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Abstract Note

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# **BI'23 Abstracts**

**(Full Papers Presented in Main Conference)**

# *Cognitive and Computational Foundations of Brain Science*

- B223** Distractor-Specific Single Neuron Activity Predicts Visual Working Memory Task Outcomes
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# **Distractor-Specific Single Neuron Activity Predicts Visual Working Memory Task Outcomes**

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## **Abstract:**

This paper explores the relationship between neural activity and behavioral performance in the form of visual working memory (VWM) task outcomes, by answering the question: Are there any significant differences in the firing rates of individual neurons during the distractor presentation period of a VWM task between success and error trials that can predict the outcome of a trial? Distractor-specific single neuron firing rates during a VWM task were analyzed to answer this question. A logistic regression was used to identify the predictive capability of neural firing rate on trial outcome with the neural activity of 51 cells from the lateral prefrontal cortex of a primate. This study found that a best-fit logistic model could predict the behavioral performance of the primate (success or error of the VWM task) with 63.01% accuracy. The logistic model was compared with decision tree, random forest, and neural network models, which produced accuracy scores of 68.04%, 69.45% and 70.26%, respectively. Moreover, greater firing rates in response to the distractor, indicating less efficient distractor suppression, accompanied the error trials of the VWM task. This suggests that stronger neural responses to task-specific distractors can hinder the attentional filtering required for efficient working memory, supporting previous research that found that distractor suppression is a mechanism that heavily influences WM efficiency. These findings indicate that people, particularly children, with disorders that affect WM capacity such as ADHD may experience stronger neural responses to distractors, and therefore inefficient distractor suppression, at the single neuron level when engaging in goal-oriented behaviors, which can significantly impact learning and other developmental processes.

## **Keywords:**

Visual Working Memory, Distractor Suppression, Single Neuron Firing Rates, Lateral Prefrontal Cortex, ADHD



## Systematic Fusion of Cognitive Networks and Its Application

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### Abstract:

With the advancement of research in the field of cognitive science, the diversity of human brain atlases from different sources, especially the differences in the definition of the same cognitive network, has brought difficulties to the selection of human brain atlas. This article proposed a systematic fusion method for multi-sourcing cognitive networks based on the diversity of the human brain atlases. Through combining the typical cognitive task with negative correlated network (default mode network) and the cognitive task with positive correlated network (fronto-parietal network), experiments were conducted to verify the effectiveness of the method, and the results findings were discussed. By integrating the instances of the cognitive network and comparing the topological properties of each instance on the combined cognitive network, this method was first utilized to distinguish the cognitive task states, selecting the instance with the optimal performance as the main cognitive network, and other instances as the supplementary cognitive networks. Next, the main cognitive network was set as the initial candidate fused cognitive network while the ROIs of all supplementary cognitive networks were sorted according to their nodal topological attributes. The ROI with the highest priority was then iteratively imported into the candidate fused cognitive network. During the iteration process, the performance of the current candidate fused cognitive network was continuously calculated. Finally, the candidate fused cognitive network with the optimal performance throughout the iteration process was selected as the final fused cognitive network, which has the most significant performance in distinguishing different cognitive states according to its topological properties. The experiment results indicated that the fused fronto-parietal network based on this method can generate better performance in distinguishing cognitive states compared to those typical machine learning methods in fusing multi-sourcing fronto-parietal networks. The application of this method also generated the most well-balanced retention rate for the numbers of ROIs in the frontal and parietal lobes.

### Keywords:

Systematic Fusion, Brain Atlas, Cognitive Network, Fronto-parietal Network, fMRI

# Patient-specific Identification and Potential Etiology of Cognitive Impairment based on a Directed Epileptic Brain Network Model

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## Abstract:

Epilepsy is a pathophysiologically induced brain network disorder characterized by recurrent seizures as well as widespread cognitive difficulties and emotional dysfunction. Functional and structural abnormalities of brain tissue in focal epilepsy have been extensively quantified, but the degree and directionality of abnormalities are highly variable and insensitive to the differentiation of epileptic patient types, which cannot be visually explored based on SEEG. Nonlinear kinetic models with directed brain functional networks are an effective means of probing the neurobiological intrinsic mechanisms and macro-connectomics of epilepsy and hold great promise in revealing the mechanisms leading to dysfunction and identifying biomarkers, however, its effectiveness in applying real EEG data to differentiate between different patient types is unclear. The purpose of this study was to investigate whether the spatial distribution of the 3D parameters of the epileptor network model differentially affects the topological characteristics of the EEG-derived dynamic directed functional network in different epilepsy patients and to explore its potential application as a novel biomarker of neuromodulation. Specifically, we derived evolved directed functional brain networks from them based on real SEEG data from eight subjects, and also performed seizure propagation simulations using the epileptor network model to obtain the simulated resultant directed functional brain networks. Immediately after, we quantitatively analyzed important global efficiency, local centrality and clustering coefficients and other network characteristics in a time-resolved manner using graph-theoretic analysis tools, and used network optimization algorithms to make an effective fit between the characteristics of the real data and the model-simulated data. Finally, the sharing and variability of brain hubs directly or indirectly involved in seizure propagation in different patients were further evaluated. Our results suggest that patients with various types of epilepsy have overlap and variability in parameter space, which may partially support an antiepileptic effect or indicate a potential compensatory response to brain function early in the disease. In addition, subjects with no distinctive features observed on SEEG may instead be visually distinguished on the three-dimensional parameter space (excitability index  $x_0$ , connectivity strength  $w$ , dominant eigenvalue  $\lambda$ ) compared to subjects with distinctive seizure features, while seizures also lead to an immediate and persistent reorganization of the features of the directed functional brain network. The present study provides insights into the intrinsic physiological pathogenesis of epileptic networks in focal epilepsy, showing promise in localizing epileptic networks and lesions to help explain cognitive deficits and psychiatric symptoms. Unlike direct analysis of SEEG data, random network configurations in 3D parameter space also allow accurate identification of epilepsy

patient specificity and may be used as biomarkers for patient selection, neuromodulatory targets and parameters, and this identification of non-pharmacological interventions for network characterization may potentially guide diagnosis or tailor treatment approaches to specific epilepsy syndromes, providing additional valid information for clinical diagnosis of epilepsy. However, large-scale clinical studies with long-term follow-up are still needed to further validate its validity and accuracy and to improve the yield and clinical value of network studies.

**Keywords:**

Epileptor Network Model, Patient Specificity, Directed Brain Function Network

# **Tools and Theoretical Frameworks for Understanding Neural Basis of Motivation and Learning**

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## **Abstract:**

Our focus lies in unraveling the intricate neural pathways that underlie motivated behavior and comprehending the brain's learning processes at a cellular level throughout its entirety. Survival heavily relies on the drive for exploration and protection against predators, necessitating a delicate equilibrium in all animal species to attain peak adaptability, right from their early developmental stages. The significance of stimulus-induced learning cannot be understated, as it initiates intrinsic mechanisms vital for future stimulus recognition and forms the bedrock for associative learning. In our experiments, we subject head-embedded tail-free larval zebrafish to repeated exposures of visual sensory stimuli that convey unique motivational values. By utilizing brain-wide calcium imaging techniques, we capture the activity patterns of individual neurons throughout the entire brain, while simultaneously recording tail movements over an extended duration of tens of minutes. This comprehensive approach enables us to obtain detailed activity traces of neurons and corresponding tail swing data, shedding light on the neural dynamics associated with sensory processing and behavioral responses in these zebrafish larvae. Our primary objective is to unravel the intricacies of high-dimensional data and uncover fundamental principles of circuitry function derived from the temporal dynamics of individual neuronal activity, which can be linked to sensory stimuli and motor outputs. These encompass a wide range of processes, including sensory detection, sensory processing, decision-making, pre-motor planning, and motor execution. To achieve this, we devise models and methodologies that integrate information across multiple levels, bridging the gap between cellular properties and organismal behavior. Additionally, we employ machine learning algorithms to identify cells that exhibit dynamic learning of visual sensory stimuli, further enhancing our understanding of the neural mechanisms involved.

## **Keywords:**

Machine Learning, Zebrafish, Brain-wide Calcium Imaging, Motivation, Learning

# Predicting Cognitive Impairment Using Brain Connectivity and Machine Learning in Multiple Sclerosis

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## Abstract:

Brain connectivity analysis provides a promising tool with which to map the effect of multiple sclerosis (MS)-related pathology on physical and cognitive impairment. Advanced imaging techniques such as diffusion and functional MRI are commonly used to quantify structural connectivity (SC) and functional connectivity (FC) networks; however, they are expensive and time-consuming. Our recent study showed that the SC and FC networks estimated using deep learning and lesion masks extracted from conventional MRI and can predict disability as well as SC and FC networks derived from advanced MRI. However, how well the estimated connectivity networks can predict cognition is unknown. Therefore, this study aims to predict cognitive scores using 1) regional structural dysconnectivity (called ChaCo scores), estimated by identifying white matter pathways in a normative database that intersect a patient's lesion mask, 2) estimated FC (eFC) derived using a pre-trained deep learning model, and 3) both ChaCo scores and eFC together using machine learning. One hundred fifty-eight MS patients (female: %72, age:  $42.40 \pm 10.50$ ) were included in our study. Symbol Digit Modalities Test (SDMT), California Verbal Learning Test (CVLT), and Brief Visuospatial Memory Test (BVMT) were used to assess cognition. Spearman's correlation ( $r$ ) between observed and predicted cognitive scores for a hold-out set of test subjects was used to assess the models' prediction performances. The model based on ChaCo scores outperformed other models in predicting SDMT ( $r=0.39$ ,  $p<0.01$  for all comparisons) and CVLT ( $r=0.42$ ,  $p<0.01$  for all comparisons). However, the eFC outperformed other models in predicting BVMT ( $r=0.38$ ,  $p<0.01$  for all comparisons). Structural disconnectivity in subcortical regions, specifically the putamen and thalamus, was associated with poorer cognitive scores in all models. Increased eFC in visual-related regions was associated with better cognitive scores, in particular with BVMT which measures visual memory. Lower eFC in the thalamus and the frontal pole was associated with poorer cognitive scores in all models. Our modeling approach predicting cognition in MS performed similarly to the highest accuracy in previous models in the literature. Our work demonstrates that lesion masks, coupled with our approach to estimating structural dysconnectivity and FC using them, can be a viable alternative to collecting advanced MRI, bringing the connectome one step closer to the clinic.

## Keywords:

Machine Learning, Cognition, Connectivity, Multiple Sclerosis, fMRI

# Optimizing Artificial Neural Networks to Predict Brain Age from Functional MRI

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## Abstract:

Large MRI datasets combined with deep learning methods have realized a new state of the art for brain age prediction, which might serve as a valuable biomarker for brain health and disease. Most of these gains have been achieved via the use of high resolution structural (T1w) scans. Brain age prediction via deep learning over large volumes of functional MRI (fMRI) data has been less well studied, but could help form a bridge between neural health biomarkers observed in MRI and more portable platforms like fNIRS that measure a hemodynamic signal similar to fMRI. In this work, we studied how to optimize deep learning models and training architectures to predict brain age from resting state fMRI data. We searched a set of parameters that included varying the number of nodes and the composition of input functional connectivity matrices, the size, depth and objective functions of the neural network models as well as timeseries sub-sampling as an augmentation strategy. We assessed model performance on both an internal validation set of held out participants from our composite training corpus, as well as numerous external corpora not seen during training that comprised health controls and clinical participants. We find a number of hyperparameters for neural network models can support very accurate brain age prediction using fMRI. However, like for other modalities and machine learning tasks, generalizing to new corpora and scanners still poses a challenge. Finally, we do not find as clear of a brain age gap (overestimation of age for clinical participants relative to healthy controls) for held out data as previous studies. This work constitutes a valuable step towards scalable, portable brain age prediction but highlights number of areas where additional work and improvement is needed.

## Keywords:

Deep Learning, Functional Connectivity, Brain Age, Brain Age Gap, Biomarkers

# Analyzing Network-Level Rhythmic Dynamics with Latent Dynamical Coherence Models

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## Abstract:

Understanding how rhythmic neural activity evolves in time and space is crucial for advancing our understanding of healthy and pathological brain states. While significant progress has been made in the development of analytical tools to study rhythmic neural activity at various scales, these methods have limited applicability in analyzing transient and fast dynamics occurring across neural nodes. In this research, we propose a novel dynamical latent modeling framework to capture fast and transient rhythmic dynamics across neural nodes, which we refer to as the Latent Dynamical Coherence Model (LDCM). The LDCM characterizes the temporal dynamics in network-level coherence, which is a measure of coordinated neural activity across nodes at a specific frequency. In LDCM, we build a parametric model of the cross-spectral matrix to capture changes in functional connectivity across neural nodes using spectral measures of neural recordings. This is achieved through a switching state space model. To characterize coherence, we employ latent discrete and continuous processes to capture the covariation across neural nodes. We argue that the LDCM expands the range of synchrony analysis tools, such as the state space coherence previously developed by our team, enabling us to capture dynamics at the sampling resolution. We demonstrate an application of the LDCM framework in the analysis of anesthesia data captured using 64-channel EEG data. The inference results from the LDCM not only corroborate with empirical results derived from global coherence analysis but also provide significantly finer temporal resolution with easily interpretable outcomes. Furthermore, we demonstrate that the utilization of the switching mechanism in the LDCM framework enables us to capture the rapid changes of oscillations more effectively at the network level.

## Keywords:

Coherence, Synchrony, State-space Model

# **Gamma Band Elevated Power in Fragile X Syndrome during Auditory Chirp is due to Higher Power Gamma Burst Events**

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## **Abstract:**

**Background** Fragile X syndrome (FXS) is a neurodevelopmental disorder caused by the silencing of the FMR1 gene on the X chromosome, resulting in a shortage of the RNA binding protein FMRP. Auditory hyperarousal is a typical symptom of FXS. Previous EEG studies have observed increased gamma band power during auditory paradigms in FXS. In this study, we utilized Bayesian inference, which offers advantages in analyzing gamma band burst features, to investigate the underlying neurophysiological mechanisms. Bayesian inference was particularly suitable for our analysis due to its ability to handle heavy-tailed data and account for variances cross different groups. **Methods** Auditory chirp stimulus induced EEG segments were studied from 36 individuals with FXS (23 Males) and 39 controls (22 Males). Source localized EEG signals were lower gamma bandpass filtered using Morlet wavelet convolution (30-55 Hz with a step size of 2 Hz). Gamma band bursts, characterized by count, peak power, duration, and frequency span, were extracted from the trial-specific time-frequency representation. We hypothesize significant feature differences between FXS and typical developing controls (TDC), with separate comparisons for males and females within each group. A Bayesian hierarchical model based on the effects model with a T location-scale distribution was applied to account for heavy-tailed data and assumed heterogeneous variances cross groups (Kruschke, 2015). The Bayesian significance was determined based on the deviation of the posterior estimate from zero or exclusion of zero from the 95% highest density interval of the contrast's posterior distribution. **Results** The Bayesian hierarchical modeling revealed that FXS males exhibited greater peak power compared to typically developing males in both the left and right temporal lobes during auditory chirp stimuli. Furthermore, FXS males showed a greater degree of dispersion in peak power compared to typically developing males in the left temporal region, known for temporal variation specialization in auditory nonspeech stimuli processing (Jamison et al., 2006). Interestingly, within the FXS group, males displayed more variability in peak power values compared to females in the right temporal region, which is related to spectral variation specialization. **Conclusions** Our results suggest that the peak power of gamma transient activities likely underlies the increased background gamma band spectral power observed during auditory processing in FXS, with individualized differences. However, the other tested features of gamma band bursts of isolated events, such as count, duration, or frequency span, did not show differences.



**Keywords:**

Gamma Band Transient Burst Mechanism, Auditory Sensory Processing, Electroencephalography, Neurodevelopmental Disorders

# ***Investigations of Human Information Processing Systems***

- B246**    The Role of Mind-Wandering in Food Satiation: A Cognitive Neuroscience Perspective
- B276**    Dual Process Model of Depression: ROC Analysis of Two Systems

# **The Role of Mind-Wandering in Food Satiation: A Cognitive Neuroscience Perspective**

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## **Abstract:**

In our previous electroencephalography (EEG) study, we explored the neural correlates of the experience of boredom using auditory stimuli. We measured the changes in EEG oscillatory activity while participants listen to a short repetitive melody and change it as they feel bored of listening to it by key pressing. The results showed that there was a significant increase in the frontal theta amplitude right before the key press response, indicating the involvement of the frontal theta activity in the occurrence of boredom. Our findings also suggested that boredom is associated with cognitive processes involved in shifting attention from demands in the environment and towards task-unrelated thoughts (i.e., mind-wandering), as previous studies have linked the frontal theta activity with internally oriented attention and mind-wandering. Although this theta increase was considered to emerge as participants are in the state of boredom (with or without conscious awareness), the relationship between theta activity and subjective experience in the state of boredom remained unclear. Therefore, in this study, we aimed to investigate the relationship between the frontal theta activity and the subjective experiences of boredom, using gustatory stimuli. We measured the changes in EEG oscillatory activity and the intensity of boredom on visual analogue scales (VAS 1-10) while participants intake the same sampling food repetitively. We hypothesized that the subjective awareness to be bored is positively correlated with theta amplitude in the frontal area. The results showed that there was a significant positive correlation between the frontal theta amplitude and the boredom intensity. Our findings confirm the involvement of the frontal theta activity in the experience of boredom, and furthermore, suggest the relationship to be modality nonspecific.

## **Keywords:**

EEG, Theta, Boredom, Mind-wandering, Food Satiation

## Dual Process Model of Depression: ROC Analysis of Two Systems

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### Abstract:

**Background:** Approach and avoidance are the two most basic forms of motivation, reflecting the way individuals interact with their environment, and are the core functions for humans to tend to avoid harm and adapt to their environment. Recognition memory, as an instinctive response to biologically recognized stimulus types, has a crucial role in biological adaptation to the environment. Inductive reasoning is an ability that is closely related to survival adaptations. Yonelinas proposed a dual-process model of recognition memory, which divides recognition memory into two processes: familiarity and recollection, with familiarity being an automated processing that allows for rapid responses to stimuli; recollection is a controlled processing that responds relatively slowly but allows for more fine-grained discrimination of stimuli. **Experimental design:** We designed a system of novel and different symbols for which individuals had no prior knowledge to prevent the effect of different individual experiences on the experiment. We drew on Sloutsky's (2004) inference-recognition paradigm to design two experiments. The learning process of inductive reasoning was used to assign positive or negative valence to the special symbols, triggering individual motivation for approach and avoidance (three special symbols representing positive or negative emotional words). The response characteristics of individuals in the approach and avoidance paradigm triggered by inductive reasoning were examined through a recognition task. We measured their immediate responses based on their experimental paradigm by increasing the difficulty of the task (shorter learning time and more difficult learning content) and by reasoning or recognition immediately after learning. In Experiment 1, we first asked subjects to learn three new and different symbols and the meanings they represented through inductive reasoning, and then asked them to complete a recognition task of the old and new symbols. In Experiment 2, we made inferential judgments about the recognition symbols before the recognition task (whether the recognition symbols also represented the meanings of the emotional words in the learned message). **RESULTS:** In Experiment 1, familiarity in the avoidance mode was significantly greater than in the approach mode, and recollection was significantly smaller than in the approach mode. In Experiment 2, the amount of recollection in the avoidance mode was zero, i.e., a rapid response based solely on familiarity. The ROC curves in the two modes were separated, with the approach mode ROC curve on the upper left of the avoidance mode ROC curve. The intercept of the ROC curve in the avoidance mode was 0, and the intercept of the ROC curve in the approach mode was the amount of recollection. **DISCUSSION:** The results of Experiment 1 suggest that the two systems in which individuals recognize stimuli in both approach and avoidance modes will have.

**Keywords:**

ROC Curves, Perceptual Recognition, Induction Reasoning, Dual Process Model, Approach-avoidance Motivation

# ***Brain Big Data Analytics, Curation and Management***

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- B288** Block Dense Weighted Networks with Augmented Degree Correction
- B289** Comparative Evaluations of Computational Neurometric and Deep-learning Methods to Estimate the Number of Intrinsic Dimensionality of High-Density EEG for Optimal Independent Component Analysis
- B297** Workshop: Time Domain Analysis of Neural Oscillations

# Application of Unsupervised Machine Learning Methodologies for the Detection of Electrophysiological Factors Predisposing to Heavy Alcohol Consumption in Teenagers

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## Abstract.

Binge Drinking (BD) has emerged as a widespread pattern of consumption among teenagers. It is characterized by the intake of large amounts of alcohol (more than 4 drinks per session) within short periods of time (2 hours), with a period of abstinence between episodes. This type of consumption entails several social and sanitary risks, altering the integrity and development of the nervous system, particularly vulnerable during adolescence. By the time, there is a scarcity of works with the advantages from the newcoming Machine Learning (ML) that study possible predisposing factors to BD consumption. In this longitudinal study, we recruited 99 students from different high schools of the Community of Madrid, Spain, aged around 14 years ( $\pm 0.9$  years). We recorded resting-state electrophysiological activity by means of Magnetoencephalography (MEG). Two years later, they fulfilled the AUDIT test to measure their alcohol consumption habits. According to this information, we subdivided the sample into control and BD groups. We conducted a source-space spectral power analysis for 78 cortical regions (based on AAL atlas), in four frequency bands: theta (4-8 Hz), alpha (8-12 Hz), beta (12-20 Hz), and gamma (30-45 Hz). Next, we analyze and clusterize the normalized power data using Unsupervised ML techniques, ascertaining the most efficient number of groups our data was divided into, we performed a preliminary K-nearest neighbors (KNN) model (K between 1-10). The similarity between ROIs' power was used to create hierarchical clusterisation, in the form of dendrograms, using Ward's method with Euclidean distance between points. The obtained results showed a different clusterisation in alpha and theta bands between groups. In alpha band, we found a clusterisation encompassing regions from the default mode network (DMN) in the BD group, while in the control group only a portion of the occipital lobe was clusterize. Regarding the theta band, we found the inverse pattern of clusterisation, with control groups clustering regions from the DMN in theta band, while the BD group only clustering in an occipital region. The results found in beta and gamma bands showed similar pattern between control and BD participants (focused on the frontal lobe in beta band; and on parieto-occipital areas in gamma band). The results shown demonstrate the capabilities of ML techniques, especially unsupervised learning algorithms. The distinctive patterns found between control and BD groups, especially in Alpha and Theta bands, might be used to understand brain organizations associated with BD predisposition, probably derived from different neuromaturation patterns. The qualities of MEG, with its significant temporal resolution, coupled with the capacities



and sensibility of ML techniques, have been shown as excellent tools to analyze neurofunctional data. In this case, focusing on Alpha and Theta bands, we found an inverse pattern of power between control and BD groups. This pattern, which is very similar to a DMN-like distribution, links with a decrease in theta and alpha bands' power in BD and control groups. In this vein, some studies have reported a progressive increment of the oscillatory frequency after puberty onset.

**Keywords:**

Binge Drinking, Machine Learning, MEG, MRI

# Estimating the Number of Active Sources in MEG based on an F-Ratio Method

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## Abstract:

Magnetoencephalography (MEG) is a powerful technique for studying brain function; however, accurately estimating the number of sources that contribute to the MEG recordings remains a challenging problem due to the low signal-to-noise ratio (SNR) of MEG signals, the presence of correlated sources, head modeling errors, and variations in individual anatomy. In this study, we introduce a precise method for accurately estimating the number of active sources in the brain based on the F-ratio statistical approach, which allows for a comparison between a full model with a higher number of sources and a reduced model with fewer sources. Using this approach, we developed a formal statistical procedure that sequentially increases the number of sources in the multiple dipole localization problem until all sources are found. We found that the selection of thresholds plays a critical role in determining the method's overall performance, and appropriate thresholds needed to be adjusted for the number of sources and SNR levels, while they remained largely invariant to different inter-source correlations, modeling inaccuracies, and different cortical anatomies. We identified these optimal thresholds and validated our proposed F-ratio-based method in simulated, real phantom, and human MEG data. Our method outperformed state-of-the-art statistical approaches, such as the Akaike Information Criterion (AIC) and Minimum Description Length (MDL), particularly in the presence of large number of active sources, highly correlated sources and low SNR. Overall, when tuned for optimal selection of thresholds, our method offers researchers a precise tool to estimate the true number of active brain sources and accurately model brain function.

## Keywords:

F-Ratio, Source Localization, Alternating Projection (AP), Source Enumeration, MEG

# A Multi-Loop Generative Adversarial Model on Brain Network Learning to Classify Alzheimer's Disease

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## **Abstract:**

Recent advancements in AI, big data analytics, and magnetic resonance imaging (MRI) have revolutionized the study of brain diseases such as Alzheimer's Disease (AD). However, most AI models used for neuroimaging classification tasks have limitations in their learning strategies, which is batch training without the incremental learning capability. To address such limitations, the systematic Brain Informatics methodology is reconsidered to realize evidence combination and fusion computing with multi-modal neuroimaging data through continuous learning. Specifically, we introduce a loop-based generative adversarial model for brain network learning, encompassing multiple techniques such as conditional generation to provide support for the generation of matrices with specified attributes in the subsequent multiple-loop-learning algorithm, patch-based discrimination to learn the implicit distribution of brain networks using block features, and Wasserstein gradient penalty to address the problems of the mode collapse and training instability. Moreover, a multiple-loop-learning algorithm is developed to combine evidence with better sample contribution ranking during training processes. The effectiveness of our approach is demonstrated through a case study on the classification of individuals with AD and healthy control groups using various experimental design strategies and multi-modal brain networks obtained from diffusion and resting-state functional MRI data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. Our experimental results demonstrate an accuracy of 83.8%, indicating that the fused brain image learning can achieve a better performance than others. Although some current studies can achieve higher accuracy, it is worth noting that the evaluation strategy is based on k-fold cross-validation which is difficult to transfer into real-world scenarios. In this paper, we consider the test samples are not seen in the training phrase. Moreover, the BNLoop-GAN model with the loop learning mode can effectively learn the implicit distribution of brain networks to reduce training complexity and improve classification performance.

## **Keywords:**

BNLoop-GAN Model, Multiple-Loop-Learning, Evidence Combination-Fusion Computing (ECFC), Brain Network Analysis, Alzheimer's Disease (AD)

# Symptom-linked Multimodal Connectivity of EEG and fMRI Reveals Clinically Relevant Dimensions in Major Depression

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## Abstract:

The complexity and heterogeneity of depressive symptoms present significant challenges in understanding the underlying neurobiological mechanisms and providing precise treatment recommendations for patients with depression. To address these challenges, we utilized multimodal neuroimaging techniques to gain insight into the complexity of depressive symptoms and establish representative bases for individual subjects. Our approach involved the application of a coupled matrix and tensor factorization model, which enabled us to jointly decompose multi-conditional electroencephalography (EEG) functional connectivity, functional magnetic resonance imaging (fMRI) functional connectivity, and clinical assessments of the 17-item Hamilton Depression Rating Scale (HAMD) into distinct latent dimensions. Through this integrated analysis, we were able to identify distinct latent dimensions that captured the interplay between different modalities and provided a comprehensive representation of each individual's depressive symptomatology. We conducted rigorous statistical analyses to investigate the relationships between the latent dimensions and various phenotypic measures. Remarkably, our results indicated that among all the symptoms assessed by the HAMD, suicidal ideation exhibited the strongest correlation with the identified latent dimensions. This finding highlights the significance of considering suicidal tendencies as a crucial aspect of depressive disorders. Additionally, we discovered significant associations between the latent dimensions and factors such as age, total scores of self-report inventories like the quick inventory of depressive symptomatology, the mood disorder questionnaire, and the NEO-five factor inventory conscientiousness. Importantly, our analysis demonstrated the predictive power of the identified latent dimensions in terms of treatment response to the antidepressant sertraline compared to a placebo. This predictive capability holds great promise for guiding treatment decisions and tailoring interventions to individual patients, ultimately improving the precision and efficacy of mental health care. By leveraging the richness of multimodal neuroimaging data, our study sheds light on the heterogeneous nature of depressive symptoms and offers valuable insights into the underlying mechanisms. These findings have the potential to transform the field of precision mental health by enabling clinicians to make more informed treatment recommendations and provide personalized care for patients with depression. This approach represents a significant step towards addressing the complexity of depression and moving towards a future where mental health interventions are optimized for each individual's unique needs.

## Keywords:

Multimodal Neuroimaging, EEG, fMRI, Functional Connectivity, Major Depression

# Modeling Implicit Musical Representation in Brain with Deep Neural Networks

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## Abstract:

Music is a complex and universal cultural phenomenon that offers a valuable framework for studying the human brain and its response to abstract structures (Levitin, 2018; Toiviainen et al., 2014). The integration of deep neural networks (DNNs) with functional magnetic resonance imaging (fMRI) has become a powerful methodology for investigating sensory information processing across various brain regions (Gómez-Herrero et al., 2021). Music tagging using task-optimized DNNs has been shown to effectively map neural network layers to auditory brain regions in the primary auditory cortex, offering a promising tool for examining neural representations of music processing (Güçlü, 2016). However, the use of short music excerpts and the task-specific DNN modeling approach limit the scope of this methodology. A generative and probabilistic paradigm has been proposed as an alternative approach for investigating music processing in the brain (Huang et al., 2020). This approach involves the use of self-supervised DNNs to model the entire music corpus and generate new musical samples. By analyzing the neural representations of these generative models, researchers can gain insights into the underlying mechanisms of music processing in the brain. Despite its potential, the generative and probabilistic paradigm has not been extensively explored in the context of music processing. In this study, we aimed to investigate the potential of unsupervised deep neural networks, specifically the variational auto-encoder (VAE), to learn latent music representations and examine brain activity patterns in a continuous music listening task. Our hypothesis is that generative computational models with a probabilistic basis, such as VAE, are better suited for capturing the complexity of neural anatomy. Previous studies by Schaefer et al. (2017) and Gómez-Herrero et al. (2021) have shown that using probabilistic generative models allowed for a more accurate and comprehensive understanding of brain networks and music processing. To examine the correspondence between the computational model activity patterns and fMRI patterns, we utilized Representation Similarity Analysis (RSA), a method previously employed in similar studies (Kriegeskorte et al., 2008) albeit in the visual modality. In addition, owing to the differences in the way musicians and non-musicians perceive and process music (Alluri et al., 2017; Patel and Iversen, 2014), we also examine differences in musicians and non-musicians. Results from the RSA analysis indicate that the STG brain region displayed the strongest correlation with the five VAE encoder layers for both musician and non-musician group, consistent with the known auditory processing mechanisms of the brain (Jones & Callan, 2003). This is followed by HG exhibiting significant correlations with the first and fifth DNN layers, with lower but still significant

correlation values observed in the second, third, and fourth hidden layers ( $p < 0.001$ ) (Griffiths et al., 2019). In conclusion, our study suggests that the VAE architecture, specifically the DNN encoder layers, can provide a powerful computational model for explaining the brain encodings of music latent representations. Our findings support the involvement of primary auditory cortex regions such as STG, Heschl's gyrus in processing musical stimuli.

**Keywords:**

Neural Networks, Representation Similarity Analysis, Music Cognition, Music Encoding, Neuromusicology

# Studying Latent Representations of Disorder of Consciousness Using Deep Learning on EEG Recordings

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## Abstract:

**Introduction:** Patients with disorder of consciousness (DoC) present a challenge for clinical diagnosis as subjective reports are not possible due to their inability to communicate with the external world. Furthermore, inter-patients and inter-etiological variability make it hard to capture DoC general properties. Different studies have shown evidence that the brain is a large-scale complex system where collective behavior emerges from nonlinear dynamics of all neuron interactions (Shine et al., 2019). This activity self-organizes into a much lower number of states (such as the wake-sleep cycle states), suggesting that a low-dimensional manifold could explain the diverse states of consciousness. Currently, the DoC diagnosis is obtained using the coma recovery scale - revised (CRS-R) and patients are diagnosed as Unresponsive Wakefulness Syndrome (UWS) and Minimally Conscious State (subcategorized into MCS+ and MCS-). Such scales are sensitive to subjectivity of the physician and rely on the patient behavioural responses. In order to obtain more accurate and objective measures comparable across patients, electroencephalogram (EEG) protocols are used to compute markers (e.g. connectivity, complexity or spectral) which are derived from predictions of current theories of consciousness, then classic machine learning algorithms are trained to predict the patients' state from those markers. In this work, we propose a novel variational autoencoder (VAE) architecture that we called Variational Translator Encoder (VTE) to obtain a low-dimensional latent representation of the raw EEG data where the decoder learns to reconstruct the previously proposed biomarkers instead of reconstructing the input as it's normally the case in VAE models. This modification to the original variational autoencoder architecture constrains the model to prioritize emergent low-dimensional general behaviors away from the individualities of each EEG signal. Using such VTE architecture, we are able to study in one hand, the dynamics of the markers and the amount of shared information between them, and in another hand, from the topology of the latent space, we can study the synergy existent in the EEG-to-biomarkers dynamics. Ultimately from the discrepancies between the latent space and the CRS-R diagnosis as well as the aforementioned study of the latent space topologies we can hint toward miss-diagnosis. Our preliminary results show that encoding from epochs of 800 milliseconds with 64 channels at 100Hz vector we are able to obtain a 3 dimensional latent space that reconstruct almost all the markers. This latent space separates the DoC categories (UWS, MCS-, MCS+ and EMCS) based on

the CRS-R diagnosis even though this information is never given to the model. Also, the gradient obtained in the latent space shows a linearity from UWS to MCS+/EMCS and this generalizes to a separated cohort of Healthy Controls (HC) and to a separated cohort of DoC patients from other centers.

**Methods: The dataset:** We used a total of 396 EEG recordings during a Local Global task (Bekinschtein et al., 2009) between 2014 and 2022 from 340 subjects from 3 datasets, One with 342 DoC recordings from 286 patients (VS = 47%, MCS-=27%, MCS+=18%, EMCS=8%) from Paris-DoC (Hôpital Pitié-Salpêtrière, Paris, France), another with 36 recordings from 36 healthy controls from Paris-HC (Hôpital Pitié-Salpêtrière, Paris, France) and a last one with 18 recordings from 18 DoC patients (VS = 17%, MCS-=5%, MCS+=78%) from Burgau-DoC (Therapiezentrum Burgau, Burgau, Germany). EEG recordings were taken at different stages (acute and chronic). Patients in the database suffered from different etiologies (traumatic brain injury, anoxia, stroke and subarachnoid hemorrhage). For each recording of DoC patients, one or multiple clinical assessments were performed by trained clinicians using the CRS-R Scale during the weeks following the recordings and the best assessment was used to diagnose the patient as UWS, MCS-, MCS+ or EMC.

All EEG recordings were taken from 2014 to 2022.

**The preprocessing and marker calculations:** The EEG data was preprocessed in python using the NICE tools (Engemann & Raimondo et al., 2018) in an automatic fashion without ICA nor other manual cleaning steps. The automatic preprocessing pipeline is as following. First, a high-low IIR Butterworth filter between 0.5Hz and 45Hz is applied, next, notch filters at 50Hz and 100Hz are applied to remove remaining noise from electrical sources, next the recordings are cut in epochs from 200ms before the onset of the first sound to 600ms after the onset of the first sound (obtaining epochs of 800ms), finally, automatic channel and epoch rejection is applied in a four-steps elimination mechanism: 1. channels where more than 50% of the epochs have a maximum peak-to-peak amplitude greater than  $100e-6$  are dropped; 2. an iterative z-score outlier detection is used to drop all channels with an overall variance greater than four standard deviation of all other channel variances; 3. epochs where more than 10% of the channels have a maximum peak-to-peak amplitude greater than  $100e-6$  are dropped; 4. once again, an iterative z-score outlier detection is used to drop all channels with an overall variance in the higher frequency bands (above 25Hz) greater than four standard deviation of all other channel variances in the same frequency bands. Finally, dropped channels are interpolated to maintain the data shape. We used a total of 22 markers from three families (spectral, information theory and connectivity), these markers are: normalized Power Spectral Density (PSD) in delta, theta, alpha, beta and gamma bands, spectral entropy, spectral edge 90 and spectral edge 95, Permutation entropy, Kolmogorov Complexity and weighted symbolic mutual information wSMI). For each marker the mean and standard deviation across all the timepoints of each epoch is calculated to obtain a summarization of each marker for each epoch. Both, preprocessed epochs and calculated markers are then normalized. The markers are z-scored per marker across all subjects, this maintains the relative differences between subjects while normalizing the scales of different markers to avoid biases toward some markers just because of their amplitude or range. EEG epochs are z-cored per recording and per channel, this allows to keep the temporal relative differences while removing the possible inter subjects and inter channel scale



and range differences. Finally, the EEG channels were recombined using a weighed neighbored average algorithm to create a virtual biosemi 64 montage, this channel recombination allowed us to reduce the model input size, to obtain more robust signal and to potentially generalize to other EEG systems. The model: The model proposed in this project is a variation of a VAE that we called Variation Translator Encoder (VTE), the VTE learns to reconstruct the markers from the latent representation of the EEG epochs. The model is composed of an encoder from epochs to a latent space and a decoder from the latent space to the corresponding markers. Results: We analysed two aspects of the proposed model. In one hand, we studied the capacity of the model to reconstruct the markers from raw EEG data using linear and non-linear decoders, while in another hand, we studied the topology properties of the obtained latent space and the generalization capacities of the encoder. The obtained Pearson correlations using the linear decoder between the real and the reconstructed markers range between 0.3 and 0.94 across markers. This results where not improved using the non-linear decoder, indicating the markers mutual information can be explained as a simple linear combination of a 3 dimensional space. The obtained latent space shows a gradient between the different conscious states where a UWS-to-MCS gradient is observed in one direction while a MCS-to-EMCS gradient is observed in an orthogonal direction. Also, in order to test the model generalization to other datasets, we encoded the Paris-HC and the Burgau-DoC datasets with the already trained encoder. We observe that the Paris-HC subjects are coherently positioned near the EMCS with a clear linear direction from UWS to HC with the MCS-/MCS+ patients placed in a more central cluster. The Burgau-DoC dataset is placed in the same space as the Paris-DoC dataset and matching the same space distribution per categories as the Paris-DoC patients. In order to quantify the latent space properties, we use a Random Forest classifier implemented with Scikit-Learn. We trained multiple OneVsRest classifiers in the Paris-DoC dataset and tested the obtained trained classifier in the Paris-HC and Burgau-DoC datasets. The XX% of the HC were classified as EMCS, which shows a coherent classification as they are conceptually the closest to a healthy conscious state. When testing the classifier in the Bugau dataset, we obtain an accuracy of 66%, showing the classifier trained in the obtained latent space is able to generalize to data from different centers and conscious states.

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## Keywords:

Disorder of Consciousness, Variational Autoencoder, Biomarkers, EEG, Manyfold

## **Artificial Intelligence: Assessment of Preclinical Developmental Neurotoxicity**

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### **Abstract:**

For new drugs where in utero, childhood or adolescent exposure occurs, the preclinical assessment of the impact in the developing brain is required by regulatory authorities, such as U.S. Food and Drug Administration. Current methodology to fulfill regulatory requirements for the assessment of developmental neurotoxicity in GLP (Good Laboratory Practice)-toxicology studies relies on a limited number of manuals, linear morphometric measurements to provide quantitative analyses of toxic effects to the cortex, caudate putamen, corpus callosum, hippocampus and cerebellum. However, such manual measurements are intrinsically associated with procedural variability and bias. We are proposing an alternative method, which utilizes image analysis-based brain region segmentation generated by a suite of supervised convolutional neural networks. Our goal was to evaluate a variety of dependent variables derived from region segmentation and analyze them for their predictive value (relative to the manual measurements) and statistical power. Digitally scanned PND 21/22 and PND 71/73 rat brain samples were imported into a GLP-validated artificial intelligence (AI)-assisted image analysis platform (Visiopharm®) at Charles River Laboratories-Durham. The rat brains were sectioned according to Garman (2016) and levels 3, 4, and 7 were assessed. We developed series of qualified Analysis Protocol Packages (APPs) that automatically generated highly reproducible and precise quantitative measurements (area, minor axis, major axis, larger diameter, lesser diameter) for the regions of interest. Data generated correlated highly with the traditional manual measurements, while producing much less variability. Further, we demonstrate the ability of a trained neural network to automatically segment brain regions in an unbiased, efficient and accurate way that can generate data sets suitable to fulfill the regulatory requirements in the assessment of neurotoxicological developmental endpoints. These data sets can be used in product development for the pharmaceutical, industrial and agrochemical industries.

### **Keywords:**

Neurotoxicity, Image Analysis, Development, Deep Learning, Whole Slide Image

# Extracting Event-Event Relation of Brain Connectivity

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## Abstract:

It is a major challenge to understanding the complex brain connectivity in neuroscience. With the development of modern tools and analytical techniques, more and more studies have focused on the brain connectivity, especially published vast and ever-expanding literature. However, it becomes difficult for a neuroscientist to engage with the breadth and depth of brain connectivity field within neuroscience. In addition, event relation extraction is an important and challenging task in natural language processing. At present, there are few researches on the extraction of brain connectivity event relation, and the published articles only focused on identify connectivity relations among brain regions in general and relations, which lacks of considering data provenance and analysis provenance, and label corpus are also insufficient. Those are not small challenge. To helping neuroscience researchers to gain quick access to research findings from fragmented information published articles about brain connectivity. This article proposes a joint extraction model of event relation for brain connectivity based on constraint learning, which considered for data and analysis provenance in the entire brain connectivity research. Firstly, a brain connectivity corpus is constructed based on brain information provenance effectively solve the problem of fragmentation information in text mining. Secondly, after encoding event pairs from context and domain knowledge, a group of constraints, including common sense constraints and domain constraints, are constructed and integrated into model learning to accelerate the convergence of the model on the small sample corpus. Finally, 100 literature abstracts on brain connectivity research on PubMed were used for validation. The experimental results show that compared with existing methods, this model can better achieve joint extraction of multi event relationships in the brain connectivity domain in low resource environments.

## Keywords:

Brain Connectivity, Event-Event Relation, Consistency Constraints Learning, Few-Shot Learning

# Multifaceted Brain Imaging Data Integration via Analysis of Subspaces

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## Abstract:

Various types of imaging, behavioral, and genetic data are often collected in contemporary neuroscience studies. However, such multifaceted or multi-block data are typically analyzed in a pairwise fashion, which hinders our understanding of the comprehensive relationships among such disparate data. By contrast, a joint analysis of all blocks yields insights into brain functioning and enables more interpretable statistical modeling of the anatomical structure therein. For instance, in the Human Connectome Project (HCP), brain structural connectivity (SC) and functional connectivity (FC) are collected and estimated through diffusion and structural MRI. Additionally information pertaining to subjects' cognitive performance, substance use habits, genetic composition, and demographic background are supplied. In this work, we study the interrelation among these data types within the HCP by decomposing data signal into fully joint, partially joint, and fully individual subspaces. Such a comprehensive joint analysis, with its accompanying variational decomposition and loadings-based biological interpretations, is previously unseen in neuroimaging literature. Here we leverage Data Integration via Analysis of Subspace (DIVAS) as a novel method for exploring disparate data. In essence, DIVAS uses iterative singular value decomposition (SVD) and carefully derived angle perturbation bounds, to distinguish noise from signal and further differentiate shared from individual signal. Accordingly, each data block included in the analysis is represented as a summation of low-rank matrices comprised of loadings (that is modes of variation) and scores (how said modes of variation are expressed across each subject) inherent to each signal subspace. Specifically, we apply DIVAS to find fully joint, partially joint, and fully individual subspaces among five HCP data blocks – FC, SC, cognitive measures, substance use measures, and genetic SNPs. We first obtain a variational decomposition of each data block. That is to say, we are able to ascribe a particular amount of variability in a given data block to each of its shared and individual spaces. Taking the SC data block as one example, approximately 25.8% of the variability in structural connectivity can be attributed to its partially joint space with functional connectivity. Put another way, over one fourth of the variability in SC can be “explained” by variability in FC. Functional Connectivity is likewise decomposed to find that roughly 19.3% and 5.0% of the variability in FC can be attributed to partially shared spaces with structural connectivity and substance use respectively. Additionally, such a variational decomposition lends credence to the precision of the DIVAS signal extraction. For instance, a mere 7.7% of the variability in FC is left attributed to noise as opposed to signal. Not only has DIVAS partitioned the data in an intuitive way, but it has done so

remarkably efficiently. Aside from explaining a percentage of variability intrinsic to a given data block, the partitioned subspaces (particularly joint and partially joint subspaces) present valuable biological findings. For example, loadings corresponding to a partially shared subspace between SC, FC, and cognitive performance can be analyzed to show cognitive measures such as picture vocabulary and delay discounting (at various time intervals) are strongly associated with both structural and functional connectivity. Similarly, loadings contributing to a partially shared space between SC, FC, and substance-use elucidate that the frequency of heavy alcohol consumption is the most salient type of substance use measure when considering brain connectivity. Collectively, these findings hold the potential to specify measures most predictive of heightened or impoverished brain connectivity. Furthermore, the FC and SC loadings involved in each of the partially joint spaces mentioned above can be analyzed to highlight regions of the brain that are particularly salient for cognitive performance and/or substance use habits. For instance, adjacency matrices and corresponding circle plots are used to highlight strength and frequency of association, commissural, and projection tracts in each of FC and SC. In its entirety, the proposed method allows for a more holistic conception of the interplay between HCP multi-block data than has been advanced by pairwise analyses alone. A novel variational decomposition makes precise the extent to which even known associations (like that of FC and SC) persist as well as illuminates associations that had previously been little more than intuitions (such as that between FC and substance use). Moreover, in viewing data integration as an angle analysis stemming from matrix factorization problem – rather than a penalized optimization problem – DIVAS boasts unique loadings and scores interpretations of shared spaces. This allows us to articulate valuable biological interactions between distinct data modalities while visualizing said data in its ambient space. Collectively, this work enriches our understanding of the human brain via application of a novel methodology.

**Keywords:**

Data Integration, Multi-block, Human Connectome Project, Angle Analysis

# A Hierarchical Latent State-space Model for Modeling Brain Activities from Electroencephalogram Data

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## Abstract:

**Background:** Mental disorders, such as Major Depressive Disorder (MDD), pose significant challenges for diagnosis and treatment due to their complex and heterogeneous nature. Unlike many physical illnesses, mental disorders often lack clear objective biomarkers, making their assessment primarily reliant on subjective measures and clinical observation. Emerging evidence suggests that electroencephalogram (EEG), a neuroimaging technique, holds promise as a potential objective biomarker for mental disorders. In recent years, there has been a growing interest in exploring the intrinsic patterns of brain activity during the absence of explicit tasks (commonly referred to as the resting state), due to its relatively low cost and convenience. Extensive literature focuses on the analysis of EEG data. These methods either neglect the correlation between different EEG electrodes or are only tailored for single-subject EEG signals, making it challenging to conduct comparative analysis in multi-group, multi-subject EEG studies. **Methods:** In this paper, we propose a novel method for analyzing large-scale multi-channel resting state EEG signals, accounting for the heterogeneity of brain connectivity patterns among clinical groups and subjects. We incorporate random effects for temporal dynamical and spatial mapping matrices and address non-stationarity by dividing signals into trials with distinct random effects so that the brain connectivity patterns can vary across trials. The model is fitted using a Bayesian hierarchical framework coupled with a Gibbs sampler. Our work effectively addresses the limitations of previous mixed-effects state space models by directly modeling high-dimensional random effects for the entire temporal dynamical and spatial mapping matrices. We introduce a novel method that effectively tackles the challenge of identifiability. The MCMC computations and model selection are also presented. Through extensive simulation studies, we demonstrate that our approach yields precise estimation and inference outcomes, and excels in correctly identifying the true model in the face of model misspecification. **Results and conclusions:** We apply our method to the EMBARC study, a large-scale clinical trial including individuals with Major Depressive Disorder (MDD) and healthy control groups. Our analysis uncovers significant differences in resting state brain temporal dynamics among MDD patients compared to healthy individuals. It is statistically significant that the autocorrelation of the latent EEG signals is stronger in the control groups compared to the MDD groups. In addition, our analysis reveals the substantial utility of the subject-level parameters derived from the MCMC method in predicting the heterogeneous treatment effect

(HTE). Furthermore, we observe that these MCMC features exhibit a superior predictive value for conditional average treatment effects (CATE) compared to EEG frequency band powers.

**Keywords:**

Bayesian Hierarchical Models, Multi-channel EEG Data, Biomarkers, Brain Connectivity, Depression

# **Neuro-molecular Imaging Biomarker Identification Pipeline for Precision Diagnosis of Brain-related Disorders: A Machine Learning Perspective**

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## **Abstract:**

Brain-related disorders such as neurological, psychiatric, and addiction are multifaceted pathologies with a conundrum nature, making them challenging to diagnose and inform therapeutic strategies effectively at a patient-specific level. It is still a global burden affecting millions of population worldwide. One promising vital aspect yet still with a large knowledge gap is the diagnosis by looking at it through the molecular window and then informing effective personalized therapeutic strategy. This approach helps tackle the problem's root cause instead of looking at it from a symptom-based approach. The etiology, particularly the underlying holistic regional neuro-molecular profiles of various brain-related disorders, mainly protein, enzyme, and receptor dysregulation, is not yet clearly delineated. Hence we need brain regional neuro-molecular biomarkers to precisely diagnose and inform effective treatment strategies on a patient-specific level. This will help identify which brain regions and their corresponding molecular system are associated with a given brain disease. This will eventually advance the holistic understanding of the disease etiology to help humanity. The neuro-biomolecular profile is vital information in disease vs. healthy classification, aging study, disease progression monitoring, and disease sub-typing, to list a few. It can guide toward effective therapeutic strategy in the context of precision medicine. Thanks to the advancement of molecular imaging, such as Positron Emission Tomography/Magnetic resonance (PET/MR) imaging, we are able to probe, visualize and quantify the underlying regional molecular profiles on an in-vivo brain non-invasively. In this study, we hypothesize that exploiting a neuro-molecular imaging pattern can yield imaging biomarkers to differentiate a healthy brain from a diseased brain or phenotype subtyping that complements the existing clinical workflows. Monitoring neurochemicals using the proposed precision diagnosis approach will be helpful in identifying the state of patients and also during therapeutics. To realize our hypothesis, we propose a neuro-molecular imaging biomarker identification pipeline for precision diagnosis of brain-related disorders by leveraging a supervised machine learning approach and PET imaging data. Machine learning algorithms are inherently multivariate data analysis tools that make them well-suited to handle multiple biological signals simultaneously. These characteristic tackles the challenge of the lack of objective imaging biomarker that considers multiple brain region interactions. Also, their capability of individual-level inference fits well in the context of precision medicine to handle subject-level analysis. Last but not least, their robustness and generalizability validation through training and testing cross-validation techniques make them well-suited to apply in a real clinical setting and in hospitals. Our pipeline



starts with identifying a molecular target of a given brain disease, followed by synthesizing a PET tracer that targets the identified neurochemical target using radio chemistry knowledge. Then the acquired PET/MR scan imaging will be used as a primary endpoint for data analysis using machine learning concepts. Finally, depending on the context, it can be applied in diagnosis/prognosis, biomarker identification, and quantification, decision support systems for medical experts, or translational science scenarios. This proof-of-concept study focuses on diagnosing or classifying healthy vs. disease brain aspects. The PET image is more than a picture; it holds a great deal of molecular information to be extracted and statistically mined. In the literature, the mainstream feature extracted from PET image intensity is the so-called standardized uptake value (SUV) that directly measures the binding of the PET tracer in various brain tissues, indirectly revealing the molecular expression density in different brain regions. We used the whole brain as a reference tissue to produce SUVR images to normalize individual variability. The machine learning block of our pipeline utilizes feature selection to identify regional neuro-molecular imaging biomarkers. We validate the differentiation capabilities of the identified markers by utilizing supervised classifiers and assessing classification evaluation metrics. In a closer look, the biomarker identification pipeline has the following modular blocks and works in the following order: 1) PET/MR scanning of subjects' brains after PET tracer injection. 2) Reconstruction of PET SUVR imaging and brain anatomical structure segmentation. 3) Quantifying SUVR in all brain regions using an anatomical atlas. 4) Feature selection to produce potential candidate regional imaging markers. 5) Validating the imaging biomarkers by building a machine learning classification model, training, testing, and cross-validation. If the classification evaluation metrics show a promising high classification score, the identified regional SUVR will be considered a potential Imaging biomarker for precision brain disorder classification or diagnosis. We can introduce an explainability block that utilizes SHAP values during the training and testing phase for the sake of model transparency and interpretability so that we can know each feature's influence on the classifier's final decision. We used leave-one-out cross-validation. We showed the application of our pipeline to investigate the neuro-epigenetic mechanisms and identify brain regions and their corresponding neuro-epigenetic imaging biomarkers in Alcohol Use Disorder (AUD) patients. Epigenetic mechanisms explain the Gene-Environment interaction. In particular, we investigated Histone Deacetylation (HDAC) enzymes in the in vivo brain. Various neurological disorders have been associated with the dysregulation of HDAC enzymes. Alterations in HDAC expression and activity have been reported in conditions such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and mood disorders. These changes may be region-specific, reflecting the neuropathological features and dysfunctions characteristic of each disorder. Alcohol use disorder (AUD) is a disorder of clinical and public health significance requiring novel and improved therapeutic solutions. The underlying molecular mechanisms remain largely unknown. In this regard, the neuro-epigenetics mechanism mainly modulated by histone deacetylases (HDAC) enzymes is becoming a promising target in filling this knowledge gap, as demonstrated in rodent models and post-mortum studies. In this proof-of-concept study, we showed the biomarker capability of non-invasive imaging of class I-HDAC enzymes in the in vivo

brain for classifying AUD patients from healthy controls using a Machine Learning approach in the context of precision medicine. Eleven participants with AUD and 16 control participants (CNT) matched for age and sex completed a simultaneous positron emission tomography – magnetic resonance (PET-MR) scan with [11C]Martinostat radiotracer. Hundred-segmented anatomical brain regions are considered. [11C]Martinostat is the first class I-HDAC epigenetic enzyme targeting PET tracer developed in our lab. We conducted two experiments i) group difference analysis and ii) machine learning feature selection and single-subject classification analysis. The result from the first experiment showed a lower HDAC enzyme in the anterior cingulate region in participants with AUD compared to matched controls (CNT). In the second experiment, by applying a model-based ‘Genetic Algorithm’ feature selection, we identified five relevant combinations of particular brain regions from hundred segmented anatomical brain regions - the left hemisphere (lh)-Cuneus, lh-Superior temporal, lh-Temporal pole, right hemisphere (rh)-Accumbens area, and rh-Posterior cingulate whose relative [11C]Martinostat standard uptake value (SUVR) features could reliably classify AUD vs. CNT. We validated those identified quantitative imaging-based biomarkers using a support vector machine (SVM) radial basis function classifier, which achieved a promising classification performance; 85% Accuracy, 80% F1- score, 0.83 AUC, 73% Sensitivity, 93.8% Specificity, 89% PPV, 83.3% NPV, 0.7 Matthew’s correlation coefficient, and 0.7 Cohen’s Kappa. These findings suggest a link between HDAC dysfunction and AUD, indicating that pharmacological agents such as HDAC inhibitors may represent a potential novel treatment for AUD. Furthermore, showing the potential of the [11C]Martinostat PET imaging biomarkers coupled with machine learning tools in the objective diagnosis of AUD that could complement the current diagnostic and statistical manual of mental disorders (DSM) based intervention to propel precision medicine forward. The proposed modular pipeline is generic (i.e., it can be applied to various molecular images and brain diseases), scalable, and flexible (i.e., any component of the modules, such as the feature selection and classifier, can be updated with a state-of-the-art technique).

**Keywords:**

Machine Learning Analysis, PET/MR Imaging, Molecular Imaging Biomarker, Neuro-Epigenetics Enzymes, Precision Diagnosis

# Neurodynamic Trait Discovery in Fragile X Syndrome: Matching Pursuit Decomposition of EEG from a Visual Discrimination Task

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## Abstract:

Background Fragile X Syndrome (FXS) is a leading inherited cause of autism and is associated with deficits in visual perception. Matching Pursuit (MP) is an iterative algorithm to greedily select a unique linear combination (book) of Gabor functions (atoms) from a redundant candidate collection (dictionary) to represent the analyzed signal. In this study, we aimed to employ the MP decomposition method to quantify electroencephalography (EEG) recorded during a visual moving grating orientations discrimination task in individuals with FXS and typically developing controls (TDC). Our primary research goal was to differentiate these groups based on MP-based EEG features, with separate comparisons for orientations within each group. Methods Twenty-seven participants, including 12 individuals with FXS and 15 TDC, contributed EEG recordings induced by visual stimuli. We selected four clusters related to visual working memory (Early Visual Cortex, EVC; Posterior Parietal Cortex, PPC; Frontal Eye Field, FEF; Lateral Prefrontal Cortex, LPFC) and analyzed data from 22 electrodes within these clusters. MP was applied to segments of EEG that represented the brain's response to the visual stimuli. Each book was divided into three categories for features development: a) the energy-dominant atom, b) the isolated spike-shape atoms, and c) EEG frequency band-specific groups of atoms. Various features, including location, duration, peak amplitude, energy ration, and count ratio, were tested at each electrode. Statistical significance at the cluster level was determined using majority voting. Results Our findings revealed the following: a) In the energy-dominant atom, individuals with FXS exhibited delayed location (135-degree stimulus in clusters EVC and LPFC) and longer duration (135-degree stimulus in EVC) compared to TDC. b) For the spike atoms, individuals with FXS showed delayed median location (135-degree stimulus in all 4 clusters; 45-degree stimulus in PPC) compared to TDC. c) Among the three EEG frequency bands of interest, theta band atoms showed that individuals with FXS had a greater count ratio (135-degree stimulus in LPFC, PPC, EVC; 45-degree stimulus in FEF, LPFC), energy ratio (135-degree stimulus in EVC, PPC, LPFC; 45-degree stimulus in LPFC), median peak amplitude (both stimuli in all 4 clusters), and median duration (135-degree stimulus in LPFC, EVC; 45-degree stimulus in LPFC) compared to TDC. Alpha band atoms did not show group-wise difference at the cluster level, while gamma band atoms exhibited greater median peak amplitude (both stimuli in FEF, EVC, PPC) and longer median duration (135-degree stimulus in all 4 clusters; 45-degree stimulus in LPFC) in individuals with FXS compared to TDC. Conclusions Our results suggest that the MP decomposition-based approach has utility in distinguishing traits between FXS and TDC on task-based EEG.

We note the group-wise differences were more frequently detected by 135-degree orientation stimulus-induced trials cross clusters and features. This finding has implication for understanding the underlying neural mechanism of FXS and potential to contribute to the development of objective diagnostic or assessment tools for FXS.

**Keywords:**

FXS Visual Perception, Visual Stimuli-induced EEG, Matching Pursuit Signal Decomposition, Neurodynamic Trait Discovery

# **Automated Processing of Neuronal Axon Initial Segment Morphology**

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## **Abstract:**

The axon initial segment (AIS) is a highly specialized compartment of neuronal cells that controls cell firing. The AIS is composed of an intricate intracellular and extracellular structure that concentrates and arranges voltage-gated ion channels and associated proteins critical for the generation of the action potential. A variety of factors can influence the probability of action potential generation at the AIS, including distance from the soma, AIS length, AIS tortuosity, and many more. These features aid in returning the cell to homeostasis. Details of AIS morphology throughout development and in nervous system pathology are lacking due to a limited ability to analyze the AISs of thousands of cells across multiple developmental points in a single project. More autonomous, unbiased methods for analyzing large datasets are required to expand our knowledge of AIS morphology throughout development and in nervous system pathology. In this project, we have developed a new Python program that can quickly and efficiently analyze immunohistochemically stained AISs in confocal images from different developmental stages and in animal models of human neurodevelopmental syndromes. It can individually label AISs, and provide readouts of morphological features and proximity measurements for each AIS. This program will prove to be a powerful tool for experimenters interested in AIS analysis by improving the efficiency and fidelity of AIS analysis, and it can easily be customized to analyze the morphological features of other subcellular compartments. This research will contribute to our understanding of the progression of AIS development and how AIS may be influenced in neurodevelopmental disorders.

## **Keywords:**

Axon Initial Segment, Morphology, AIS, Neurodevelopment, Python

# Estimation of Upper Extremity Function in Stroke via Fractional Anisotropy Derived from Diffusion Tensor Imaging based on Regression Tree

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## Abstract:

Introduction. Stroke is one of the leading causes of disability in adult populations worldwide, where the loss of upper extremity motor function is an impactful consequence of the disease. Upper extremity motor rehabilitation, ranges from physiotherapy to experimental therapies including, for example, brain computer interfaces (BCI). Clinical assessments of the motor function of stroke patients involve a range of scales and are crucial for stroke rehabilitation. The Fugl-Meyer assessment of the upper extremity (FMA-UE) is one of the most used scales to evaluate the upper extremity sensorimotor function in stroke. This scale has been used clinically and in multiple research studies to assess the degree of functional recovery following a therapy program. However, FMA-UE must be performed by trained clinical personnel and can be affected by inter-rater variability. On the other hand, it has been reported that brain structural integrity is diminished in the affected hemisphere after stroke. Thus, patients' neuroanatomy could be assessed as part of their clinical evaluation of the upper extremity. To this end, diffusion tensor imaging (DTI) has shown potential as a useful tool to evaluate white matter (WM) integrity. This assessment is commonly done in DTI data by computing fractional anisotropy (FA) values in brain tissue, which increases in presence of highly oriented fibers, like tracts, and decreases in areas of WM injuries. In many studies, the FA has been measured in the lesion site, or in anatomical regions of interest (ROIs) like the corticospinal tract (CST). Also, this metric has been reported as a FA ratio (rFA) to compare the brain structural integrity between the affected (ipsilesional) and the unaffected (contralesional) hemispheres. Moreover, associations between upper extremity sensorimotor function and neuroanatomical integrity in selected brain areas have been reported. However, it remains unclear if measuring WM integrity in certain anatomical regions is more relevant than in others to estimate the upper extremity motor function. In this work, a regression tree (RT) was implemented with rFA values of multiple WM ROIs in order to estimate FMA-UE scores for stroke patients. In addition, this estimation would not be affected by a rater's experience. Furthermore, the RT could provide an assessment of the importance that the structural integrity in each included anatomical region had in the estimation of the FMA-UE score. This, in turn, could provide valuable information about which brain areas are more related with the upper extremity motor function in stroke. Methods. Thirteen stroke patients (5 females) were included in this study. All patients signed an

informed consent approved by the Ethical and Research Committees of the National Institute of Rehabilitation “Luis Guillermo Ibarra Ibarra” (registry number: 25/19AC) as part of their enrollment in a clinical trial (clinical registry: NCT04724824). Patients underwent BCI therapy for upper-extremity motor rehabilitation, and were assessed at three time points: pre-therapy, mid-therapy, and post-therapy. At each assessment session ( $n=39$ ), DTI data and clinical scores from the FMA-UE were obtained. The diffusion weighted data was acquired along 15 gradient encoded directions with a b-value of 800 s/mm<sup>2</sup>, alongside a non-diffusion weighted image (b-value of 0 s/mm<sup>2</sup>). Using the FMRIB software library (FSL, v6.0.4), the DTI data was corrected for motion and eddy current distortion, and a diffusion tensor was fitted at each voxel. Then, FA values were calculated from the diffusion tensor data at each pair ( $m=21$ ) of ROIs included in the JHU ICBM-DTI-81 WM labels atlas provided in FSL. To this end, the atlas’ ROIs were registered to native diffusion space for each assessment session. Subsequently, the mean FA values in the ipsilesional (FA\_IH) and contralesional (FA\_CH) ROIs were used to compute a rFA in each pair of ROIs according to  $rFA = FA\_IH / FA\_CH$ . Afterwards, a regression tree (RT) was implemented in MATLAB to estimate the FMA-UE score given the ROIs rFA values of a single assessment session. In total, 39 samples were used to perform a leave-one-out cross-validation of the RT. Each sample was comprised by the data obtained in a specific assessment session, i.e., the 21 ROIs rFA values (characteristics) and the observed FMA-UE score. For the hyperparameters of the RT, leaves were not merged, and the minimum number of branch node observations was 1. Additionally, the estimated FMA-UE scores were obtained during the testing stage of the model. In order to determine performance, the mean absolute error (MAE) was computed between the estimated and the real FMA-UE scores. Also, after a normality test, a Wilcoxon signed rank test was performed to assess differences between these clinical scores ( $\alpha = 95\%$ ). Moreover, the discrepancy in clinical capacity categories assigned by the estimated and the real scores was evaluated. These categories were defined as stated in the study of Hoonhorst et al., as “no capacity” (FMA-UE score of 0-22), “poor capacity” (23-31), “limited capacity” (32-47), “notable capacity” (48-52), and “full capacity” (53-66). Finally, the importance of the rFA value at each pair of ROIs in the estimation of the FMA-UE scores was assessed as the characteristics’ frequency of appearance in the nodes of the cross-validated RT. Results. The validated model achieved a MAE of 6.15 points. Also, of the 39 estimated FMA-UE scores, 8 (20.5%) were over, 6 (15.4%) were under, and 25 (64.1%) were within the MAE of the corresponding real score. In addition, the Wilcoxon signed rank test showed no statistically significant differences between the estimated and the real FMA-UE scores ( $p=0.60$ ). Only 15 of the estimated FMA-UE scores (38.5%) fell under a different capacity category than the real scores, where 7 of them fell in a higher category. Lastly, the importance of the rFA value in the estimation of the FMA-UE scores was concentrated around specific pairs of ROIs. The rFA at the ROIs labeled in the atlas as CST (36.1%), medial lemniscus (ML, 15.5%), inferior cerebellar peduncle (ICP, 9.3%), cerebral peduncle (CP, 7.6%), fornix (cres)/stria terminalis (FST, 5.5%), and the retrolenticular part of the internal capsule (RPIC, 5.1%) accounted for 79.1% of the nodes in the cross-validated RT. Conclusion. With the RT, an acceptable estimation of FMA-UE scores using rFA data was achieved.

This was implied by the lack of significant differences between both estimated and real FMA-UE scores, and by the MAE, which was within the range of measurement error of FMA-UE scale of  $\pm 7.2$  points. Additionally, almost two thirds of the estimated FMA-UE scores fell in the same capacity category as the real scores. Moreover, specific pairs of ROIs provided key WM integrity data for the regression, implying that the rFA values obtained in these brain areas can provide useful information to estimate FMA-UE scores. Also, this suggests that DTI analysis could focus on these regions, reducing computation time. These six atlas' ROIs, labeled as CST, ML, ICP, CP, FST, and RPIC, are included in or located near the CST pathway, whose structural integrity has been shown as an important metric for motor function in stroke patients. Different studies have reported that the integrity of this tract, often measured by FA, is correlated with motor outcome after stroke. Additionally, increases in either the ipsilesional or contralesional CST FA have been associated to motor improvements of the upper extremity in different stroke populations after a therapy program. Thus, this indicates that the RT was able to primarily use ROIs relevant to motor function in stroke to estimate the FMA-UE scores. These results suggest that the proposed method could be used in the development of a complementary clinical evaluation tool that is not affected by the rater's experience.

**Keywords:**

Diffusion Tensor Imaging, Fugl-Meyer Assessment of the Upper Extremity, Machine Learning, Regression Tree, Stroke



## Real Time EEG Brain State Classification Using MUSE 2

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### Abstract:

Brain computer interface (BCI) is a real-time brain-machine interface that interacts with external devices and allows the direct connection between human brain and outside environment (Mridha et al., 2021). With its capability to provide a new form of communication mechanism controlled by brain signals, BCI becomes extremely helpful for people with impairments (Nicolas-Alonso & Gomez-Gil, 2012). While Electroencephalography (EEG), Electrocorticography (ECoG) and Near-Infrared Spectroscopy (NIRS) are methods used for acquiring brain signals, EEG is one of the most frequent methods used for BCI application (Chamola et al., 2020; Pfurtscheller et al., 2000). Traditionally data collection for EEG-based BCIs uses wet Ag/AgCl electrodes that are uncomfortable and require considerable time to apply (Matthews et al., 2007; Zhang et al., 2019). Recently, low-cost portable wireless EEG devices like MUSE 2 have achieved signal stability on par with traditional EEG alternatives (Krigolson et al., 2021; Krigolson et al., 2017). We therefore propose a BCI system using portable EEG to classify people's motor states in real-time. We employed the MUSE 2 headset for EEG classification and collected EEG data from participants during motor tasks. To preprocess the EEG data, we applied a notch filter at 60 Hz together with a band-pass filter. We then demeaned the EEG signals and dropped samples by percentage of outliers. After preprocessing, we used common spatial pattern (CSP) on the covariance matrix to extract features and used linear discriminant analysis (LDA) to perform classification. This study offers a solution for people with motor impairment, whose nervous system is not able to execute per the brain's signals. The potential application provides new communication possibilities for those who are paralyzed or suffered from various bodily disabilities.

### Keywords:

Brain-computer Interface, Electroencephalography (EEG), Biomedical Signal Processing, Motor Imagery, Portable Electronics

# Graph Convolutional Learning of Multimodal Brain Connectome Data for Schizophrenia Classification

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## Abstract:

Schizophrenia is a severe psychiatric disorder which causes impairments in memory, attention, and other high-order cognitive dysfunctions. Recent advances in magnetic resonance imaging (MRI) have made it possible to examine the changes in white and grey matter in the brain of patients suffering from schizophrenia. Various functional neuroimaging techniques are also being used to understand the abnormalities in neural activities of schizophrenia patients. A recent promising research direction in context of neuroimaging analysis is the conceptualization of a particular disorder as a dysconnectivity syndrome. The long term goal of this work is to develop powerful tools for brain network analysis in order to study structural and functional connectivity abnormalities in psychiatric disorders like schizophrenia. Graph convolutional neural networks (GCNN) are quite effective for learning complex discriminate features in graph-structured data. Here, we explore the GCNN to learn the discriminating features in multimodal human brain connectomes for the purpose of schizophrenia disorder classification. We propose a graph convolutional neural network which learns to distinguish between brain networks of schizophrenia patients and healthy controls. From a conceptual view of graph network, we use a structural connectome as the underlying graph structure and the concerned input graph signal is derived from the functional connectomes. In particular, the graph signal at each node is the vector containing functional similarity to rest of the nodes in brain. In particular, we train and validate a network using both structural connectivity graphs obtained from diffusion tensor imaging data and functional connectivity from functional magnetic resonance imaging data. We compare the GCNN method with a support vector machine based classifier and other popular classification benchmarks. We demonstrate that the proposed graph convolution method has the best performance compared to existing benchmarks with F1 scores of 0.75 for schizophrenia classification. This demonstrates the potential of this approach for multimodal diagnosis and prognosis in mental health disorders.

## Keywords:

Brain Connectivity, Schizophrenia Disorder, Classification, Deep Learning, Graph Convolutional Network

## **Sponsored Workshop: ANT-Neuro Workshop Session**

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### **Abstract:**

We are excited to announce a workshop on EEG (Electroencephalography) scheduled for August. Hosted by ANT North America, a leading provider of EEG research solutions, this comprehensive workshop will equip participants with the knowledge and practical skills necessary to prepare, record, and analyze EEG data using Matlab. As part of the workshop, participants will have the unique opportunity to work with state-of-the-art equipment provided by ANT North America, including EEG amplifiers and gel-based and saline-based EEG electrodes. The primary objective of the workshop is to empower participants to conduct EEG research, interpret collected data, and apply advanced analysis techniques. We will begin the workshop with a discussion on the fundamental principles of EEG, tracing its historical development and highlighting its significance and diverse applications. This segment will explore the pioneering work of Hans Berger in the 1920s and the subsequent advancements in techniques like ERP analysis, as elucidated in Steven J. Luck's book "An Introduction to the Event-related Potential Technique." Further, we will delve into the relationship between the brain's organization and EEG signals. Participants will gain a deeper understanding of the brain's structural folds, such as gyrus and sulcus, with a specific focus on the central sulcus and lateral sulcus. Additionally, we will explore the role of pyramidal cells in the neocortex, emphasizing their contribution to generating the EEG signal. To kick-start the practical aspects of the workshop, participants will be guided through the process of preparing participants for EEG recordings. They will gain hands-on experience in setting up and operating the EEG recording equipment to ensure the acquisition of high-quality data. In a follow-up analysis section, we will run an EEG analysis using Matlab, where participants will learn essential tasks such as data preprocessing, artifact removal, and basic analysis techniques, including spectral analysis and event-related potential (ERP) analysis. As the workshop progresses, we will introduce more advanced topics, including source localization and connectivity analysis. These topics will enable participants to explore the intricacies of EEG data analysis and gain valuable insights from their research. Overall, this EEG workshop aims to provide participants with a comprehensive understanding of EEG methodology and analysis. By the end of the workshop, participants will be well-equipped to undertake their own EEG studies and contribute to the field of neuroscience. With hands-on experience in preparing, recording, and analyzing EEG data using Matlab, participants will have the necessary skills to conduct research, interpret collected data, and apply advanced analysis techniques. We look forward to welcoming all participants to this exciting workshop hosted by ANT North America.

### **Keywords:**

EEG Singal Preccessing, EEG Device, Brain Imaging

# Automatic Segmentation of Insular Cortex using Computational Super-Resolution and 3D-UNet Deep Learning Methods

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## Abstract:

The insular cortex, often called the insula, is a unique brain region involved in diverse functions, including emotion processing, self-awareness, cognitive control, and interoceptive awareness. Its fundamental role in these essential cognitive and emotional processes underscores the importance of insula-focused studies, as understanding its precise structure and functioning can elucidate its involvement in numerous neurological and psychiatric disorders. FreeSurfer, one of the most popular MRI processing tools, provides automatic parcellation of cerebral cortices, including the insula. However, the results often have substantial errors, so it is not recommended to use the fully automated insula segmentation for structural and functional MRI studies analyzing insula volumes or functional activation patterns. The reasons for the inaccuracy include limited MRI quality, substantial individual differences in the brain anatomy, and the algorithms designed as a general tool to parcellate all major cortical regions, which is not accurate enough for segmenting the insular cortex. Developing a fully automated computational algorithm for segmenting the insular cortex is challenging due to its complex morphology, the relatively deep location surrounded by the operculum, and anatomical proximity to nearby subcortical gray matter structures, including the claustrum. With this difficulty, to our knowledge, there is no alternative, accurate, and fully automated method for segmenting the insula. To overcome the limitations of the current MRI processing tools and limited spatial resolutions (~1.0 mm isotropic voxels), we developed a semi-automatic processing pipeline utilizing a computational super-resolution technique called Non-Local MRI Upsampling (NLMU) that accurately enhances the spatial resolution to an ultra-high resolution (0.5 mm isotropic voxels), the current state-of-art whole brain segmentation tools (FreeSurfer and FSL), computational algorithms based on anatomical landmarks, the most advanced cellular-level Allen brain atlas, and multiple steps of visual inspection and manual correction. Furthermore, we developed a fully automated deep learning algorithm using the semi-automatically created insular label, ultra-high resolution T1-weighted MRIs, and 3D U-Net deep-learning algorithm that generates highly accurate insular cortical labels. To this end, we used our 30 T1w MRIs with 1.0 mm resolution MRIs and 30 T1w Human Connectome Project (HCP) 0.7 mm high-resolution MRIs. We conducted a study for the development of a semi-automatic insula segmentation program using the following 7 steps; 1) AC-PC alignment of T1 MRI using AFNI 3dresample and the MNI152 standard brain, 2) upsampling to 0.5 mm resolution using NLMU algorithm, 3) FreeSurfer recon-all processing to generate cortical gray and white matter (GM/WM) label maps, 4) fsl\_anat processing to generate the probability maps of GM, WM, and CSF, 5) automatic segmentation, visual inspection, and manual

correction of the Sylvian Fissure that delineates boundaries of the insular cortex, 6) the final automatic segmentation, visual inspection, and manual segmentation of insular cortex, and 7) evaluation of the inter-rater reliability of the semi-automatic segmentation results obtained from two independent operators using intra-class correlation. Using a 3D U-Net model, an ideal choice for 3D volumetric data, with an encoder-decoder architecture to capture context while allowing for precise localization, we developed a fully automated insula segmentation algorithm. First, we divided the 60 MRIs into 40-10-10 sets to train, validate, and test the model to mitigate overfitting and evaluate the model's accuracy. Second, we trained the model using the preprocessed and annotated MRI scans with Adam optimizer and a loss function. Third, we used 5-fold cross-validation procedure with the Dice coefficient as the accuracy metric. Fourth, we optimized the model by adjusting hyperparameters, dropout, and batch normalization layers. Last, we evaluated the final model accuracy using the 10 test dataset. We will discuss the final results highlighting the pros and cons of the computational semi-automatic and fully automatic deep-learning algorithm in segmenting the insular cortex. Developing a novel automatic insula segmentation method will substantially improve the accuracy of insular measures in the neuroimaging field and facilitate novel findings.

**Keywords:**

Insula, Structural MRI, Super-Resolution, Deep Learning, 3D U-Net

# Block Dense Weighted Networks with Augmented Degree Correction

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## Abstract:

Two common types of structure appearing in most real networks are communities, broadly understood as sets of nodes whose edges exhibit similar connectivity patterns, and degree correction, broadly understood as certain nodes having consistently more edges than other nodes. Dense networks with weighted connections often exhibit a community like structure, where although most nodes are connected to each other, different patterns of edge weights may emerge depending on each node's community membership. That is, community is defined by the patterns of edge weights, rather than the presence or absence of edges between particular pairs of nodes. We propose a new framework for generating and estimating dense weighted networks with potentially different connectivity patterns across different communities. The proposed model relies on a particular class of functions which map individual node characteristics to the edges connecting those nodes, allowing for flexibility while requiring a small number of parameters relative to the number of edges. By leveraging the estimation techniques, we also develop a bootstrap methodology for generating new networks on the same set of vertices, which may be useful in circumstances where multiple data sets cannot be collected, or can be expensive, as in the case of brain scans. Performance of these methods are analyzed in theory, simulations, and real data, including applications to structural and functional brain network data. The proposed approach provides an alternative perspective of certain datasets, and is able to uncover certain dynamics that would be missed by using existing approaches, which may lead to new potential diagnostic tools.

## Keywords:

Dense Networks, Weighted Networks

# Comparative Evaluations of Computational Neurometric and Deep-learning Methods to Estimate the Number of Intrinsic Dimensionality of High-Density EEG for Optimal Independent Component Analysis

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## **Abstract:**

Electroencephalography (EEG) is an essential tool for cognitive neuroscience and neurology, but EEG recording contains large systematic noises from physiological and environmental origins. As numerous studies have demonstrated, independent component analysis (ICA) provides the best solution for blind source separation of noises from brain signals if the two primary assumptions are met. First, the source locations are fixed and stationary. Second, the number of channels is equal to the number of sources. Unlike the first assumption that is usually fulfilled in EEG recordings, the equal number assumption cannot be met because the number of brain and noise sources should be way larger than that of EEG channels. Therefore, ICA decomposition always results in mixed ICs. The problems of mixed ICs are nontrivial since selective inclusion/exclusion of mixed ICs can lead to the removal of genuine neurogenic signals as well as imperfect deletion of noises, distorting rather than denoising the data. To overcome this fundamental problem of ICA, the most effective method is to estimate the number of intrinsic dimensions (nID) of EEG recordings and transform the original data into latent variable data with a dimensionality of the estimated nID using a dimensionality reduction method, such as principal component analysis (PCA), before running ICA. This approach is called probabilistic ICA, originally developed for the ICA of functional MRI data to minimize the mixed IC problems caused by overfitting. Despite the strengths, this approach has not been widely used for EEG due to the difficulty in estimating the nID of EEG data. Although several methods have been used in the field (e.g., eigenvalue-based methods, information criteria-based methods), they tend to over- or under-estimate nID, leading to overfitting or underfitting problems in the subsequent ICA. Also, their estimates largely vary according to the data quality. More problematically, no well-established and objective way of evaluating the nID estimates exists. To provide objective and computationally straightforward solutions to this fundamental problem in the field, we conducted a study to develop an automatic nID estimation method using extensive computational algorithms based on neurometric principles and a deep learning model using a Generative Adversarial Network (GAN). To this end, we used 64-channel EEG recordings collected from 30 subjects during resting and a cognitive control task and 128-channel EEG recordings from another 30 subjects during resting and a similar but distinct cognitive control task. Our EEG model assumes that scalp EEG recordings are linear combinations of numerous latent (independent source) signals, and the number of major sources explaining the majority of EEG signal variance represents nID, which

is smaller than the original number of EEG channels. Our strategy was to determine nID based on the following 4 neurometric criteria; 1) nID latent variables should explain majority of the data variance ( $>90\%$ ), 2) nID latent variables should parsimoniously explain the data, 3) the test-retest reliability of an ICA with nID latent variables should be high enough across all the ICs, and 4) an ICA with nID latent variables should generate minimal number of mixed ICs. The first and second criteria contradict each other as the greater number of dimensions should explain the more data variance. For the first criterion, we calculated the proportion of variance explained (Pev: range 0-1) by the nID latent variables (i.e., ICs). We also calculated the proportion of nID to the original EEG dimensionality ( $N=64$  or  $128$ ;  $P_n = nID/N$ ). To evaluate the reliability, we used a Matlab toolbox called ICASSO, which runs FastICA multiple times on the same data and estimate a quality index (Iq: range 0-1), quantifying the homogeneity of similar IC clusters across the multiple ICA results. We used the mean of Iq scores of all IC clusters () as a proxy of test-retest reliability of ICA with an nID. To evaluate the “mixedness” of ICs, we conducted EEG dipole source modeling of each IC using a head model derived from the MNI152 standard brain template, calculating the proportion of explained variance by a single dipole (Pdv: range 0-1). As an unmixed IC is supposed to be well localized to a single source location with small residual variance, the larger Pdv should indicate the less “mixedness” of the IC. Since the mean of Iq and the mean of Pdv tend to be smaller with larger number of EEG dimensions, we calculated the weighted indices of them (Iqw and Pdvw) by multiplying each of them with  $P_n$ . Finally, we calculated a composite quality score (Qc: range 0-1) as the mean of Pev, Iqw, and Pdvw values. We implemented our study with the neurometric quality indices in the following steps. First, we preprocessed EEG data, including bad electrode and bad time-segment deletion. Second, we obtained the initial estimation of nID using the Bayesian model order selection method developed by Rajan & Rayner (1997), which estimated the most reasonable nID compared to other methods in our prior extensive evaluations. Third, we selected the range of candidate nID estimates ( $\pm 10$  of the initial nID estimate; total 21 nIDs) for the optimal nID and ran ICASSO with 20 iterations. Fourth, we calculated the quality indices and selected an nID with the highest qc as the optimal nID of the EEG data. We conducted another study employing a GAN model to develop an accurate and computationally light nID estimation method. First, we built the GAN architecture with two main components: a generator network and a discriminator network. The generator produced synthetic data samples, while the discriminator attempted to distinguish between real and synthetic data. Applying the GAN to the EEG nID estimation problem, we aimed to generate the lower-dimensional latent space synthetic data. The generator network took a random vector drawn from a multivariate normal EEG sample distribution as input and mapped it to the data space. In this process, the GAN model learned a transformation from the lower-dimensional latent space to the high-dimensional EEG data space. This latent space is supposed to ideally capture the most relevant variances in the EEG data, effectively learning a compressed, lower-dimensional representation. Second, we randomly divided the 60 EEG data into 40-10-10 sets to train, validate, and test the model to mitigate overfitting and evaluate the model's accuracy. Third, we trained the generator trying to map the latent vectors to data that the discriminator cannot



distinguish from real EEG recordings. With this approach, the nID of EEG data can be estimated as the dimensionality of the latent space of the generator. Fourth, we conducted 5-fold cross-validation. As the larger nID tends to be more similar to the real EEG, we calculated a new quality index by dividing the similarity with the nID and used it for cross-validation. Fifth, we optimized the model by adjusting hyperparameters and regularization. Last, we evaluated the final model accuracy using the 10 test dataset. We will discuss the results highlighting the pros and cons of the computational neurometric and GAN deep-learning algorithms in estimating optimal nID. Developing a novel nID estimation method will substantially contribute to establishing the gold standard ICA protocols for EEG denoising.

**Keywords:**

EEG, ICA, Intrinsic Dimensionality, Neurometrics, Generative Adversarial Networks (GAN)

## Workshop: Time Domain Analysis of Neural Oscillations

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### Abstract:

Cortical oscillations are one of the essential part of brain functionality. In human electrophysiological recordings such as scalp electroencephalogram (EEG), magnetoencephalogram (MEG) these oscillations manifest visible rhythmic patterns or equivalently as a local concentration or narrowband peaks in power spectral density. Some of the commonly used tools to characterize these oscillations are band-pass filters and frequency domain analysis of the signal. Unfortunately, results of these ad-hoc methods are difficult to interpret since they do not adhere to any generative models to formally represent oscillations. For example, bandpass filters can produce spurious oscillations when applied on a broad-band signal. In general, these methods suffer from confounding from cooccurring oscillations and broadband activities, loss of spatio-temporal resolution due to windowing, leading to noisy, inefficient measures of derived metrics, such as amplitude, phase etc. In this context, this session focuses on time domain or state space modeling of neural oscillations to decompose time series in multiple oscillations and trend components. We start with a new conceptual construct that makes clear, from a dynamical systems perspective, when oscillations are present or not. Using that construct, a novel method is developed to identify and characterize neural oscillations distinct from broad-band noise. We then demonstrate how these extracted component oscillations improve statistical efficiency in parametric, time-varying cross frequency phase amplitude coupling analysis. Next, we show the utility of state space models of rhythms in estimation of phase, i.e., the local time index of the waves of a rhythm, that is tolerant of model misspecification. Using this model, we can improve on how current state-of-the-art real-time methods of phase estimation deal with common confounds such as broadband rhythms, phase resets and co-occurring rhythms. Moreover, for offline phase analysis, we found that while phase can be multiply-defined, different methods converge during times of low uncertainty. State space models can be ubiquitous even when neural signals exhibit time-varying activity, precluding adequate model specification with stationary parameters. One flexible approach to model such time-varying signal is by using switching state-space models. A set of parallel state-space models with different linear dynamics are constructed from domain knowledge, capturing multiple target neural states of interest, while a switching process determines the presence of a particular dynamics at a given point of time. We show that these switching state-space models provide numerous analytical advantages and enable more rigorous characterization of time-varying neural signals. Lastly, we demonstrate how state-space modeling provides a convenient and compact way to model signals simultaneously recorded at multiple sensors. With a generative model where an unknown number of hidden oscillation sources undergo linear mixing to produce multichannel recordings, we can effectively pool information across channels

while taking the temporal (i.e. oscillatory) structure of neural data into consideration. That provides inference of oscillation source time-courses and their explicit distribution over the scalp as an interpretable dimensionality reduction. In a nutshell, this session offers a glimpse into how the state space modeling approach of linear dynamical systems can lead to significant methodological advancements in analyzing neural electrophysiology signals.

**Keywords:**

Oscillations, EEG, State Space

# ***Informatics Paradigms for Brain and Mental Health Research***

- B256** Liver Cancer Knowledge Graph Construction based on Dynamic Entity Replacement and Masking Strategies RoBERTa-BiLSTM-CRF Model
- B267** CalciumZero: A User-friendly Prep Processing Pipeline for Fluorescence Calcium Imaging
- B281** Exploring Brain Tumors with Deep Learning: A Cause of Air Pollution
- B285** Multimodal Augmented Sensory Feedback for Neural Engagement in Virtual Reality Rehabilitation
- B286** WORKSHOP: BI 2023 Workshop on External Sources of Brain Stimulation to “Inform” Motor Function
- B292** Alteration in the Resting-state MRI Functional Connectivity Associated with the Development of Post-traumatic Epilepsy (PTE) after Traumatic Brain Injury (TBI)
- B293** Trajectory Analysis of EEG Response in Optogenetic Induced Mesial Temporal Lobe Seizures

# **Liver Cancer Knowledge Graph Construction based on Dynamic Entity Replacement and Masking Strategies RoBERTa-BiLSTM-CRF Model**

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## **Abstract:**

**Background:** Liver cancer, the fifth most common malignant tumor and the second leading cause of death in China presents a significant challenge to the healthcare system. Medical knowledge graph (KG) is attracting attention from both the academic and healthcare industries due to its power in intelligent healthcare applications. This study introduces a novel approach dynamic entity replacement and masking strategies RoBERTa-BiLSTM-CRF(DERM-RoBERTa-BiLSTM-CRF) to recognize medical entities and build liver cancer KG from Chinese electronic medical records (EMRs) and medical website www.XYWY.com. **Challenge:** Building KG for specific medical fields is challenging due to the difference between public data sources and real-world electronic medical records. Integrating these records effectively remains a key issue. Besides that, non-standard and insufficient electronic medical record data can lead to poor model training results, as it introduces noise and inconsistency. **Materials and Methods:** The original data set contains 310 medical electronic records of liver cancer patients from 2015 to 2020 in Zhujiang Hospital. The KG construction procedure contains 6 steps, which are conceptual layer design, data preprocessing, entity recognition, entity normalization, knowledge fusion and graph visualization. The methodology involves the construction of KG's conceptual layer by defining 11 concepts and 15 semantic relationships. A novel and unique aspect of the entity recognition method DERM-RoBERTa-BiLSTM-CRF in this study is the use of dynamic entity replacement and masking strategies(DERM), enhancing the model's generalization ability and fault tolerance in the test set. To further expand the knowledge of electronic medical records, data extracted from the EMRs were normalized by ICD-10 and Commonly used clinical medical terms. To extend the liver cancer knowledge and better interact with other medical knowledge bases, the Term frequency-inverse document frequency (TF-IDF) was used to fuse the knowledge from EMRs and the medical website www.XYWY.Com. The fusing data were integrated into the Neo4j graphic database to construct the liver cancer KG. **Results:** A liver cancer KG with 11 entity types including disease, symptom, body condition, etc. was established, which contains 1495 entities. DERM-RoBERTa-BiLSTM-CRF exhibits a recognition accuracy of 93.23%, a recall rate of 94.69%, and an F1 score of 93.96%. Compared with RoBERTa-BiLstm-CRF, the F1 score increases by 4.3%, which is proven to be effective in entity recognition. Based on the structure of the conceptual

layer of KG, this study imports extra knowledge from the medical website and liver cancer entities extracted from EMRs into the neo4j graph database to complete the construction of liver cancer KG. Compared with other Chinese liver cancer KG, this study's KG can represent more normalized entities and more comprehensive liver cancer knowledge. Conclusion: In conclusion, this study successfully constructs Liver Cancer KG based on DERM-RoBERTa-BiLSTM-CRF from Chinese EMRs and the third knowledge base. The proposed method DERM-RoBERTa-BiLSTM-CRF achieve high performance under most entity recognition model. Moreover, this study demonstrates the rationality, effectiveness, and practicality of the KG in specific disease domains, providing a valuable reference for the rapid design and construction of other disease diagnoses and related knowledge graphs.

**Keywords:**

Liver Cancer, Knowledge Graph, Electronic Medical Records, Name Entity Recognition, Knowledge Fusion

# CalciumZero: A User-friendly Prep Processing Pipeline for Fluorescence Calcium Imaging

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## Abstract:

The relationship between neuronal activity and psychiatric disorders such as schizophrenia and autism spectrum disorders (ASD) is complex. Abnormal neuronal activity patterns, including hyperactivity and hypoactivity, have been observed in these disorders in various brain regions affecting information processing, sensory integration, and social interactions. These irregularities in neuronal firing can disrupt the balance of neurotransmitters, such as dopamine and glutamate, leading to cognitive impairments, hallucinations, and delusions characteristic of the disorder. Understanding the precise mechanisms linking neuronal activity to psychiatric disorders like schizophrenia and autism is an ongoing area of research. gCAMP is a synthetic fusion protein of green fluorescent protein (GFP), calmodulin (CaM), and M13, a peptide sequence from myosin light-chain kinase, which is a genetically encoded calcium indicator. gCAMP calcium imaging is a technique that utilizes the genetically encoded calcium indicators to visualize and monitor neuronal activity in real-time. By introducing the gCAMP protein into neurons, it fluoresces in response to changes in intracellular calcium levels, providing a direct measure of neuronal firing. This imaging method enables researchers to study the dynamics of individual neurons or neuronal populations, helping to unravel the complexities of neural circuits and their involvement in various cognitive processes and disorders. Analyzing calcium imaging data poses challenges in extracting reliable information due to noise and artifacts, as well as the need to accurately separate neuronal activity from confounding factors. Developing robust algorithms for noise reduction, artifact removal, and automated cell segmentation is crucial for accurate interpretation of the recorded signals. This study, we introduce CalciumZero, a user-friendly standalone software with a graphical user interface (GUI) designed for fluorescence calcium imaging. With minimal programming experience required, CalciumZero offers a hassle-free experience and operates seamlessly across various platforms and software packages. It provides an automated, parallel processing pipeline that handles batch data processing, incorporating pre-processing and post-processing steps. Users have the flexibility to run the complete pipeline or selectively execute specific tasks based on latency and energy considerations, allowing for interrupted workflows and task prioritization. In addition, we introduce novel peak detection techniques aimed at identifying sudden changes in calcium levels from time series signals obtained from the CaImAn package. Unlike existing algorithms that require careful parameter tuning, our improved approach utilizes a filtering mechanism that robustly detects desired peaks without the need for extensive parameter adjustments. Additionally, our classification method effectively distinguishes signals with prominent

peaks from those dominated by noise. By training the classification algorithm on existing manually labeled data, a score of 80% can be achieved in both precision and recall, allowing for meaningful statistical analysis and reliable results in fluorescence calcium imaging.

**Keywords:**

Fluorescence Calcium Imaging, Pre-processing, Cell Segmentation, Peak Detection



## Exploring Brain Tumors with Deep Learning: A Cause of Air Pollution

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### Abstract:

Air pollution has been a significant key for numerous human brain diseases, right from childhood to elderly old age. The fact that the Industrial Revolution has led to the inventions of technology, chemicals, and energies and in turn increased global warming and impact on climate change. Invention and innovation improved the economic, socio-cultural, and urbanization of humans. But, at the same time, the leading cause of pollution, and global warming. In this study, the air quality index and PM quality for Delhi (India) is analyzed using a machine learning algorithm (GLM) for three different months namely April, July and December 2022, the model is statistically fit with a p-value less than 1. The z-score value obtained are April PM<sub>2.5</sub> (0.29), July PM<sub>2.5</sub> (4.03) and December PM<sub>2.5</sub>(6.2) and April CO (0.45), July CO(-0.25), and December CO (-0.00). PM<sub>2.5</sub> is found to be higher in April and December due to dry climate, in July month PM<sub>2.5</sub> is low and AQI is good. It means the rain washes away the pollutants in the atmosphere. Hence, PM<sub>2.5</sub> is leading cause for different diseases, one such as cancers, childhood autism and autism spectrum disorders, brain tumors, asthma and so on. Next, ResNet 50 transfer learning, a deep learning model was implemented on brain tumors which achieved nearly 96% accuracy. The training acc. (0.9635) and loss (0.0622) and validation acc. (1.0000) and loss (0.0133) were obtained on applying transfer learning. The air pollutant data was collected from open source and tumors (Dicom images) were collected from Vijaya Diagnostic Centre, Secunderabad, India. Hence, the study proved that pollution is endangering the human brain and needs to reduce and control the pollutants emitted.

### Keywords:

Air Quality Index, Brain Tumors, ResNet 50 Transfer Learning, Generalized Linear Model, Global Warming

# Multimodal Augmented Sensory Feedback for Neural Engagement in Virtual Reality Rehabilitation

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## Abstract:

**INTRODUCTION:** Neurological traumas (i.e., injury to the brain or spinal cord) can severely impair upper-extremity function and the ability to perform activities of daily living. Rehabilitation of functional capabilities typically requires the repetitive practice of rigorous physical training, which can challenge a patient's participation and engagement with training. Computerized interfaces such as virtual reality (VR) are increasingly prevalent for motor rehabilitation, given their leading feature to motivate participants through gamification and immersion. Despite their scope and customizability, computerized rehabilitation methods are not sufficiently well deployed to surpass the efficacy of conventional therapies when normalizing for dosage. This research examines how augmented sensory feedback (ASF) about performance during VR-based training can accelerate gains in movement function through measurable cognitive mechanisms. It has been suggested that multimodal ASF (visual combined with haptic cues) can accelerate motor learning [Sigrist 2013] by enhancing the patterns of neural activation occurring with movement training. In this ongoing study, we investigate the effects of multimodal ASF training on the performance of a motor rehabilitation task with a myoelectric VR interface. Furthermore, we will observe the impact of multimodal ASF on physiological measures that indicate different dimensions of mental and physical engagement. **MATERIALS AND METHODS:** We have created a custom brace that adjusts the isometric arm position (based on physical therapist recommendations) to perform resistance exercises. The brace system (Figure 1) includes electromyography (EMG) sensors (Delsys Trigno) at the skin surface to record muscle activation patterns used as inputs to a machine learning classifier (regression support vector machine). The classifier detects intended command directions for a VR robot arm (with a spherical end-effector) performing a point-to-point touch task. Participants must guide the arm to move the end-effector and contact highlighted spherical targets efficiently (i.e., take shorter pathlengths) while moving quickly (i.e., complete task in less time). Feedback to mitigate performance error is provided in two ways: 1) visual feedback of a guide end-effector positioned halfway along the optimal (shortest) pathlength to the target, and 2) haptic feedback encoding the optimal direction to move the arm towards the target. We repeat training under four conditions: 1) no ASF (control case), 2) visual ASF, 3) haptic ASF, and 4) multimodal ASF (concurrent visual and haptic cues). We examine how these variations in ASF affect performance and physiological measures indicative of user training experience. We employ skin-surface sensors to measure electroencephalography (EEG, g.tec USBamp), electrocardiogram (ECG, Shimmer 3 ECG), and electrodermal activity (EDA, Shimmer3 GSR), which together indicate levels of cognitive, body, and

emotional arousal. We also examine whether changes in ASF produce changes in the perception of control, i.e., the sense of “agency” [Haggard 2002]. We hypothesize that multimodal ASF will generate the largest changes in post-training performance and measures for cognitive engagement. To date, we have collected data with 7 of 20 planned participants who were healthy (no reported or observable signs of upper-extremity or cognitive dysfunction) and have signed an informed consent approved by the Stevens Institutional Review Board (IRB, protocol 2021-036). We are similarly evaluating this platform with persons having incomplete cervical-level spinal cord injury as part of two funded studies (VA SPiRE I21 RX003582-01, NSF CAREER award no. 2238880).

**RESULTS:** Our current study examines the effects of multimodal ASF training on movement performance and cognitive factors for a myoelectric control task in VR. From power analysis on preliminary data, our planned recruitment of twenty neurotypical participants for this study will result in 95% power at  $\alpha = 0.05$ . In applying a one-way ANOVA on our current data sets, we have observed a significant increase in performance (reduced motion pathlength) with visual ASF, increased neural activity (higher EEG alpha power), and increased heart rate with multimodal ASF, as seen in Figure 2. Preliminary survey results have also suggested that participants prefer multimodal ASF based on a greater sense of agency being reported.

**DISCUSSION:** Based on several of our previous works, ASF guidance during movement training enhances post-training motor performance compared to no or sub-optimal feedback. We have demonstrated this result with other motor tasks, such as free reaching [Nataraj 2020], two-legged squatting [Sanford 2021], and pinch force modulation [Nataraj 2021]. We also observe such trends in persons with neurological injuries receiving ASF training for grasp while using a custom-built smart glove [Liu 2021] as part of recently funded studies (New Jersey Health Foundation, PC 53-19; Department of Veterans Affairs, I21 RX003582-01). Our previous works [Nataraj 2020, Nataraj 2021] have also shown a positive correlation between the sense of agency and performance, but whether other cognitive factors (cognitive loading, emotional arousal) follow suit will be newly elucidated in this study. Our previously published work with the bracing platform [Sanford 2022] suggested that varying the complexity/intensity (i.e., more information) or the intermittency (i.e., how often presented) of visual ASF can affect short-term post-training performance and alter EEG and EDA activity. More specifically, simpler and more intermittent feedback resulted in significantly ( $p < 0.05$ ) better performance, reduced cognitive loading, and increased arousal. Therefore, the current study employs simpler and more intermittent forms of ASF in examining and directly comparing visual, haptic, and multimodal ASF for neurotypical participants. In comparison to our previous works, we may be able to conclude whether neurotypicals will interpret the new feedback streaming from haptic activation as either simple or more complex, whether in isolation or combined with visual ASF. Based on our current and preliminary results, despite the increased neural activity and positive perceptions being reported with multimodal ASF, the best short-term retention in performance is derived with visual ASF specifically. While haptic ASF in VR can contribute to greater immersion [Rose 2018] and user perceptions of engagement, it may not contribute positively to performance pending the specific task being trained [Collaco 2021]. As demonstrated in our recent works using mixed-mode reality and an instrumented glove

system [Conferences: Liu 2023 - ICVR, Liu 2023 IEEE CBMS], persons with neuropathology (e.g., spinal cord injury, traumatic brain injury) may need the additional multisensory cueing for improved post-training performance. On the other hand, neurotypicals may experience cognitive overloading that hinders performance or rates of learning when presented with redundant sensory cueing. Ensuring user engagement during motor training requires investigating how cognitive factors change in response to systematic variations (e.g., ASF) in the computerized interface. Such user states can indicate vigilance and well-being that promote better rehabilitation outcomes. In future work, these measures could be utilized in real-time control systems that monitor cognitive engagement to adapt computerized interfaces and facilitate better motor performance.

**Keywords:**

Motor Rehabilitation, Neural Engagement, Virtual Reality, Brain and Spinal Cord Injury

## **WORKSHOP: BI 2023 Workshop on External Sources of Brain Stimulation to “Inform” Motor Function**

Raviraj Nataraj<sup>1</sup>, George McConnell<sup>1</sup>, Noam Harel<sup>2</sup>, Soha Saleh<sup>3</sup>, and Kasia Bieszczad<sup>3</sup>

1. Stevens Institute of Technology, USA

2. Icahn School of Medicine at Mount Sinai, USA

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### **Abstract:**

1) Workshop/special session title:

BI 2023 Workshop on External Sources of Brain Stimulation to “Inform” Motor Function

2) Length of the workshop (half/full day)

Half-day (~4 hours)

3) Names, main contact, and a short bio of the workshop organizers

Raviraj Nataraj, Ph.D. (main contact):

Currently an Assistant Professor in the Department of Biomedical Engineering at Stevens Institute of Technology. Background in developing musculoskeletal simulations and creating sensor-based feedback control systems for real-time operation of powered assistive neuroprostheses. Currently develops computerized interfaces, e.g., virtual reality, and instrumented wearables for motor rehabilitation after brain or spinal cord trauma.

Noam Y. Harel, M.D./Ph.D.

Currently, Associate Professor and Physician (Neurology) with James J. Peters VA Medical Center and Icahn School of Medicine at Mount Sinai. Focus on rehabilitation from and treatment of spinal cord injury (SCI) and amyotrophic lateral sclerosis (ALS). Specializes in methodologies to reactivate weakened nerve circuits, including physical exercises, electrical stimulation, drug repurposing, and ischemic conditioning.

Soha Saleh, Ph.D.

Currently an Assistant Professor in the Department of Rehabilitation and Movement Sciences, School of Health Professions. Focus on improving function and quality-of-life of persons with motor and cognitive disabilities (e.g., stroke, traumatic brain injury). Research areas include neuroimaging-based prognosis models, cognitive-motor interactions driven by novel rehabilitative and assistive technologies, and neuromodulation methods for neuroplasticity in humans.

Kasia Bieszczad, Ph.D.

Currently an Associate Professor in the Department of Psychology at Rutgers University. Focus on neurobiological substrates of learning and memory, including brain processes supporting long-term memory. Research areas include identifying circuit and molecular mechanisms that regulate auditory systems and remodeling cortical and subcortical representations of sounds. Employs advanced electrophysiological and pharmacological techniques to analyze animal models for functional, molecular, and genetic markers of brain-behavior relationships.

George McConnell, Ph.D.

Currently an Assistant Professor in the Department of Biomedical Engineering at Stevens Institute of Technology. Focus on designing and implementing innovative electrical therapies to treat neurological and psychiatric disorders. Research areas include employing implantable neural stimulation, e.g., deep brain stimulation, to recover motor and cognitive function, model-based analysis of motor behaviors, electrophysiological signals, and histological patterns to characterize post-therapeutic gains in motor (gait) function with rats. Student contributors (from Nataraj lab):

Mingxiao Liu, M.S., Sophie Dewil, M.S.

4) Brief description of the workshop scope and timeline

5-6 talks, each ~30 minutes, including Q&A. • Topics will touch upon a broad array of applications of neural stimulation to alter (presumably improve) motor function. External sources of neural stimulation that may be discussed include (but are not restricted to) electrical/magnetic stimulation to modulate neuromotor circuitry, robotic devices actively injecting power to affect motor function and associated neuroplasticity responses, and sensory-driven human-computer interfaces, including virtual reality, to affect neural engagement during rehabilitative training. • Each talk will conclude its scientific portion (i.e., explanation of application/context whereby the brain is “stimulated” and movement function subsequently affected) with suggestions outlining how artificial intelligence, machine learning, or general data mining techniques can be applied to improve related clinical or preclinical paradigms.

5) Prior history of the workshop (if any): N/A

6) Potential program committee members and invited speakers

Mainly the above-listed organizers and potentially other interested parties

7) Any other relevant information

N/A

**Keywords:**

Brain Stimulation, Sensorimotor Rehabilitation, Movement Learning, Neural Dysfunction

# **Alteration in the Resting-state MRI Functional Connectivity Associated with the Development of Post-traumatic Epilepsy (PTE) after Traumatic Brain Injury (TBI)**

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Spencer Chen<sup>2</sup>, Bharat Biswal<sup>3</sup>, and Hai Sun<sup>2</sup>

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2. Department of Neurosurgery, Rutgers Robert Wood Johnson Medical School, Piscataway, NJ, USA

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## **Abstract:**

**Rationale** - Post-traumatic epilepsy (PTE) is associated with cognitive and general brain dysfunction. PTE is known to occur at a delayed onset after traumatic brain injury (TBI), but there is no reliable predictor for PTE. Studies have shown clinical parameters such as age, injury type, or Glaucoma Stroke Scale (GCS) scores predispose TBI patients to epilepsy, but functional aspects of the brain that may predispose patients to PTE have not yet been studied. **Method** - We obtained resting-state (i.e. in the absence of stimulus or task) MRI scans of TBI (16 subjects), PTE (4 subjects), and healthy subjects (19 subjects) to investigate differences in resting-state functional connectivity between these cohorts. Schaefer atlas was used to identify 100 brain parcellations and temporal correlation between the different brain regions was computed to obtain the functional connectivity [1] [2]. Brain regions that are functionally connected to one another would exhibit high correlation values. Using the Fisher z-transformed correlation values, we performed a two-sample t-test ( $\alpha < 0.05$  for significance) to assess for any significant connectivity disparity between control vs TBI and control vs PTE subjects. Then to identify the specific brain networks that are more affected by changes in functional connectivity, we tallied significant alterations of the connectivity in the context of the Yeo 7-Network parcellation [3]. This analysis provides an indication of the networks that may improve or worsen in progression from TBI to PTE. **Result** - Functional connectivity analysis showed that 11% of the connectivity have significantly altered in TBI subjects when compared to control subjects. This is reduced to 5% in PTE subjects when compared to controls. The default mode and visual networks had the largest number of significantly altered connections between control and TBI subjects with 19.6% and 19.3% respectively, and the limbic network had the fewest with 3.8%. Between control and PTE subjects, the visual network showed the largest number of significantly altered connections with 27.2%, and the ventral-attention network showed the lowest with 5.5%. Increased numbers of significantly different connections from TBI to PTE when compared to control may indicate progression to worse outcomes in PTE, most notably in the default mode network from 16.5% to 22.6%, limbic system from 3.1% to 6.9%, and visual network from 19.3% to 27.2%. Interestingly, decreased numbers of significantly different connections from TBI to PTE when compared to control were seen in dorsal-attention, fronto-parietal,

and ventral-attention networks. These differences may be indicators of areas of epileptogenesis in TBI patients that may warrant targeted treatment. Conclusion - Our study is a benchmark for future comparisons of brain network changes associations in the brain predicting the development of PTE after TBI which will improve our understanding of epileptogenesis associated with PTE.

**Reference:**

[1] Chen K, Azeez A, Chen DY, Biswal BB. Resting-State Functional Connectivity: Signal Origins and Analytic Methods. *Neuroimaging Clin N Am*. 2020 Feb;30(1):15-23. doi: 10.1016/j.nic.2019.09.012. PMID: 31759568.

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[3] B. T. Yeo et al., "The organization of the human cerebral cortex estimated by intrinsic functional connectivity," *J Neurophysiol*, vol. 106, no. 3, pp. 1125 – 1165, Sep. 2011.

**Keywords:**

Human, Resting-state MRI, Brain Injury, Epileptogenesis, Yeo 7-Network Parcellation



## Trajectory Analysis of EEG Response in Optogenetic Induced Mesial Temporal Lobe Seizures

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### Abstract:

Mesial temporal lobe epilepsy (mTLE) is a prevalent type of epilepsy with a high rate of drug resistance and surgery relapse. The ictogenesis of mTLE is not well understood. A better understanding of how mTLE seizures begin may offer new therapeutic opportunities. We modeled mTLE seizures with optogenetic stimulation to the hippocampus. In mice, we transduced ChR2 in putative glutamatergic neurons unilaterally in CA1 of the hippocampus. A fiber cannula was implanted at the site of ChR2 transduction for optical stimulation. We demonstrate that focal to bilateral tonic-clonic seizure can be induced in awake-behaving mice by 10Hz optical activation of unilateral CA1 glutamatergic neurons. Altogether we recorded from 8 mice, 120 sessions, and acquired a total of 243 seizures. Using a co-implanted electrode attached to the cannula to simultaneously monitor the EEG activity as the neural tissue underwent optical stimulation, we observed an extraordinary evolution of the optically driven EEG response leading to the seizure. At first, optical stimulation of the ChR2-expressing neurons evoked a consistent reactive response. However, the evoked response evolved into more complex patterns with subsequent stimulation pulses, then eventuating into a seizure. We investigated the dynamics of this EEG response patterns phased-locked with respect to each stimulation pulse. We took snippets of the EEG -10 to 60ms around each stimulation pulse and rearranged them into a 3D matrix with the pulse-relative time in the y-dimension, successive snippets in time on the x-dimension, and the EEG voltage in the z-dimension; thus built a time-vs-time visualization of how the driven EEG response change over time and into the seizure – so called the “pulsogram”. This representation revealed that optical pulse trains initially evoked an immediate, reactive EEG activity within 10ms of the stimulation. To continual stimulation, a stereotypical secondary discharge emerged in EEG, delayed 20-50ms from each stimulation pulse. The secondary discharge led into the seizure onset and thus denotes a critical transition from a reactive, stimulation-driven neural response to a self-sustaining seizure, which was characterized by unsynchronized EEG activity to the stimulation pulse. Treating each pulsogram snippet as an n-dimensional vector, we then applied several trajectory analysis approaches to examine and compare the pulsogram evolution patterns between seizures. PCA analysis of the pulsogram demonstrated that the first (nascent) seizure induced each day exhibited a distinct pulsogram pattern to subsequent (breakthrough) seizures induced by repeated stimulation trains every 120s. We demonstrate that nascent seizures have more complex response trajectories – compared to breakthrough seizures, nascent seizure pulsogram required more PCA components to capture 90% of the response variance ( $p < 0.0001$ ), contained more trajectory segments from both angular analysis ( $p < 0.0001$ )

and using Ramer – Douglas – Peucker trajectory reduction algorithm ( $p < 0.0001$ ). This could mean that more neural ensembles would need to be activated or a more complex sequence of activation is required to initiate a nascent seizure – the first seizure of each day. When administered the same stimulation train repeatedly, we did not always induce a seizure, but often we observed evolution of the pulsogram and the appearance of a secondary discharge similar to the seizure onset patterns for breakthrough seizures. We labeled these as “evolving” responses as opposed to a completely reactive “flat” response to the stimulation train. PCA dimension reduction revealed that flat, evolving response and breakthrough seizures appear to be a continuation of the same response trajectory. Using dynamic time warping, we demonstrate that indeed the trajectory of a flat response can be considered the leading segment of an evolving response, which in turn can be considered the leading segment to a breakthrough seizure. This identified critical response transitions in the initiation of a seizure – from the reactive response to the secondary discharge (flat to evolving), and from the secondary discharge phase to a seizure (evolving to breakthrough). These may represent operating states of neural substrate that can be exploited to prevent the progression of the neural activity towards a seizure. In conclusion, we demonstrate that optically stimulation as a controlled mean to generate on-demand seizures. Trajectory analytical approaches revealed the neural activity progression over which seizures are initiated, through which we have identified different types of seizure onset and the phases of neural activity in seizure initiation. Through better understanding of the required neural activation by which seizures are initiated, we hope to be able to detect and pre-emptively prevent seizures before they initiate.

**Keywords:**

Mouse, Hippocampus, Optical Stimulation, Epilepsy, Ictogenesis

# ***Brain-Machine Intelligence and Brain-Inspired Computing***

- B247**     Workshop Proposal
- B252**     Developing a Hidden Markov Model - Gaussian Mixture Model Framework to Classify Gait Patterns in Huntington's Disease
- B264**     Visual Cortex Doesn't Change, Why should Convolutional Layers?
- B274**     A Bayesian Hierarchical Method for Mental Disorders Subtyping Using Integrated Multi-modality Data
- B291**     Biologically Plausible Credit Assignment with Top-down Dendritic Gating of Plasticity
- B298**     Differential Neural Activity During Decision Making Reflects Both Reward-Impulsivity and Decision Difficulty

## Workshop Proposal

Lu Zhang<sup>1</sup>, Lin Zhao<sup>2</sup>, and Bo Zhou<sup>3</sup>

1. The University of Texas at Arlington, USA

2. United Imaging Intelligence, USA

3. Yale University, USA

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### Abstract:

#### Proposal for Brain Informatics (BI) 2023 Workshop

The Intersection of Artificial Intelligence and Human Intelligence (IAIHI) Objective Artificial Intelligence (AI) has been a long-standing goal of humanity, with the aim of creating machines capable of performing any intellectual task that humans can do. To achieve this, AI researchers draw inspiration from the human intelligence (HI) and seek to replicate its principles in intelligent machines. In light of this, we propose to organize a workshop that serves as a platform to explore the dynamic relationship between AI and HI, fostering interdisciplinary discussions that delve into their intersection and uncover potential synergies. Scope The scope of this workshop is to explore how the intersection of AI and HI can contribute to two specific areas of research: the analysis and interpretation of brain data and the design of more efficient AI models. Firstly, in this workshop, we will discuss how AI technologies can be leveraged to facilitate the analysis and interpretation of brain data, allowing researchers to process, analyze, and interpret large-scale brain data more efficiently. This includes the application of AI techniques in uncovering brain fundamental organization principles and assisting in the diagnosis and understanding of various brain disorders. Secondly, we will delve into the applications and advancements in designing brain-inspired AI models and explore how neuroscience knowledge can inform AI development. The study of the human brain provides valuable insights into cognitive processes, learning mechanisms, and information processing. Researchers can leverage this knowledge to design more efficient AI models and algorithms that mimic or are inspired by the brain's mechanisms. By incorporating neuroscience principles, AI models can potentially achieve higher performance, improved interpretability, and better adaptability to complex tasks.

### Timeline

We propose to hold a full-day workshop following the agenda below:

8:30am - 9:00am Breakfast

9:00am - 9:15am Welcome

9:15am - 10:15am Plenary Session (invited talk 1)

10:15am - 10:30am Coffee break

10:30am - 12:30pm Oral Session 1

12:30pm - 1:30pm Lunch

1:30pm - 2:30pm Plenary Session (invited talk 2)

2:30pm - 3:30pm Poster Session

3:30pm - 3:45pm Coffee break

3:45pm - 5:45pm Oral Session 2

5:45pm - 6:00pm Closing remarks

### **Space requirements and technical support**

A room that accommodates 50-60 people with multimedia equipment: laptop projector/screen, microphone/speaker (wireless would be desirable). A nearby poster area with approximately 10 poster boards is preferred.

### **Workshop organizers**

Lu Zhang, The University of Texas at Arlington, USA

Lin Zhao, United Imaging Intelligence, China

Bo Zhou, Yale University, USA

### **Program committee members**

Yuzhi Guo – Postdoctoral, The University of Texas at Arlington (UTA)

Yuan Yang – PhD Candidate, Vanderbilt University

Haixing Dai – PhD Candidate, The University of Georgia (UGA)

Xiaowei Yu – PhD Candidate, UTA

Yanjun Lyu – Senior PhD, UTA

Saiyang Na – Senior PhD, UTA

Zihao Wu – Senior PhD, UGA

Zhenliang Liu – Senior PhD, UGA

### **Keynote speakers**

Our workshop will feature two exceptional keynote speakers who are renowned experts in the fields of AI and Brain Science. They will bring their exceptional expertise and insights to enrich the experience for all attendees.

### **Keywords:**

Proposal for Brain Informatics (BI) 2023 Workshop, The Intersection of Artificial Intelligence and Human Intelligence (IAIHI), A Full-day Workshop

## **Developing a Hidden Markov Model - Gaussian Mixture Model Framework to Classify Gait Patterns in Huntington's Disease**

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### **Abstract:**

**Background:** Gait abnormality is a potential diagnostic sign which can occur even in the early, pre-manifest stages of neuro-degenerative diseases such as Huntington's disease (HD). Gait patterns in such patients are characterized by irregular, shortened stride lengths and jerky movements. Hidden Markov Models (HMMs) offer a straightforward and effective framework for disease progression prediction and pattern recognition. **Methods:** We propose a two-class Hidden Markov Model (HMM) where a stride model and a transition model were trained individually to identify distinct patterns and abnormalities during the gait-phase transition to distinguish between HD patients with moderate to severe motor dysfunctions and healthy controls. A left to right HMM was used to represent the stride model. The HMM for the transition model was extended to allow transitions to occur at any point. A 2-dimensional Gaussian Mixture Model was chosen to represent the hidden states of the HMM due to their ability to model diverse and personalised gait patterns. To estimate the parameters of the GMMs, the hidden states were initialized by dividing the strides into 2 equally spaced sections. The parameters were then optimized using the Baum-Welch algorithm with a maximum of 15 iterations. The threshold of convergence was set to 0.0001. Our HMM-GMM approach was applied on pre-existing data from an open source dataset from physio.net. 25% of the records was used to train the model while the other 75% was used during the recognition phase. **Results:** Our proposed HMM-GMM approach outperformed most standard algorithms, achieving the highest average F1 score of 81.76%. The results obtained by the HMM model is almost the same as the highest performing SVM classifier with only a 0.55% difference in terms of F1 score (81.21%). Moreover, it achieved the highest accuracy rate of 86.66%, suggesting that the use of HMM is suitable for classifying time-varying motion such as gait. Additionally, we observed that both supervised algorithms, Support Vector Machine (SVM) and k-Nearest Neighbours (kNN) achieved relatively high classification accuracy rates of 81.00% and 76.66% respectively. Only 54.04% of instances were classified correctly using k-means clustering with a significantly high standard deviation of 3.429, possibly due to its high sensitivity to outliers and the irregular distribution of data points. **Conclusion:** The obtained results are very promising since the HMM-GMM performs within an unsupervised context and do not require labelled data during the training phase, making them much easier to implement. In the future, the study could initially be undertaken without the effect of medication and the changes in gait patterns should be monitored continuously either as the disease progresses or with the use of medication.

**Keywords:**

Machine Learning, Neurodegeneration, Huntington's Disease, Gait Analysis, Hidden Markov Models

# Visual Cortex Doesn't Change, Why should Convolutional Layers?

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## Abstract:

1. Introduction The last two decades have been marked by major advances in Artificial Intelligence, due in large part to convolutional neural networks (CNN) [1]. Traditionally, neural networks only included dense layers (Dense-only), and employed backpropagation for training. CNN frameworks add filter layers in front of dense layers, but continue to employ backpropagation for all layers. Unfortunately, backpropagation is extremely expensive in terms of training times, required hardware, and electricity consumption. This research investigated the necessity of backpropagation for the filter layers in CNNs. The question of whether backpropagation is necessary for convolutional layers is largely inspired by the human and animal brains. To be specific, the primary visual cortex, the area of the brain where convolutional layer -like filters are located, does not change during learning in adult humans and animals (e.g., [2]). Earlier cortical layers are subject to synaptogenesis during early childhood, but outside abnormal development, these brain areas are myelinated and stable during all following adult learning. Artificial neural network frameworks, such as Tensorflow, enable researchers to turn off learning for specific neural network layers. In the current work, we employ this feature to enable and disable backpropagation learning in convolutional layers for various image categorization simulations. Ultimately, the question we are asking is whether transfer learning in artificial neural networks (e.g., [3,4]) will work as well as it does in biological brains. That is, if early visual filters are trained on some subset of visual stimuli, and then frozen, to what degree does that early training transfer to future problems? In Simulation 1, we examine whether backpropagation can be turned off altogether, and to what degree would this affect training speed and prediction accuracy. In Simulation 2 we attempt to simulate normal development of human and animal brains - turning on learning in early convolutional layers during early learning exposures, and then turning it off for later learning trials; once again focusing on the degree to which this affects training speed and prediction accuracy.

2. Simulation 1 - turning off backpropagation In this simulation we examine the necessity of training in convolutional layers. Given that backpropagation is highly resource-intensive, we wanted to examine whether randomly initialized convolutional layers may provide enough of an advantage without any training. We ran simulations comparing efficiency and accuracy of Dense-only, CNN, and CNN without backpropagation (CNN-nobp) neural networks using two datasets commonly used to evaluate neural nets: MNIST handwritten digits (MNIST) [5] and MNIST fashion images (Fashion) [6]. We used Python and TensorFlow to implement all models with the same hyperparameters, and Keras to visualize their performance during training. All networks had a single dense layer and were trained for 5 epochs. CNN and CNN-nobp also had 3 convolutional layers each (each convolutional layer had 32 3x3 filters). Final test accuracy and total training+testing times after five epochs of training are displayed below (run times will



vary depending on hardware): Accuracy Total Run Time Fashion MNIST Fashion MNIST CNN 0.91 0.99 221.3s 219.1s CNN-nobp 0.88 0.98 69.3s 69.5s Dense-only 0.83 0.93 8.7s 8.8s Results of this simulation suggested that convolutional filter layers provide accuracy advantages for neural networks, even in the case of CNN-nobp, where these filter layers are randomly initialized and never trained. CNN-nobp was more accurate than Dense-only (+5% on MNIST, +5% on Fashion). However, CNN-nobp was less accurate than the standard CNN with backpropagation turned on (-1% on MNIST, -3% on Fashion). This may be extremely encouraging for problems where 1-3% of accuracy loss is not a major issue. However, in the next simulation we explore how we may be able to get rid of this loss of accuracy while retaining the speed advantages gained from turning off backpropagation. As expected, CNN-nobp provides major advantages over CNN in terms of training times (3.2x speedup for each of the datasets, though this number will vary depending on hardware configuration), confirming once again that backpropagation is very resource-consuming, and should be avoided, if at all possible.

### 3. Simulation 2 - transfer learning

Human and animal brains do not retrain early visual filter layers during learning in adulthood. Rather, early visual filter layers in the primary visual cortex are updated early during development, and are stable during later learning. Taking biological brains as inspiration, this simulation is set up to evaluate how CNN's would perform if convolutional filter layers were trained during early learning stages, and frozen during later neural network training. In this simulation we trained and tested three models using the same datasets as the prior simulation - MNIST and Fashion. The major difference is that in this simulation we would train the same model on one of the datasets, followed by the other dataset. We ran three models in this fashion - CNN, CNN-nobp, and one more model which acted like a normal CNN for the first of the two datasets, and then had its convolutional layers frozen for the second dataset (CNN-transfer). All models were identical in structure to the convolutional models from Simulation 1 (3 convolutional layers, 32 3x3 filters in each layer, followed by a single Dense output layer). Test accuracy and total training+testing times after a single epoch of training are displayed below (run times will vary depending on hardware):

Direction	Model	Accuracy	Accuracy	Run Time
Fashion -> MNIST	CNN	0.89	0.98	45.9s
	CNN-nobp	0.82	0.95	14.8s
	CNN-transfer	0.89	0.98	15.2s
MNIST -> Fashion	CNN	0.98	0.88	44.9s
	CNN-nobp	0.95	0.82	14.3s
	CNN-transfer	0.98	0.88	14.6s

Results show no difference between CNN and CNN-transfer on either the first or second datasets. It is not surprising that there is no difference between CNN and CNN-transfer on the first of the datasets, since the two models are set up identically during that part of the simulation. However, for the second dataset CNN-transfer had all convolutional layer training turned off, and this resulted in 3x training speed improvements (though this number will vary depending on hardware configuration) without any impact on test accuracy. Similar to how the human visual cortex trained in early childhood would help a person learn and identify objects faster in adulthood without any backpropagation, early training and later freezing of filter layers in artificial neural networks seems to provide the same benefits.

### 4. Summary and Conclusions

This research highlights the resource-intensive nature of backpropagation in convolutional neural networks. Training convolutional layer filters does provide accuracy advantages over models where backpropagation is turned off completely. By drawing inspiration from the development of the primary visual cortex in biological brains, we can

restructure weight updates in artificial neural networks. Simulation 1 revealed that convolutional layers aid in accuracy, regardless of whether they are trained at all, but training of convolutional layers definitely improves accuracy. Simulation 2 revealed that when convolutional layers are trained during early development, this is enough training for those filter layers, and turning off training for those layers during later learning stages does not impact accuracy. Whether the models were trained on handwritten digits first and then trained on recognizing clothing, or vice versa, turning off backpropagation between the two training stages had no impact on accuracy while providing 3x improvements in training speed. Future work will focus on identifying how speedup improvements vary given different numbers of convolutional layers and the numbers of filters in these layers. Additionally, we aim to explore how different datasets with more complex image types will impact transfer learning, and whether “unnecessary” convolutional layer filters can be pruned in the same way that the biological brain prunes neurons in the primary visual cortex during early stages of development. In sum, our findings emphasize the importance of taking inspiration from biological brain function and development for designing more efficient AI. Backpropagation is a neat mathematical optimization technique, but it is far from efficient or biologically realistic. In paying greater attention to why and when neural connections are strengthened and pruned in biological brains we are likely to achieve far more practical artificial learners. 5.

## References:

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## Keywords:

Brain-inspired Artificial Intelligence, Transfer Learning, Convolutional Neural Networks, Image Recognition, Primary Visual Cortex

# A Bayesian Hierarchical Method for Mental Disorders Subtyping Using Integrated Multi-modality Data

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## Abstract:

**Background:** The current diagnostic criteria for mental disorders are based on symptoms or clinical variables, which face significant challenges due to substantial heterogeneity of these disorders and a lack of objective biomarkers. The National Institute of Mental Health (NIMH)-led Research Domain Criteria (RDoC) initiative proposes to integrate biological and behavioral measures from various sources of analysis and different domains of functioning for disease classifications. In this sense, mental disorders will be reorganized by the measures collected across multiple domains (e.g., clinical, genomics, brain, and behavioral) at multiple levels and thus more closely align with the underlying biology. **Existing approaches:** The increasing availability of high-dimensional biological and behavioral measurements provides promising opportunities to test theoretical constructs within the RDoC framework and compare them with data-driven constructs and clustering techniques. However, most applications of biological markers for reorganizing mental disorders, often referred to as 'biotyping', have relied on 'off-the-shelf' clustering techniques such as K-means clustering, finite mixture modeling, and graph-based clustering. Unfortunately, these methods have not yet been successfully replicated or externally validated. Furthermore, none of them can handle the integration of heterogeneous data-type modalities in subtyping or address unbalanced missing data across modalities. **Methods:** In this paper, we develop novel methods for subtyping mental disorder patients by integrating measures across multiple modalities with different data types (e.g., categorical clinical measures and continuous neuroimaging measures). We propose a Bayesian hierarchical mixture model with latent variables for simultaneous dimension reduction of high dimensional measures across different modalities while also learning patient clusters. Our proposed method generalizes the Item Response Theory (IRT) for categorical modalities and allows the integration of both continuous and categorical modalities. Furthermore, we propose two algorithms for estimation: (a) a Gibbs sampling algorithm with Polya-Gamma augmentation which constructs conjugate posteriors for random parameters and allows exact inference; (b) a computationally and memory-efficient stochastic black-box variational inference algorithm, which avoids high-dimensional integration of heterogeneous random variables from multiple modalities. We compare these two proposed algorithms through extensive simulations. **Results and conclusions:** We apply our developed methods to cluster adolescent participants from the Adolescent Brain Cognitive Development (ABCD) Study. We account for children's multi-dimensional modality-specific latent constructs (e.g., cognitive control and attention), shared covariates, and shared latent constructs across different modalities. We integrate categorical clinical measures, Kiddie Schedule for Affective Disorders and Schizophrenia (KSADs) modality, and continuous brain image measures (cortical

thickness measures from structural MRI modality and sub-cortical volumes) to identify potential subtypes of Attention-Deficit/Hyperactivity Disorder (ADHD) and Obsessive-Compulsive Disorder (OCD). Our analysis offers novel insights into the subtyping of mental disorder patients.

**Keywords:**

Mental Disorder Subtyping, Bayesian, Multi-modality Integration

# Biologically Plausible Credit Assignment with Top-down Dendritic Gating of Plasticity

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## Abstract:

A central problem in biological learning is how information about the outcome of a decision or behavior can be used to reliably guide learning across distributed neural circuits while obeying biological constraints. This “credit assignment” problem is commonly solved in artificial neural networks through supervised gradient descent and the backpropagation algorithm. In contrast, biological learning is typically modelled using unsupervised Hebbian learning rules. While these rules only use local information to update synaptic weights, and are sometimes combined with weight constraints to reflect a diversity of excitatory (only positive weights) and inhibitory (only negative weights) cell types, they do not prescribe a clear mechanism for how to coordinate learning across multiple layers and propagate error information accurately across the network. In recent years, several groups have drawn inspiration from the known dendritic non-linearities of pyramidal neurons to propose new learning rules and network architectures that enable biologically plausible multi-layer learning by processing error information in segregated dendrites. Meanwhile, recent experimental results from the hippocampus have revealed a new form of plasticity—Behavioral Timescale Synaptic Plasticity (BTSP)—in which large dendritic depolarizations rapidly reshape synaptic weights and stimulus selectivity with as little as a single stimulus presentation (“one-shot learning”). Here we explore the implications of this new learning rule through a biologically plausible implementation in a rate neuron network. We demonstrate that regulation of dendritic spiking and BTSP by top-down feedback signals can effectively coordinate plasticity across multiple network layers in a simple pattern recognition task. By analyzing hidden feature representations and weight trajectories during learning, we show the differences between networks trained with standard backpropagation, Hebbian learning rules, and BTSP.

## Keywords:

Synaptic Plasticity, Dendrites, Credit Assignment, Continual Learning, Hebbian Learning

# Differential Neural Activity During Decision Making Reflects Both Reward-Impulsivity and Decision Difficulty

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## Abstract:

**Introduction:** The concept of impulsivity is a complex construct that requires careful definition. We define decision making impulsivity (DM-impulsivity) to be choices that are made quickly and involve fast responses executed by quick neural processes. DM-impulsivity is measured by reaction time (RT) in choice tasks. In contrast, we define Reward-impulsivity (R-impulsivity), as a preference for smaller rewards sooner (SS) over larger rewards later (LL) as assessed by delay discounting (DD) tasks. There have been insufficient studies on the relationship of DM-impulsivity and R-impulsivity. Here we will use RT to investigate this relationship. RT in DD tasks, as in perceptual and cognitive tasks, should reflect the difficulty of the decision, with very fast responses corresponding to easy decisions regardless of the choices (SS and LL). Typically, in DD tasks choice difficulties depends on both the reward amount and time difference. Therefore, in DD task fast choices may depend on both the individuals R-impulsivity and DM-impulsivity. We tested the hypotheses that fast and slow choices in the DD task involve either R-impulsivity focusing on reward and disregarding the time information, or scenario evaluation assessing both reward amount and time to maximize reward. We expect these two possible processes to be also reflected in differential neural activities.

**Methods:** Participants (N=20; age:  $22.5 \pm 4.0$ ; female=7) performed a DD task (on average 124 trials). in an MRI scanner. The data were analyzed at the trial level without aggregation. A Bayesian generalized linear mixed-effects model was tested on SS vs. LL choices as a function of reward immediacy, framing, SS and LL time difference (2 or 4 weeks), SS reward magnitude, SS and LL relative reward difference (RRD), RT, and their interactions. In addition, we performed the same analysis with Group as an additional factor based on individuals' prior performance on the same task. We defined the R-impulsive group (N=10) as those who made more SS choices, and the R-patient group as those who made fewer SS choices. For the neuroimaging analysis, we used a standard preprocessing including slice timing correction, motion correction, normalization, and smoothing. A generalized linear model (GLM) was used for the whole brain analysis of the individual subject data, with SS and LL responses, and 3 RT lengths as regressors, which were used in the group level contrasts. Regions of interests (ROIs) analysis was conducted in decision-making areas defined on the AAL atlas.

**Results:** When Group was not included in the model, a significant main effect of RT showed that with increased RT participants made more LL choices. In a model that included Group, there was an interaction between RT and RRD, indicating that, when

RRDs were small (harder choices) RTs were longer and were associated with LL choices, whereas when RRDs were large the LL choices were not associated with RT. We also found that RT interacts with Group. The R-impulsive group showed a steeper increase of LL choices with increased RT compared to the patient group. No group differences were found in neural activation. In ROI analysis, however, the insula showed stronger BOLD activity for short versus long RT, while the hippocampus and the inferior parietal show the reverse pattern.

**Conclusions:** The behavioral data demonstrate that in a DD task, RT is related to the specific choice made and to an individual's discounting propensities, as well as the reward difference. In contrast, the MRI data suggest that for choices with short RTs, the insula, which is part of the reward network, is more active. Whereas choices associated with long RTs, engaged the hippocampus and the inferior parietal cortex, brain regions that are involved in context processing including time-to-reward assessment and cognitive control, respectively. Our findings point to complex processes during the DD tasks that do not only reflect R-impulsive choices but differentiate between easy and difficult choices. Fast choices which are based on the reward valuation network are active either when the amount options are easy to differentiate (both SS or LL choices) or when the choice is driven by R-impulsivity (SS choices only). The anticipatory and cognitive control processes are engaged when the choices require more complex computation of the RRD over time and thus generate longer RTs. This study provides a novel demonstration of the complex interaction of fast and slow cognitive processes involved in DD choices, reflecting the mobilization of different decision-making mechanisms within the same task..

**Keywords:**

Delay-discounting, Impulsivity, Reaction-Time, Decision-making, fMRI

# **BI'23 Abstracts**

**(Workshop /Special Session)**



# ***The 5th International Workshop on Cognitive Neuroscience of Thinking and Reasoning***

**S03201** Effects of Time Pressure and Cognitive Load on the Effect of Belief Bias in Syllogistic Reasoning: Evidence from Eye Tracking Studies

# Effects of Time Pressure and Cognitive Load on the Effect of Belief Bias in Syllogistic Reasoning: Evidence from Eye Tracking Studies

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## Abstract:

Dual mechanism theory (DMT) supports that the reasoning process is a game of two different cognitive processing methods, in which heuristic processing responds based on existing knowledge and experience, and analytical processing responds based on logical rules. However, the theoretical model and processing mechanism of the belief bias effect are still controversial. In recent years, emerging logical intuition model has suggested that there may be automatic analytical processing and heuristic processing in syllogistic reasoning at the same time. In order to solve this problem, different experimental manipulations and conflict detection paradigms will be used to provide empirical evidence for the logical intuition model. In addition, previous studies have concluded that the reasoning accuracy rate of logically valid tasks is greater than that of logically invalid tasks, but it ignores that logically invalid tasks can be divided into logically inconsistent (IC) and logically indeterminate (ID) tasks, which makes the internal mechanism of logically invalid tasks in the belief bias effect still unclear. In response to this problem, this study will test the effects of two logic invalid tasks through behavioral and eye tracking experiments. This study can be divided into 1 pre-experiment and 3 formal experiments. Experiment 1 is 3 (validity: logically valid / logically inconsistent / logically indeterminate)  $\times$  2 (believability: believable / unbelievable) two-factor experimental design, this experiment is based on the materials prepared by the pre-experiment, to investigate the belief bias effect of the participant completing the category syllogism reasoning without additional conditions, and explore the processing mechanism of the bias effect. It was found that the reasoning process showed a tendency to belief bias: there were significant differences between congruent tasks and incongruent tasks ( $p < 0.05$ ). Reasoning tasks with logically invalid and believable conclusions have lower accuracy rates, longer reaction time, and lower confidence ratings, especially when there are tasks with logically indeterminate and believable conclusions. Another finding is that the main effect of validity is significant ( $p < 0.01$ ), which is reflected in the lower reasoning accuracy rate, longer reaction time, and lower confidence rating of logically invalid tasks, especially in logically indeterminate tasks. In addition, through the calculation of the size of conflict detection, it can be concluded that most of the participants (66.67%) with belief bias can successfully detect conflicts, and the results basically support the conflict inhibition failure theory. Experiment 2 is 3 (validity: logically valid / logically inconsistent / logically indeterminate)  $\times$  2 (believability: believable / unbelievable)  $\times$  2 (time

pressure: limit/no limit) three-factor mixed experimental design, experiment three is 3 (validity: logically valid / logically inconsistent / logically indeterminate)  $\times$  2 (believability: believable / unbelievable)  $\times$  2 (cognitive load: high load/low load) three-factor mixed experimental design. Formal experiments 2 and 3 add eye tracking technology on the basis of experiment 1 to continue to explore the belief bias effect of syllogistic reasoning tasks. The results of experiment 2 showed that there was a belief bias effect in the reasoning process, and the reasoning performance of congruent tasks and incongruent tasks were significantly different ( $p < 0.05$ ), and congruent tasks were significantly better than incongruent tasks. Compared with the no limit condition, the reasoning accuracy rate was lower, the reaction time was longer, and the confidence rating was lower under the time limit condition, but it didn't not change the conflict detection mode under no time pressure, and the time pressure excluded analytical processing to a certain extent, proving that the conflict comes from the existence of logical intuition and intuition, and the difference between ICB and IDB task performance under the conflict detection paradigm further supported the logical intuition model. In the conflict task, the greater the total fixation time, the larger the Ht value, indicating that the reasoning process consumes more resources and the more frequent the eye movement switching, indicating that there was a difference between the ID task and the IC task and the former was more difficult, which is in line with the theory of mental model theory. The fixation time and Hs values of different regions of interest (ROI) indicated that the participants paid more attention to the ROI1 where the two premises were located, indicating that the participants paid more attention to the logical relationship between the arguments, while the influence of beliefs was small, which could also reflect that the participants strictly followed the requirements of the instructions and the material settings were more reasonable, and the meaningless middle terms had less impact on reasoning. At the same time, the difference in fixation time between the two regions of interest under the ICB and IDB tasks was greater, indicating that the participants found the conflict more obviously, and then spent more resources on the premise. Although the resources were spent a lot, the behavioral results showed that the accuracy rate of IDB was much lower than that of ICB, indicating that although the participant found the conflict but failed to inhibit it, it also supported the conflict inhibition failure theory. The results of experiment 3 showed that the main effect of validity was significant ( $p < 0.01$ ), and compared with V and IC tasks, the reasoning accuracy rate of ID tasks was lower, the confidence rating was lower, and there was no difference in reaction time, which verified the different reasoning performance and mechanism of IC tasks and ID tasks. Under the same kind of tasks, the participants' fixation time in ROI1 was longer than that of ROI2 ( $p < 0.001$ ), and the Hs value in ROI1 was less than that of ROI2 ( $p < 0.001$ ), indicating that the participant paid more attention to logic than belief. The trend of the results of experiment 3 was the same as that of experiment 2, which was basically in line with expectations. However, the belief bias effect was not reflected, and the main effect of cognitive load was not significant ( $p > 0.05$ ), which was speculated to be due to the different resources occupied by secondary tasks and reasoning tasks, or due to insufficient cognitive load intensity. Finally, through the above experiments, the following main conclusions are drawn: (1) Based on experiment 1 and Weenig (2002), the calculation method shows that the reaction time under time pressure should be 7.5s; (2) There is a belief bias effect

in syllogistic reasoning; (3) The main effect of validity is significant, and the reasoning performance and mechanism of IC tasks and ID tasks are different; (4) Through the gaze time and entropy value of eye movement, it is found that the participants pay more attention to the logical relationship between the premise propositions and the conclusion proposition in the process of completing the task, and the believability of the conclusion has less impact on the subject's judgment; (5) The conflict inhibition failure theory supporting the belief bias effect is found; (6) the comparative study of the ICB tasks and the IDB tasks supports the logical intuitive model. In this study, the use of behavioral and eye movement experiments basically supports the logical intuition model and the view of conflict inhibition failure, which has an important impact on the interpretation of belief bias effect and the updation and improvement of the doubleprocessing theory.

**Keywords:**

Logical Intuition Model, Belief Bias, Time Pressure, Cognitive Load

# ***International Workshop on the Intersection of Artificial Intelligence and Human Intelligence***

**S02201** Generalized Cross-Domain Brain Segmentation via Domain Randomization

# Generalized Cross-Domain Brain Segmentation via Domain Randomization

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## Abstract:

**Background:** Brain image segmentation has been studied widely, where recent years have witnessed great success of convolutional neural networks (CNNs), particularly the U-Net and its variants. However, these CNN-based methods generally suffer from the performance degeneration on cross-domain data collected from different healthcare centres. **Purpose:** To prevent the performance degeneration, we propose to reform the existing brain-segmentation CNNs via domain randomization to improve their generalization ability across multiple-centre data. **Materials:** The initial-visit T1-weighted MRI scans of a total of 3464 subjects from ADNI cohorts were included in this perspective study. These scans were acquired from 67 sites. All these scans were preprocessed by the widely-used FreeSurfer software via the command “recon-all”. The major steps include internal resampling, bias correction, intensity normalization, skull stripping, brain parcellation, etc. These skull-stripped brain scans were used as the inputs and their corresponding brain-parcellation maps are used as the ground truth. **Methods:** Two algorithms, the 3D UNet and 3D ResUNet were used as our baselines and we enhance them by integrating a domain randomization strategy on the features after the first and second layers to learn the domain-invariant representations explicitly. Under this strategy, an unprecedented search space is constructed to strength the model’s generalization by randomly sampling the statistics of intermediate features from a uniform distribution, and the feature styles are perturbed by randomly mixing the augmented and original statistics along the channel wise. The performance of these two algorithms and their enhanced versions was evaluated quantitatively using the Dice coefficients and qualitatively by 3D visualization of the brain surfaces. **Results:** These 3464 subjects were divided into three folds according to different sites, and these algorithms are trained on the data from a select fold and tested on the data from the rest two folds. The overall Dice coefficients of these four methods {UNet, ResUNet, UNet-w, ResUNet-w} are {76.51, 79.42, 77.93, 83.92}, which demonstrate that the proposed domain randomization strategy efficiently improved the generalization of existing segmentation methods. When delving into the brain regions, it can be seen that some regions (e.g., bankssts, pericalcarine) not segmented well by the baseline methods are obviously improved by our domain randomization strategy. We further visualize the surface of an example of the segmentation results and find that the better segmentation results can also lead to better surface visualization. **Conclusion:** The generalization ability of CNN-based methods for brain image segmentation can be improved by our proposed domain randomization strategy, which may lead to a superior tool for generalized cross-domain brain-image segmentation.

**Keywords:**

Brain Segmentation, Medical Image Analysis, Domain Generalization

# ***Special Session on Recent Advances in Artificial Intelligence for Brain Research***

**S11201** Computational Modeling of Brain Functional Dynamics



# Computational Modeling of Brain Functional Dynamics

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## **Abstract:**

Understanding brain functional dynamics, and how they are affected in neurological disorders, is one of the key problems in neuroscience today. This talk will describe advances in theoretical and biophysically grounded tools to understand the functional activity of the entire brain. Specifically, it will demonstrate a graph-based mathematical model that captures the spectral and spatial features of the brain's functional activity. This modeling approach revealed biophysical alterations in Alzheimer's disease, different stages of sleep, and spontaneous fluctuations in electrophysiological functional activity. Together, these results aim to highlight the importance of such modeling techniques in identifying the underlying biophysical mechanisms of neuronal dynamics, which can be intractable to infer using neuroimaging data alone.

## **Keywords:**

Magnetoencephalography, Spectral Graph Theory, Mathematical Modeling, Brain Activity