.58 \times 10^{-4}$). Beta- and gamma-band power also increased at seizure onset, with beta-band activity persisting through ES (Figure 7.2B). In the SOZ, beta- and gamma-band power showed significant increases at seizure onset and ES, whereas slow-band power increased primarily during ES (Figure 7.2D). Beta- and gamma-band activity in the SOZ decreased postictally toward baseline.

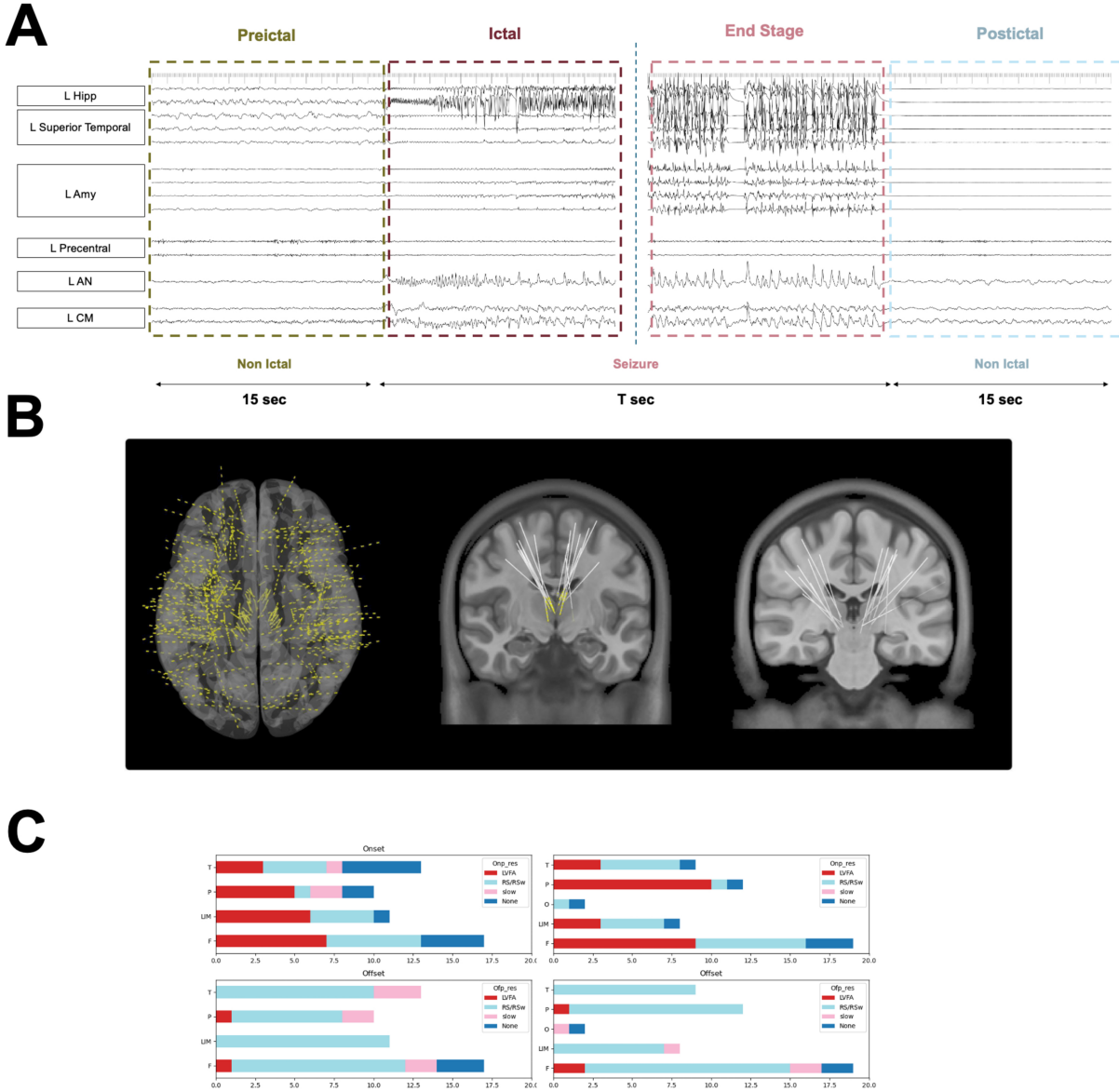


Figure 7.1: Overview of approach and visual characterization of thalamic ictal patterns. (A) Representative SEEG seizure example illustrating the analysis epochs: preictal (15 s), ictal (seizure duration, T s), end-of-seizure (15 s preceding termination), and postictal (15 s). Traces are shown from representative cortical regions and ipsilateral thalamic contacts (AN and CM). Vertical dashed lines denote seizure onset and seizure termination. (B) Example electrode localization demonstrating widespread cortical sampling and thalamic depth electrode trajectories targeting AN and CM (all subjects combined). (C) Distribution of visually classified thalamic ictal patterns at seizure onset (top) and seizure termination (bottom), shown separately for AN contacts (left) and CM contacts (right), stratified by SOZ focus (F, frontal; LIM, limbic; T, temporal; P, parietal; O, occipital). Patterns are categorized as LVFA, RS/RSw, slow, or none.

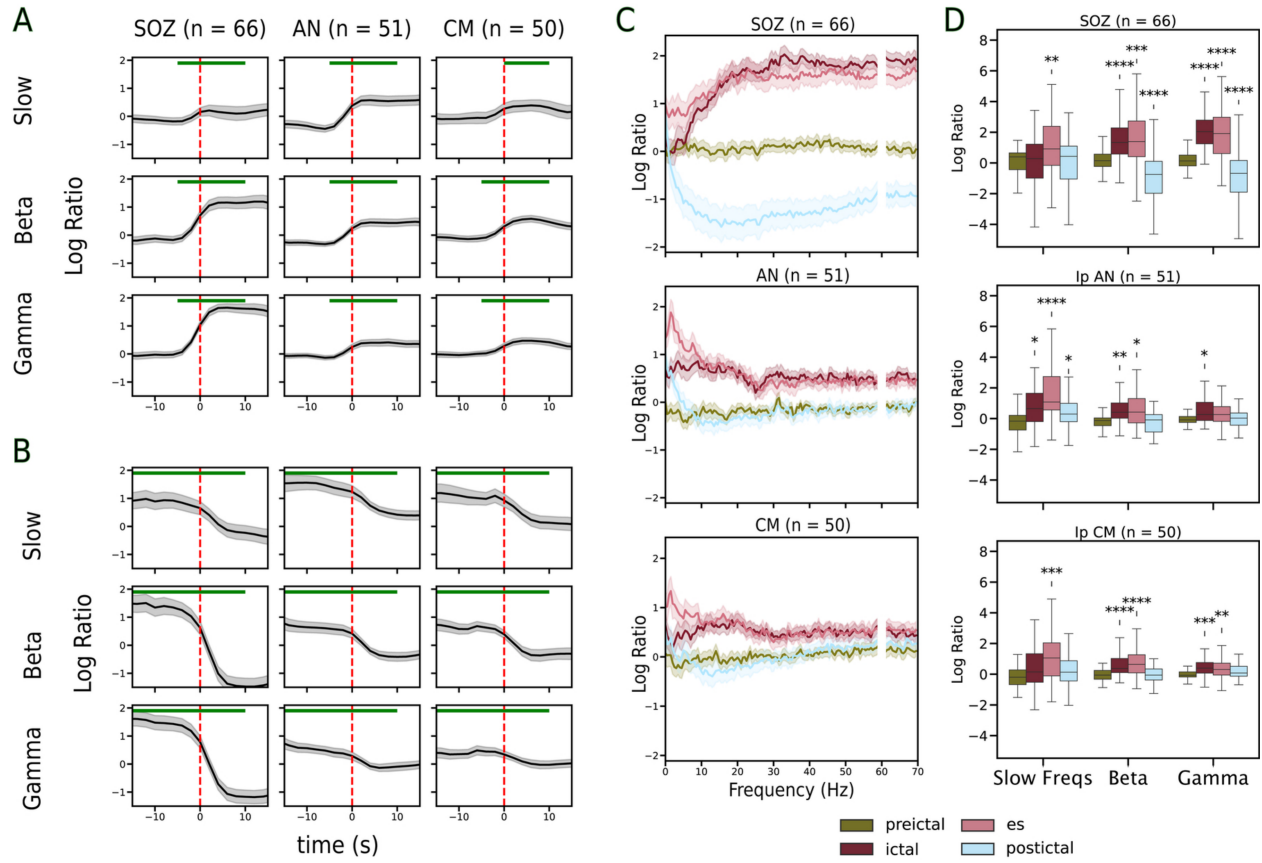


Figure 7.2: Frequency-specific spectral power dynamics in thalamus and seizure onset zone across seizure evolution. Spectral power was computed in canonical frequency bands (slow, 1–12 Hz; beta, 13–30 Hz; gamma, 30–70 Hz) and expressed as log-ratio relative to an interictal baseline. (A) Time-resolved spectral power changes aligned to seizure onset for the SOZ, ipsilateral AN (Ip AN), and ipsilateral CM (Ip CM), averaged across seizures. The vertical dashed line denotes seizure onset. (B) Same as (A), but time-aligned to seizure termination. The vertical dashed line denotes seizure termination. (C) Broadband spectral power changes in the SOZ, Ip AN, and Ip CM across seizure phases (preictal, ictal, end-of-seizure [ES], and postictal). (D) Box plots showing frequency-band-specific spectral power changes for each region and seizure phase. Statistical significance was assessed relative to the interictal baseline. *: $1.00\text{e-}02 < p \leq 5.00\text{e-}02$; **: $1.00\text{e-}03 < p \leq 1.00\text{e-}02$; ***: $1.00\text{e-}04 < p \leq 1.00\text{e-}03$; ****: $p \leq 1.00\text{e-}04$

7.3.4 Thalamocortical Connectivity Increased from Seizure Onset to Termination

Undirected connectivity between each thalamic nucleus and the SOZ was quantified using iCoh. Time-series analyses showed significant increases in thalamocortical iCoh during seizures, particularly in the slow and beta bands during ictal and ES periods (Figure 7.3A,B). Period-wise analyses further showed significant increases in thalamocortical slow- and beta-band iCoh during the ictal, ES, and postictal periods, whereas gamma-band iCoh increased significantly only between the CM and SOZ during the ES period (Figure 7.3C).

Similarly, directed connectivity assessed using GCA demonstrated bidirectional increases between the thalamic nuclei and the SOZ during both the ictal and ES periods, again most prominently in the slow and beta bands (Figure 7.4A,B). Box-plot analyses confirmed significant bidirectional increases relative to the interictal baseline (Figure 7.4C). During the ictal period, no significant difference was observed between inflow and outflow in the AN for either the slow band ($p = 0.052$) or beta band ($p = 0.759$). Similarly, CM slow-band connectivity showed no significant inflow–outflow difference ($p = 0.205$), whereas CM beta-band inflow was significantly greater than outflow ($p = 0.000325$). At the ES period, no significant differences between inflow and outflow were observed in either frequency band for AN (slow: $p = 0.0506$; beta: $p = 0.752$) or CM (slow: $p = 0.299$; beta: $p = 0.108$), indicating balanced bidirectional thalamocortical coupling toward seizure termination.

We additionally examined intra-thalamic connectivity between ipsilateral AN and CM ($n = 40$ pairs). Slow- and beta-frequency iCoh between AN and CM increased at seizure onset, remained elevated throughout the seizure, and declined at seizure termination.

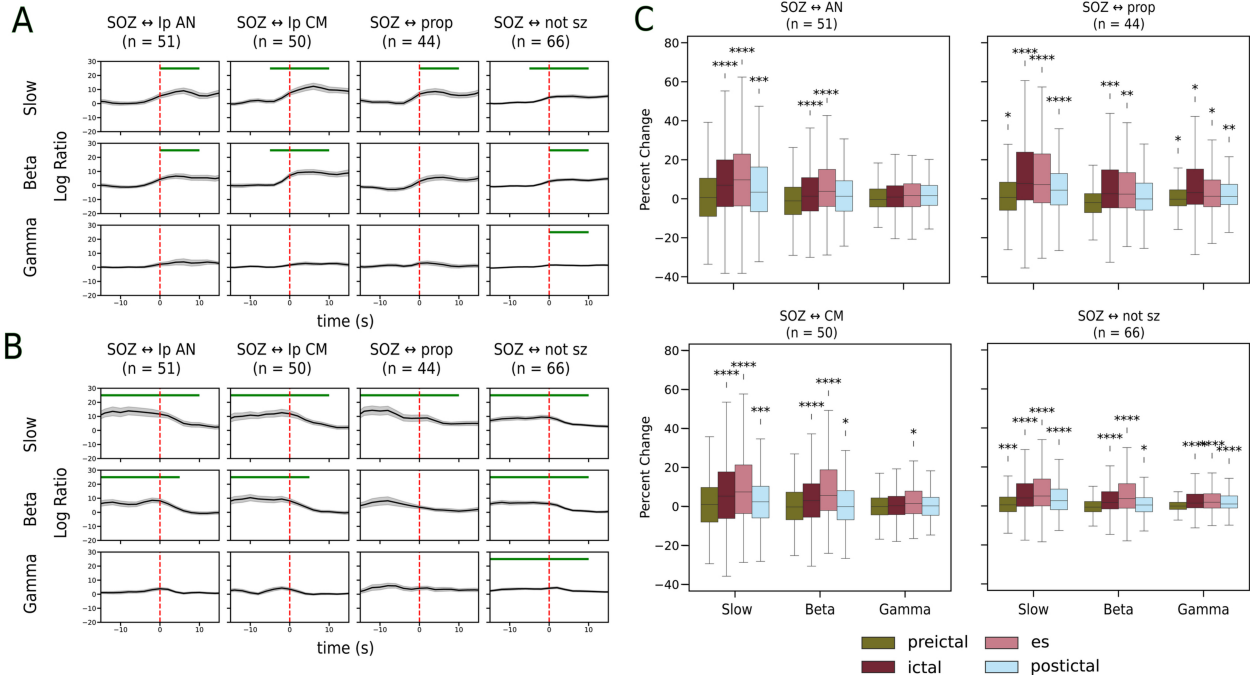


Figure 7.3: Thalamocortical and cortico-cortical connectivity dynamics assessed using imaginary coherence. Imaginary coherence (iCoh) was computed between the SOZ and ipsilateral thalamic nuclei (Ip AN and Ip CM), as well as between the SOZ and cortical regions (propagation and non-seizure areas), in canonical frequency bands and expressed as percent change relative to an interictal baseline. (A) Time-resolved iCoh changes aligned to seizure onset for thalamocortical (AN–SOZ, CM–SOZ) and cortico-cortical (SOZ–propagation, SOZ–non-seizure) interactions, averaged across seizures. The vertical dashed line denotes seizure onset. Horizontal bars indicate time periods with statistically significant increases relative to baseline. (B) Same as (A), but time-aligned to seizure termination. The vertical dashed line denotes seizure termination. Horizontal bars indicate time periods with statistically significant increases relative to baseline. (C) Box plots showing frequency-specific iCoh changes for thalamocortical and cortico-cortical interactions across seizure phases (preictal, ictal, end-of-seizure [ES], and postictal). Statistical significance was assessed relative to the interictal baseline. *: $1.00\text{e-}02 < p \leq 5.00\text{e-}02$; **: $1.00\text{e-}03 < p \leq 1.00\text{e-}02$; ***: $1.00\text{e-}04 < p \leq 1.00\text{e-}03$; ****: $p \leq 1.00\text{e-}04$

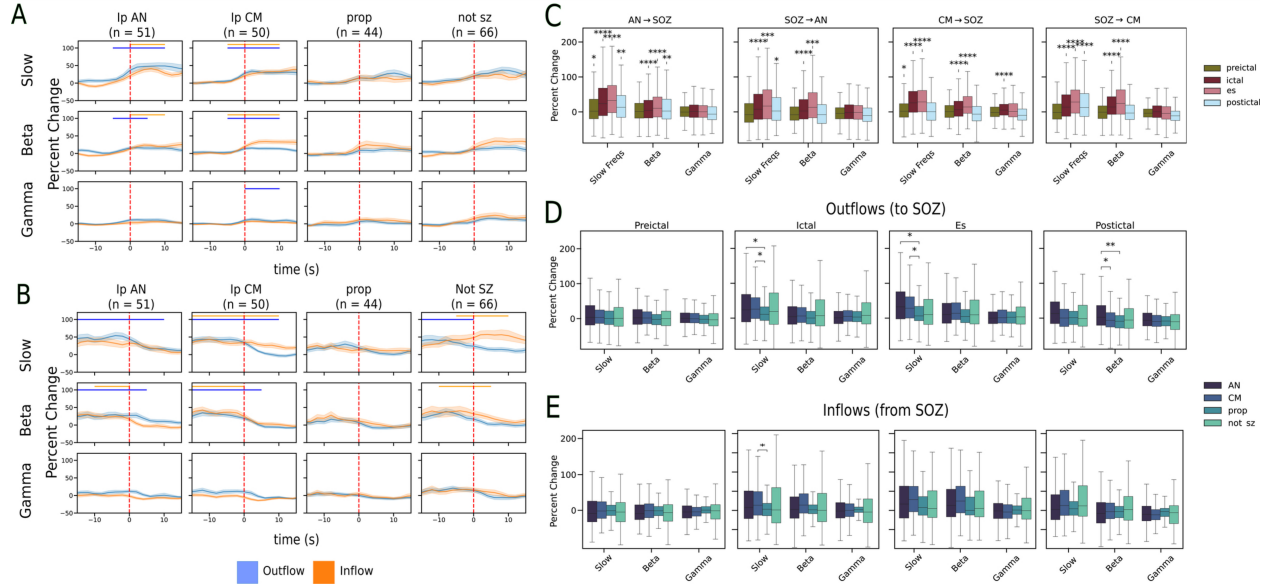


Figure 7.4: Directed thalamocortical and cortico-cortical connectivity dynamics assessed using spectral Granger causality. Spectral Granger causality (GCA) was computed to quantify directed connectivity between the SOZ and ipsilateral thalamic nuclei (Ip AN and Ip CM), as well as between the SOZ and cortical regions (propagation and other non-seizure cortical regions), in canonical frequency bands and expressed as percent change relative to an interictal baseline. Directed connectivity was separated into inflow (SOZ $\rightarrow$ target region) and outflow (target region $\rightarrow$ SOZ). (A) Time-resolved spectral GCA aligned to seizure onset for both thalamocortical (AN-SOZ, CM-SOZ) and cortico-cortical (SOZ-propagation, SOZ-other cortical) interactions, showing inflow and outflow. The vertical dashed line denotes seizure onset. Horizontal bars indicate time periods with statistically significant increases relative to baseline. (B) Same as (A), but time-aligned to seizure termination. The vertical dashed line denotes seizure termination. Horizontal bars indicate time periods with statistically significant increases relative to baseline. (C) Box plots showing frequency-specific spectral GCA changes for thalamocortical and cortico-cortical inflow and outflow across seizure phases (preictal, ictal, end-of-seizure [ES], and postictal), relative to the interictal baseline. (D) Box plots comparing slow-band outflow directed toward the SOZ from thalamic nuclei (AN and CM) and from cortical regions (propagation and other cortical regions) across seizure phases. (E) Box plots comparing slow-band inflow directed from the SOZ to thalamic nuclei (AN and CM) and to cortical regions (propagation and other cortical regions) across seizure phases. Statistical significance was assessed relative to the interictal baseline or between network types, as appropriate. *: $1.00\text{e-}02 < p \leq 5.00\text{e-}02$; **: $1.00\text{e-}03 < p \leq 1.00\text{e-}02$; ***: $1.00\text{e-}04 < p \leq 1.00\text{e-}03$; ****: $p \leq 1.00\text{e-}04$

7.3.5 Comparison Between Thalamocortical and Cortico-Cortical Ictal Dynamics

Directed connectivity analyses showed bidirectional thalamocortical coupling during seizures, with prominent slow-band thalamus-to-SOZ outflow and greater thalamocortical than cortico-cortical slow-band outflow toward the SOZ (Figure 7.4D,E). Specifically, slow-band outflow from AN to the SOZ exceeded outflow from propagation zones to the SOZ during the ictal period ($p = 9.06 \times 10^{-3}$) and ES period ($p = 8.80 \times 10^{-3}$). Similarly, slow-band outflow from CM to the SOZ exceeded cortico-cortical outflow during the ictal period ($p = 3.30 \times 10^{-3}$) and ES period ($p = 5.7 \times 10^{-3}$). Moreover, slow-band inflow from the SOZ to the CM was significantly greater than cortico-cortical inflow from the SOZ to propagation regions. No significant differences were observed between thalamocortical and SOZ–other cortical networks across frequency bands.

To contextualize thalamocortical effects, power and iCoh were also quantified in propagation and non-seizure cortical regions. Spectral power in propagation and non-seizure regions increased from seizure onset to termination, but to a lesser magnitude than in the SOZ and thalamus (Figure 7.5). Similarly, coherence increased in both thalamocortical and cortico-cortical networks, including SOZ–propagation and SOZ–non-seizure interactions (Figure 7.3C).

7.3.6 Subgroup Analyses of Thalamocortical Connectivity by Seizure Focus and Onset Patterns

Exploratory subgroup analyses suggested that thalamocortical connectivity varied by seizure focus and ictal onset pattern. Limbic seizures showed the most prominent increases in AN–SOZ connectivity, particularly in the slow and beta bands, whereas CM–SOZ connectivity increased across seizure foci with significant effects in limbic and parietal seizures (Figure 7.6A). Seizures with RS/RSw onset patterns demonstrated greater thalamocortical slow-band con-

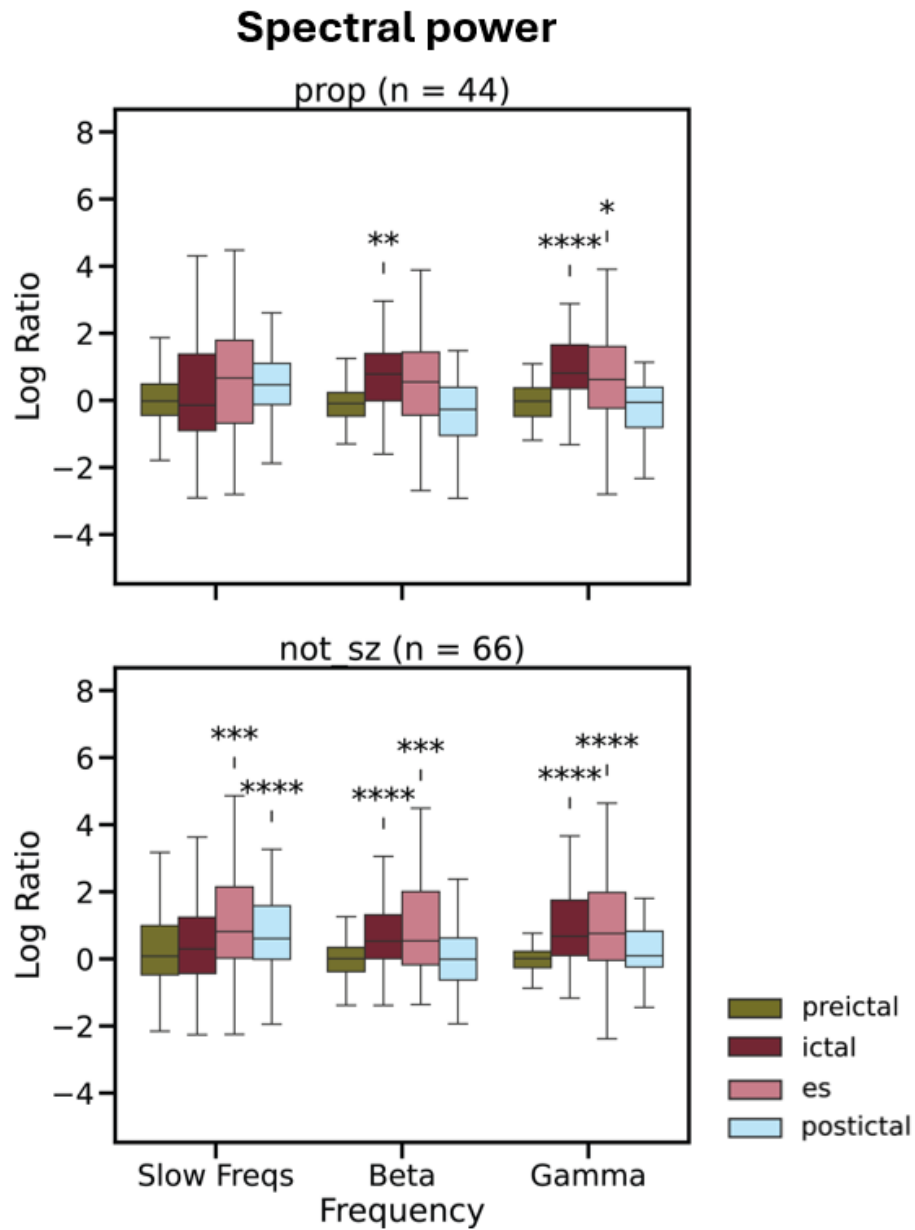


Figure 7.5: Frequency-specific spectral power dynamics in non-seizure onset zone cortical regions across seizure evolution. Box plots show frequency-band-specific spectral power changes for each region and seizure phase. Statistical significance was assessed relative to the interictal baseline.

nectivity increases than LVFA and other onset patterns (Figure 7.6B). In contrast, seizures with diffuse cortical involvement at onset showed relatively lower thalamocortical activity during the ictal period (Figure 7.7).

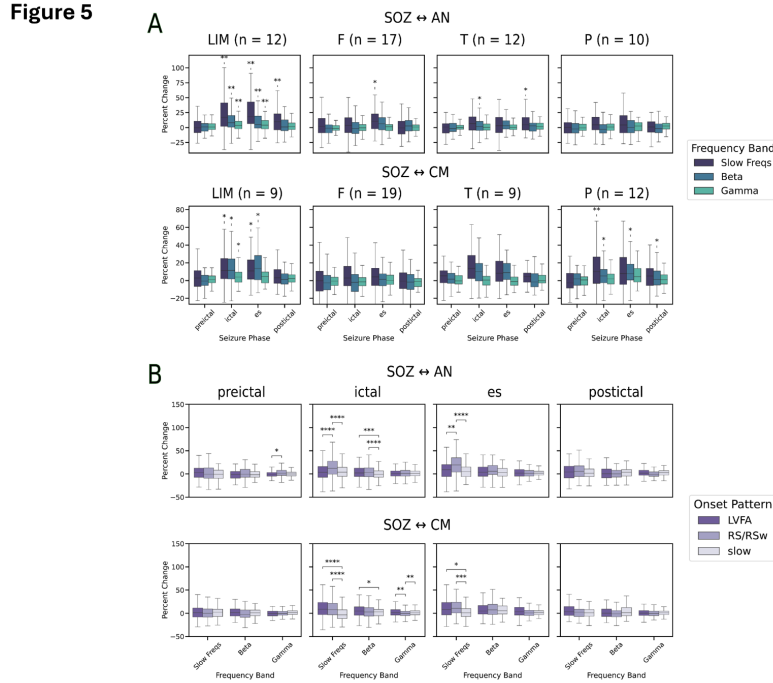


Figure 7.6: Subgroup analysis of thalamocortical connectivity using imaginary coherence by seizure focus and onset patterns. (A) Seizure focus. Frequency-specific iCoh changes for AN–SOZ and CM–SOZ interactions stratified by seizure focus across seizure phases. (B) Ictal onset pattern. Frequency-specific iCoh changes stratified by ictal onset pattern (LVFA, RS/RSw, and other) across seizure phases.

7.3.7 Seizure State Classification Using Thalamic Features

We next tested whether thalamic spectral and connectivity features could distinguish ictal from non-ictal states using leave-one-patient-out random forest classifiers (Figure 7.8A). Mean $\pm$ standard deviation AUROC values across patients quantified classification performance. To avoid extreme cases that could bias model evaluation, very short (<10 s) and very long (>300 s) seizures were excluded from this analysis ($n = 15$ seizures excluded). For the AN-based model, spectral features alone achieved an AUROC of 0.785 ± 0.182 ,

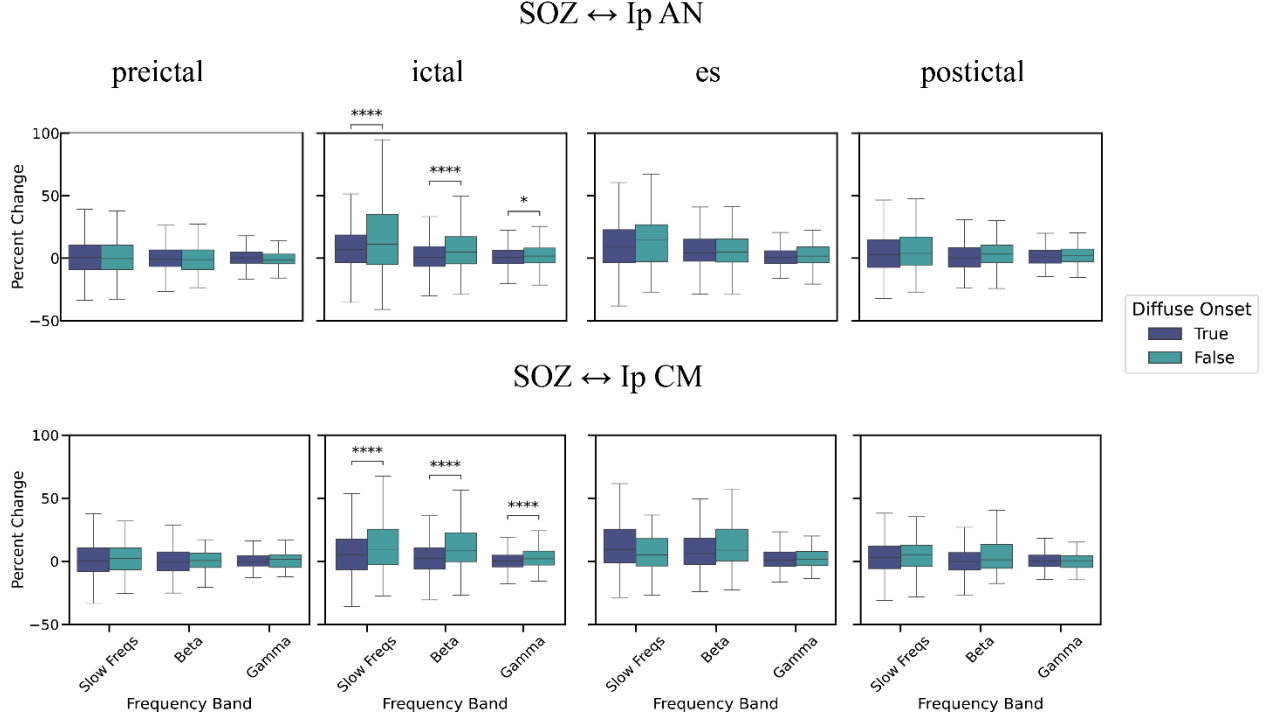


Figure 7.7: Subgroup analysis based on onset pattern for thalamocortical connectivity dynamics across seizure phases. iCoh changes for AN–SOZ and CM–SOZ interactions stratified by seizure onset pattern (diffuse vs. not diffuse).

which increased to 0.803 ± 0.176 with the addition of iCoh and to 0.817 ± 0.168 with the inclusion of GCA. The full feature set (spectral power + iCoh + GCA) yielded the highest AN performance, with an AUROC of 0.825 ± 0.163 (Figure 7.8B). A similar performance pattern was observed for the CM-based model. Spectral features alone achieved an AUROC of 0.777 ± 0.176 , increasing to 0.793 ± 0.171 with iCoh and to 0.840 ± 0.147 with GCA. The full CM feature set produced the highest performance, with an AUROC of 0.839 ± 0.149 (Figure 7.8C).

To identify features contributing to seizure classification, SHAP values were computed and averaged across cross-validation folds. For the AN model, the most predictive features included broadband AN spectral power (slow, beta, and gamma bands), slow-band outflow from the AN to the SOZ, and beta-band inflow from the SOZ to the AN. For the CM model, the strongest predictors included slow- and beta-band CM spectral power, slow-band outflow from the CM to the SOZ, beta-band inflow from the SOZ to the CM, and bidirectional slow-

band iCoh.

7.4 Discussion

Across 66 focal seizures from 19 patients with pediatric-onset drug-resistant epilepsy, we demonstrate that human focal seizures engage dynamic, frequency-specific thalamocortical interactions that evolve from seizure onset to termination (Figure 7.9). Early thalamic involvement was observed on both visual inspection and broadband power analysis. Thalamocortical connectivity increased predominantly in slow and beta bands and peaked near seizure termination. Directed analyses revealed bidirectional thalamocortical coupling, with prominent slow-frequency thalamus-to-SOZ outflow exceeding that of the cortico-cortical (SOZ-prop) network. In addition, thalamic features supported seizure-state classification, indicating that thalamic activity carries clinically relevant information about seizure evolution. Together, these findings support thalamocortical network recruitment as an important feature of focal seizures and highlight the thalamus as a potential source of biomarkers for adaptive neuromodulation.

7.4.1 Clinical and Translational Implications for Personalized Thalamic Neuromodulation

Our findings inform thalamic neuromodulation strategies used in patients who are not candidates for curative resection. The efficacy of DBS targeting the AN in focal epilepsy has been established,[6] and additional thalamic stimulation strategies have been explored, including CM targeting in generalized and multifocal phenotypes such as Lennox–Gastaut syndrome and pediatric-onset epilepsy.[25, 181, 182] Our results add to this literature by showing that the thalamus carries frequency- and direction-specific seizure-state signatures that are measurable during ongoing seizures. These findings are consistent with emerging concepts that the thalamus can exert frequency-coded control over telencephalic ictal organization.[200]

Figure 5

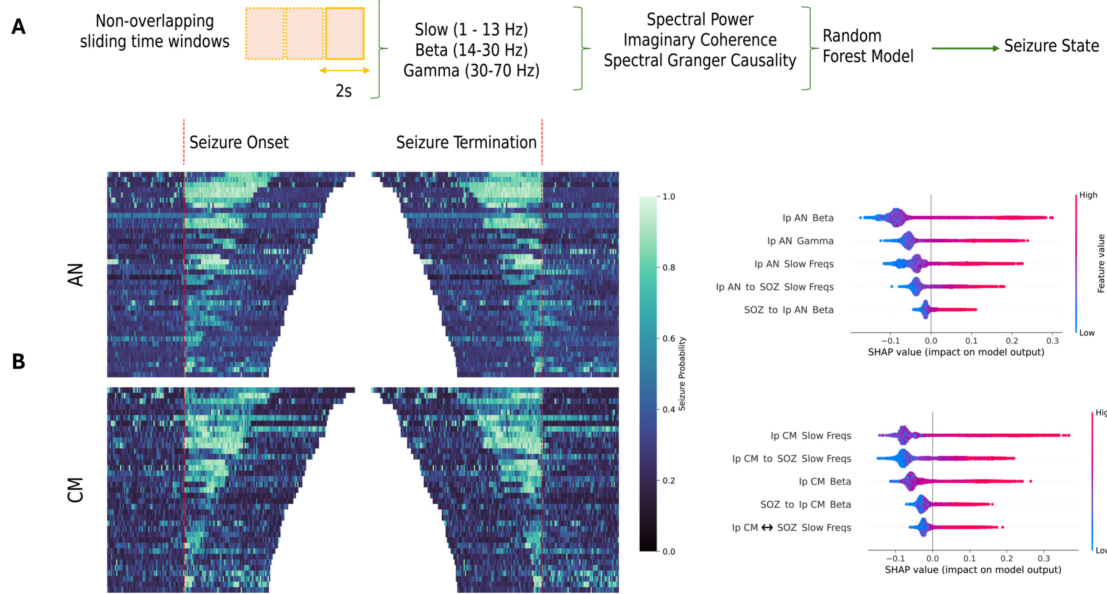


Figure 7.8: Seizure state identification using thalamic spectral power and thalamocortical connectivity features. (A) Overview of the seizure state prediction pipeline. Each seizure was segmented into non-overlapping two-second windows spanning one minute before seizure onset to one minute after seizure termination. For each window, thalamic spectral power, iCoh, and GCA between the thalamus and SOZ were computed. Random Forest classifiers were trained to classify ictal versus non-ictal states using leave-one-patient-out cross-validation. (B) AN-based classifier performance and feature importance. Left: Heatmaps showing predicted seizure probabilities for each two-second window using AN features, ordered by seizure duration. Data are aligned to seizure onset (left panel) and seizure termination (right panel). Right: SHAP summary plot showing feature importance for the AN classifier. Features are ordered by mean absolute SHAP value; the x-axis indicates the direction and magnitude of each feature's contribution to ictal classification (positive values indicate higher ictal probability), and color denotes feature magnitude (red, high; blue, low). (C) CM-based classifier performance and feature importance. Same format as (B), but using CM features. Heatmaps display predicted seizure probabilities aligned to seizure onset and termination, and SHAP summary plots illustrate feature importance for the CM classifier.

Figure 6

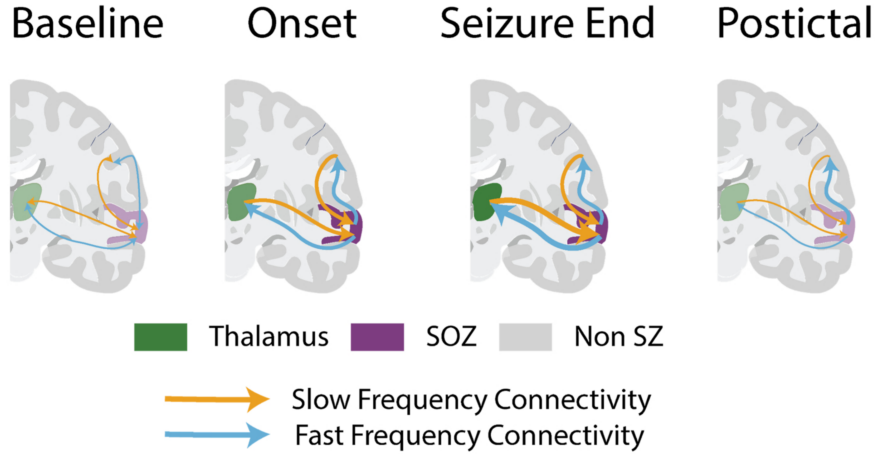


Figure 7.9: Hypothesized model of frequency-specific thalamocortical network dynamics during focal seizures. Schematic illustration summarizing a hypothesized model of frequency-specific thalamocortical and cortico-cortical network dynamics across seizure evolution. At seizure onset, cortical regions within the SOZ exhibit prominent fast-frequency activity that is primarily organized around the SOZ, with concurrent engagement of thalamocortical networks. As seizures progress toward the end-of-seizure (ES) period, slow- and beta-band thalamocortical connectivity—particularly slow-frequency outflow from the thalamus (AN and CM) to the SOZ—reaches maximal expression, with bidirectional thalamocortical interactions maintained during this late ictal phase. At seizure termination, this organized thalamocortical coupling rapidly collapses, consistent with a loss of frequency-specific thalamocortical network engagement rather than gradual attenuation. Findings from seizure state classification models converge with this framework: ictal states are characterized by the presence of slow-frequency thalamus-to-SOZ outflow together with fast-frequency inflow from the SOZ to the thalamus, whereas the absence of this bidirectional, frequency-specific signature corresponds to non-ictal states, including the post-termination period. Cortico-cortical interactions are also engaged throughout seizures but exhibit comparatively weaker, consistent with an ictal cortical network that remains primarily organized around the SOZ. Collectively, this conceptual model highlights frequency- and direction-specific thalamocortical interactions—and their abrupt disengagement at seizure termination—as potential targets for adaptive neuromodulation strategies.

This aligns with the broader push toward network-guided neuromodulation[201] and with emerging methodology-driven personalization of stimulation targets and parameters.[202] These data suggest that adaptive stimulation strategies may benefit from incorporating thalamocortical interaction patterns, rather than relying on local thalamic power alone. In addition, exploratory subgroup findings, such as stronger AN–SOZ interactions in limbic seizures, suggest that known anatomical connectivity may help guide nucleus selection and patient-specific stimulation approaches, although these observations require validation in larger cohorts.

7.4.2 Relationship Between Ictal Thalamocortical and Cortico-Cortical Networks

The concept that seizures engage thalamocortical loops dates back to classic “centrencephalic” frameworks proposed by Penfield to modern mechanistic views in which pathological activity hijacks physiological thalamocortical circuitry.[187, 189, 203] Animal studies of absence epilepsy provided early causal insights, demonstrating that a cortical focus can drive widespread corticothalamic networks.[142] In focal epilepsies, a growing human SEEG literature has documented early thalamic recruitment and thalamocortical coupling,[143, 148, 144, 186] including evidence that thalamic recruitment can vary across seizures within individuals.[144, 185] Our study extends our understanding of the thalamocortical dynamics within a frequency-resolved and directionally resolved framework, while also comparing these dynamics with cortico-cortical networks. Our data suggest a nuanced relationship between thalamocortical and cortico-cortical dynamics: both networks are engaged, but slow-frequency outflow toward the SOZ was comparatively stronger in thalamocortical networks than in propagation-zone→SOZ cortico-cortical interactions. This may reflect subcortical constraints mediated through thalamocortical circuitry.[26, 204] Further, these findings relate to cortico-cortical interictal network frameworks such as the interictal suppression hypothesis, which proposes that non-SOZ regions can suppress SOZ

activity,[205, 206] as well as to recent work further evaluating such disruption of suppression-related networks during seizure evolution.[207] Visual EEG analysis patterns further support state dependence: LVFA was common at onset, a pattern associated with reduced synchrony and local microcircuit changes early in seizures,[208, 209] whereas RS/RSw patterns were more prominent near ES, aligning with the emergence of synchronized slow/beta thalamocortical engagement that may be particularly relevant to seizure termination (Figure 7.6). Consistent with this interpretation, LVFA-onset and diffuse-onset seizures showed relatively reduced thalamocortical engagement in specific frequency bands during the ictal period, whereas RS/RSw-associated connectivity increases were more prominent later in the seizure course (Figure 7.7).

7.4.3 Mechanistic Considerations and Implications for Seizure Termination

Corticothalamic inputs shape thalamocortical network activity during physiological rhythms such as sleep spindles[203] and, under pathological conditions, during epileptic synchronization.[26] Whether the thalamus amplifies seizures, restrains them, or performs both roles likely depends on seizure state and network context. Experimental studies support such a state-dependent role. Closed-loop optogenetic inhibition of the thalamus interrupts seizures in a rat model of post-cortical injury epilepsy,[210] and another animal study suggests that the thalamus exerts frequency-dependent control over large-scale ictal coherence.[200] Our findings are consistent with the possibility that seizure termination is associated with collapse of organized, frequency-specific thalamocortical coupling.[188] However, because our data are observational, they do not establish a specific causal mechanism or prove recruitment of inhibitory thalamic circuitry, including thalamic reticular nucleus-mediated suppression.[211, 212] Rather, they suggest that late seizure stages are characterized by prominent structured thalamocortical engagement that rapidly dissipates after termination. This interpretation aligns with stimulation studies empha-

sizing network-level therapeutic mechanisms,[213] and with CM-targeted DBS experience in Lennox–Gastaut syndrome, which further supports the relevance of thalamocortical network targeting and connectivity-informed programming.[172] Together, these findings support the hypothesis that adaptive thalamic neuromodulation could leverage frequency- and direction-specific thalamocortical signatures for seizure tracking and potentially for stimulation timing, but this will require prospective validation.[201, 202]

7.4.4 Limitations

Several limitations should be considered. The cohort size was modest and clinically heterogeneous, with anatomically diverse seizure onset zones, limiting detailed subgroup analyses even though this heterogeneity may improve generalizability across focal epilepsy phenotypes. Thalamic sampling was restricted to AN and CM and was clinically determined, limiting inference about other nuclei such as the pulvinar. In addition, the classifier results demonstrate translational promise but do not establish real-time clinical performance in prospective settings. Finally, the retrospective design limits causal inference regarding the role of any single network feature in seizure initiation or termination.

7.4.5 Future Perspectives

Future studies should include larger multicenter cohorts with broader thalamic and cortical sampling, including additional nuclei implicated in seizure propagation and termination, and integrate structural and functional imaging to relate intracranial electroencephalography dynamics to individualized connectomes. Prospective studies should test whether frequency- and direction-specific thalamocortical signatures improve adaptive stimulation compared with conventional power-based detectors. Broader future directions building on this work are discussed in Chapter 9.

7.4.6 Data Availability Statement

The EEG dataset supporting this study is publicly available through OpenNeuro (<https://openneuro.org/datasets/ds007445>). Analysis code used to support the findings of this study is publicly available as described in the Methods.

Patient characteristics are provided in Appendix Section A.2.

CHAPTER 8

Alap: Towards a World Model for Seizures

This chapter proposes a Seizure World Model (SWM): a single model that learns a shared latent space across patients and seizures, conditions its predictions on stimulation parameters, and rolls out latent trajectories to predict seizure onset, predict response to stimulation, and ultimately reason about which parameters would stop a seizure in progress. Such a model would enable better closed-loop control and may provide insight into the brain states that cause seizures.

8.1 Introduction

Approximately one-third of people with epilepsy develop drug-resistant disease [3], and many are not candidates for curative resection because their seizures are multifocal, poorly localized, or arise from a distributed network, leaving neuromodulation as the only remaining therapeutic option. Responsive neurostimulation (RNS) and deep brain stimulation (DBS) reduce seizures in controlled trials [5, 6]. The benefit is partial: after nine years of responsive stimulation the median seizure reduction is 75%, and only 18% of patients experience a seizure-free year [7]. DBS stimulates on a fixed schedule regardless of the brain’s state. RNS stimulates when it detects a seizure, after the seizure has begun. In both, the stimulation parameters are set at clinic visits rather than chosen per event, and neither predicts what a given stimulation will do. The brain’s state when the stimulation arrives changes what the stimulation does. Stimulation delivered during periods of lower epileptiform burden

gives better long-term seizure control [214], and whether a stimulation moves the network toward or away from seizure depends on the baseline risk, the stimulation parameters, and the anatomical target [215].

Choosing a stimulation per event requires knowing, before delivering it, how it would change the brain’s activity over the next seconds. No current device makes this prediction. Making it requires a model of how the brain’s activity evolves under stimulation.

A world model is a learned model of a dynamical system: it compresses each observation into a compact state and forecasts how that state evolves under a given input, so that candidate inputs can be compared by simulation before any is applied [216, 217, 63]. Joint-embedding predictive architectures (JEPAs) train such models entirely in the compact state space, without reconstructing the raw signal [63, 66], and in EEG this objective yields embeddings that track seizure onset under frozen linear probing [218]. Here the observation is intracranial EEG (iEEG), the state is a compact summary of the brain’s activity, and the input is electrical stimulation. This framing sidesteps the search for a single seizure biomarker: the world model learns one state trajectory from the raw recording.

Forecasting spontaneous seizures is an established field [219]: an implanted advisory system has predicted seizure likelihood prospectively over months [220], and multiday cycles of epileptiform activity support forecasts days ahead [221]. These systems estimate when a seizure is likely given the brain’s current dynamics. In neuroimaging, NeuroWorld [222] rolls a latent brain state forward under naturalistic movie stimuli, but its inputs are passive sensory streams rather than interventions. Neither line of work predicts how an intervention would change the trajectory, which is the prediction a closed-loop device needs.

In this work, we present Alap,¹ a world model of iEEG trained jointly across patients on passive and stimulation recordings. No single patient can supply such a model: each electrode montage samples a fraction of the brain, and a monitoring stay yields few seizures. Alap therefore conditions on electrode coordinates rather than fixed channel orderings, so

¹In Hindustani classical music, an *alap* is the opening improvisatory section in which a musician introduces and freely explores a raga within its melodic framework.

that partial views from many patients aggregate into one model of dynamics. To predict the effect of a stimulation, Alap runs two rollouts from the same starting window, one stimulated and one unstimulated. The difference between the two rollouts, measured as movement toward the region of latent space that recorded seizures occupy, is the predicted effect, which we call the ictal shift.

This chapter makes four contributions:

- The rollouts match what was recorded: the unstimulated rollout tracks held-out recordings, and the rollout conditioned on the delivered stimulation tracks the recorded response.
- The ictal shift predicts whether a stimulation induces a seizure (AUROC 0.662) and outperforms every baseline that sees only the recording before the stimulation.
- Occluding channels of the learned representation localizes the seizure onset zone with no localization labels.
- One recorded seizure from a never-seen patient recalibrates seizure detection for that patient.

Together these are a first step toward a device that tests candidate stimulations in simulation and delivers the one predicted to keep the brain farthest from seizure.

8.2 Methods

Alap adapts LeWorldModel [223], a video world model, to intracranial EEG, following Laya [218], which applied the LeJEPa objective to EEG. An encoder maps each observation to a latent state, and an autoregressive predictor rolls that state forward under a sequence of actions. Here the observations are multi-channel voltage recordings and the actions are stimulation parameter vectors.

8.2.1 Data

We use three cohorts. HUP [224, 225] contributes passive iEEG from 58 subjects with annotated interictal and ictal periods and clinically marked onset channels, with no stimulation (OpenNeuro ds004100). MESA [226, 227] contributes SEEG from 32 patients with 83 annotated seizures, 46 spontaneous and 37 stimulation-induced. Each MESA stimulation train carries amplitude, frequency, pulse width, duration, and electrode coordinates. A stimulation-mapping cohort from a third academic medical center (hereafter the academic cohort) contributes 29 sessions from 24 patients, and the same site contributes 66 spontaneous seizures from 19 subjects through OpenNeuro ds007445 [228].

Six academic-cohort patients, P1 through P6, are held out of both training stages by subject identifier and used only for evaluation. P6 is the one academic-cohort patient whose seizure was triggered by stimulation. Per-cohort detail, preprocessing, the coordinate caveats, and a stage-by-stage split table are in Section 8.6.

8.2.2 Alap

The encoder maps a window of multi-channel iEEG to one latent vector per one-second patch. The predictor models how these latent states evolve, conditioned on the stimulation parameters. Figure 8.1 shows the pipeline.

The encoder embeds each channel’s one-second patch with a one-dimensional convolution shared across channels, which accommodates any channel montage. Because montages differ across patients, channels are identified by position rather than by order: each channel embedding is tagged with its electrode’s three-dimensional MNI coordinates, encoded as Fourier positional features [229]. A transformer then mixes across channels, and masked mean-pooling yields one vector per patch.

Stimulation is represented as a seven-dimensional vector per patch: four waveform parameters (amplitude, frequency, pulse width, duration) and the three MNI coordinates of the stimulating electrode. A separate stimulation encoder maps this vector to an embedding

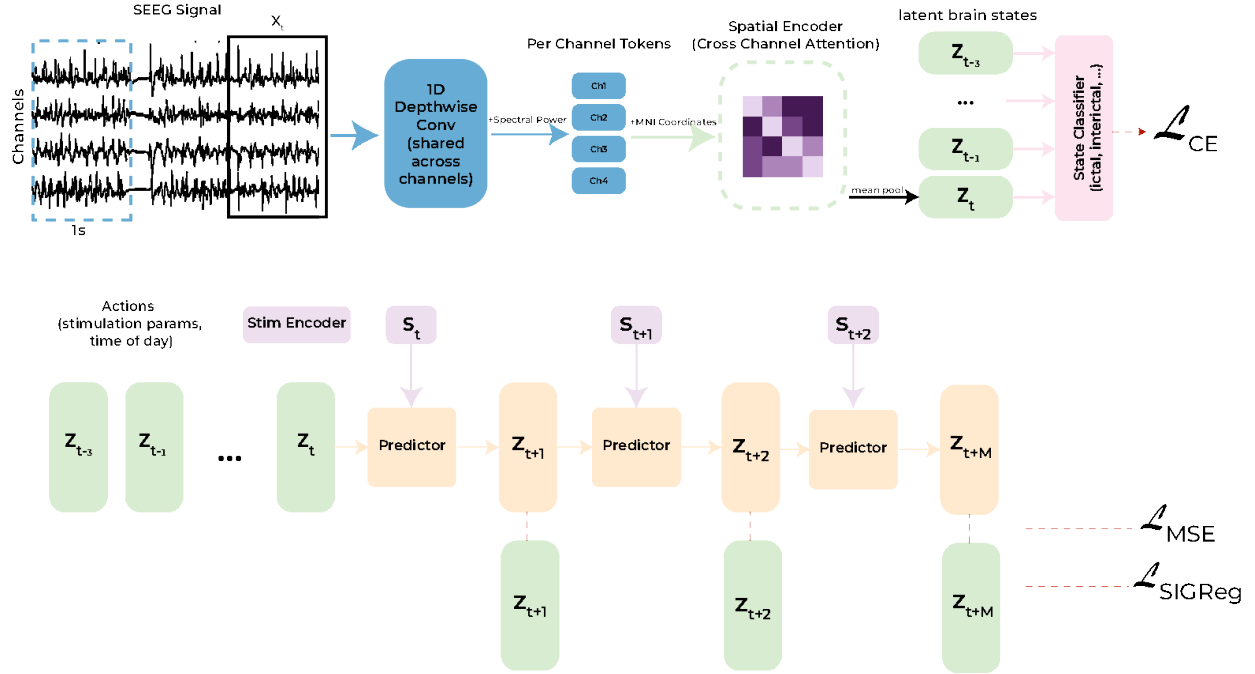


Figure 8.1: **Alap architecture and training objectives.** Top: the encoder embeds each one-second patch per channel with a depthwise one-dimensional convolution shared across channels, mixes across channels using learned 3D electrode-coordinate embeddings, and mean-pools to a sequence of latent frames $z_{t-3}, \dots, z_t$. A state classifier on those frames supplies the detection loss $\mathcal{L}_{CE}$. Bottom: a causal transformer predictor, conditioned on stimulation parameters via AdaLN-zero modulation, rolls forward from a short latent context to produce predicted latents $\hat{z}_{t+2}, \hat{z}_{t+4}, \dots$, each two patches ahead of the last, trained against the encoder’s own latents with MSE and SIGReg.

that is near zero when no stimulation is active, so the predictor defaults to unconditional dynamics. The predictor is a causal transformer over a 16-second context window that predicts the latent state two patches ahead. The stimulation embedding is injected at each block through Adaptive Layer Normalization with zero initialization [230].

Training minimizes the mean squared error between the predictor’s output at time t and the encoder’s output at time $t + 2$, plus two auxiliary terms. The SIGReg regularizer from LeJEPa [66] enforces an isotropic Gaussian prior across the batch, which prevents representational collapse. A linear seizure-detection head on the patch embeddings supplies the second term, which keeps ictal activity in a distinct region of latent space. The head is discarded at evaluation.

Training proceeds in two stages. In Stage 1, the encoder and predictor are trained jointly on all three cohorts under the losses above. In Stage 2, the encoder is frozen and the predictor and stimulation encoder are fine-tuned on the stimulation data alone, against multi-step rollout error rather than a single prediction step. The representation and unconditional-forecasting results use the Stage 1 model, and the stimulation-response results use the Stage 2 model. Architectural detail, loss weights, and hyperparameters are in Section 8.7.

8.2.3 Manifold score and ictal shift

We call the region of latent space occupied by seizure states the *ictal manifold*, and we measure a patch embedding’s proximity to it with a scalar *manifold score*: the median Euclidean distance from the embedding to its 25 nearest background reference patches, minus the median distance to its 25 nearest ictal reference patches. Higher scores indicate greater proximity to the ictal manifold. Each experiment states which recordings supply the reference patches.

At inference the predictor runs autoregressively. From a context window of encoded patches and a specified stimulation sequence, it predicts the next embedding, appends it to the context, and repeats. Each step advances two seconds, so the ten-step rollouts of Section 8.3.1 span 20 s.

To predict the effect of a stimulation, two rollouts run from the same pre-stimulation context. The *stimulated rollout* is conditioned on the stimulation parameters that were delivered, and the *unstimulated rollout* on a null stimulation vector at every step. The *ictal shift* is the stimulated-rollout manifold score minus the unstimulated-rollout score at the same step, averaged over the ten steps. It measures how much closer to the ictal manifold the stimulation is predicted to move the brain than no stimulation would.

8.2.4 Evaluation

Stimulation outcome. The ictal shift is used as a predictor of stimulation outcome with no classifier trained on top of it. Stage 1 model selection used the MESA validation loss, and Stage 2 model selection used validation rollout error alone. The stimulation-outcome numbers were computed once, on the selected model.

Baselines. Two baselines are fitted on the same 3 s pre-stimulation window the rollouts start from: a logistic classifier on the mean patch embedding (the learned snapshot baseline) and a logistic classifier on band powers and line length (the classical baseline). Both are evaluated under leave-one-recording-out cross-validation. Classifier settings, fold structure, and permutation schemes are in Section 8.10.

Statistics. Confidence intervals are bootstrapped by subject, and p -values are two-sided permutation tests over 10,000 shuffles run under the cohort layout being tested.

Seizure onset localization. Each held-out recording is re-embedded once per channel with that channel zeroed and masked, and channels are ranked by how much their removal lowers the manifold score. The ranking is scored against clinician-marked onset channels. No localization labels are used in training, and nothing is fitted at evaluation.

Patient adaptation. Seizure detection scores every patch of a held-out recording by its manifold score and measures, by AUROC, how well that score separates the patches inside a seizure from background. The model weights are unchanged. Only the recordings that build the ictal reference manifold change: the reference is built from zero, one, or two of the patient’s own seizure recordings, and detection is scored on the recordings not used for the reference, averaged over every choice.

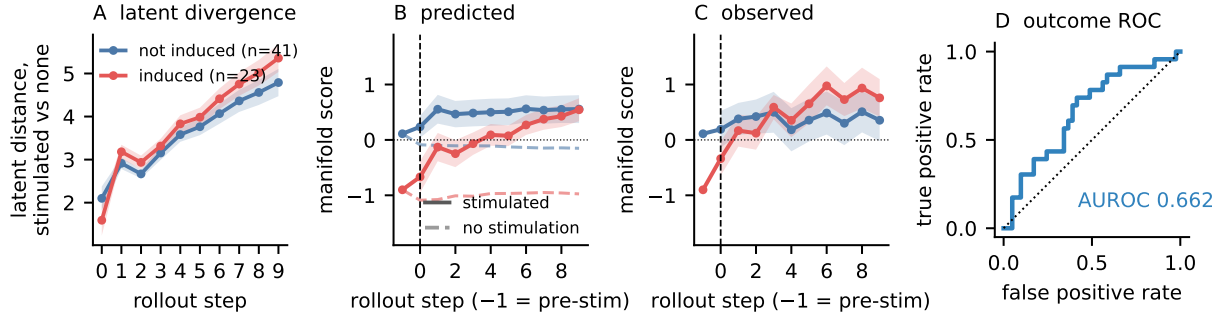


Figure 8.2: **Simulating the stimulation predicts its outcome.** All panels cover the same 64 MESA stimulation events, 23 that induced a seizure within 20 s and 41 that did not. Lines are means with standard error. **A:** latent distance between the stimulated and unstimulated rollouts. **B:** predicted manifold score under the stimulated (solid) and unstimulated (dashed) rollouts, from the shared pre-stimulation state one step before stimulation onset. Only the stimulated rollout of an induced event rises. **C:** the same score on the recording that actually followed, on B’s axes. **D:** the ictal shift, the gap between B’s two rollouts averaged over the ten steps, as a predictor of outcome: AUROC 0.662. Baselines on the same pre-stimulation window span 0.30 to 0.47 (Section 8.10).

8.3 Results

8.3.1 The rollouts track held-out recordings

We evaluate on all 64 stimulation trains in MESA. The academic cohort is not used here because only one of its stimulations triggered a seizure. Both rollouts start from 3 s of pre-stimulation recording, since many events have no more stimulation-free recording than that before the train. An event counts as induced if a seizure onset follows the stimulation onset within 20 s, the rollout horizon, which gives 23 induced and 41 non-induced events. Induced means a seizure followed within the window, not that a clinician judged the stimulation to have caused it.

We first test the unstimulated rollout on stimulation-free recording. Rolled forward from 124 background windows in 17 held-out recordings, it predicts the ten-step horizon better than repeating the last observed state (mean squared error ratio 0.70), and its predicted manifold score matches the recorded one ($r = 0.77$, $p = 7 \times 10^{-26}$; median per-recording $r = 0.45$).

We then test the stimulated rollout on the stimulation events. Only the stimulated rollout of an induced event rises toward the ictal manifold, and the recording that followed does the same (Figure 8.2B,C). Event by event, the predicted shift correlates with the recorded one ($r = 0.45$, $p = 0.0002$, $n = 63$), and within the 23 induced events $r = 0.70$ ($p = 0.0002$). One event lacks 20 s of clean post-stimulation recording and is excluded here.

8.3.2 The ictal shift predicts whether a stimulation induces a seizure

The ictal shift averages 1.06 over induced events and 0.62 over non-induced ones. As a scalar predictor it gives AUROC 0.662 (95% CI [0.515, 0.788], permutation $p = 0.0099$; Figure 8.2D). It stays above chance at every response window from 5 to 60 s (Table 8.4, Section 8.10). The latent distance between the two rollouts is also larger for induced events, by a smaller margin (Figure 8.2A).

We compare against four baselines on the same 3 s pre-stimulation window: the manifold score of the last patch (0.429), its mean over the window (0.458), a logistic classifier on the mean patch embedding (0.471), and a logistic classifier on band powers and line length (0.304). The shift beats the pre-stimulation manifold score by +0.204 (95% CI [+0.023, +0.371]) and the classical baseline by +0.36 (95% CI [+0.13, +0.56]). Adding the strongest baseline to the shift (0.670) does not improve on the shift alone. Simulating the stimulation with Alap’s world model therefore extracts information about the outcome that the pre-stimulation recording alone does not carry.

The stimulation parameters alone do not predict the outcome (0.295), as expected when 63 of 64 events share one protocol. The rollout still depends on them: giving each event’s rollout another event’s parameters lowers the AUROC to 0.600 on average, below 0.662 in all ten permutations. Neither rollout predicts on its own (0.453 stimulated, 0.355 unstimulated), and the result does not rest on stimulation duration alone (0.624 to 0.647 with duration removed). The prediction comes from the difference between the two rollouts. The full

control table is in Section 8.10.

8.3.3 Occluding channels localizes the seizure onset zone

We next test whether the representation itself localizes the seizure onset zone. Ranking channels by occlusion (Section 8.2.4) scores the clinician-marked onset channels at a mean AUROC of 0.754 across 28 held-out recordings from two datasets (permutation $p = 0.0001$ on each). On the 11 held-out academic-cohort seizures, the mean is 0.795 and the top-ranked channel is a true onset channel in 8 of 11 (chance 29%, since the cohort’s labels are region-level). On 17 recordings from held-out MESA patients, with per-contact labels and a median of 5 onset contacts out of roughly 130 channels, the mean is 0.727 and the top-ranked contact is a true onset contact in 4 of 17 (chance 5.9%). The ranking uses no localization labels, and nothing is fitted at evaluation. Within-hemisphere specificity, the per-patient spread, and the failure cases are in Section 8.8.

8.3.4 One recorded seizure recalibrates the reference manifold

Finally, we test how Alap transfers to a new patient. The task here is seizure detection, not stimulation outcome: every patch of a held-out recording receives its manifold score, and the AUROC measures how well that score separates the patches inside a seizure from background. The score depends on the reference manifold, so we vary what the reference is built from. Each held-out patient has three seizure sessions. The reference is built from zero, one, or two of them, and detection is scored on the remaining sessions, averaged over every choice (Table 8.1). The median session is 68 minutes of monitoring containing about 38 s of seizure.

With the reference built only from training patients, detection in the held-out patients averages AUROC 0.516. One of the patient’s own sessions raises it to 0.861, and a second adds about 0.01. A few minutes around the seizure are enough: two minutes gives 0.829, five gives 0.856, and the remaining hour adds 0.005 (Figure 8.3). The patient’s own data

Table 8.1: **Detection AUROC by number of the patient’s own recordings in the reference manifold.** Per-recording AUROCs, averaged over held-out patients and over every choice of reference recordings.

Reference built from	0	1	2
Own recordings	0.516	0.861	0.871
Own plus population	0.516	0.798	0.820

should replace the population reference rather than join it: keeping the population recordings alongside lowers the result to 0.798. The benefit is specific to patients unlike the training set: on 12 never-trained subjects from the pretraining hospital, zero-shot detection already reaches 0.721, and building the reference from their own recordings lowers it to 0.651. Alap therefore adapts to a new patient from one recorded seizure, with no change to the model weights.

8.4 Discussion

The preceding chapters developed two views of seizure dynamics that are each incomplete on their own. The representation learning chapters produced compact brain-state embeddings, but these are static snapshots with no notion of how a state will evolve or how an intervention would change its trajectory. The thalamocortical chapters identified frequency-specific signatures at seizure onset and termination, but these are summary statistics computed after the fact. Neither arc can answer the question that closed-loop neuromodulation requires: if stimulation is applied with these parameters at this moment, where will the brain state be in five seconds? Answering that question demands three components in concert: learned representations that compress high-dimensional iEEG into a shared latent space, a dynamics model that projects forward in time, and action conditioning that makes those projections sensitive to stimulation parameters. The contribution of this chapter is their integration into a single trainable system.

This work develops a proof of concept of a world model for the epileptic brain. Alap learns

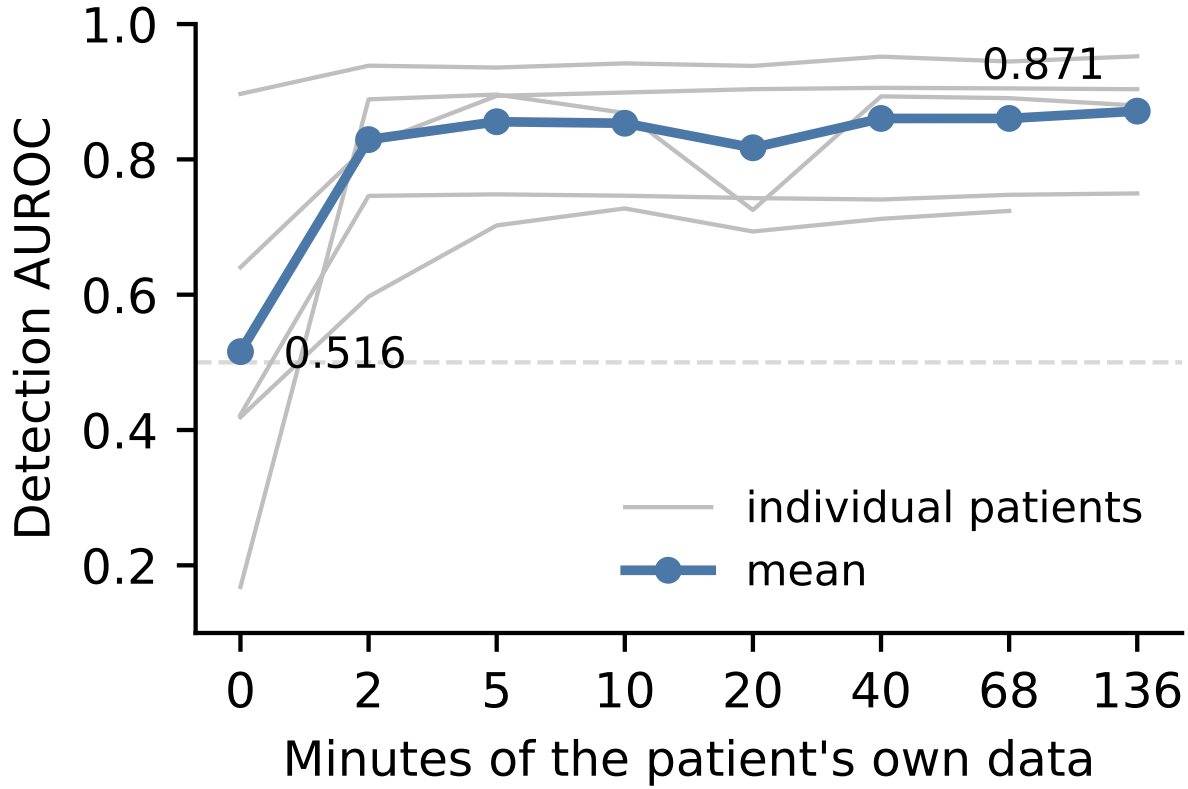


Figure 8.3: **Detection AUROC by the amount of the patient’s own data in the reference manifold.** Gray lines are individual held-out patients. The bold line is the mean over recordings and reference choices, as in Table 8.1. Zero minutes is the zero-shot score. The 2- to 40-minute points crop one of the patient’s seizure sessions to a window around the seizure. The 68-minute point is the median full session, and 136 minutes is two sessions.

a shared latent space for iEEG across patients, predicts how the latent state evolves, and conditions that prediction on stimulation parameters. We tested it in two experiments. The rollouts track held-out recordings, with and without stimulation. The difference between the two rollouts, the ictal shift, predicts whether a stimulation induces a seizure and outperforms every baseline that sees only the recording before the stimulation. The ictal shift has a direct clinical interpretation. It measures how much more ictal a candidate stimulation makes the brain than no stimulation, and it can be computed for a stimulation that has not been delivered. A closed-loop device requires exactly this quantity.

Two further findings show that the representation encodes more than a spectral thresh-

old. Occluding channels recovers the clinician-marked onset channels without localization labels, so the learned state is anchored on the tissue clinicians identify. This procedure adapts occlusion attribution from computer vision [231] and parallels virtual resection [232, 233, 234, 235, 236]. Virtual resection fits a separate model to each patient. Alap’s representation is pretrained across patients and needs no per-patient fitting. Band powers and line length explain little of the manifold score. The score rises as low-frequency power falls, which matches the low-voltage fast-activity pattern clinicians read at seizure onset [237] (Section 8.9).

8.4.1 Limitations

Modest training scale. The training data spans three institutions but remains modest. Passive iEEG comes from 77 patients, stimulation recordings from 56, and only 37 MESA seizures and one academic-cohort event are stimulation-induced. Whether robust stimulation-response mappings can be learned from this volume remains open.

A single stimulation protocol. Every comparison in this work is stimulation against no stimulation, never one stimulation against another. Shuffling the delivered parameters lowers the shift’s AUROC by about 0.06, so the conditioning contributes. Separating one parameter set from another requires recorded outcomes across varied parameters, which neither cohort provides.

No patient-level holdout. All patients who contribute induced events appear in pre-training. Holding out MESA patients would have left roughly two positive events. Refits that score each induced subject out of sample give a similar AUROC (Section 8.10), but confirming the result requires a prospectively held-out stimulation cohort.

Untested on chronic implants. Alap has not been evaluated on recordings from chronic RNS devices. There the stimulation paradigm, timing, and brain state differ from clinical

mapping, and only four contacts record against the dense montages trained on here. The evaluation is also retrospective. We have not shown that the model runs within closed-loop timing constraints.

8.5 Future work

Alap is a small step toward a world model of seizure neurostimulation. Future work will first aggregate stimulation recordings from more centers, giving more induced seizure events, a more diverse patient set, and a wider range of montages and protocols. Further, to move from prediction to planning, we will train and evaluate on mapping sessions that vary amplitude, frequency, and site. These sessions provide the comparison closed-loop selection requires, one candidate stimulation against another. Finally, the true test of Alap’s efficacy is on chronic RNS recordings, where stimulation aims to steer the brain away from seizures rather than to provoke a response. That is the setting in which this work would be applied.

8.5.1 Latent Planning for Stimulation

Once the SWM can reasonably model the latent trajectories into and out of a seizure state, two applications follow directly. First, by rolling out the predictor with null stimulation, we can monitor whether the current brain state is approaching the ictal manifold, providing a trajectory-level seizure warning rather than a threshold-based detection. Second, by rolling out under candidate stimulation parameters, we can predict how stimulation would bend or redirect that trajectory. Together, these capabilities frame stimulation selection as goal-directed planning: define a goal state z_g as the latent embedding of the patient’s own interictal activity, then search over candidate stimulation sequences to find the one whose predicted rollout arrives closest to z_g .

The Cross-Entropy Method (CEM) [223] provides a natural search procedure for this problem. CEM maintains a distribution over stimulation parameter sequences, samples a

population of candidates, scores each by the predicted distance between the rollout endpoint and z_g , refits the distribution to the top-scoring candidates, and iterates. Because the rollout and scoring are performed entirely in latent space, the search is computationally lightweight relative to approaches that require decoding back to voltage traces.

For this approach to be practical, the rollout must remain predictive over a long enough horizon for stimulation to take effect. The ten-step rollouts in Section 8.3.1 span 20 s. Whether this horizon is sufficient for planning depends on the timescale of stimulation effects, which varies across paradigms. For slower interventions or pre-ictal steering, a longer horizon would be needed, and the autoregressive error accumulation would need to be characterized over minutes rather than seconds. Retrospective evaluation on existing recordings can partially address this; prospective validation with RNS data would be the definitive test.

8.5.2 Per-Patient Adaptation

Section 8.3.4 demonstrates reference-manifold recalibration from one recorded seizure without changing model weights. Beyond this recalibration, the pretrained SWM may not immediately generalize to a new patient’s specific seizure dynamics and may require some amount of calibration. One approach is to use the rollout prediction error on a short baseline recording as a fine-tuning signal: the model attempts to predict its own next latent states on the new patient’s data, and the prediction error drives parameter updates. An interictal baseline may suffice for calibrating the encoder’s representation of that patient’s normal dynamics, but a recording that includes at least one seizure would provide a stronger signal by exposing the model to the patient’s ictal trajectory.

This leads to two open questions. First, how much of the model should be fine-tuned? Fine-tuning the full model risks overwriting the shared dynamics learned during pretraining, while training only a lightweight adapter may not capture enough patient-specific structure. Second, how much baseline data is required for good calibration? Whether a few minutes of recording suffice or whether longer monitoring is needed will determine how practical this

adaptation step is in a clinical workflow. Empirical results on held-out patient data, where we can retrospectively test calibration quality as a function of both adapter size and baseline duration, will be essential to answer these questions.

8.5.3 Validation Against RNS Trajectories

The MESA dataset provides stimulation that *induces* seizures: cortical stimulation mapping pushes the brain toward the ictal state. But the clinical goal of responsive neurostimulation is the opposite: stimulation that steers the brain *away* from seizures. Whether the SWM’s action-conditioning pathway generalizes to this reversed direction is the central empirical question that RNS data would answer. Given an RNS recording in which responsive stimulation was delivered with known parameters, we can encode the pre-stimulation context, roll out the predictor under those same parameters, and ask whether the model correctly predicts a trajectory that moves away from the ictal manifold. If it does, the model has learned something about how stimulation perturbs brain-state dynamics in both directions, not just the seizure-induction direction present in the training data. If it does not, the gap between MESA’s stimulation paradigm and RNS’s responsive paradigm is too large for the current action-conditioning pathway to bridge, and the RNS recordings themselves would provide a training signal for further calibration.

RNS data would also serve as a source of naturalistic stim-response pairs collected during chronic, ambulatory use. Each stimulation event produces a (state, stimulation, next-state) triplet under realistic clinical conditions, complementing the controlled but artificial setting of MESA’s stimulation mapping. No RNS data has been acquired for this project yet; obtaining such recordings is the target for the next phase of data collection. RNS devices record from only four electrode contacts at a reduced sampling rate, so this validation would simultaneously test whether the spatial encoder produces meaningful representations under the extreme channel sparsity of the chronic-implant regime.

8.5.4 Seizure Taxonomy in Latent Space

Clinicians classify seizures by their electrographic onset pattern: low-voltage fast activity (LVFA), rhythmic spiking, burst suppression, and others. If the SWM has learned meaningful seizure dynamics, these categories should show up as distinct trajectory families in the latent space. We can test this directly: embed a set of seizures with known clinical onset classifications, project them into the SWM’s latent space, and ask whether LVFA seizures cluster separately from rhythmic-spiking seizures, and whether their trajectories evolve differently over time.

This matters for planning because different seizure types likely require different intervention strategies. A seizure that evolves slowly through rhythmic spiking may be steerable over a longer prediction horizon than one that begins with abrupt LVFA. If the latent space captures this distinction, the planning procedure described in Section 8.5.1 could use seizure-type-specific cost functions or prediction horizons rather than treating all seizures the same way. On a longer timescale, the same latent space could be used to track slow interictal drift and flag pre-ictal approach before a seizure begins, operating over minutes to hours rather than the seconds-scale rollout described in Section 8.2.3.

8.5.5 Grounding Latent Geometry in Thalamocortical Biomarkers

The earlier chapters of this dissertation identified frequency-specific thalamocortical signatures at seizure onset and termination. The SWM learns latent representations from the same recording modality, but it is trained to predict next states, not to recover connectivity measures. The question is whether the model has implicitly learned the mechanistic structure that those chapters characterized, and we can answer it by probing.

The idea is straightforward: train lightweight probes on the SWM’s latent representations and ask whether known biomarkers are recoverable. This is analogous to recent work in other domains. Lehn-Schiøler et al. [238] applied sparse autoencoders to EEG foundation models and found interpretable features grounded in clinical concepts like abnormality and

medication status. They introduced a spectral decoder that maps latent manipulations back to frequency-domain signatures, which is exactly the kind of bridge we would need: map the SWM’s latent features back to frequency signatures and compare them to the thalamocortical spectra from the earlier chapters. Tang et al. [239] audited what EEG foundation models learn through ridge probing and subspace erasure, finding that classical spectral features explain roughly 79% of the models’ advantage on easier tasks but leave significant unexplained residual on harder ones. That residual is where novel biomarkers may live.

For the SWM specifically, we could regress thalamocortical coherence values from patch embeddings at matched time points, classify seizure onset type from the encoder’s representation at the first ictal patch, and track whether ictal-manifold distance correlates with coherence changes across the seizure. If these probes recover thalamocortical signatures, the planning objective (minimize distance to interictal) gains a physiological interpretation, and the two arcs of the dissertation connect concretely. If they do not, that is also informative: it would mean the learned representations and the coherence-based biomarkers capture genuinely different aspects of seizure dynamics, which points toward complementary rather than redundant views of the same process.

8.6 Data detail

HUP [224, 225] comprises intracranial EEG from 58 subjects with drug-resistant epilepsy, recorded with subdural grid, strip, and depth electrodes (ECoG) or stereotactically placed depth electrodes (SEEG). Electrode locations are given in ICBM152 MNI space. Interictal and ictal periods are annotated, and clinically determined seizure onset channels are included. The dataset contains no stimulation and is distributed through OpenNeuro (ds004100).

MESA [226, 227] comprises SEEG from 32 patients (19 from the University of Pennsylvania, 13 from Children’s Hospital of Philadelphia) with 83 annotated seizures, 46 spontaneous

and 37 stimulation-induced. Eighty of those onsets survive our preprocessing, and 35 of them follow a stimulation onset at some delay. How many of the 35 count as induced depends on the response window (Table 8.4). Three board-certified epileptologists annotated each seizure independently, giving consensus labels for onset timing and onset channels. Each stimulation train carries its parameters (amplitude, frequency, pulse width, and per-train duration) and electrode coordinates.

The academic cohort is a stimulation-mapping dataset from a third academic medical center, converted to the MESA format. It contributes 29 sessions from 24 patients, 2152 bipolar depth channels, about 30.5 hours of iEEG, and 1889 stimulation trains. Each train carries amplitude, frequency, duration, and the coordinates of the stimulated contact pair, with pulse width fixed at 200 microseconds across the cohort. Two protocols are represented, 1 Hz for 40 s and 50 Hz for 5 s, and 22 of the 29 sessions carry clinician-marked seizure onset channels. One session contains a seizure triggered by stimulation. The same site contributes spontaneous seizures through OpenNeuro ds007445 [228]: 19 subjects and 66 annotated seizures, with hour-scale context around each seizure and no stimulation.

Six academic-cohort patients, P1 through P6, are held out of both training stages by subject identifier, which removes their stimulation and seizure sessions from every training stream. Table 8.2 lists each stream’s role by stage.

Channel coordinates in both academic-cohort streams are MNI centroids of each channel’s anatomical-region label rather than per-contact positions, so contacts in the same region share a coordinate. Channel occlusion still names individual channels, but the spatial information behind the ranking is region-level. HUP and MESA carry per-contact coordinates.

All recordings are resampled to 250 Hz. Each channel is centered at its median and scaled by its interquartile range, with values clipped to ± 20 . Each time sample is labeled background, ictal, stimulation, or co-occurring stimulation and ictal activity. Training, validation, and test sets are split by subject.

Table 8.2: **Data streams by training stage and evaluation role.** Stage 1 trains on the training split of every stream and Stage 2 on the stimulation streams only. P1–P6 are held out of both stages and supply the localization, zero-shot detection, and adaptation evaluations. The 64 stimulation-outcome events are every delivered MESA train, and all patients contributing induced events appear in the training data.

Stream		Stage 1	Stage 2	Evaluation only
HUP (58 sub-jects)		training split	not used (no stimulation)	12 never-trained sub-jects (recalibration check)
MESA (32 patients)	pa-	training split	training split	validation and test subjects (no-stimulation check, localization)
Academic hort, stimulation (24 patients)	co-stim-	training split	training split	P1–P6
Academic hort, ds007445 (19 subjects)	co-seizures,	training split	not used (no stimulation)	P1–P6

8.7 Architecture and training detail

8.7.1 Patch embedding

A depthwise one-dimensional convolution with kernel size and stride of 250 samples (one second at 250 Hz) maps each channel’s voltage trace to a sequence of d_e -dimensional patch embeddings. The weights are shared across channels, so the same temporal feature extractor applies to any electrode and any channel count.

8.7.2 Spatial encoder

The spatial encoder aggregates the per-channel embeddings into one vector per patch. Each electrode’s three-dimensional MNI coordinates are encoded as Fourier positional features [229], projected to d_e , and added to that channel’s patch embedding. A pre-layer-norm transformer encoder then mixes across channels (Table 8.3). Masked mean-pooling over valid

channels followed by layer normalization gives one vector per patch, a linear projection maps it from d_e to d , and sinusoidal temporal positional embeddings encode each patch’s position in the recording.

8.7.3 Stimulation encoder

The stimulation vector per patch has seven dimensions: amplitude in milliamperes, frequency in hertz, pulse width in microseconds, duration in seconds, and the MNI x , y , z coordinates of the stimulating electrode. Separate MLPs process the waveform and spatial groups, and a linear layer maps their concatenated outputs to a d -dimensional stimulation embedding. An all-zero input, meaning no active stimulation, produces a near-zero embedding, so the predictor defaults to unconditional dynamics.

8.7.4 Action-conditioned predictor

The predictor is a causal transformer over a sliding window of 16 patches (16 seconds) that predicts the latent state two patches ahead (Table 8.3). Stimulation conditioning enters through Adaptive Layer Normalization with zero initialization (AdaLN-zero) [230]. At each block, the stimulation embedding passes through a SiLU activation and a linear layer to produce six modulation vectors: a shift and scale for the attention sublayer, a shift and scale for the feedforward sublayer, and a gate for each. The modulated pre-norm computation is $\hat{x} = (1 + \gamma) \cdot \text{LN}(x) + \beta$, where γ and β are the predicted scale and shift, and the gated residual is $x + g \cdot f(\hat{x})$, where g is the predicted gate and f is the attention or feedforward function. The modulation weights start at zero, so the predictor begins training as an unconditional predictor.

8.7.5 Training objective

Alap is trained with the latent prediction objective of LeWorldModel [223], as Laya [218] did for EEG. Encoder and predictor outputs pass through separate projection MLPs before the loss, which decouples the prediction target from the raw encoder representation. The primary loss is the mean squared error between the predictor’s output at time t and the encoder’s output at time $t + 2$, averaged over valid patch pairs in each window, with padded pairs masked out.

The SIGReg regularizer from LeJEPA [66] prevents representational collapse by enforcing an isotropic Gaussian prior on the representations. It compares their projections onto random unit directions against a standard Gaussian in the Fourier domain and is applied across the batch at each temporal position.

An auxiliary seizure detection loss keeps the ictal manifold consistent across patients. A linear head maps each patch embedding to three classes, background, ictal, and stimulation, with co-occurring stimulation and ictal activity labeled ictal, supervised by the per-patch labels. The head is discarded at evaluation. The total loss is

$$\mathcal{L} = \mathcal{L}_{\text{pred}} + \lambda_{\text{SIGReg}} \cdot \mathcal{L}_{\text{SIGReg}} + \lambda_{\text{det}} \cdot \mathcal{L}_{\text{det}} \quad (8.1)$$

with $\lambda_{\text{SIGReg}} = 0.02$ and $\lambda_{\text{det}} = 1.0$. The model is optimized with AdamW under a cosine schedule with linear warmup for a fixed 40 epochs, and model selection uses the MESA validation loss. Table 8.3 lists all hyperparameters.

8.7.6 Two-stage training

Stage 1 is the joint pretraining above. The encoder and predictor train together on all three datasets, each optimizer step draws a roughly equal share of its batch from HUP, MESA, and the academic cohort, and the reported loss is the unweighted mean of the three per-stream losses.

Table 8.3: Stage 1 architectural and training hyperparameters.

Component	Hyperparameter	Value
Patch embedding	Kernel / stride	250 samples (1 s @ 250 Hz)
	Output dimension	$d_e = 128$
Spatial encoder	Transformer layers	4
	Attention heads	4
	FFN expansion	$4\times$
	Attention dropout	0.3
Stim encoder	MLP layers per branch	2
	Hidden dimension	256
	Activation	GELU
Predictor	Transformer blocks	6
	Attention heads	8
	Head dimension	64
	FFN dimension	2048
	Dropout	0.1
	Context window	16 patches (16 s)
Projection MLP	Architecture	$d \rightarrow 2048 \rightarrow d$, batch normalization
Training	Optimizer	AdamW
	Learning rate	1×10^{-4}
	Weight decay	10^{-3}
	LR schedule	cosine, 10% warmup, min 10^{-6}
	Epochs	40 (fixed)
	SIGReg weight λ_{SIGReg}	0.02
	Detection weight λ_{det}	1.0
	Precision	16-bit mixed

Stage 2 fine-tunes the action conditioning on the stimulation data alone. The Stage 1 encoder is frozen, and the predictor and stimulation encoder are updated against a multi-step rollout error: the predictor is unrolled 8 steps from a 3-patch history and compared against the encoded future. It runs on the combined MESA and academic-cohort stimulation recordings, holds out the same subjects as Stage 1, and uses a learning rate of 1×10^{-5} for at most 50 epochs.

8.8 Occlusion localization detail

The academic-cohort result is bimodal. P2 and P4 reach 1.0 on several of their seizures, while P5 scores 0.0 on two of its three, ranking true onset channels last. With 11 seizures the mean is not a stable summary. The permutation null shuffles channel scores within each recording, 10,000 shuffles under a fixed seed.

The ranking is more than lateralization. Restricted to channels in the seizure-onset hemisphere, the result barely moves (0.784, with the top-ranked channel still correct in 8 of 11), whereas asking the same score to pick the onset hemisphere gives only 0.643. P5’s failures persist under the within-hemisphere restriction, so they are a per-patient failure and not a laterality artifact.

On MESA, the nine validation recordings score 0.693 and the eight test recordings 0.766, together 0.727. The top-ranked contact is a true onset contact in 4 of 17 and in the top three in 7 of 17. The 63 training recordings score 0.634, no higher than the held-out recordings, and the weakest held-out recording scores 0.19. All MESA runs use the same occlusion score and the MESA training-split reference manifold.

8.9 What the model treats as a seizure

Six band powers and line length, computed on the same windows and regressed jointly onto the manifold score across held-out seizure sessions, explain $R^2 = 0.11$ of it. The manifold score is therefore not a band-power readout. Every feature correlates negatively with the score (delta -0.24 , theta -0.29): the score rises as low-frequency power falls, the low-voltage fast-activity pattern clinicians read at seizure onset.

This also indicates where the model’s advantage lies. The classical baseline detects seizures in unseen patients at about 0.53, on par with the zero-shot manifold score in Section 8.3.4. The stronger results come after recalibration (0.861) and from the dynamics (0.662 for stimulation outcome).

Table 8.4: **Response window against positive count and result.** An event counts as induced if a seizure onset follows the stimulation onset within the window. The 20 s row is what we report and matches the ten-step rollout horizon. At 60 s some seizures follow two stimulations inside the window, so the 39 counts stimulation events labeled induced (33 distinct seizures). At 10 and 20 s the mapping is one-to-one.

Window	Induced events	Shift AUROC
5 s	5	0.583
10 s	9	0.717
20 s	23	0.662
30 s	31	0.646
60 s	39	0.707

8.10 Controls on the stimulation-outcome result

All rows in Table 8.5 use the same 64 stimulation events and the same 20 s response window, 23 of them induced, over 36 recordings from 29 subjects. Fitted rows are cross-validated leave-one-recording-out. The rest have no training set. Confidence intervals are bootstrapped by subject, and p -values are two-sided permutation tests that exchange label blocks across subjects, both over 10,000 resamples.

The response window selects the cohort, so we report the whole sensitivity curve rather than one window. MESA records 80 seizure onsets, 35 of which follow a stimulation at some delay, and the window decides how many of the 35 are attributed to the stimulation that preceded them. The ictal shift separates the outcomes above chance at every window from 5 to 60 s (Table 8.4).

Learned snapshot baseline. The mean of the three pre-stimulation patch embeddings, 3 s of context in 512 dimensions, classified by `LogisticRegression(C=0.1, class_weight="balanced")` on standardized features over the 36 recordings. Leave-one-recording-out is not leave-one-patient-out, since 17 of the 23 induced events come from subjects contributing other events, but grouping the folds by subject moves this baseline by only 0.006.

Table 8.5: **Predictors of stimulation outcome on the same 64 events, 20 s window.** AUROC for the ictal shift, for baselines that see only the 3 s pre-stimulation window, and for controls that change what the rollouts receive. Rows marked * are logistic classifiers scored leave-one-recording-out. Every other row uses one scalar directly as the predictor. Events in the top quartile of the shift induced a seizure 9 times in 16, against 2 in 16 in the bottom quartile.

Predictor	AUROC
<i>Ictal shift</i>	
Reported model	0.662
Stage 1 model, no fine-tuning	0.638
Leave-one-patient-out refits	0.637
<i>Baselines on the pre-stimulation window</i>	
Manifold score, last patch	0.429
Manifold score, window mean	0.458
Learned snapshot baseline*	0.471
Classical baseline*	0.304
<i>Controls</i>	
Stimulation parameters alone*	0.295
Parameters shuffled across events	0.600
Duration removed	0.624–0.647
Stimulated rollout alone	0.453
Unstimulated rollout alone	0.355
Shift and pre-stimulation score*	0.670

Classical baseline. Seven features per event: six $\log_{10}$ mean band powers from the power spectrum of each 1 s patch (delta 1–4, theta 4–8, alpha 8–13, beta 13–30, gamma 30–70, high gamma 70–120 Hz) and $\log_{10}$ line length, the mean absolute first difference per patch. Each feature is averaged over valid channels and over the three pre-stimulation patches, then classified with L_2 -regularized class-weighted logistic regression under leave-one-recording-out cross-validation. At the 20 s window this classifier scores 0.304 (0.554 at 10 s), and the subject-bootstrapped paired difference between the shift and it is +0.36 (95% CI [+0.13, +0.56]).

Leave-one-induced-patient-out Stage 2. Nine Stage 2 models were retrained, each excluding one induced event’s subject from the rollout objective (validation MSE 0.0389 to

0.0404, all converged). Each held-out subject's events were rescored with the model that never saw them, and the rest keep the reported model. Out of sample the shift gives 0.637 (95% CI [0.495, 0.771], $p = 0.020$). A Stage 1 model, whose predictor was never fine-tuned on stimulation rollouts, gives 0.638 on the same events. Neither differs meaningfully from the reported 0.662, so training exposure does not produce the result.

Confidence-interval width. Twenty-three induced events put a roughly 0.27-wide confidence interval on every stimulation-outcome AUROC. The shift's paired advantage over the pre-stimulation manifold score, +0.204 with 95% CI [+0.023, +0.371], excludes zero only narrowly. It is evidence of a gap, not a measurement of its size.

CHAPTER 9

Conclusions

9.1 Summary

I find that latent prediction learns more semantically organized and transferable latent representations of EEG than masked reconstruction does. More broadly, this work shows that the choice of pretext task shapes both what can be represented and what is clinically useful.

I find that focal seizures engage structured, frequency-specific thalamocortical interactions that evolve across the ictal trajectory. At ictal onset, both AN and CM are recruited bidirectionally, with broadband inflow from the seizure onset zone to the thalamus and slow-frequency (delta) outflow from the thalamus to cortex; CM is preferentially recruited in frontal seizures and AN in limbic seizures. As seizures progress, slow- and beta-band thalamocortical coupling builds and is sustained through the late ictal phase, then disengages at termination. These results support a model in which ictal states carry a bidirectional, frequency-specific thalamocortical signature (slow thalamus-to-SOZ outflow paired with fast SOZ-to-thalamus inflow), and termination is marked by the loss of this organized coupling. Thalamic spectral and thalamocortical connectivity features classify seizure state, supporting their evaluation as candidate biomarkers for adaptive thalamic stimulation.

Alap learns a shared latent space for iEEG across patients, predicts how the latent state evolves, and conditions that prediction on stimulation parameters. The simulations track held-out recordings, with and without stimulation. The difference between the two simulations, the ictal shift, predicts whether a stimulation induces a seizure and outperforms

every baseline given the same pre-stimulation recording. These results establish retrospective stimulation-outcome prediction. Selecting among candidate stimulations remains future work.

9.2 Future Work

9.2.1 Representation learning

One direction is to ground EEG foundation models in what the brain is responding to. Current foundation models, including Laya, are pure observation models: they learn from the signal but not from the context that produced it. Brain state is fundamentally a response to something (a stimulus, a behavior, an internal goal), and a representation that ignores this context can only go so far. The natural next step is to bring these conditioning signals into pretraining, not one paradigm at a time but in concert, so that a single foundation model learns brain state across the full range of contexts in which it is measured.

A second direction is more systematic and comprehensive evaluation of EEG foundation models. The current evaluation landscape is fragmented: models are assessed on narrow task sets with incompatible preprocessing pipelines, making it hard to know which approaches actually generalize. NeuralBench [240] is a step toward addressing this, providing a unified framework across 36 tasks and 94 datasets spanning cognitive decoding, BCI, clinical prediction, and sleep. An early finding is that current foundation models only marginally outperform task-specific baselines, and that many complex tasks remain highly challenging even for the best models. Beyond breadth, benchmarks also need to better reflect real-world deployment: clinical tasks should be evaluated in terms of how a clinician would actually use them (e.g., sensitivity at low false-positive rates, performance on rare phenotypes), and BCI tasks should account for practical constraints like latency and calibration time. Closing this gap between benchmark performance and clinical utility is a prerequisite for foundation models to matter outside the lab.

9.2.2 Mechanistic analysis

A third direction is understanding what EEG foundation models actually learn. Current models are evaluated on downstream benchmarks, but the structure of their learned representations remains largely opaque. Applying mechanistic interpretability tools to these representations (probing latent geometry, tracing which input features drive which representations, testing whether the model recovers known structure such as the thalamocortical signatures characterized in Chapter 6 and Chapter 7) would begin to answer whether foundation models are discovering neuroscientifically meaningful organization or fitting superficial statistical patterns. Interpretability is the bridge that closes the loop between foundation model training and neuroscience. Models that encode meaningful brain structure become tools for hypothesis generation, not just prediction. The goal is for learned representations to return insights to the field, not just improve benchmark scores.

9.2.3 Translation

A fourth direction moves the SWM from retrospective analysis toward prospective clinical use. The rollouts in Chapter 8 retrospectively predict stimulation-associated outcomes on recorded data; ranking candidate stimulation parameters and prospective prediction of seizure termination remain future work. The longer-term goal is a trial in which the model selects stimulation parameters in real time, predicts whether a candidate intervention will terminate a seizure, and adapts to the individual patient over the course of the recording. Chapter 8 develops the steps that would close this gap: latent-space planning (Section 8.5.1), per-patient adaptation (Section 8.5.2), validation against chronic RNS recordings (Section 8.5.3), seizure taxonomy in latent space (Section 8.5.4), and probes that ground latent geometry in thalamocortical biomarkers (Section 8.5.5). The shared challenge is patient-specific generalization: whether a model pretrained on a cohort can adapt to a new patient quickly enough to be useful in real time.

9.3 Closing remarks

Overall, this dissertation has shown that EEG foundation models can learn useful, transferable representations of brain state from unlabeled EEG data. It has also shown that thalamocortical network dynamics during seizures are structured and frequency-specific, and that a learned model of seizure dynamics can predict stimulation outcomes, providing a foundation for future closed-loop planning. These results are a step toward a mechanistic understanding of epilepsy and a foundation for personalized neurostimulation.

APPENDIX A

Supplementary Material

A.1 Epilepsia Patient Characteristics

Table A.1: Epilepsia cohort characteristics

Pt. ID	Age	Sex	Epilepsy type/etiology	Current AED use	MRI/PET	Prior surgery	Thalamic electrode (no. contacts)	Sampling location (no. contacts)
1	18.3	M	Focal / Unknown	LEV, LMT, RFM, CLB	NL/NL	None	RAN (4) / RCM (4)	R: F, T, LIM, P; L: F, T, LIM (total: 62)
2	28.1	M	Focal / Structural (FCD)	CNB, OXC, CZP	L P & PV WM T2 FLAIR hyperintensity / L P	L hemicraniotomy	LAN(4) / LCM(4)	R: T, P, LIM; L: T, P, LIM (total: 80)
3	12.9	F	Focal / Unknown	FBM, CLB, KD	NL/R T	VNS	RAN(4) / RCM(4)	R: F, T, LIM; L: F, T, LIM (total: 72)
4	25.7	F	Focal / Unknown	LTG, LEV	NL / L T	VNS	LAN(4) / LCM(4)	L: F, T, LIM, BG (total: 66)
5	10.5	M	Focal / Structural (R ethmoid encephalocele)	CLB, LTG, CNB	R F gliosis / R F	R F pole resection	RAN(4) / RCM(4)	R: F, T, P, LIM; L: F, T, P, LIM (total: 110)

Pt. ID	Age	Sex	Epilepsy type/etiology	Current AED use	MRI/PET	Prior surgery	Thalamic electrode (no. contacts)	Sampling location (no. contacts)
6	21.9	M	Focal / Structural (Encephalitis & FCD)	CNB, LCM, LEV	L T FLAIR hyperintensity / NL	VNS	LAN(4) / RAN(4)	R: F, T, P, LIM; L: F, T, P, LIM (total: 120)
7	18.4	F	Rasmussen syndrome / Structural	BRV, CBD, CLB, ESL, FBM, ZNS	L putamen FLAIR hyperintensity; L F, T, BG atrophy (& L lateral ventricle dilation) / L F	VNS	LAN(4) / LCM(4)	R: T; L: F, P, T, BG (total: 32)
8	16.1	M	Focal / Unknown	CBD, OXC, CLB	NL / L T, P	none	LAN(4) / LCM(4)	R: F, P, O, T, LIM; L: F, P, O, T, LIM (total: 140)
9	25.2	F	Focal / Structural (FCD)	BRV, CLB, CNB	L T, P, O gliosis / L TPO	L T resection, VNS	LAN(4) / LCM(4)	L: F, P, O, T, LIM, BG (total: 30)

Pt. ID	Age	Sex	Epilepsy type/etiology	Current AED use	MRI/PET	Prior surgery	Thalamic electrode (no. contacts)	Sampling location (no. contacts)
10	2.7	M	LGS / Genetic-Structural (TSC)	CBD, CLB, FBM, LEV	L cortical & subcortical Tub, subependymal nodules along L F, T, P / L F, O Tub resection T, P	L Tub laser ablation, CC, L T lobectomy, & L	RAN(4)/ RCM(4)	R: F, P, T; L: F (total 78)

Table A.2: Epilepsia seizure characteristics

Pt. ID	Seizure type	Seizure onset	Onset (anatomical)*	Semiology
1	1_1	R F (n=3)	R pars triangularis, R supramarginal, R middle temporal	FMS
1	1_2	R F (n=1)	R pars triangularis	FMS
2	2_1	L P (n=3)	L supra marginal	FNMS (+/- FBTCS)
2	2_2	R P (n=2)	R supra marginal	FMS to FBTCS
3	3_1	L F (n=1)	L middle frontal & L anterior cingulate	MS
3	3_2	R F (n=2)	R middle frontal, R anterior cingulate	MS
4	4_1	L LIM_1 (n=3)	L hippocampus	FMS
4	4_2	L LIM_2 (n=1)	L hippocampus, L superior temporal	FNMS
5	5_1	R P (n=3)	R superior parietal	FMS
6	6_1	L LIM (n=1)	L hippocampus, L superior temporal	FNMS
6	6_2	L T (n=2)	L superior temporal	FNMS
6	6_3	R T (n=1)	R superior temporal	FNMS
7	7_1	L F (n=3)	L pars opercularis/trangularis, L superior temporal, L middle temporal, L postcentral	FMS

Pt. ID	Seizure type	Seizure onset	Onset (anatomical)*	Semiology
7	7_2	L T (n=1)	L superior temporal, L middle temporal, L pars opercularis, L pars triangularis, L postcentral	FMS
8	8_1	L P (n=3)	L inferior parietal	FBTCS
8	8_2	L P (n=1)	L inferior parietal	FNMS
9	9_1	L LIM (n=2)	L anterior insula	FMS
10	10_1	R F (n=1)	R superior frontal	FMS
10	10_2	R F (n=1)	R superior frontal	FMS to FES
10	10_3	R F (n=1)	L pars opercularis	FES
AN: anterior nucleus of thalamus; BG: basal ganglia; BRV: brivaracetam; CC: corpus callosotomy; CBD: cannabidiol (epidiolex); CLB: clobazam; CM: centromedian nucleus of thalamus; CNB: cenobamate; CZP: Clorazepate; ESL: eslicarbazepine; F: female; F: frontal; FBM, felbamate;				
FBTCS: focal to bilateral tonic-clonic seizure; FCD: focal cortical dysplasia; FES: focal epileptic spasms; FNMS: focal nonmotor seizure; FMS: focal motor seizure; KD: ketogenic diet; LCM: lacosamide; L: left; LEV: levetiracetam; LIM: limbic system;				
LTG: lamotrigine; M: male; MS: myoclonic seizure; NL: normal; O: occipital; OXC: oxcarbazepine; P: parietal; PV: periventricular; R: right; RFM: rufinamide; T: temporal; TSC: tuberous sclerosis; complex; Tub: tuber; ZNS: zonisamide; VNS: vagus nerve stimulator				
* bold area is used as an onset for connectivity analysis.				

A.2 Termination Patient Characteristics

Age category*	Sex	Etiology	ASMs during SEEG	MRI/PET hypo metabolism	Prior Surgery	Onset	Non-thalamic coverage	Thalamic Coverage	Seizure Onset Pattern	Seizure End Semiology	Outcomes (intervention)
0-2	M	LGS /Genetic-Structural(TSC)	CBD, CLB, FEB, LEV	Bilateral cortical & subcortical Tub, subependymal nodules/L F,T,P	L Tub laser ablation, CC, L T lobectomy, & L O Tub resection	R F: 1 R F: 3	R: F, P, T L: F	RAN, RCM	RAN:none, RCM: LVFA	FMS	No surgery
6-12	M	Focal /Structural (R ethemoid encephalocoele)	LCM, LEV, BTM	R F gliosis / R F FLAIR	R F pole resection	R P:3	R: F, T, P, LIM L: F, T, P, LIM	RAN, RCM	RAN:LVFA/ Slow, RCM: LVFA	RAN:RS/ RSsw, slow RCM: RS/RSw	RNS (Incl. RCM)
18-29	F	Rasmusussen syndrome / Structural	BTM, CBD, CLB, ESL, FBM, ZNS	L putamen FLAIR hyperintensity; L F, T, BG atrophy(& L lateral ventricle dilation)/ L F	VNS	L T:3	R: T L: F, P, T	LAN, LCM	LAN: LVFA, none; LCM: LVFA, none	FMS	RNS (Incl. LCM)
18-29	F	Focal / Structural (FCD)	BVT, CLB, CNB	L T,P,O gliosis/ L TPO	L T resection, VNS	L L: 2	L: F, P, O, T, LIM	LAN, LCM	LAN: LVFA RS/RSw	FMS FNMS	RNS (Incl. LAN)
0-2	M	Focal / Structural (FCD/NRPL3)	OXC, VGB	None/ R T	none	R T:3	R: F, T, LIM L: F	RCM	RCM: LVFA, RS/RSw	FNMS	Laser ablation for FCD

Age category* (yr)	Sex	Etiology	ASMs during SEEG	MRI/PET hypo metabolism	Prior Surgery	Non-thalamic coverage	Thalamic Coverage	Seizure Onset Pattern	Seizure End Semiology	Outcomes (intervention)	
0-2	M	FS+ post IESS/Genetic-structural (TSC)	CLB,	Bilateral	none	R F: 3 R: F, T L: O, LIM	RAN,RCM	RAN: LVFA,	RAN:	Right	
			LEV,	cortical &			none	RS/RSw			
			PER,	subcortical			RCM:LVFA,	RCM:			
			VGB	Tub,			none	RS/RSw		tuberectomy	
13-17	F	Focal / Structural (FCD)	LTG,	None (lack of	L subtotal	L F: 2, L: F, P, L P: 3 LIM	LCM	LCM:	LCM:	FMS, RNS (Incl. LCM)	
			OXC	left brain) /L F	hemispherectomy;			RS/RSw, LVFA	RS/RSw	FBTCS	
					L sensorimotor						
					resection						
13-17	F	LGS /Genetic-Structural(Bandheterotopia)	FFA,	Posterior	VNS	L O: 3 R: O, L: O	RAN,RCM	RAN: LVFA,	RAN:	FMS	
			CNB,	dominant				RS/RSw, none	RS/RSw		RNS (LCM & RPUL)
			CLB,	bandheterotopia/ NL				RCM: LVFA	RCM:		
			RUF						RS/RSw		
3-5	M	Focal/Structural (perinatal ischemia)	CLB,	RF	none	L O: 2 R: F, P, T, O	LCM	LCM:	LCM: slow,	FNMS	
			LTG,	Porencephalic				RS/RSw, none	none		RNS (Incl. LPUL)
			PER	syst / L T		L: P, O, LIM					

Age category* (yr)	Sex	Etiology	ASMs during SEEG	MRI/PET hypo metabolism	Prior Surgery	Onset	Non-thalamic coverage	Thalamic Coverage	Seizure Onset Pattern	Seizure End Semiology	Outcomes (intervention)
6-12	M	Focal/Structural (periventricular gray matter heterotopia)	LTG	LF Gray matter heterotopia/NL	none	L F:3	R: F, LIM L: F, P, T, LIM	LAN, LCM	LAN: RS/RSw LCM: RS/RSw slow, none LCM: RS/RSw, slow, none	FNMS	RNS (Incl. LCM)
13-17	F	Focal/Genetic-structural (TSC)	CNB, LTG, ZNS	Subcortical Tub L F & R F, T, P, subependymal nodules/L F	none	L F:3	R: F, T, P L: F, T, LIM	LAN, LCM	LAN: LVFA, NA LCM: None	FNMS	Left tuberectomy
18-29	M	Focal/Unknown	CLB, LTG	R T FLAIR hy-perintensity(or none?)/ NL	none	R F:3	R: F, T, LIM L: F, T, LIM	RAN, RCM	RAN: RS/RSw RCM: RS/RSw RCM: RS/RSw	FNMS, FBTCS	No surgery
13-17	M	Focal/Structural (FCD)	CBD, CBZ, CLB, LCM, Ketogenic Diet	L insula FCD / L insula	none	L	L: F, P, T, LIM	LAN, LCM	LAN: LVFA, NA LCM: LVFA, NA	FMS, FBTCS	RNS (Incl. LAN)
18-29	M	Focal/Unknown	BTM, CNB, LCM	NL / NL	R T lobectomy	R T:3	R: F, P, T, O, LIM	RAN, RCM	RAN: RS/RSw RCM: RS/RSw RCM: RS/RSw	FNMS	RNS (Incl. RAN)

Age category* (yr)	Sex	Etiology	ASMs during SEEG	MRI/PET hypo metabolism	Prior Surgery	Non-thalamic coverage	Thalamic Coverage	Seizure Onset Pattern	Seizure End Semiology	Outcomes (intervention)
18-29	M	Focal / Structural (Encephalitis & FCD)	CNB, LCM, LEV	L T FLAIR hyperintensity / NL	VNS	R T: 3 R: F, T, P, LIM R P:1 L T:4 L: F, T, P, LIM	RAN, LAN LAN: LVFA, RS/RSw, Slow, none LAN: slow, none RAN: LVFA, RS/RSw, none RS/RSw, none	LAN: FNMS	RNS (bil. AN)	
	13-17	M	Focal / Unknown	NL / L T, P	none	L P:3 R: F, P, O, T, LIM L LIM:1 L: F, P, O, T, LIM	LAN, LCM LAN: LVFA, RS/RSw LCM: LVFA	LAN: FNMS, FBTCS RS/RSw FBTCS LCM: RS/RSw	RNS (Incl. RCM)	
						L L: F, T, LIM LIM: 4 LIM, BG	LAN, LCM LAN: RS/RSw LCM: RS/RSw, slow	FMS, FNMS	RNS	
18-29	F	Focal / Unknown	LTG, LEV	NL / L T	VNS					
18-29	M	Focal / Structural (FCD)	CNB, OXC, CZP	L P & periventricular white matter T2 FLAIR hyperintensity	L hemisphericotomy	R P: 3 R: T, P, (L P: 2) L P: LIM L: T, P, LIM	LAN, LCM LAN: LVFA, RS/RSw, none LCM: LVFA, RS/RSw, none	LAN: LVFA, RS/RSw LCM: LVFA, RS/RSw	FNMS, FBTCS	RNS (Incl. LCM)
	18-29	M	Focal / Unknown	NL/NL	None	R F: 4 R: F, T, LIM, P, L: F, T, LIM	RAN, RCM RAN: LVFA RCM: LVFA	RAN: FMS RS/RSw RCM: RS/RSw	RNS (Incl. RCM)	

ASMs: antiseizure medications; AN, anterior nucleus of the thalamus; BTM, brivaracetam; CBD, cannabidiol; CBZ, carbamazepine; CLB, clobazam; CM, centromedian nucleus of the thalamus; CNB, cenobamate; CZP, clorazepate; ESL, eslicarbazepine; F, frontal; FBM, felbamate; FBTCS, focal to bilateral; FFA, fenfluramine; FMS, focal motor seizure; FNMS, focal non-motor seizure; IEES, Infantile Epileptic Spasms Syndrome; LEV, levetiracetam; LGS, Lennox-Gastaut Syndrome; LTG, lamotrigine; L left; LCM, lasocamide; LIM, limbic system; LVFA, low voltage fast activity; NL, non-lesion; O, occipital; OXC, oxcarbazepine; P, parietal; PER, perampanel; PUL, pulvinar; T, temporal; TSC, Tuberous Sclerosis Complex ; Tub, tuber; R; right; RS/RSw, rhythmic spike, spike-and-wave, or slow wave; RNS, responsive neurostimulation; RUF, rufinamide; Slow, slow wave without rhythmicity; VGB, vigabatrine; VNS

*Age categories were defined as inclusive intervals based on chronological age at evaluation, with the “0–2 years” category encompassing ages from birth through 2 years 11 months.

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