Medical/Bio Research Topics Ⅱ: Week 12 (23.11.2023)

Brain disease diagnosis artificial intelligence models (1-2): data and prediction problem, model construction

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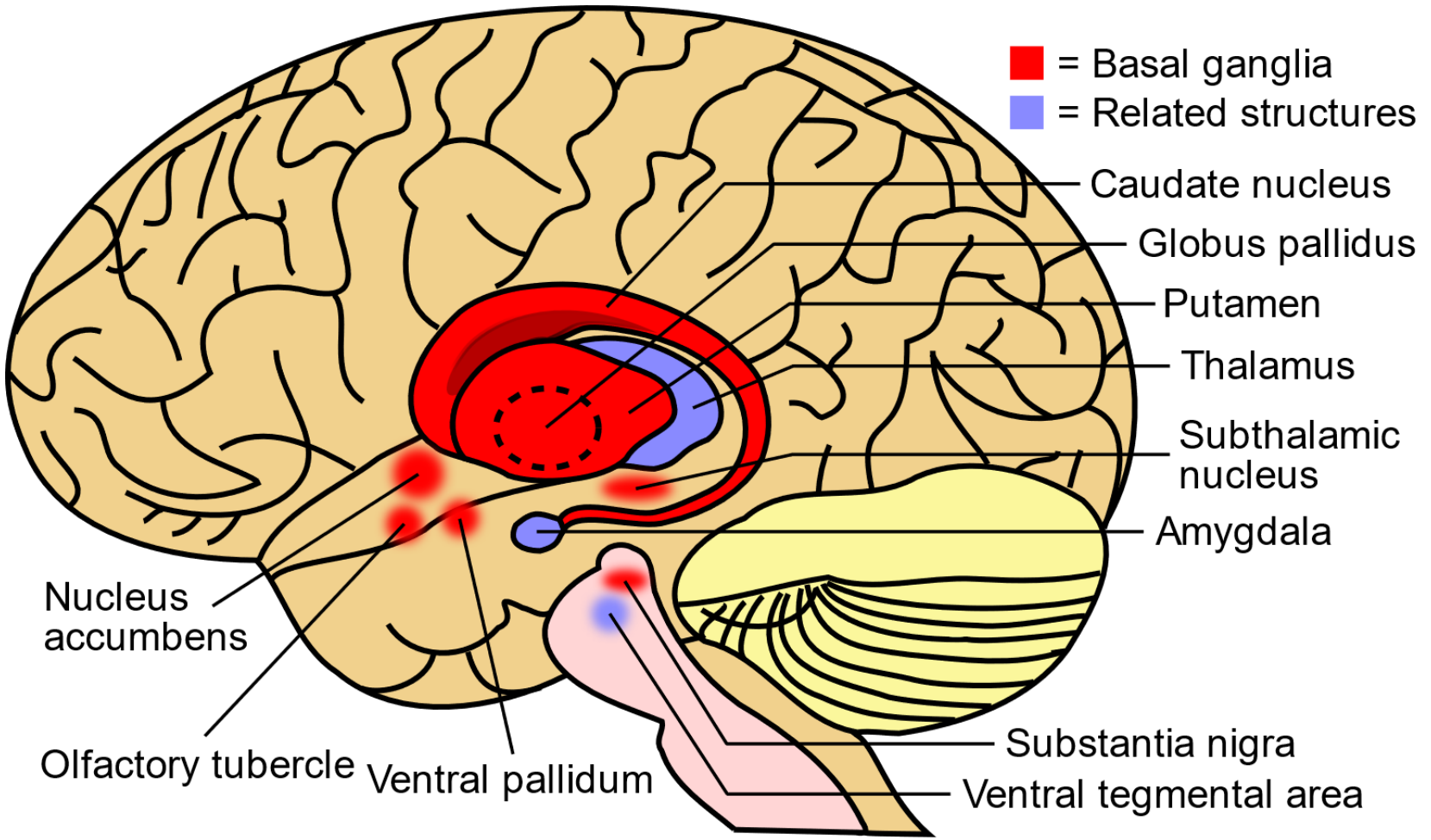
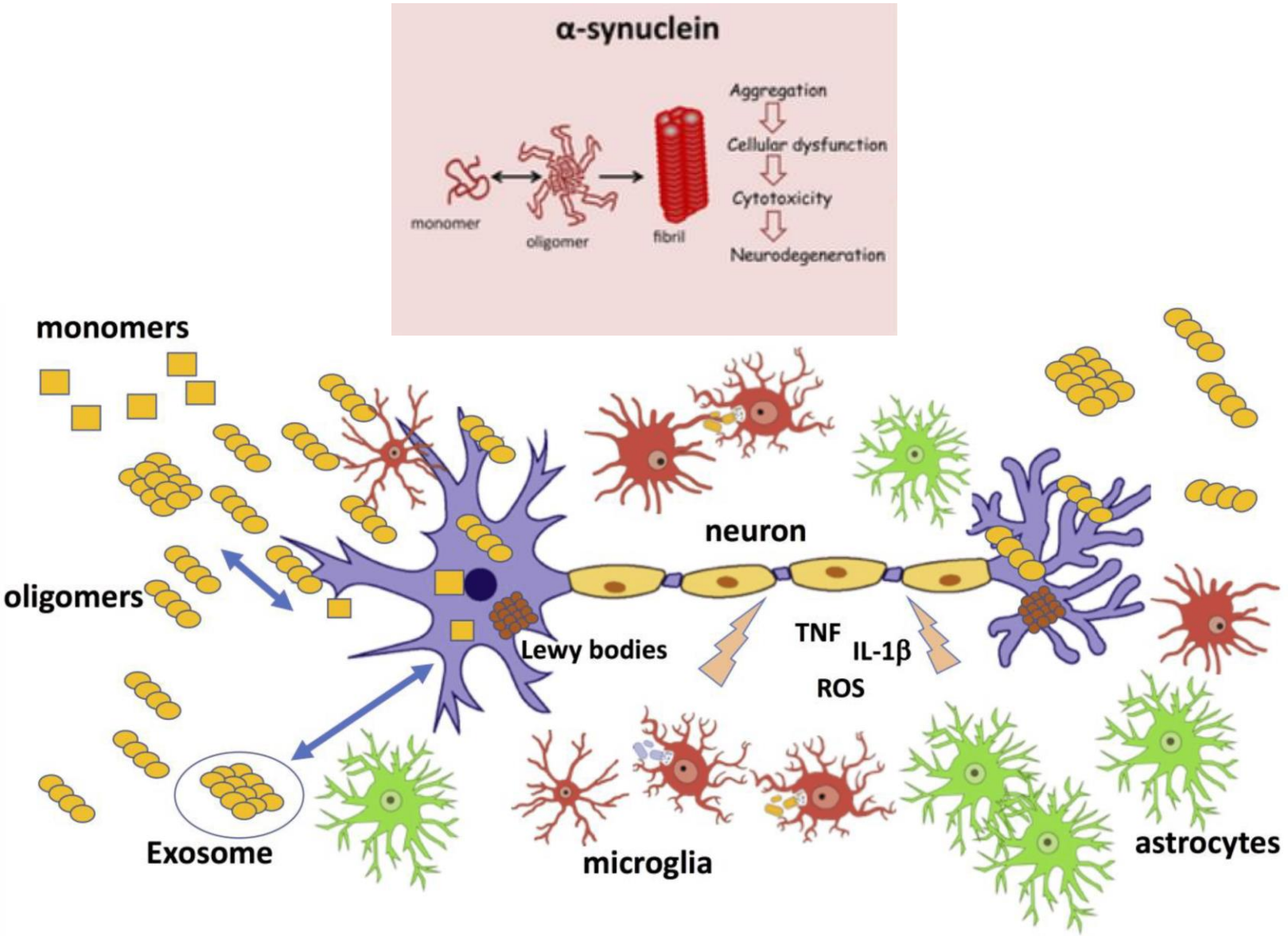
Parkinson's Disease

- Neurodegenerative disease that affects the nervous system and the parts of the body controlled by the nerve
  - Primarily manifests abnormalities of movement
- Resulted from the death of nerve cells in the substantia nigra (region of the midbrain that supplies dopamine to the basal ganglia)
  - Involves the aggregation of α-synuclein proteins into Lewy bodies (clumps of abnormal protein particles) within neurons and their spread throughout the brain



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

Anatomical locations of the substantia nigra and basal ganglia

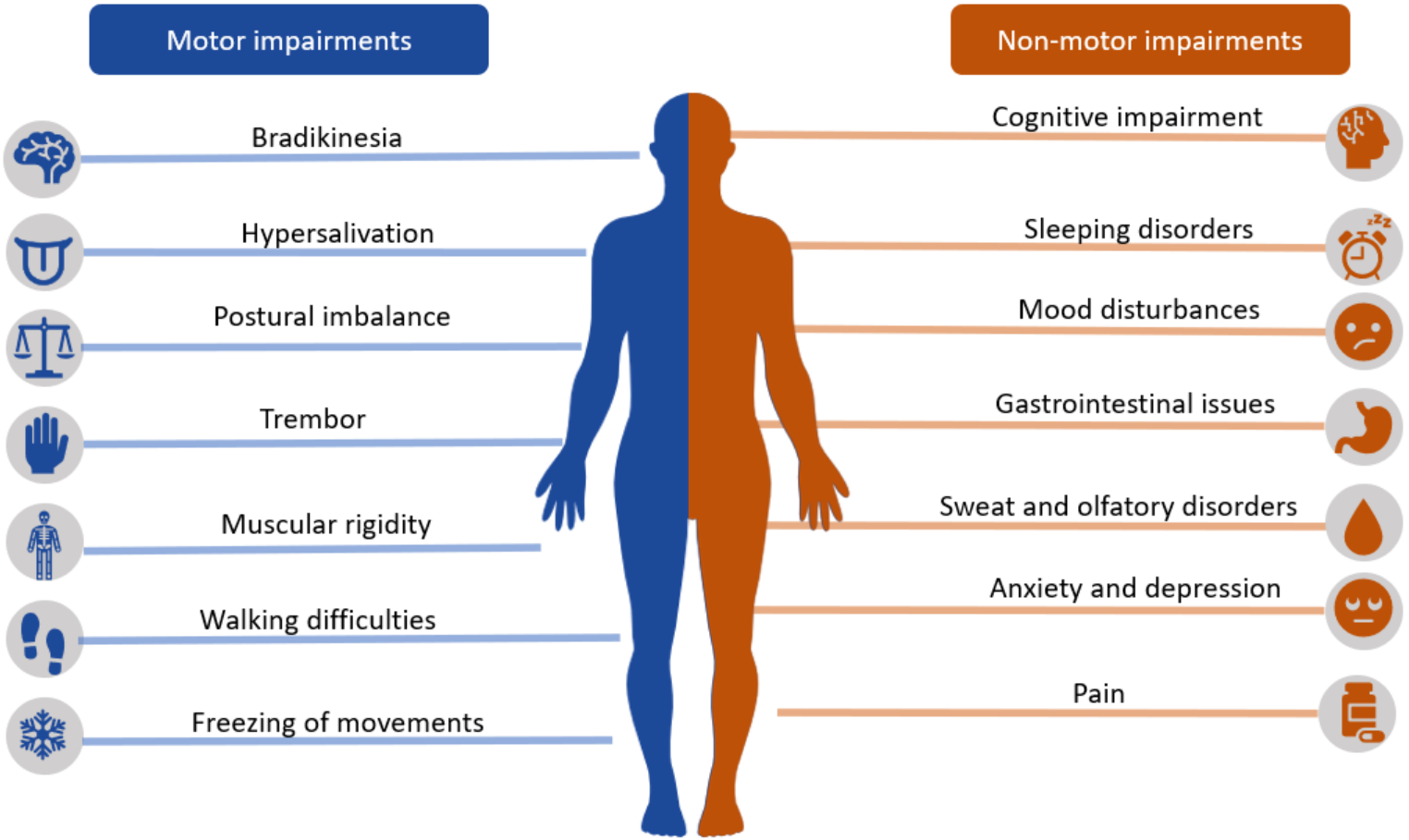


[Delenclos et al., 2019, Forloni, 2023]

Scenario in the pathogenesis of Parkinson's disease

- Prevalence
  - Commonest form of parkinsonism (group of neurological disorders that cause similar symptoms to those seen in Parkinson's disease)
  - Typically occurs in individuals over the age of 60
    - About 1% of individuals over the age of 60 are affected [Reeve et al., 2014]
  - More frequently in males than in females
  - Average life expectancy of 7-15 years following diagnosis

- Signs and symptoms
  - Usually start and develop slowly over years
  - Motor symptoms
    - Cardinal signs and most recognizable symptoms of Parkinson's disease
    - Tremor (rhythmic shaking), rigidity (limb stiffness), bradykinesia (slowed movement), and postural instability (gait and balance problems)
  - Non-motor symptoms
    - Dysautonomia (autonomic dysfunction), neuropsychiatric problems (mood, cognition, behaviour, or thought alterations), and sensory (especially altered sense of smell) and sleep difficulties

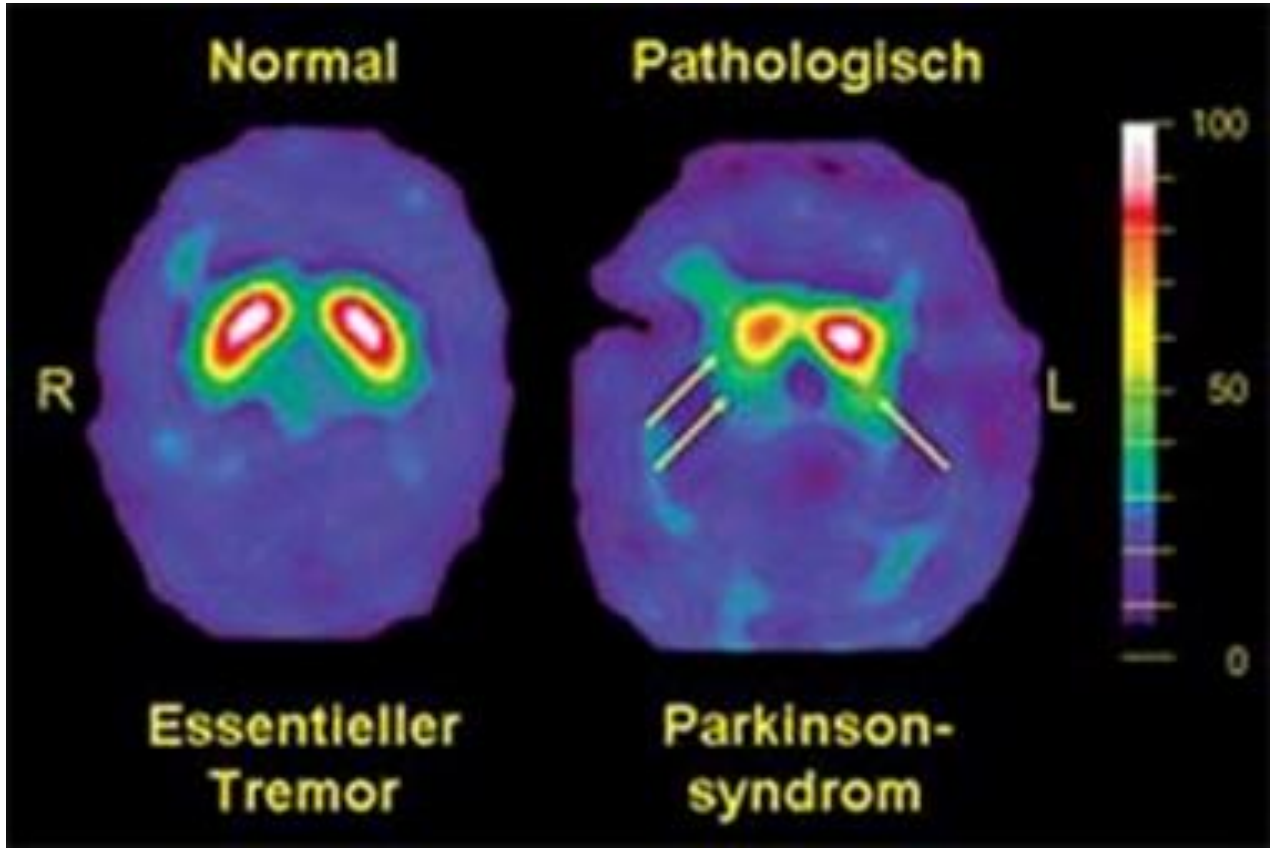


[https://en.wikipedia.org/wiki/Parkinson's_disease]

Signs and symptoms of Parkinson's disease

- Cause
  - Remains largely unknown
    - Called idiopathic (no identifiable cause) parkinsonism
  - Possibly combination of genetic and environmental factors
    - Genetic risks
      - Affected family member
        - » Around 15% of individuals with Parkinson's disease have a first-degree relative who has the disease [Samii et al., 2004]
      - Certain genes
    - Environmental risks
      - Exposure to pesticides
      - Prior head injuries
      - History of exposure to trichloroethylene

- Diagnosis
  - Mainly based on medical history and neurological examination
    - By assessing motor symptoms using clinical diagnosis criteria
  - Brain imaging to rule out other diseases
    - MRI
    - Dopamine transporter (DaT) scan
      - Measures the metabolic activity of dopamine transporters in the basal ganglia by using single-photon emission computed tomography (SPECT)
  - Checked by the finding of Lewy bodies in the midbrain on autopsy
    - Usually considered final proof that an individual had Parkinson's disease
    - 80.6% of Parkinson's disease diagnoses are accurate [Rizzo et al., 2016]



[https://movementdisorders.ufhealth.org/2012/04/11/should-i-get-a-dat-scan-to-confirm-my-parkinsons-disease/]

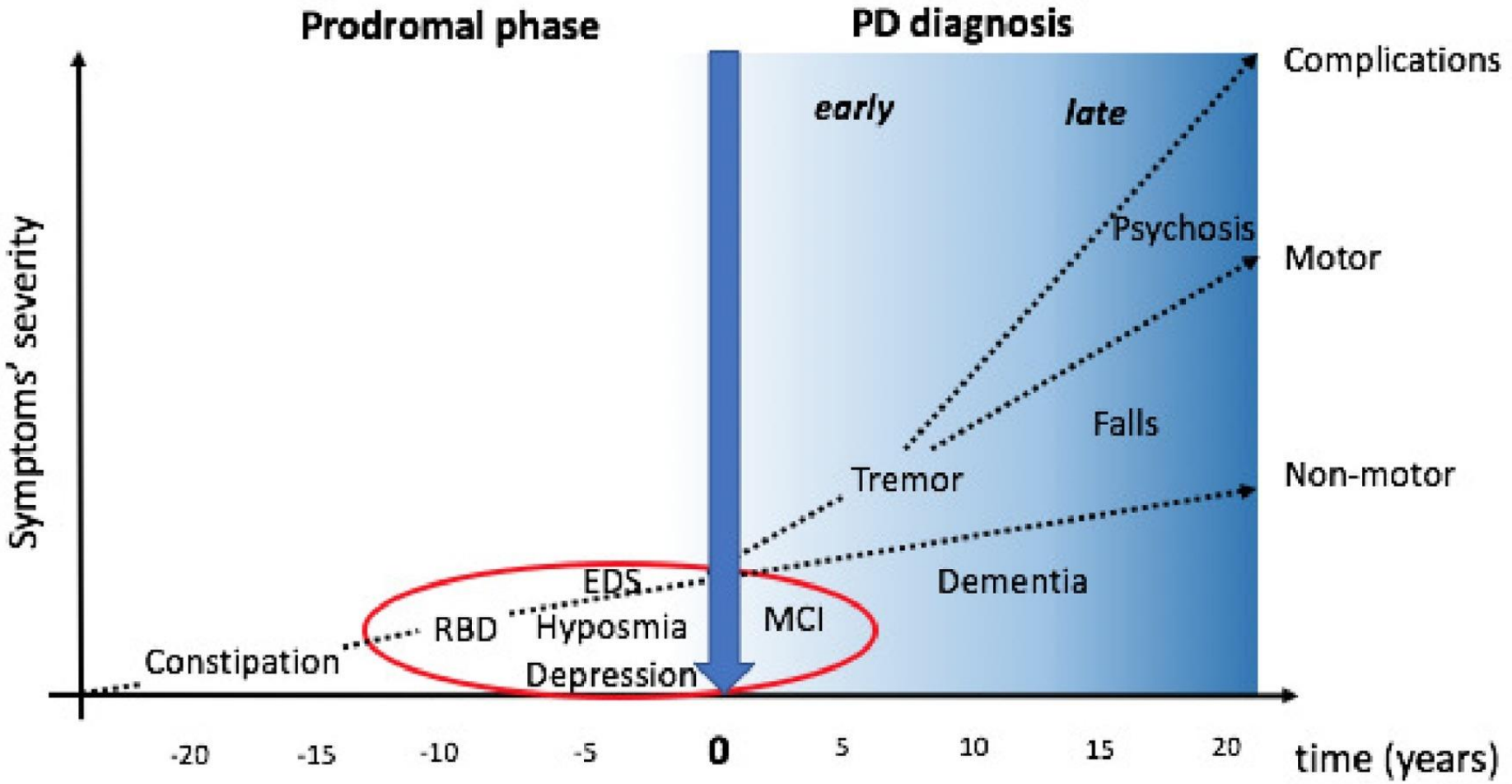
DaT scans for essential tremor (normal) and parkinsonism (decreased)

- Treatment
  - No known cure
  - Aims to reduce the effects of symptoms and improve the quality of an individual's life
    - Medications
    - Diet and certain forms of rehabilitation
    - Surgery to place microelectrodes for deep brain stimulation
  - Much more effective than treatment for other neurological disorders such as Alzheimer's disease [Connolly et al., 2014]

Prodrome

- Early signs or symptoms that often indicate the onset of a disease before more diagnostically specific signs and symptoms develop
  - In several psychiatric diseases such as schizophrenia and bipolar disorder
  - In several neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease

- Prodromal Parkinson’s disease
  - Prodromal phase of Parkinson’s disease
    - Progressive neurodegenerative pathology is initiated, but motor symptoms necessary for the diagnosis of Parkinson's disease are not yet manifested
  - May begin several years before the onset of motor symptoms
    - Disease course modifying treatment may be given before motor symptoms occur
  - Characterized by a range of non-motor symptoms as well as subtle motor symptoms
    - Hyposmia, constipation, depression, anxiety, rapid eye movement (REM) sleep behavior disorder (RBD), and excessive daytime sleepiness (EDS)
  - Increased risk of Parkinson's disease in case of genetic variants



[Amoroso et al., 2018]

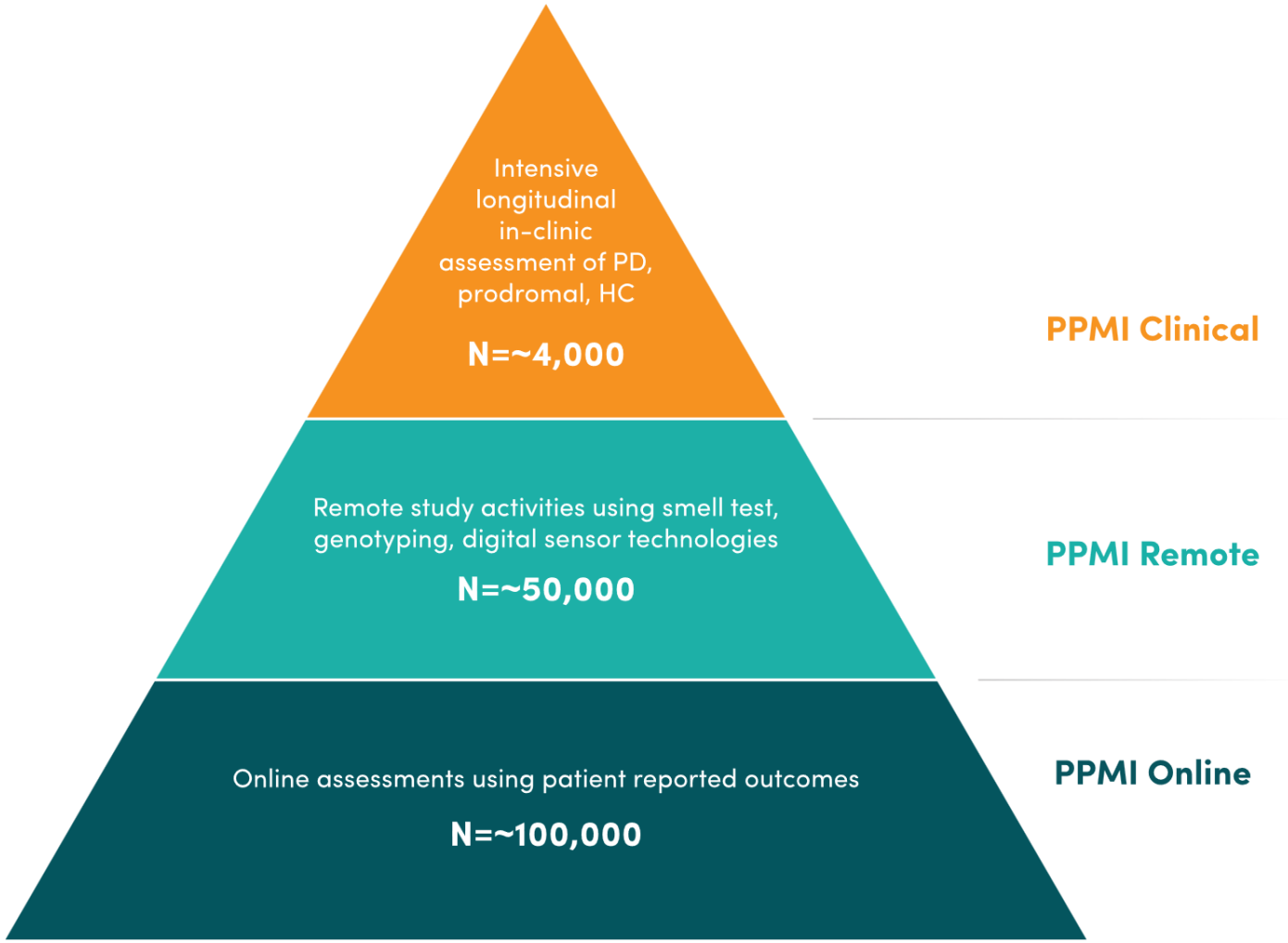
Symptoms characterizing prodromal Parkinson's disease

Parkinson's Progression Markers Initiative (PPMI)

- Launched in 2010 by the Michael J. Fox Foundation and a core group of academic scientists and industry partners
- Assesses progression of clinical features, imaging outcomes, biologic and genetic markers, and digital outcomes of Parkinson’s disease across its all stages from prodromal to moderate disease

- Aims to identify biomarkers of Parkinson's disease progression
  - By assessing multiple cohorts to develop the largest collection of clinical, imaging, and biologic specimens ever created in the Parkinson's community
  - To accelerate therapeutic trials to reduce progression of disability
  - Diagnostic vs. progression marker
    - Diagnostic marker: any objectively measurable physical characteristic associated with the presence of the disease
    - Progression marker: any characteristic that changes over time in a way that can be tied to the progression of the disease

- Study design
  - Longitudinal, observational, multi-center natural history study
    - Comprehensive longitudinal within-participant data in approximately 4,000 participants enrolled at about 50 sites worldwide
    - By enrolling individuals with (diagnosed with Parkinson's disease in the past two years and not yet taking medication) and without Parkinson's disease
  - Through the pathway from PPMI online to PPMI Remote and finally to PPMI clinical



[https://www.ppmi-info.org/study-design]

Prodromal pyramid

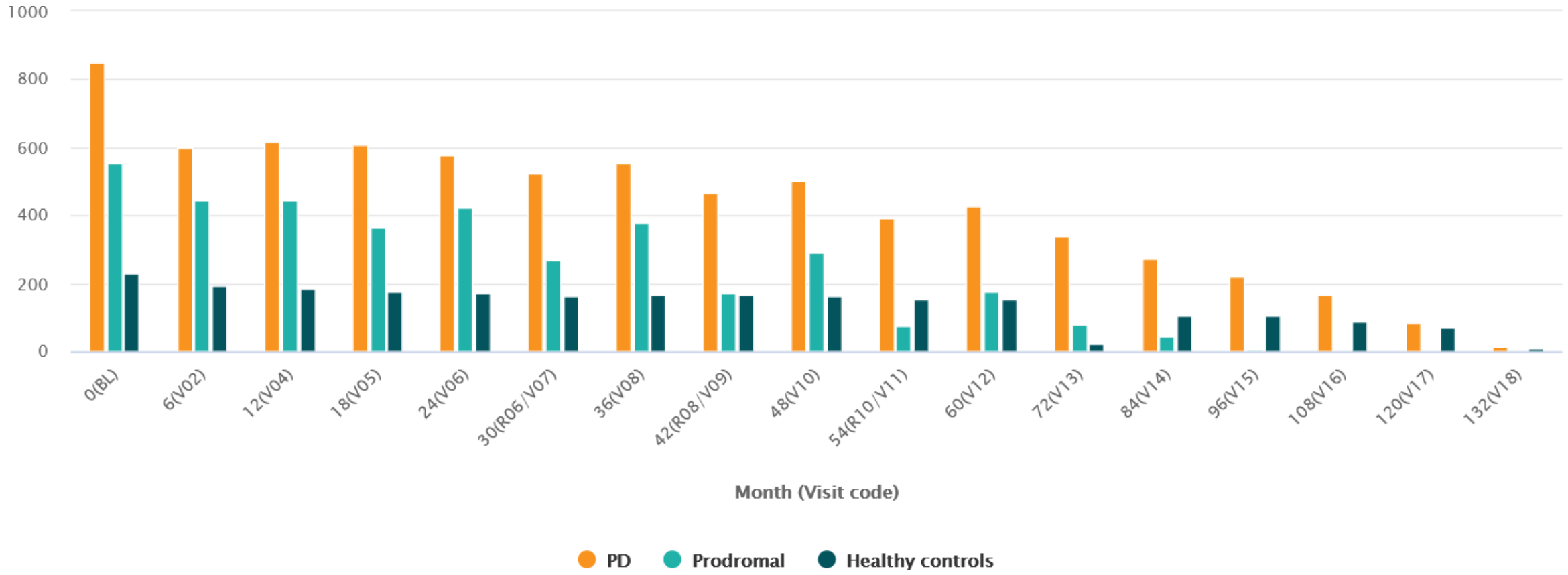
- Data
  - Imaging data
    - Structural MRI
    - Diffusion-weighted MRI
    - DaT scan
  - Clinical information and assessment results
    - Medical and family history (including demographics)
    - Physical examination
    - Neurological examination
    - Vital signs
    - Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) scores (including Part III and Hoehn & Yahr)

- Modified Schwab & England Activities of Daily Living (ADL)
- University of Pennsylvania Smell Identification Test (UPSIT, olfactory testing)
- Hopkins Verbal Learning Test
- Benton Judgment of Line Orientation
- Semantic fluency
- Letter number sequencing
- Symbol digit modalities
- Montreal Cognitive Assessment (MoCA)
- Epworth Sleepiness Scale
- REM Sleep Behaviour Questionnaire
- Geriatric Depression Scale (GDS-15)
- State-Trait Anxiety Inventory for Adults

- Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP)
- Scale for Outcomes in Parkinson's disease for Autonomic Symptoms (SCOPA-AUT)
- Current medical conditions review
- Concomitant medication review

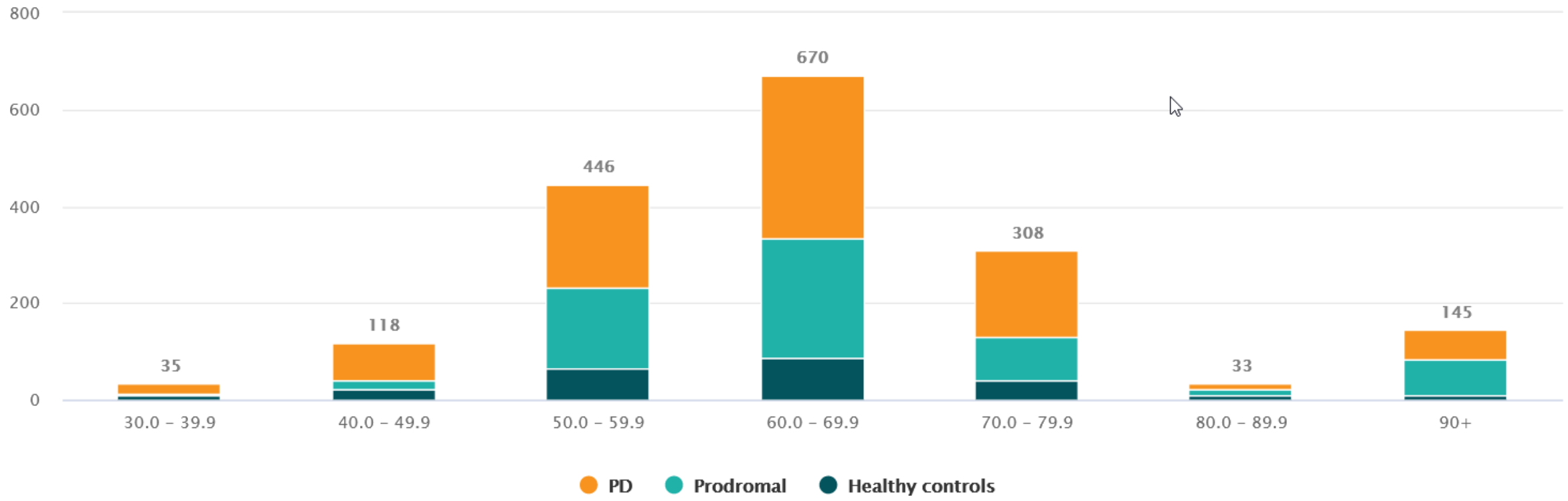
- Study cohorts
  - Parkinson’s disease cohort
    - Clinical diagnosis of Parkinson’s disease
    - Positive DaT scan
    - Comprised of subgroups:
      - Untreated Parkinson’s disease
      - Parkinson’s disease and pathogenic genetic variant(s) in LRRK2, GBA, SNCA
  - Healthy controls
    - No current or active clinically significant neurologic disorder
    - No first-degree relative with Parkinson’s disease
    - Normal DaT scan

- Prodromal cohort
  - No clinical diagnosis of Parkinson's disease or other parkinsonism or of dementia
  - At risk of Parkinson's disease based on clinical features, genetic variants, or other biomarkers
    - REM sleep behaviour disorder (RBD)
    - Known genetic risk variants including LRRK2, GBA, SNCA, or other rare genetic variants (e.g., PRKN, PINK1)
    - Hyposmia based on UPSIT testing
    - First-degree family history of Parkinson's disease
    - Other known Parkinson's disease risk criteria including those based on questionnaires in PPMI Online
  - Positive DaT scan



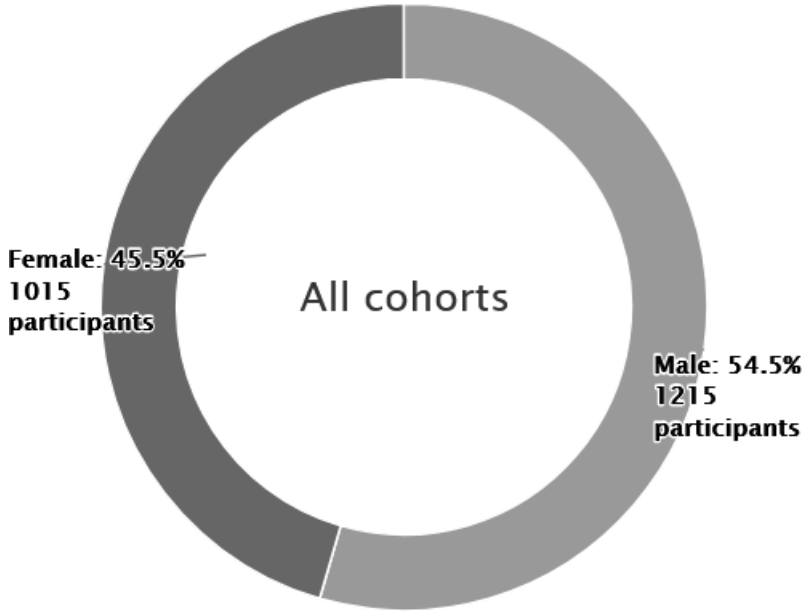
[https://www.ppmi-info.org/access-data-specimens/data]

PPMI participants by visit



[https://www.ppmi-info.org/access-data-specimens/data]

PPMI participants by age



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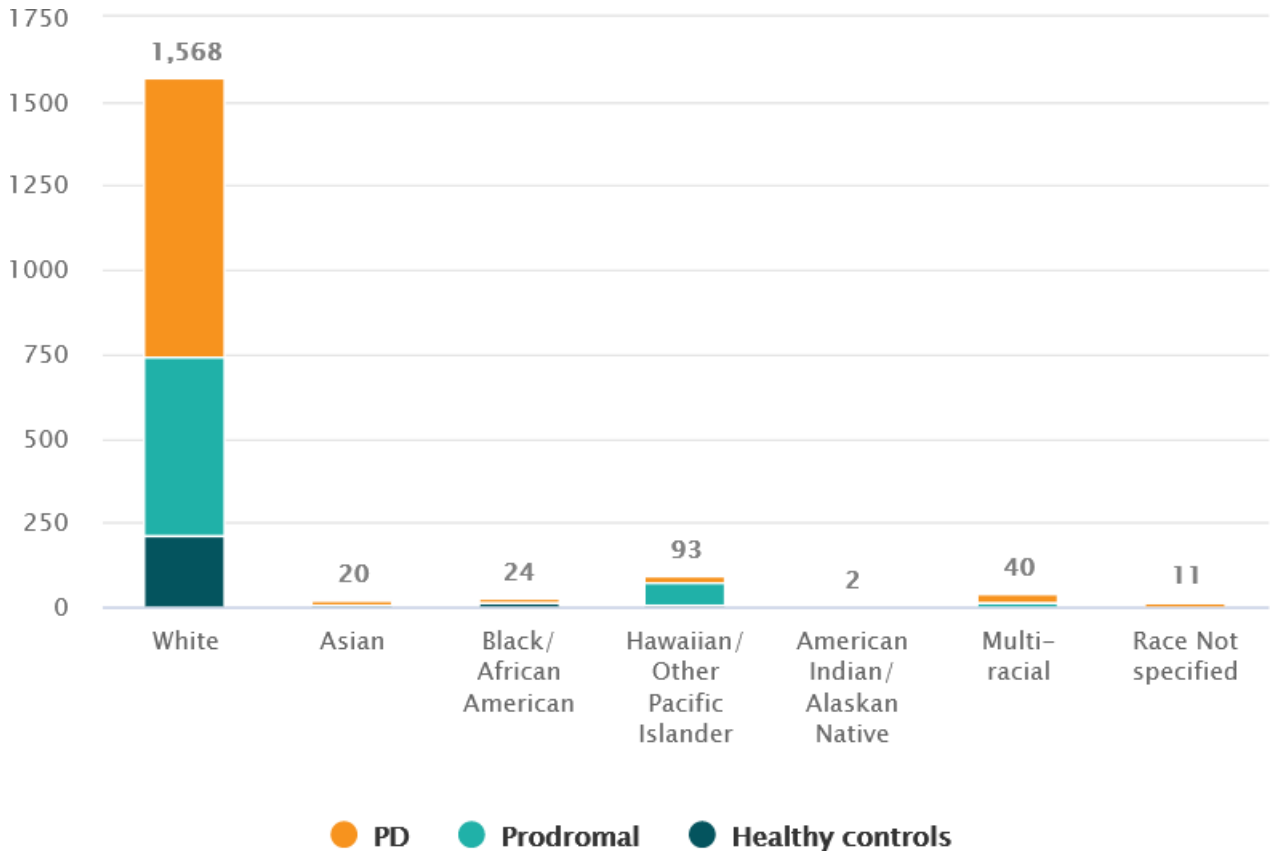
PPMI participants by sex

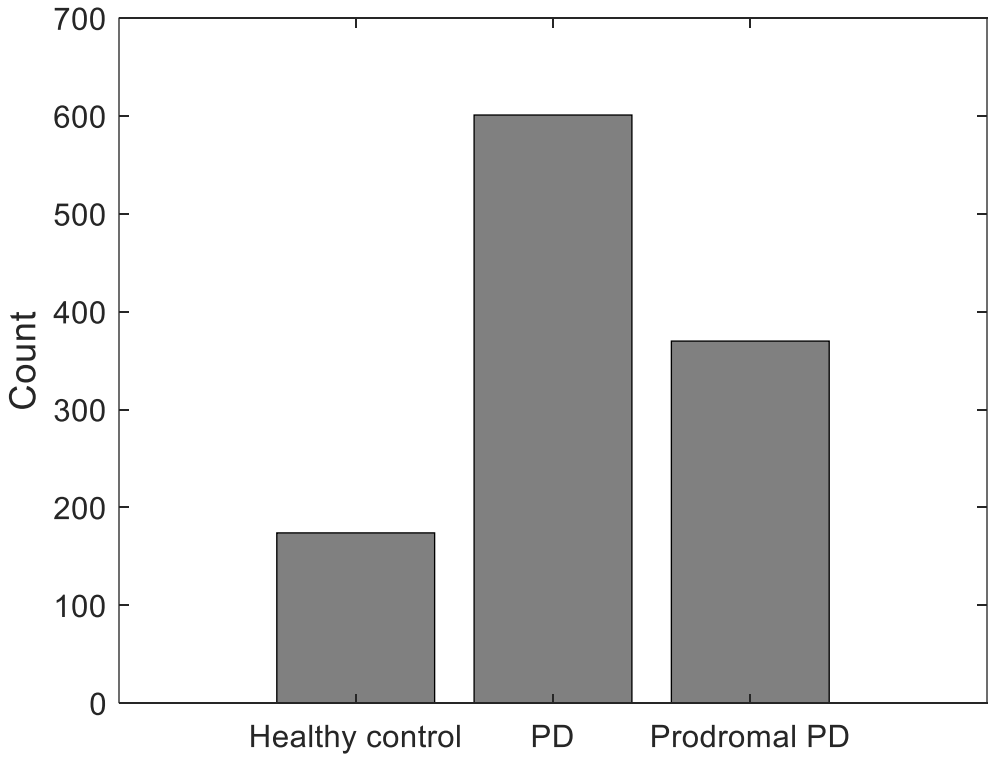


[https://www.ppmi-info.org/access-data-specimens/data]

PPMI participants by race

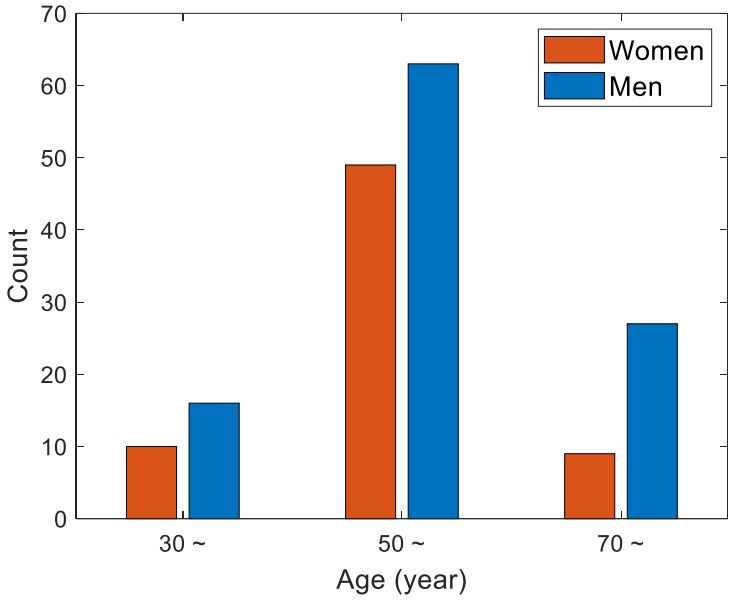
Dataset

- Data from PPMI (n = 1,145)
  - T1-weighted MRI scans at baseline
  - Demographic information including chronological age and sex

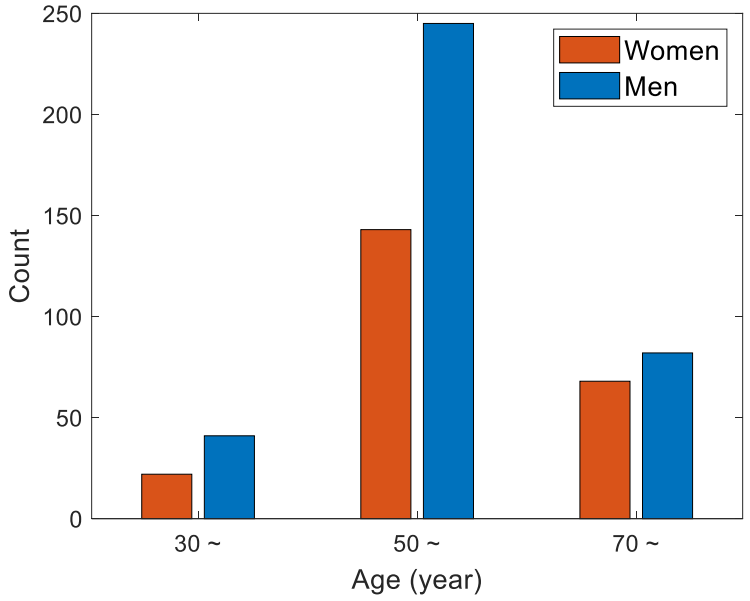


Distribution of cohorts for the whole data

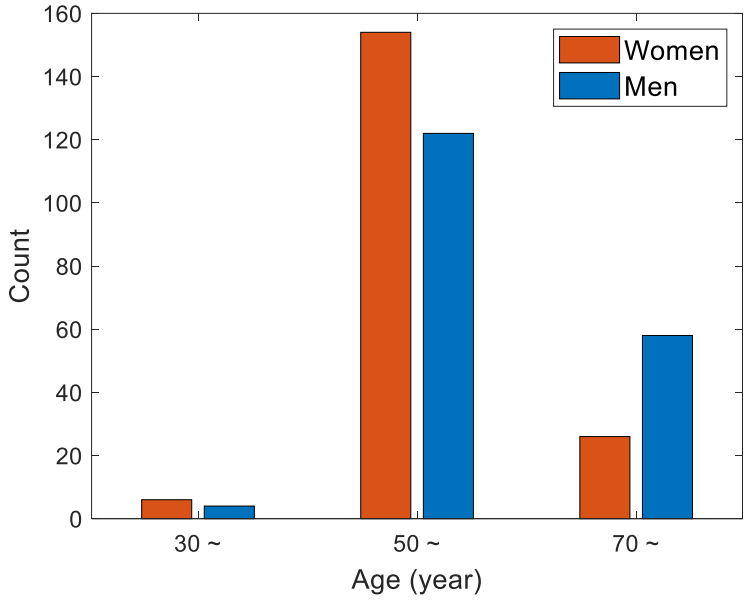
- HealthyControl (healthy individuals): *n* = 174
  - Age: 60.8±11.5 years
  - Sex: 68 women and 106 men
- PD (individuals with Parkinson's disease): *n* = 601
  - Age: 62.9±9.7 years
  - Sex: 233 women and 368 men
- ProdromalPD (individuals with prodromal Parkinson's disease): *n* = 370
  - Age: 64.6±7.3 years
  - Sex: 186 women and 184 men



HealthyControl

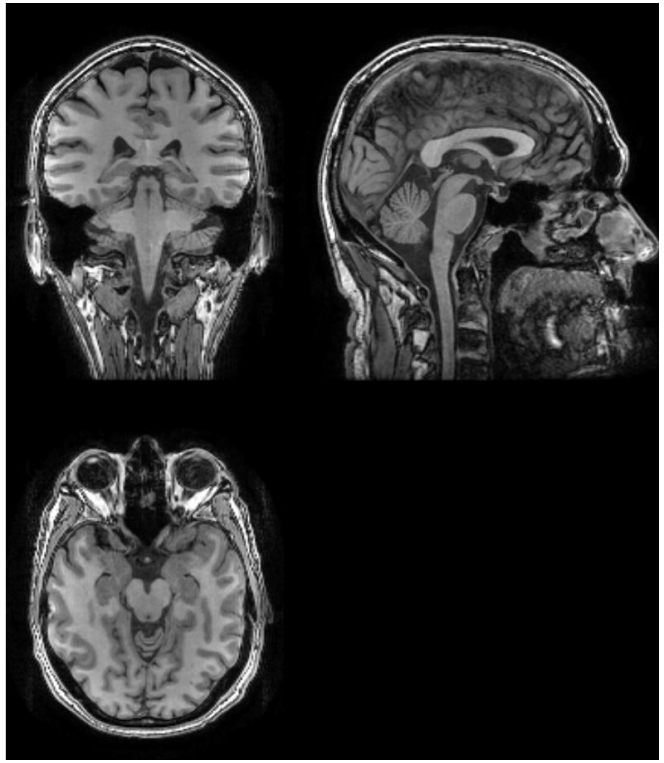


PD

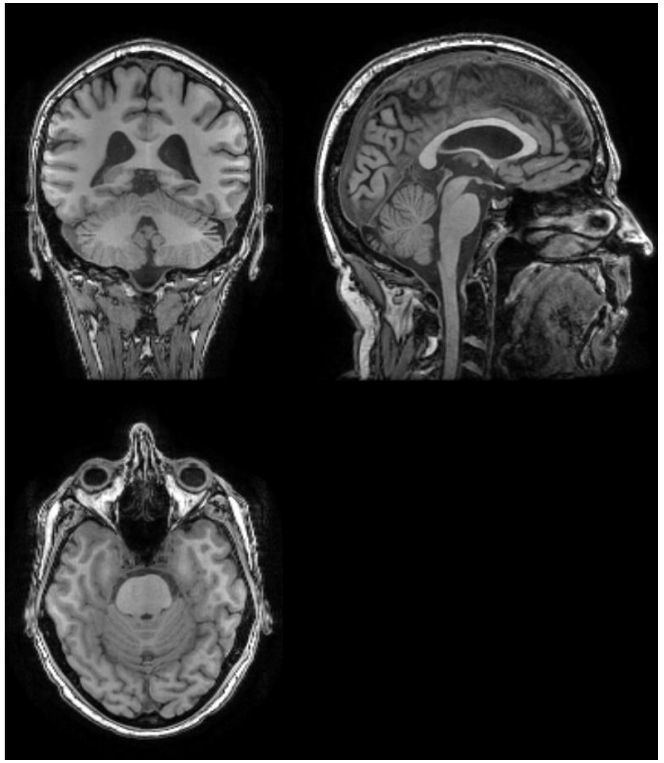


ProdromalPD

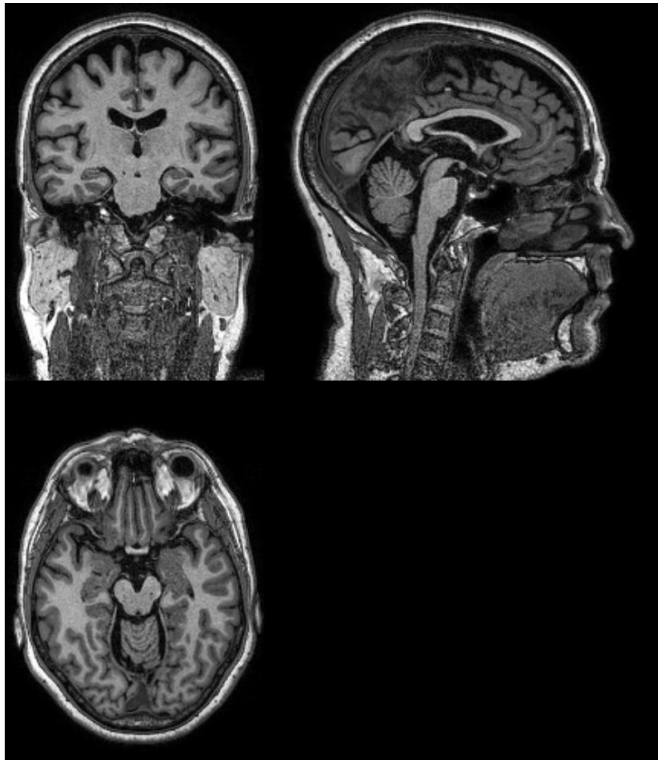
Distribution of age and sex for three cohorts



HealthyControl



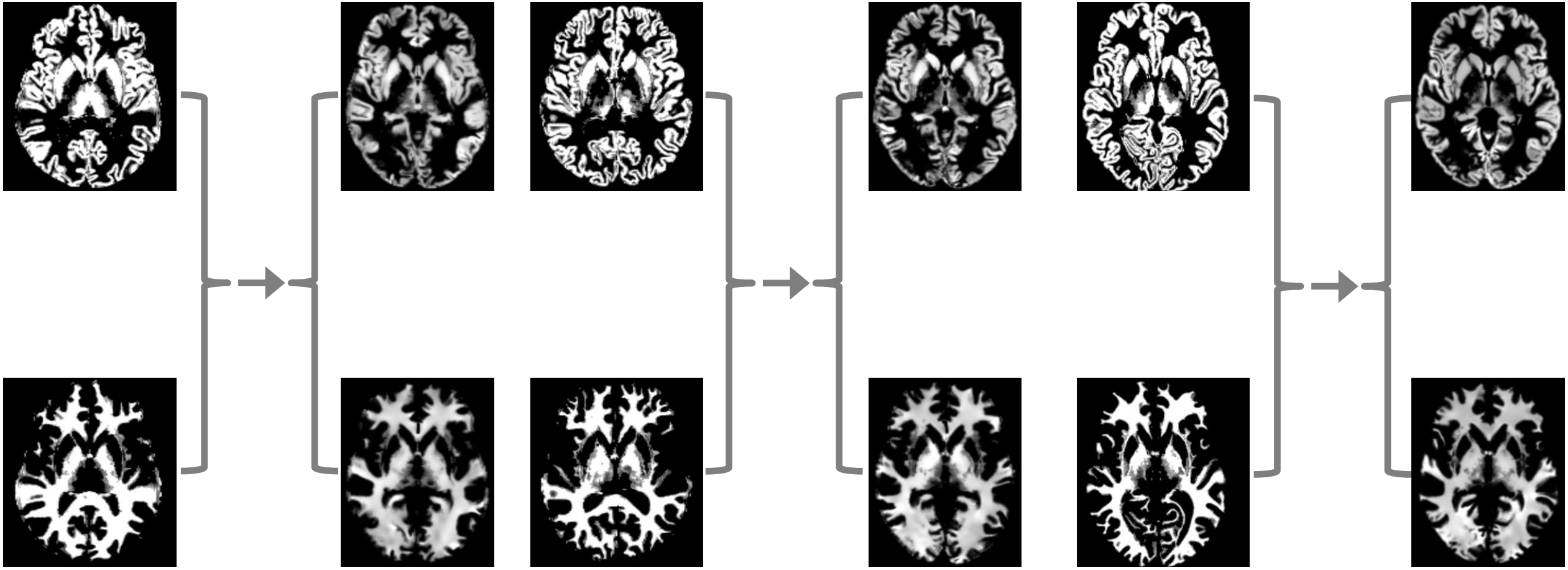
PD



ProdromalPD

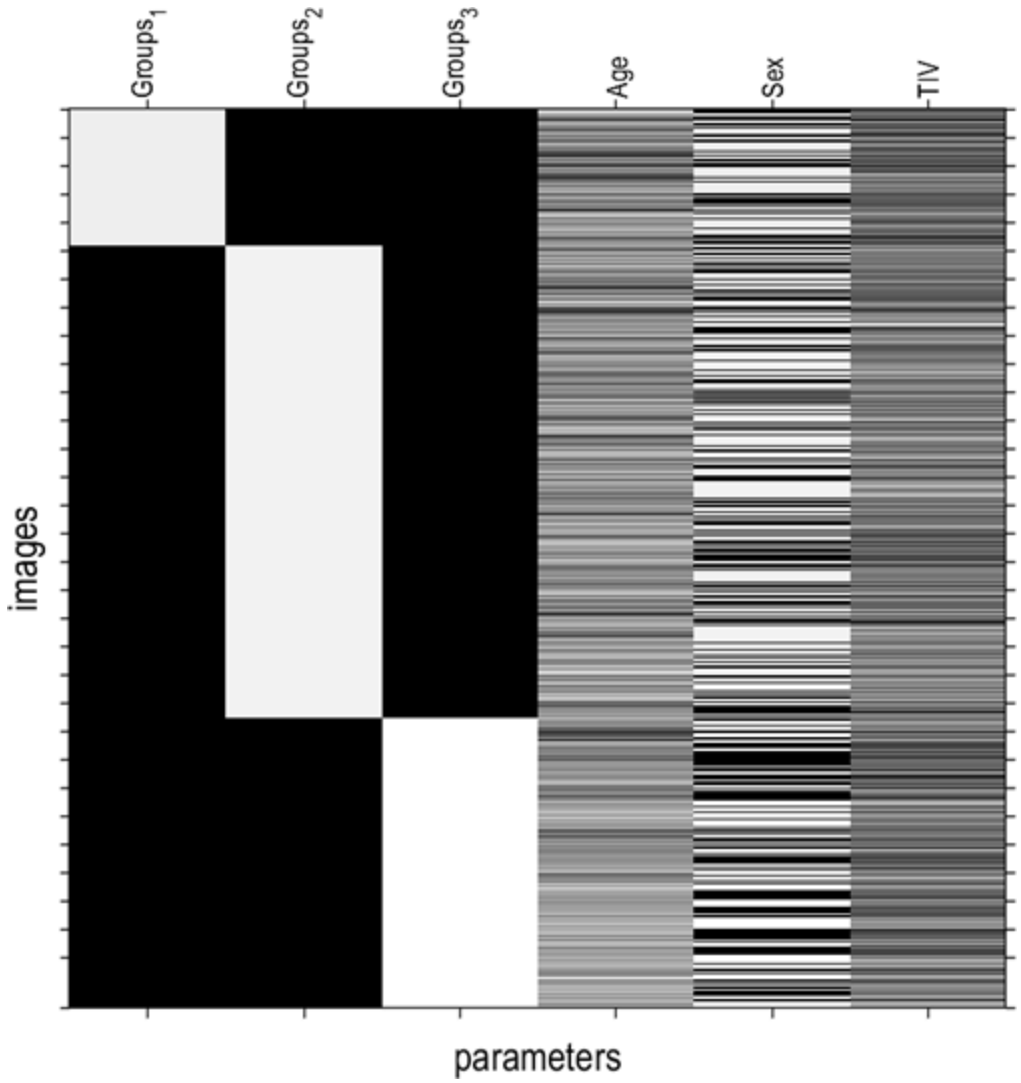
T1-weighted MRI scan

- Preprocessing
  - Correction for intensity non-uniformity (bias field)
  - Segmentation into grey matter, white matter, and cerebrospinal fluid
  - Normalisation into the MNI standard brain space



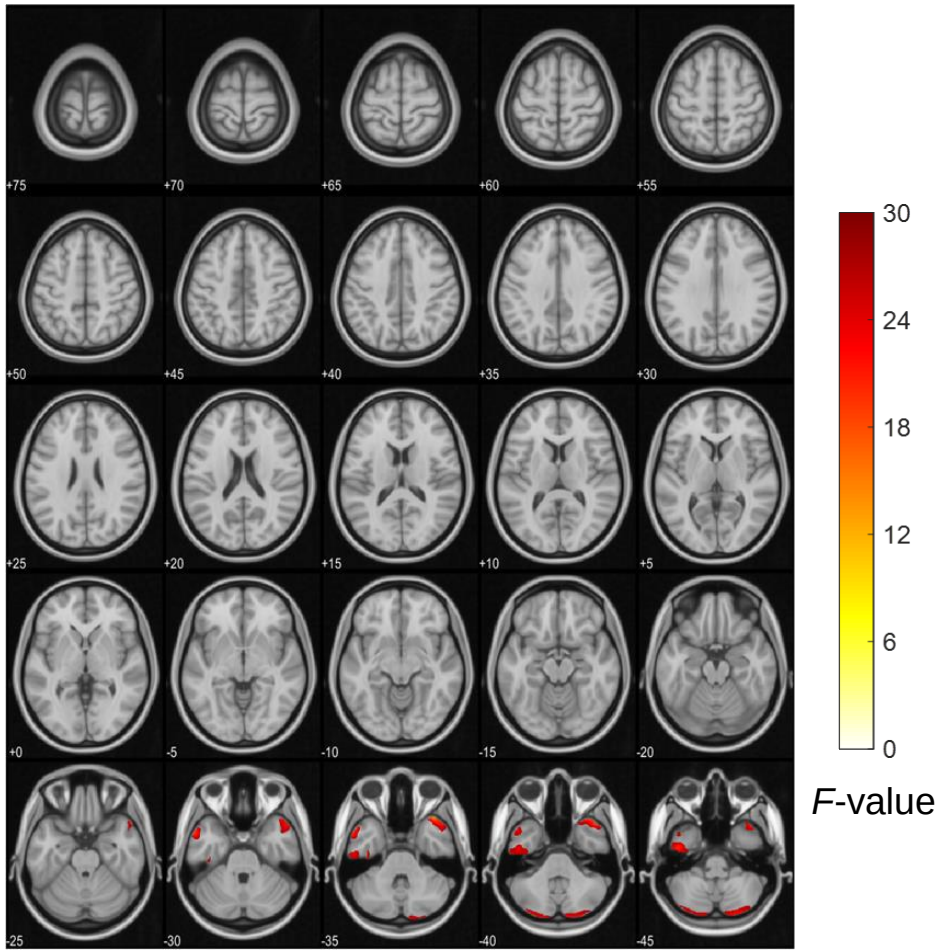
Segmentation and normalisation

- Statistical inferences on processed maps: group differences in brain structure
  - Grey matter volume ~ HealthyControl + PD + ProdromalPD + age + sex + total intracranial volume (TIV)
  - White matter volume ~ HealthyControl + PD + ProdromalPD + age + sex + TIV

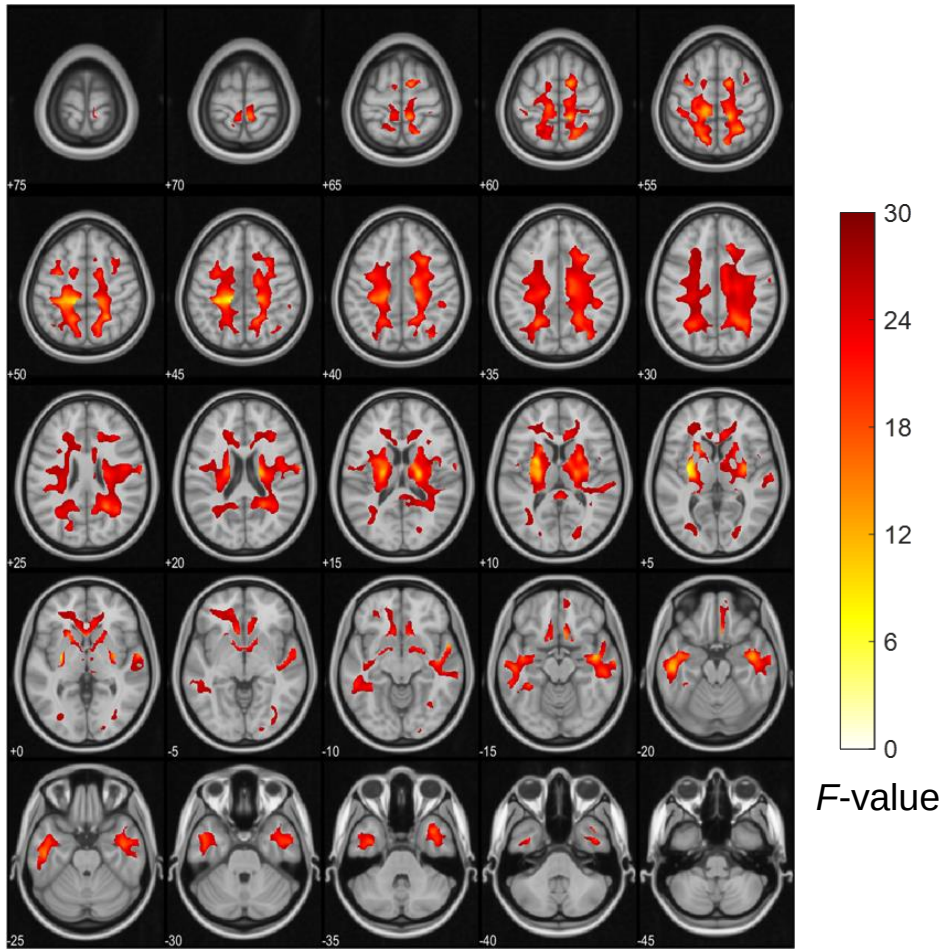


Design matrix for group comparison

Main effect of ANOVA



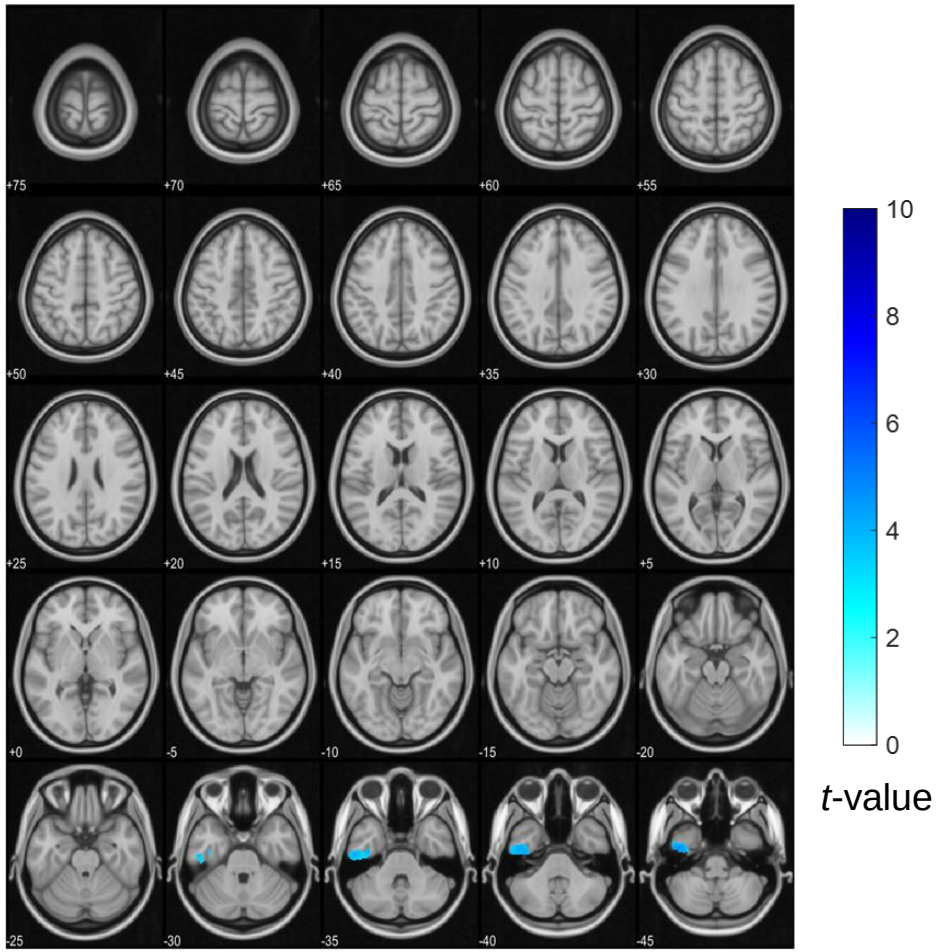
Grey matter volume



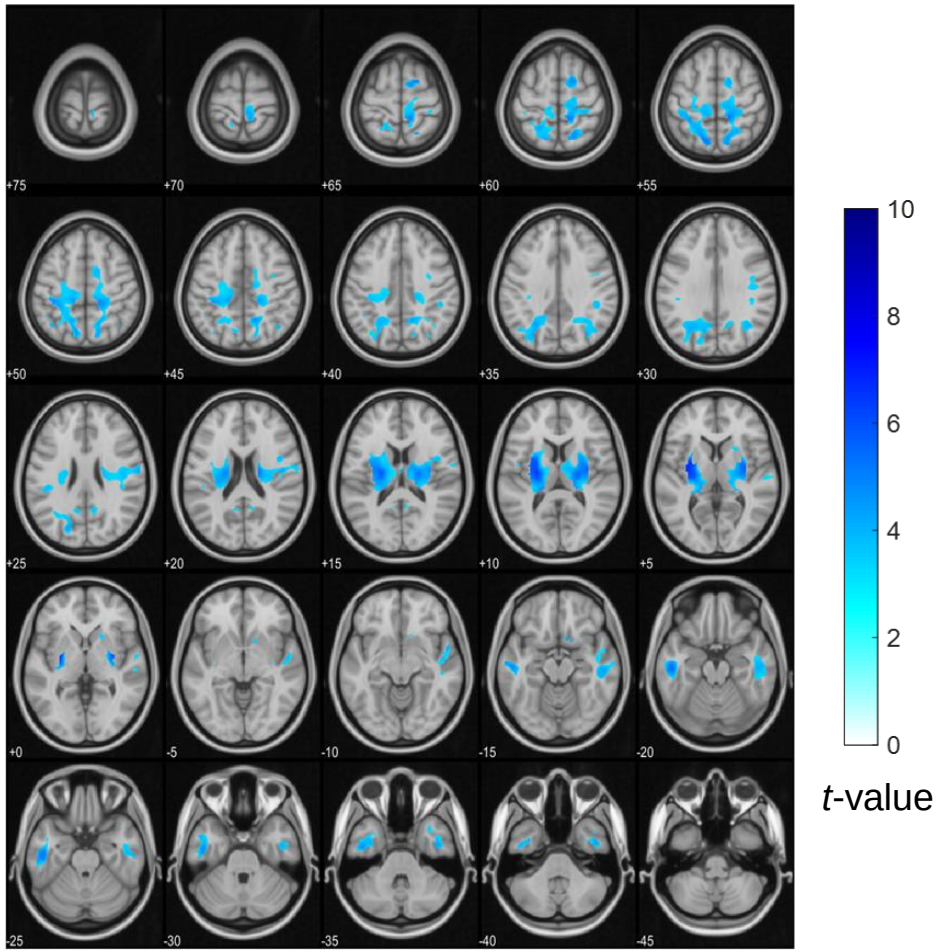
White matter volume

Thresholded at FDR corrected $p = 0.05$ at the cluster level and uncorrected $p = 0.001$ at the voxel level

Healthy control > PD



Grey matter volume



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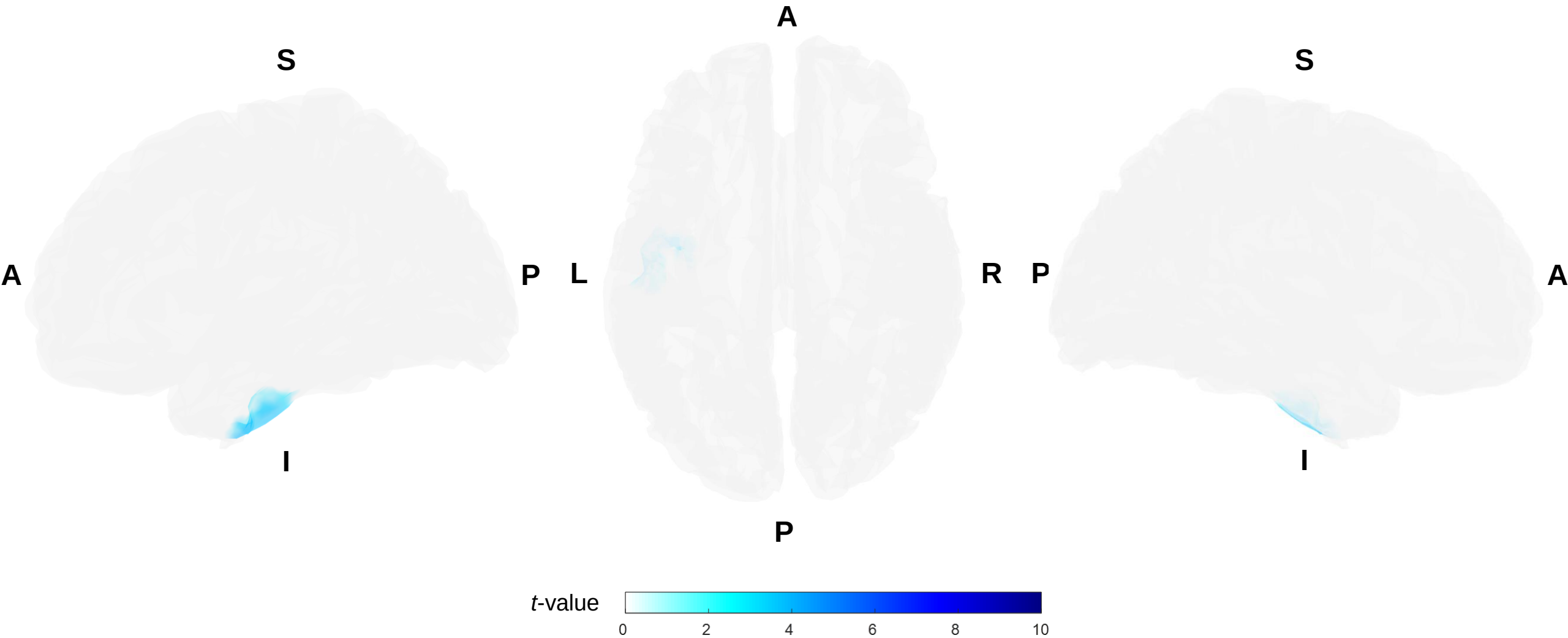
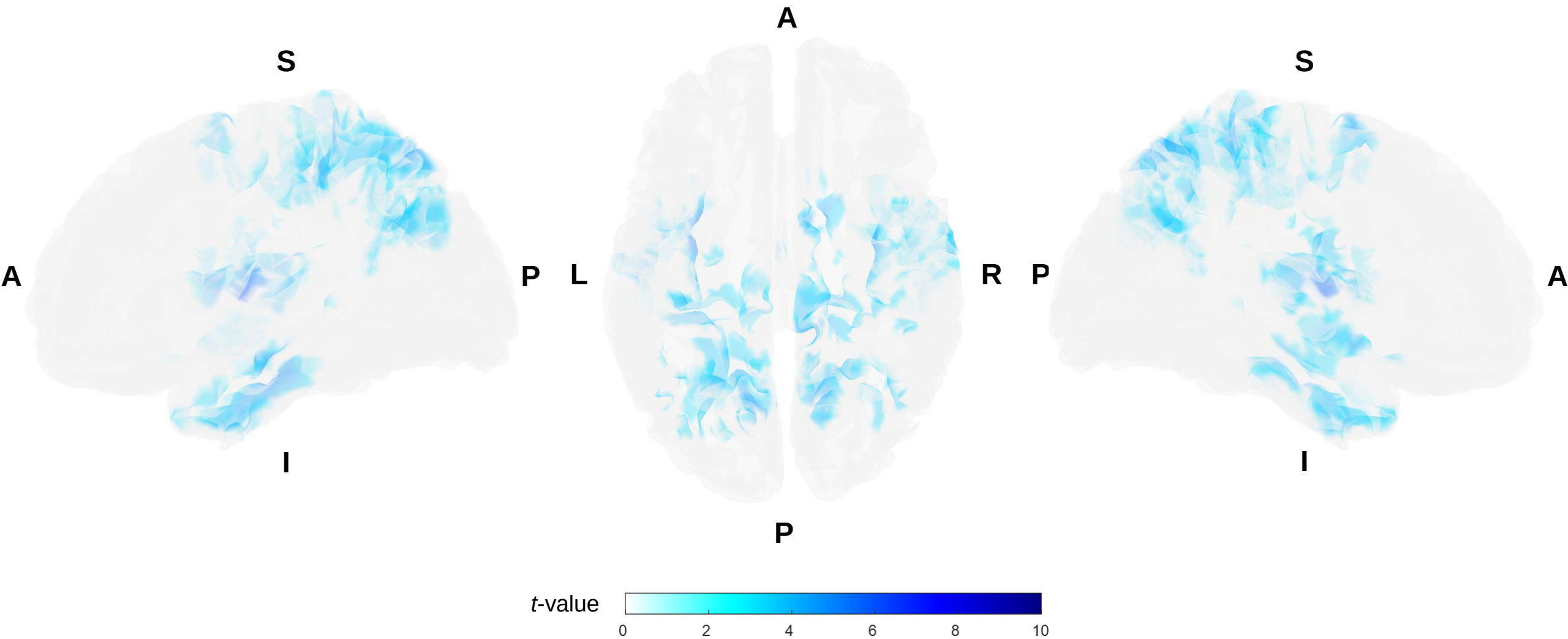
Healthy control > PD: grey matter volume



t-value

0 2 4 6 8 10

Healthy control > PD: white matter volume



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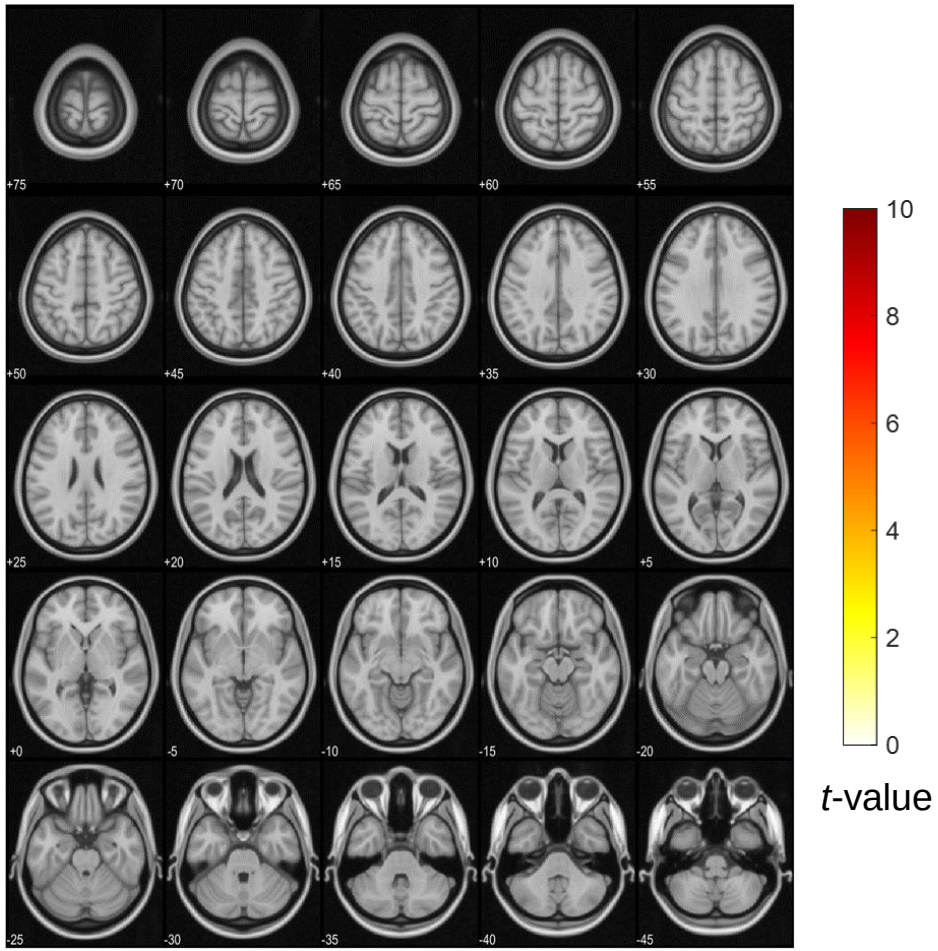
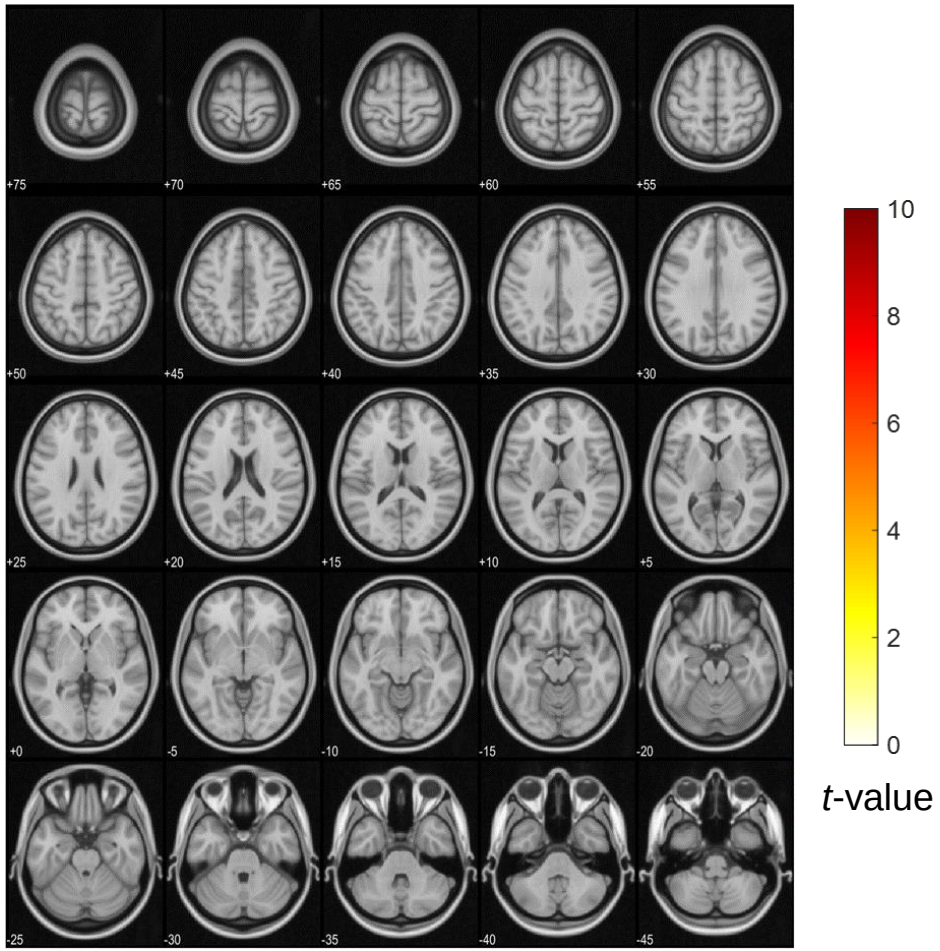
Healthy control < PD



Grey matter volume



White matter volume

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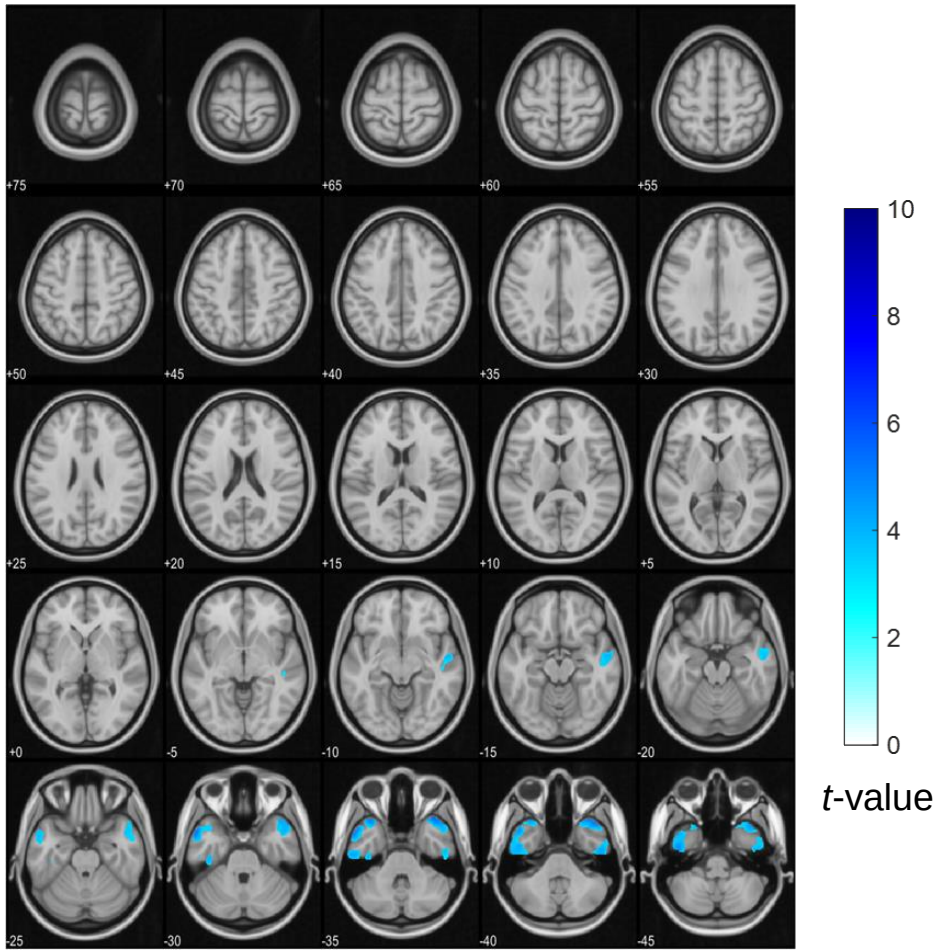
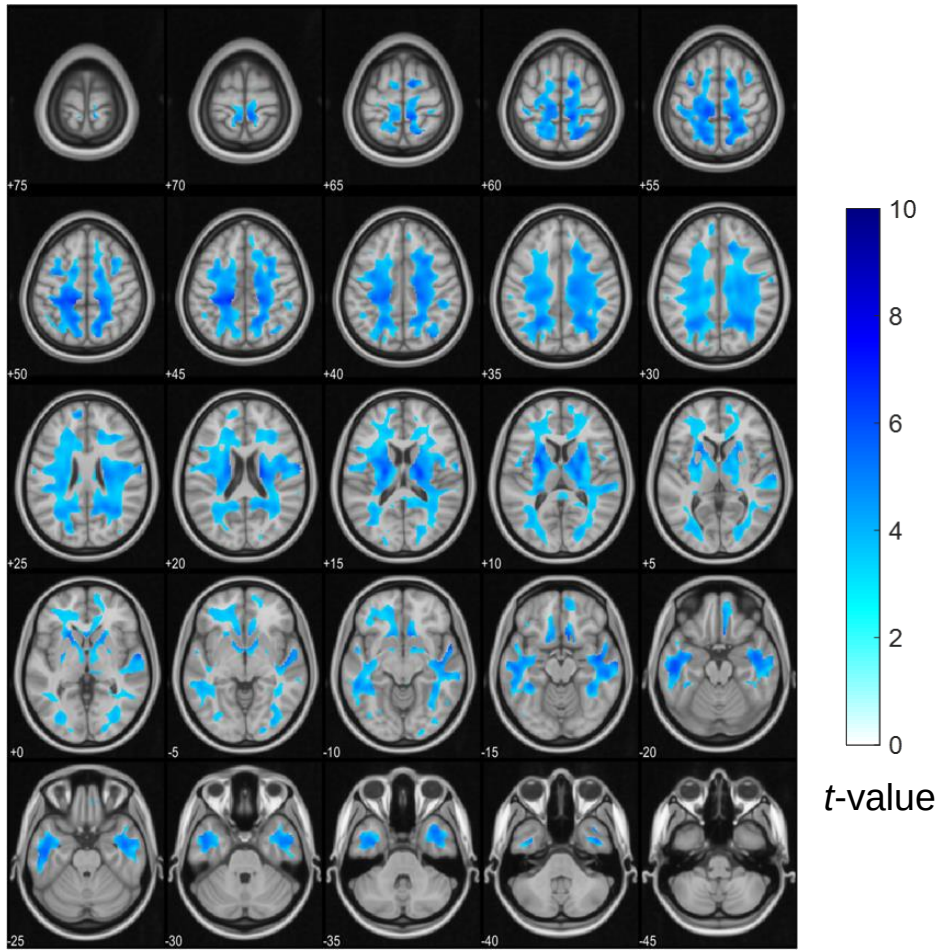
Healthy control > Prodromal PD



Grey matter volume



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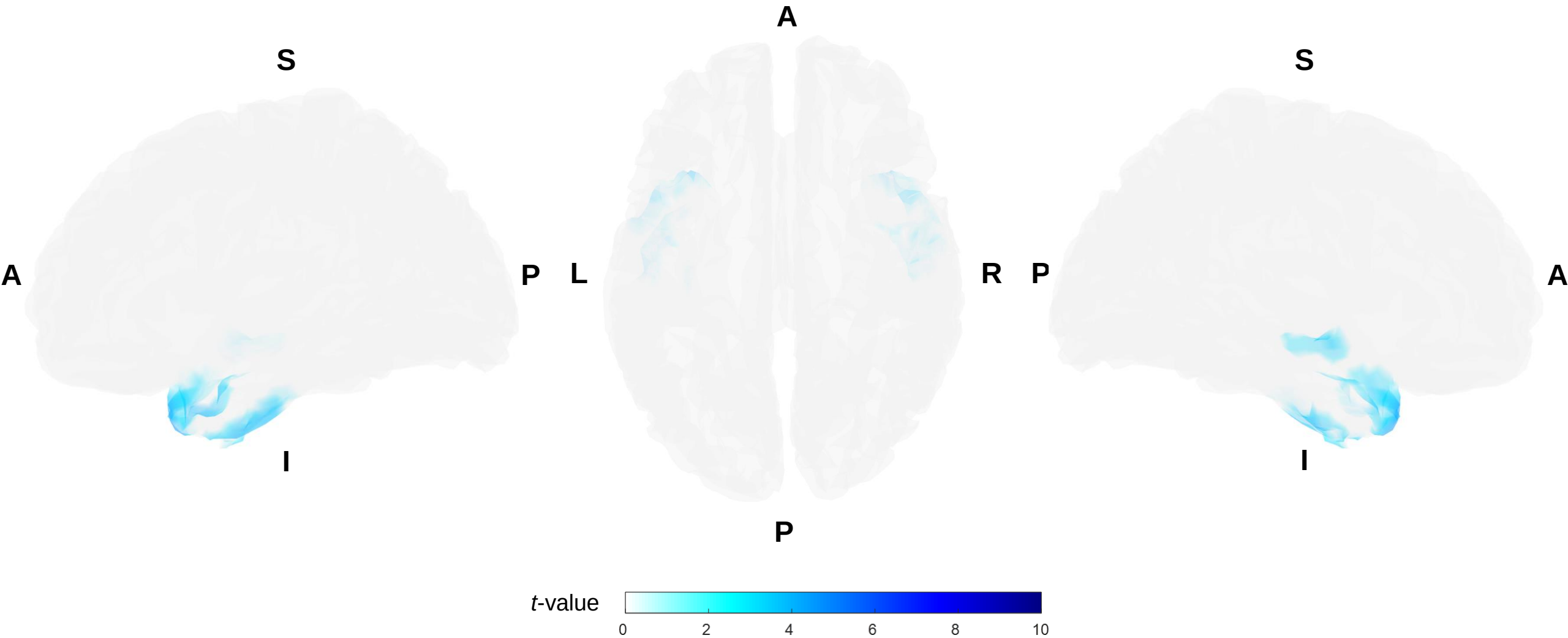
Healthy control > Prodromal PD: grey matter volume



t-value

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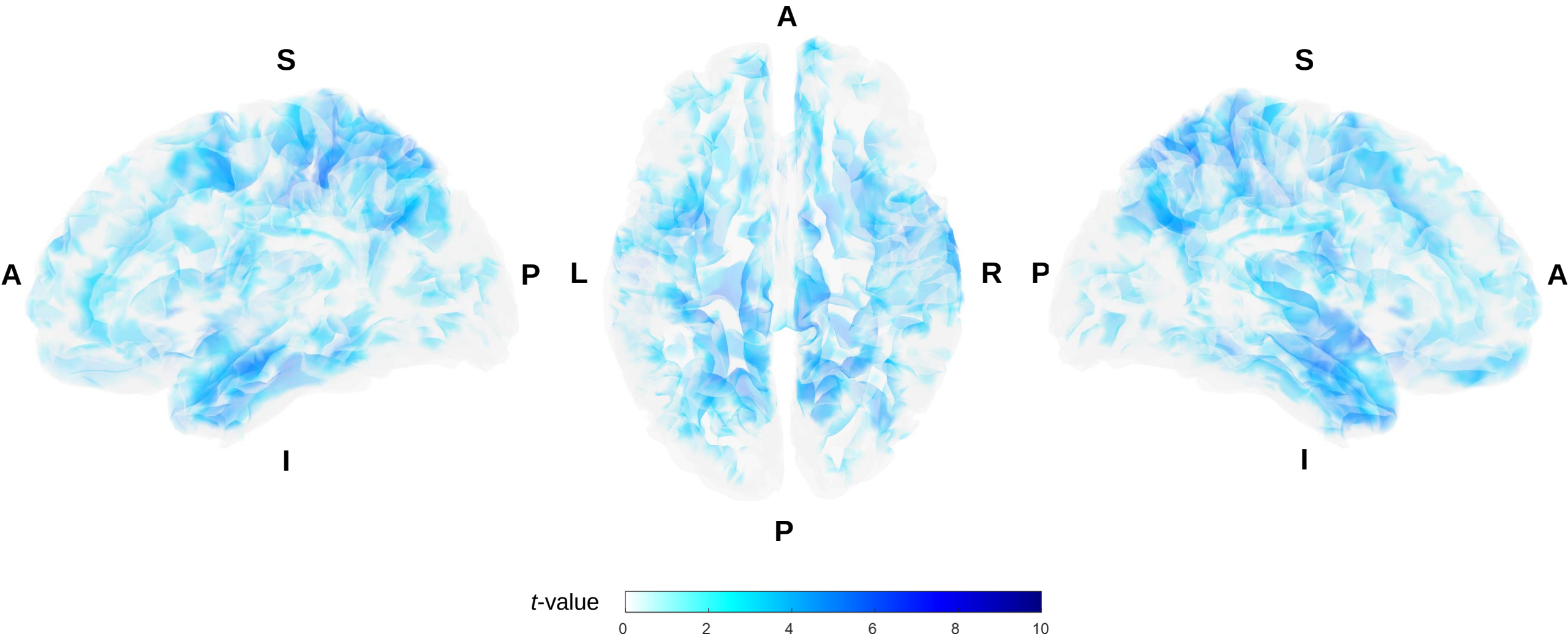
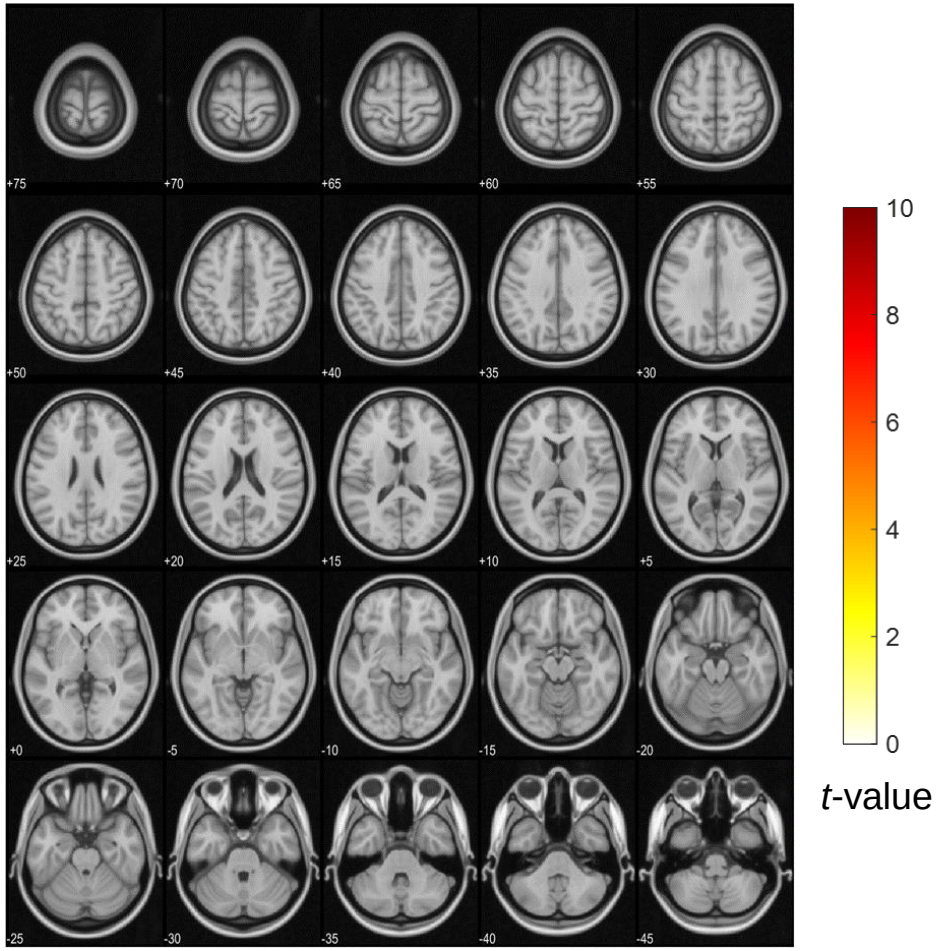
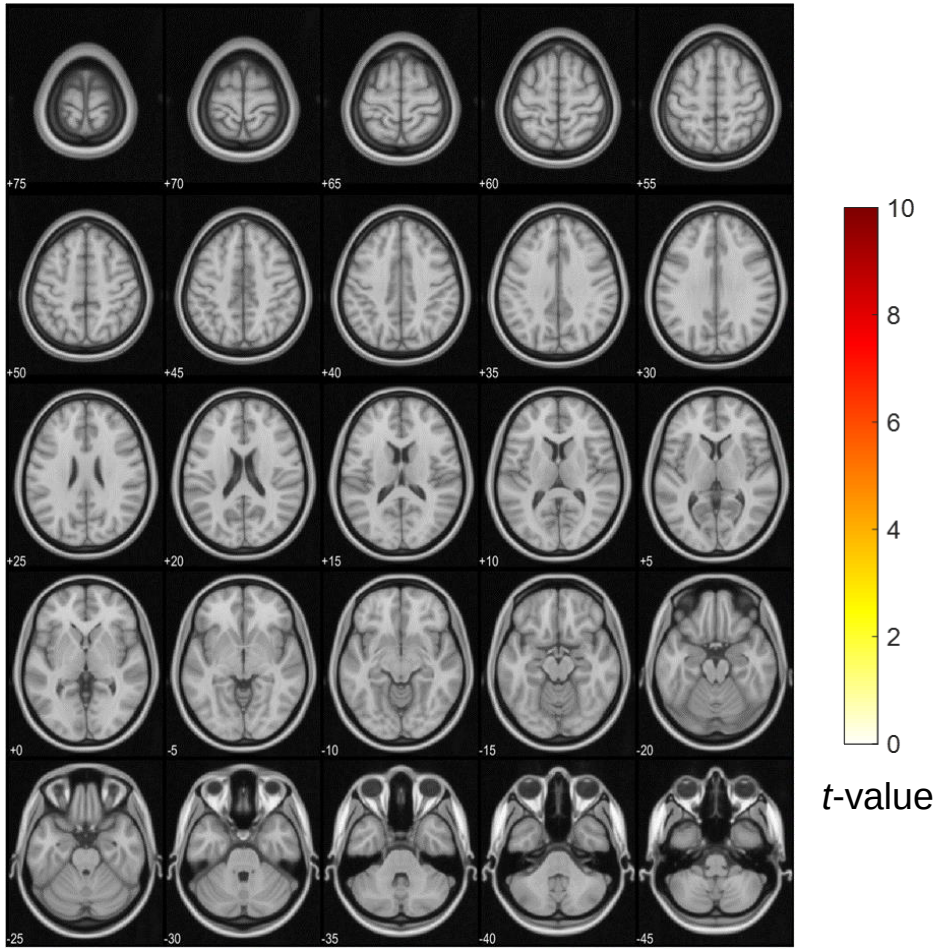
Healthy control > Prodromal PD: white matter volume



Healthy control < Prodromal PD



Grey matter volume



White matter volume

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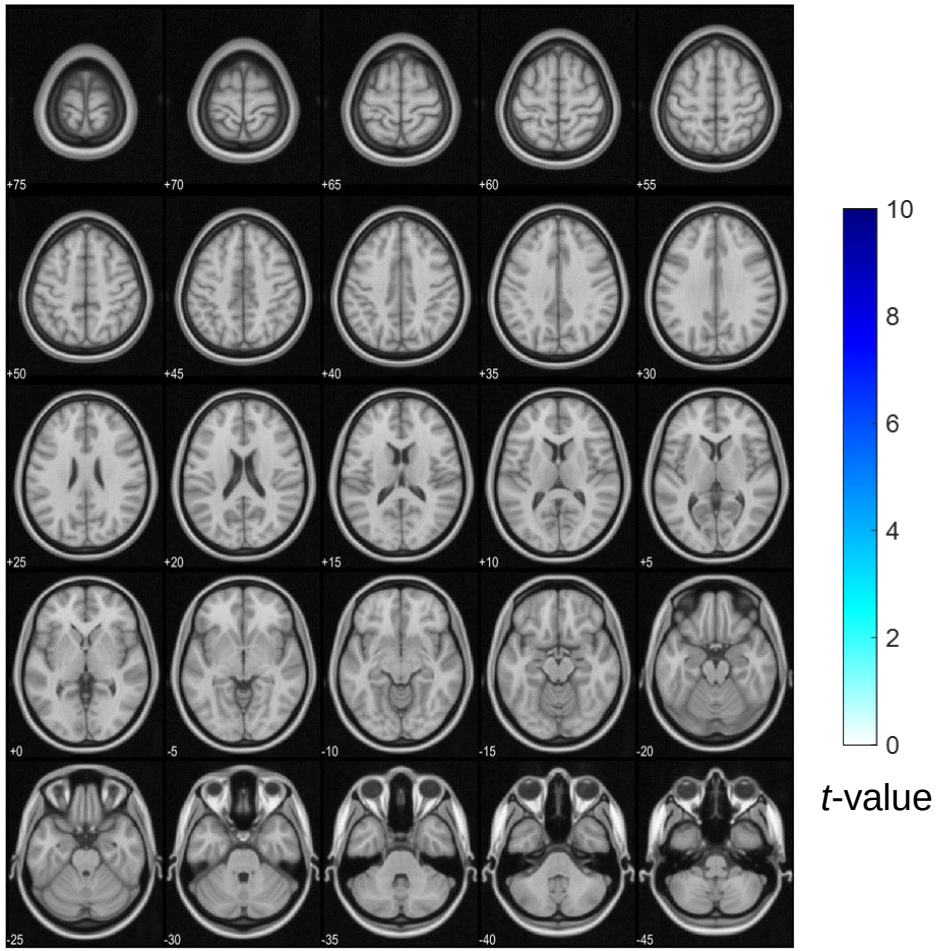
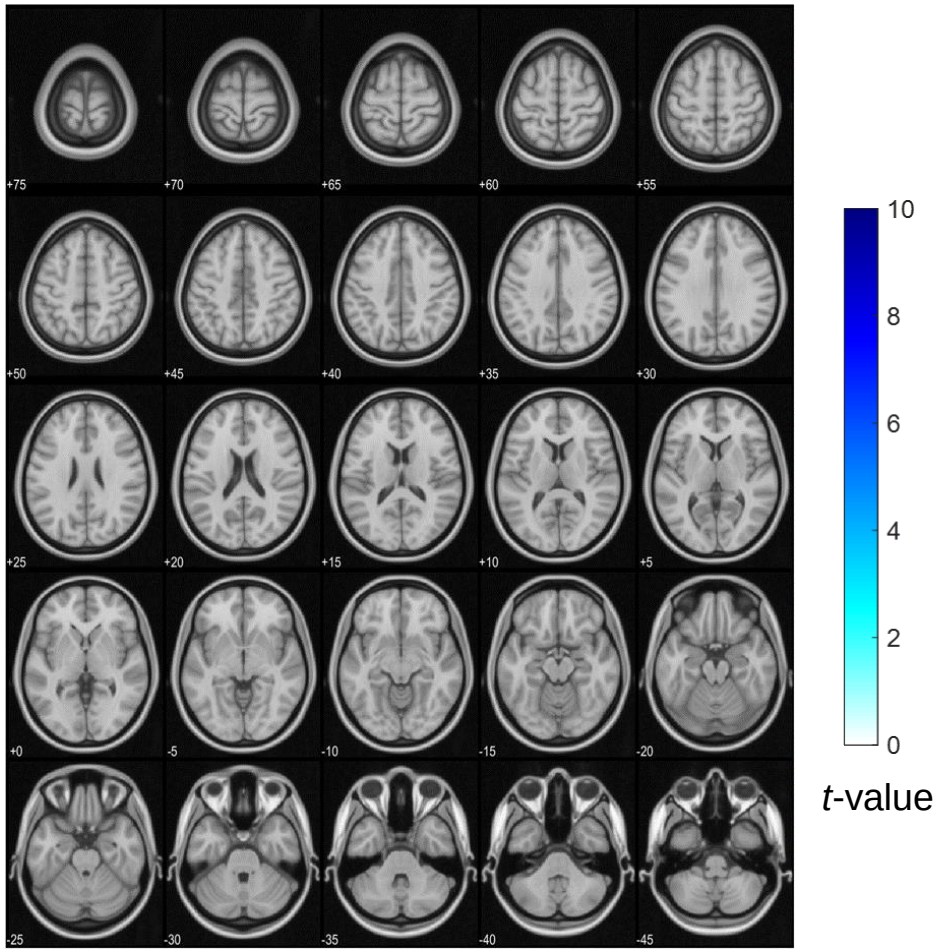
PD < Prodromal PD



Grey matter volume



White matter volume

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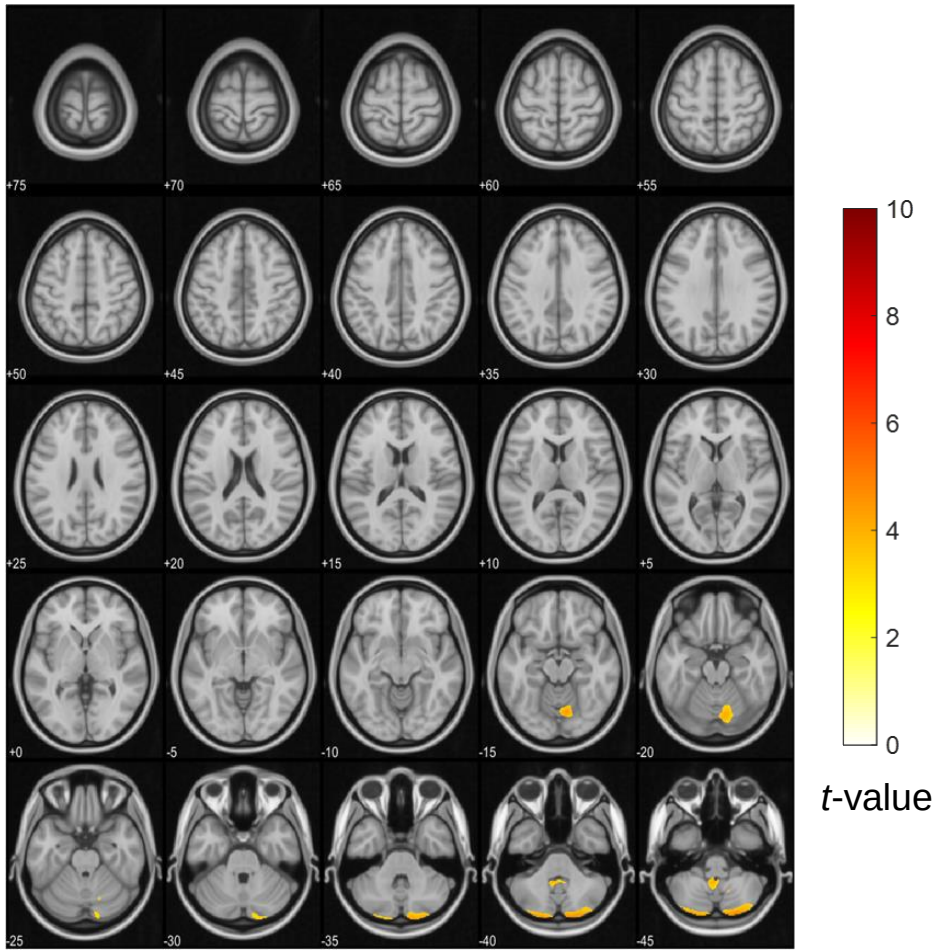
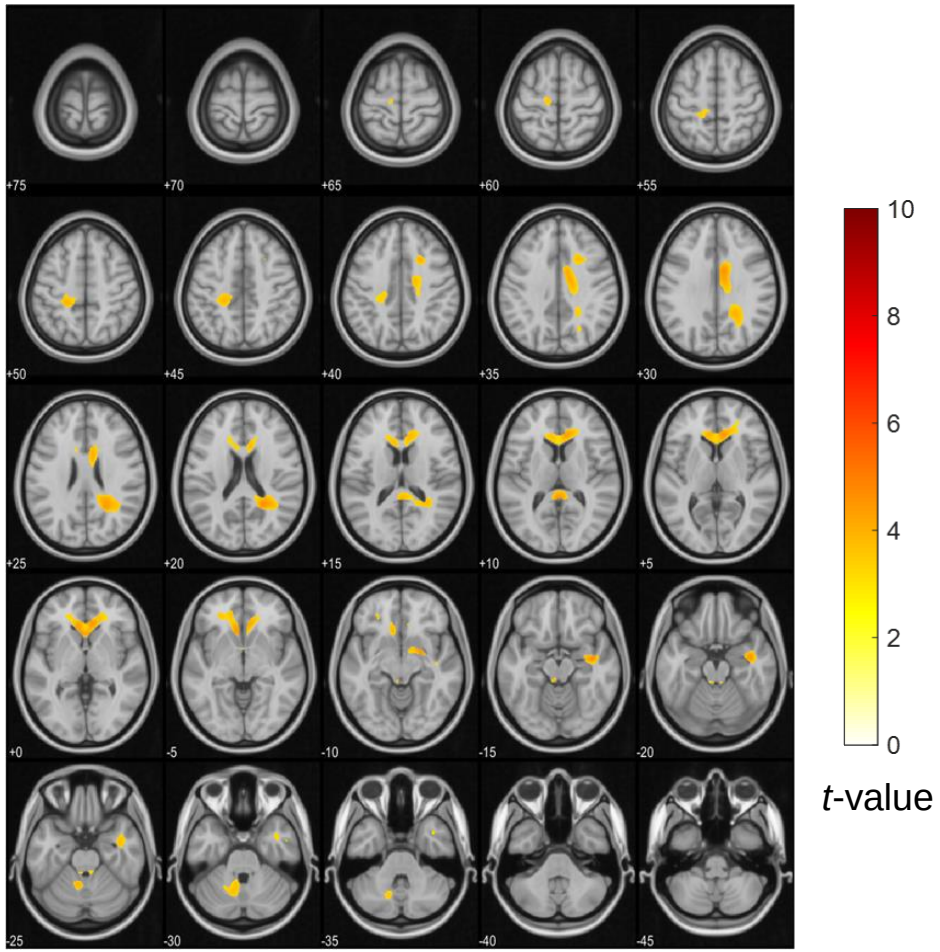
PD > Prodromal PD



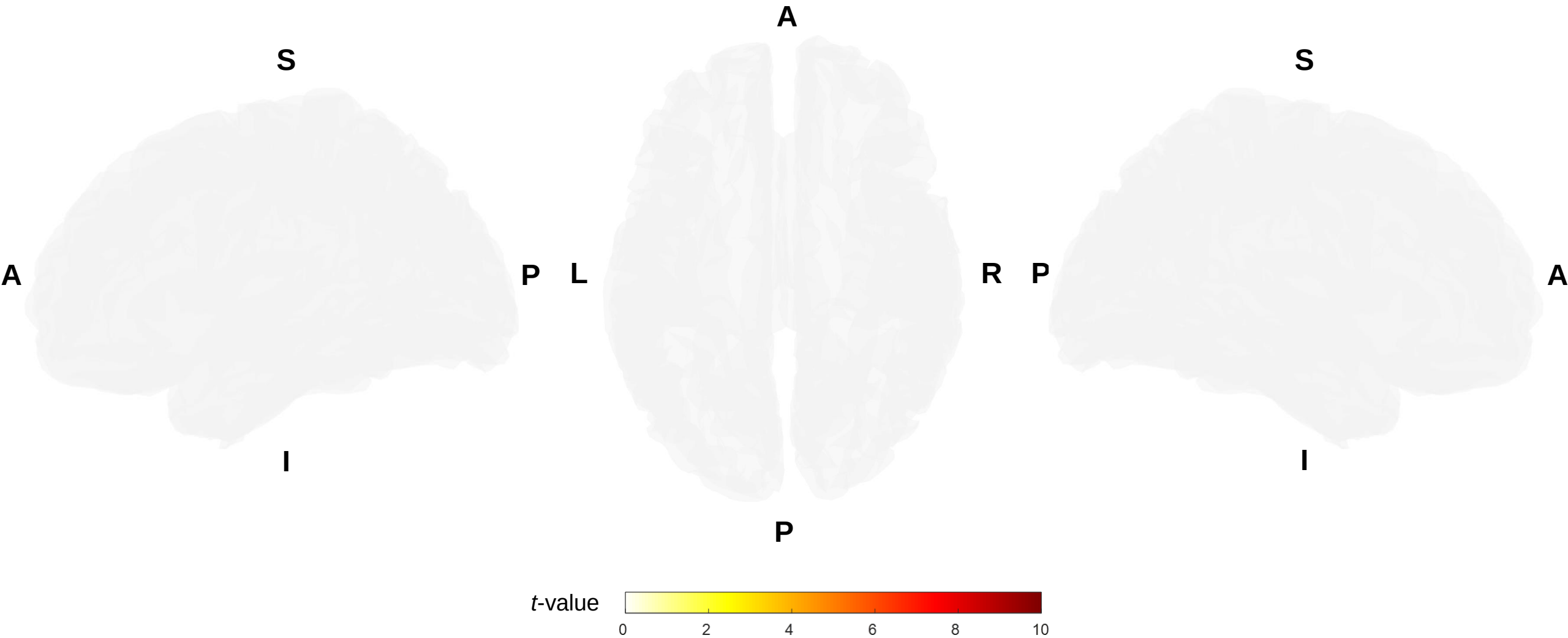
Grey matter volume



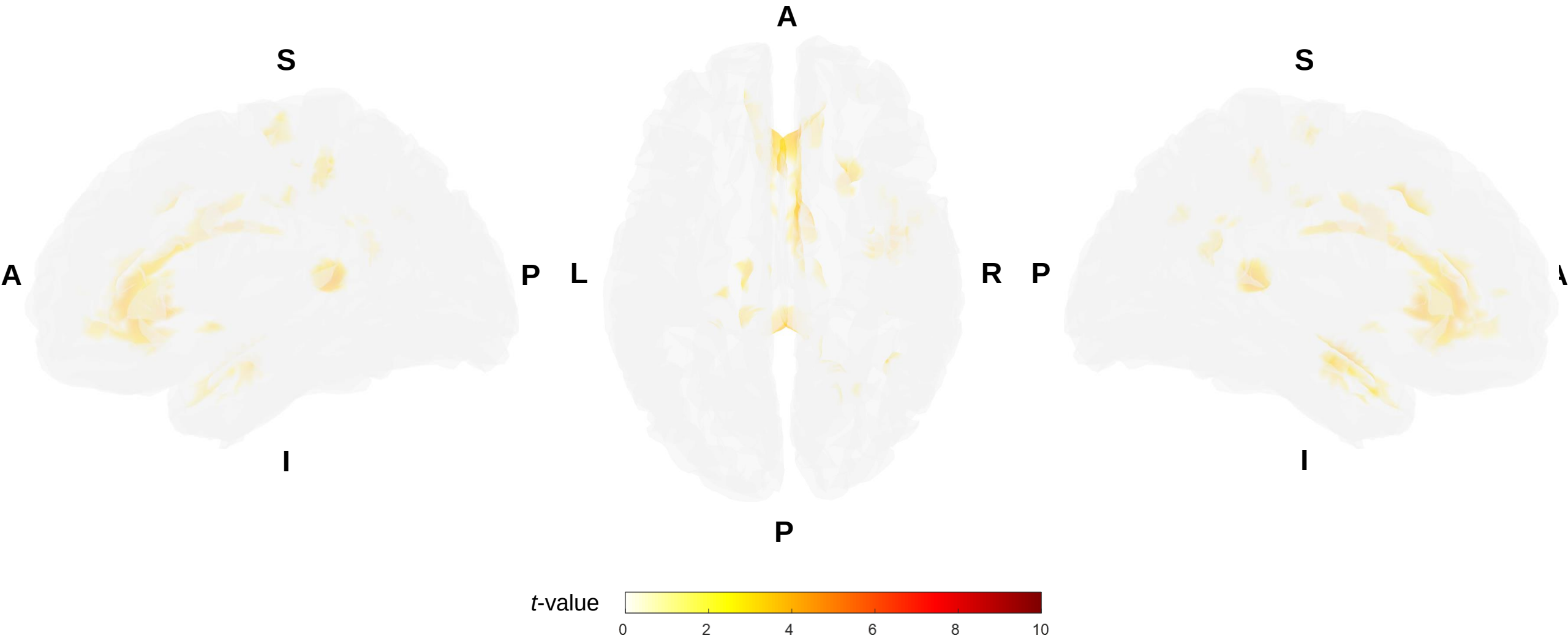
White matter volume

Thresholded at FDR corrected $p = 0.05$ at the cluster level and uncorrected $p = 0.001$ at the voxel level

PD > Prodromal PD: grey matter volume

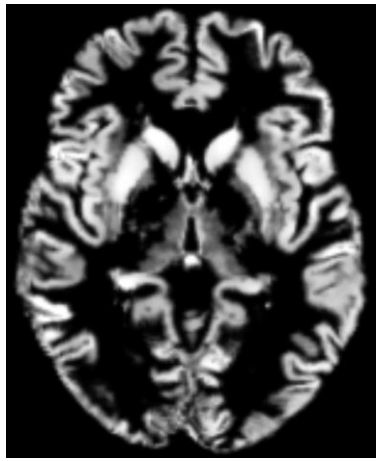


PD > Prodromal PD: white matter volume

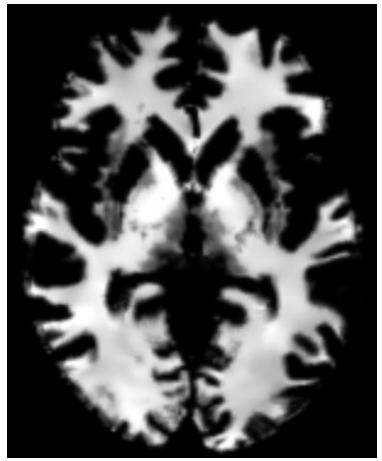


Brain Disease Diagnosis

- Input data
  - Grey matter probability (partial volume fraction) image after segmentation and normalisation
  - White matter probability (partial volume fraction) image after segmentation and normalisation



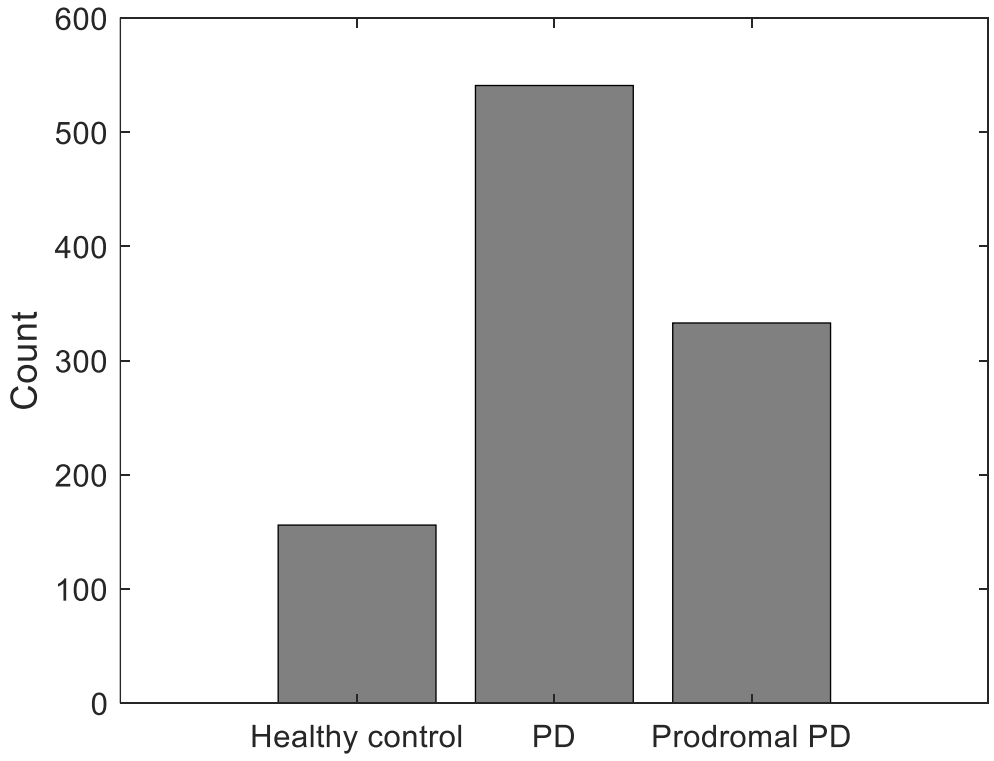
Grey matter
probability image



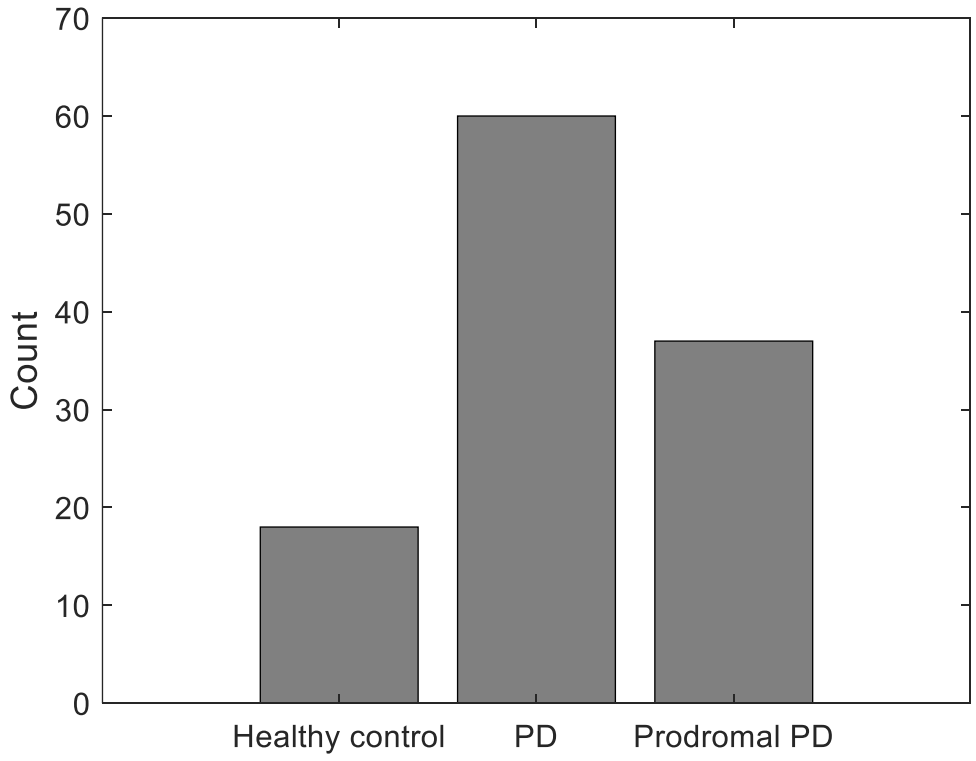
White matter
probability image

Input data for brain disease diagnosis

- Training and test datasets
  - Training dataset: n = 1,030
    - Grey matter probability image: GM/train/0001-1030.nii.gz
    - White matter probability image: WM/train/0001-1030.nii.gz
    - Cohort label
      - 0: HealthyControl
      - 1: PD
      - 2: ProdromalPD
  - Test dataset: n = 115
    - Grey matter probability image: GM/test/0001-0115.nii.gz
    - White matter probability image: WM/test/0001-0115.nii.gz



Training dataset



Test dataset

Distribution of cohorts for training and test datasets

- Brain disease diagnosis performance
  - Accuracy
    - Proportion of correct predictions

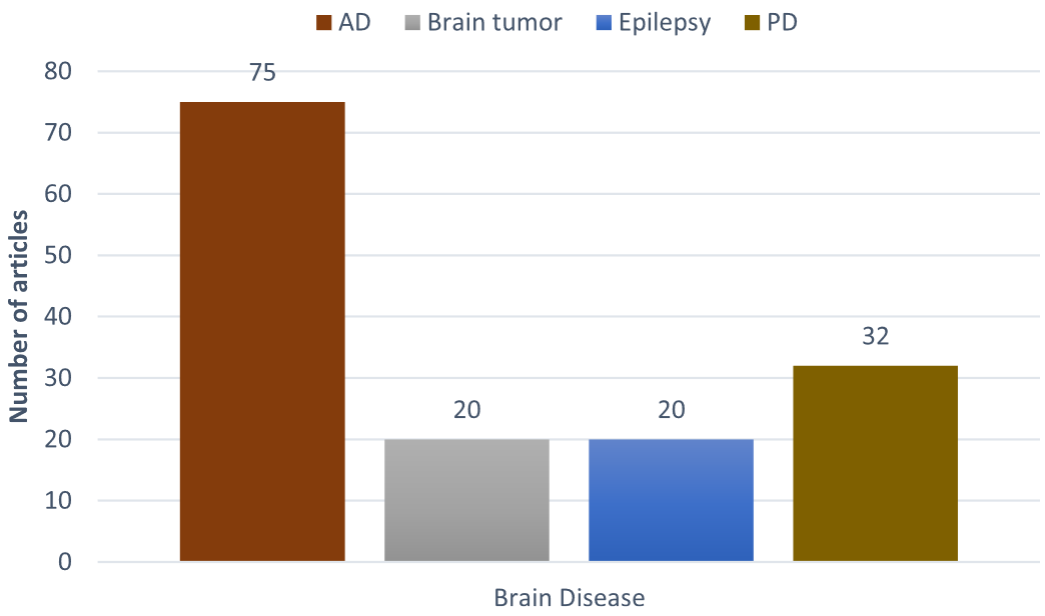
		Predicted condition			
	Total population $= P + N$	**Positive (PP)**	**Negative (PN)**	Informedness, bookmaker informedness (BM) $= TPR + TNR - 1$	Prevalence threshold (PT) $= \frac{\sqrt{TPR \times FPR} - FPR}{TPR - FPR}$
Actual condition	**Positive (P)**	**True positive (TP),** hit	**False negative (FN),** type II error, miss, underestimation	True positive rate (TPR), recall, sensitivity (SEN), probability of detection, hit rate, power $= \frac{TP}{P} = 1 - FNR$	False negative rate (FNR), miss rate $= \frac{FN}{P} = 1 - TPR$
	Negative (N)	**False positive (FP),** type I error, false alarm, overestimation	**True negative (TN),** correct rejection	False positive rate (FPR), probability of false alarm, fall-out $= \frac{FP}{N} = 1 - TNR$	True negative rate (TNR), specificity (SPC), selectivity $= \frac{TN}{N} = 1 - FPR$
	Prevalence $= \frac{P}{P + N}$	Positive predictive value (PPV), precision $= \frac{TP}{PP} = 1 - FDR$	False omission rate (FOR) $= \frac{FN}{PN} = 1 - NPV$	Positive likelihood ratio (LR+) $= \frac{TPR}{FPR}$	Negative likelihood ratio (LR−) $= \frac{FNR}{TNR}$
	Accuracy (ACC) $= \frac{TP + TN}{P + N}$	False discovery rate (FDR) $= \frac{FP}{PP} = 1 - PPV$	Negative predictive value (NPV) $= \frac{TN}{PN}$ $= 1 - FOR$	Markedness (MK), deltaP (Δp) $= PPV + NPV - 1$	Diagnostic odds ratio (DOR) $= \frac{LR+}{LR-}$
	Balanced accuracy (BA) $= \frac{TPR + TNR}{2}$	F_1 score $= \frac{2PPV \times TPR}{PPV + TPR} = \frac{2TP}{2TP + FP + FN}$	Fowlkes–Mallows index (FM) $= \sqrt{PPV \times TPR}$	Matthews correlation coefficient (MCC) $= \sqrt{TPR \times TNR \times PPV \times NPV} - \sqrt{FNR \times FPR \times FOR \times FDR}$	Threat score (TS), critical success index (CSI), Jaccard index $= \frac{TP}{TP + FN + FP}$

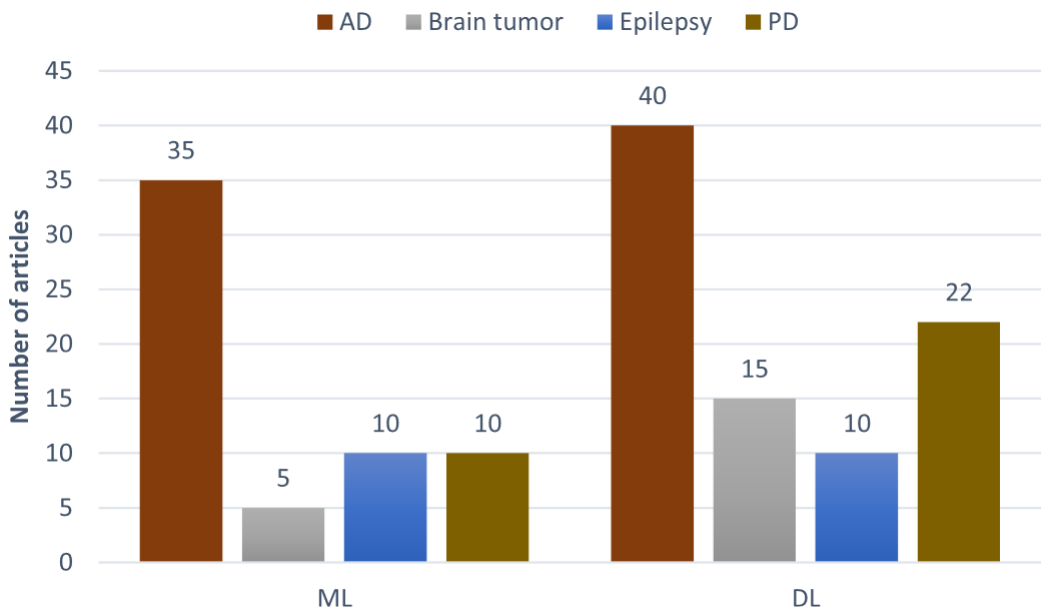
[https://en.wikipedia.org/wiki/Confusion_matrix]

Accuracy in a confusion matrix

Machine Learning for Brain Disease Diagnosis

- Reviews
  - Mei et al., 2021
  - Nissar et al., 2021
  - Khan et al., 2021





[Khan et al., 2021]

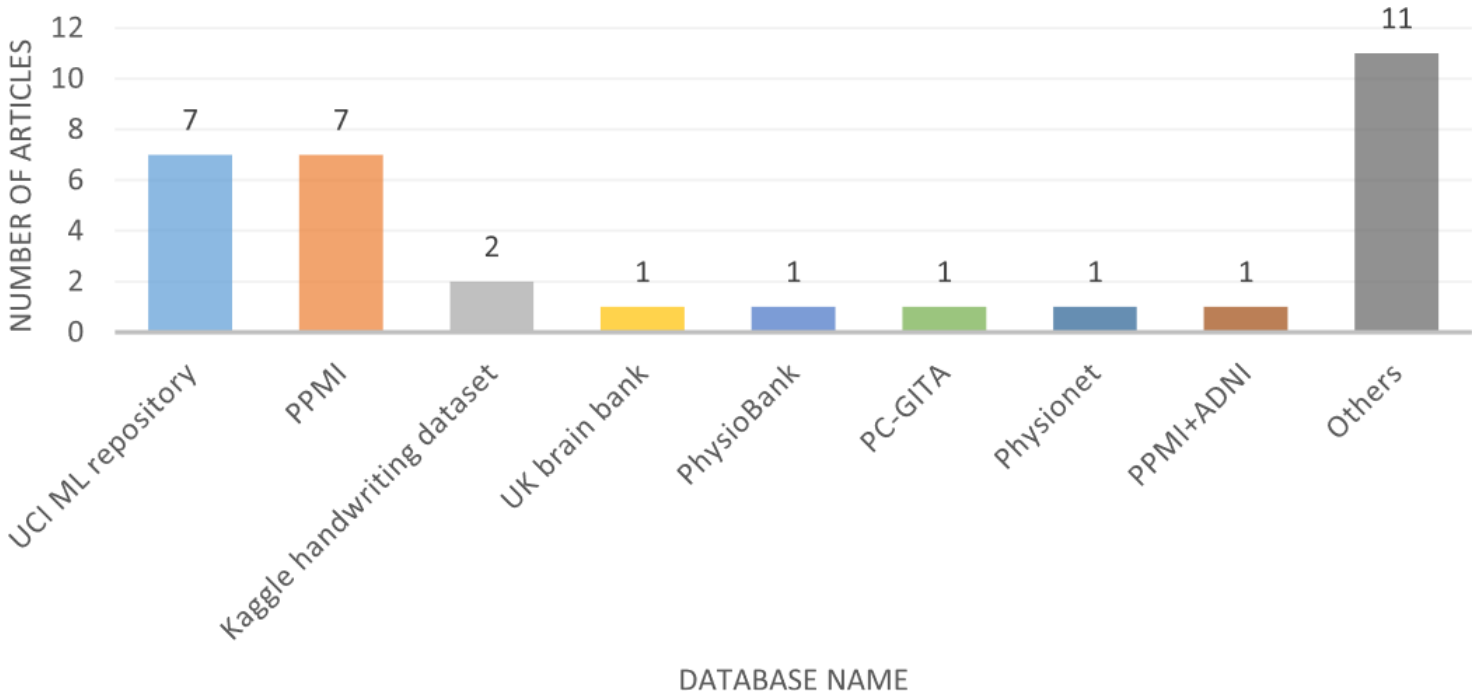
Machine learning for brain disease diagnosis

Data source/Database	Number of studies	Percentage
independent recruitment of human participants	93	43.06%
UCI Machine Learning Repository	44	20.37%
PPMI database	33	15.28%
PhysioNet	15	6.94%
HandPD dataset	6	2.78%
mPower database	4	1.85%
Other databases (1 PACS, 1 PaHaW, 1 PC-GITA database, 1 PDMultiMC database, 1 Neurovoz corpus, 1 The NTUA Parkinson Dataset)	6	2.78%
Collected postmortem	1	0.46%
Commercially sourced	1	0.46%
Acquired at another institution	1	0.46%
From another study	1	0.46%
From the author's institutional database	1	0.46%
Others (1 PPMI + Sheffield Teaching Hospitals NHS Foundation Trust; 1 PPMI + Seoul National University Hospital cohort; 1 UCI + collected from participants)	3	1.39%

PACS, Picture Archiving and Communication System; PaHaW, Parkinson's Disease Handwriting Database.

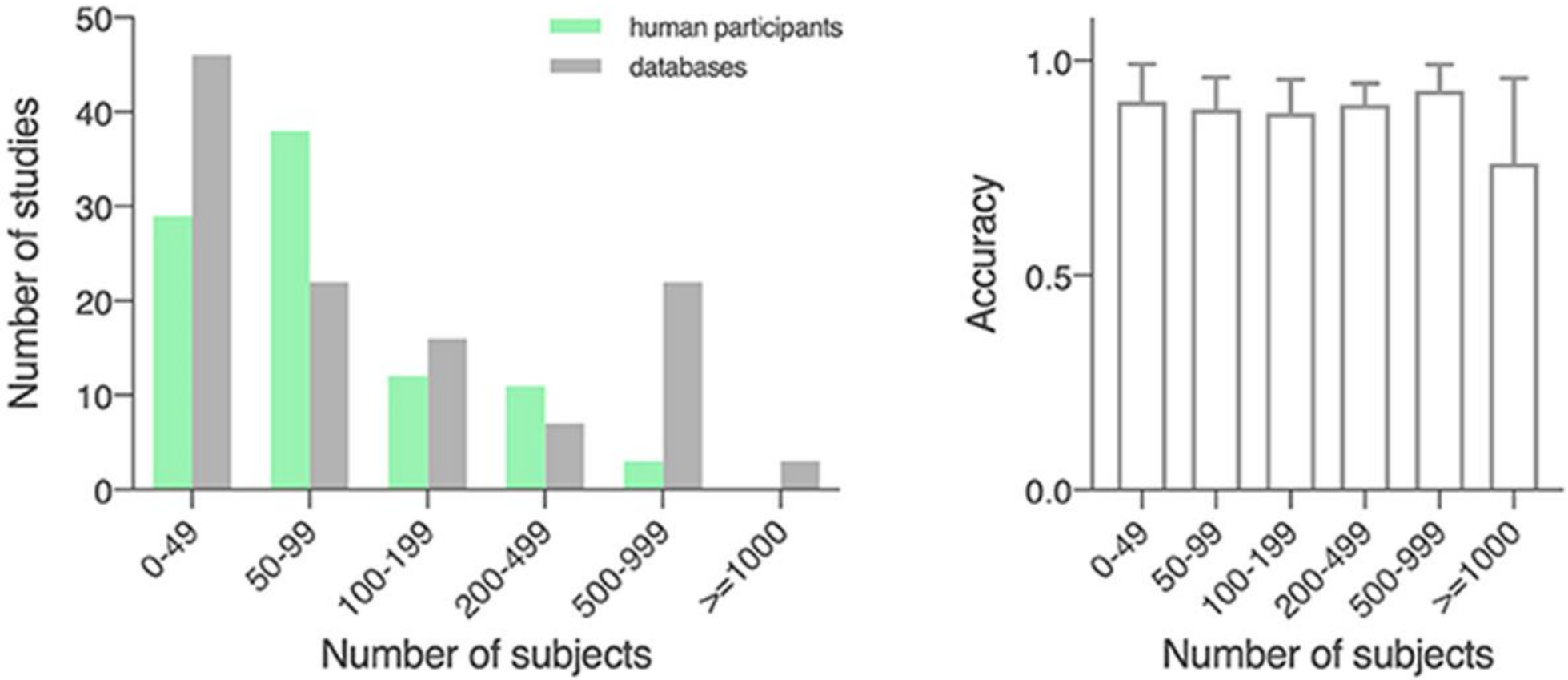
[Mei et al., 2021]

Data sources in machine learning for Parkinson's disease diagnosis



[Khan et al., 2021]

Data sources in machine learning for Parkinson's disease diagnosis



[Mei et al., 2021]

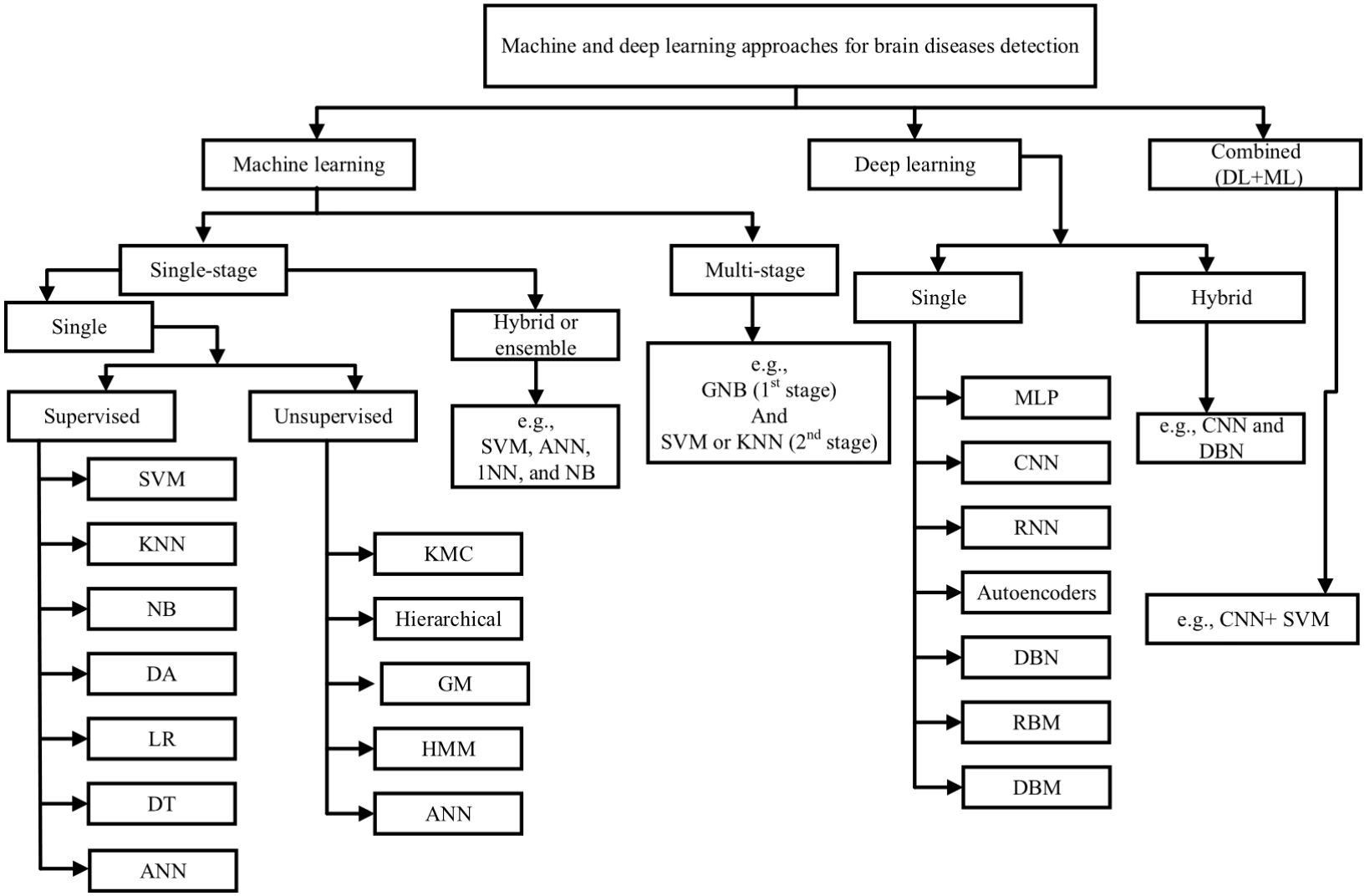
Sample sizes in machine learning for Parkinson's disease diagnosis

Performance metric	Definition	Number of studies
Accuracy	$\frac{TP+TN}{TP+TN+FP+FN}$	174
Sensitivity (recall)	$\frac{TP}{TP+FN}$	110
Specificity (TNR)	$\frac{TN}{TN+FP}$	94
AUC	The two-dimensional area under the Receiver Operating Characteristic (ROC) curve	60
MCC	$\frac{TP\times TN-FP\times FN}{\sqrt{(TP+FP)(TP+FN)(TN+FP)(TN+FN)}}$	9
Precision (PPV)	$\frac{TP}{TP+FP}$	31
NPV	$\frac{TN}{TN+FN}$	8
F1 score	$2\times\frac{precision\times recall}{precision+recall}$	25
Others (7 kappa; 4 error rate; 3 EER; 1 MSE; 1 LOR; 1 confusion matrix; 1 cross validation score; 1 YI; 1 FPR; 1 FNR; 1 G-mean; 1 PE; 5 combination of metrics)	N/A	28

TNR, true negative rate; AUC, Area under the ROC Curve; MCC, Matthews correlation coefficient; PPV, positive predictive value; NPV, negative predictive value; EER, equal error rate; MSE, mean squared error; LOR, log odds ratio; YI, Youden's Index; FPR, false positive rate; FNR, false negative rate; PE, probability excess.

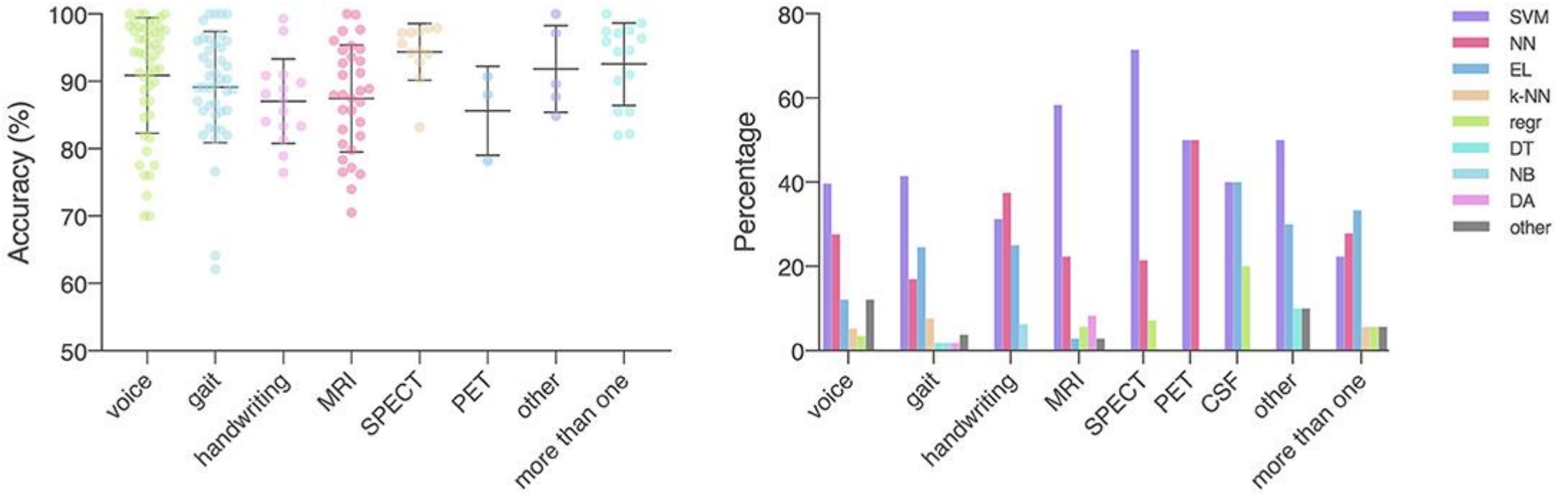
[Mei et al., 2021]

Performance measures in machine learning for Parkinson's disease diagnosis



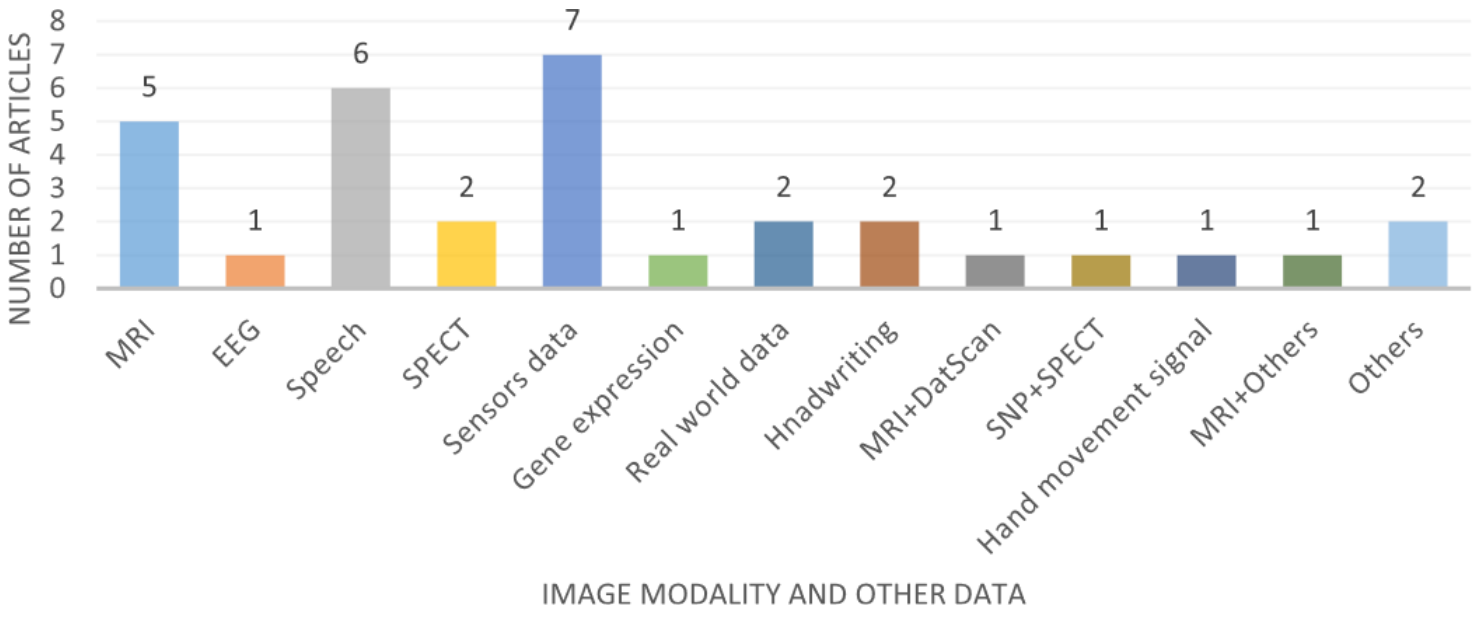
[Khan et al., 2021]

Machine learning algorithms for Parkinson's disease diagnosis



[Mei et al., 2021]

Data types and algorithms in machine learning for Parkinson's disease diagnosis



[Khan et al., 2021]

Data types and in machine learning for Parkinson's disease diagnosis

Conventional machine learning

Author	*Technique Applied*	*Highest Accuracy Achieved (%)*
Little et al (2009)	SVM	91.4
David Gil A. et al (2009)	SVM	93.33
Resul Das (2010)	Neural network	92.9
Ipsita Bhattacharya et al (2010)	Linear SVM	65.21
R. Arefi Shirvan et al (2011)	k-NN	98.2
R. Geetha Ramani et al (2011)	Random tree	100
Uma Rani et al (2012)	SVM (RBF)	87.5
A. Ozcift et al (2012)	IBk	96.93
B.E Sakar et al (2013)	Linear SVM	85.0
Mohammad Shahbakhi et al (2014)	SVM	94.50
Achraf Benba et al (2015)	Linear SVM	91.17
Achraf Benba et al (2016)	Linear SVM	90.0
Richa Mathur et al (2018)	k-NN + Adaboost.M1	91.28
Salama A. Mostafa et al (2019)	Random forest	99.49
Diogo Braga et al (2019)	Random forest	99.94
Amin ul Haq et al (2019)	SVM	99.0
C.O. Sakar et al (2019)	SVM (RBF)	86.0
I.Nissar et al (2020)	XGBoost	95.39
C.D. Anisha (2020)	AdaBoost	94.0
O. Asmae et al (2020)	ANN	96.7
Z.K. Senturk (2020)	SVM	93.84
Tuncer et al (2020)	k-NN	96.83

Deep learning

Author	*Technique Applied*	*Highest Accuracy Achieved (%)*
Ali H. Al-Fatlawi et al (2016)	DBN	94
Alex Frid et al (2017)	CNN	83.63
Abdullah Caliskan et al (2017)	DNN classifier	86.09
Savitha S. Upadhya et al (2018)	NN classifier	98.0
Srishti Grover et al (2018)	DNN	81.66
Chitra Rajagopal et al (2019)	NN classifier	99.49
D. R . Rizvi et al (2020)	LSTM	99.03
S. Kaur et al (2020)	DNN	91.69
K. Akyol (2020)	DNN	95.15

[Nissar et al., 2021]

Performance of Parkinson's disease diagnosis depending on machine learning algorithms

SN	Ref	Year	Image Modality/other data	Database	Extracted Feature	Classifier/Detector (Single-stage)	Performance measurement						Others
							A_{cy} (%)	S_{ny} (%)	S_{py} (%)	AUC (%)	P_m (%)	F1 (%)	
Machine Learning													
1	[146]	2020	Tremor at rest	UCI ML repository	Feature vectors	RF	99.79	99.91	99.61	--	--	--	PD vs NC
			Bradykinesia			RF	97.50	100	100				
			Rigidity			RF	83.12	81.03	89.47				
			Voice impairment			KNN	97.96	100	97.50				
2	[147]	2020	Hand movement signal	Federal State Budget Scientific Institution + Scientific and Educational Medical and Technological Center	Speed, frequency, and amplitude estimates	KNN (K=11)	81.30	--	--	--	--	--	PD vs non-PD
						SVM	98.40						
						DT	82.80						
						RF	94.10						
3	[148]	2020	R-fMRI	Wuhan Children's Hospital	Discriminative features	Linear SVM	80.75	73.61	86.52	81.09	--	--	PD vs NC
4	[149]	2020	SPECT	E-Da Hospital, I-Shou University	Pixel-based features	SVM	52.50	--	--	--	--	37	PD vs NC
						RF	54.50					38.50	
						Deep CNN-VGG16	65.30					60.60	
5	[150]	2020	Voice	UCI ML repository	Phonetic features	CART	90.76	--	--	--	--	--	PD vs NC
						SVM	93.84						
						ANN	91.54						
6	[151]	2020	Sensors data	John Radcliffe Hospital, Oxford	Clinical features	RF	88	86	90	--	--	--	PD vs Progressive supranuclear palsy (Combined tasks)
						LR	80	85	75				
7	[152]	2020	Sensors data related to gait patterns	Vertical ground reaction force datasets	Statistical features	DT	99.40	99.60	99.80	--	--	99.25	Cumulative performance for different stages of PD detection
					Kinematic features	DT	99.40	99.60	99.80			99.25	
8	[153]	2020	16S rRNA gene sequencing data	Sequencing Read Archive	Metagenomic data	RF	71	69	--	80	78	71	PD vs NC
						ANN	66	66		67	70	66	
						SVM	60	55		54	68	60	
9	[154]	2020	Voice	Data collected from Synapse research portal	Paralinguistic features	LR	--	75.90	--	91	81.10	78.40	Mild PD vs NC
						RF		69.30		94	90.20	78.30	
						GBT		79.70		95	90.10	83.60	
10	[155]	2020	sMRI	Data collected at Beijing Tiantan Hospital, Capital Medical University, China	Brain features	SVM	Pearson correlation coefficient = 75.16% Coefficient of determination=56.49%						HD severity prediction

[Khan et al., 2021]

Conventional machine learning studies for Parkinson's disease diagnosis

SN	Ref	Year	Image Modality/other data	Database	Extracted Feature	Classifier/Detector (Single-stage)	Performance measurement						Others
							A_{cy} (%)	S_{ny} (%)	S_{py} (%)	AUC (%)	P_m (%)	F1 (%)	
Deep Learning													
11	[156]	2020	Speech	PC-GITA	Deep features	CNN-AlexNet + MLP	99.30	--	--	--	--	--	PD vs NC
						CNN-AlexNet + RF	98.30						
12	[157]	2020	Sensors data	Self-generated	Feature maps	CNN	67.39	--	--	--	--	--	PD motor state detection
13	[158]	2020	Rapid Eye Movement and olfactory loss, CSF, dopaminergic imaging	PPMI	Feature vectors	Deep ensemble model based on feed-forward ANN	96.68	97.52	94.84	98.86	97.67	97.58	PD vs NC
14	[159]	2020	Sensors data related to left and right gait patterns	PhysioBank	Discriminative features	CNN-LSTM + Softmax	99.31	99.35	99.23	--	--	--	PD vs NC
15	[160]	2020	Voice	UCI ML repository	Feature vectors	Sparse autoencoder + LDA	95	96	98	--	--	--	PD vs NC
16	[161]	2020	Real-world data	UCI ML repository	Feature map	DBN + ELM	Root mean square error=53.70% Coefficient of determination=88.90%						Motor-UPDRS
							Root mean square error=52.20% Coefficient of determination=90.70%						Total-UPDRS
17	[162]	2020	sMRI, DaTscans	PPMI	Feature vectors	CNN-RNN	99.76	--	--	--	--	--	PD vs non PD
18	[163]	2020	Sensor data	UK Brain Bank	Feature vectors	CNN-LSTM	--	84.90	84.90	92.30	--	--	Freezing of gait detection
19	[164]	2020	Real-world data	UCI ML repository	Feature vectors	DNN	Root mean square error=14.22% Coefficient of determination=97%						Motor-UPDRS
							Root mean square error=22.21% Coefficient of determination=95.60%						Total-UPDRS
20	[165]	2020	Speech	UCI ML repository	Feature vectors	DNN	91.69	--	--	--	--	--	PD vs NC
21	[166]	2020	MRI	PPMI	Mean diffusivity, fractional anisotropy	Spatial variational autoencoder	--	--		80	--	--	PD vs NC (WM)
						Spatial autoencoder				83			
						Dense variational autoencoder				74			
22	[167]	2020	Handwriting	Kaggle handwriting dataset	Spiral patterns	CNN-VGG19	88.50	86.50	92.20	91.60	--	--	PD vs non PD
					Wave patterns		88	89.20	87.90	88.60			
23	[168]	2020	SNPs and DaT-SPECT	PPMI	Genetic features	DNN	--	--	--	84.75	--	--	Biomarker identification for PD
24	[169]	2020	Speech	UCI ML repository	Vocal features	Autoencoder	96.11	98.15	89.78	--	96.78	97.45	PD vs NC
25	[170]	2020	EEG	Henan Provincial People's Hospital repository	Non-linear features	RNN	--	84.84	91.81	--	88.31	--	PD vs NC
26	[171]	2020	Sensors data	Self-generated	Motion signals	LSTM	Pearson correlation coefficient = 86% Mean absolute error=6%						Dyskinesia severity estimation
27	[172]	2020	Handwriting	Kaggle handwriting dataset	Spiral patterns, Wave patterns	CNN-RF and CNN-LR with ensemble voting	93.30	94	--	--	93.50	93.94	PD vs NC
28	[173]	2020	sMRI (T2), clinical data	PPMI and ADNI	ROI	CNN + Softmax	77.90	--	--	--	--	--	PD detection
29	[174]	2020	sMRI (T1)	PPMI	Brain features	Autoencoder	85	100	80	--	--	--	NC vs. mild impairment
30	[175]	2020	DaT-SPECT	PPMI	Feature vectors	3D-CNN	97	--	--	96	--	--	PD vs NC
31	[176]	2020	sMRI (T1)	PPMI	Feature vectors	3D-CNN	95.29	94.30	94.30	98	92.70	93.60	PD vs NC
32	[177]	2020	Sensors data related to gait patterns	Physionet	Discriminative features	DNN	98.70	98.10	100	--	--	--	PD detection
							85.30	85.30	--		87.30	85.30	Parkinson severity prediction

[Khan et al., 2021]

Deep learning studies for Parkinson's disease diagnosis