BRAINGNNet: Graph Models for Chronic Pain Detection through EEG Biomarkers

Introduction

Despite the advancements in healthcare and the surge in emerging clinical technologies, there has yet to be progress concerning the methods of assessment of pain in general and chronic pain in particular due to the complications involved in the identification of specific neuro markers. In clinical settings, the measurement of perceived pain continues to rely primarily on subjective assessments and traditional tooling tightly coupled with various rating scales with none sufficiently developed and proven to provide broader applicability, accuracy, and reproducibility to be recommended for use in clinical practice or research.

This article explores our preliminary analysis of a novel approach to chronic pain detection leveraging electroencephalographic (EEG) biomarkers. As part of the discovery stage of our effort, we developed BRAINGNNet: a graph model and a framework that integrates brain topology with EEG channel read and extracted features using data from publicly available studies and data sets (i.e., cpCGX-BIDS and MBB-LEMON). The proposed model aims to effectively differentiate between healthy and chronic pain subjects by applying Graph Neural Networks (GNNs) to detect and classify chronic pain states. The preliminary analytics findings indicate considerable potential for improving chronic pain monitoring and management in clinical applications through this data-driven, lightweight, resource-preserving approach.

Motivation and Background

Chronic pain affects millions worldwide and often co-occurs with a wide range of cognitive and emotional contributors, including mental disorders. The impact of the inability to objectively measure an individual's experience of pain is manifold, presenting numerous challenges in pain management concerning medication availability or overuse, clinical care, treatment, monitoring, and clinical trials. As such, reliable, ethical, non-invasive detection and continuous measurement (e.g., patient-side) are crucial for effective treatment.

Despite the uncertainties in establishing pain correlations and the difficulties in fully capturing the dynamics of neural circuits involved in pain processing, brain imaging shows promise in identifying the mechanisms that underlie chronic pain. Electroencephalographic (EEG), in particular, with its high temporal resolution enabling the detection of specific brain areas associated with chronic pain through the correlation of oscillatory activities across different regions, stands out as a portable, easy-to-perform alternative that is more cost-effective than fMRI and PET [11,12].

Some of the evolving and recent EEG-based methods and approaches to the detection and measurement of pain include:

- *Univariate approaches*: Focus on individual metrics and features, including location, magnitude, spatial extent of activation, or functional connectivity in a network or between specific brain areas, and how they are correlated with behavioral measures, such as reported pain experiences, to determine their relationship to pain perception.
- *Multivariate Approaches and Machine Learning (ML)*: Focus on combining multiple features of brain imaging data into a comprehensive predictive model leveraging statistical techniques leading to pattern identification with the application of ML to brain imaging data to predict pain-related outcomes.

While promising, these approaches, particularly ML, require careful interpretation and validation to ensure specificity, accuracy, and applicability across different pain types and patient populations [3].

Other more recent efforts leverage Deep Learning (DL) frameworks trained on EEG recordings and other multimodal data, looking at coherence, functional correlations, and connectivity expanding from an isolated “pain cortex” to pain as a distributed, dynamic, and non-linear brain network activity. One such effort combines Signal Processing with Artificial Neural Networks (ANN) for severity-level classification [5], identifying the alpha band activity as a potential indicator and revealing a direct correlation between the Alpha frequency band power and pain intensity. It is important to note that approaches dealing with aspects of chronic pain present a more complex proposition compared to predictive ML frameworks and techniques targeting the detection of acute pain perception. Similar complexity in chronic vs. acute pain classification applies to differentiating neuropathic pain-related brain activity from nociceptive patterns.

To our best knowledge, no study has yet considered the topological relationships between EEG channels and band power activity within the context of pain detection and classification leveraging graph-based learners [2]. In our approach, we propose reducing the chronic pain detection and measurement problem space to a graph representation of topological relationships and features from EEG data, leveraging a Heterogeneous Graph Neural Network (HGNN) learner to differentiate between healthy and chronic pain subjects through the classification of *graphs or nodes*. As part of the discovery and planning stage, we have conducted a preliminary analysis with available open datasets to explore the proposed approach and develop a framework for assessing the specificity and effectiveness of leveraging EEG biomarkers.

Our focus on achieving high efficiency while minimizing computational complexity differentiates the proposed pain measurement approach from similar efforts. Our proof-of-concept (POC) projects target the development of a cost-effective and sustainable measurement apparatus, primarily relying on non-invasive EEG recordings and an innovative computational model where we reduce the detection problem to optimized GNN algorithm(s), learning and modeling the subtle and complex patterns through graph connectivity, to address and overcome the staggering DL complexities in working with EEG and potentially with other multimodal neuroimaging data, system performance problems due to heavy reliance on computing resources, and brittleness in the ML/DL model performance and specificity in analyzing brain states.

Biomarker Assessment Framework and Model Development

EEG Study Datasets

To assess the effectiveness of the proposed HGNN learner and inference framework in capturing EEG biomarkers, we developed a graph model aligning the brain topology with the International 10–10 system for EEG electrode placement and Absolute Band Powers as the key EEG feature. This model combines Brain Imaging Data Structure (BIDS) compliant datasets from two critical EEG studies:

- **cpCGX-BIDS: Chronic Pain Data EEG Dataset** (Technical University of Munich [15])
    - Raw resting-state EEG data -- conditions: eyes closed (EC) or eyes open (EO), Electrodes: 29, in BIDS format for 74 chronic pain patients
    - Recorded between March 2022 and November 2022 in the Klinikum Rechts der Isar (Munich, Germany)
- **MBB LEMON: Control (Healthy) EEG Dataset** (Max Planck Institut Leipzig [1])
    - Preprocessed resting state EEG data -- conditions: eyes closed (EC) or eyes open (EO), Electrodes: 59, in BIDS format for 228 Participants (from which we sampled 92).
    - Digitized EEG channel locations Polhemus leveraging PATRIOT Motion Tracking System (Polhemus, Colchester, VT, USA) localizer with the Brainstorm toolbox.

In working with these datasets, to establish a baseline for chronic pain versus control subject reads, we solely relied on the Eyes-Closed resting-state EEG reads, excluding, for the time being, the temporal aspect and to limit band activity associated with alertness and visual processing.

Data Processing Methodology, Pipelines and Tools

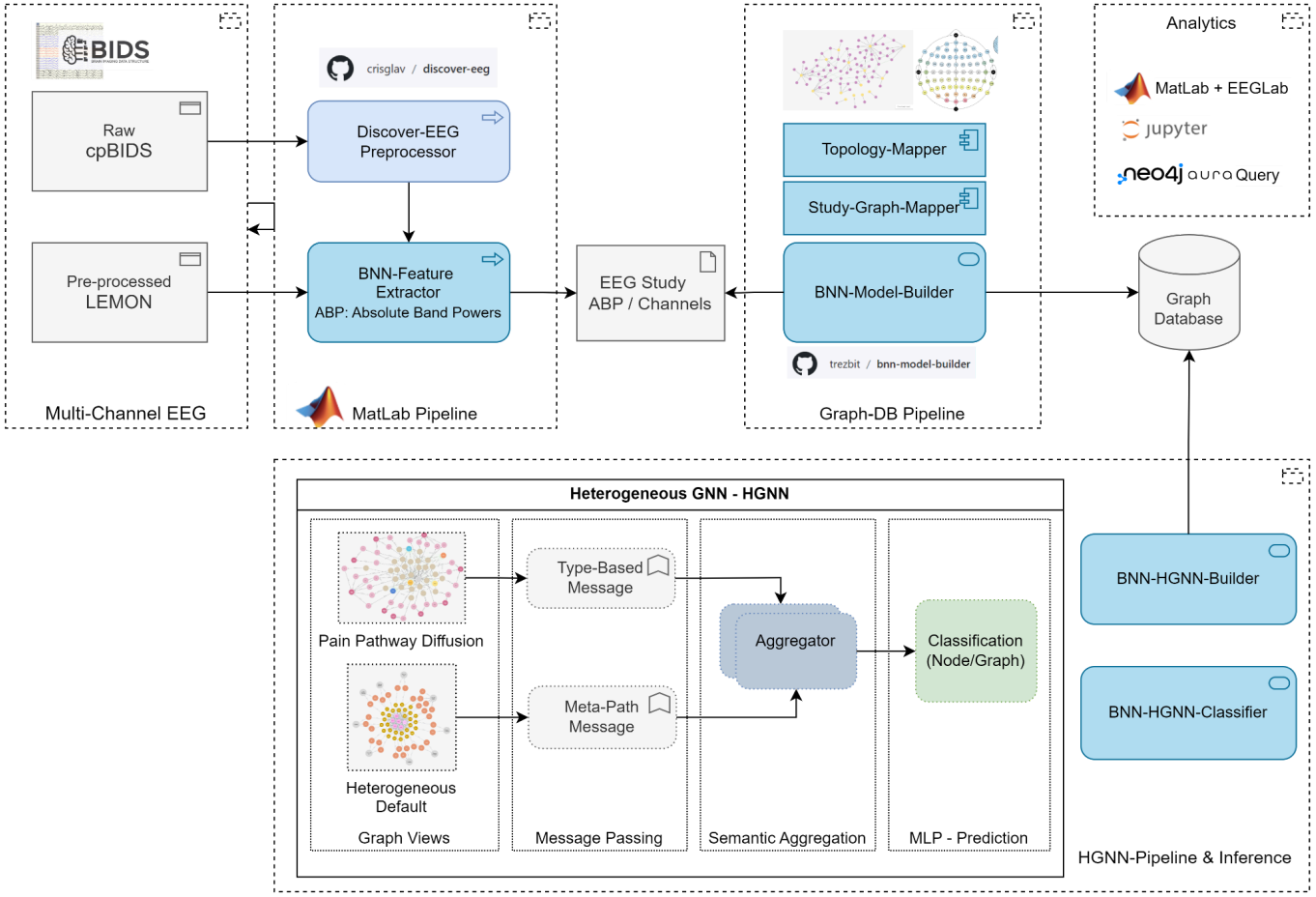


Figure 1: BRAINGNN Processing Pipelines

Preprocessing and EEG Feature Extraction

In our EEG data processing pipeline, we leveraged DISCOVER-EEG [2], an open-source EEG pipeline for biomarker discovery for MATLAB (version R2024a with Signal Processing Toolkit, EEGLAB 2024.0, Fieldtrip v.20240110, BCT: Brain connectivity toolbox v.20190303). The preprocessing steps included:

1. *Line noise removal*
2. *High pass filtering and bad channel removal*
3. *Re-referencing to the average reference*
4. *Detection and removal of artifactual independent components*
5. *Interpolation of rejected bad channels*
6. *Detection of bad time segments*

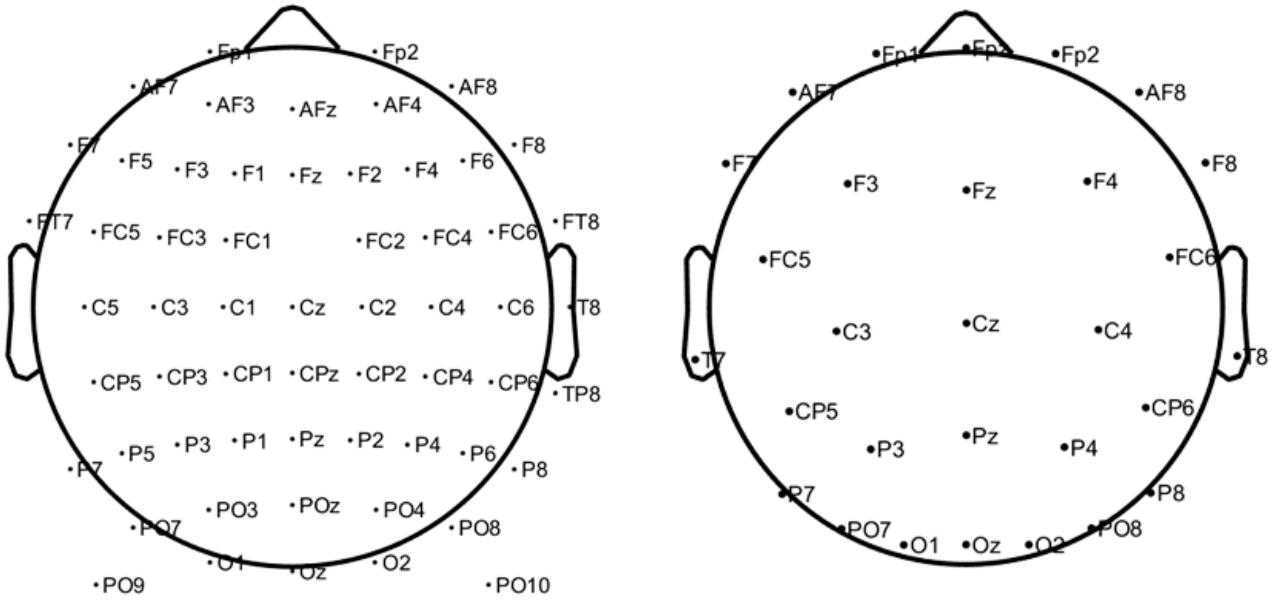
A custom EEG feature-extraction pipeline follows the preprocessing stage, implemented in MATLAB (version R2024a with Signal Processing Toolkit, EEGLAB 2024.0. To identify a baseline for a graph model that is robust and optimally expressive, we have focused on *Absolute Band Power* (ABP: Total energy intensity of an electrode on a specific region at different frequency bands [Miana L]) as the feature of interest with frequency bands:

- Delta (1–4 Hz)
- Theta (4-8 Hz)

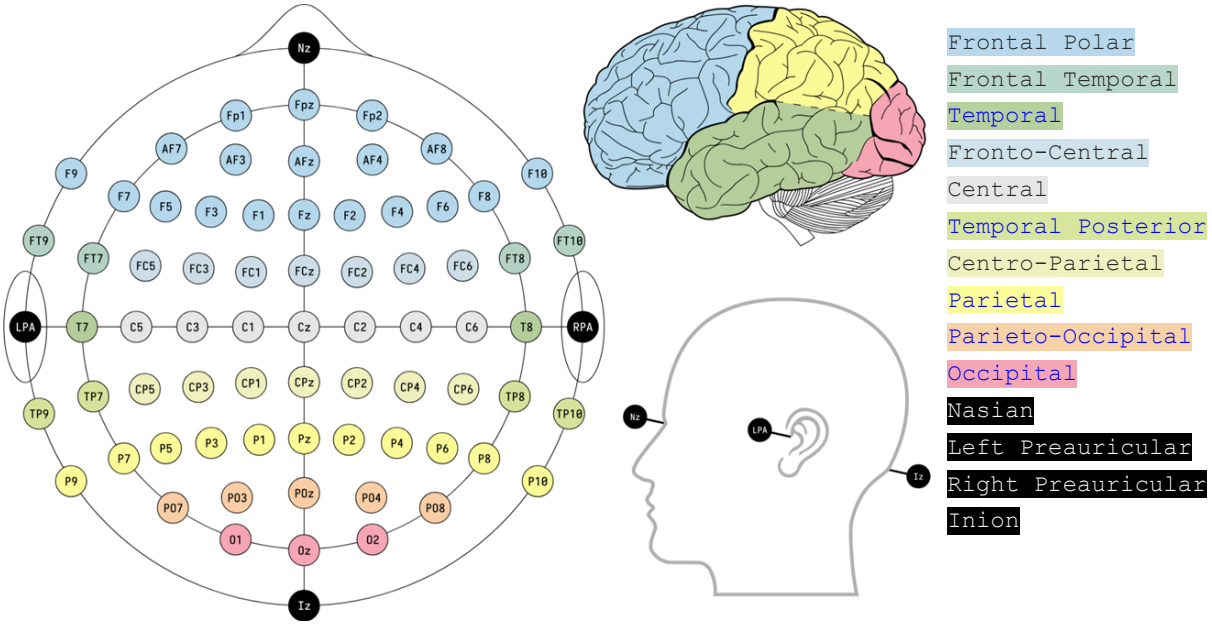
- Alpha (8-13 Hz)
- Beta (13-30 Hz)
- Gamma (30-80 Hz)

Topology Mapping

As a step leading to creating a *Reference Brain Topology Map* that can allow us to compare activation paths, we aligned the International 10–20 system for EEG electrode placement with EEG Channel locations and labels from both cpCGX-BIDS and MBB LEMON data in MATLAB (version R2024a with Signal Processing Toolkit, EEGLAB 2024.0)



The reference topology uses the labeling at 10-10 (10% precision of the 10-20) system to accommodate channel locations from control and chronic pain subjects for reliable comparison highlighting activations in or near regions:



The reference topology also includes the *electrode chains* (left *parasagittal*, right *parasagittal*, left *temporal*, right *temporal*, and a small *central* chain formed by the "z" electrodes) for potential pattern discovery, e.g., bursts of band power along the chains.

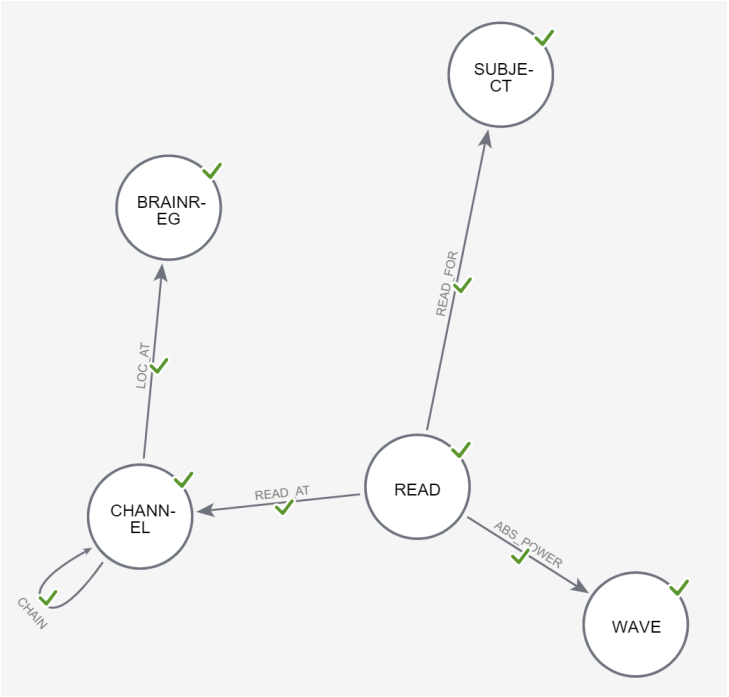


Figure 4: Graph Database Schema

We developed a graph database schema as a reduced representation of our problem space with the following:

- A subgraph capturing the *Reference Brain Topology Map* outlined in the previous section, along with ABP *marker* nodes for frequency bands.
- Subgraphs representing EEG Channel Reads clustered around the control vs. chronic pain study subjects, tying each subject to the reference brain topology and ABP to represent an activation network.

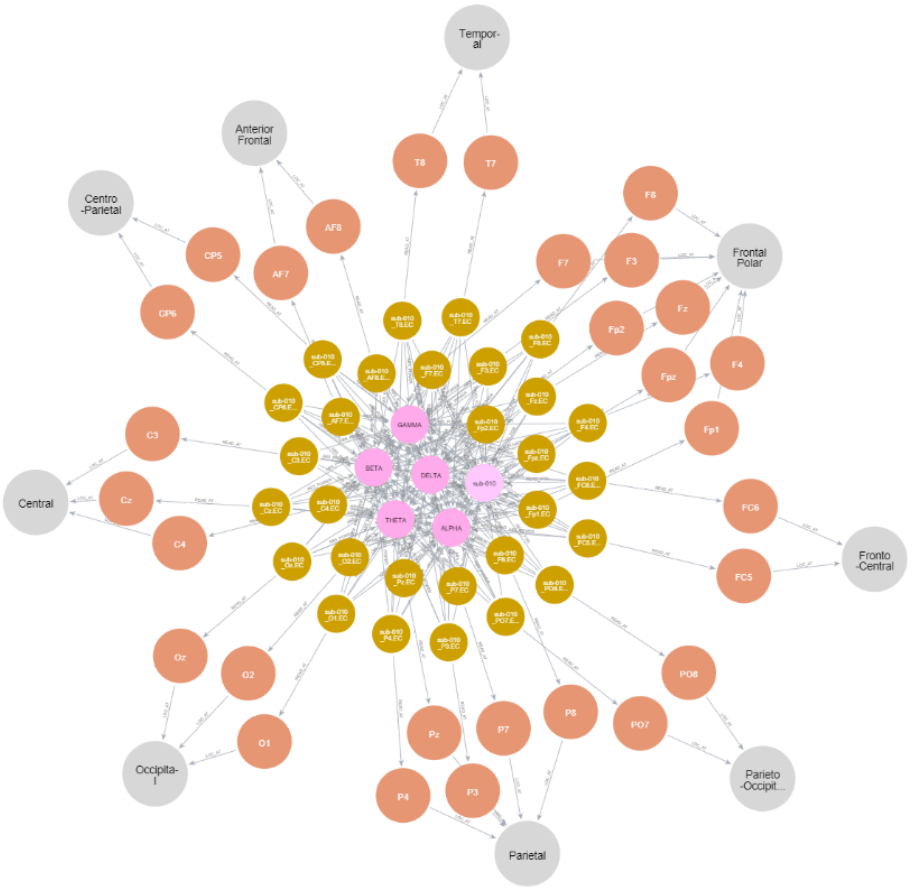


Figure 5: Subject EEG Data Graph Representation

Graph Database Statistics

NODES	Count	Property Count	Rel Count (Mean)	Rel Count (Min)	Rel Count (Max)
SUBJECT (Study Data: Participant)	166	3	89	29	118
BRAINREG (Ref: Brain Region)	15	2	5	1	14
CHANNEL (Ref: EEG electrode position in International 10–20 system)	73	10	205	1	330
WAVE (Ref: ABS for Frequency Band - Delta, Beta, Alpha, Theta, Gamma)	5	4	14814	14814	14814
READ (Study Data: EEG Data for Channel)	14814	3	7	7	7

EDGES	Count	Property Count

LOC_AT (Ref: CHANNEL→ BRAINREG [Property: alignment-central, right, left])	146	4
CHAIN (Ref: CHANNEL→ BRAINREG [Property: type, right, left])	76	7
READ_FOR (Study Data: READ → SUBJECT)	29628	3
READ_AT (Study Data: READ → CHANNEL)	29628	3
ABS_POWER (Study Data: READ → WAVE [Property: weight-measured power])	148140	4

GNN Architecture and Inference

The second phase of our discovery involves outlining the computational approach to implement Graph Neural Networks (GNN) to effectively enable learning patterns to predict chronic pain through various classification tasks.

In the context of the BRAINGNNet, we favor Heterogeneous GNN architectures as they are better suited for the proposed EEG Biomarker approach, which encapsulates rich type information both at the edge and the node level and requires specialized message-passing mechanisms, semantically augmented aggregators, and strategies like meta-paths to guide the information flow and structural matching. It is also essential to consider the extensibility of the potential inclusion of new and extended feature networks in BRAINGNNet through the seamless augmentation of the graph model with new node and edge types for improved predictive performance.

Consequently, the candidate architectures for POC efforts include message-passing neural networks (MPNNs) with improved expressiveness to:

- Handle heterogeneous graphs with different types of nodes and edges through a flexible framework for learning on complex graphs, e.g.:
    - Multi-view Heterogeneous Graph Neural Networks [17]
    - Heterogeneous Graph Attention Network (HAN) [13]
- Overcome the limitations of traditional GNNs in distinguishing between graph structures, providing higher representational power in fitting the training data, e.g.
    - Graph Isomorphism Networks (GIN) [14]
- Simplify and improve the scalability of the architecture leveraging Category Theory formalisms and structures (e.g., monoids) [9, 4]

For the targeted candidate architectures, the POC scope extends to:

1. Outlining an evaluation and benchmarking scheme/framework capturing predictive performance (i.e., Specificity and Sensitivity) and operational efficiency and effectiveness in low-resource environments with limited connectivity, focusing on metrics around energy consumption and latency in Real-Time performance.
2. Development iterations for pipelines supporting shortlisted architecture alternatives, components, and services for the Heterogenous GNN Model Build - Training and Inference
3. Evaluation of the prototyped GNN Model architecture, looping back to development iterations.

Preliminary Analysis and Findings

Method

Following the Graph Database build with all notes and edges available for both Topography and Study subgraphs, we performed comparative analysis for Control (MBB-LEMON) and Chronic Pain (cpCGX-BIDS) Subject EEG Graphs investigating:

- Absolute Band Power (ABP) Mean, Median, and Standard Deviation variations across Brain Regions by Band - (Figure 6)
- Absolute Band Power (ABP) asymmetries across the Right and Left Hemisphere contrasted with regions along the Central Chain by Band - (Figure 7)
- Sampled Subject EEG Graphs' Node and Edge visualization with conditional rendering based on ABP strength (Figure 8-9)

For this exercise, we used Cypher extracts from the Graph Database, which we then pulled into Pivot tables with aggregations using Jupyter Notebooks. The source data and the Notebook are available on GitHub: BNN-MODEL-BUILDER.

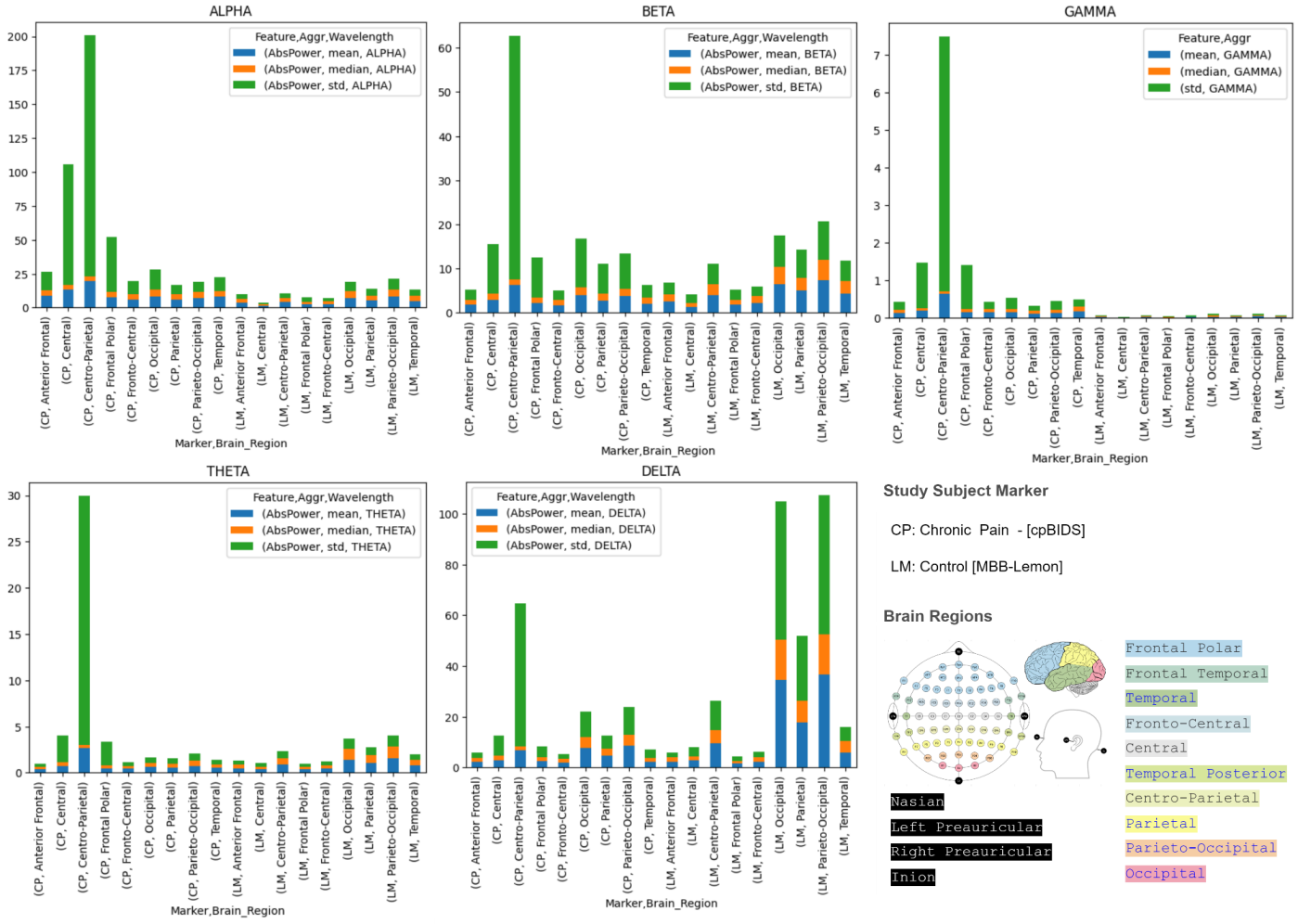


Figure 6: Comparative view of Mean and Standard Deviation regional variations for ABP

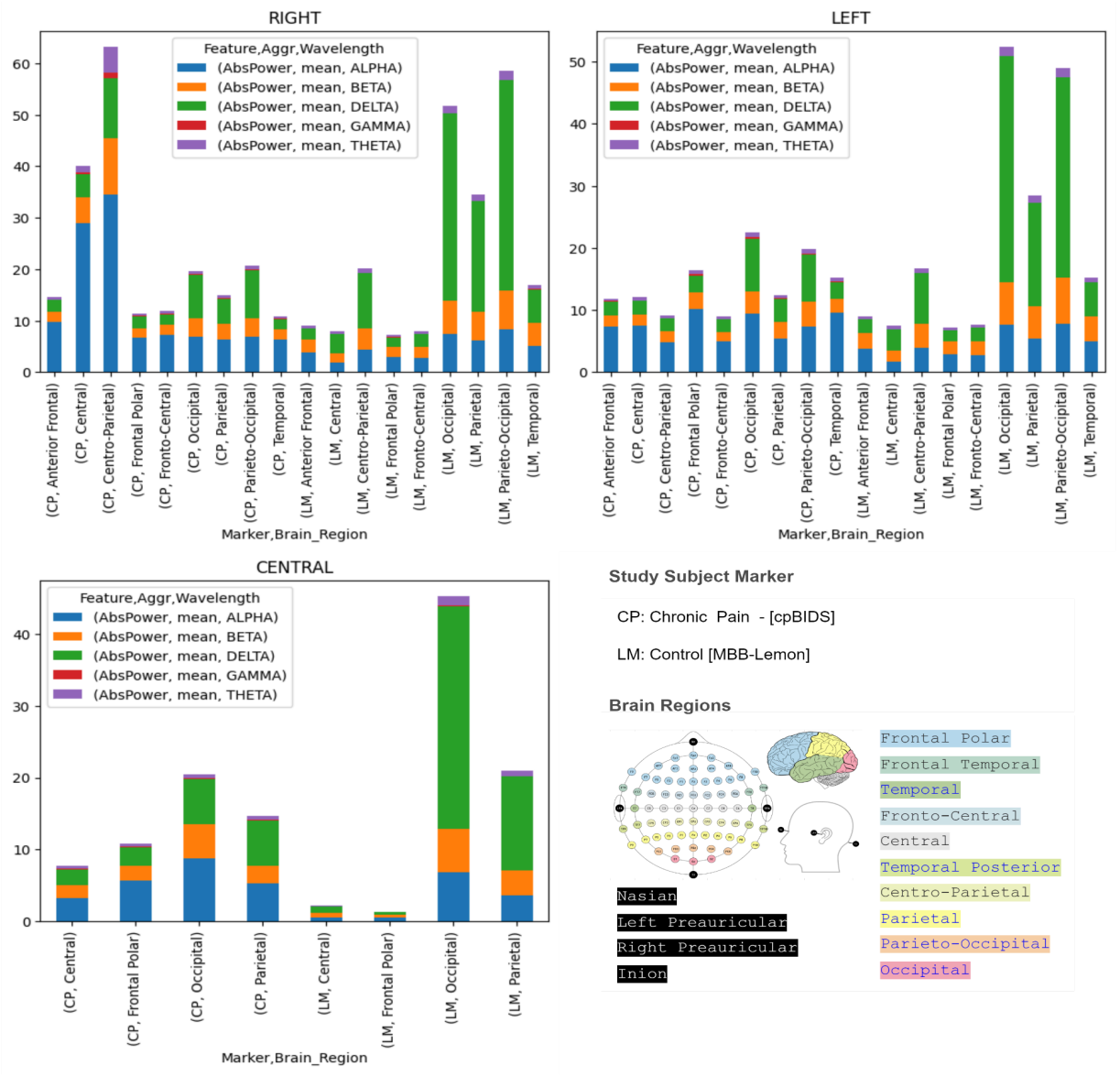


Figure 7: A comparative view of Absolute Band Power (ABP) Mean regional variations for the Right and left Hemispheres and Central Chain.

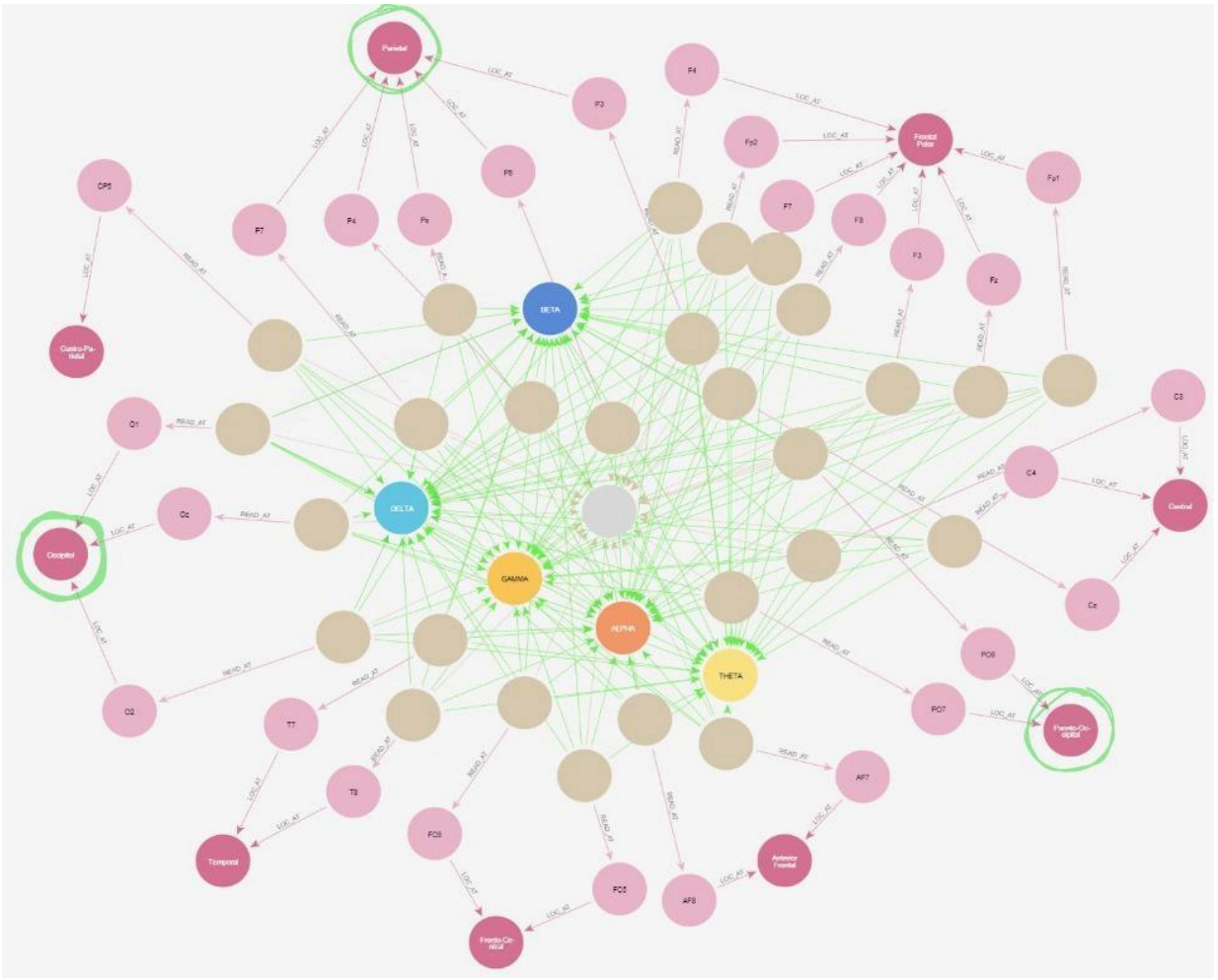


Figure 8: MBP-Lemon (Healthy) representative sample BRAINGNNet Graph Visualization with ABP edges rendered based on the value

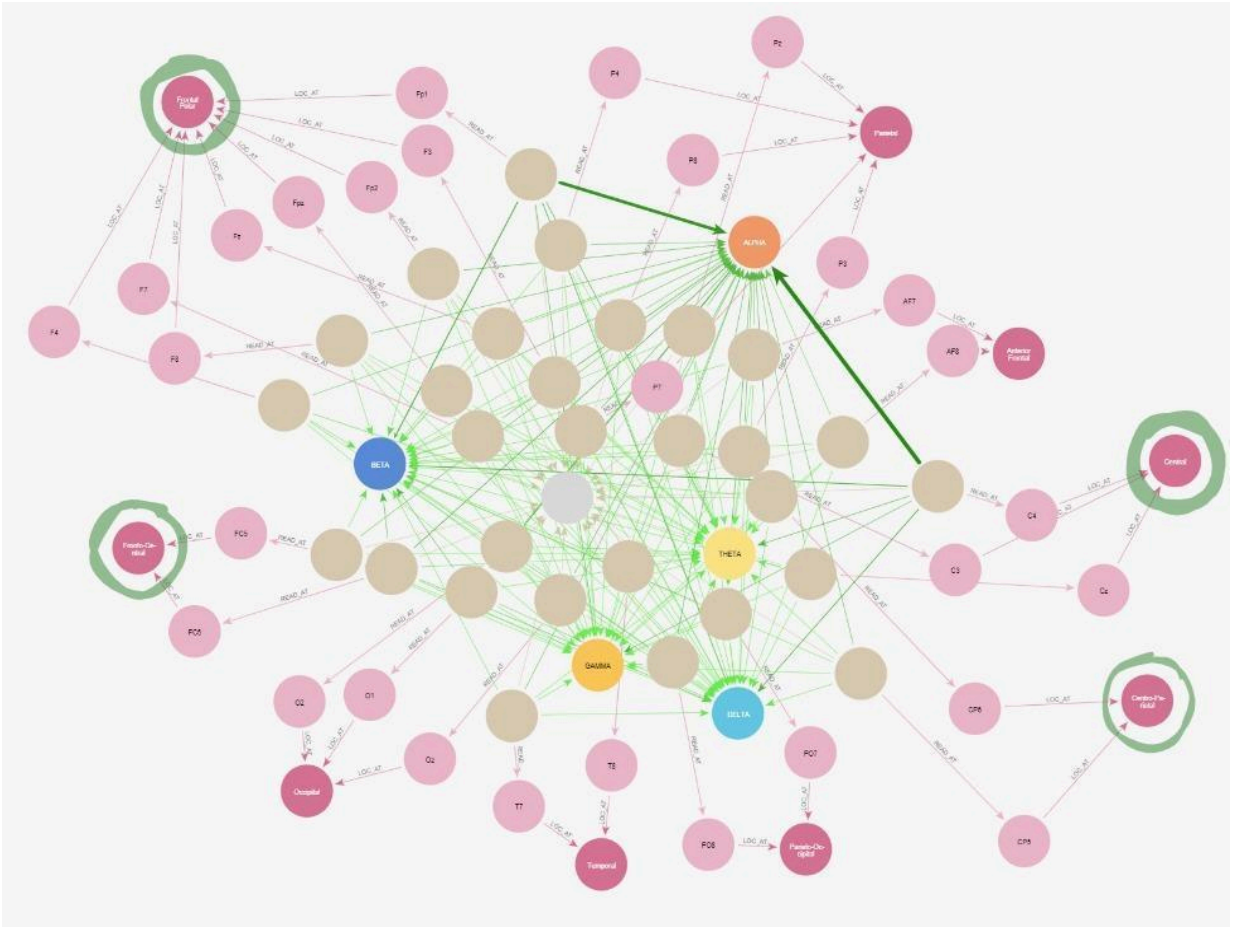


Figure 9: cpCGX-BIDS representative sample BRAINGNNet Graph Visualization with ABP edges rendered based on the value

Main Findings

We observed higher standard deviations than the mean for the chronic pain subjects, indicating high variation between values and abnormal data distribution; this could be attributed to potential variations of clinical characteristics and sources for chronic pain for the participants in cpCGX-BIDS study data, which is not available at present.

Consequently, we have primarily relied on the median to create effective distinguishing thresholds for computed ABP intensities where we observe higher deviations. Yet, we also observe a correlation between chronic pain and ABP based on the region where the peak means and deviations occur consistently across the bands, most prominently for Alpha, Theta, and Gamma Bands in (CP Regions), in contrast to healthy subjects in MBB-Lemon with relatively higher deviations and mean peaks for Delta and Beta bands in (LM Regions) [Figures 6, 8, 9].

Significance	CP Region	LM Region
1	`Centro-Parietal`	`Parieto-Occipital`
2	`Central`	`Occipital`
3	`Frontal Polar`	`Parietal`

ABP, a potential EEG biomarker, does not appear to be significantly different for chronic pain patients in every study, irrespective of its specific placement in the topology graph and as an aggregation over all topologies or lobes. However, with particular topology alignment, patterns that would discriminate chronic pain from healthy subject graphs emerge favoring ABP:

- Increase - Significant for Gamma and relatively for Theta and Alpha bands in CP regions.
- Reduction - Significant for Delta and relatively for Beta in LM Regions

Following spatial (topologic) aspects of power activations (Figure 7) to hemispheric electrode alignment, ABP asymmetries emerge as potential differentiators for chronic pain patient graphs. Specifically, asymmetries favor the right hemisphere across the bands, most prominently for Theta, closely followed by Gamma for `Centro-Parietal` and `Central` CP Regions, which does not exist for healthy subject graphs.

Discussion: Alignment, Limitations, and Challenges

Our preliminary results are generally in line with findings reported in the survey [10], most consistently with the increase in Gamma, Theta, and Alpha powers. The survey covered numerous studies indicating:

- Increased Theta power at resting state in prefrontal, medial areas, and anterior cingulate cortex potentially represent a biomarker of chronic severe neuropathic pain and migraine.
- Increased Alpha power at resting state for cancer patients and patients with neuropathic pain, yet conversely, it may reduce in painful conditions (i.e., acute pain or acute crisis in chronic pain) potentially related to excessive alertness. This finding was also supported by [5], indicating a decrease in Alpha band power for acute physical pain.

In alignment with the findings in [10], [18] provides supporting EEG characterization involving the suppression of Alpha band oscillations and enhancement of Gamma band oscillations in pathological chronic pain, which is more severe and common in clinical practice.

There is weaker alignment with findings reported by cross-sectional studies in [16], particularly concerning the Beta power increase, where central findings are:

- Higher theta and beta power in chronic pain patients, with lower or non-significant results for other bands.
- Higher than lower gamma power in patients with chronic pain: this finding is also supported by [5] in the context of acute physical pain.

To establish a more robust baseline for our analytics efforts to avoid obscure contributions of specific brain regions and networks to the neural representation of chronic pain, we limited our scope to resting-state EEG Eyes Closed (EC) reads. Yet, limitations for studies on EEG biomarkers of pain in general apply to our limited analysis as well:

1. In the absence of clinical specifics, we assume that cpCGX-BIDS potentially includes patients with different types of chronic pain (e.g., severe neurological conditions, neuropathic pain, nociplastic pain), a realistic clinical sampling, yet the source of high variations in computed ABP intensities, along with increased difficulty in identifying patterns and impacting specificity.
2. Reverse inference fallacy [3], a common obstacle for decoding brain states, requires the assessment to extend to larger EEG data sets and studies, (1) capturing pattern occurrence frequency for the individual, and (b) ensuring its absence when the individual is not experiencing pain, effectively to establish specificity and sensitivity for the inference.
3. Our exclusive reliance on publicly available EEG datasets: having no leverage in establishing and altering parameters related to the study design and neuroimaging protocols.

Next Steps

Our preliminary comparative analysis of graph-based representations for healthy versus chronic pain subjects in BRAINGNNet strongly indicates that our model can effectively support chronic pain detection with a Heterogeneous GNN-based approach for graph isomorphism identification and classification.

Considering the identified limitations and challenges and supporting the design, development, and evaluation of the POCs and Pilots for the EEG Chronic Pain Biomarker Heterogenous GNN Architecture and Inference, we have identified the following R&D streams:

⇒ *Data Collection:* Initiating institutional collaborations to leverage expertise in signal processing, medical neurology, and clinical context and access to study parameters and specifics concerning the EEG protocols, to establish baseline HGNN models.

⇒ *Real-Time Inference and Monitoring in Limited Resource Environments:* Initiating research collaborations and open-source projects for:

- Optimizing GNN models and inference for limited-resource environments
- Investigating adaptive Transfer Learning techniques for individual specific and fine-tuned HGNN models.

⇒ *Monitoring Device Prototype*: Acquisition of research-grade (16+ electrodes) developer-friendly EEG Headset with BIDS-standard support for raw recordings (e.g., Open-BCI) for developing real-time EEG processing pipelines.

The proposed R&D streams can significantly impact future research in chronic pain management and clinical practices, paving the way for advanced and affordable BCI consumer devices for clinical applications.

References

1) Babayan, A., Erbey, M., Kumral, D., Reinelt, R. D., Reiter, A. M. F., Röbbig, J., Schaare, L. H., Uhlig, M., … Gaebler, M., Villringer, A. (2019). A Mind-Brain-Body dataset of MRI, EEG, cognition, emotion, and peripheral physiology in young and old adults. Scientific Data, 6, 180308.
2) Cai S, Schultz T, Li H. Brain Topology Modeling With EEG-Graphs for Auditory Spatial Attention Detection. IEEE Trans Biomed Eng. 2024 Jan;71(1):171-182. doi: 10.1109/TBME.2023.3294242. Epub 2023 Dec 22. PMID: 37432835
3) Davis, K., Flor, H., Greely, H., et al. Brain imaging tests for chronic pain: medical, legal and ethical issues and recommendations. Nat Rev Neurol 13, 624–638 (2017). https://doi.org/10.1038/nrneurol.2017.122
4) Dudzik, A., & Veličković, P. (2022). Graph Neural Networks are Dynamic Programmers. *ArXiv*. /abs/2203.15544
5) Elsayed, Mahmoud & Sim, kok swee & Tan, Shing. (2020). A Novel Approach to Objectively Quantify the Subjective Perception of Pain Through Electroencephalogram Signal Analysis. IEEE Access. 8. 199920-199930. 10.1109/ACCESS.2020.3032153
6) Gil Ávila, C., Bott, F.S., Tiemann, L. et al. DISCOVER-EEG: an open, fully automated EEG pipeline for biomarker discovery in clinical neuroscience. Sci Data 10, 613 (2023). https://doi.org/10.1038/s41597-023-02525-0
7) Kenefati, G., Rockholt, M., Ok, D., McCartin, M., Zhang, Q., Sun, G., Maslinski, J., Wang, A., Chen, B., Voigt, E., Chen, Z., Wang, J., & Doan, L. (2023). Changes in alpha, theta, and gamma oscillations in distinct cortical areas are associated with altered acute pain responses in chronic low back pain patients. Frontiers in Neuroscience
8) Miana, L., Bastos, V. H., Machado, S., Arias-Carrión, Ó., Nardi, A. E., Almeida, L. C., Ribeiro, P., Machado, D., King, H. H., & Silva, J. G. (2013). Changes in alpha band activity associated with the application of the compression of fourth ventricular (CV-4) osteopathic procedure: A qEEG pilot study. Journal of Bodywork and Movement Therapies. https://doi.org/10.1016/j.jbmt.2012.10.002
9) Ong, E., & Veličković, P. (2022). Learnable Commutative Monoids for Graph Neural Networks. *ArXiv*. /abs/2212.08541
10) Pinheiro, S., Montoya, P., Santos, C. L., Ito, C. H., Silva, M., Nunes Santos, D. B., Benevides, S., Vivas Miranda, J. G., Sá, K. N., & Baptista, A. F. (2016). Electroencephalographic Patterns in Chronic Pain: A Systematic Review of the Literature. *PLOS ONE*, *11*(2), e0149085. https://doi.org/10.1371/journal.pone.0149085
11) Rahman, S.; Kidwai, A.; Rakhamimova, E.; Elias, M.; Caldwell, W.; Bergese, S.D. Clinical Diagnosis and Treatment of Chronic Pain. Diagnostics 2023, 13, 3689. https://doi.org/10.3390/diagnostics13243689
12) Rockholt MM, Kenefati G, Doan LV, Chen ZS, Wang J. In search of a composite biomarker for chronic pain through EEG and machine learning: where do we currently stand? Front Neurosci. 2023 Jun 14;17:1186418. doi: 10.3389/fnins.2023.1186418. PMID: 37389362; PMCID: PMC10301750.
13) Wang X, Ji H, Shi C, Wang B, Ye Y, Cui P, Yu PS (2019) Heterogeneous graph attention network. In: The world wide web conference, pp 2022–2032
14) Xu, K., Hu, W., Leskovec, J., & Jegelka, S. (2018). How Powerful are Graph Neural Networks? ArXiv. /abs/1810.00826
15) Zebhauser, P. T., Gil Ávila, C., & Ploner, M. (2023). cpBIDS: Chronic Pain Data EEG Dataset. https://doi.org/10.17605/OSF.IO/M45J2
16) Zebhauser, P. T.; Hohn, Vanessa D.; Ploner, Markus*. Resting-state electroencephalography and magnetoencephalography as biomarkers of chronic pain: a systematic review. PAIN 164(6):p 1200-1221, June 2023. | DOI: 10.1097/j.pain.0000000000002825

17) Zeng, X., Lei, FY., Wang, CD. et al. Multi-view Heterogeneous Graph Neural Networks for Node Classification. Data Sci. Eng. (2024). https://doi.org/10.1007/s41019-024-00253-y
18) Zhou, R., Wang, J., Qi, W., Liu, F., Yi, M., Guo, H., & Wan, Y. (2018). Elevated Resting State Gamma Oscillatory Activities in Electroencephalogram of Patients With Post-herpetic Neuralgia. *Frontiers in Neuroscience*, *12*, 378140. https://doi.org/10.3389/fnins.2018.00750
19) Wikipedia 10-20 System EEG https://en.wikipedia.org/wiki/10%E2%80%9320_system_%28EEG%29#/media/File:EEG_10-10_system_with_additional_information.svg