What New Insights Artificial Intelligence Can Tell Us About How PTSD Lives in the Brain

February 22, 2023

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In Cognitive and Behavioral Modeling

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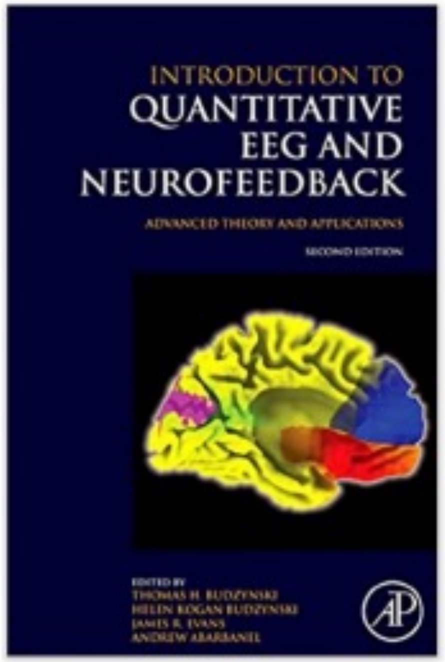
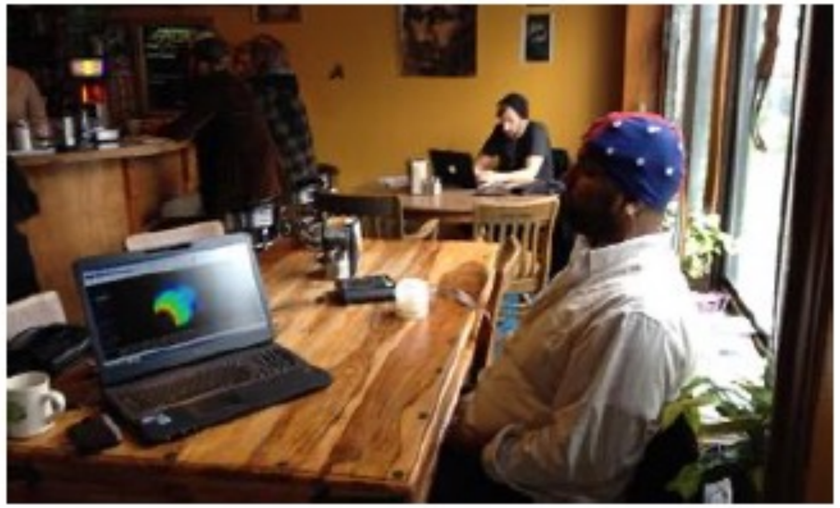
My Background

- PhD in Computational Neuroscience
  - Medical School / Supercomputing Institute
  - Machine learning on electrophysiological data
  - Postdoc Caltech
  - UW Comp Science Professor
  - PNNL Multiscale Mathematics
- Brain-focused detour
  - Saw a book on QEEG
  - Bought gear and practiced in coffee shops
  - MHC coursework for DOH requirements
  - Co-founder, Brain Health Northwest
    - ✓ Neurofeedback, Clinical neuroscience/psychology
  - Consultant/Principal Northwest Neuro Pro





Outline of Today's Talk

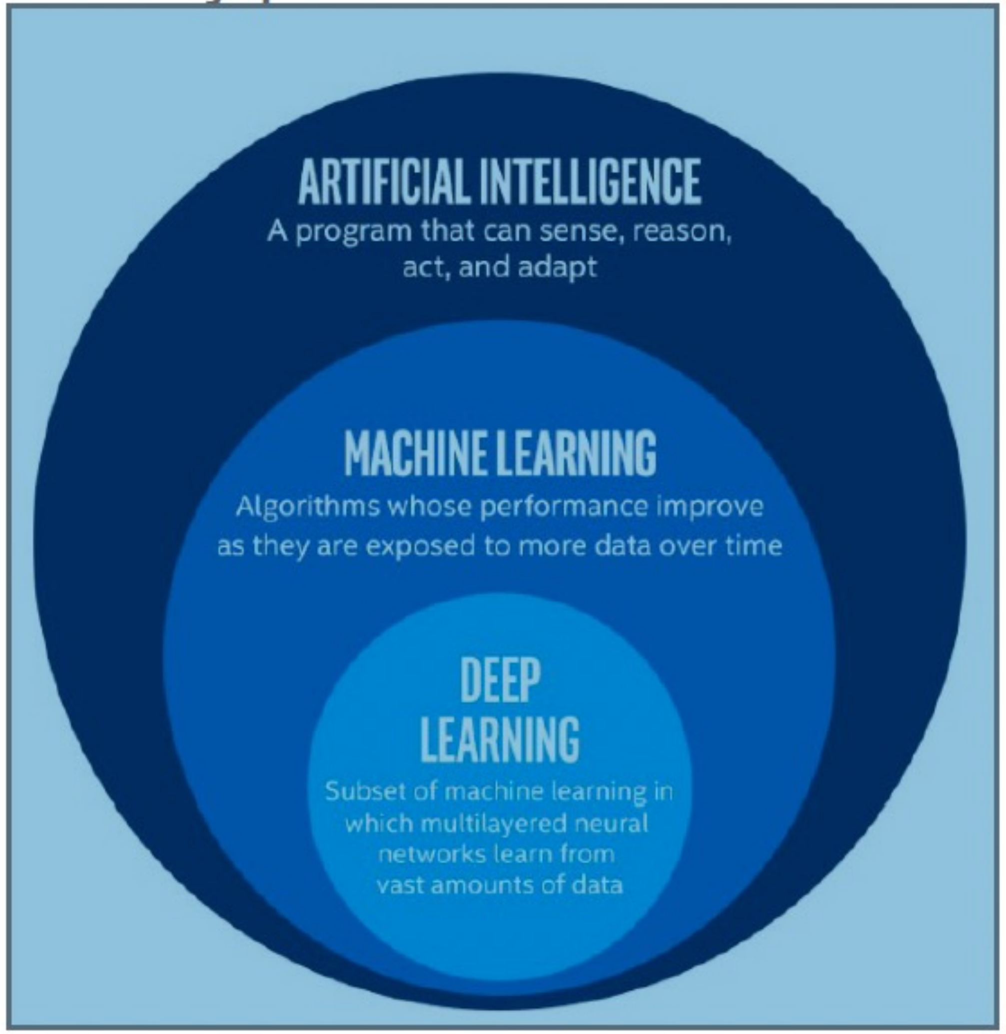
- What is Machine Learning (Artificial Intelligence)?
- The Origins of Machine Learning as Brain-inspired Algorithms
- Relationship Between Statistics and Machine Learning
- How Machine Learning is Used to Classify and Predict EEG Data
- Biggest Take Homes Machine Learning Research in PTSD for Brain Data
- Consumer Targeted Tools to Improve Dx and Tx in PTSD

What is Machine Learning (Artificial Intelligence)?

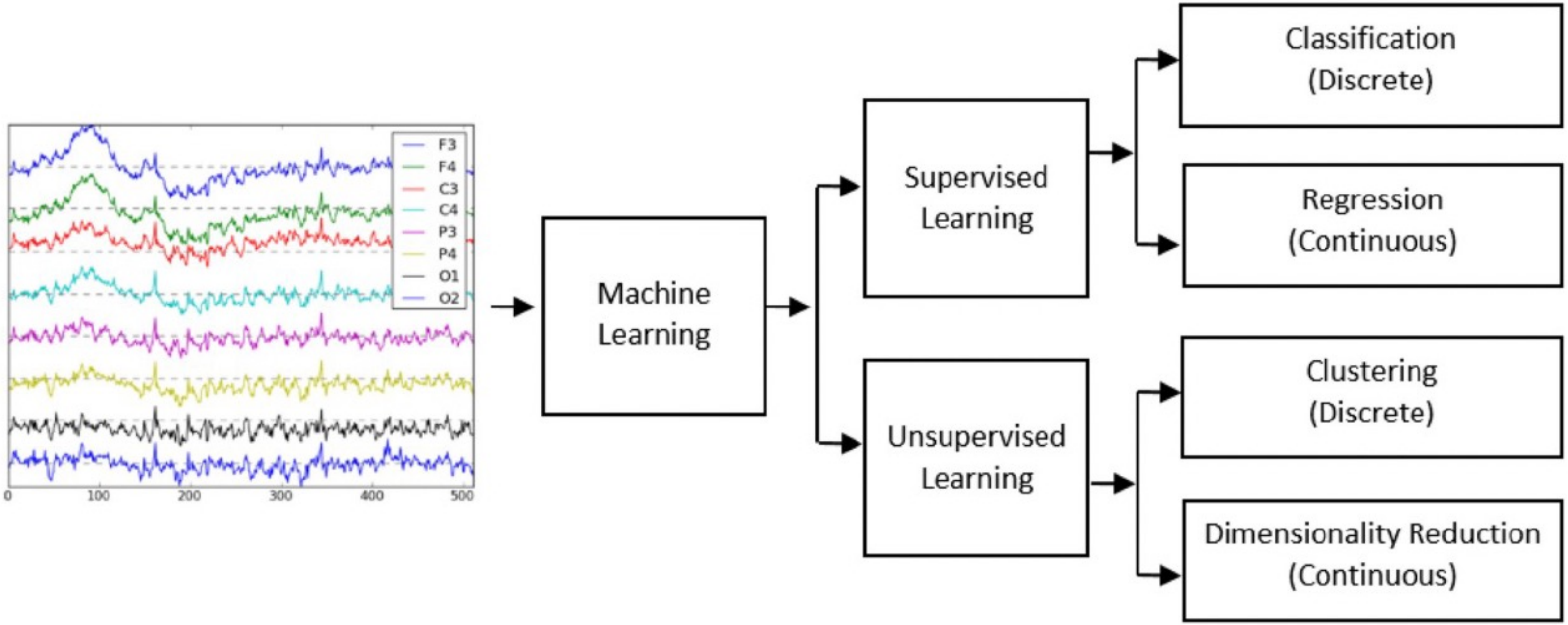
Machine learning is a set of methods that give computers the ability to learn to recognize and classify patterns, without being explicitly being programmed to do so. The more data they process, the better they perform.

A subset of machine learning known as deep learning methods (neural networks) are inspired by a very simplistic notion of brain function.

- Voice recognition (Siri, Alexa)
- Image and facial recognition
- Personalized marketing
- Financial services
- Autonomous vehicles
- Gaming
- Healthcare



What is Machine Learning (Artificial Intelligence)?



What is Machine Learning (Artificial Intelligence)?

Generative AI

ChatGPT Demo

https://chat.openai.com/chat

Transformer technology – it learns to predict the next word in the sentence, based on the context of previous words

10 years to train (355 years on a single computer)

300 billion tokens (words and positions)

174,600 internal parameters

It can generate text on topics, it has never been explicitly trained on (zero-shot learning)

Stable Diffusion (Art from Words)

https://huggingface.co/spaces/stabilityai/stable-diffusion

MakeAVideo (Video from Words)

MusicML (Music from Words)

The Origins of Machine Learning as Brain-inspired Algorithms

- McCulloch and Pitts, 1943

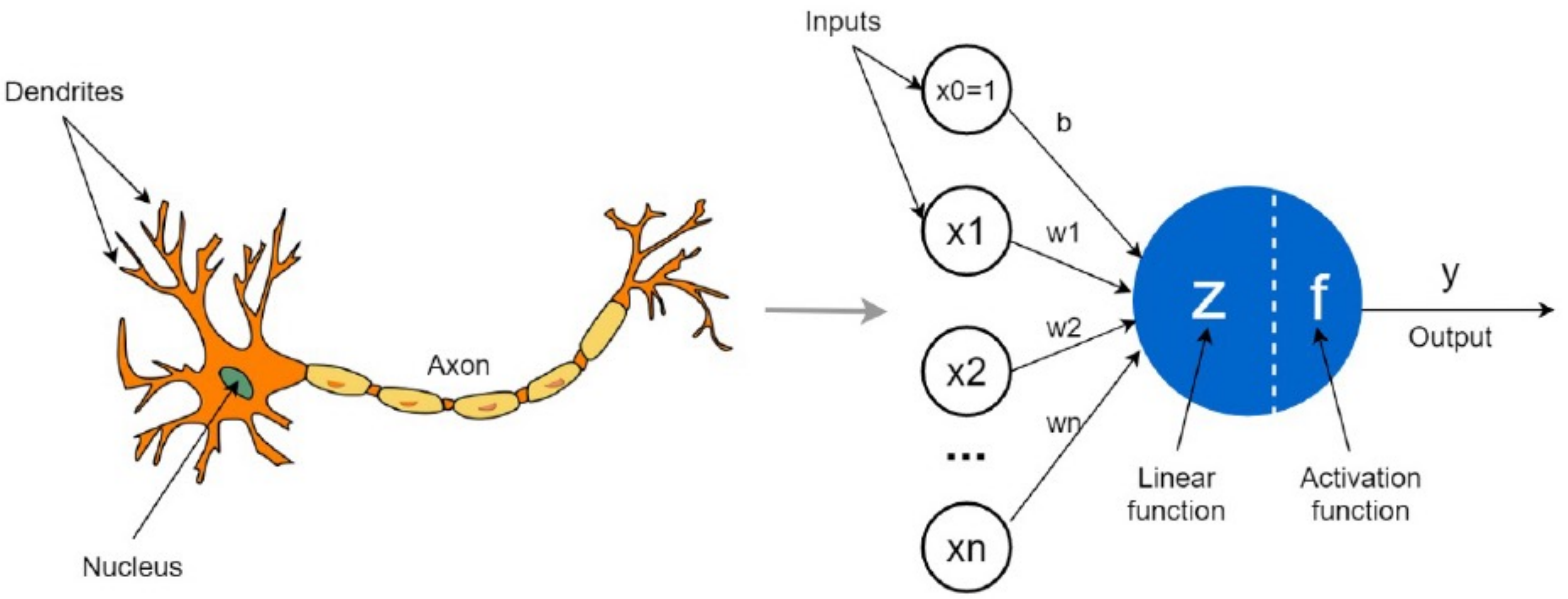
  Theoretical – the kinds of computations that were possible

- Rosenblatt, 1958 - The Perceptron

  Machine implementation

- Rumelhart and McClelland, 1986

  Research into ”connectionism” - resurgence of interest w computer access

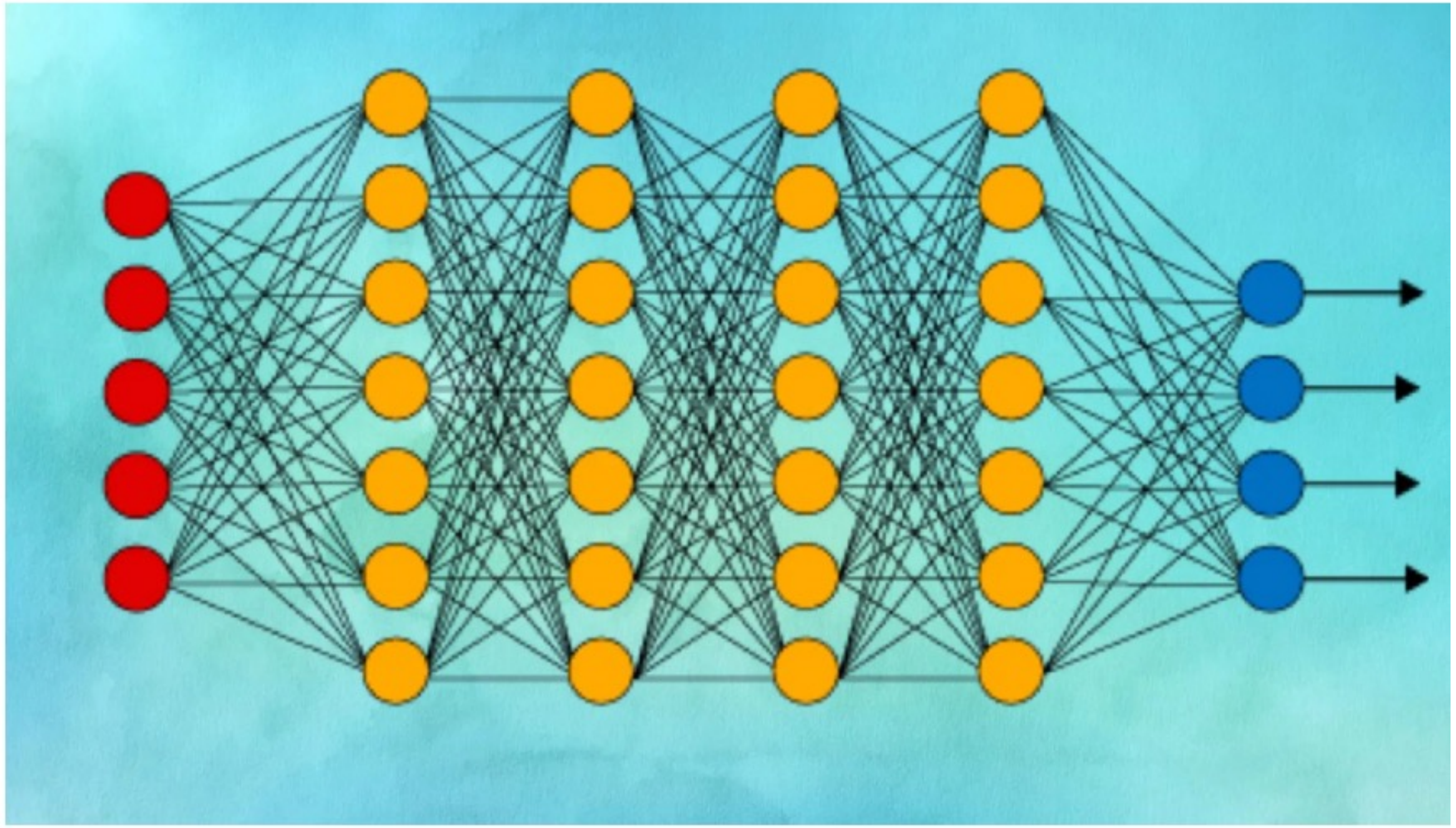


The Origins of Machine Learning as Brain-inspired Algorithms

Neural units
Layers/architecture
    input layer – size of feature space
    output layer - categories
Weighted connections
Summation function
Activation function

Loss function
Retrograde function to change the weights

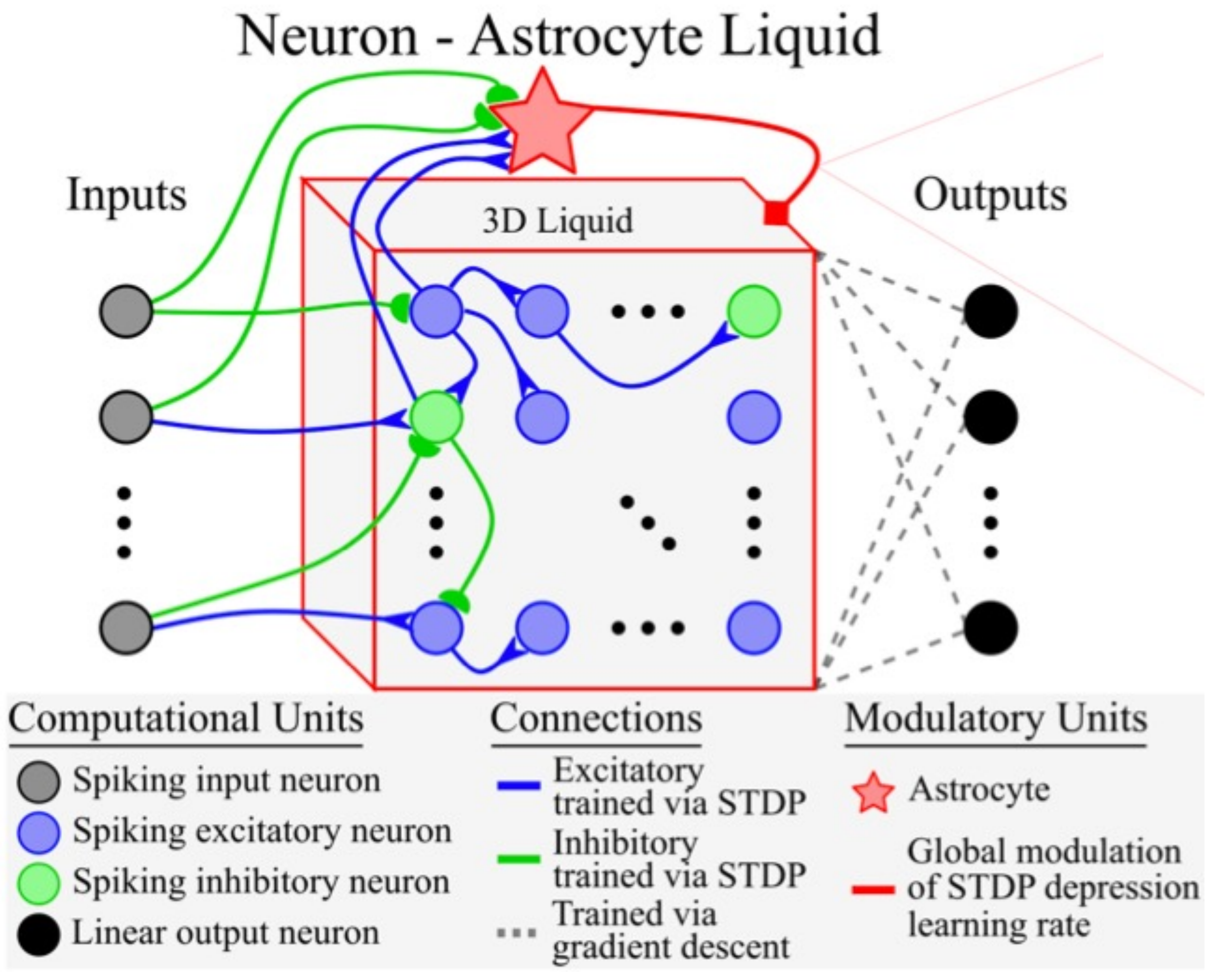
Learning rate



The Origins of Machine Learning as Brain-inspired Algorithms

Deep Connectome

- Evolution and Functional connectivity-based approaches
- Liquid State Machines
- Neuromorphic Computing



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Kinds of ML Algorithms

- Logistical Regression
- Linear Regression
- Nonlinear Regression
- Support Vector Machines
- K-Nearest Neighbors
- K-Contractive Maps
- Artificial Neural Networks
- Convolutional Neural Networks
- Recurrent Neural Networks
- Deep Learning Networks
- Decision Trees
- Random Forests
- Principle Component Analysis
- Independent Component Analysis
- Linear Discriminant Analysis
- Fuzzy Logic
- Ensemble Learning
- Reinforcement Learning
- Genetic/Evolutionary Algorithms
- Naïve Bayes

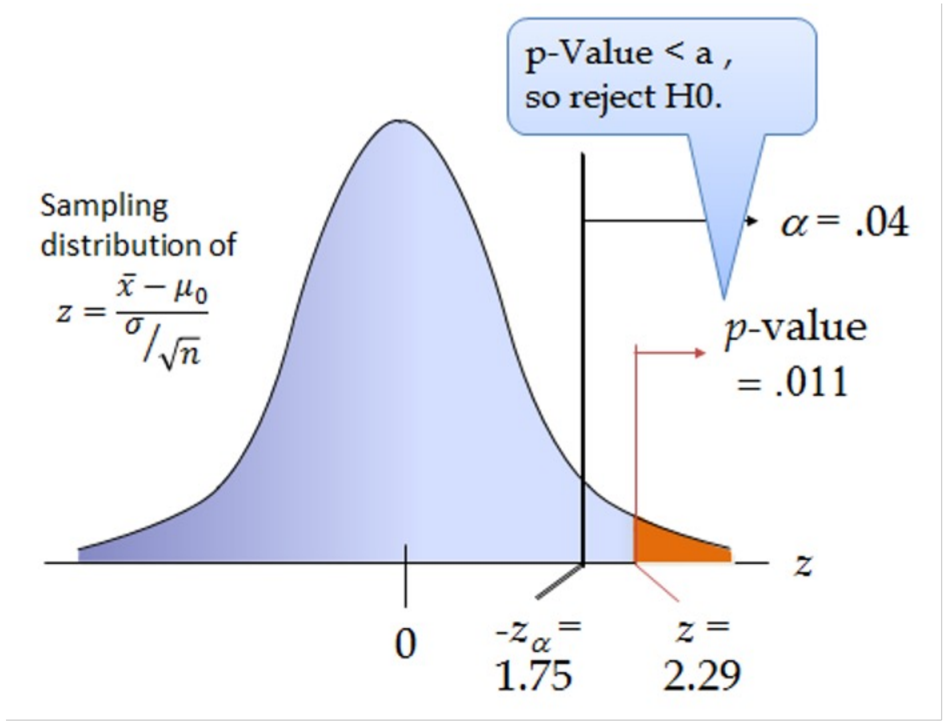
Differences Between Statistics and Machine Learning

Statistics: Hypothesis-Driven

Hypothesis: Individuals who receive cognitive-behavioral therapy (CBT) for post-traumatic stress disorder (PTSD) will experience a greater reduction in PTSD symptoms compared to individuals who receive standard supportive counseling.

The study would involve randomly assigning individuals with PTSD to either the CBT or supportive counseling group and measuring the change in PTSD symptoms over time using a validated measure.

While more data strengthens the conclusions, one only needs two data points to calculate a mean and a standard deviation.



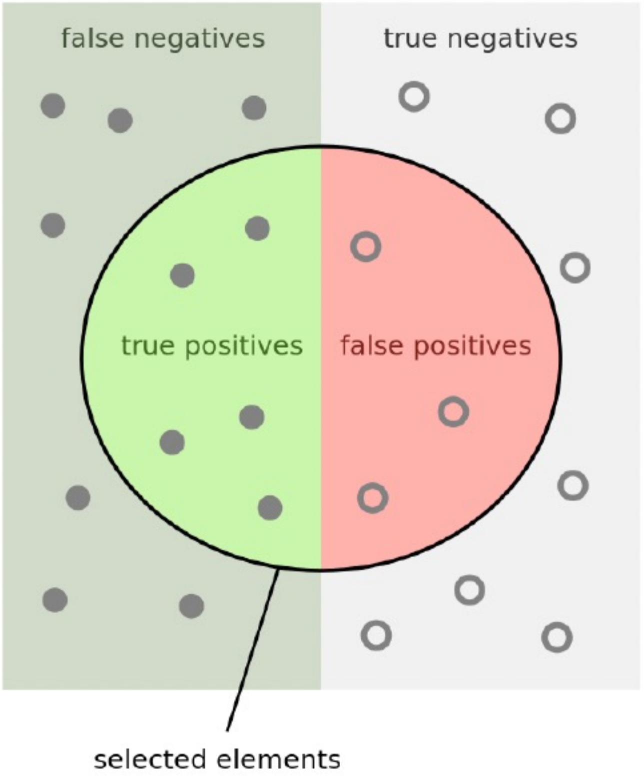
Differences Between Statistics and Machine Learning

Machine Learning: Data-Driven Classification

The study would involve associating each individual with features and outcomes.

The features might include demographics, co-morbidities, number of counseling sessions, and the outcomes might be change in PTSD symptoms over time using a validated measure, or perhaps whether they still qualify for the diagnosis.

We divide the individuals into a training set and a testing set. The network is trained using the training set, then we measure how well the machine classifies using the testing set.



Specificity $= \frac{(True\ Negative)}{(True\ Negative + False\ Positive)}$

Recall [aka **Sensitivity**] $= \frac{(True\ Positive)}{(True\ Positive + False\ Negative)}$

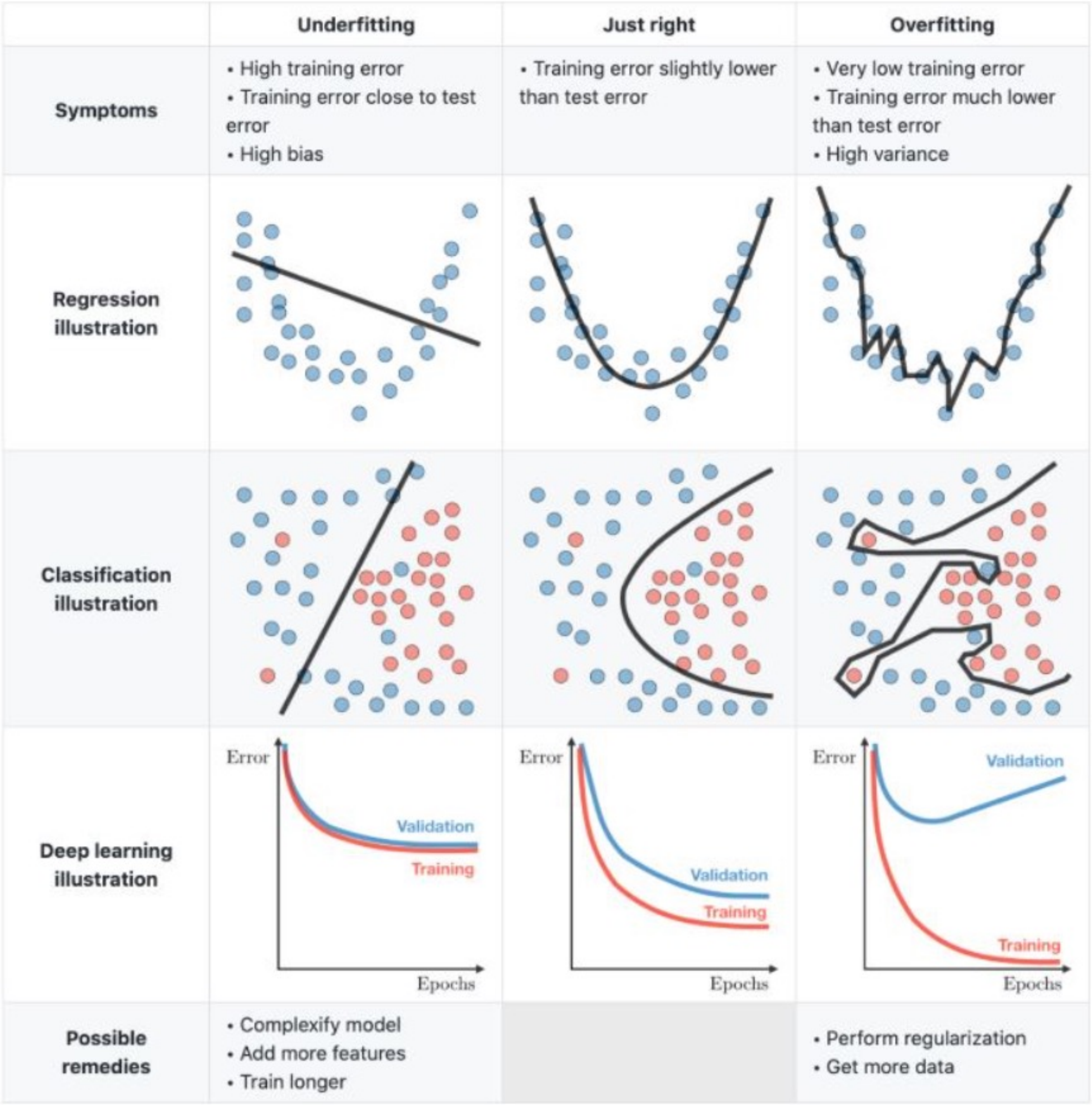
Differences Between Statistics and Machine Learning

Is there a big difference between the training error and the validation/testing error?

The model has not seen enough examples to generalize.

Are both the training error and the validation/testing errors high?

This feature space doesn't provide enough distinction to predict.



	Underfitting	Just right	Overfitting
Symptoms	• High training error • Training error close to test error • High bias	• Training error slightly lower than test error	• Very low training error • Training error much lower than test error • High variance
Regression illustration			
Classification illustration			
Deep learning illustration	Error / Validation / Training / Epochs	Error / Validation / Training / Epochs	Error / Validation / Training / Epochs
Possible remedies	• Complexify model • Add more features • Train longer		• Perform regularization • Get more data

Differences Between Statistics and Machine Learning

Statistics is hypothesis testing based on applied probability theory. We are testing whether something is likely true.

Machine Learning is based on engineering and needs lots of data to learn relationships. We assume that a relationship exists, rather than testing that one does; and we want to create a model that will classify features into outcomes with a high accuracy.

The strongest studies have an element of both.

How Machine Learning is Used to Classify and Predict EEG Data

- Abnormal Waveform Classification
- Epilepsy Classification/Seizure Probability
- Artifact Identification and Removal
- Visual Attention
- Motion Discrimination
- Emotional state classification
- Fatigue Detection
- EEG-based biometrics for authentication
- Classification of clinical conditions
    - ADHD, Autism, MS, Dementia, Alcohol Use Disorder, Depression, Schizophrenia
- Meditation States
- Cognitive Load
- Sleep Scoring
- BCI decoding

3200 entries in PubMed

*** No one has (so far) used ML to classify phenotypes!**

How Machine Learning is Used to Classify and Predict EEG Data

Original Investigation | Psychiatry

January 3, 2020

Use of Machine Learning for Predicting Escitalopram Treatment Outcome From Electroencephalography Recordings in Adult Patients With Depression

Andrey Zhdanov, PhD[1,2]; Sravya Atluri, PhD[3,4]; Willy Wong, PhD[5]; et al

Author Affiliations | Article Information

JAMA Netw Open. 2020;3(1):e1918377. doi:10.1001/jamanetworkopen.2019.18377

IPEG International Pharmaco-EEG Society

ELSEVIER

Clinical Neurophysiology

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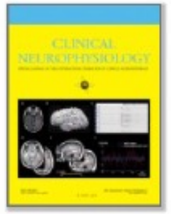


Machine learning for predicting levetiracetam treatment response in temporal lobe epilepsy

Pierpaolo Croce [a, 1], Lorenzo Ricci [b, 1], Patrizia Pulitano [c], Marilisa Boscarino [b], Filippo Zappasodi [a, d], Jacopo Lanzone [e, f], Flavia Narducci [b], Oriano Mecarelli [c], Vincenzo Di Lazzaro [b], Mario Tombini [b], Giovanni Assenza [b]

How Machine Learning is Used to Classify and Predict EEG Data

The Challenge is Feature Space Selection!

EEG Signal Acquisition → Preprocessing → Feature Extraction → Feature Selection → ML Training → ML Testing

*** ***

Raw data –

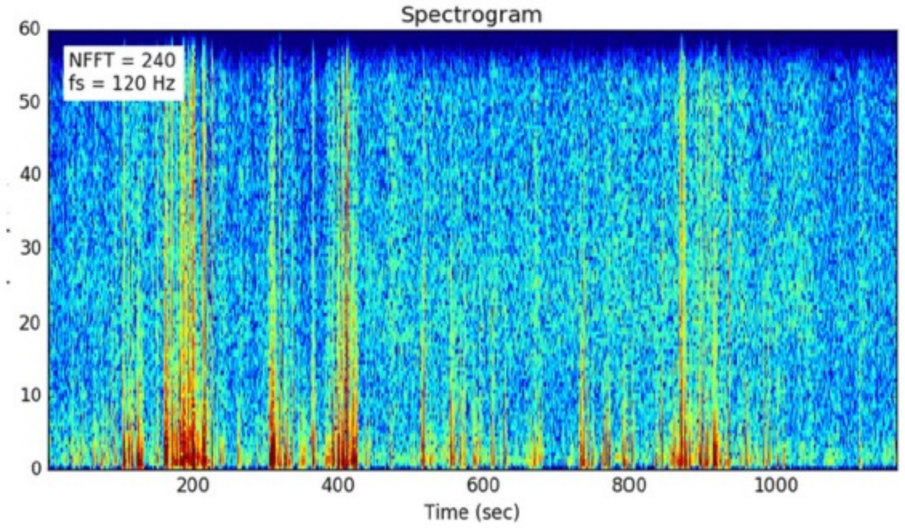
Are you teaching your algorithm to identify waveforms?
Or perhaps focal patterns that would otherwise be averaged out in an FFT?
(20 minutes at 200 sps = 240,000)

Power Spectra –

Is compressing down to 40 bins at 19 locations enough information?
(760 dimensions)

Spectrogram -

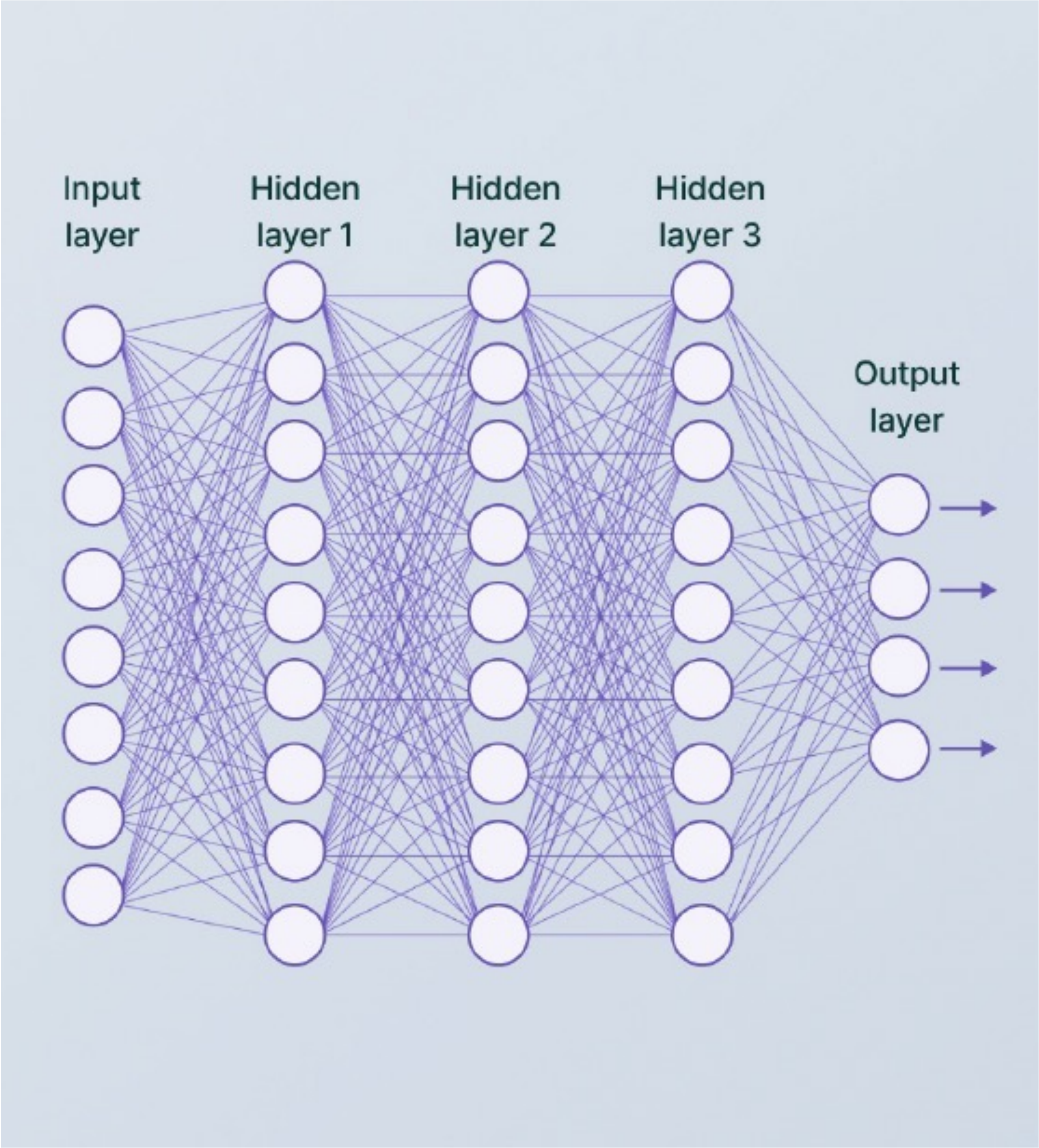
Do you expect your FFT to change over time?
(1200 seconds times 240 bins = 288,000)



How Machine Learning is Used to Classify and Predict EEG Data

Input layer should be features that classify the outputs.

Generally, we want this layer to be a reasonable size (< 1000) both for the time it takes to train a large network and for our ability to understand the importance of features.



The output layer is the diagnosis or the sleep stage or whether a spike occurred or the treatment outcome

Summarize Machine Learning Research in PTSD for Brain Data

There have only been 195 publications applying ML to EEG or MRI to date for PTSD.

Only three EEG models and four MRI models performed better than ~80%. This is not a criticism of the ML approach, but it speaks to the difficulty in identifying a predictive feature space.

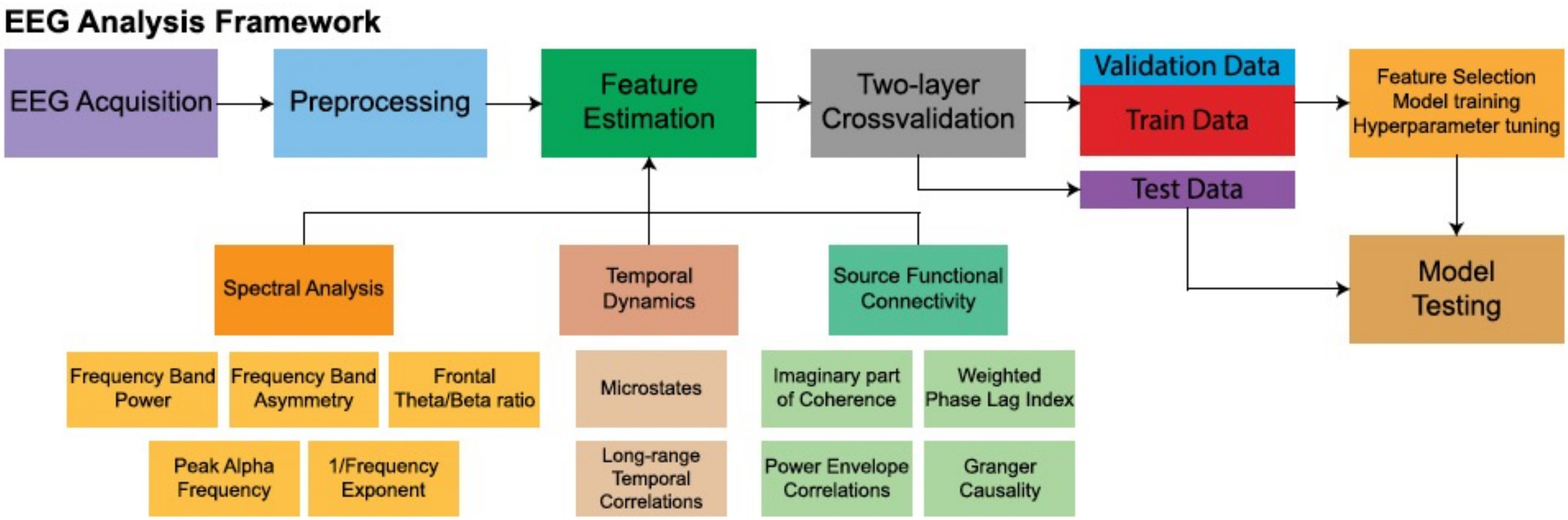
What can we know from those seven studies?

Summarize Machine Learning Research in PTSD for Brain Data

Li, Q., Theodorsen, M. C., Konvalinka, I., Eskelund, K., Karstoft, K. I., Andersen, S. B., & Andersen, T. S. (2022). Resting-state EEG functional connectivity predicts post-traumatic stress disorder subtypes in veterans. Journal of neural engineering, 19(6), 066005.

They developed a machine learning framework to investigate a wide range of commonly used EEG biomarkers.

They also explored a large number of models such as logistic regression, random forest, and support vector machines to classify PTSD.



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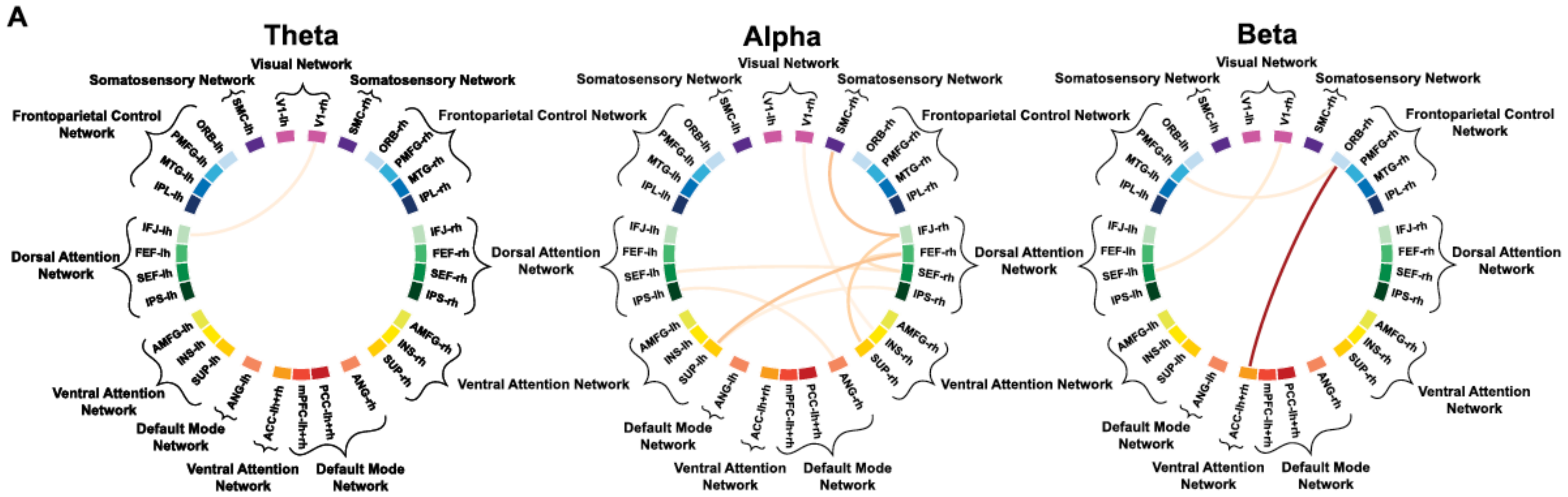
Their classifier obtained an accuracy of 79.4% when classifying PTSD from controls.

Alpha connectivity in the dorsal and ventral attention network was particularly important for the prediction, and these connections were positively correlated with arousal symptom scores, a central symptom cluster of PTSD.



Take Home: Alpha functional connectivity measures are more predictive than most other measures, including power spectra

Summarize Machine Learning Research in PTSD for Brain Data

Tahmasian, M., Jamalabadi, H., Abedini, M., Ghadami, M. R., Sepehry, A. A., Knight, D. C., & Khazaie, H. (2017). Differentiation chronic post traumatic stress disorder patients from healthy subjects using objective and subjective sleep-related parameters. Neuroscience letters, 650, 174-179.

- Subjective (i.e. from three self-reported **sleep questionnaires**) and objective sleep-related data (i.e. from **actigraphy** scores) were collected from each participant. Subjective, objective, and combined (subjective and objective) sleep data were then analyzed using support vector machine classification.
- The classification accuracy, sensitivity, and specificity for **subjective** variables were 89.2%, 89.3%, and 89%, respectively.
- The classification accuracy, sensitivity, and specificity for **objective** variables were 65%, 62.3%, and 67.8%, respectively.
- The classification accuracy, sensitivity, and specificity for the **aggregate** variables (combination of subjective and objective variables) were 91.6%, 93.0%, and 90.3%, respectively.
- Our findings indicate that classification accuracy using subjective measurements is superior to objective measurements and **the combination of both assessments appears to improve the classification accuracy for differentiating PTSD patients from healthy individuals**.

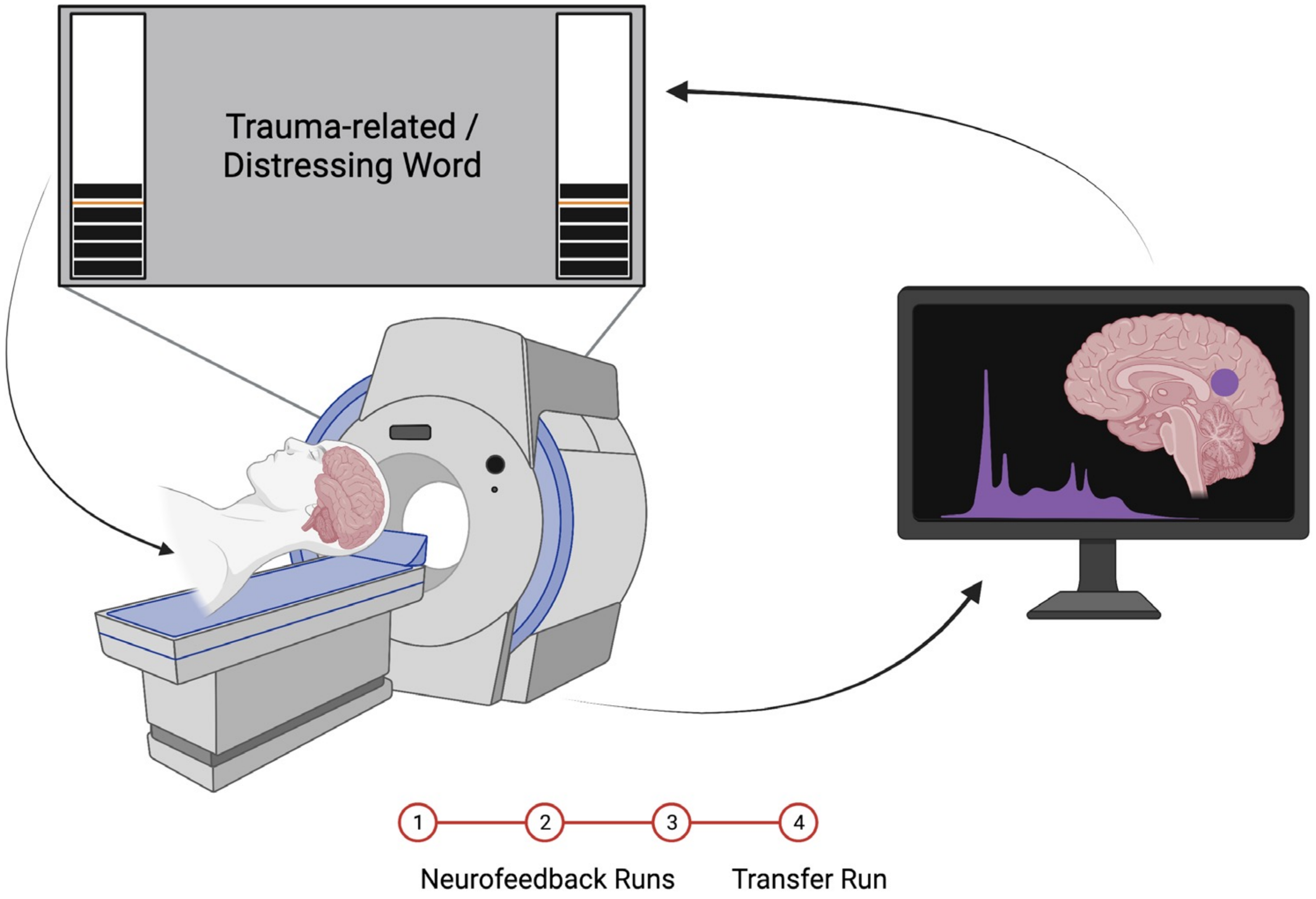
Take Home: Ask your clients about their sleep!

Summarize Machine Learning Research in PTSD for Brain Data

Nicholson, A. A., Rabellino, D., Densmore, M., Frewen, P. A., Steyrl, D., Scharnowski, F., ... & Lanius, R. A. (2022). Differential mechanisms of posterior cingulate cortex downregulation and symptom decreases in posttraumatic stress disorder and healthy individuals using real-time fMRI neurofeedback. *Brain and Behavior*, *12*(1), e2441.

This is the first study to investigate **PCC downregulation with real-time fMRI NFB** in both PTSD and healthy controls.

Our results reveal acute decreases in symptoms over training and provide converging evidence for EEG-NFB targeting brain networks linked to the PCC.



Schematic of the real-time fMRI neurofeedback set-up. Brain activity in the neurofeedback target region (posterior cingulate cortex) was processed in real-time and presented to participants in the fMRI scanner as thermometers that increased or decreased as activation fluctuated. Participants completed three neurofeedback training runs and a transfer run without neurofeedback signal.

Summarize Machine Learning Research in PTSD for Brain Data

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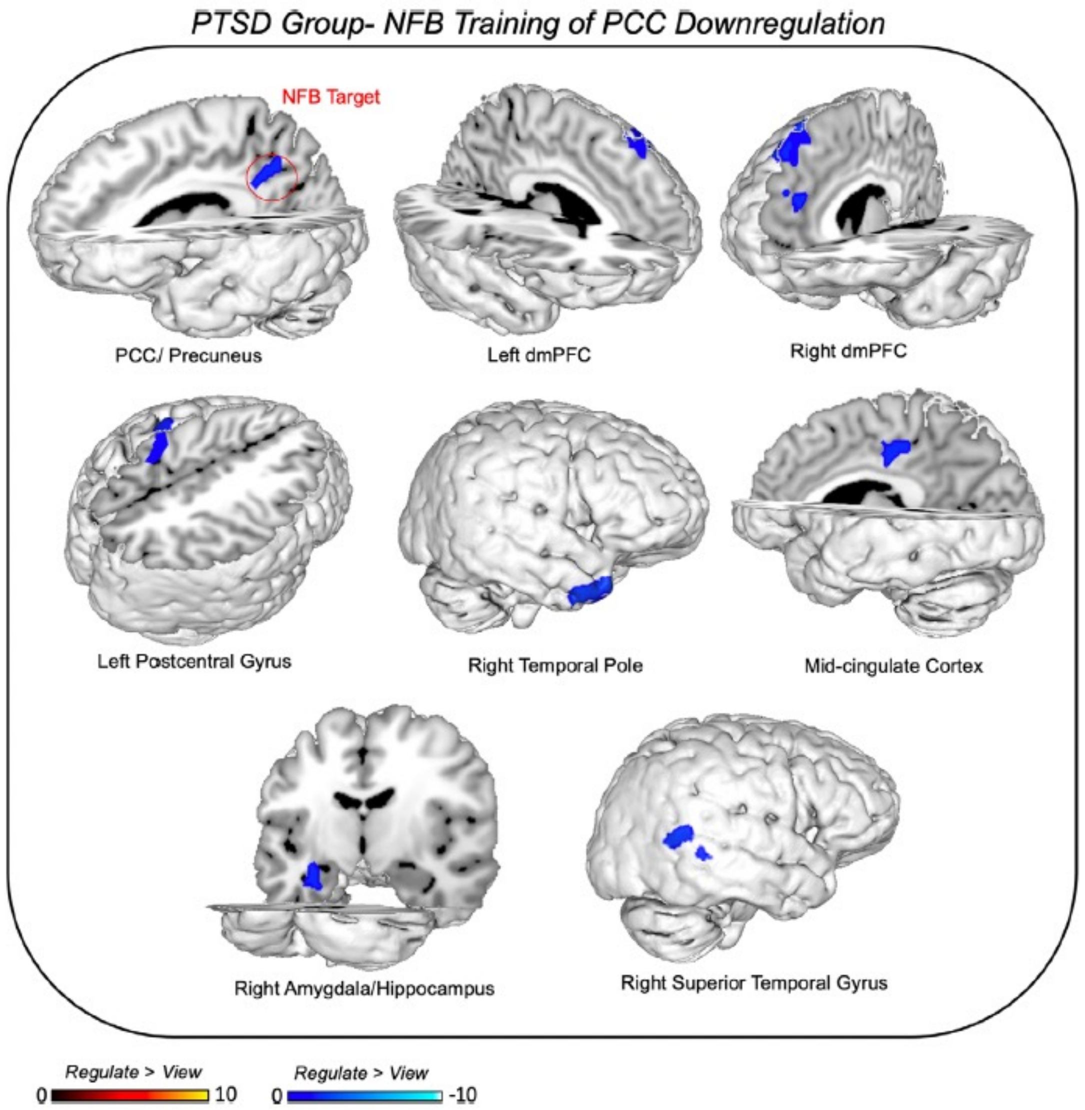
- Both the PTSD and healthy control groups demonstrated reduced reliving symptoms in response to trauma/stressful stimuli
- The PTSD group additionally showed reduced symptoms of distress.
- Both groups were able to downregulate the PCC with similar success over NFB training and in the transfer run
- Downregulation was associated with decreases in activation within the bilateral dmPFC, bilateral postcentral gyrus, right amygdala/hippocampus, cingulate cortex, and bilateral temporal pole/gyri.



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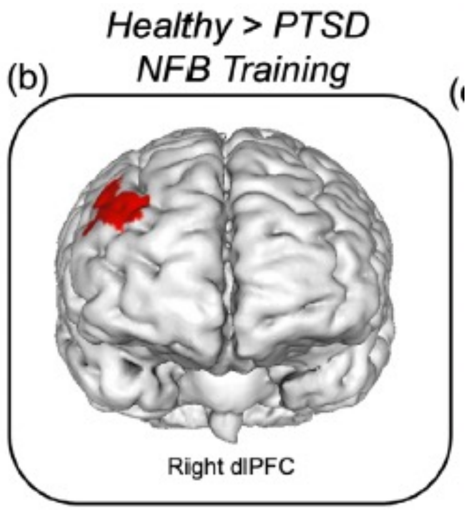
By contrast, **downregulation was associated with increased activation in the right dlPFC among healthy controls as compared to PTSD**.

During PCC downregulation, right dlPFC activation was negatively correlated to PTSD symptom severity scores and difficulties in emotion regulation.



Machine learning algorithms were able to classify PTSD versus healthy participants based on brain activation during NFB training with 80% accuracy.

Take Home: More evidence that Pz is an important training target for trauma. However, perhaps it should be trained concurrently with a right dlPFC activation protocol.

Summarize Machine Learning Research in PTSD for Brain Data

Rangaprakash, D., Dretsch, M. N., Venkataraman, A., Katz, J. S., Denney Jr, T. S., & Deshpande, G. (2018). Identifying disease foci from static and dynamic effective connectivity networks: illustration in soldiers with trauma. *Human brain mapping*, *39*(1), 264-287.

We identified three disrupted foci (middle frontal gyrus [MFG], insula, hippocampus), and an aberrant prefrontal-subcortical-parietal network of information flow.

We found the MFG to be the pivotal focus of network disruption, with aberrant effective connectivity to the insula, amygdala and hippocampus.

These connectivities also possessed high predictive ability (giving a classification accuracy of 81%); and they exhibited **significant associations with symptom severity** and neurocognitive functioning.

This mechanism likely contributes to the reduced control over traumatic memories leading to re-experiencing, hyperarousal and flashbacks observed in soldiers with PTSD and mTBI.

Path
L_MFG → L_Insula
L_Insula → L_Amygdala
L_Amyg → R_Hippocampus
L_MFG → L_OFC
L_OFC → L_Insula
L_MFG → R_Ant_Cingulate
R_Ant_Cingulate → L_Insula
R_Hippocampus → L_Insula
R_Hippocampus → L_Precuneus
R_Hippocampus → L_Striatum
L_MFG → R_TPJ
L_MFG → R_DLPFC

Summarize Machine Learning Research in PTSD for Brain Data

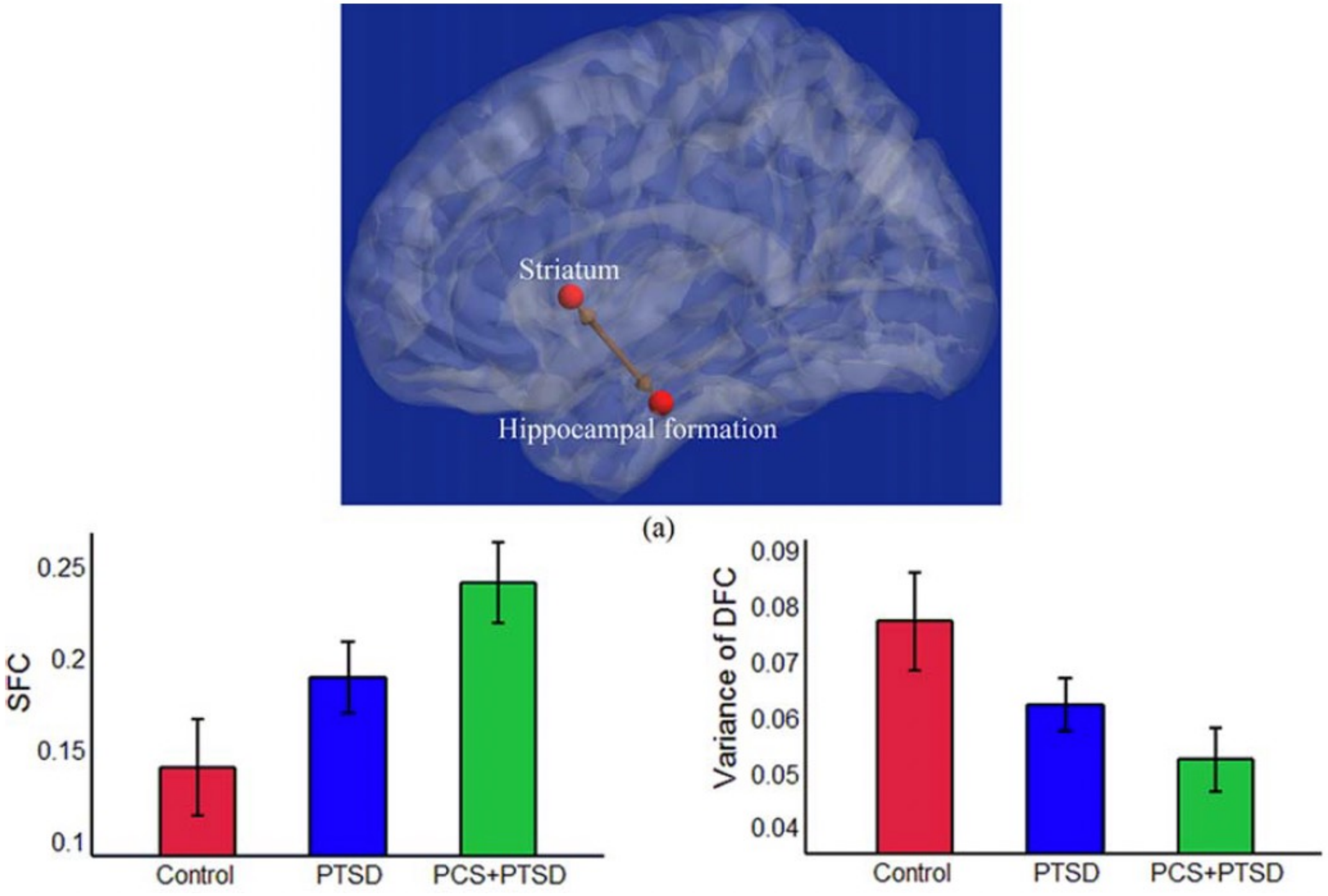
Rangaprakash, D., Deshpande, G., Daniel, T. A., Goodman, A. M., Robinson, J. L., Salibi, N., ... & Dretsch, M. N. (2017). Compromised hippocampus-striatum pathway as a potential imaging biomarker of mild-traumatic brain injury and posttraumatic stress disorder. *Human brain mapping*, *38*(6), 2843-2864.

[Same research group as the last paper, but asking about measures differentiating comorbid posttraumatic stress disorder (PTSD) and mild-traumatic brain injury (mTBI)]

PTSD/mTBI are associated with hippocampal-striatal hyperconnectivity from which it is difficult to disengage, leading to a habit-like response toward episodic traumatic memories, which fits well with behavioral manifestations of combat-related PTSD/mTBI.

Diffusion tractography revealed compromised white-matter integrity between the hippocampus and striatum regions only in the PCS + PTSD group, suggesting a structural etiology for the PCS + PTSD group rather than being an extreme subset of PTSD.

The hippocampus-striatum connectivities were found to be top predictors and thus a potential biomarker of PTSD/mTBI.



Summarize Machine Learning Research in PTSD for Brain Data

Harricharan, S., Nicholson, A. A., Thome, J., Densmore, M., McKinnon, M. C., Théberge, J., ... & Lanius, R. A. (2020). PTSD and its dissociative subtype through the lens of the insula: Anterior and posterior insula resting-state functional connectivity and its predictive validity using machine learning. *Psychophysiology*, *57*(1), e13472.

Individuals with post-traumatic stress disorder (PTSD) typically experience states of reliving and hypervigilance; however, the dissociative subtype of PTSD (PTSD+DS) presents with additional symptoms of depersonalization and derealization.

Moreover, machine learning analyses were able to classify PTSD, PTSD+DS, and controls using insula subregion connectivity patterns with 80.4% balanced accuracy ($p < .01$). These findings suggest a neurobiological distinction between PTSD and its dissociative subtype with regard to insula subregion functional connectivity patterns.

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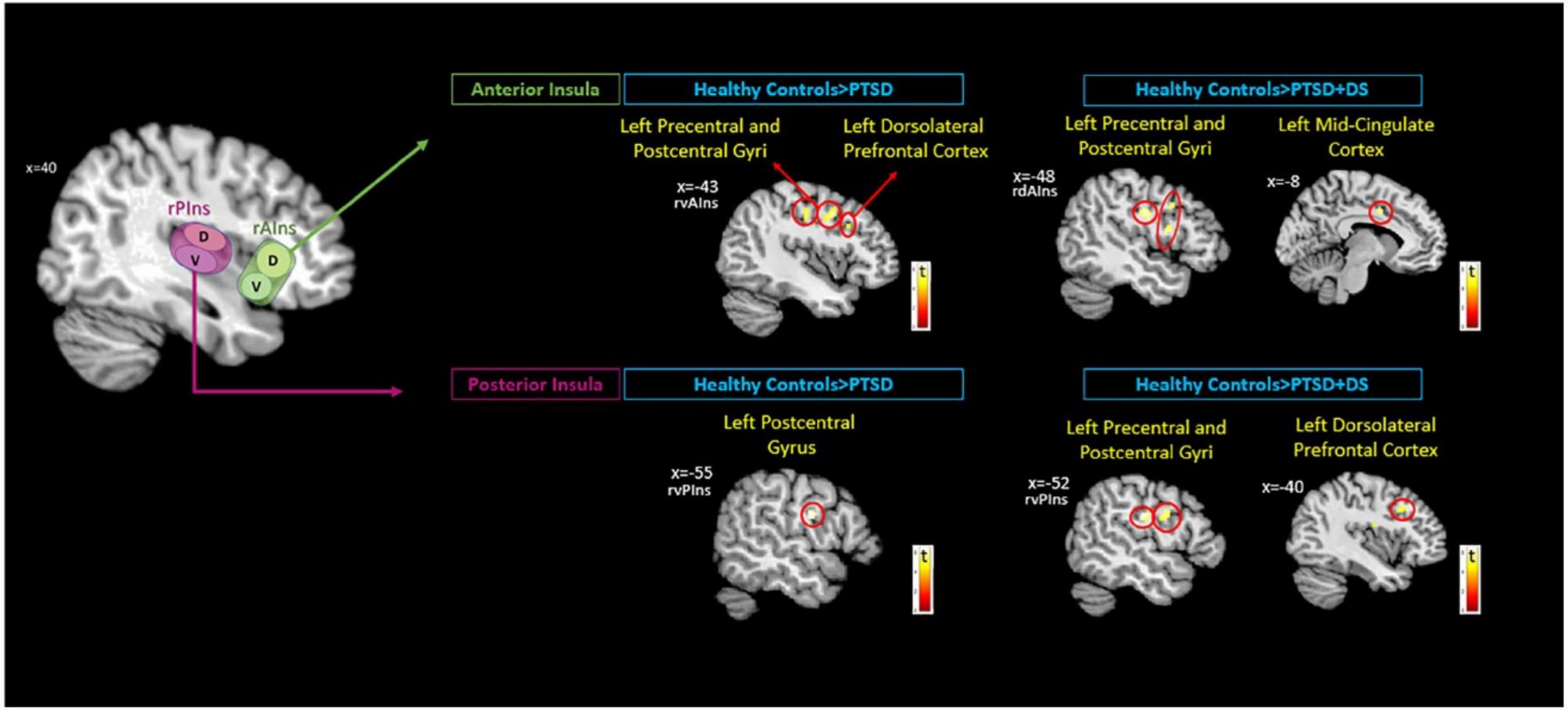
- As compared to PTSD and PTSD+DS, **healthy controls showed increased right anterior and posterior insula connectivity with frontal lobe structures**.



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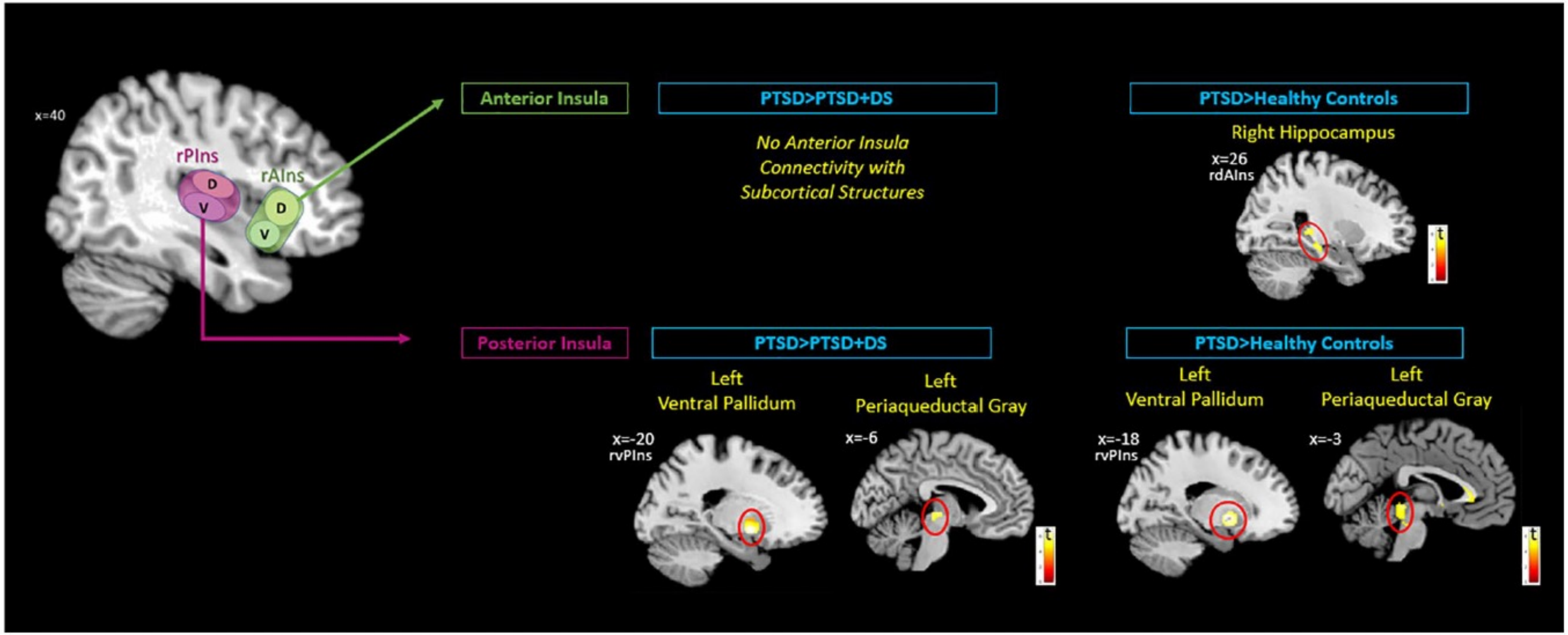
- By contrast, **PTSD showed increased bilateral posterior insula connectivity with subcortical structures**, including the periaqueductal gray.



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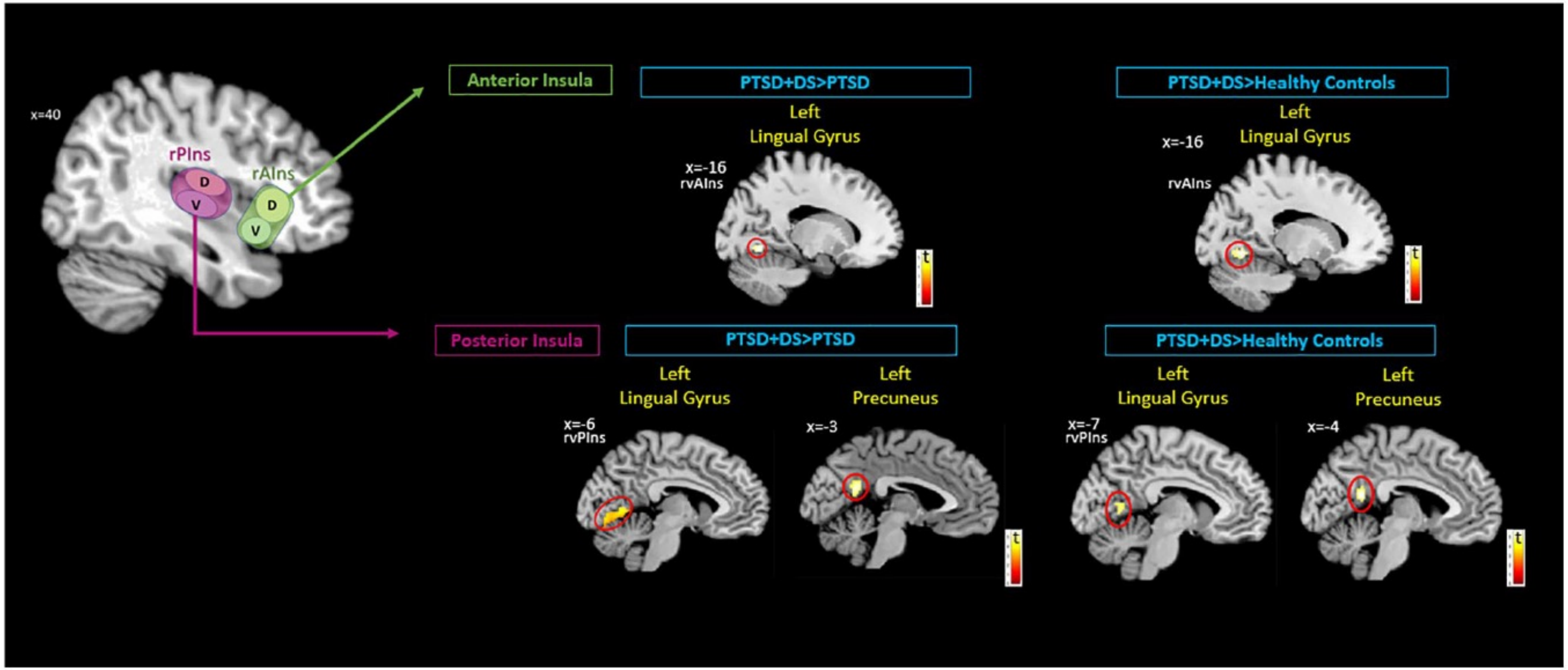
- Strikingly, as compared to PTSD and controls, **PTSD+DS showed increased bilateral anterior and posterior insula connectivity with posterior cortices, including the left lingual gyrus and the left precuneus.**



Summarize Machine Learning Research in PTSD for Brain Data

*** Saba, T., Rehman, A., Shahzad, M. N., Latif, R., Bahaj, S. A., & Alyami, J. (2022). Machine learning for post-traumatic stress disorder identification utilizing resting-state functional magnetic resonance imaging. *Microscopy Research and Technique*, *85*(6), 2083-2094.

The rs-fMRI data of 10 ROI was extracted from 14 approved PTSD subjects and 14 healthy controls. The rs-fMRI data of the selected ROI were used in ANOVA to measure performance level and Pearson's correlation to investigate the interregional functional connectivity in PTSD brains.

The **performance level in brain regions** of PTSD deviated as compared to the regions in the healthy brain. In addition, **significant positive or negative functional connectivity** was observed among ROI in PTSD brains.

The KNN and SVM with radial basis function kernel were outperformed for classification among other methods with high accuracies (96.6%, 94.8%, 98.5%) and (93.7%, 95.2%, 99.2%) to train, validate, and test datasets, respectively.

*** Highest performance, but not as specific as other findings – this is the only paper to which I didn't have access.

Summarize Machine Learning Research in PTSD for Brain Data

- Alpha band functional connectivity measures are more predictive than power spectra.
- Ask your clients about their sleep.
- More evidence that Pz is an important training target for trauma. However, perhaps it should be trained concurrently with a right dlPFC activation protocol.
- Disruptions between middle frontal gyrus, insula, amygdala, and hippocampal connectivity are highly predictive of PTSD.
- A static hippocampus-striatum hyperconnectivity distinguishes mTBI/PCS from PTSD only.
- A progressive posteriorizing of insula connectivity distinguishes normal from PTSD and from PTSD/DS.
- [Again, dysregulation of functional connectivity (high or low) is predictive.]

Machine Learning Tools to Improve Dx and Tx in PTSD

- Wearables
  - Accelerometer gesture detection in a population of veterans predicted impulse control issues
  - GPS predicts degree of avoidance behaviors – issues of ethics and compliance?
  - HRV… no surprise to anyone in this audience!
- Speech characteristics predict with 89% accuracy - but the paper is light on details re: specificity and sensitivity

Limitations

- Not enough well curated brain data for the same kind of tipping point as other machine learning applications.
- Too many papers where computer scientists are not working with clinicians. The data is poorly deartifacted and the feature space does not make sense. The point of their papers is the accuracy of the model, not the interpretability.

Thank you

dr.west@nwneuro.pro

Discord Server for further discussion:
https://discord.gg/u8f5bxVq8P