Medical/Bio Research Topics Ⅱ: Week 01 (05.09.2025)

Overview of Brain Imaging and Brain Imaging-based AI Models

뇌영상 및 뇌영상 기반 인공지능 모델 개요

Course Introduction

- Course: AI Convergence Medical/Bio Research Topics II
  - Introduction to:
    - Brain imaging as medical data
    - Brain imaging data processing methods for AI model development
  - Hands-on exercises in developing brain imaging-based AI models

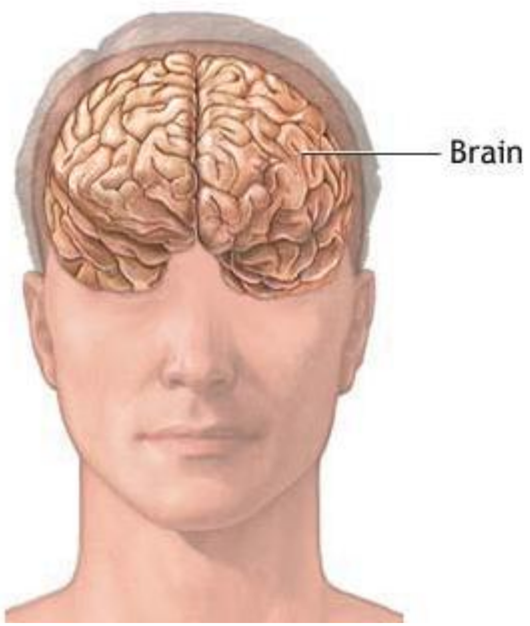
- Objectives
  - To understand the clinical utility of brain imaging
  - To gain knowledge/experience in brain imaging-based AI model development
- Format
  - Lecture: 60%
  - Presentation/Discussion: 40%

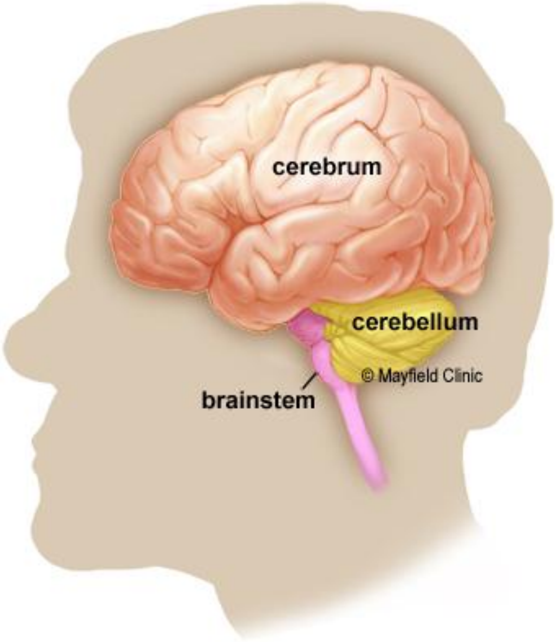
- Evaluation
  - Presentation: 90%
    - Brain imaging-based AI model development process and results
  - Participation: 10%
    - Attendance and tardiness

- Course schedule
  - [Week 1] Introduction
  - [Weeks 2-4] Brain imaging basics
    - Structural MRI
    - Functional MRI
    - Diffusion-weighted MRI
  - [Weeks 6-14] Hands-on AI model development
    - Segmentation: Lesion segmentation
    - Regression: Age prediction
    - Classification: Sex classification
  - [Week 15] Course summary

Brain

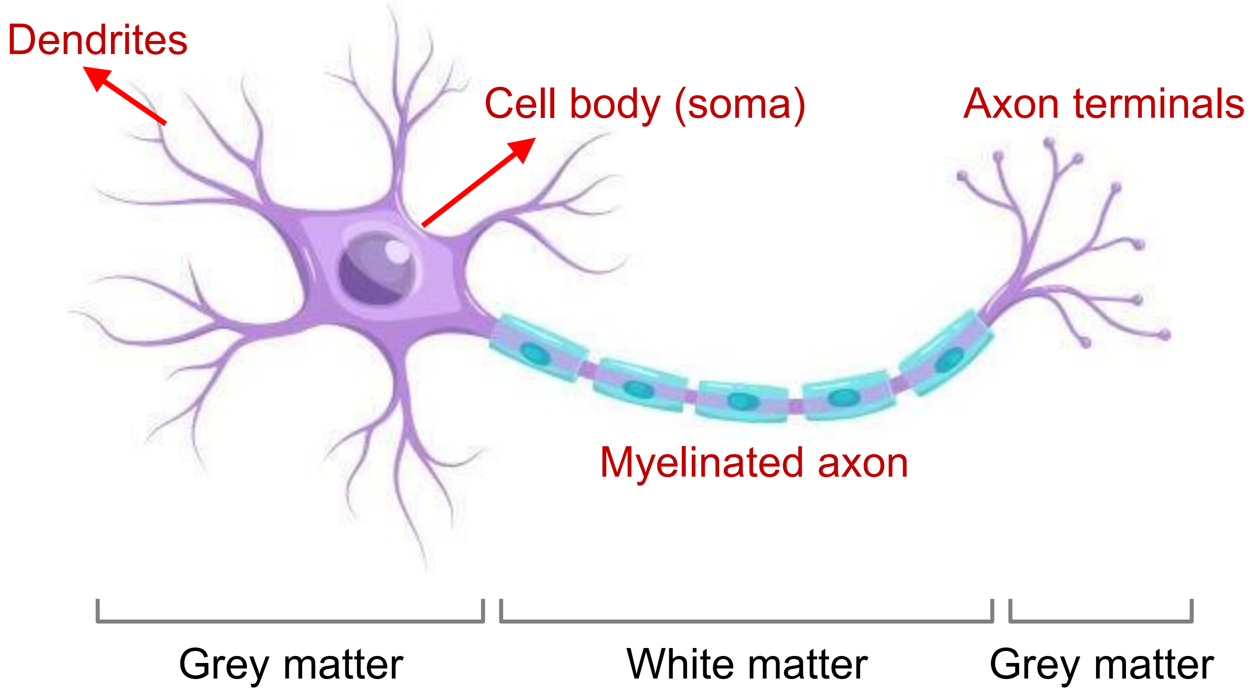
- Centre of the nervous system located in the head

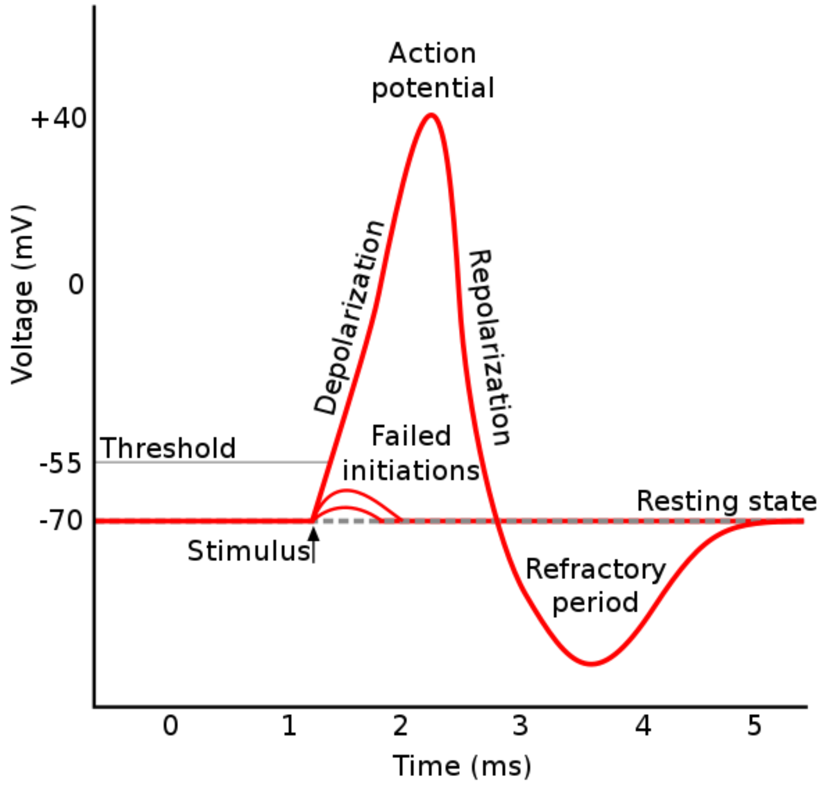




[https://medlineplus.gov/ency/imagepages/8738.htm;
https://mayfieldclinic.com/pe-anatbrain.htm]

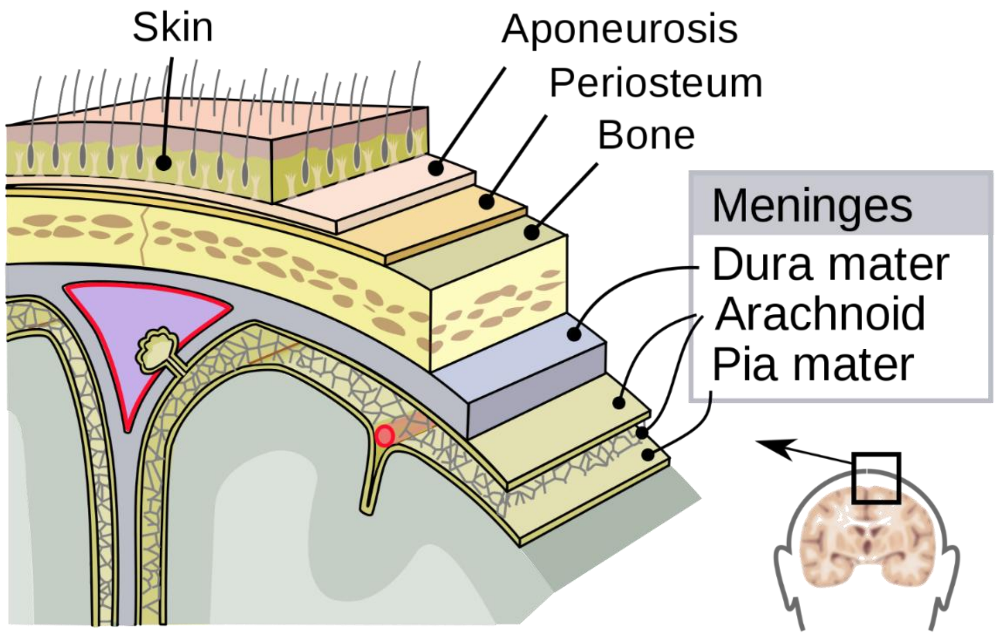
- Composed of tens of billions of neurons
  - Interconnected neurons communicate with each other by axons

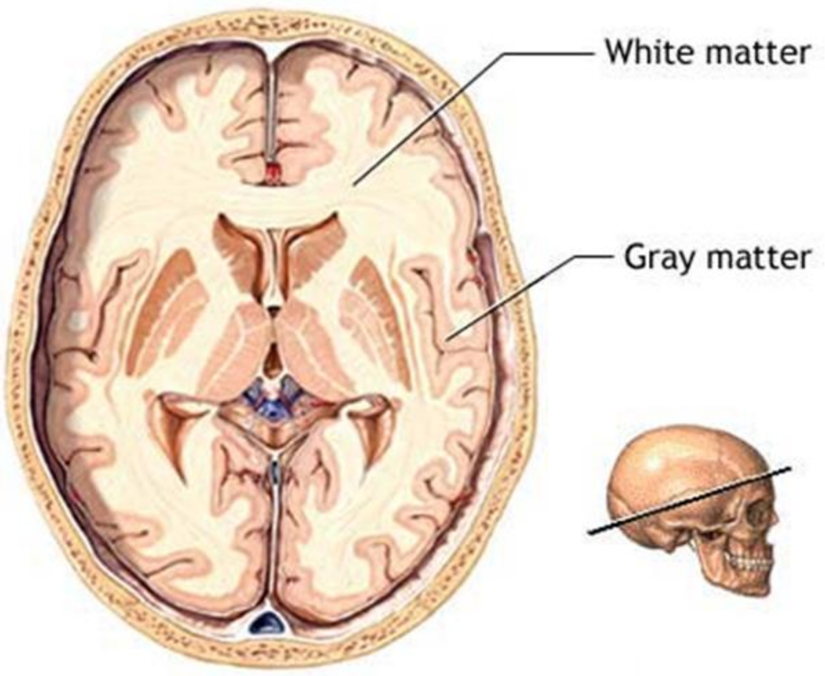




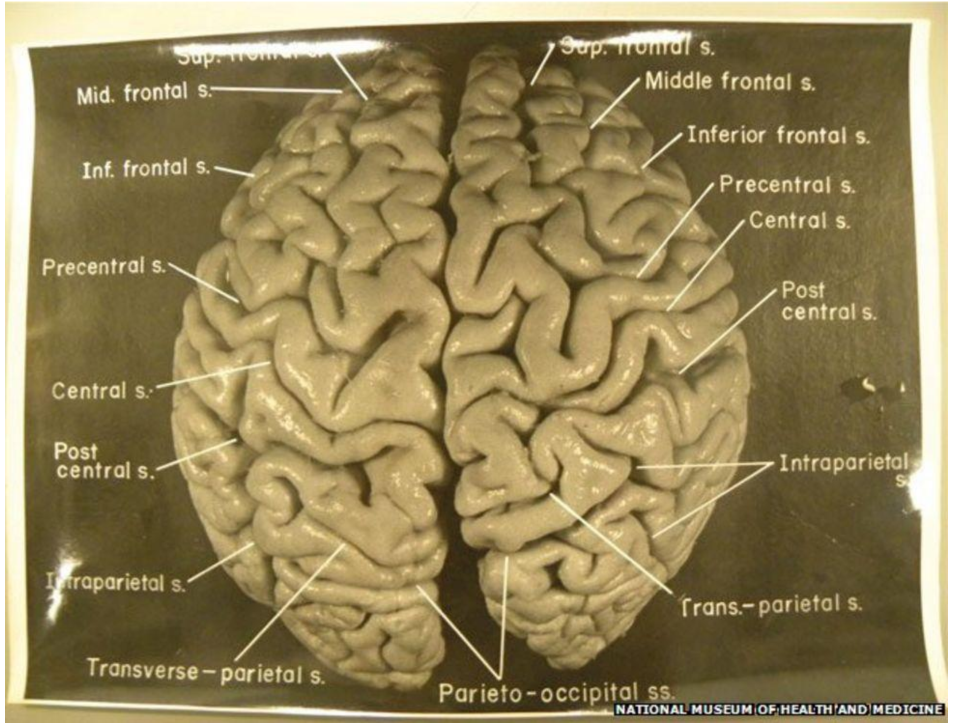
[https://en.wikipedia.org/wiki/Action_potential]

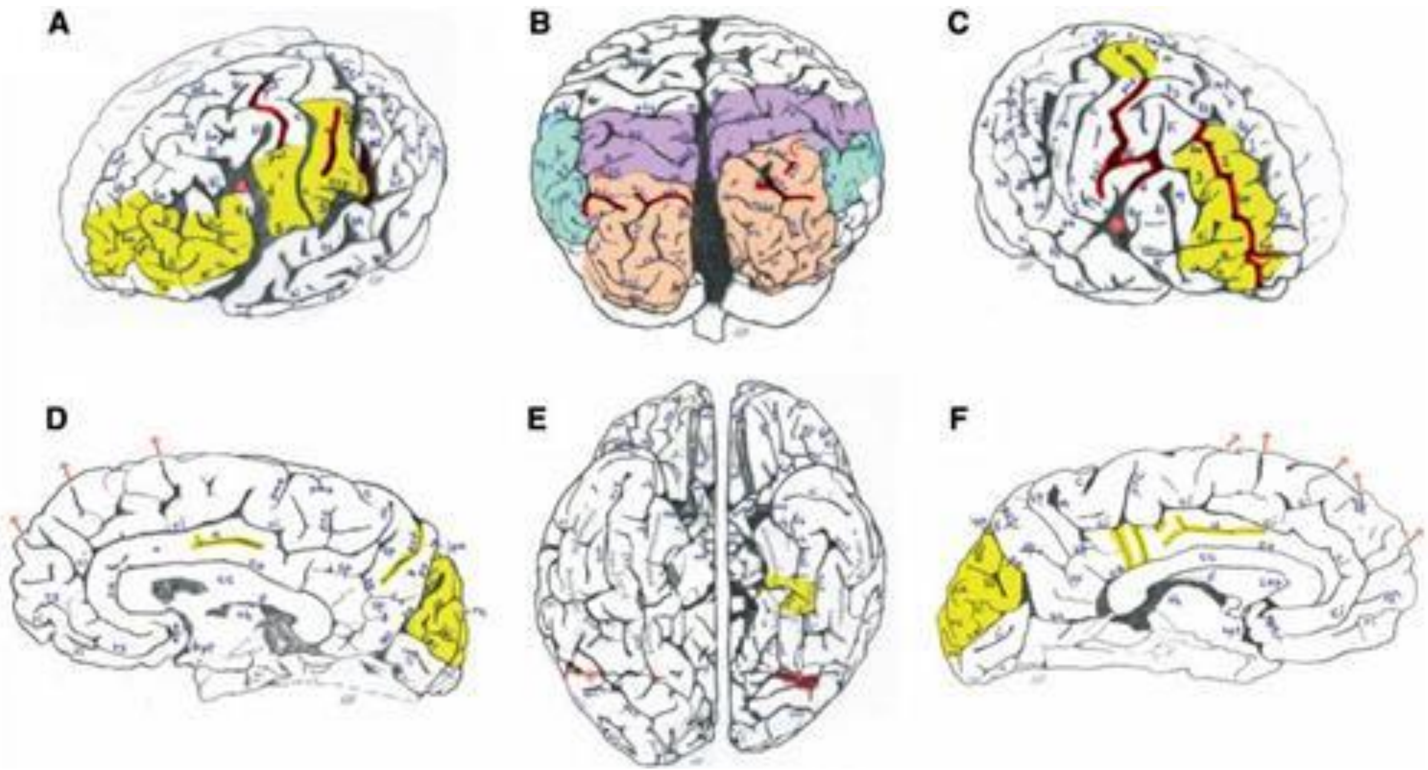
- Anatomy of the brain





[https://www.physio-pedia.com/Meninge;
https://medlineplus.gov/ency/imagepages/18117.htm]



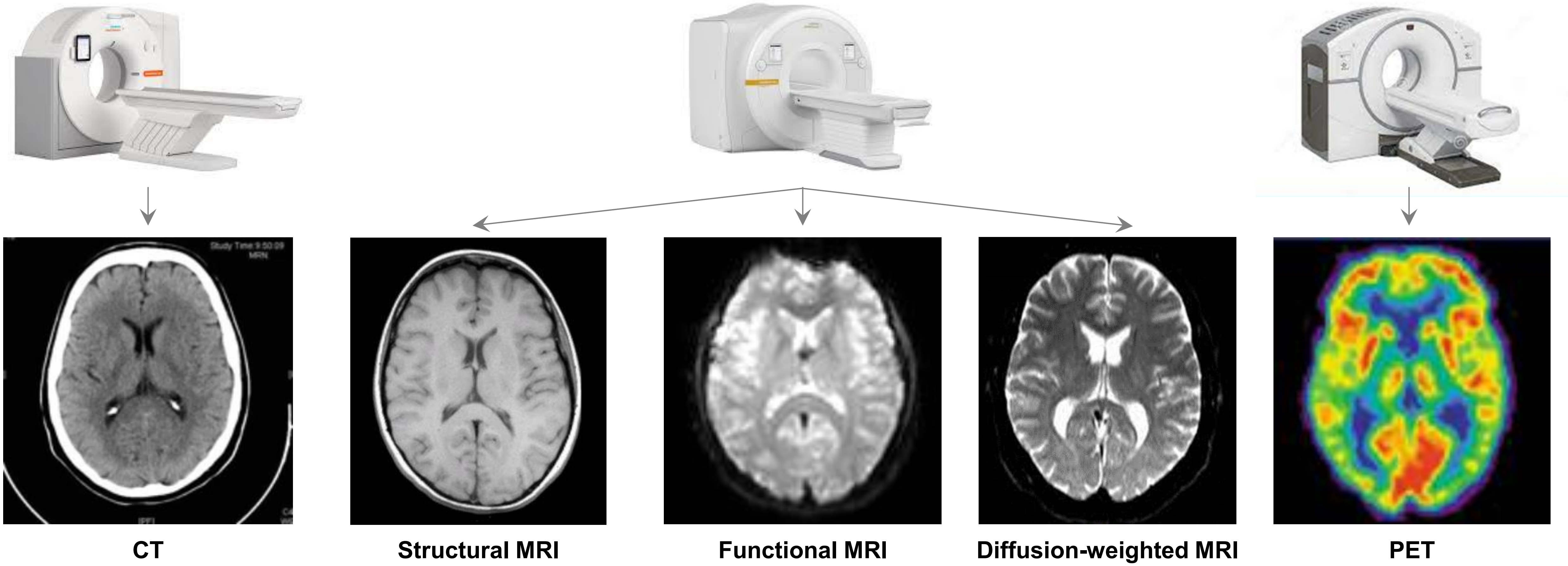


[Falk et al., 2019]

Unusual Features of Einstein's Brain

Brain Imaging

- Various quantitative techniques for imaging the structure or function of the brain
  - Computed tomography (CT)
  - Magnetic resonance imaging (MRI)
    - Structural MRI (sMRI)
    - Diffusion-weighted MRI (dMRI)
    - Functional MRI (fMRI)
  - Positron emission tomography (PET)

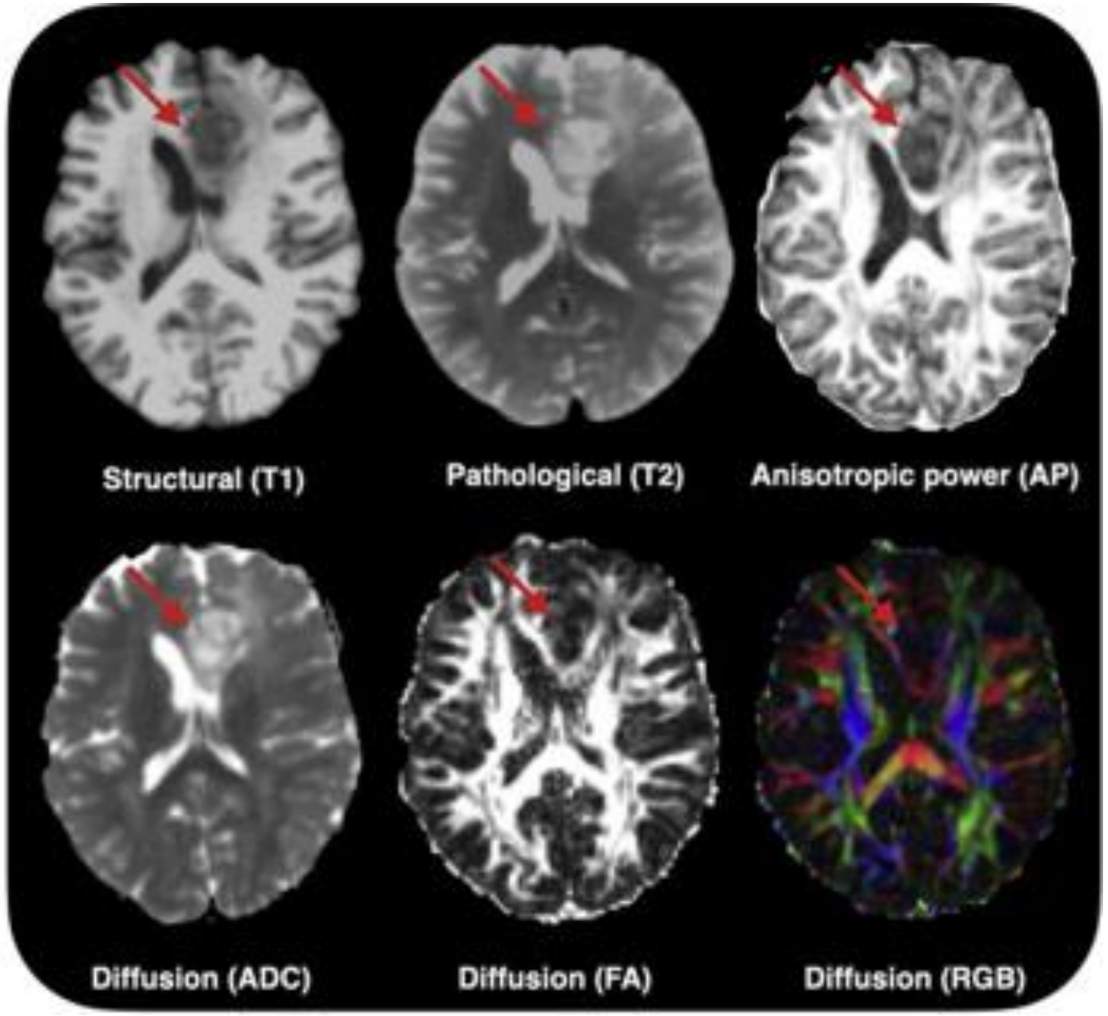

CT
Structural MRI
Functional MRI
Diffusion-weighted MRI
PET

Clinical Uses of Brain Imaging

- CT
  - Uses X-rays to create detailed cross-sectional images of the brain
  - Fast and widely available, making it a first-line imaging technique in emergencies
- MRI
  - Uses a magnetic field and radio waves to produce detailed images of the brain
  - Employed to visualize brain structure and function

- PET
  - Involves the injection of a radioactive tracer into the bloodstream, which is then taken up by active brain tissue
  - Utilized to assess brain function by imaging metabolic processes
- The choice of imaging techniques depends on:
  - Patient's condition
  - Specific clinical question to be answered
  - Imaging facilities available

- Clinical utility in radiology
  - Precise diagnosis
  - Informed prognosis
  - Effective treatment planning
  - Ongoing management



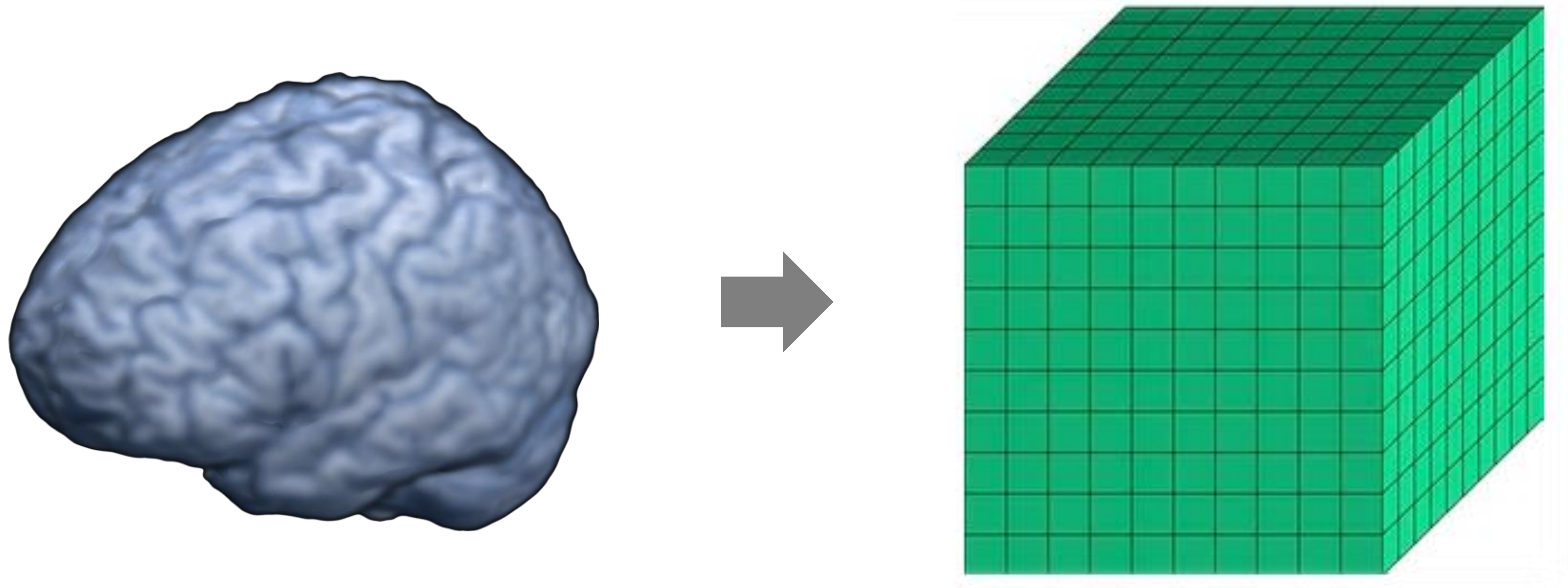
Brain Lesion Detection

Brain Imaging Data

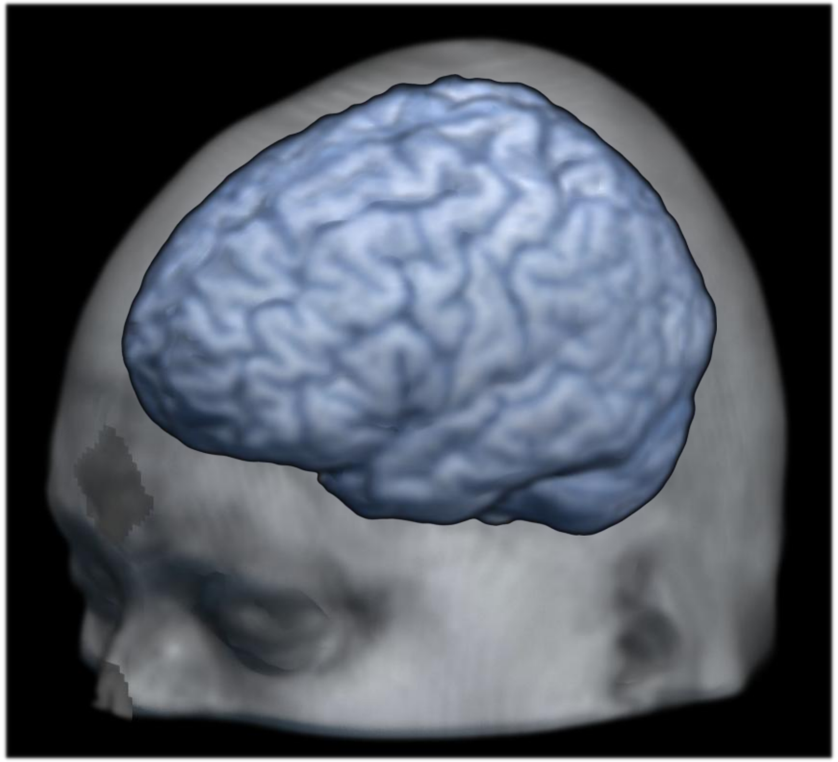
- Volumetric description of the brain as a 3D array

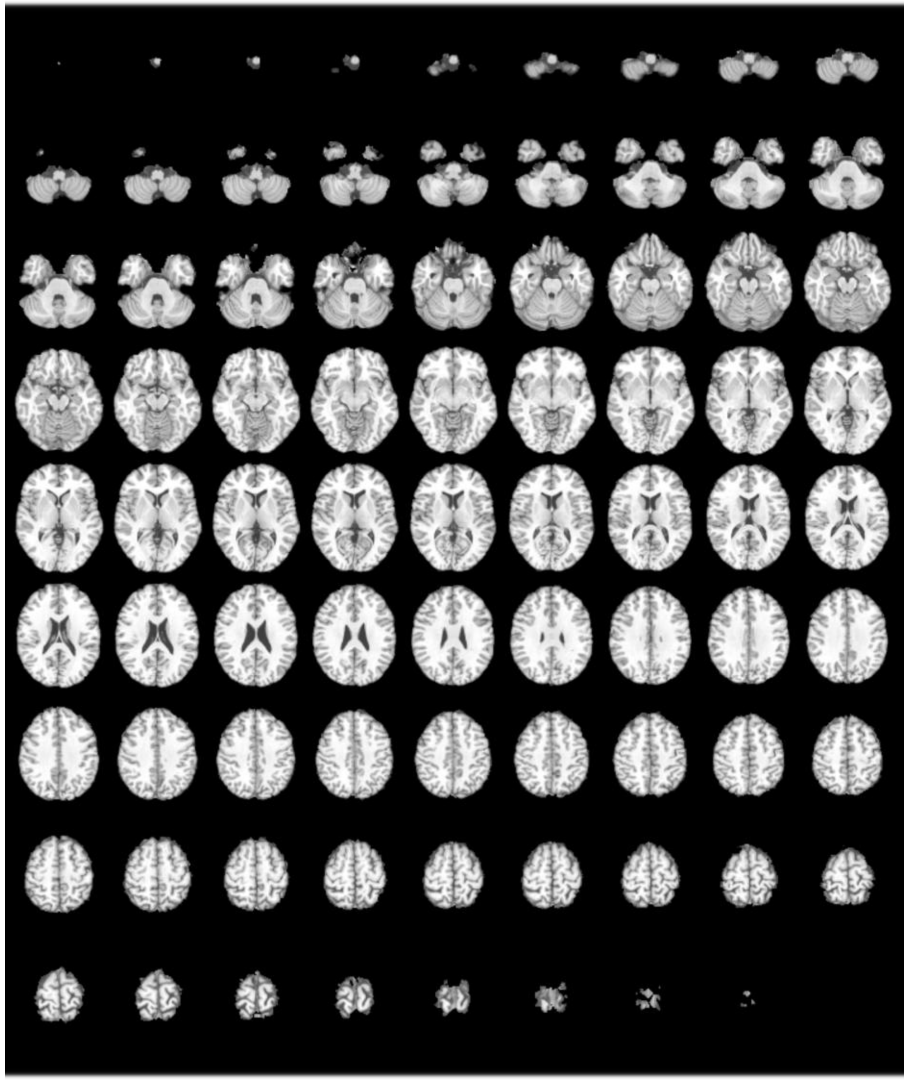
[Larobina and Murino, 2014]

  – Representation of the structure or function of the brain in the form of an array of voxels
  – Discrete representation resulting from a sampling/reconstruction process that maps numerical values to positions of the space



Brain Volumetric Data as a 3D Array

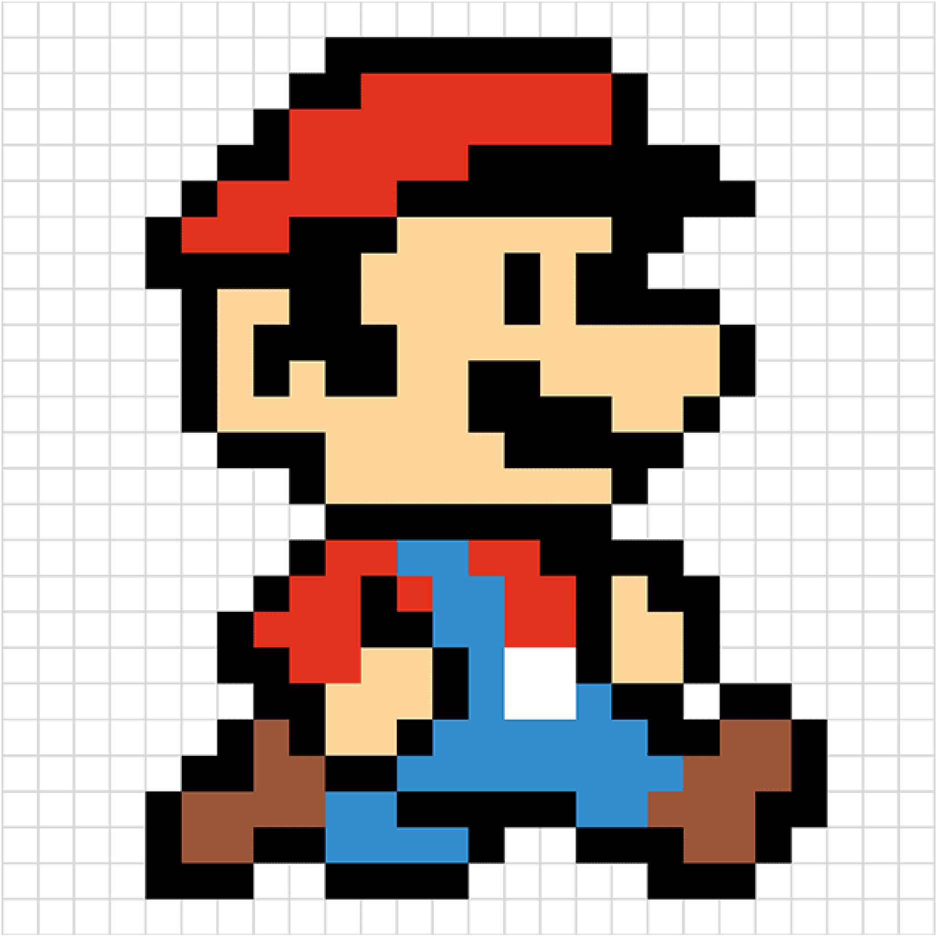




Brain Volume as a Series of Slices in a Stack

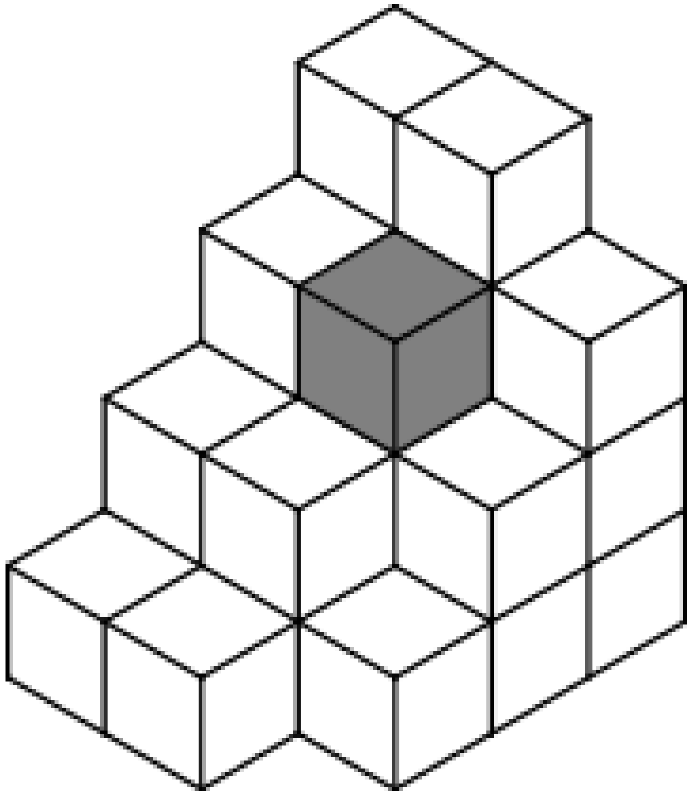
Voxel

- Volume element or volumetric pixel
  - Analogous to a pixel in 2D space
  - Smallest volumetric unit in 3D space



[https://easydrawingguides.com/how-to-draw-mario-pixel-art/]

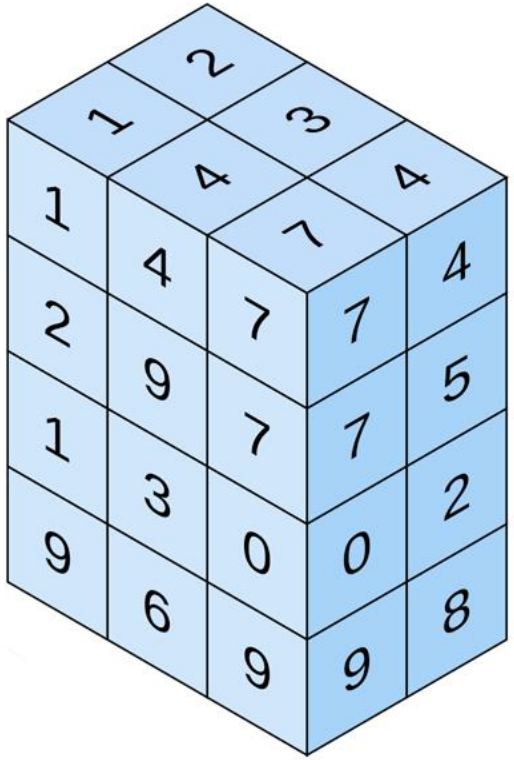
2D Raster Image Composed of Pixels

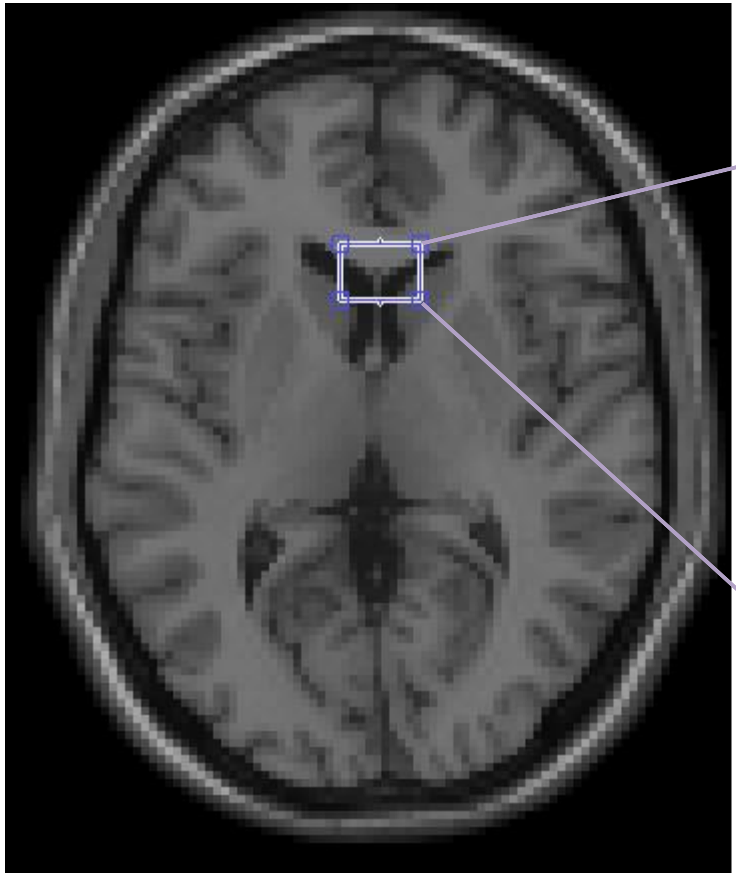


[https://en.wikipedia.org/wiki/Voxel]

Discrete Sampling of 3D Space Using Voxels

- Represents a value on a regular grid in 3D space
  - Sub-volume box with a constant value inside

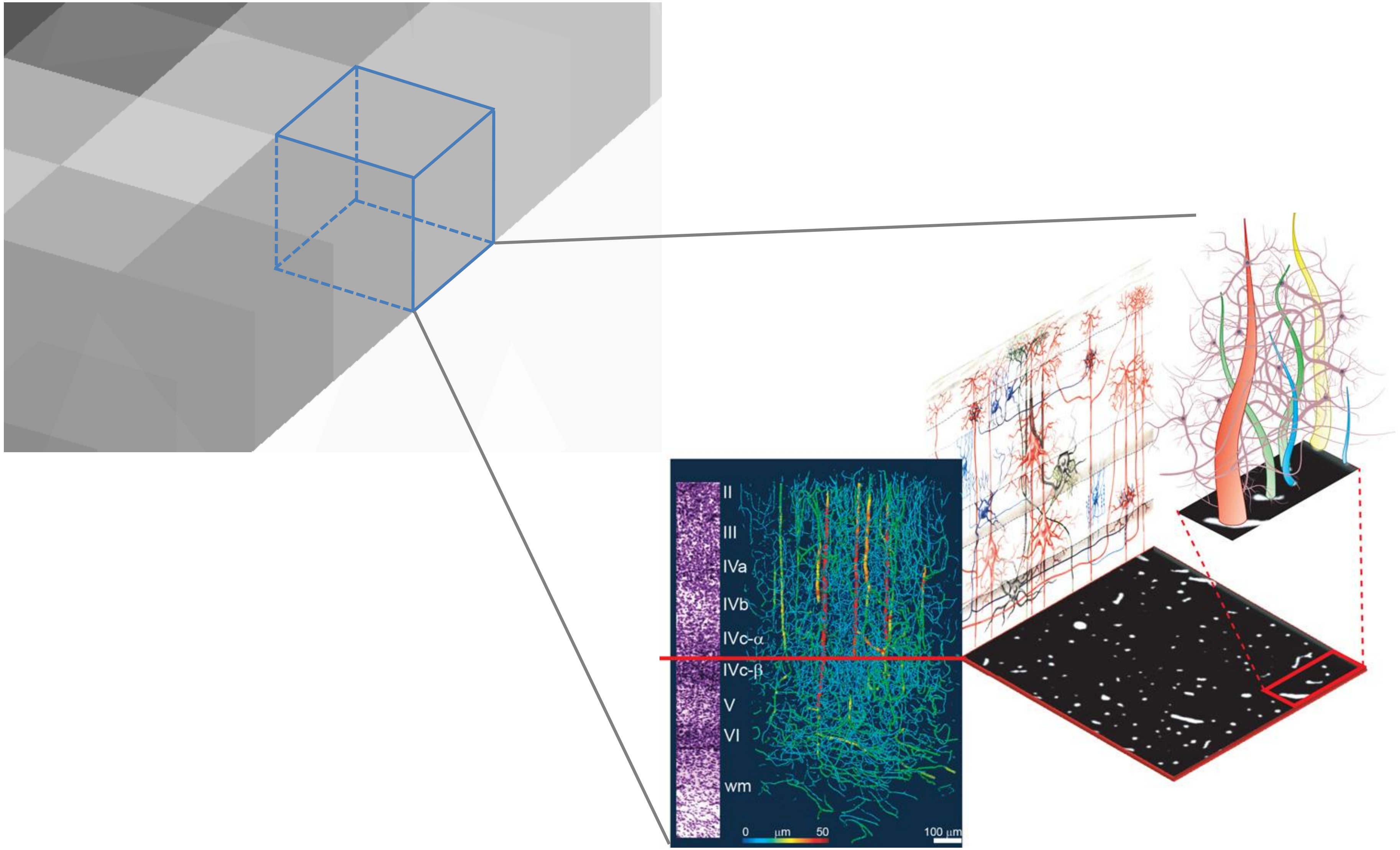




0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.45
0.41	0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.44
0.16	0.28	0.40	0.45	0.45	0.43	0.43	0.41	0.29	0.15
0.12	0.12	0.17	0.33	0.29	0.37	0.24	0.13	0.12	0.13
0.12	0.11	0.12	0.15	0.31	0.18	0.11	0.11	0.17	0.31
0.18	0.12	0.11	0.11	0.27	0.11	0.11	0.14	0.31	0.33
0.32	0.12	0.11	0.11	0.22	0.11	0.11	0.24	0.32	0.33

MRI Voxels Containing Image Data

- Typical fMRI voxel [Logothetis, 2008]
  - In-plane resolution: 2×2 mm^2 to 4×4 mm^2
  - Slice thickness: 3 mm to 7 mm
  - Occupied by:
    - Vessels for less than 3% of the volume
    - Neural elements for the rest
  - Contains:
    - 5.5 million neurons
    - $2.2 - 5.5 \times 10^{10}$ synapses
    - 22 km of dendrites
    - 220 km of axons



[Logothetis, 2008]

Neural and Vascular Contents within a Voxel

Image File Format

- Provides a standardized way to store the information describing an image in a computer file [Larobina and Murino, 2014]
  - How image data are organized inside an image file
  - How image data should be interpreted by a software for the correct loading and visualization

- Basic concepts common to all image file formats
  - Voxel depth: number of bits used to encode the information of each voxel
    - Integer, real number, or complex number in different bits
  - Photometric interpretation: how image data should be interpreted for the correct image display as a monochrome or color image
    - Samples per voxel: number of channels
    - MRI data has a grey scale photometric interpretation

- Metadata: Information that describe an image
  - Typically stored at the beginning of the file as a header
  - Contains at least image matrix dimensions, spatial resolution, voxel depth, and photometric interpretation
  - Enables a software to recognize and correctly open an image in a supported file format
  - Tool to annotate and exploit image-related information for clinical and research purposes
- Image data: Section where numerical values of voxels are stored
  - Usually stored as integers or floating-point numbers using the minimum number of bytes required to represent values according to a designated data type

- Image file size = header size + image data size
  - Metadata and image data may be contained in a single file or in separate files
- Major file formats currently used in brain imaging
  - Intended to standardize images generated by diagnostic modalities
    - Digital Imaging and Communications in Medicine (DICOM)
  - Aimed to facilitate and strengthen post-processing analysis
    - Neuroimaging Informatics Technology Initiative (NIfTI)

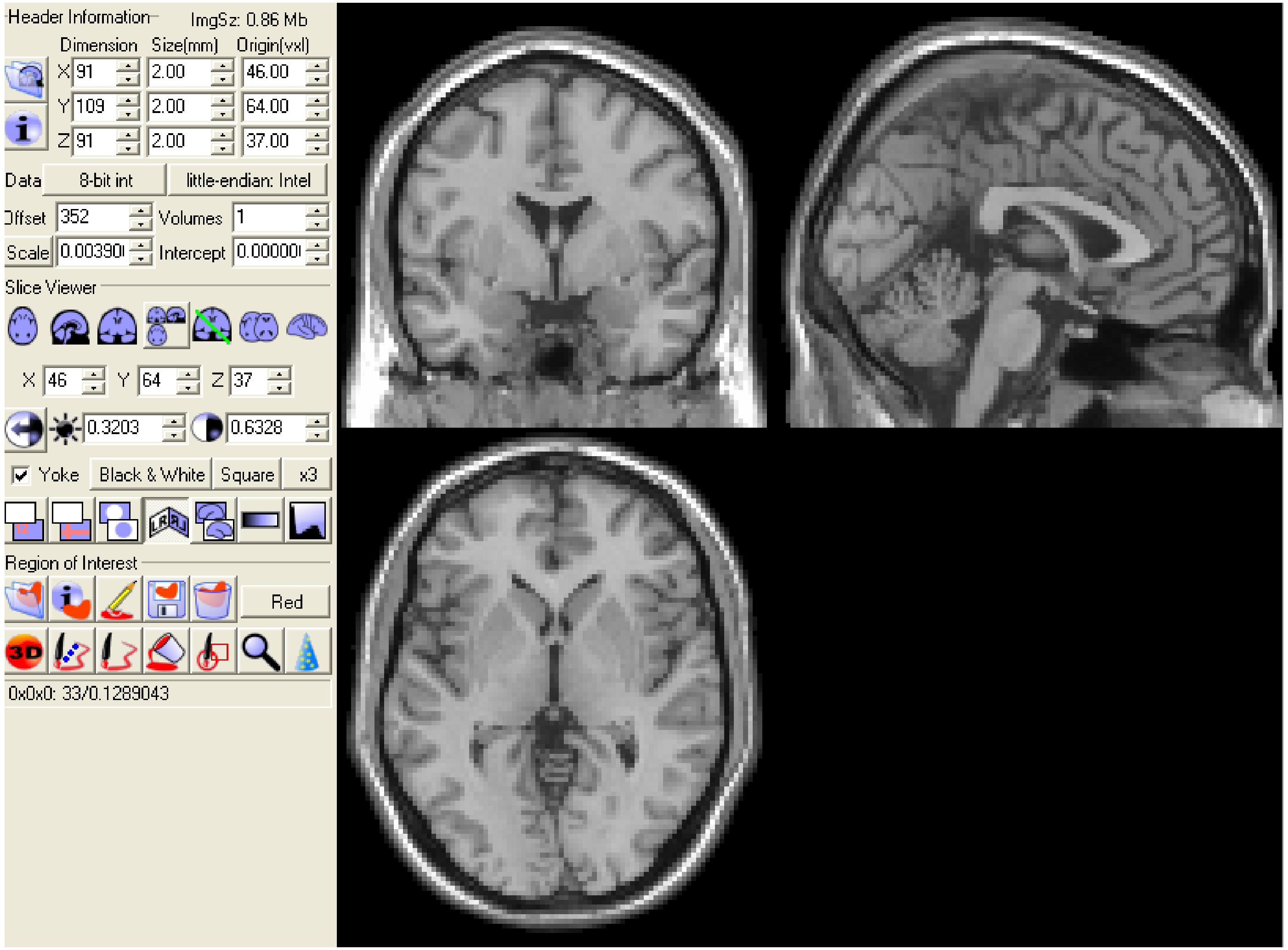
Format	Header	Extension	Data types
Analyze	Fixed-length: 348 byte binary format	.img and .hdr	Unsigned integer (8-bit), signed integer (16-, 32-bit), float (32-, 64-bit), complex (64-bit)
Nifti	Fixed-length: 352 byte binary format[a] (348 byte in the case of data stored as .img and .hdr)	.nii	Signed and unsigned integer (from 8- to 64-bit), float (from 32- to 128-bit), complex (from 64- to 256-bit)
Minc	Extensible binary format	.mnc	Signed and unsigned integer (from 8- to 32-bit), float (32-, 64-bit), complex (32-, 64-bit)
Dicom	Variable length binary format	.dcm	Signed and unsigned integer, (8-, 16-bit; 32-bit only allowed for radiotherapy dose), float not supported

[Larobina and Murino, 2014]

Characteristics of Image File Formats

- DICOM
  - Origin and development
    - Developed by the National Electrical Manufacturers Association (NEMA) and the American College of Radiology (ACR)
    - First introduced in 1985 as ACR/NEMA 1.0
  - Version evolution
    - DICOM 3.0 (1993) - First official DICOM standard
    - Regular updates and supplements with backward compatibility
    - Current edition - DICOM 2025c (as of September 2025)
  - Primary uses
    - Standard format for medical imaging
    - Includes a network protocol for image transmission

- NIfTI
  - Origin and development
    - Developed by the National Institutes of Health Data Format Working Group
    - Created to address limitations in the ANALYZE 7.5 format
    - First released in 2003
  - Version evolution
    - ANALYZE 7.5 (1980s-1990s) - Predecessor format with orientation issues
    - NIfTI-1 (2003) - Initial release
    - NIfTI-2 (2011) - Extended to support larger image dimensions
  - Primary uses
    - Specifically designed for neuroimaging research
    - Supports both single-file (.nii) and dual-file (.hdr/.img) formats



Dimensions: 91 × 109 × 91
Voxel depth: 8-bit integer
Voxel size: 2 mm × 2 mm × 2 mm
Origin: [46, 64, 37]

File size:
Header = 352 B
Image data = 91 × 109 × 91 × 8 bits
Total = 352 B + 902,629 B
= 902,981 B
= 0.86 MB

MRI Data Stored in NIfTI Format

MRI Coordinate System

- Reference frame in a 3D space that assigns *x*, *y*, and *z* coordinates to anatomical positions [https://www.fieldtriptoolbox.org/faq/coordsys/]
  - What is the definition of the origin, *i.e.* [0, 0, 0]?
  - In which directions are the *X*-, *Y*- and *Z*-axis pointing?
  - In what units are coordinates expressed?
  - Is the geometry scaled to some template or atlas, or does it still match the individual's brain size?

system	units	orientation	origin	scaling	notes
ACPC	mm	RAS	anterior commissure	native, i.e., not normalized to a template	
Allen Institute	mm	RAS	Bregma point		
Analyze	mm	LAS		native	
BTi/4D	m	ALS	between the ears	native	
CTF MRI	mm	ALS	between the ears	native	voxel order can be arbitrary
CTF gradiometer	cm	ALS	between the ears	native	
CapTrak	mm	RAS	approximately between the ears		
Chieti ITAB	mm	RAS	between the ears	native	
DICOM	mm	LPS	centre of MRI gradient coil	native, see here	
EEGLAB	mm	ALS	between the ears	native	
FreeSurfer	mm	RAS	center of isotropic 1 mm 256x256x256 volume		
MNI	mm	RAS	anterior commissure	scaled to match averaged template	
NIfTI	mm	RAS		see here, search for "Orientation information".	
Neuromag/Elekta/Megin	m	RAS	between the ears	native	
Paxinos-Franklin	mm	RSP	Bregma point		
Scanner RAS (`scanras`)	mm	RAS	scanner origin	native	
Talairach-Tournoux	mm	RAS	anterior commissure	scaled to match atlas	
Yokogawa		ALS	center of device		

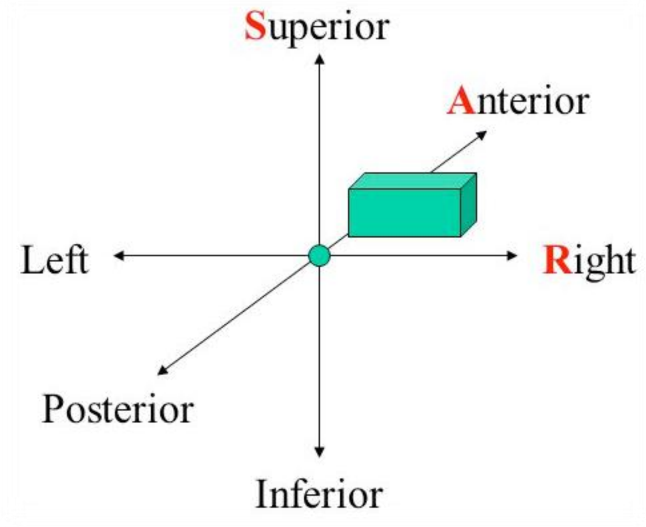
[https://www.fieldtriptoolbox.org/faq/coordsys/]

Different MRI Coordinate Systems

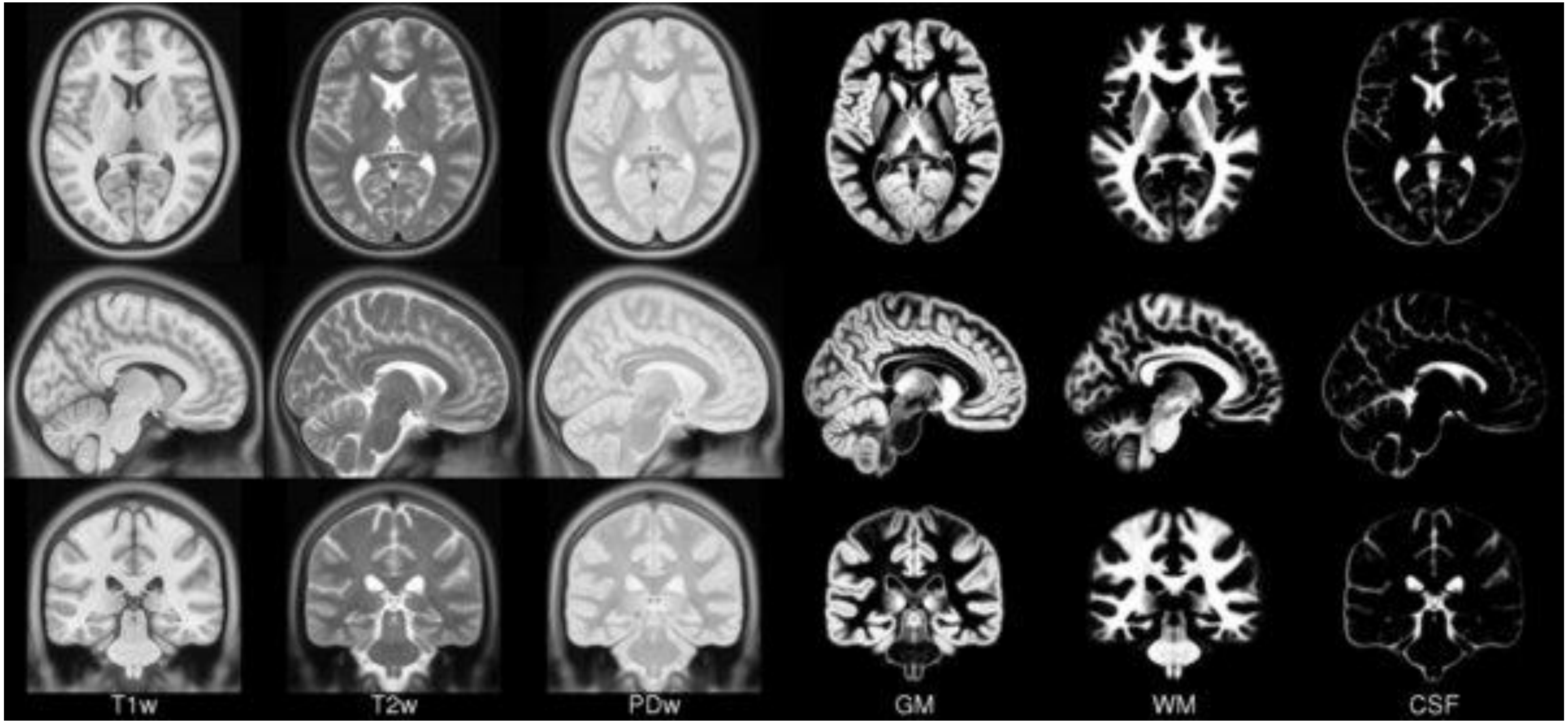
- Montreal Neurological Institute (MNI) coordinate system

[https://www.fieldtriptoolbox.org/faq/coordsys/]

  - The origin is the anterior commissure
  - The *X*-axis points from left to right
  - The *Y*-axis points from posterior to anterior
  - The *Z*-axis points from inferior to superior



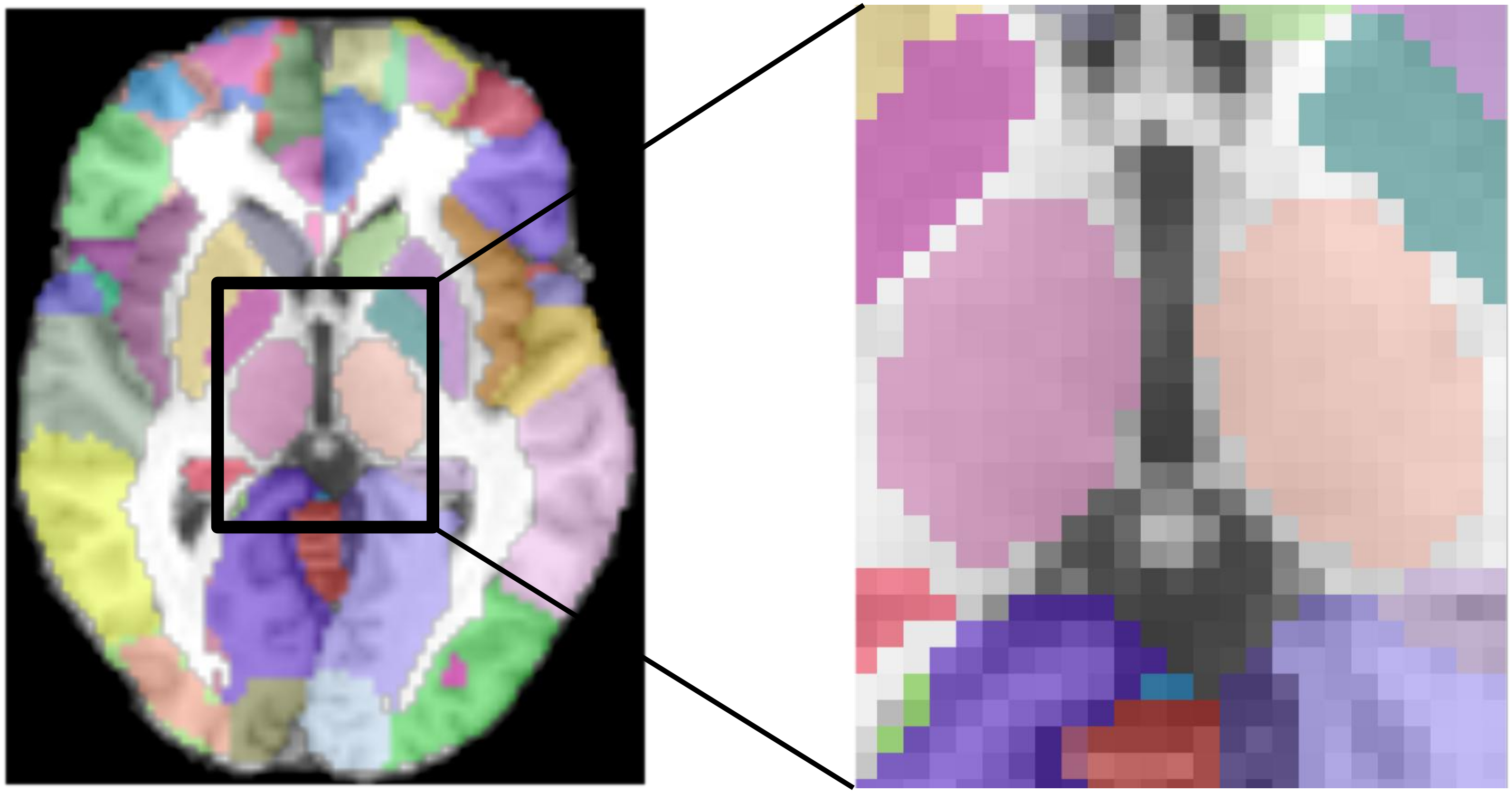
- Used if the geometry is spatially warped to the template brain
  - MNI152 Linear Template: Based on linearly co-registered 152 healthy brains
  - MNI152 Nonlinear Template, 6th Generation: Based on nonlinearly co-registered 152 healthy brains
  - MNI152 2009a/b/c Nonlinear Symmetric/Asymmetric Template: Based on nonlinearly co-registered 152 healthy brains with improved resolution and registration methods



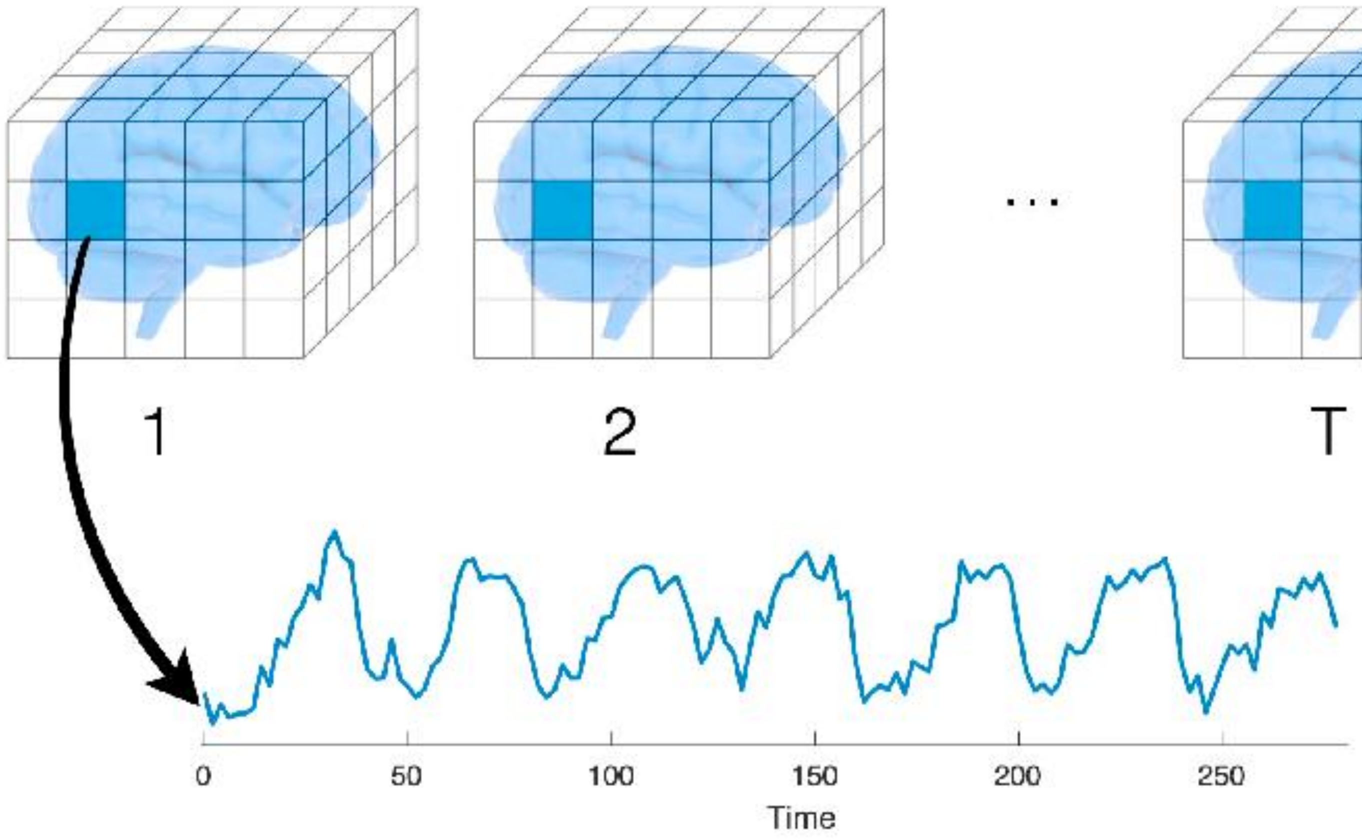
[https://www.bic.mni.mcgill.ca/ServicesAtlases/ICBM152NLin2009]

MNI152 2009c Nonlinear Asymmetric Template

- Applications of 3D coordinates in brain imaging
  - Identifying voxels within specific brain regions based on their 3D spatial coordinates

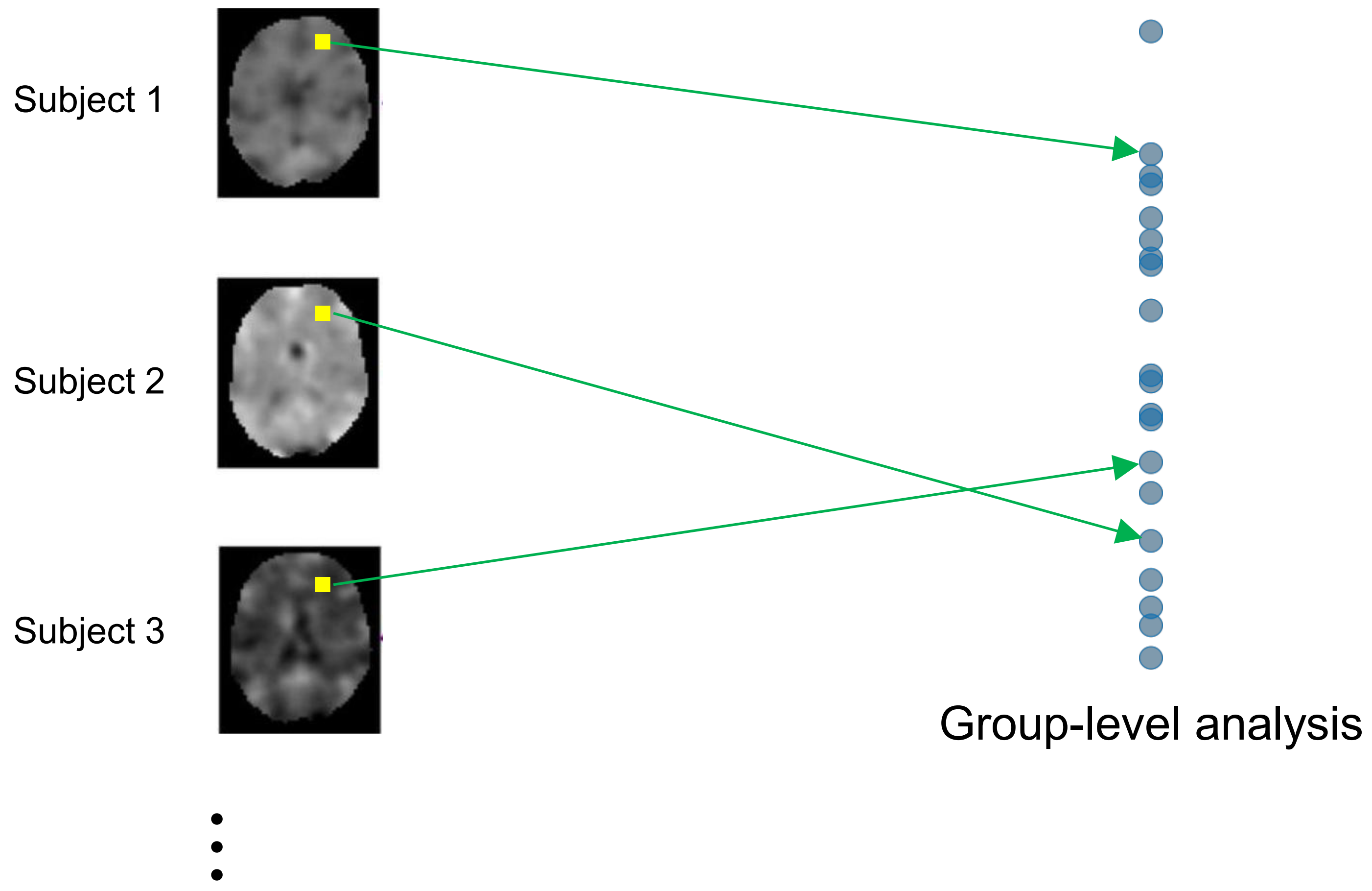


– Extracting voxel time series data from consistent 3D locations across multiple time points in a single subject's brain volumes



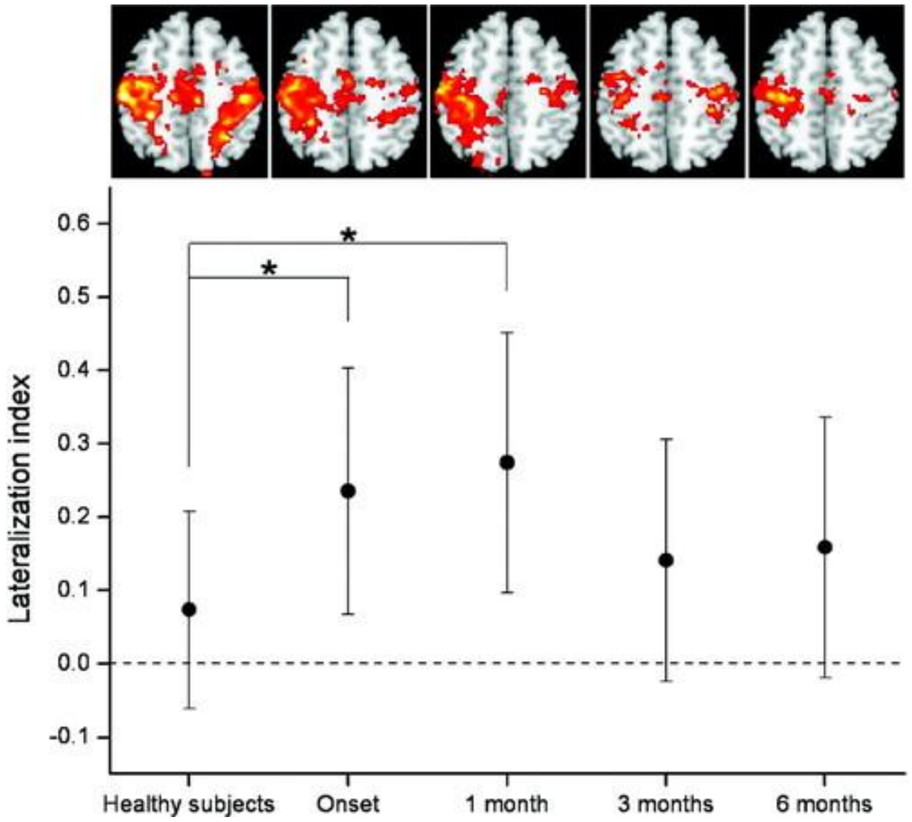
[Sidén, 2020]

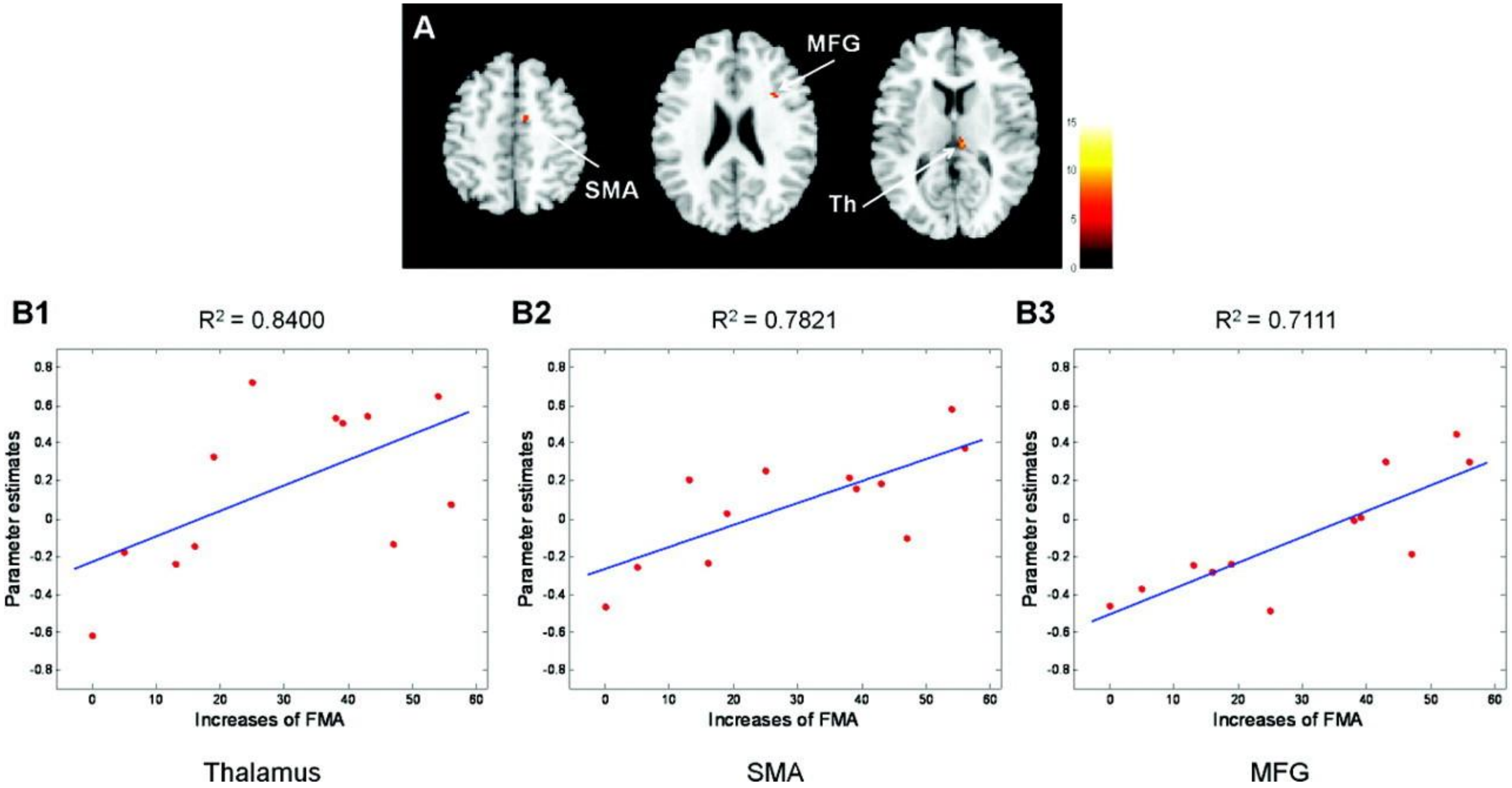
– Acquiring voxel values from corresponding 3D coordinates across multiple subjects' brain volumes for group-level analyses



Clinical MRI Studies

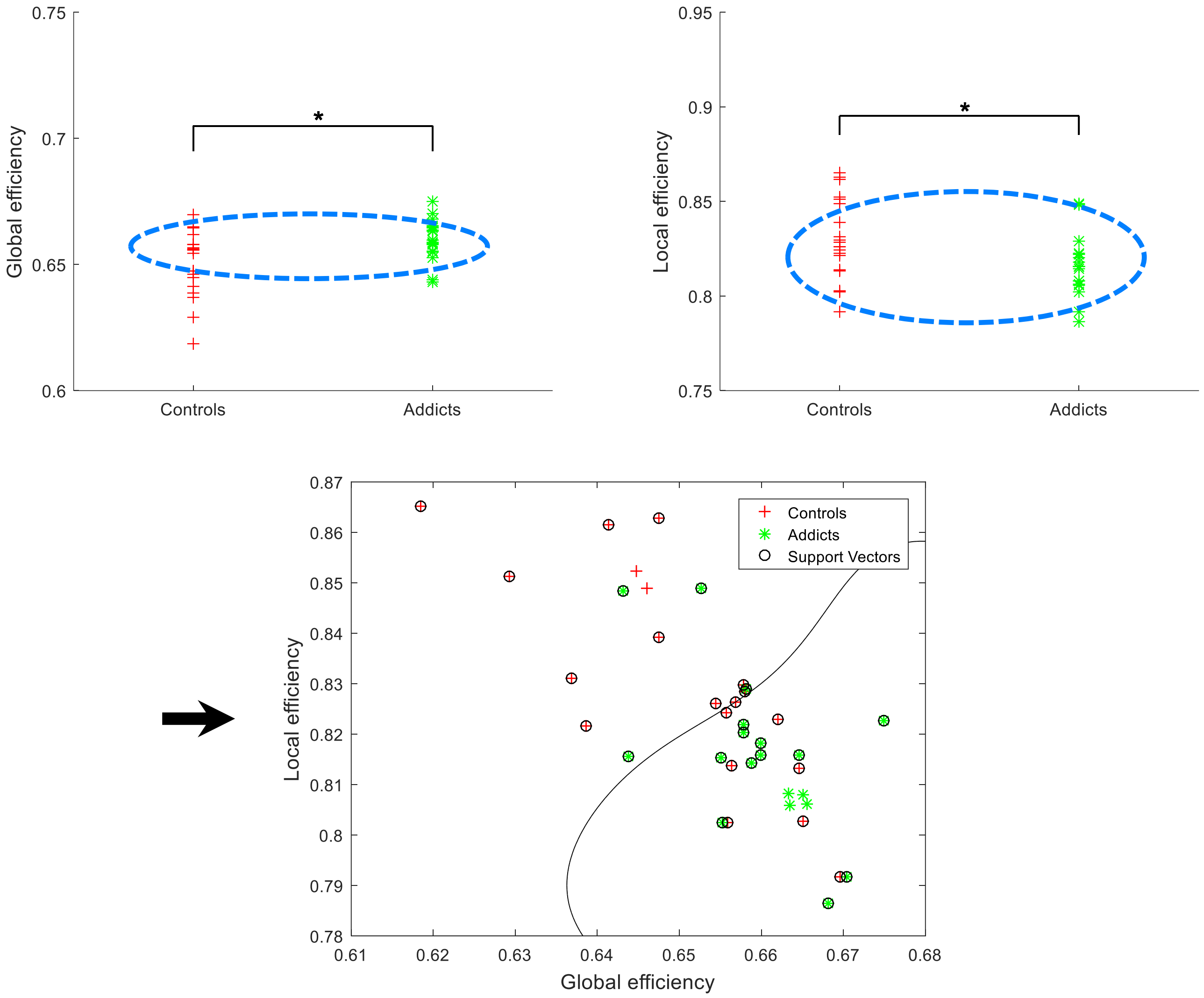
- Brain changes in recovery after stroke [Park et al, 2011]





A
MFG
SMA
Th
B1
$R^2 = 0.8400$
Parameter estimates
Increases of FMA
Thalamus
B2
$R^2 = 0.7821$
Parameter estimates
Increases of FMA
SMA
B3
$R^2 = 0.7111$
Parameter estimates
Increases of FMA
MFG

- Classification beyond describing group differences



Machine Learning (ML)

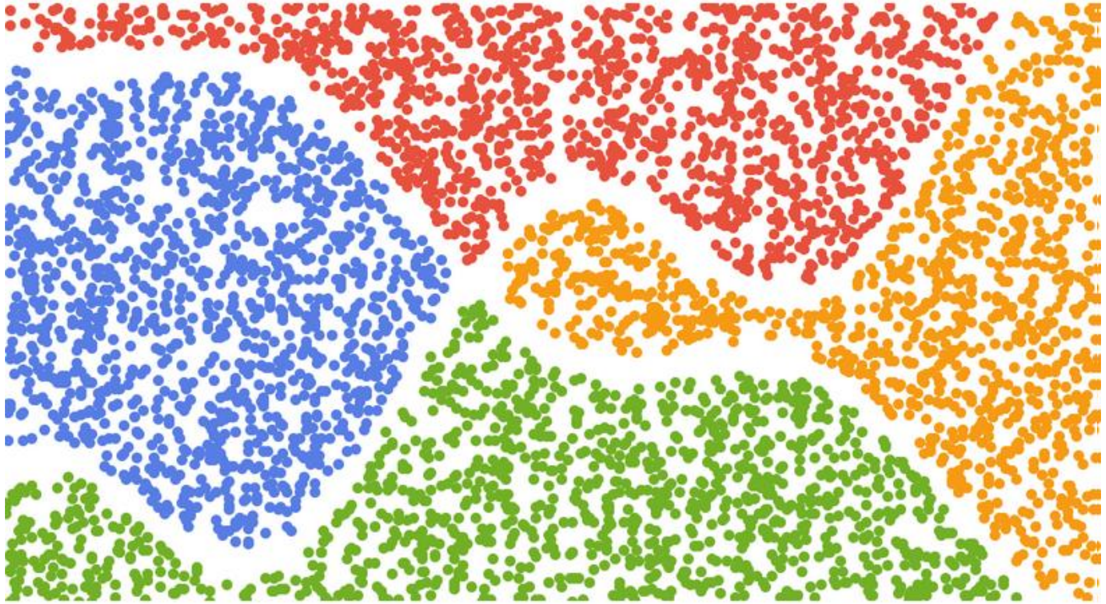
- Subset of AI that enables systems to learn patterns from data and make predictions or decisions without being explicitly programmed
- Key characteristics:
  - [Data-driven learning] Learns from structured or unstructured data rather than relying on rule-based programming
  - [Generalization ability] Aims to generalize from training data to unseen data, making accurate predictions on new inputs

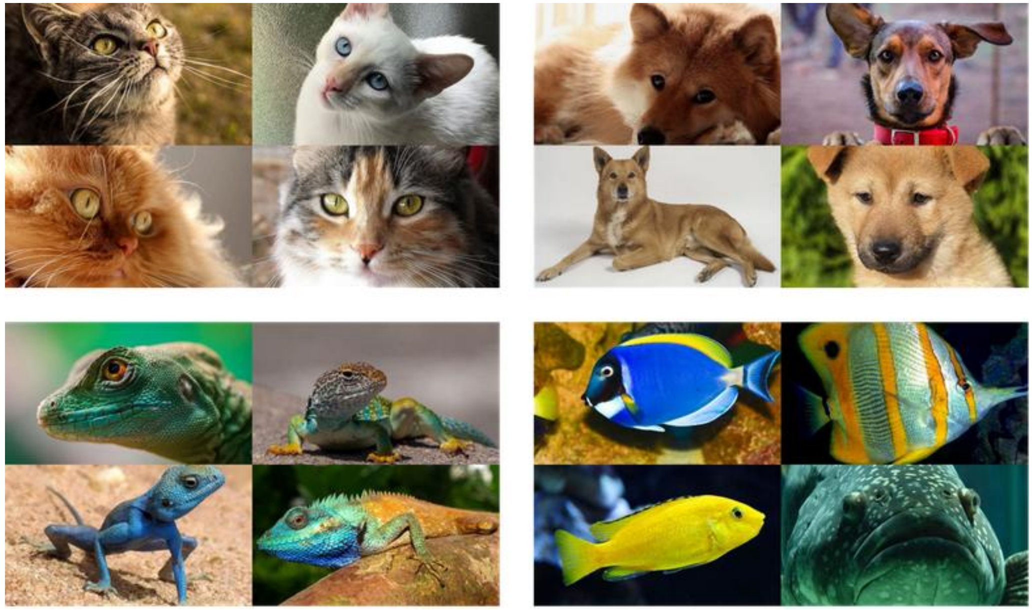
- Based on learning paradigm
  - Supervised learning
    - Learns from labeled data to make predictions
  - Unsupervised learning
    - Discovers patterns and structures in unlabeled data
  - Semi-supervised learning
    - Uses a mix of a small amount of labeled data and a large amount of unlabeled data
  - Reinforcement learning
    - Learns through interaction with the environment through rewards and penalties

- Based on data supervision
  - Online learning
    - Learns incrementally from continuously arriving data
  - Batch learning (offline learning)
    - Trains on entire dataset at once
- Based on model purpose
  - Discriminative models
    - Learns the direct mapping from inputs to outputs by estimating $P(Y|X)$
  - Generative models
    - Learns the joint probability distribution $P(X,Y)$, enabling to generate new data samples by drawing from the estimated distribution

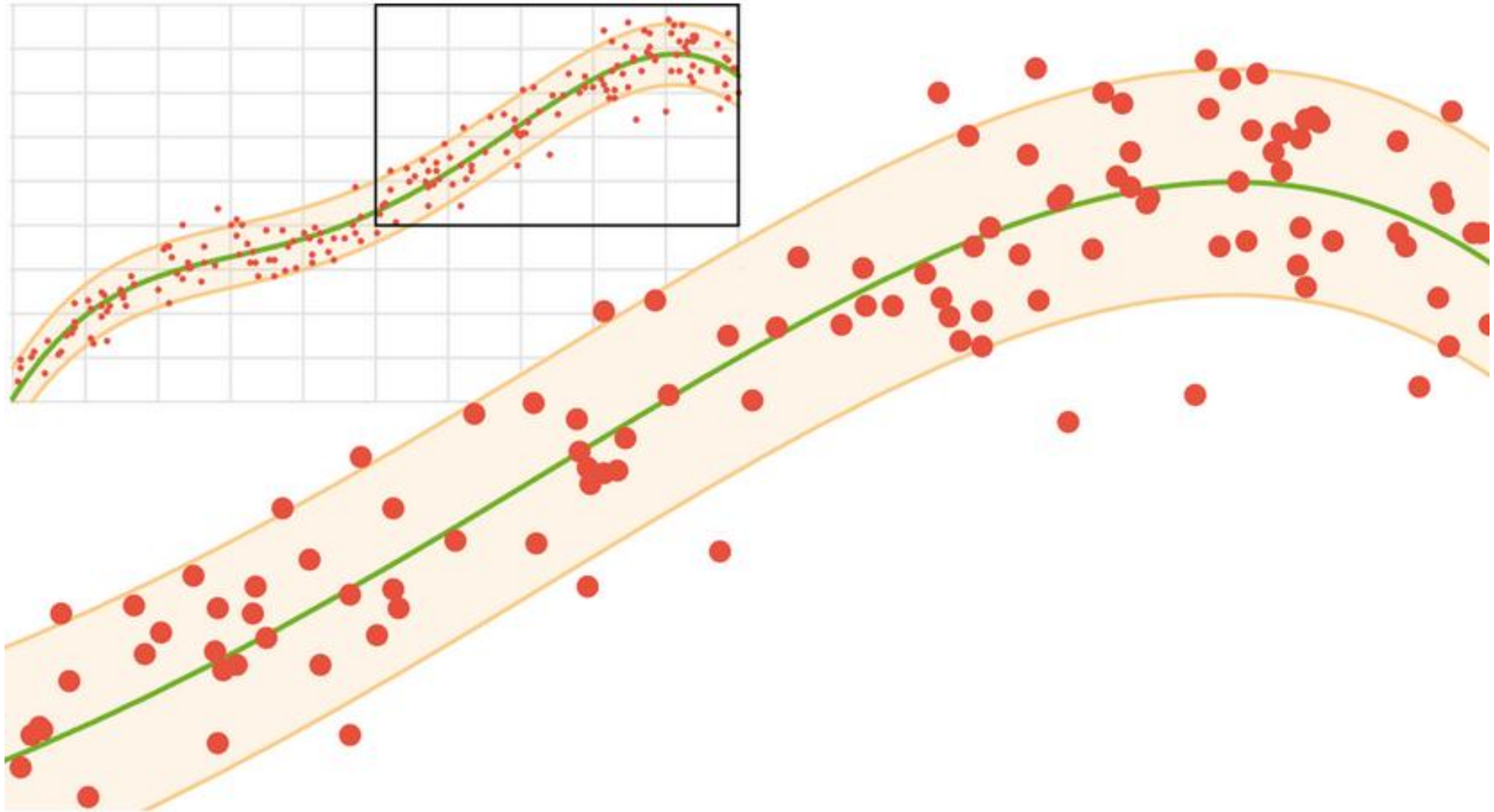
- Based on model architecture
  - Traditional ML (shallow learning)
    - Relies on statistical methods and simpler architectures
    - Often requires manual feature extraction and engineering
    - Linear models (linear regression, logistic regression), tree-based models (decision trees, random forest, gradient boosting machines (GBMs) like XGBoost, LightGBM, CatBoost), support vector machines (SVMs), etc.
  - Deep learning
    - Composed of multiple hidden layers
    - Capable of learning hierarchical features automatically
    - Feedforward neural networks (FNNs), convolutional neural networks (CNNs), recurrent neural networks (RNNs), transformers, etc.

- Based on application domains
  - Predictive modeling
  - Clustering
  - Dimensionality reduction
  - Anomaly detection
  - Natural language processing (NLP)
  - Computer vision
  - Speech processing

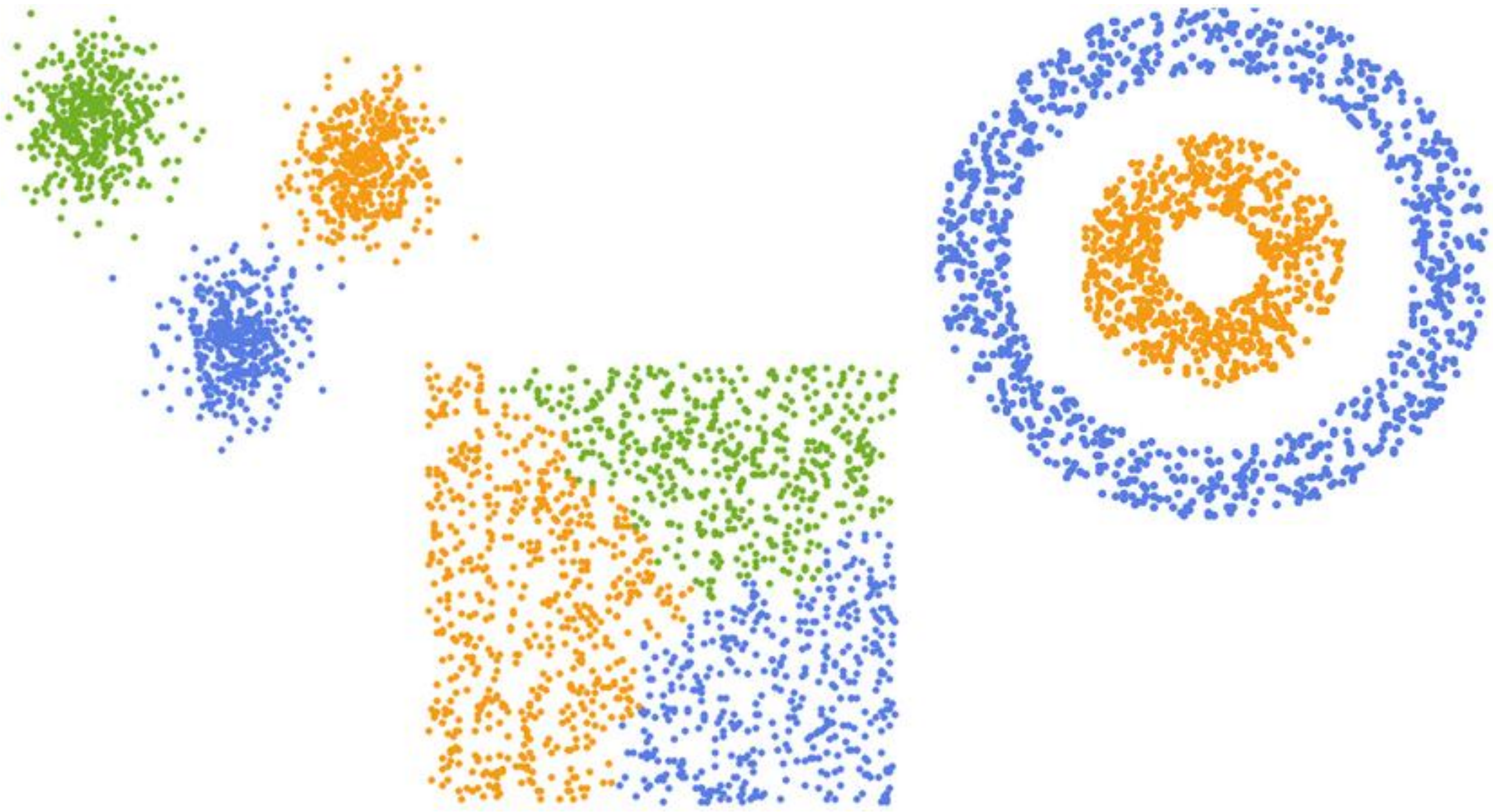




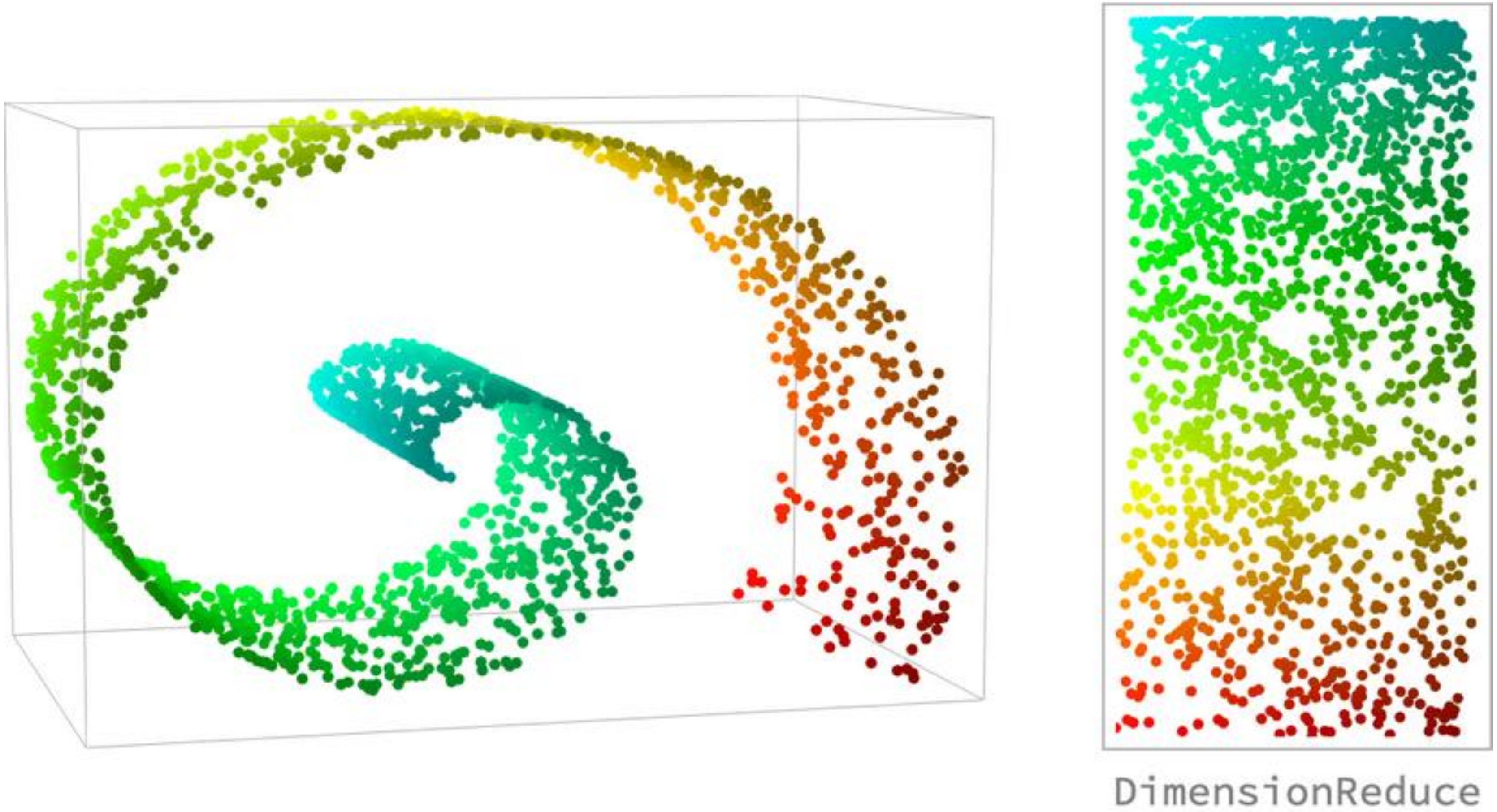
Predictive Modeling: Classification



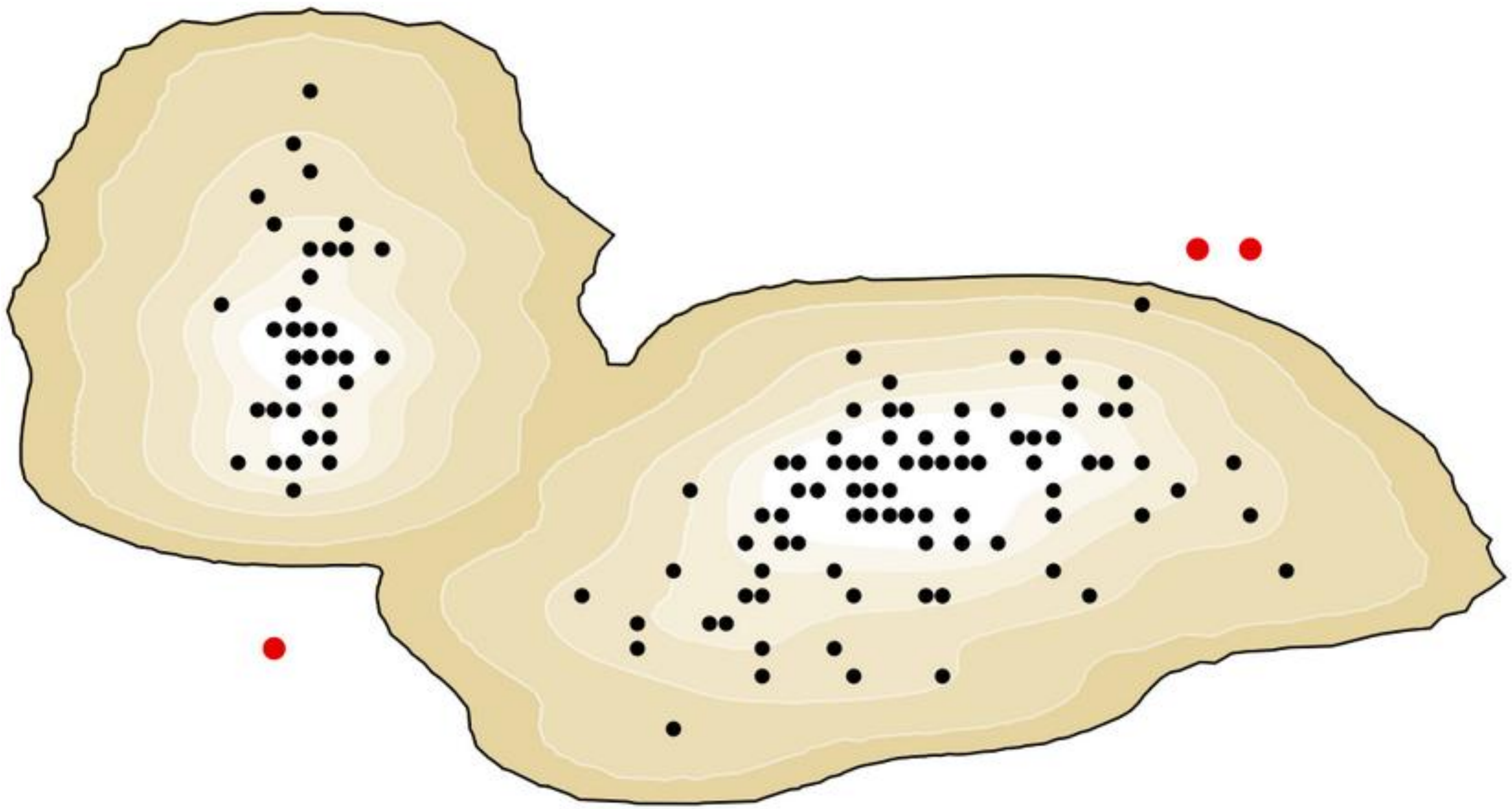
Predictive Modeling: Regression



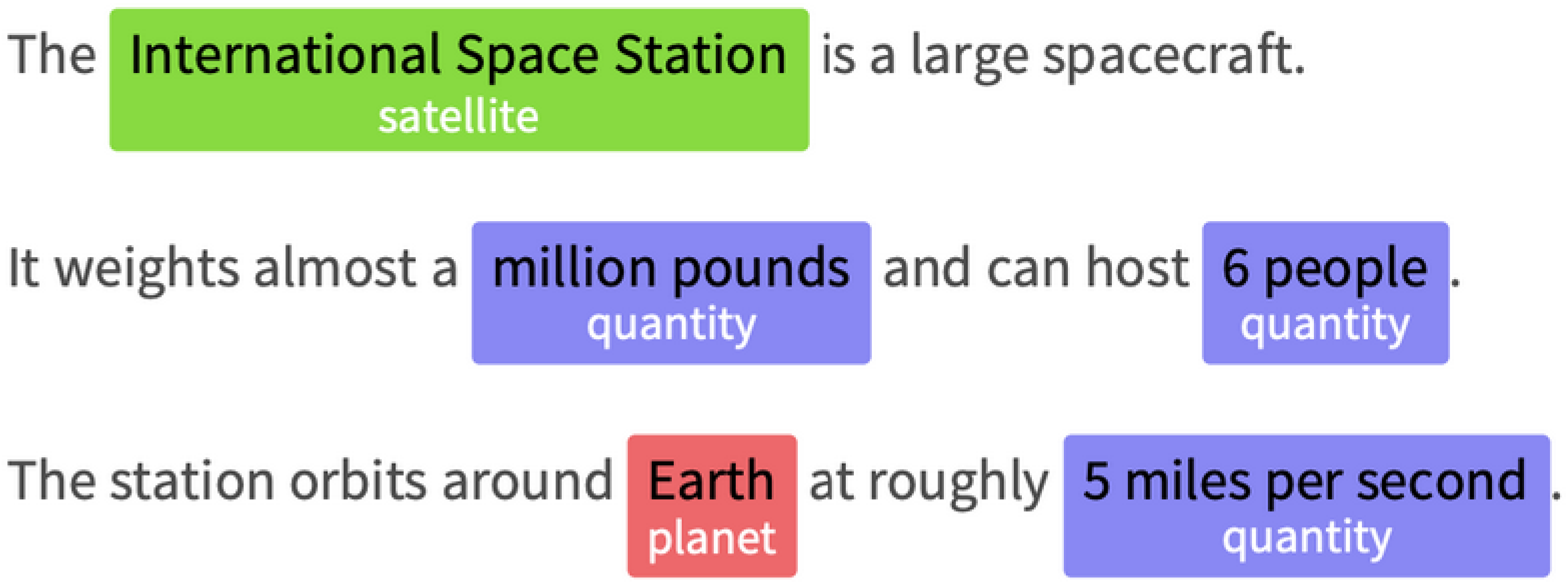
Clustering



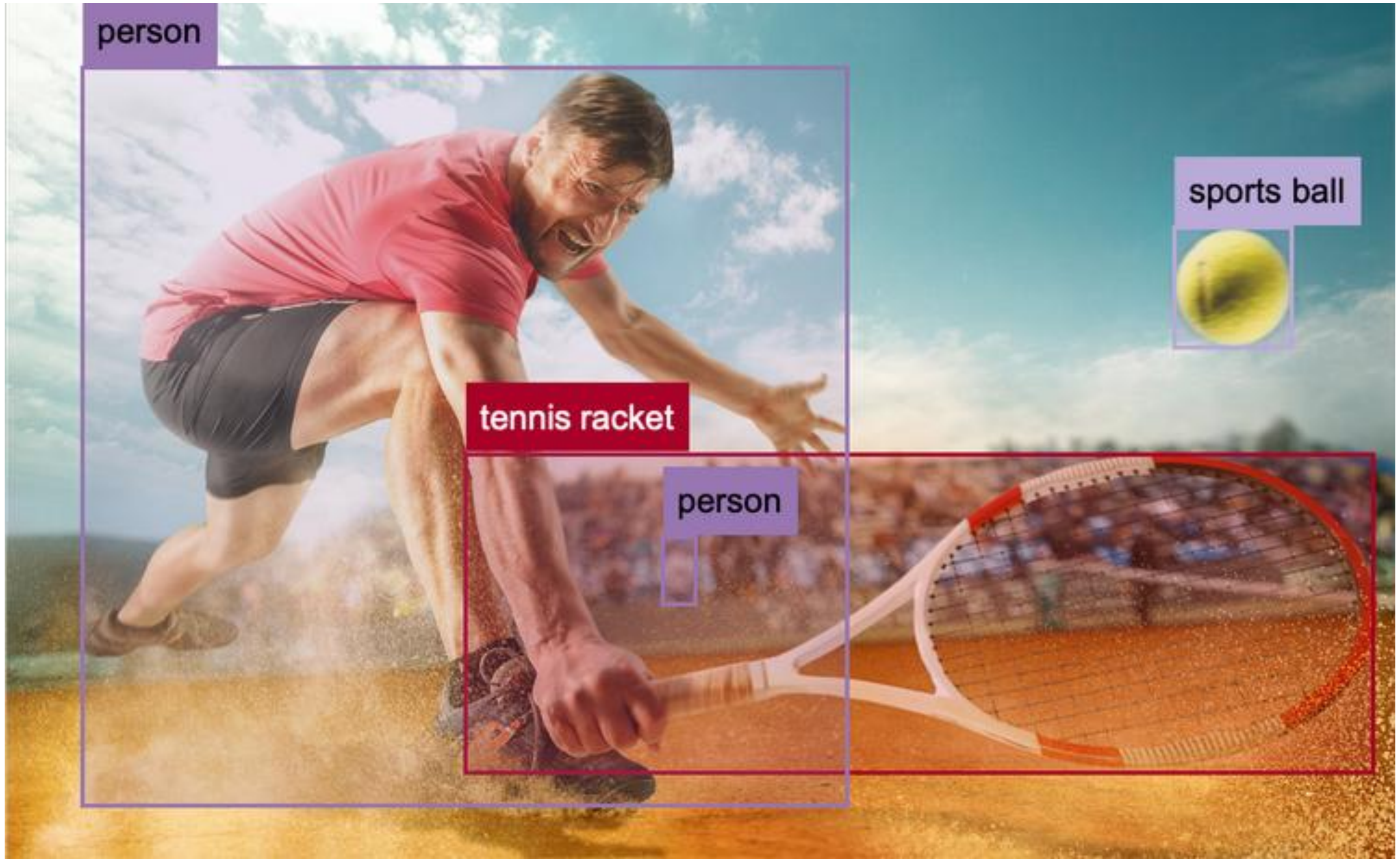
Dimensionality Reduction



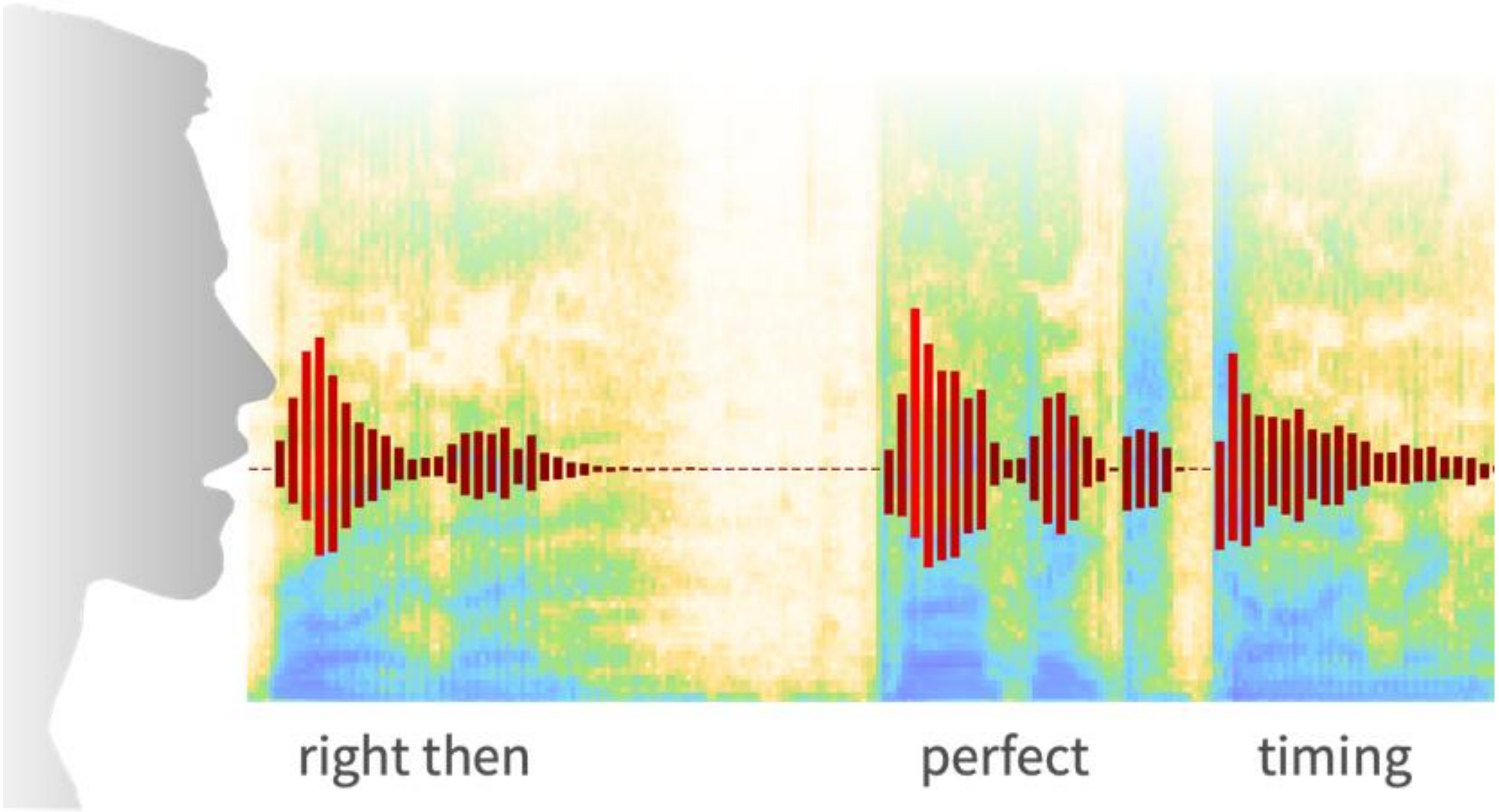
Anomaly Detection



Natural Language Processing



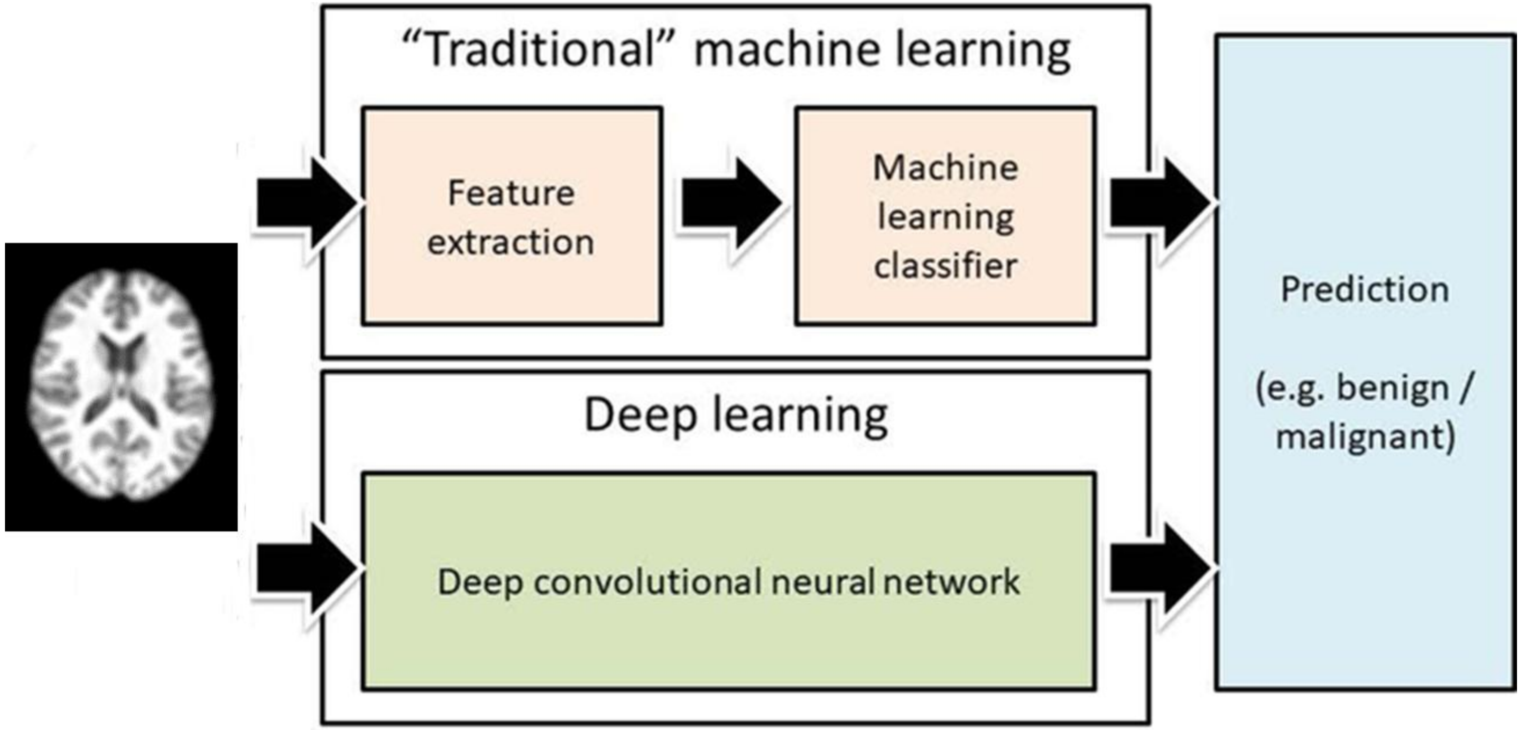
Computer Vision



Speech Processing

- ML models to be covered in this course
  - Based on learning paradigm: Supervised learning
  - Based on data supervision: Batch learning
  - Based on model purpose: Discriminative models
  - Based on model architecture: Deep learning
  - Based on application domains: Predictive modeling

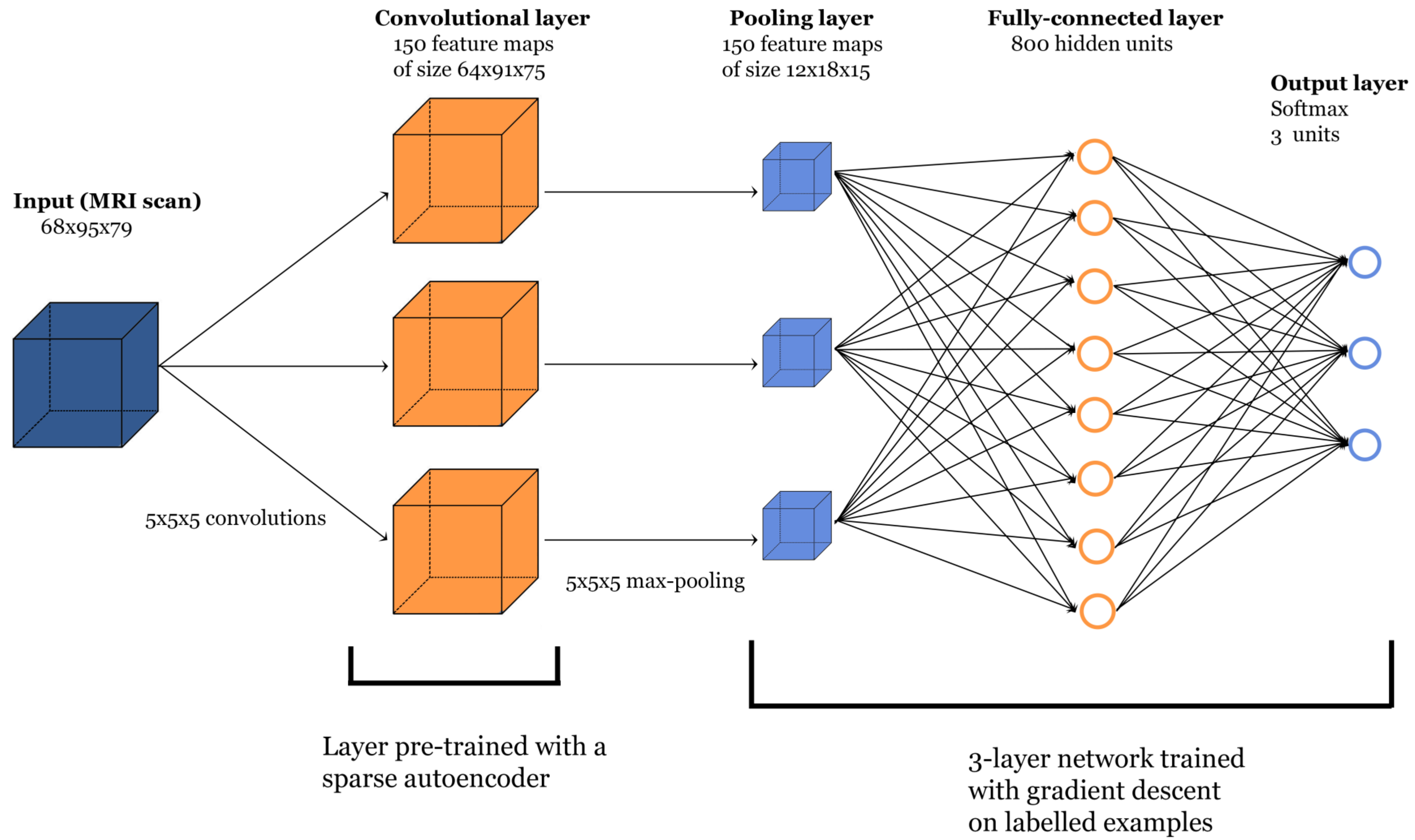
MRI-based ML Studies



[Mazurowski et al., 2018]

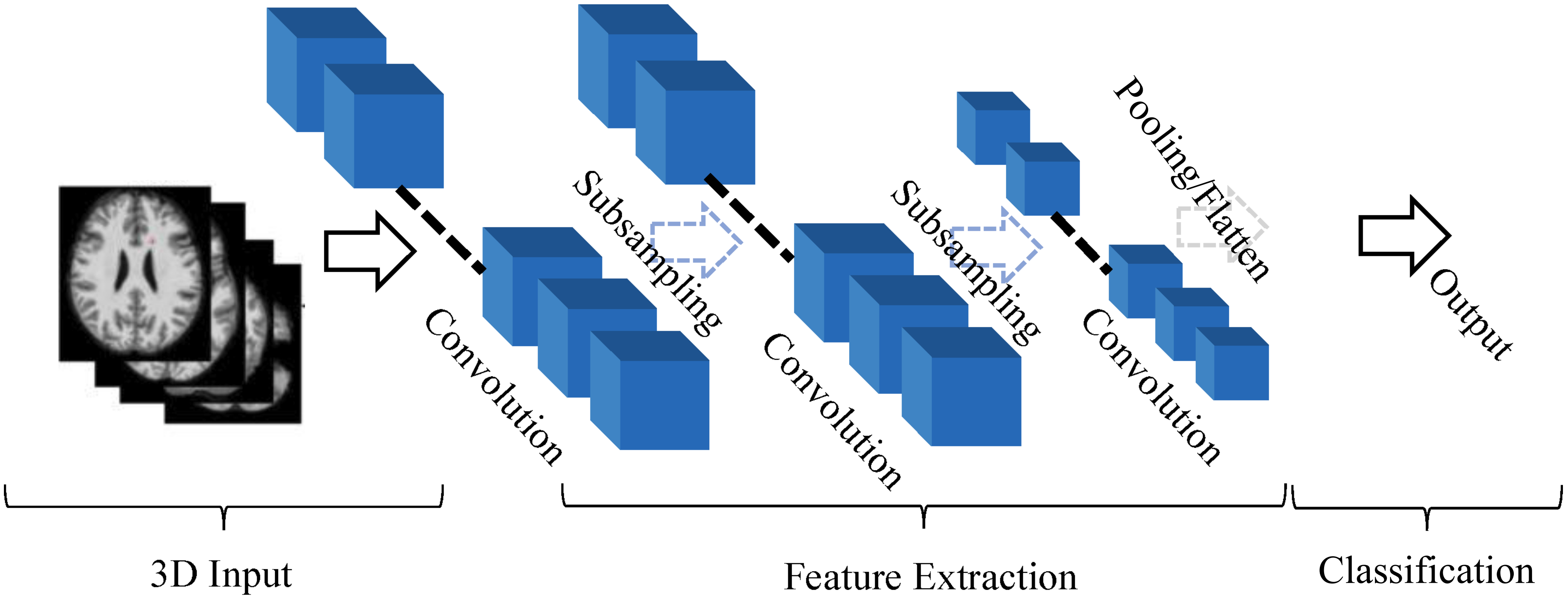
Difference between Traditional ML and Deep Learning

- Classification
  - Demographic classification
  - Disease vs. health classification
  - Risk stratification
  - Treatment response prediction



[Payan & Montana, 2015]

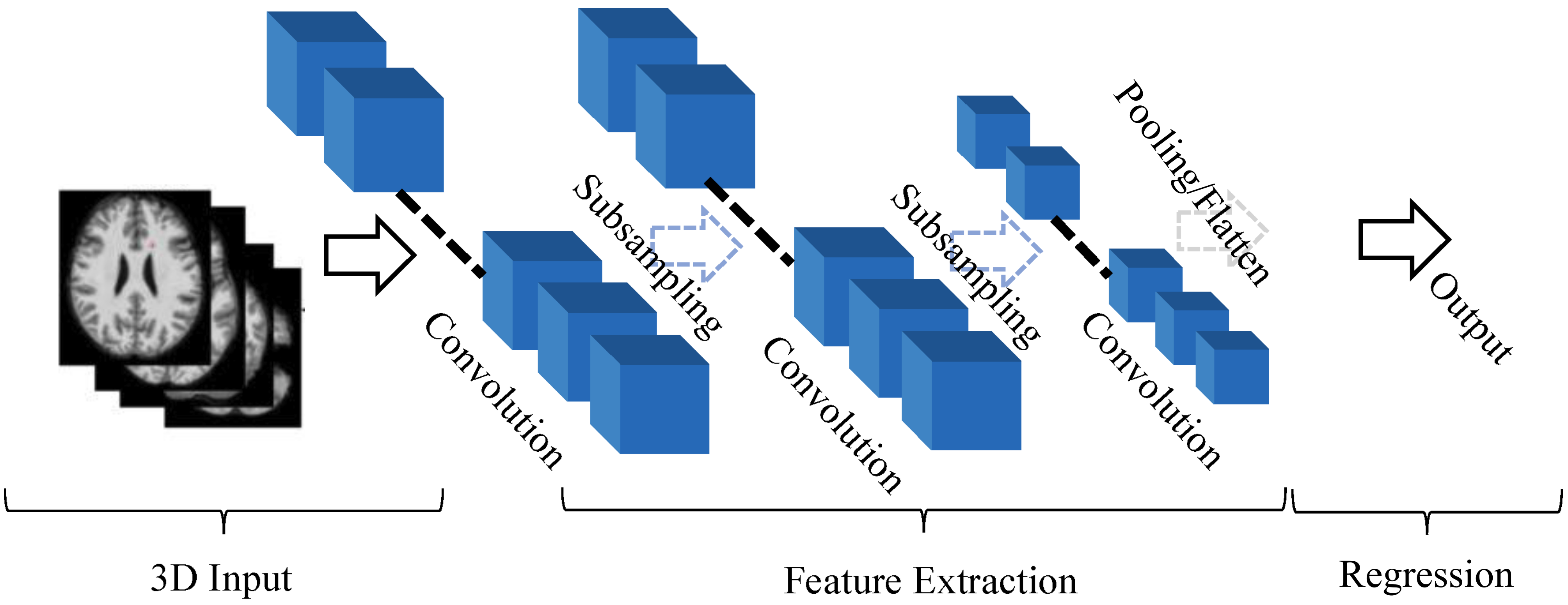
3D Convolutional Neural Network (CNN) Architecture



Feature Extraction (Convolutional, Transformer, or Hybrid Layers) → Pooling/Flatten → Prediction Head (FC Layers + Output Activation)

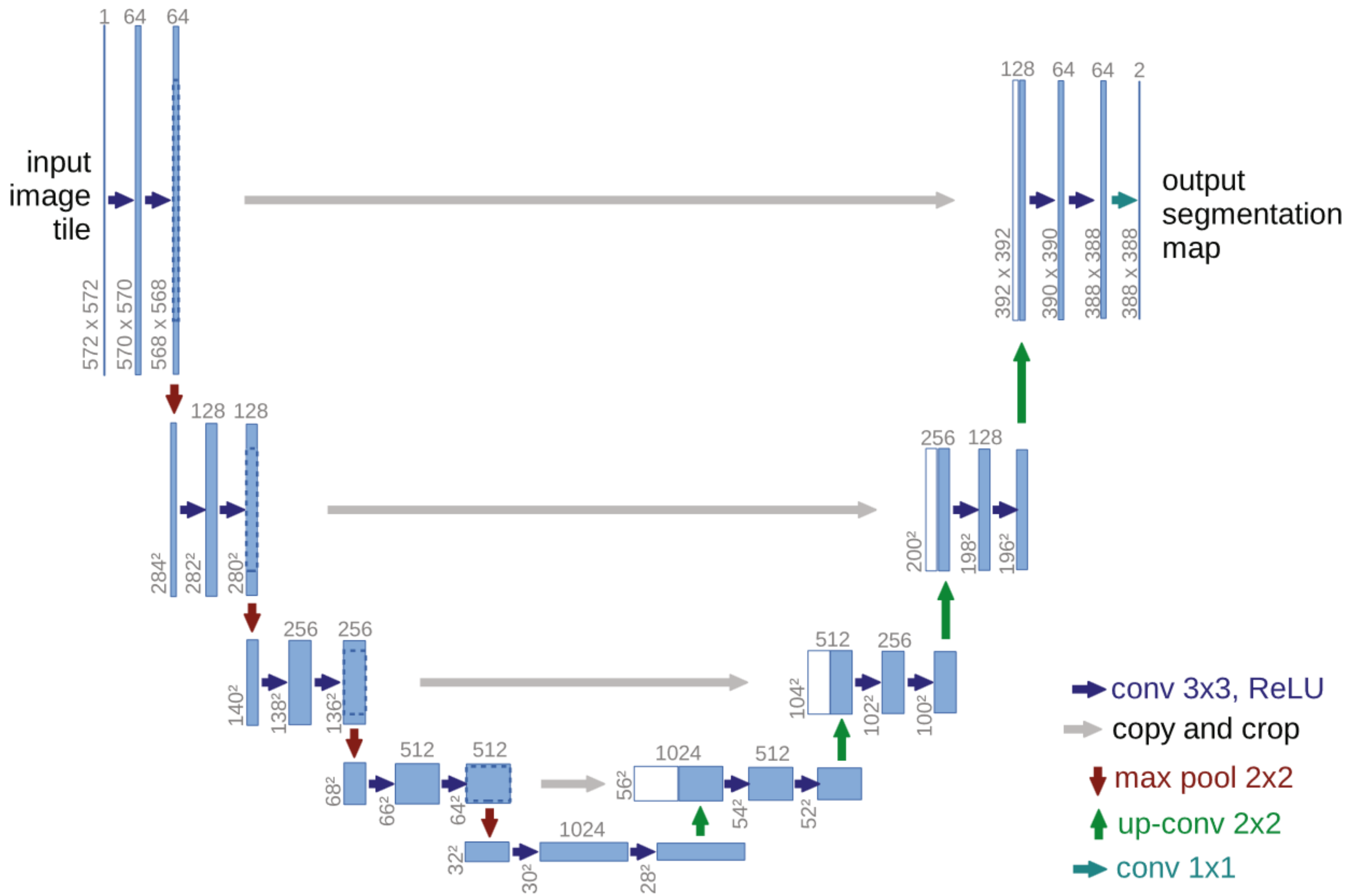
- Regression
  - Age prediction
  - Cognitive performance prediction
  - Disease severity prediction
  - Biomarker quantification

[Yin et al., 2023]



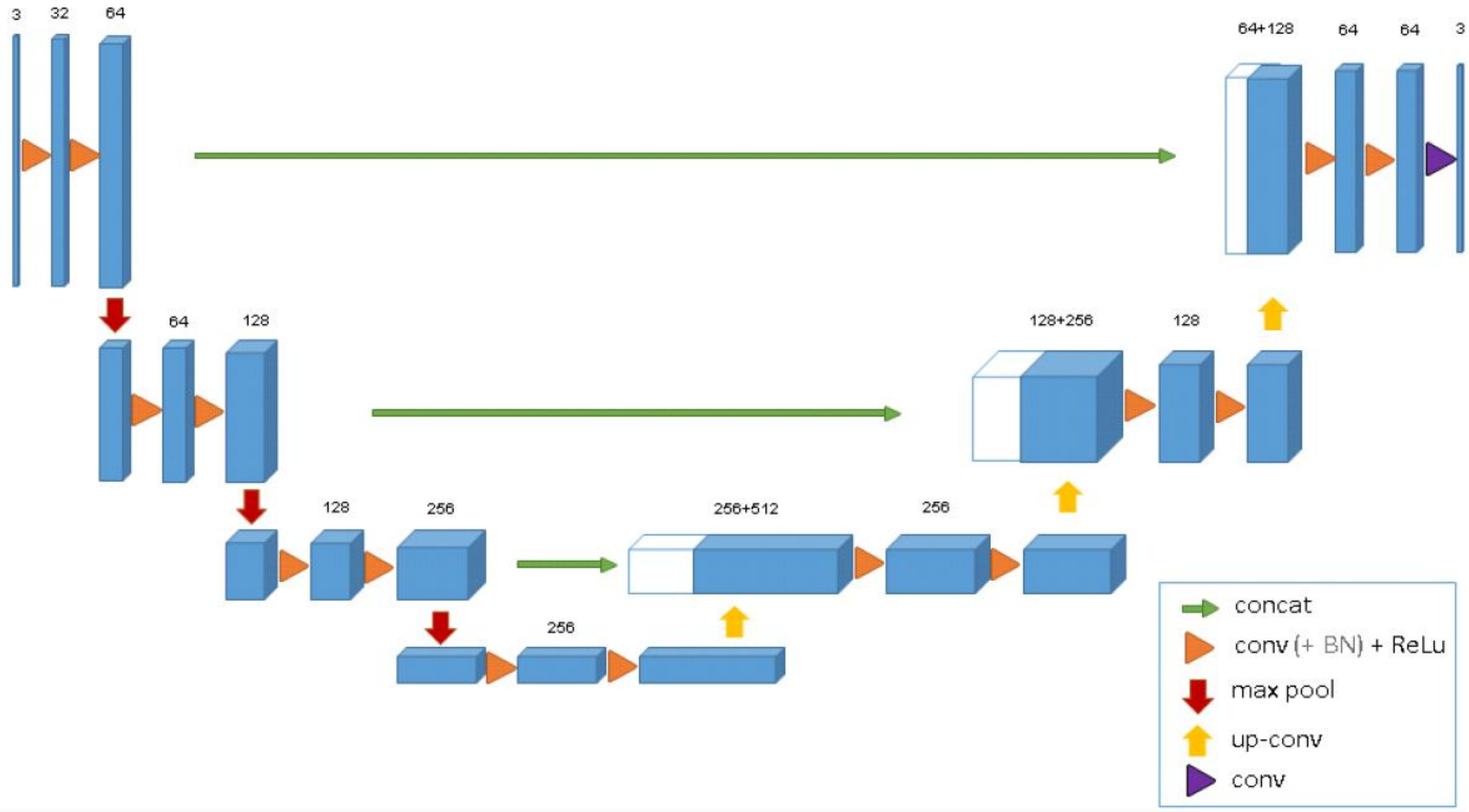
Feature Extraction (Convolutional, Transformer, or Hybrid Layers)
→ Pooling/Flatten → Prediction Head (FC Layers)

- Segmentation
  - Brain lesion segmentation
  - Anatomical structure segmentation
  - Pathological region segmentation
  - Vascular structure segmentation



[Ronneberger et al., 2015)]

U-Net Architecture



[Çiçek et al., 2016]

Feature Extraction (Convolutional, Transformer, or Hybrid Encoder)
→ Spatial Prediction Head (Decoder)

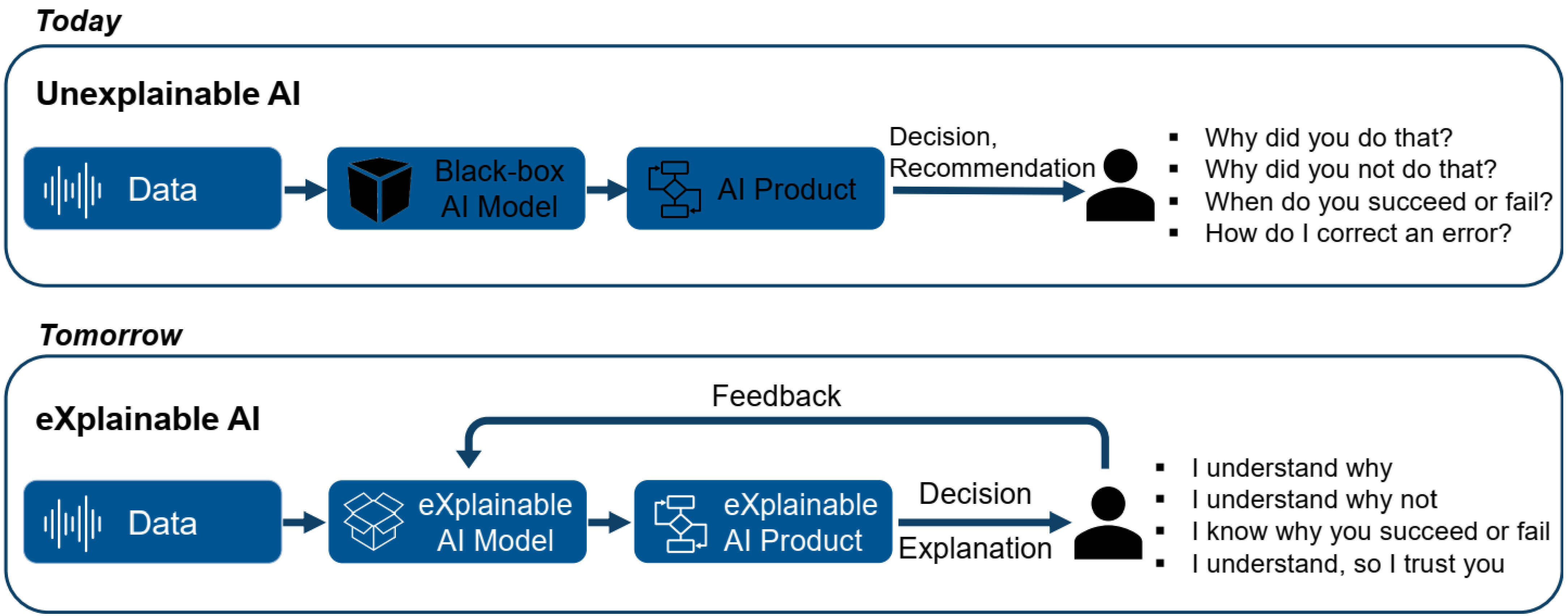
Demands for MRI-based ML

- Good Machine Learning Practices (GMLPs)
  - Standardized guidelines and best practices for developing, validating, and implementing ML systems in healthcare
- Explainable AI (XAI)
  - AI systems designed to make their decisions transparent and interpretable to humans

Checklist of GMLPs for brain MRI		
1.	Are neuroradiologists, neuroimaging scientists, MR technician and data scientist working together throughout the whole life cycle of the product?	
2.	Is the patient's personal information anonymous in the brain MR images?	
3.	Is the metadata being filled for each patient scan with proper details of all parameters?	
4.	Does training and testing MR datasets contain different scans? There shouldn't be any common scan in both datasets.	
5.	Does reference MR dataset for validation of model have completely unique scans with same parameters as training and testing dataset?	
6.	Are you using the model for segmenting brain structures from the specific contrast for which it has been trained for? If so, don't use it for other contrasts.	
7.	Is the output of the model accepted and readable by the neuroradiologist?	
8.	Has the model been tested in the neuroradiology department under the supervision of an expert neuroradiologist before deployment?	
9.	Are the precautions and potential dangers of using the model explicitly mentioned?	
10.	Is the model being updated frequently for incorporating the changes in the new scans that may occur naturally?	

[Aggarwal et al., 2023]

GLMPs for Brain MRI

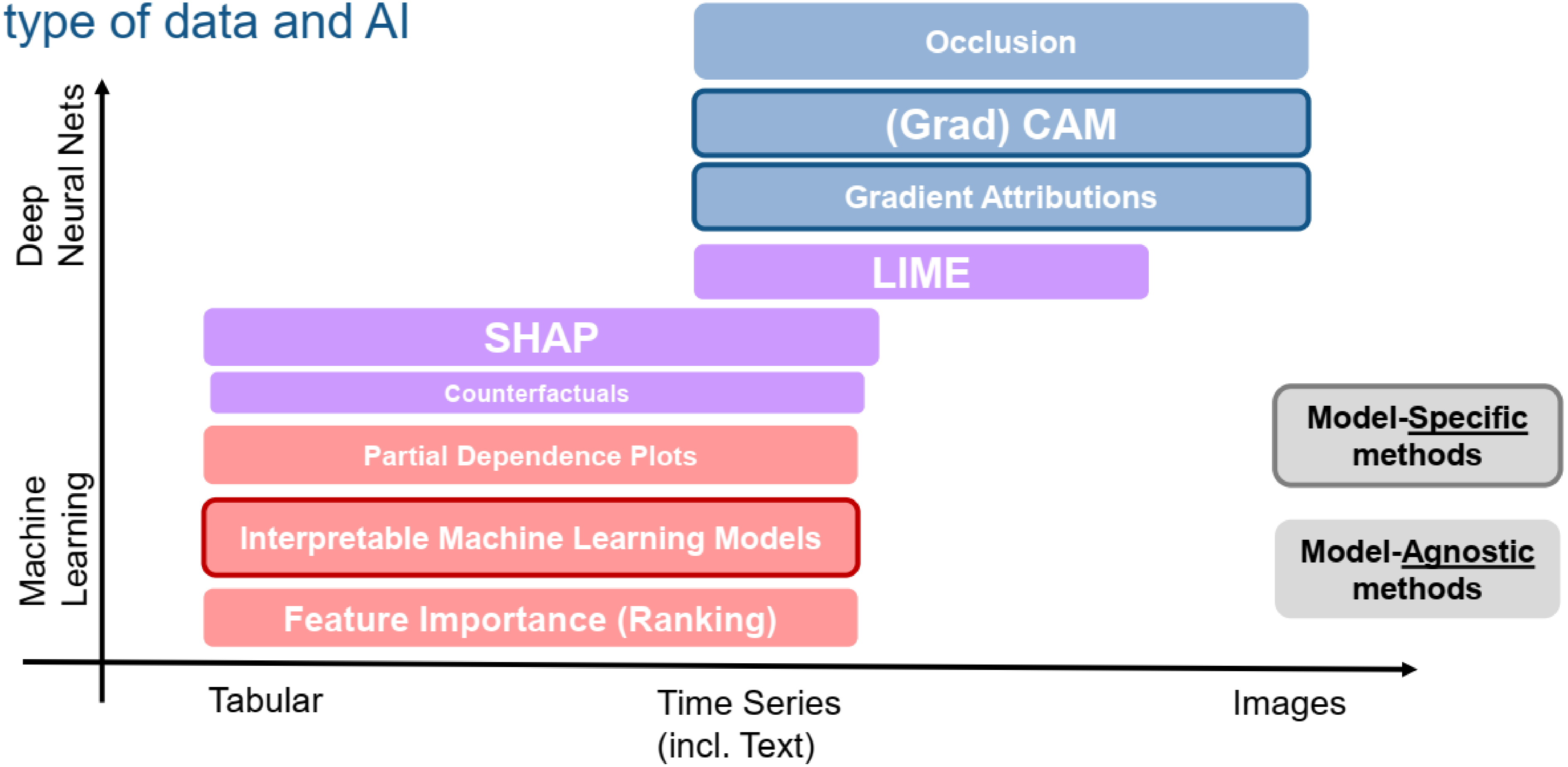


[MathWorks Online Seminar: eXplainable AI and AI V&V]

Unexplainable AI vs. XAI

- Critical importance of XAI in healthcare
  - Clinical trust
    - Helps medical professionals trust AI recommendations
    - Enables validation of AI decisions
  - Regulatory compliance
    - Complies with comprehensive AI regulations (EU AI Act 2024) and specialized healthcare AI requirements (US FDA AI/ML guidance for medical device approval)
    - Supports transparency requirements for high-risk AI systems in healthcare
    - Facilitates compliance with GDPR's automated decision-making provisions
  - Error detection
    - Helps identify potential biases
    - Enables troubleshooting of incorrect outputs

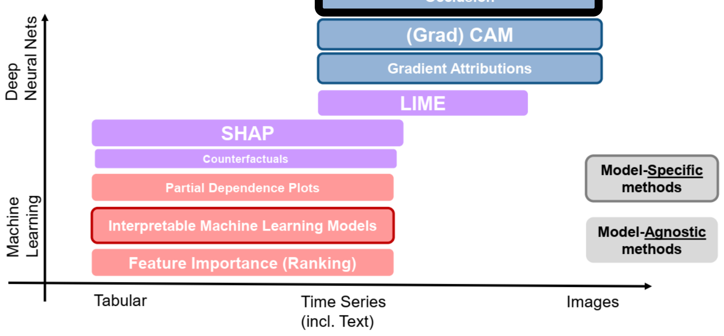
Wide range of techniques with varying applicability depending on type of data and AI

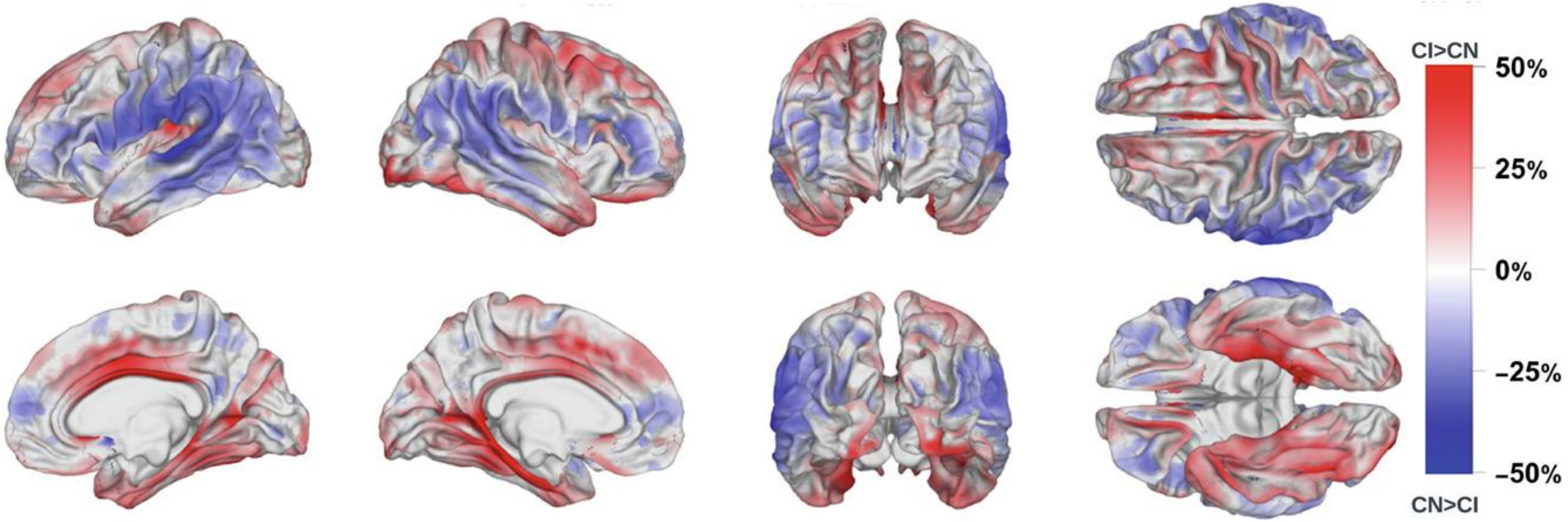


[MathWorks Online Seminar: eXplainable AI and AI V&V]]

Techniques for XAI

Wide range of techniques with varying applicability depending on type of data and AI





[Yin et al., 2023]]

XAI through Sensitivity Analysis

Summary: MRI-based Predictive Analytics