

The role of neuroimaging beyond T1-weighted MRI in the diagnosis and prediction of neuropsychiatric disorders

Esten H. Leonardsen

26.10.23



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Overview

1. Background: Defining the scope of the lecture.
2. State-of-the-art: How is neuroimaging beyond T1-weighted MRI currently being used to predict neuropsychiatric disorders.
3. The future: Challenges and opportunities in using neuroimaging for predicting neuropsychiatric disorders moving forward.



Background

The role of neuroimaging beyond T1-weighted MRI in the diagnosis and prediction of neuropsychiatric disorders



Background

The role of **neuroimaging** beyond T1-weighted MRI in the diagnosis and prediction of neuropsychiatric disorders



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The role of **neuroimaging** beyond T1-weighted MRI in the diagnosis and prediction of neuropsychiatric disorders



Bert from FreeSurfer 7.3

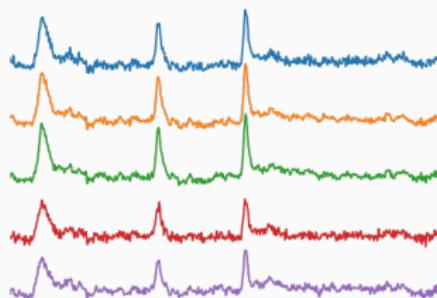


Background

The role of **neuroimaging** beyond T1-weighted MRI in the diagnosis and prediction of neuropsychiatric disorders



Bert from FreeSurfer 7.3



Sample from the MNE library



Background

The role of neuroimaging beyond T1-weighted MRI in the diagnosis and prediction of neuropsychiatric disorders



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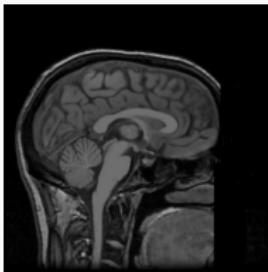


Bert from FreeSurfer 7.3

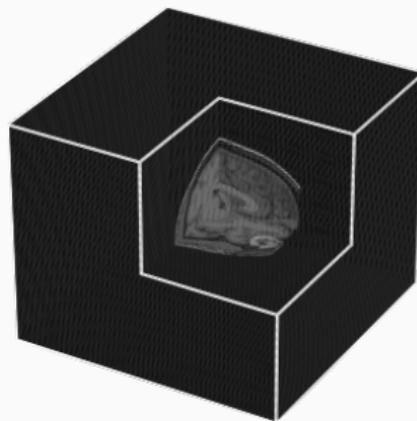


Background

The role of neuroimaging beyond T1-weighted MRI in the diagnosis and prediction of neuropsychiatric disorders



Bert from FreeSurfer 7.3

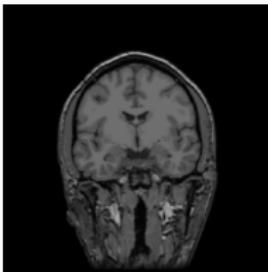


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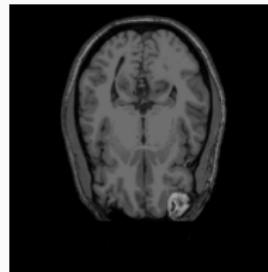
The role of neuroimaging beyond T1-weighted MRI in the diagnosis and prediction of neuropsychiatric disorders



Bert from FreeSurfer 7.3



Front



Above

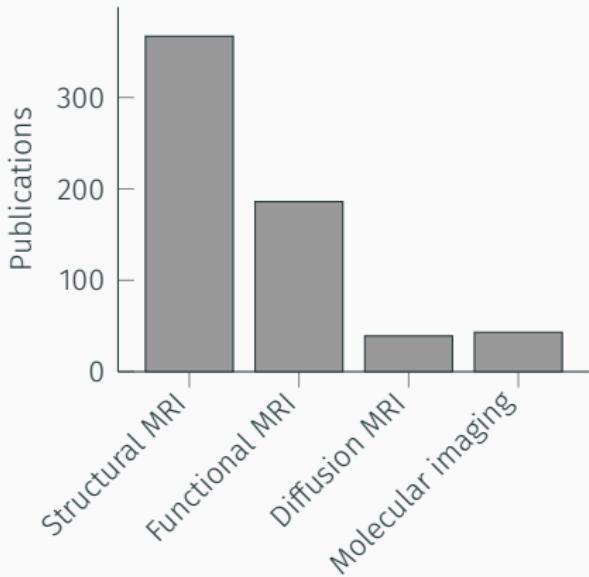


Background

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Bert from FreeSurfer 7.3



Background

The role of neuroimaging beyond T1-weighted MRI in the diagnosis and prediction of neuropsychiatric disorders



Background

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Alzheimer's disease (AD) and other causes of dementia (DEM)

Multiple Sclerosis (MS)
Parkinson's Disease (PD)



Background

The role of neuroimaging beyond T1-weighted MRI in the diagnosis and prediction of neuropsychiatric disorders

Alzheimer's disease (AD) and other
causes of dementia (DEM)

Multiple Sclerosis (MS)

Parkinson's Disease (PD)

Bipolar Disorder (BP)
Schizophrenia (SCZ)

Depressive disorders, including
major depressive disorder (MDD)



Background

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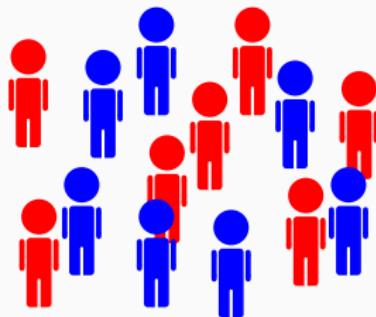


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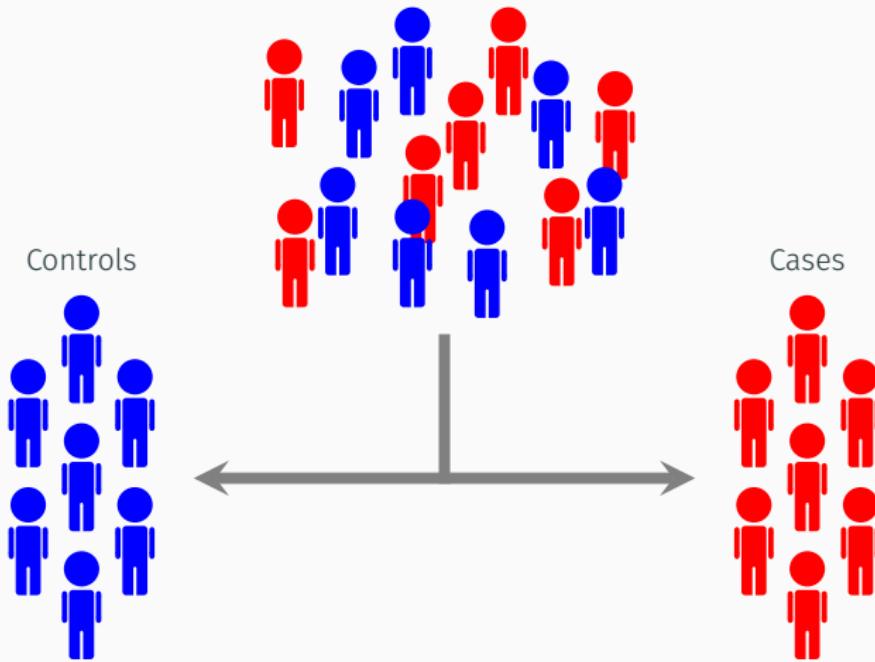
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The role of neuroimaging beyond T1-weighted MRI in the diagnosis and prediction of neuropsychiatric disorders



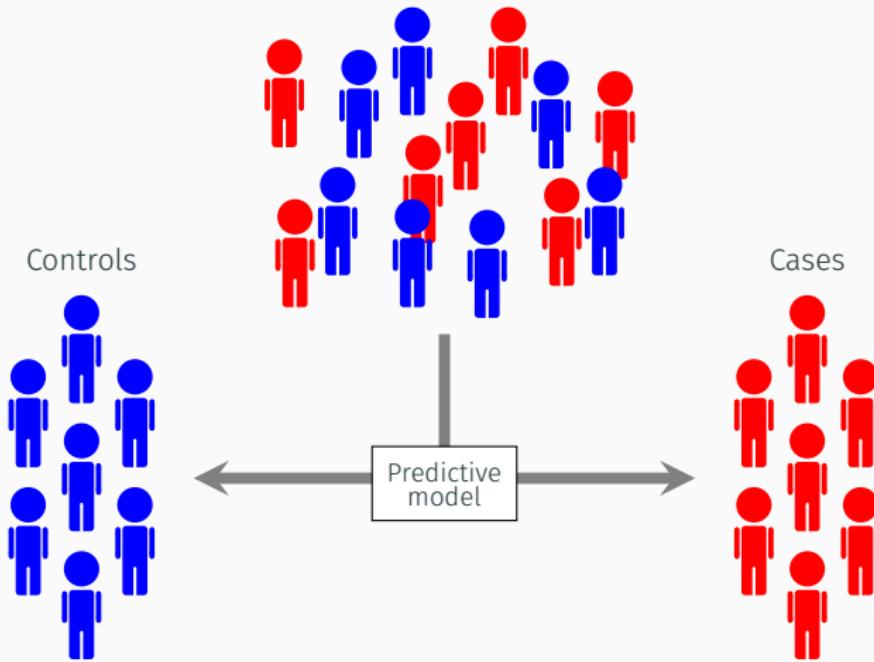
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Background

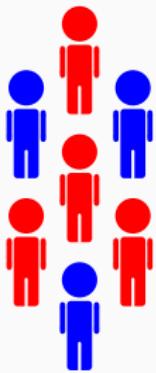
The role of neuroimaging beyond T1-weighted MRI in the diagnosis and prediction of neuropsychiatric disorders



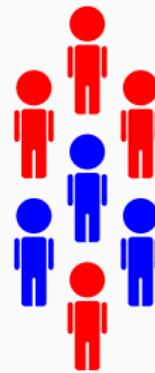
Background

The role of neuroimaging beyond T1-weighted MRI in the diagnosis and prediction of neuropsychiatric disorders

Controls



Cases

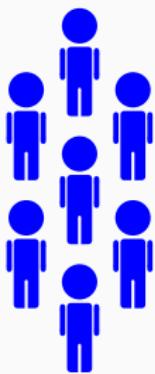


Accuracy
50%

Background

The role of neuroimaging beyond T1-weighted MRI in the diagnosis and prediction of neuropsychiatric disorders

Controls



Cases



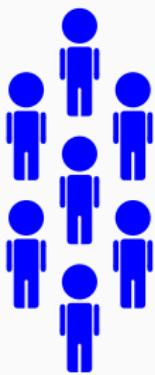
Accuracy
100%



Background

The role of neuroimaging beyond T1-weighted MRI in the diagnosis and prediction of neuropsychiatric disorders

Controls



Cases



Neuroimaging modalities for diagnostic predictions



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Approach



DEM MS PD SCZ MDD BP
Diagnosis



Approach



DEM MS PD SCZ MDD BP
Diagnosis

(Non T1w) structural MRI (sMRI)
Diffusion MRI (dMRI)
Functional MRI (fMRI)
Molecular imaging (MOL)

sMRI dMRI fMRI MOL
Modality



Approach



From estimating activation locality to predicting disorder: A review of pattern recognition for neuroimaging-based psychiatric diagnostics

Thomas Wolters^{a,b}, Jon K. Buitelaar^{c,d}, Christian F. Beckmann^{b,c,e}, Barbara Franke^{a,f}, Andre F. Marquand^{b,g}

Single subject prediction of brain disorders in neuroimaging: Promises and pitfalls

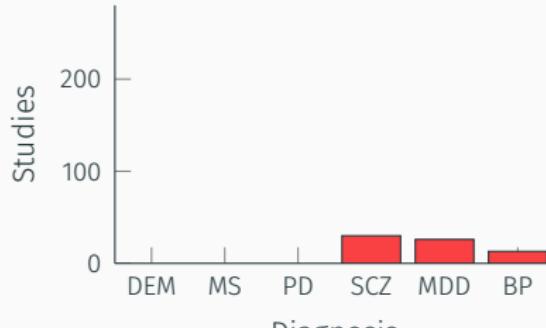
Mohammad R. Arbabi Shirani^{a,b}, Sergey Pliushch^b, Jing Sui^{a,c}, Vince D. Calhoun^{a,d}

Towards a brain-based predictome of mental illness

Barnaly Rashid, Vince Calhoun

Deep learning applications for the classification of psychiatric disorders using neuroimaging data: Systematic review and meta-analysis

Mirjam Quaak¹, Laurens van de Mortel³, Rajat Mani Thomas³, Guido van Wingen²



Approach



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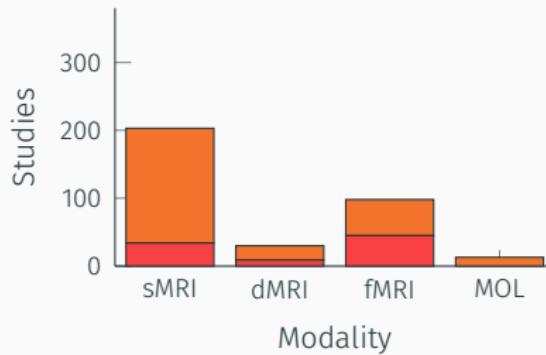
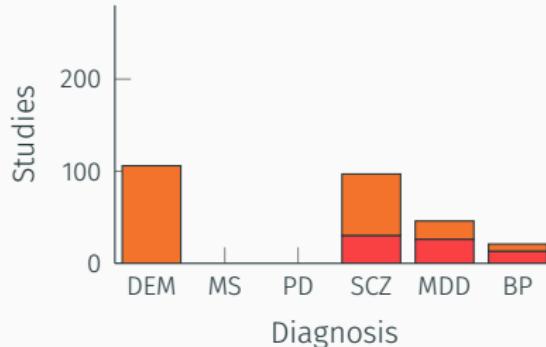
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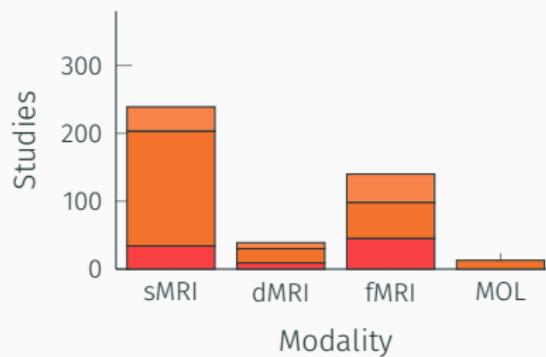
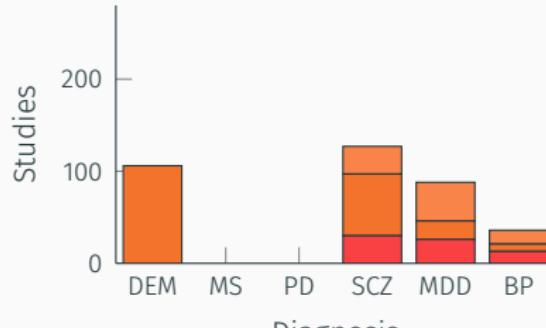
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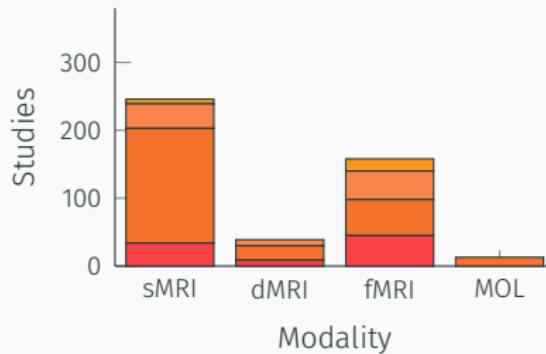
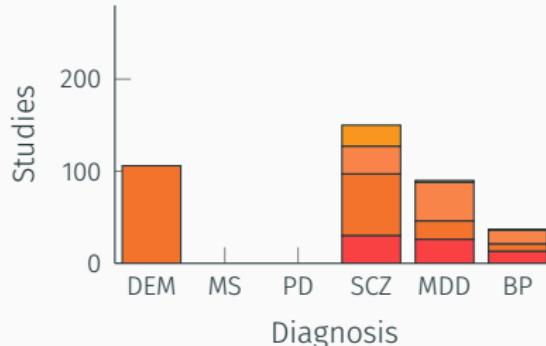
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Approach



Deep learning to detect Alzheimer's disease from neuroimaging: A systematic literature review

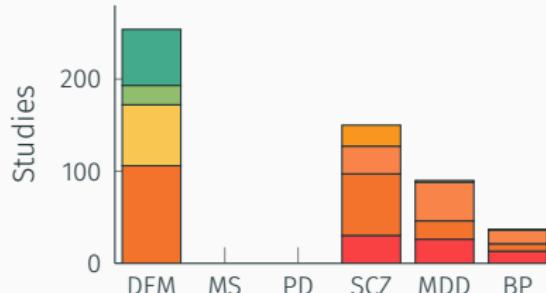
Mr Amir Ebrahimighavvaghieh ¹, Suhuai Luo ¹, Raymond Chiong ²

Machine learning techniques for diagnosis of alzheimer disease, mild cognitive disorder, and other types of dementia

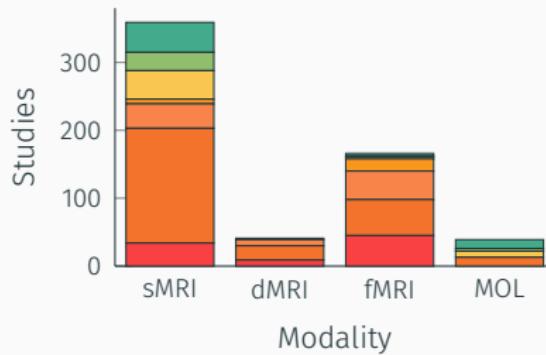
Golrokh Mirzaei ³, R. Hojjat Adeli ³

Early diagnosis of Alzheimer's disease based on deep learning: A systematic review

Sina Fathi ¹, Maryam Ahmadi ², Alsaneh Dehnad ³



Diagnosis

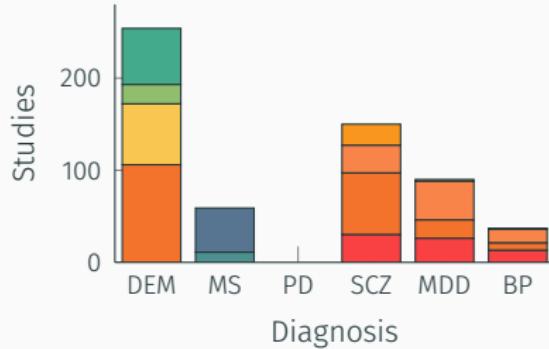


Approach



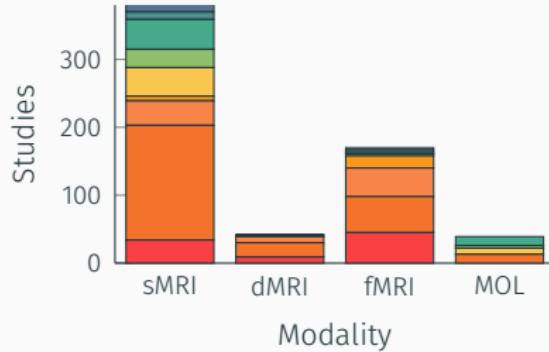
Applications of deep learning techniques for automated multiple sclerosis detection using magnetic resonance imaging: A review

Afshin Shoibei¹, Marjane Khodatian², Mahboobeh Jafari³, Parisa Mordinian⁴, Mitra Rezaei⁵, Roohallah Alizadehsani⁶, Fahime Khozeinreh⁶, Juan Manuel Gorric⁷, Jonathan Heras⁸, Maryam Panahazar⁹, Saeid Nahavandi⁸, U Rajendra Acharya¹⁰

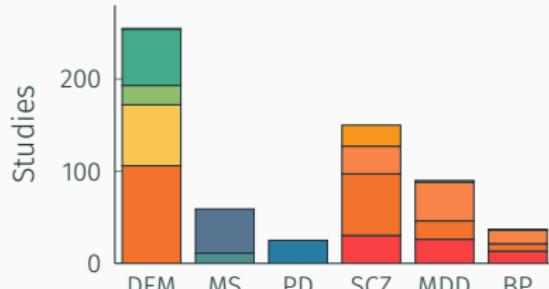


Multiple Sclerosis Diagnosis Using Machine Learning and Deep Learning: Challenges and Opportunities

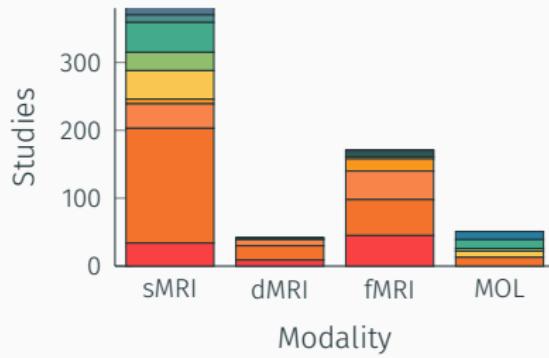
by Nida Aslam^{1,*} , Irfan Ulta Khan¹ , Asma Bashashati¹, Fatima A. Alghool¹, Menna Abouelrour¹ , Noorah M. Alsuwaiyan¹, Rawaa K. Alturaiif¹, Samira Brahimi², Sumayyah S. Aljamees¹ and Khaloud Al Ghandi³



Approach



Diagnosis



Role of Artificial Intelligence Techniques and Neuroimaging Modalities in Detection of Parkinson's Disease: A Systematic Review

Nikita Aggarwal¹ · B. S. Saini¹ · Savita Gupta²

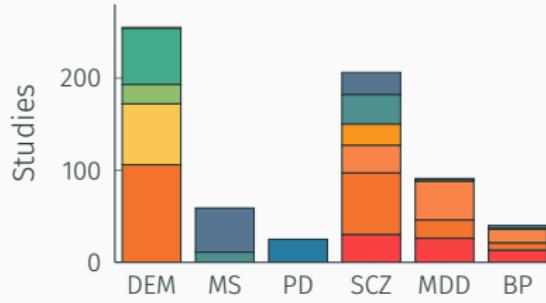


Approach

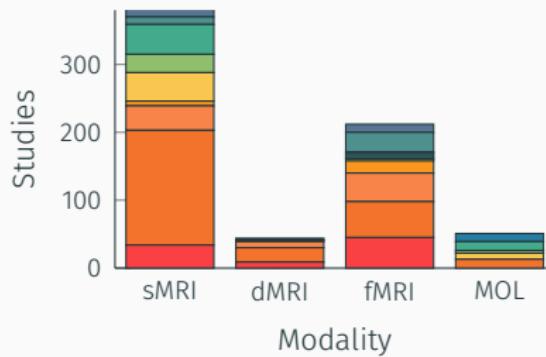


Machine learning techniques in a structural and functional MRI diagnostic approach in schizophrenia: a systematic review
Renato de Filippi,^{1*} Elvira Anna Carboni,^{1†} Raffaele Gaetano,¹ Antonella Bruni,¹ Valentina Puglisi,¹ Cristina Sepura-Garcia,² and Pasquale De Fazio¹

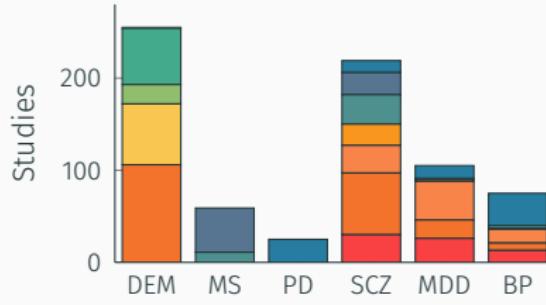
Machine learning techniques for the Schizophrenia diagnosis:
a comprehensive review and future research directions
Shradha Verma¹ · Tripti Goel¹ · M. Tanveer² · Weiping Ding³ · Rahul Sharma¹ · R. Murugan¹



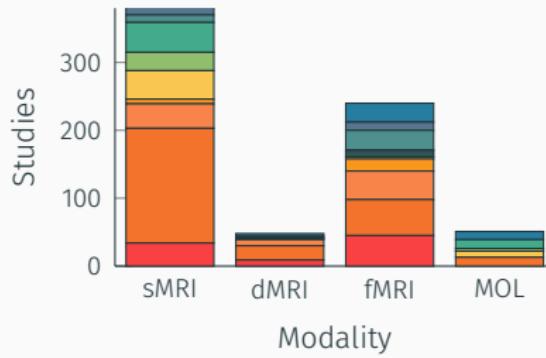
Diagnosis



Approach



Diagnosis

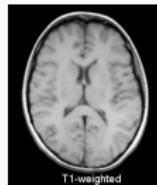


Will machine learning applied to neuroimaging in bipolar disorder help the clinician? A critical review and methodological suggestions

Laurie-Anne Claude, Josselin Houenou, Edouard Duchesnay, Pauline Favre



Other structural MRI modalities



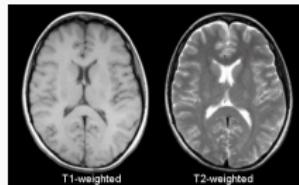
T1-weighted



Preson D. C., (2006), MRI Basics, <https://case.edu/med/neurology/NR/MRI%20Basics>



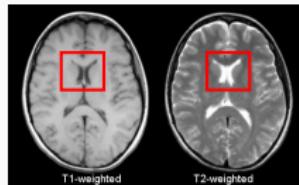
Other structural MRI modalities



Preson D. C., (2006), MRI Basics, <https://case.edu/med/neurology/NR/MRI%20Basics>



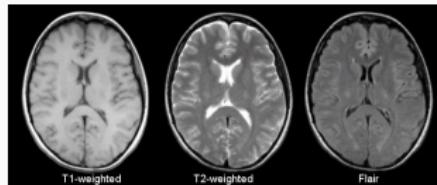
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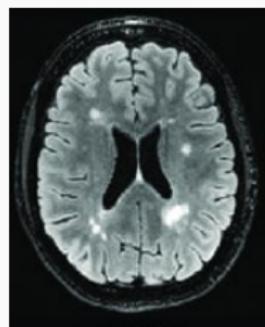
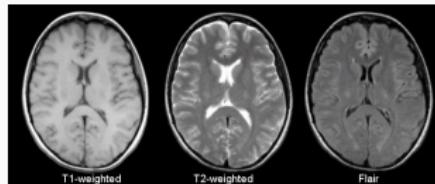
Other structural MRI modalities



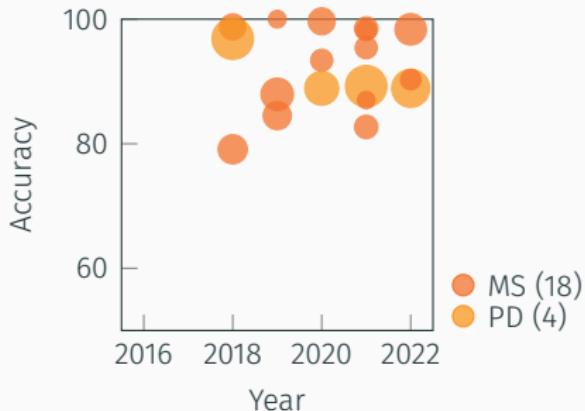
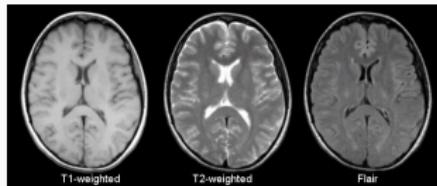
Preson D. C., (2006), MRI Basics, <https://case.edu/med/neurology/NR/MRI%20Basics>



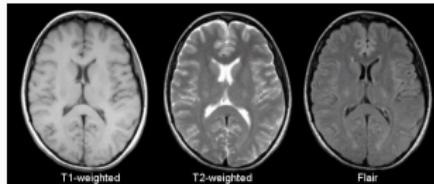
Other structural MRI modalities



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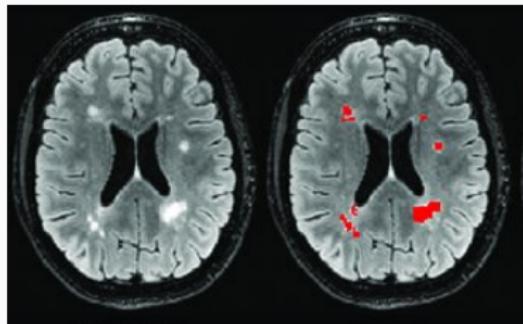
Other structural MRI modalities



T1-weighted

T2-weighted

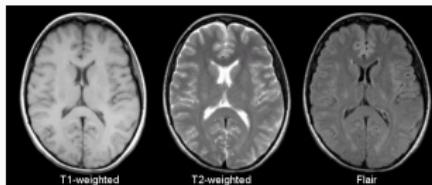
Flair



Weeda, M. M., Brouwer, I., de Vos, M. L., de Vries, M. S., Barkhof, F., Pouwels, P. J. W., & Vrenken, H. (2019). Comparing lesion segmentation methods in multiple sclerosis: Input from one manually delineated subject is sufficient for accurate lesion segmentation. *NeuroImage: Clinical*, 24, 102074.



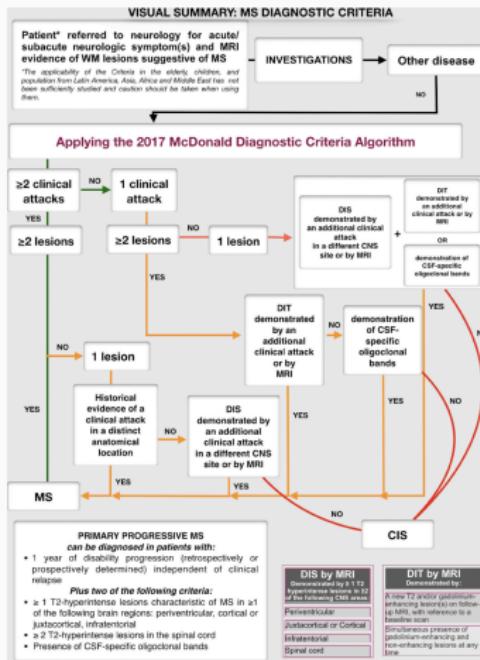
Other structural MRI modalities



T1-weighted

T2-weighted

Flair



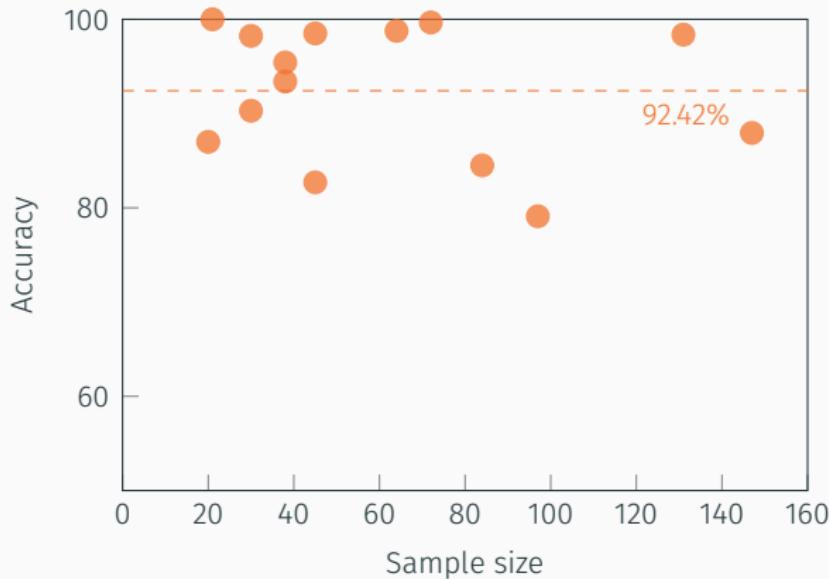
De Angelis, F., Brownlee, W. J., Chard, D. T., & Trip, S. A. (2019). New MS diagnostic criteria in practice. *Practical Neurology*, 19(1), 64-67



Other structural MRI modalities



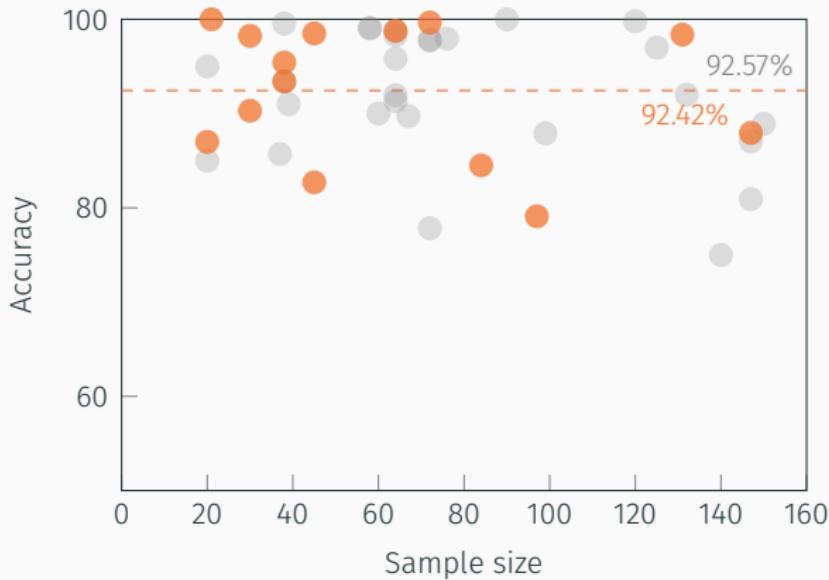
MS classification studies using non-T1w sMRI



Other structural MRI modalities



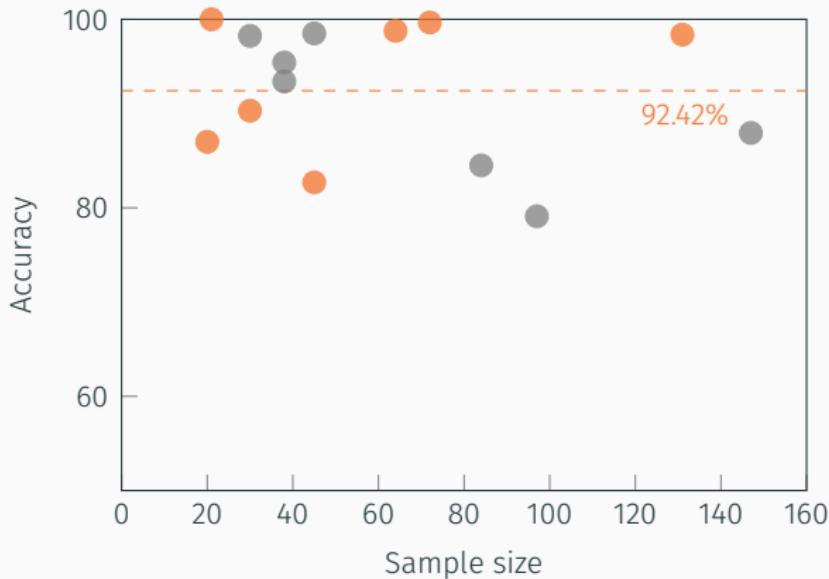
MS classification studies using non-T1w sMRI



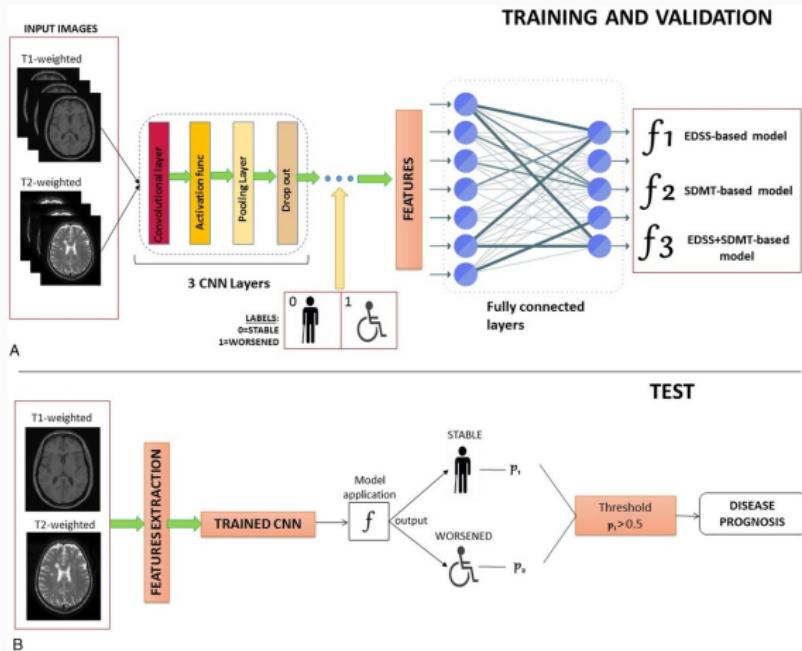
Other structural MRI modalities



MS classification studies using non-T1w sMRI



Other structural MRI modalities



Storelli, L., Azzimonti, M., Gueye, M., Vizzino, C., Preziosa, P., Tedeschi, G., ... & Rocca, M. A. (2022). A deep learning approach to predicting disease progression in multiple sclerosis using magnetic resonance imaging. *Investigative Radiology*, 57(7), 423-432



Other structural MRI modalities



		Prediction of Clinical Worsening (EDSS Model)	Prediction of Cognitive Worsening (SDMT Model)	Prediction of Clinical and Cognitive Worsening (EDSS + SDMT Model)	p*
CNN deep learning	Accuracy (%)	83.3	67.7	85.7	—
	Sensitivity (%)	57.1	60.0	75.0	—
	Specificity (%)	90.0	81.8	87.5	—
Expert raters consensus	Accuracy (%)	—	—	70.0	<0.001
	Sensitivity (%)	—	—	14.3	<0.0001
	Specificity (%)	—	—	80.0	<0.01

*P value for the comparisons between the expert raters consensus and the deep learning model.



Storelli, L., Azzimonti, M., Gueye, M., Vizzino, C., Preziosa, P., Tedeschi, G., ... & Rocca, M. A. (2022). A deep learning approach to predicting disease progression in multiple sclerosis using magnetic resonance imaging. *Investigative Radiology*, 57(7), 423-432



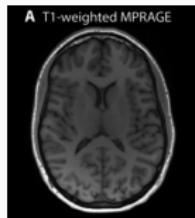
Other structural MRI modalities

Structural MRI beyond T1-weighted: Picturing different, stable, properties of tissue.

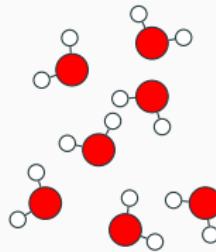
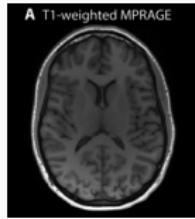
- Most prevalent in studies classifying MS and PD, yielding high accuracies (~90%).
- T2 intimately linked with MS due to its efficacy at exposing characteristic lesions.
- Machine learning models trained on T1 and T2-weighted scans shown by Storelli et al. to predict prognosis in MS better than expert humans.



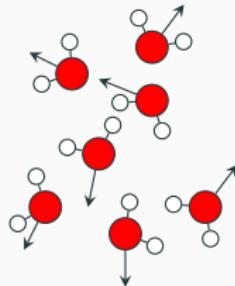
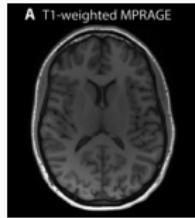
Diffusion MRI



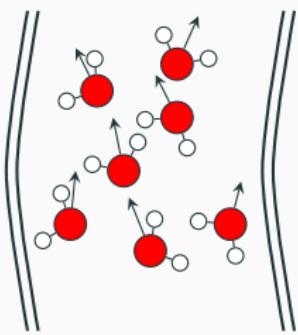
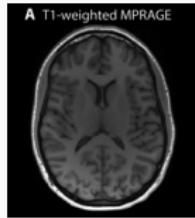
Diffusion MRI



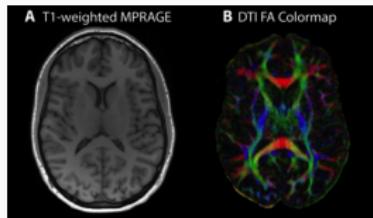
Diffusion MRI



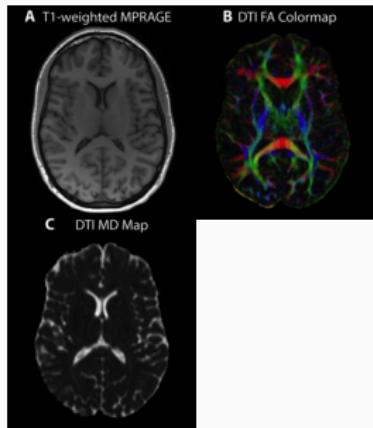
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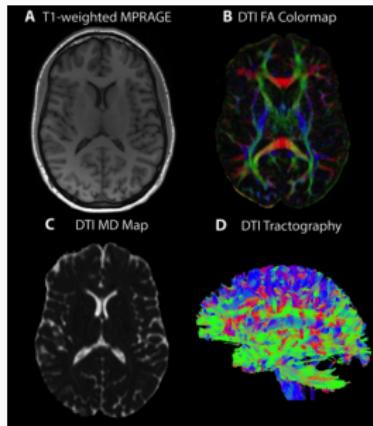
Diffusion MRI



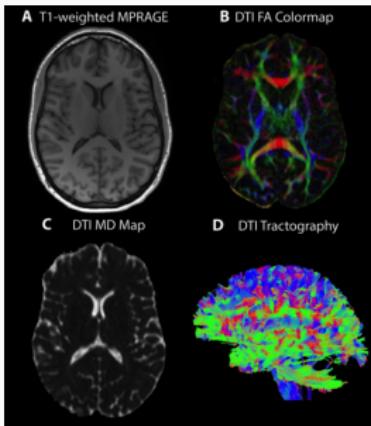
Diffusion MRI



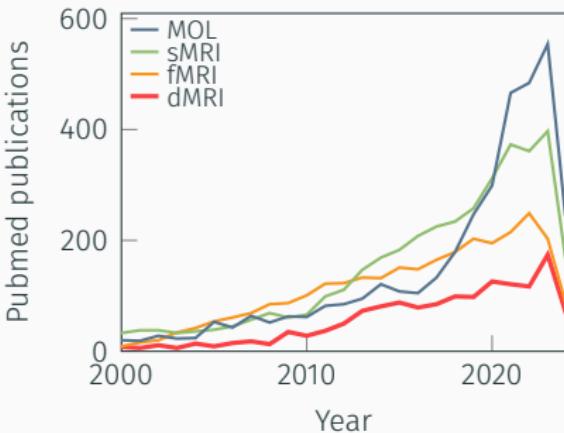
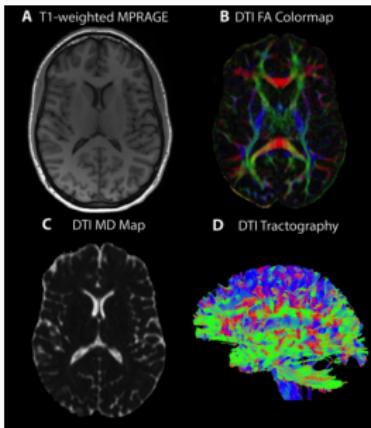
Diffusion MRI



Diffusion MRI



Diffusion MRI



MOL: ((molecular[Title] AND imaging[Title]) OR PET[Title] OR SPECT[Title]) AND (machine learning OR ML OR deep learning OR DL OR prediction)"

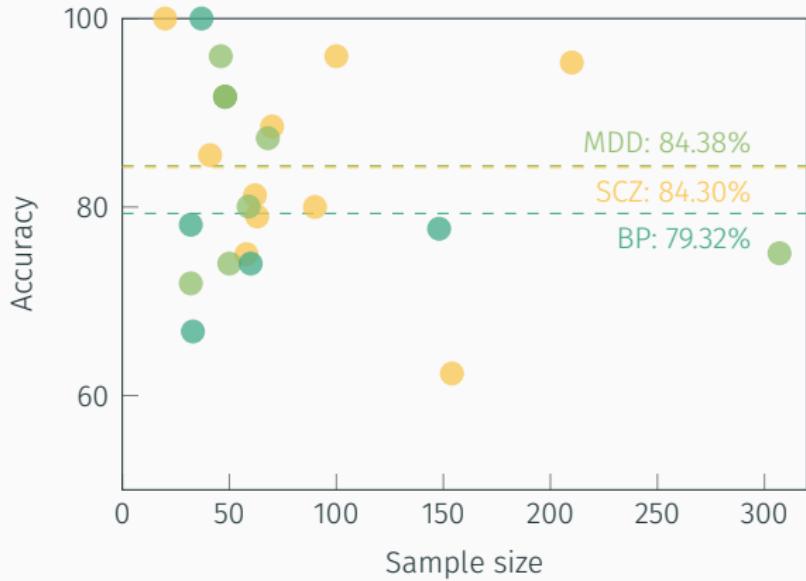
sMRI: ((structural[Title] AND MRI[Title]) OR smRI[Title] OR T1[Title] OR T2[Title]) AND (machine learning OR ML OR deep learning OR DL OR prediction)

fMRI: ((functional[Title] AND MRI[Title]) OR fmRI[Title]) AND (machine learning OR ML OR deep learning OR DL OR prediction)

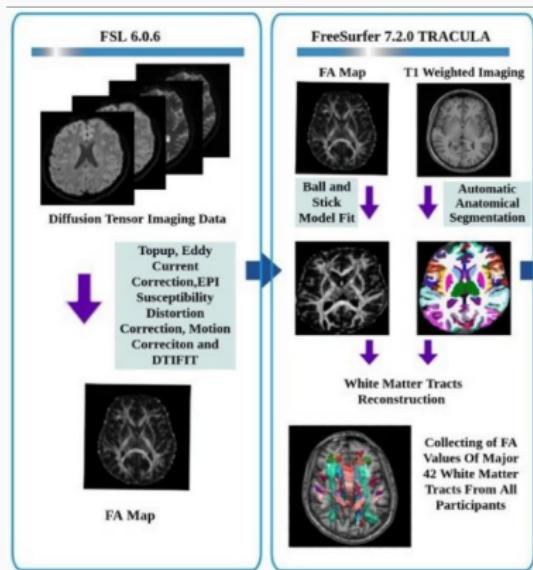
dMRI: ((diffusion[Title] AND MRI[Title]) OR dMRI[Title] OR DTI[Title]) AND (machine learning OR ML OR deep learning OR DL OR prediction)



Classification studies of mental disorders using dMRI



Diffusion MRI



Saglam, Y., Oz, A., Yildiz, G., Ermis, C., Kargin, O. A., Arslan, S., & Karacetin, G. (2023). Can diffusion tensor imaging have a diagnostic utility to differentiate early-onset forms of bipolar disorder and schizophrenia: A neuroimaging study with explainable machine learning algorithms. *Psychiatry Research: Neuroimaging*, 335, 111696.



Diffusion MRI

Classifier	AUC	Accuracy	Sensitivity	Specificity	Precision	F1 score	MCC
SVM-linear	0.85	0.80	0.75	0.86	0.79	0.77	0.74
Random forest	0.82	0.79	0.72	0.81	0.76	0.74	0.70
SVM-Gaussian	0.83	0.78	0.71	0.80	0.75	0.73	0.70
LR	0.78	0.76	0.70	0.79	0.73	0.71	0.68
Naive Bayes	0.75	0.72	0.65	0.74	0.68	0.66	0.62

Saglam, Y., Oz, A., Yildiz, G., Ermis, C., Kargin, O. A., Arslan, S., & Karacetin, G. (2023). Can diffusion tensor imaging have a diagnostic utility to differentiate early-onset forms of bipolar disorder and schizophrenia: A neuroimaging study with explainable machine learning algorithms. Psychiatry Research: Neuroimaging, 335, 111696



Diffusion MRI: Depicting white matter tracts and their integrity

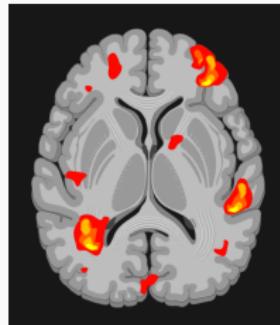
- Relatively few prediction studies found, most studies appear to focus on deriving biological insights.
- Most studies for mental disorders, specifically SCZ and MDD, with high mean accuracies (~85%) but a large spread (60-100%).
- Used by Saglam et al. to differentially diagnose SCZ and BP with 80% accuracy, approaching the threshold for predictive utility.



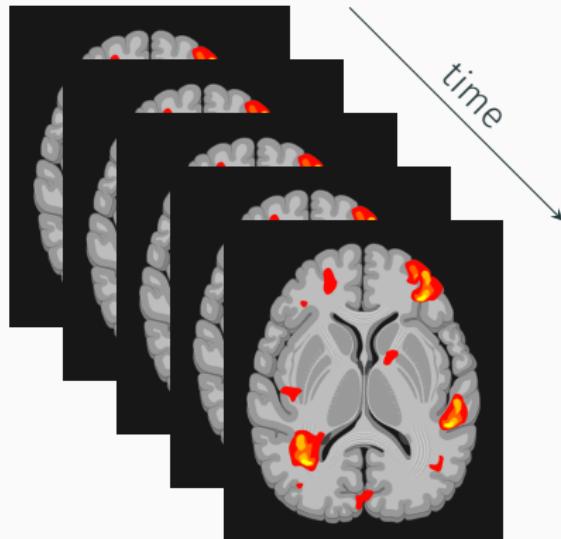
Functional Magnetic Resonance Imaging (fMRI)



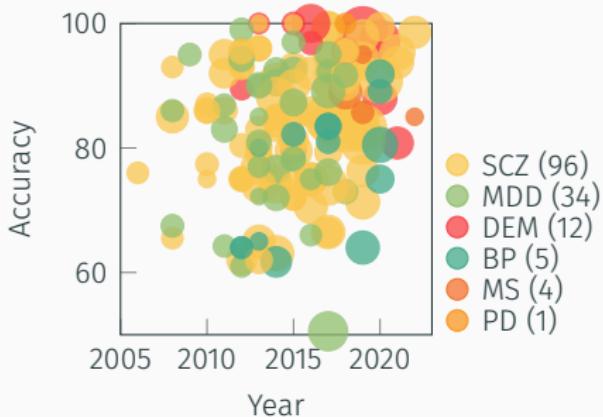
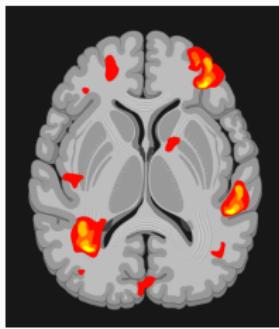
Functional Magnetic Resonance Imaging (fMRI)



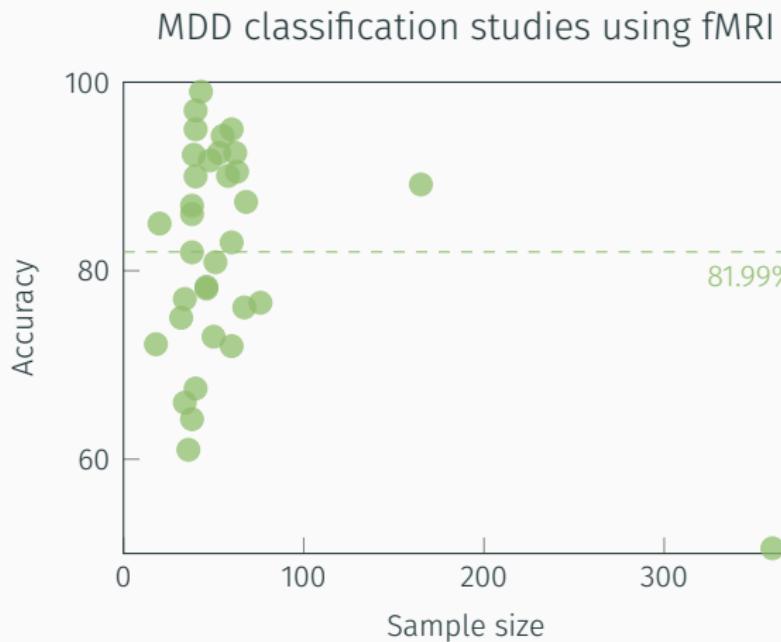
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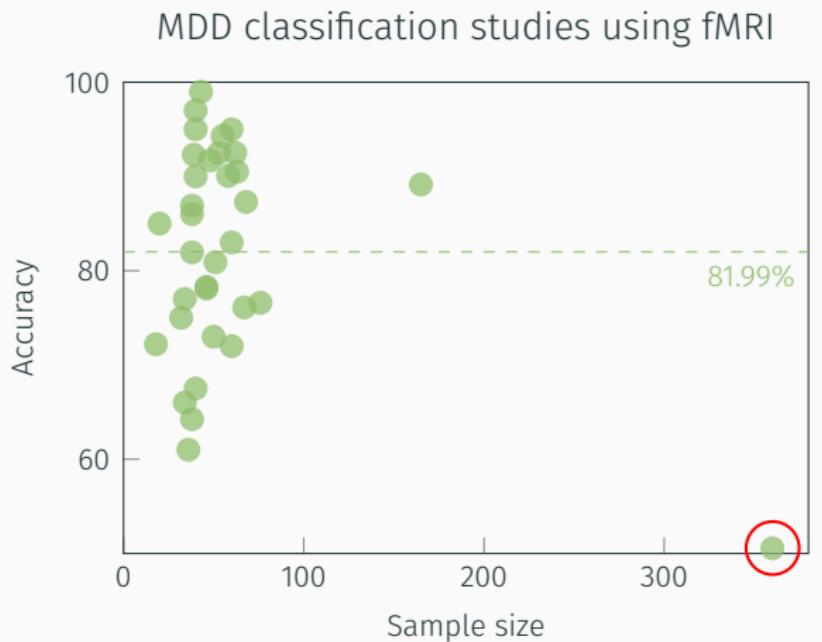
Functional Magnetic Resonance Imaging (fMRI)



Functional Magnetic Resonance Imaging (fMRI)



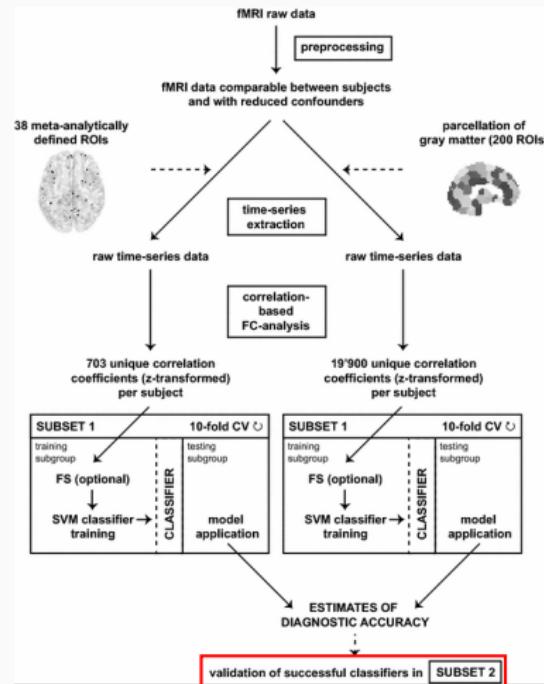
Functional Magnetic Resonance Imaging (fMRI)



Sundermann, B., Feder, S., Wersching, H., Teuber, A., Schwindt, W., Kugel, H., ... & Pfleiderer, B. (2017). Diagnostic classification of unipolar depression based on resting-state functional connectivity MRI: effects of generalization to a diverse sample. *Journal of Neural Transmission*, 124, 589-605



Functional Magnetic Resonance Imaging (fMRI)



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Functional Magnetic Resonance Imaging (fMRI)

(a) Main analysis Yielded no positive results									
(b) Subgroup analysis [most severely depressed patients ($n = 60$) and their corresponding controls ($n = 60$)]									
FS	Features (n)	C-SVC-classifier	CV in subset 1			Validation in subset 2			$p(FDR)$ ACC
			ACC (%)	SENS (%)	SPEC (%)	ACC (%)	SENS (%)	SPEC (%)	
<i>Models based on connectivity of meta-analytically defined regions</i>									
./.	703	RBF ($\gamma = 0.01$), C = 10	60.0	60.0	60.0	55.0	46.7	63.3	0.171
t test ^a	141	lin, C = 0.1	65.0	63.3	66.7	57.5	45.0	70.0	0.087
t test ^a	141	RBF ($\gamma = 0.01$), C = 10	61.7	60.0	63.3	55.8	45.0	66.7	0.140
SVM ^b	141	RBF ($\gamma = 0.01$), C = 1	61.7	71.7	51.7	61.7	58.3	65.0	0.046*

Sundermann, B., Feder, S., Wersching, H., Teuber, A., Schwindt, W., Kugel, H., ... & Pfeiferer, B. (2017). Diagnostic classification of unipolar depression based on resting-state functional connectivity MRI: effects of generalization to a diverse sample. Journal of Neural Transmission, 124, 589-605



Functional Magnetic Resonance Imaging (fMRI)



Functional Magnetic Resonance Imaging (fMRI)



Functional Magnetic Resonance Imaging (fMRI)



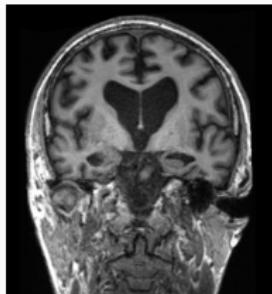
Functional Magnetic Resonance Imaging (fMRI)

Functional MRI: An indirect measure of brain activity

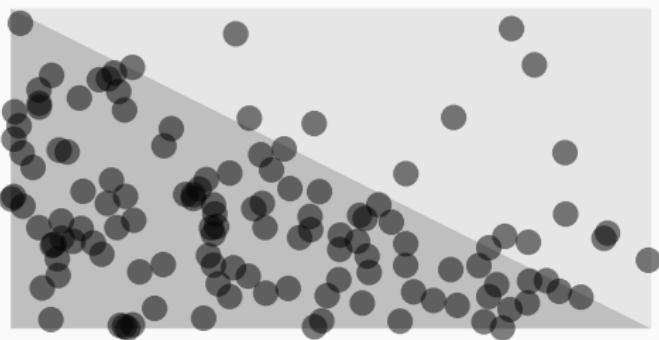
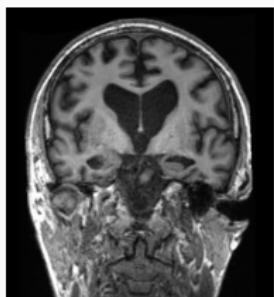
- A large number of predictive studies found, mostly for mental disorders.
- Generally high mean accuracies (80-85%) but a large spread(60-100%).
- Sundermann et al. struggled to find signal in a sample of diverse patients, but saw predictive efficacy when restricted to those with the most severe symptoms.



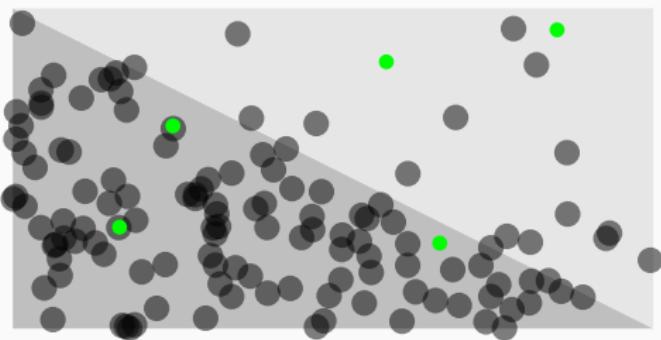
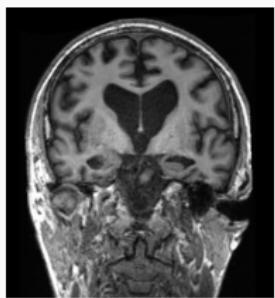
Molecular imaging



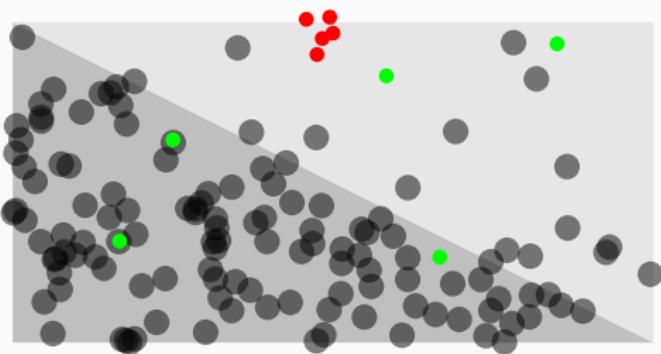
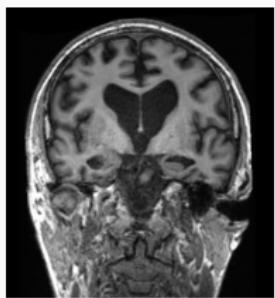
Molecular imaging



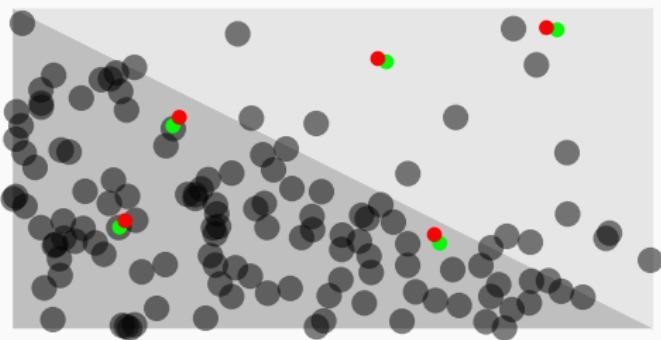
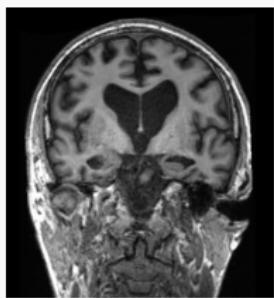
Molecular imaging



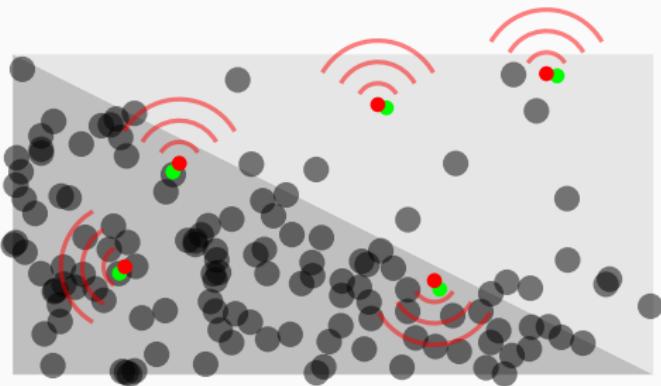
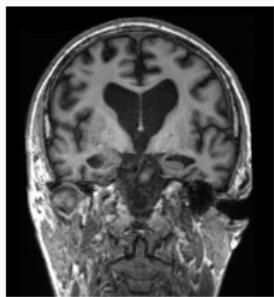
Molecular imaging



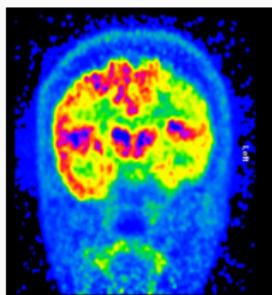
Molecular imaging



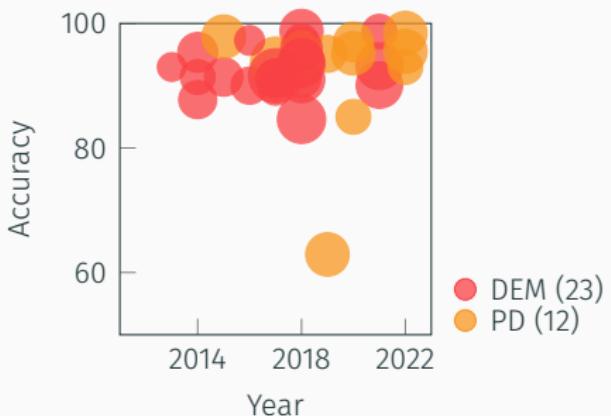
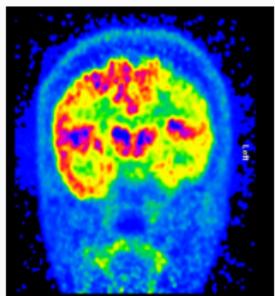
Molecular imaging



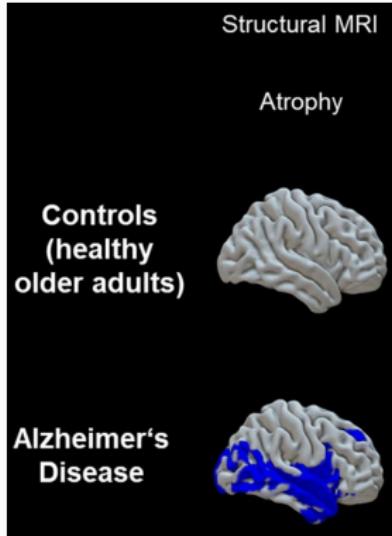
Molecular imaging



Molecular imaging



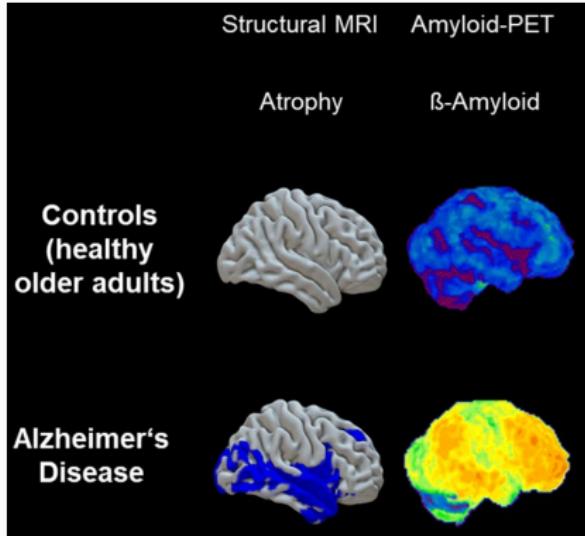
Molecular imaging



Chételat, G., Arbizu, J., Barthel, H., Garibotto, V., Lammertsma, A. A., Law, I., ... & Drzezga, A. (2021). Finding our way through the labyrinth of dementia biomarkers. European journal of nuclear medicine and molecular imaging, 48, 2320-2324



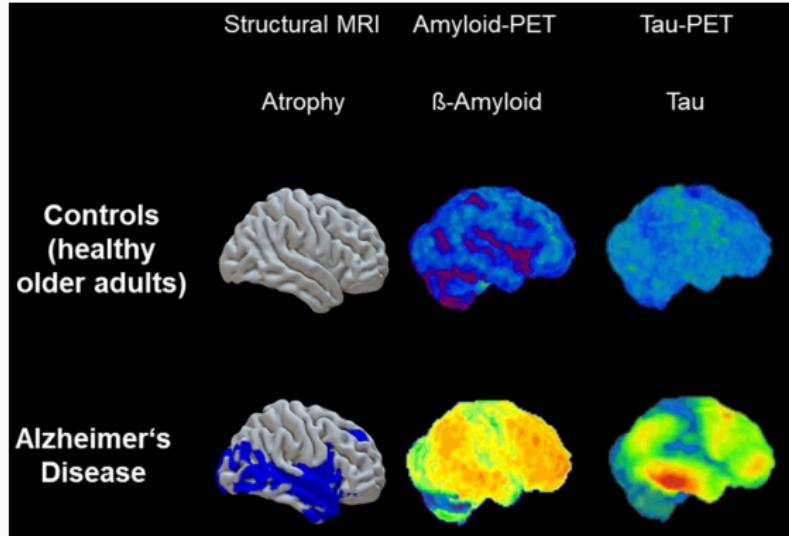
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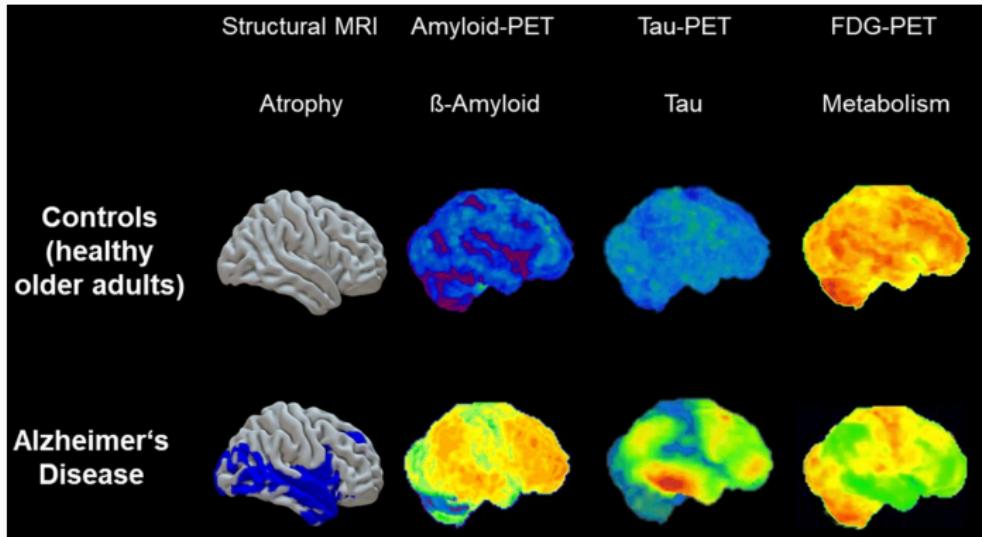
Molecular imaging



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Molecular imaging

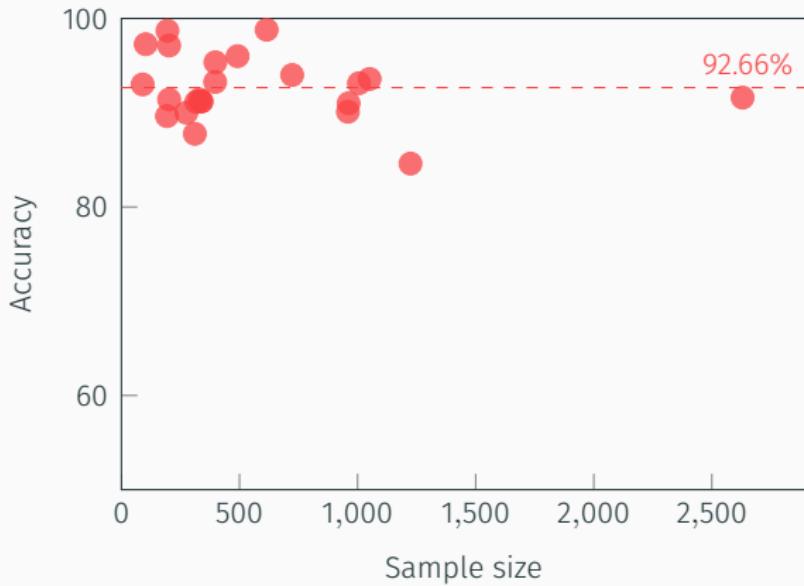


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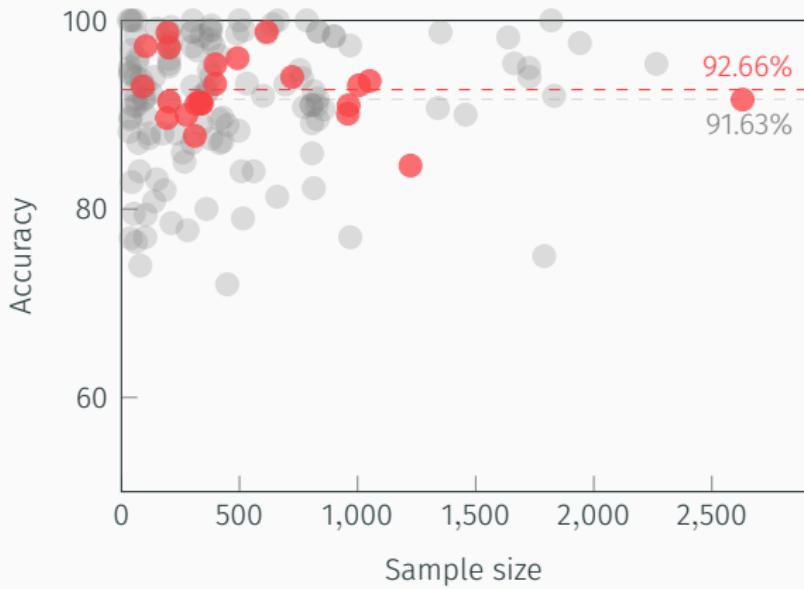
Molecular imaging

DEM classification studies using molecular imaging

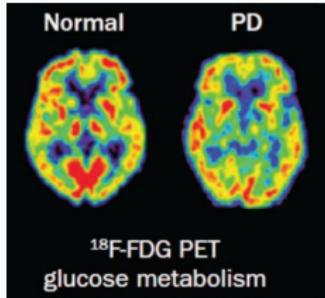


Molecular imaging

DEM classification studies using molecular imaging

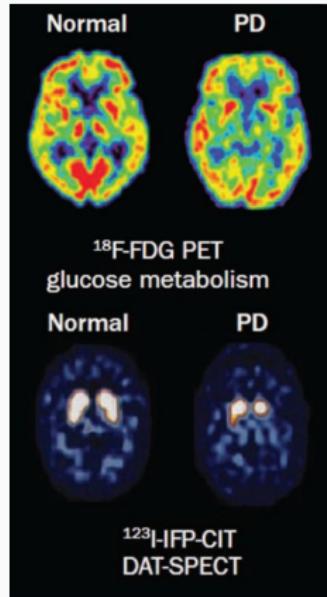


Molecular imaging



Pagano, G., Niccolini, F., & Politis, M. (2016). Imaging in Parkinson's disease. Clinical Medicine, 16(4), 371

Molecular imaging

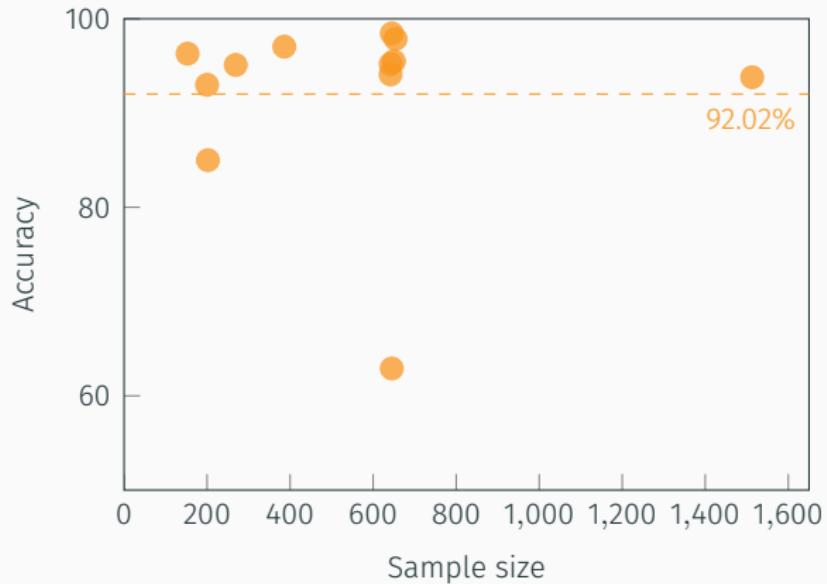


Pagano, G., Niccolini, F., & Politis, M. (2016). Imaging in Parkinson's disease. Clinical Medicine, 16(4), 371



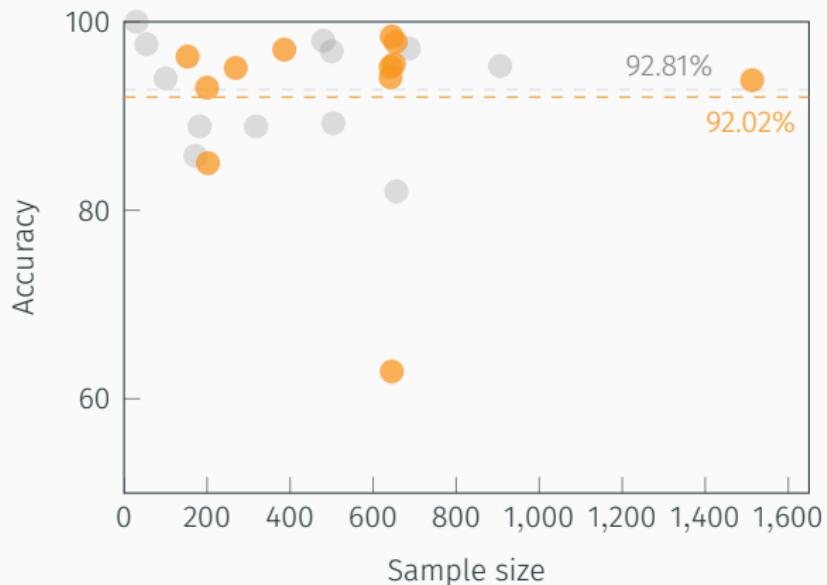
Molecular imaging

PD classification studies using molecular imaging



Molecular imaging

PD classification studies using molecular imaging



Molecular imaging

"It is necessary to separate syndrome (clinically identified impairment) from biology (etiology)

AD is defined by its biology with the following implications

The disease is first evident with the appearance of β-amyloid plaques, and later neocortical tau tangles, while people are asymptomatic. Pathophysiologic mechanisms involved with processing and clearance of protein fragments may be involved very early in the disease process, but these are not yet well understood.

In living people the disease is diagnosed by disease specific core biomarkers

Unimpaired individuals with abnormal biomarker testing are at risk for symptoms due to AD.

They are not at risk for a disease they already have.

Symptoms are a result of the disease process and are not necessary to diagnose AD

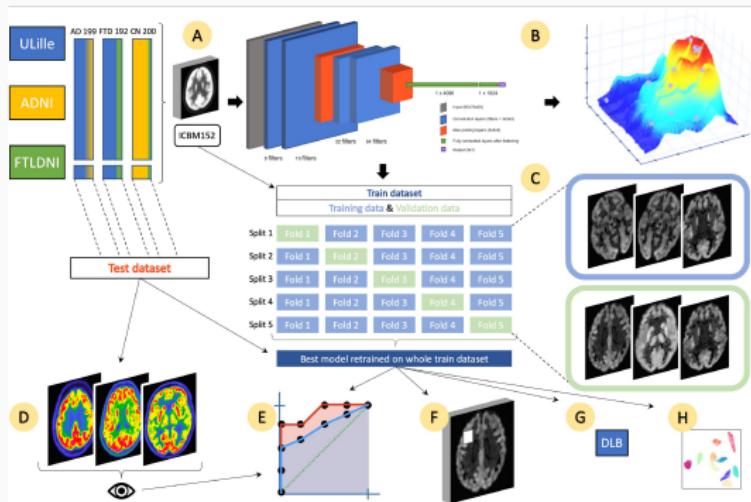
AD exists on a continuum not as discrete clinically defined entities

Clinical syndromes commonly seen with AD may also be caused by disorders other than AD and therefore clinical presentation alone is not diagnostic of AD

The same AD biology may result in different phenotypic presentations"



Molecular imaging



Rogeau, A., Hives, F., Bordier, C., Lahousse, H., Roca, V., Lebouvier, T., ... & Lopes, R. (2024). A 3D convolutional neural network to classify subjects as Alzheimer's disease, frontotemporal dementia or healthy controls using brain 18F-FDG PET. *NeuroImage*, 120530



Molecular imaging

		Metrics				
		Se	Sp	Precision	F1-score	Support
Model	AD	75 % (15/20)	97 % (38/39)	94 % (15/16)	83 %	20
	FTD	95 % (18/19)	90 % (36/40)	82 % (18/22)	88 %	19
	CN	100 % (20/20)	97 % (38/39)	95 % (20/21)	98 %	20 ^{acc} <u>89.8%</u>
		Se	Sp	Precision	F1-score	Support
Physician	AD	70 % (14/20)	87 % (34/39)	74 % (14/19)	72 %	20
	FTD	47 % (9/19)	92 % (37/40)	75 % (9/12)	58 %	19
	CN	90 % (18/20)	74 % (29/39)	64 % (18/28)	75 %	20 ^{acc} <u>69.5%</u>

Rogeau, A., Hives, F., Bordier, C., Lahousse, H., Roca, V., Lebouvier, T., ... & Lopes, R. (2024). A 3D convolutional neural network to classify subjects as Alzheimer's disease, frontotemporal dementia or healthy controls using brain 18F-FDG PET. *NeuroImage*, 120530



Molecular imaging

Molecular imaging: Detects the presence of specific molecules

- Used in studies classifying PD and DEM with good results (accuracies >90%), although (potentially surprisingly) not substantially better than other modalities.
- PET is a natural choice for detecting AD-related pathology, both A β plaques and TAU tangles.
- SPECT useful to characterize degeneration of dopamine-producing cells in PD
- Useful for differentially diagnosing neurological disorders underlying DEM, as shown by Rogeau et al.

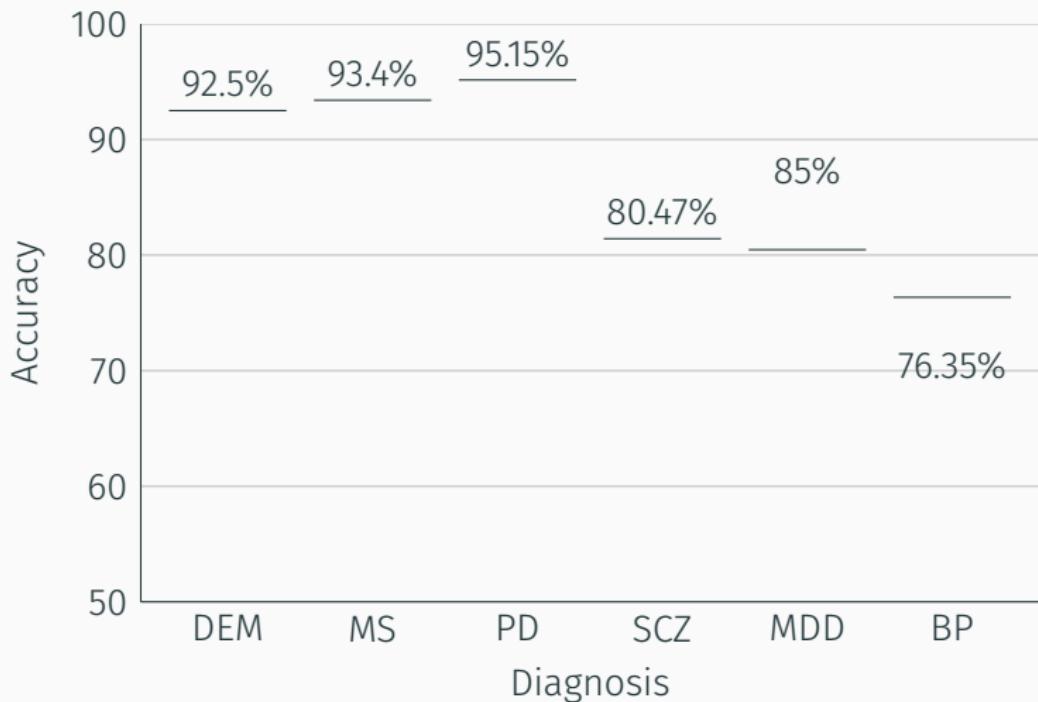


An overview of neuroimaging for diagnostic predictions

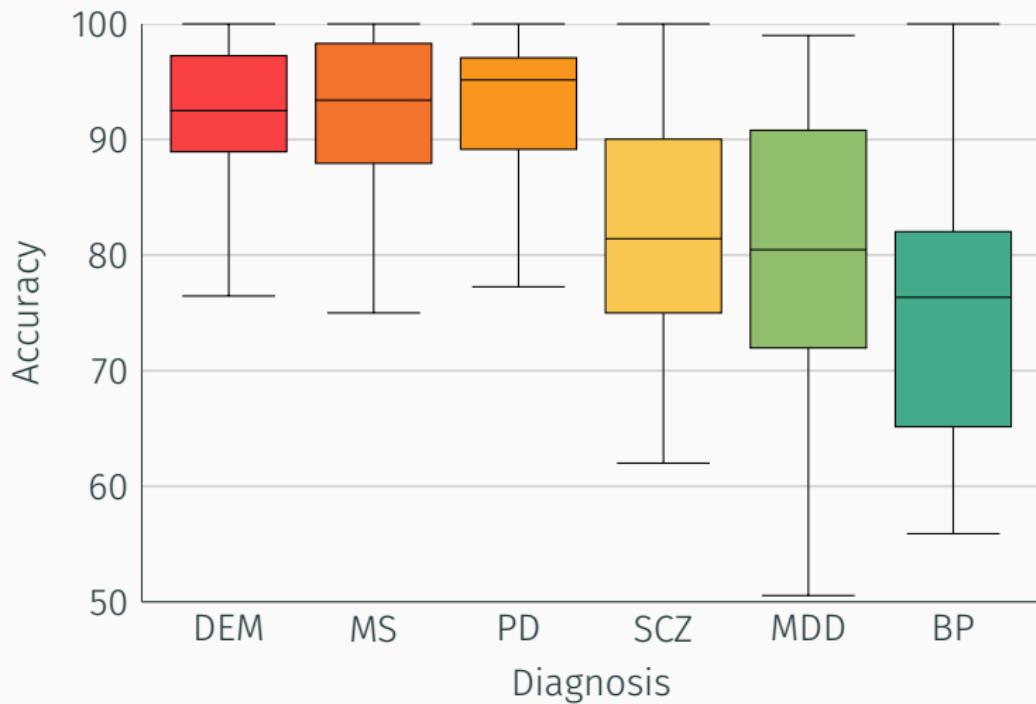


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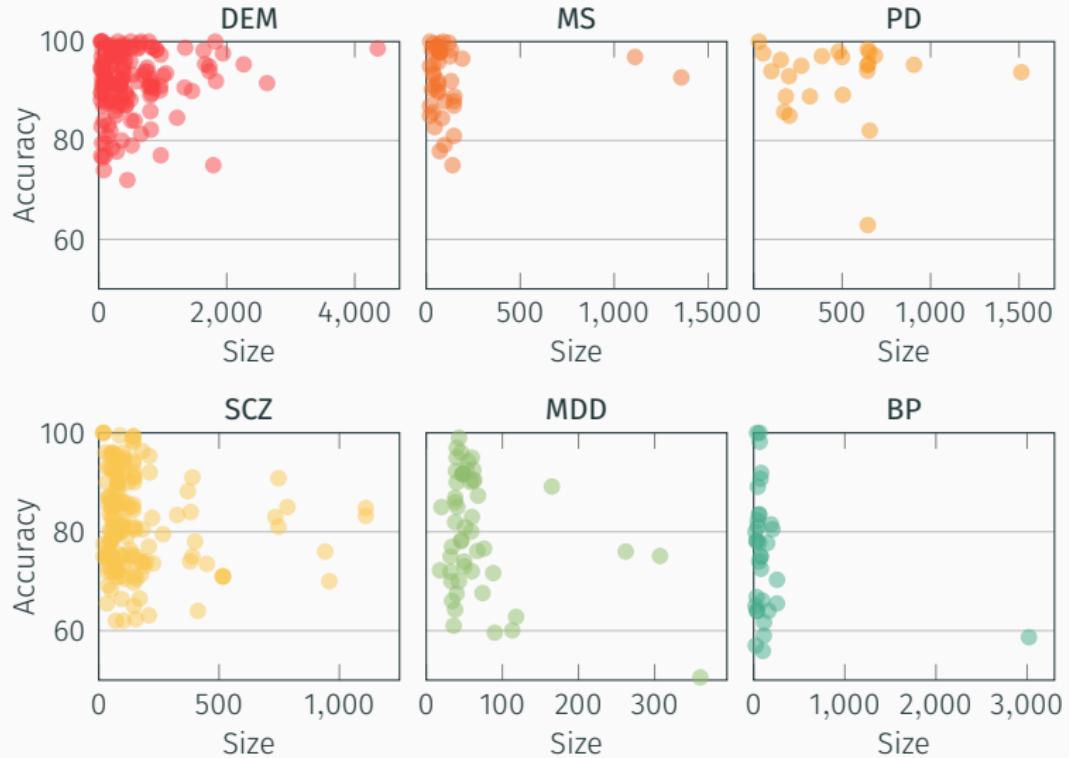
Challenges: Predictiveness



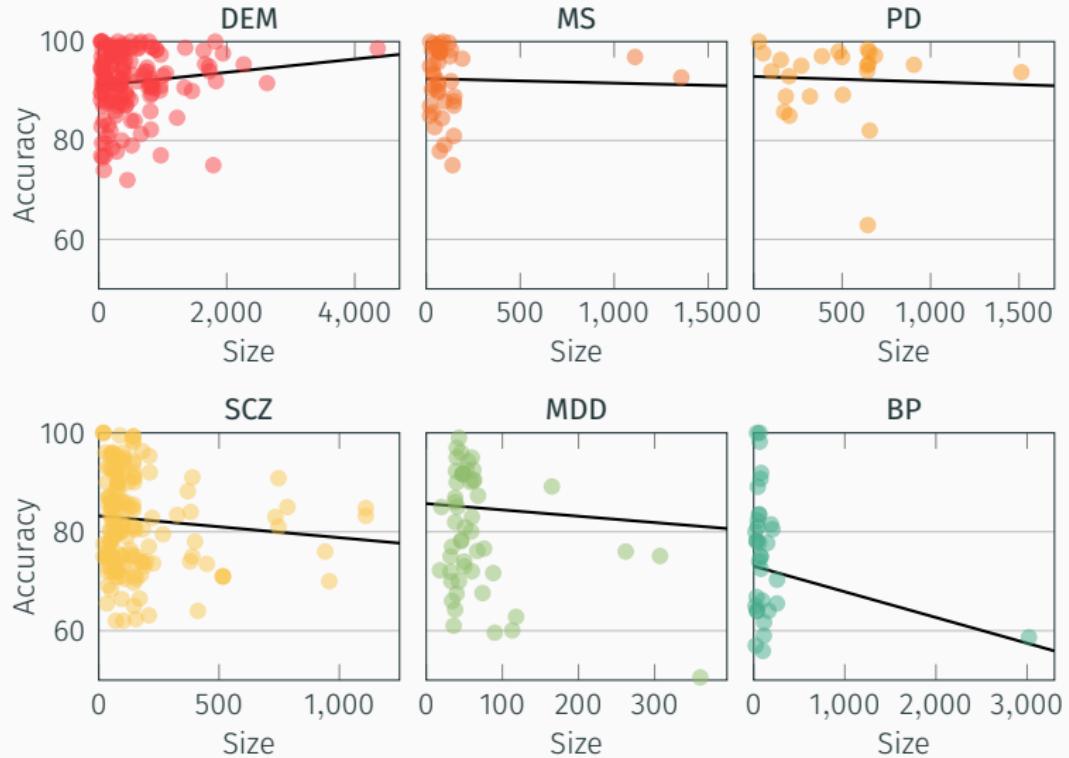
Challenges: Predictiveness



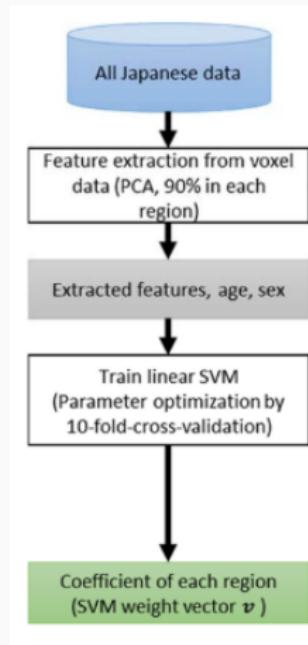
Challenges: Predictiveness



Challenges: Predictiveness



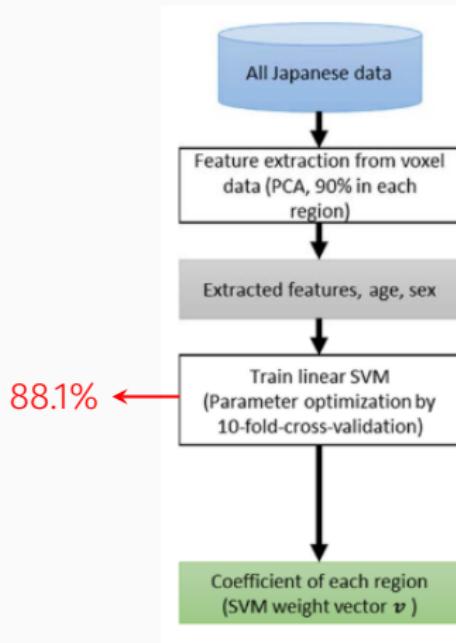
Challenges: Generalization



Matsuo, K., Harada, K., Fujita, Y., Okamoto, Y., Ota, M., Narita, H., ... & Watanabe, Y. (2019). Distinctive neuroanatomical substrates for depression in bipolar disorder versus major depressive disorder. *Cerebral Cortex*, 29(1), 202-214



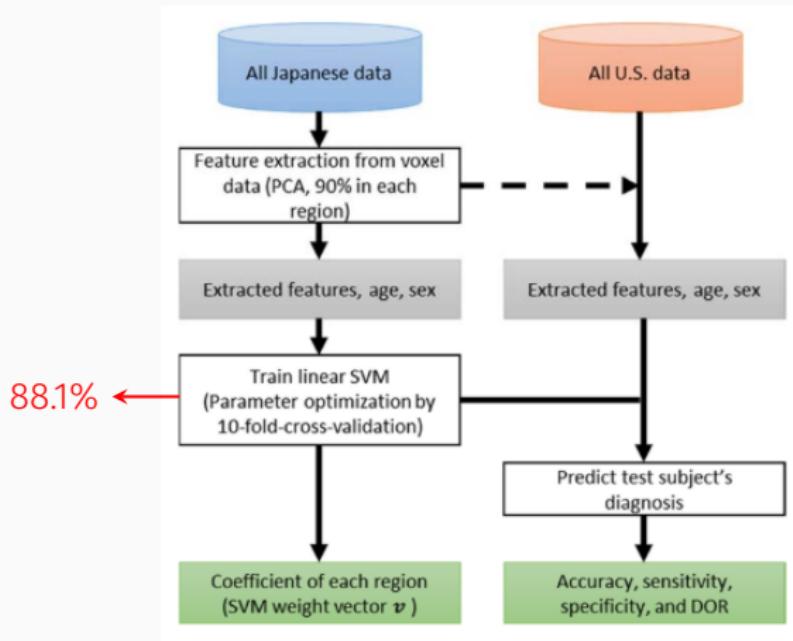
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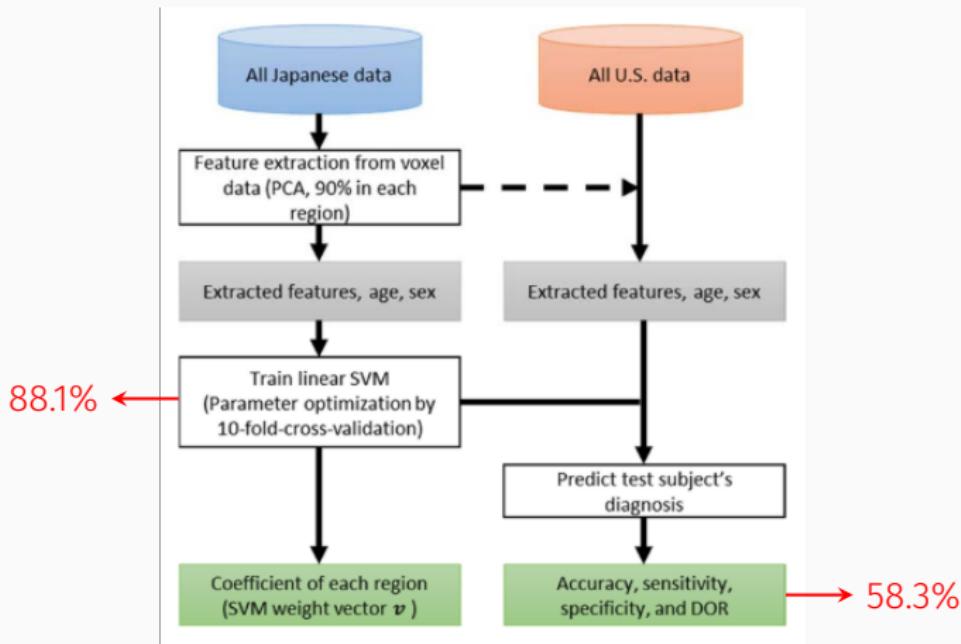
Challenges: Generalization



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Challenges: Generalization



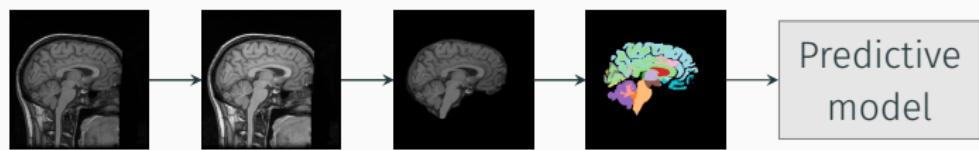
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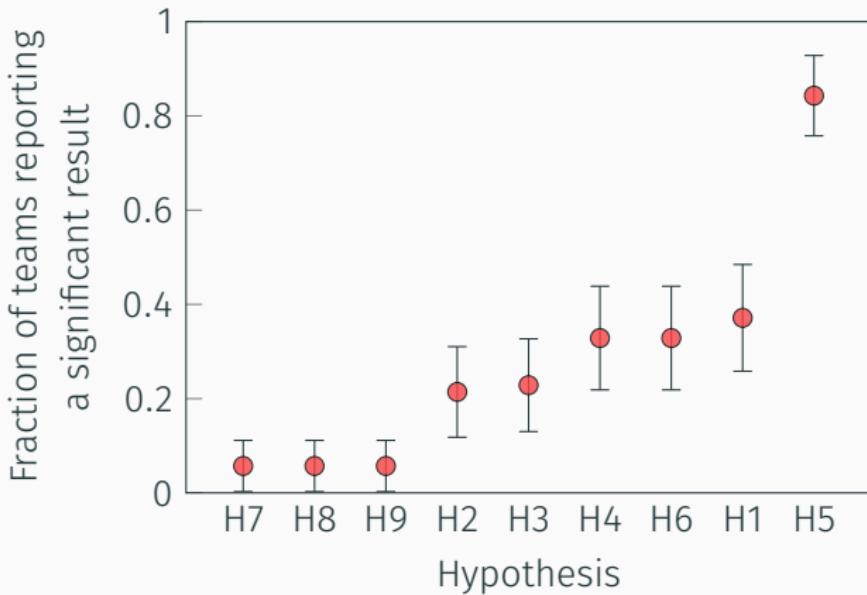
Challenges: Researcher degrees of freedom



Challenges: Researcher degrees of freedom



Challenges: Researcher degrees of freedom

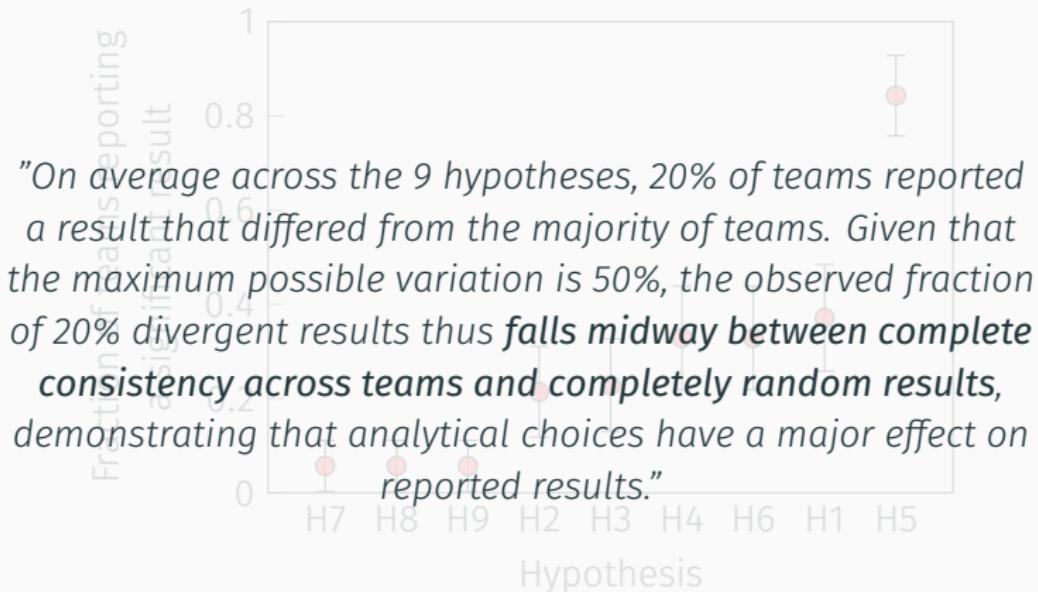


Adapted from Botvinik-Nezer et al., 2020

Botvinik-Nezer, R., Holzmeister, F., Camerer, C. F., Dreber, A., Huber, J., Johannesson, M., ... & Rieck, J. R. (2020). Variability in the analysis of a single neuroimaging dataset by many teams. *Nature*, 582(7810), 84-88



Challenges: Researcher degrees of freedom

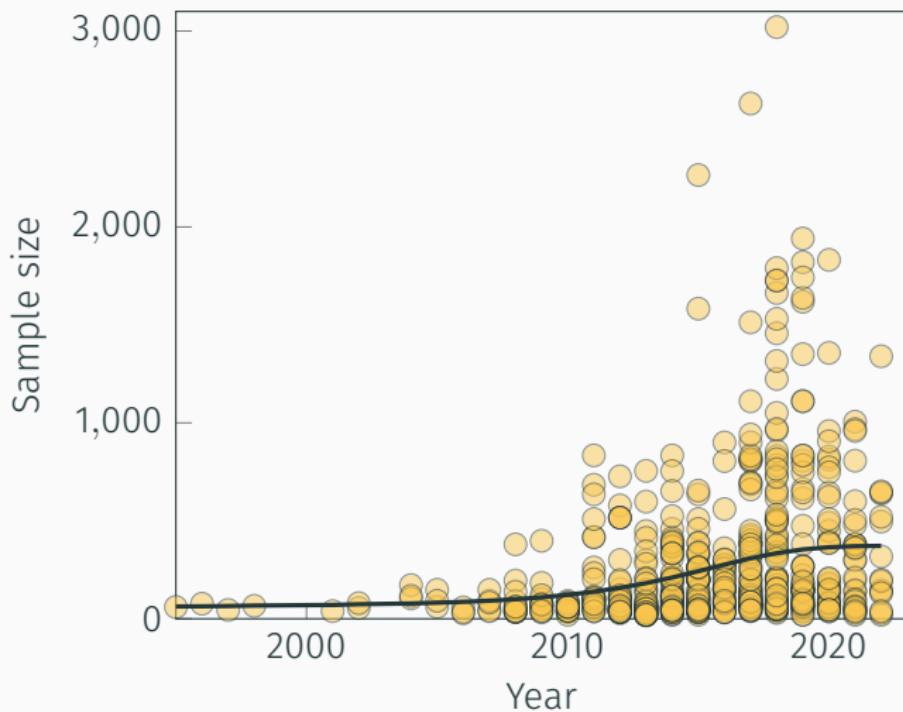


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Opportunities: Larger datasets



Opportunities: Better methods

