Discovering Injury-Specific Brain States After Traumatic Brain Injury Through Deep Learning Network Analysis

AZAD AZARGUSHASB[1], Samuel Vander Dussen[2], Afshin Paydar[2,3], Neil G. Harris[2,3]

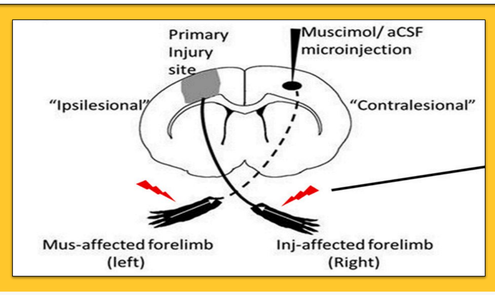
[1] Departmental Scholar, Computational and Systems Biology B.S. and Bioinformatics M.S., UCLA [2] UCLA Brain Injury Research Center, Department of Neurosurgery, David Geffen School of Medicine, UCLA [3] Intellectual Development and Disabilities Research Center, UCLA

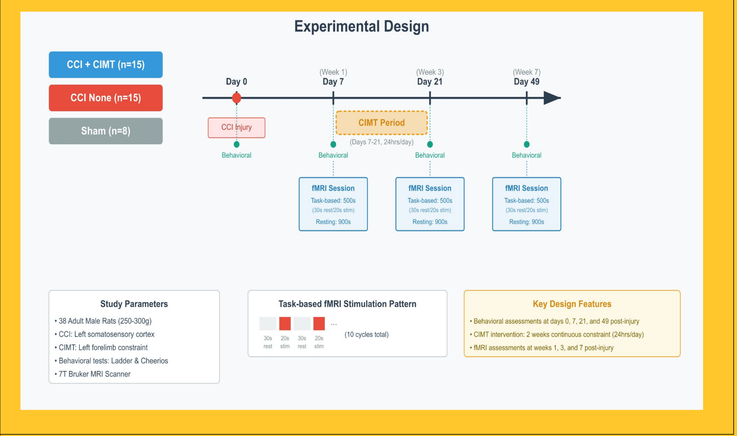
ABSTRACT

Functional brain networks reorganize dynamically following traumatic brain injury (TBI), but understanding how, why and when post-injury they occur remains to be determined. We hypothesized that TBI induces distinct, measurable brain states that differentially evolve during recovery. One of the main issues is how to characterize these network-level changes since there is no agreed upon methodology. We applied Gaussian Mixture Variational Autoencoder (GMVAE) to forelimb-evoked and resting state functional magnetic resonance imaging (fMRI) data from rats with controlled cortical impact injury, comparing the effects of constraint-induced movement therapy (CIMT) to untreated and sham- injured rats across three post-injury timepoints (7, 21, 49 days). GMVAE identified 9 distinct brain states from forelimb-evoked fMRI data. State 6 emerged exclusively within injured animals and was absent in all sham animals, representing an injury-specific network configuration. State distributions shifted temporally. Graph theory analysis revealed state-specific network topologies through modularity and clustering metrics. These brain states could provide biomarkers for tracking TBI progression and evaluating therapeutic interventions.

BACKGROUND

- **Functional connectivity** (FC) in the brain, which refers to the synchronization of activity between different brain regions, undergoes region-specific changes following a traumatic brain injury (TBI) induced in experimental settings.
- Dynamic Functional Connectivity Analysis, which captures the temporal evolution of functional connectivity patterns from brain imaging data, is increasingly being used by many laboratories to gain a more comprehensive understanding of the complex neurological processes following traumatic brain injury and to identify potential biomarkers for diagnosis, prognosis, and targeted interventions.
- **Brain states**, which are defined as distinct patterns of brain activity that exhibit consistent functional connectivity profiles, have been identified using dynamic functional connectivity analysis.





METHODOLOGY

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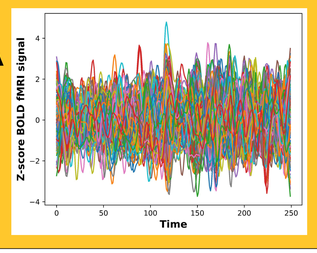

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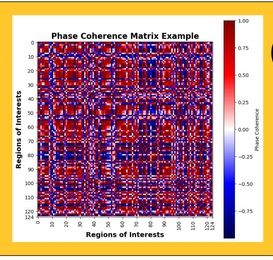

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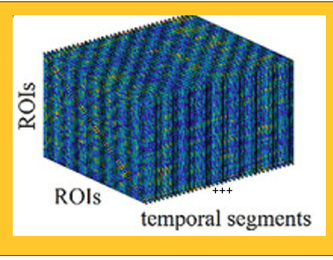

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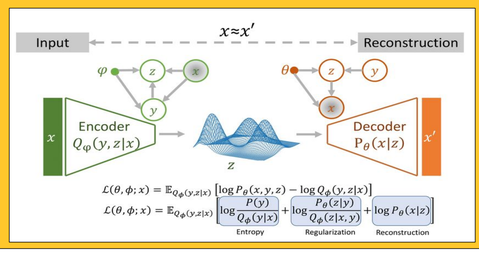

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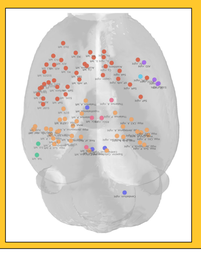
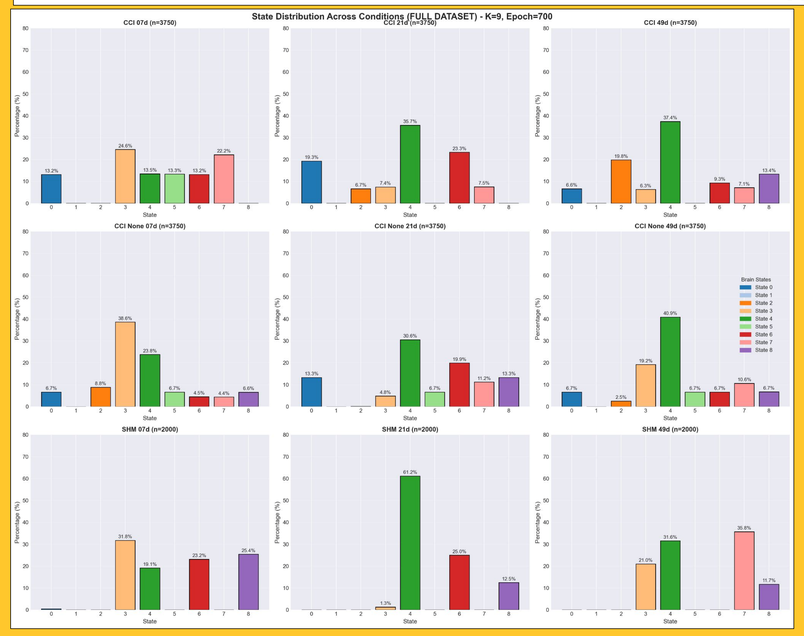


A. BOLD Signal Acquisition Functional MRI data was collected from 114 subjects across two conditions: resting-state (450 scans) and task-based stimulation (250 scans). Each scan captures neural activity across 114 anatomically-defined regions of interest (ROIs). Time series were extracted for each ROI, representing fluctuations in blood oxygen level-dependent (BOLD) signals. **B. Phase Coherence Matrix Construction** The Hilbert transformation was applied to each BOLD time series to extract instantaneous phase information. Phase coherence was then calculated between all pairs of ROIs, measuring synchronization strength between brain regions. This results in a 114 × 114 symmetric matrix for each scan, with values ranging from -1 (anti-phase) to +1 (perfect synchrony). **C. 4D Tensor Organization** Individual phase coherence matrices were stacked across time and subjects to create comprehensive datasets. The resting-state data forms a 4D tensor with dimensions (114 subjects × 450 scans × 114 ROIs × 114 ROIs), while the stimulation data forms a 4D tensor with dimensions (114 subjects × 250 scans × 114 ROIs × 114 ROIs). This organization preserves both temporal dynamics and individual subject variability. **D. GMVAE Processing** The Gaussian Mixture Variational Autoencoder (GMVAE) performs simultaneous dimensionality reduction and clustering on the input tensors. The model learns compressed representations of brain connectivity patterns in a lower-dimensional latent space. The clustering component automatically identifies distinct brain states without prior labeling. **E. Brain State Extraction** The trained model generates cluster centroids representing prototypical brain states. The decoder network reconstructs full connectivity matrices from these latent representations. These extracted brain states enable downstream analyses including state occupancy, transition dynamics, and network modularity assessment.

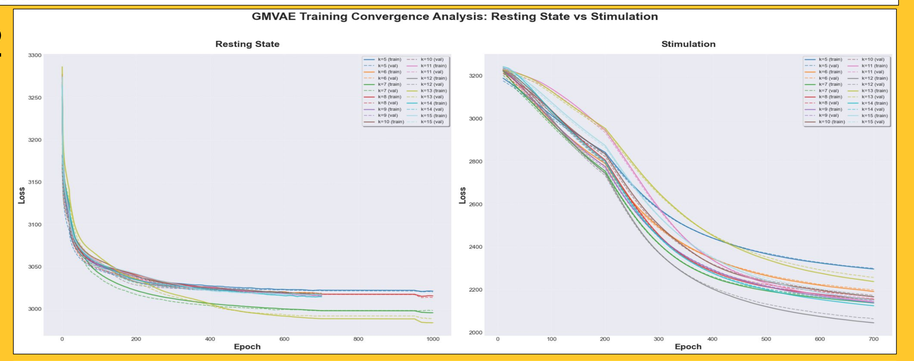
Results

1



In Figure 1, there are the k = 9 state distributions from the GMVAE model trained on stimulation data. There are a total of 3 groups, Sham, CCI + CIMT, and CCI None. State 5 is present for only CCI None and CCI CIMT during week 1 and then only present during week 3 and 7 for CCI None.

2



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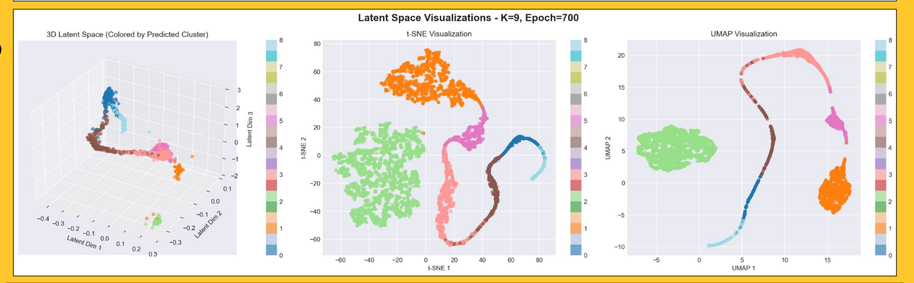

Figure 2 shows GMVAE training convergence for k=5-15 brain states. Resting state data (left) trained for up to 1000 epochs; stimulation data (right) for 700 epochs. Smooth loss curves indicate successful learning across different k values.

Figure 3 visualizes the learned latent space for k=9 at epoch 700 (resting state). The GMVAE maps brain connectivity patterns to 3D space (left), with 2D projections via t-SNE (center) and UMAP (right). Despite targeting k=9, the model identified 8 distinct brain states (shown by color clusters), suggesting this represents the natural organization of resting state brain networks in our data.

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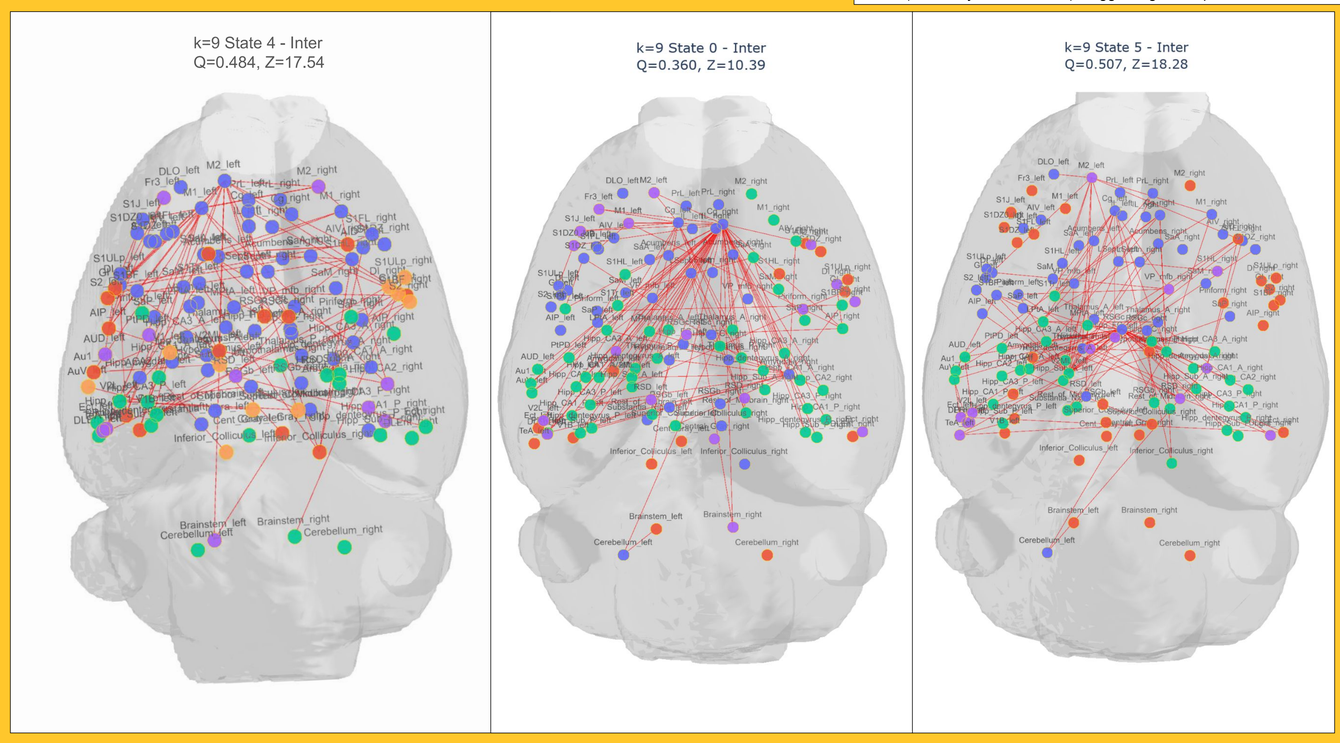

Figure 4 shows modular organization of rodent brain networks mapped onto anatomical brain space. Colored nodes represent brain regions grouped into functional modules (communities) that are more densely connected internally than between modules.

- **Module Detection:** Consensus clustering via netneurotools (10000 iterations of Louvain algorithm) to identify stable modules
- **Orthogonal Minimal Spanning Tree** were used as a data driven way to threshold the brain states before assigning module assignments
- **Statistical Validation:** Z-scores calculated from 1000 permutation tests; Z>3 indicates significant modularity above chance
- **Q-values:** Modularity strength (0-1 scale); Q>0.3 indicates strong community structure
- **Inter** (left): Shows only connections between different modules
- **Nodes Only** (center): Module membership without connections displayed
- **All** (right): Complete network with both within- and between-module connections

Red edges indicate network connections. Each color represents a distinct functional module. Results shown for k=9 clustering states with varying modularity strengths (Q=0.484-0.507, all highly significant with Z>17).

Discussion/Future Works

- GMVAE of phase coherence networks from stimulation fMRI is able to classify distinct brain states associated with persistent injury (brain state 0), recoverable injury (brain state 2), and a global network (brain state 5).
- Previous work has shown that CIMT improves the somatosensory behavior occupation of the injured subjects. GMVAE has identify a brain state (brain state 2) that leaves following treatment, thus showing how treatment effects the brain.
- GMVAE model benefits from having an interpretable latent space with clear separation that can effectively perform dimensionality reduction and clustering
- Future work entails using functional Ultrasound Imaging (fUSI) data, as fMRI functional connectivity studies requires sedation of the rodent before scanning and fUSI data can be acquired without sedation.
- While the Rodents are awake, they are able to be placed under different cognitive loads and we plan on exploring whether we can connect brain states to cognitive inflexibility or learning deficits.

Acknowledgements