From machine learning to deep learning,

how do we ensure objective and reproducible evaluations?

ARAMIS LAB
BRAIN DATA SCIENCE

www.aramislab.fr

www.clinica.run

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OHBM – ML4NI

2020

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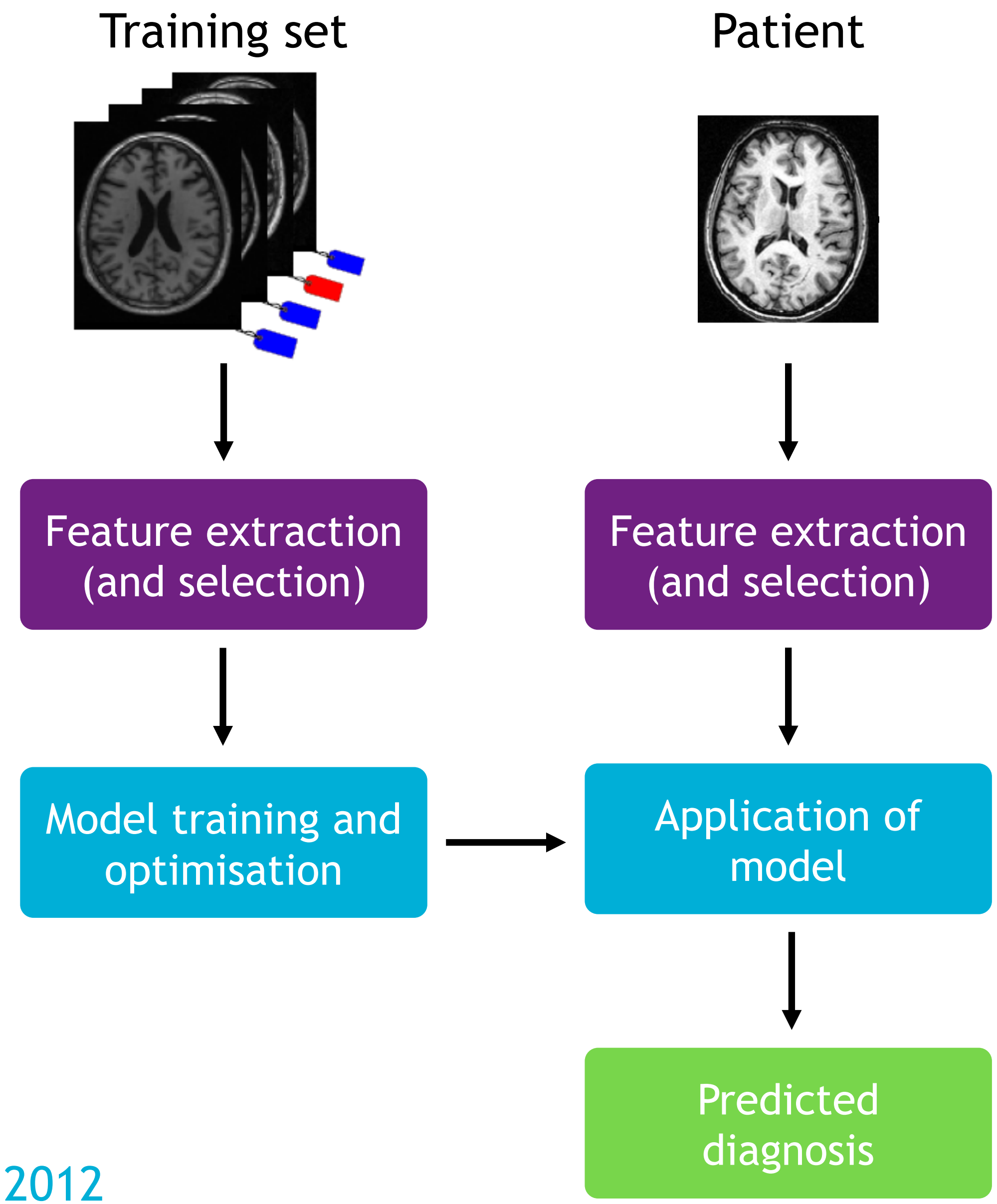
Clinical pattern recognition

Basic elements of a machine learning classification pipeline

- Training data set
- Feature extraction from raw data and dimensionality reduction
- Model training and optimization
- Application to test data



Klöppel et al., NeuroImage, 2012

Clinical pattern recognition

Basic elements of a deep learning classification pipeline

- Training data set
- Feature extraction from raw data and dimensionality reduction
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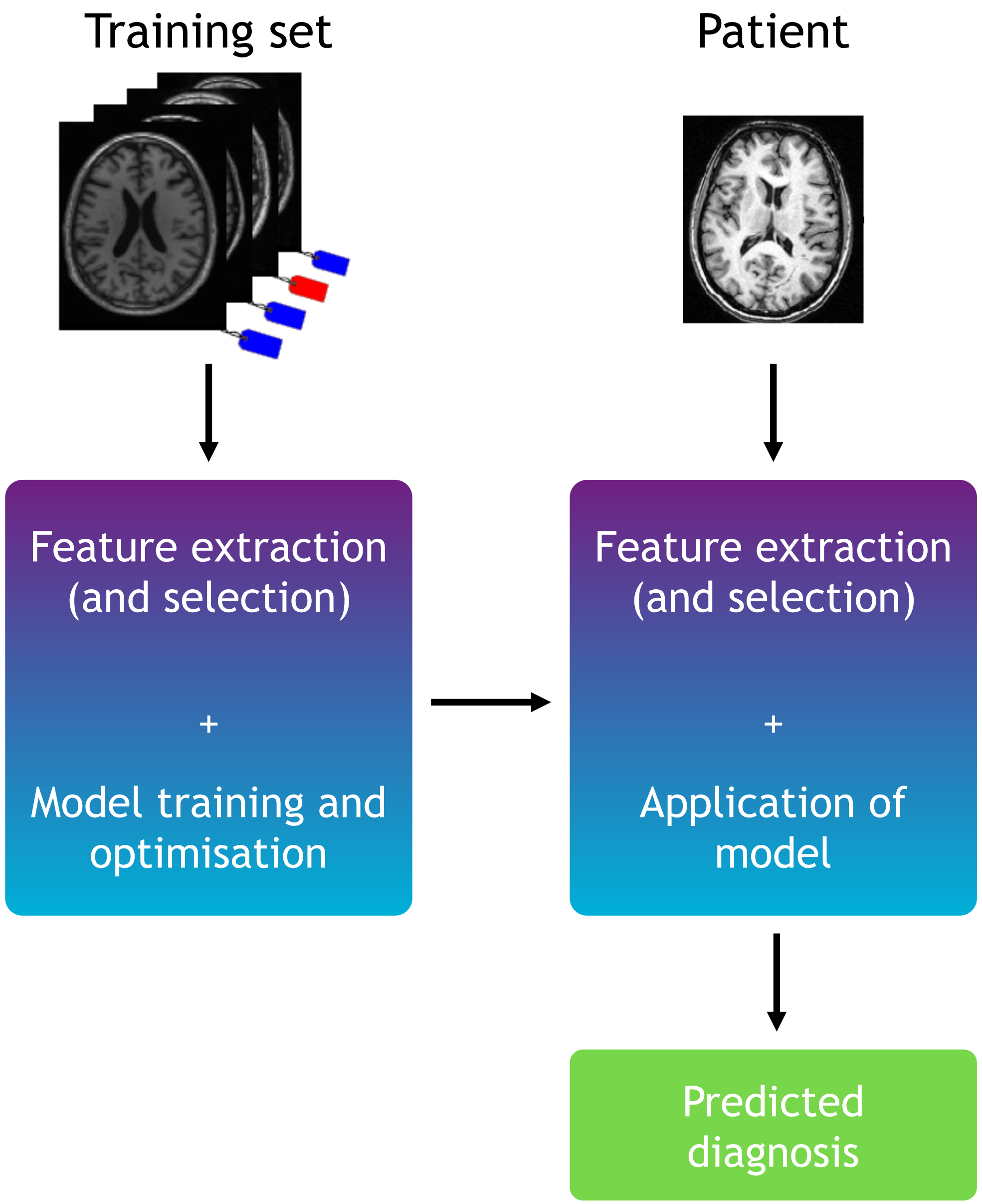
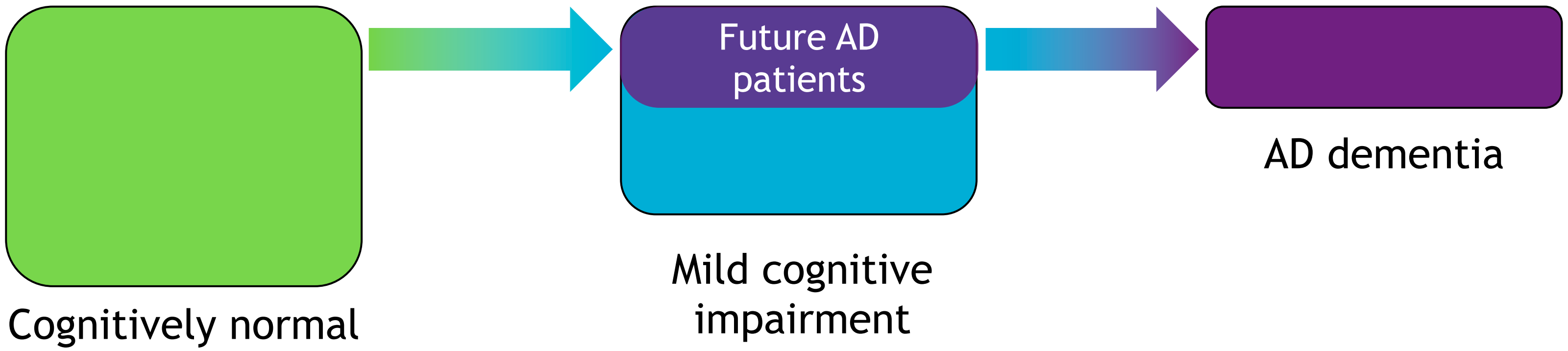


Use case: Alzheimer’s disease (AD)

What is Alzheimer’s disease?

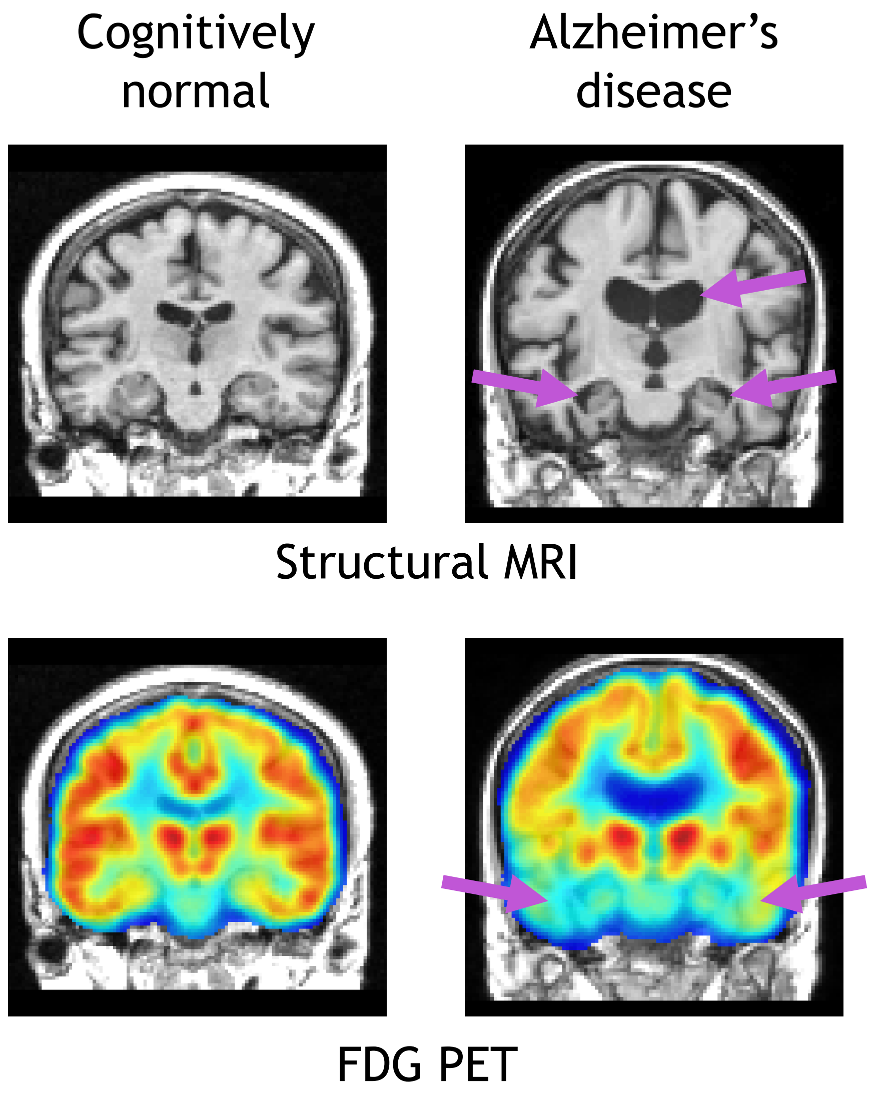
- Most common cause of dementia
- Disorder caused by abnormal brain changes
- Trigger decline in cognitive abilities, severe enough to impair daily life
- Affect behaviour, feelings and relationships
- Progressive disease



Use case: Alzheimer’s disease (AD)

AD-related biomarkers

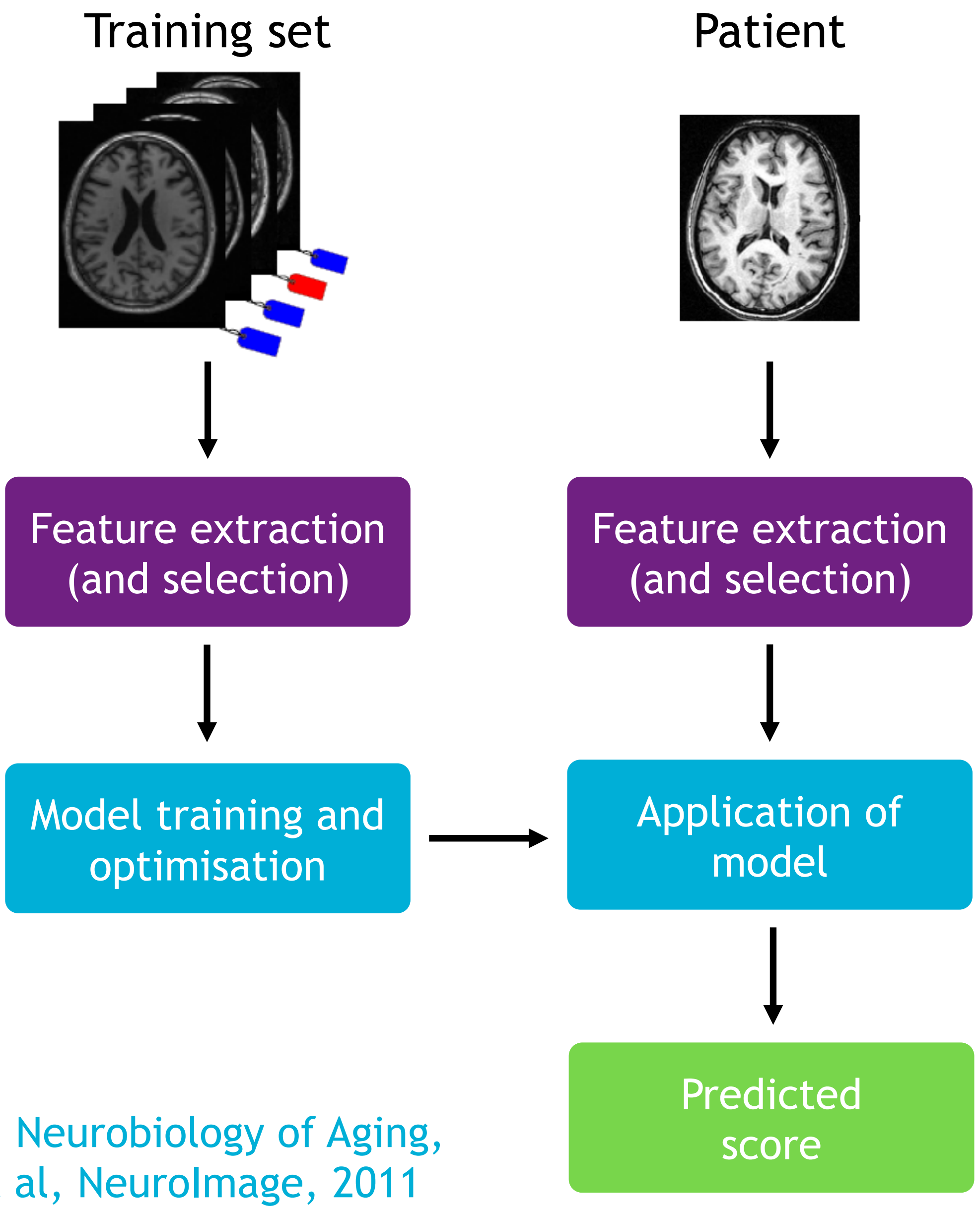
- **Clinical/cognitive tests**
  - Neuropsychological testing of cognitive functions (memory, language, etc.)
- **Structural MRI**
  - Atrophy
- **FDG PET**
  - Hypometabolism
- **CSF Aß42, CSF tau, amyloid PET, tau PET, diffusion MRI, etc.**



Clinical pattern recognition

Use case: Alzheimer's disease (AD)

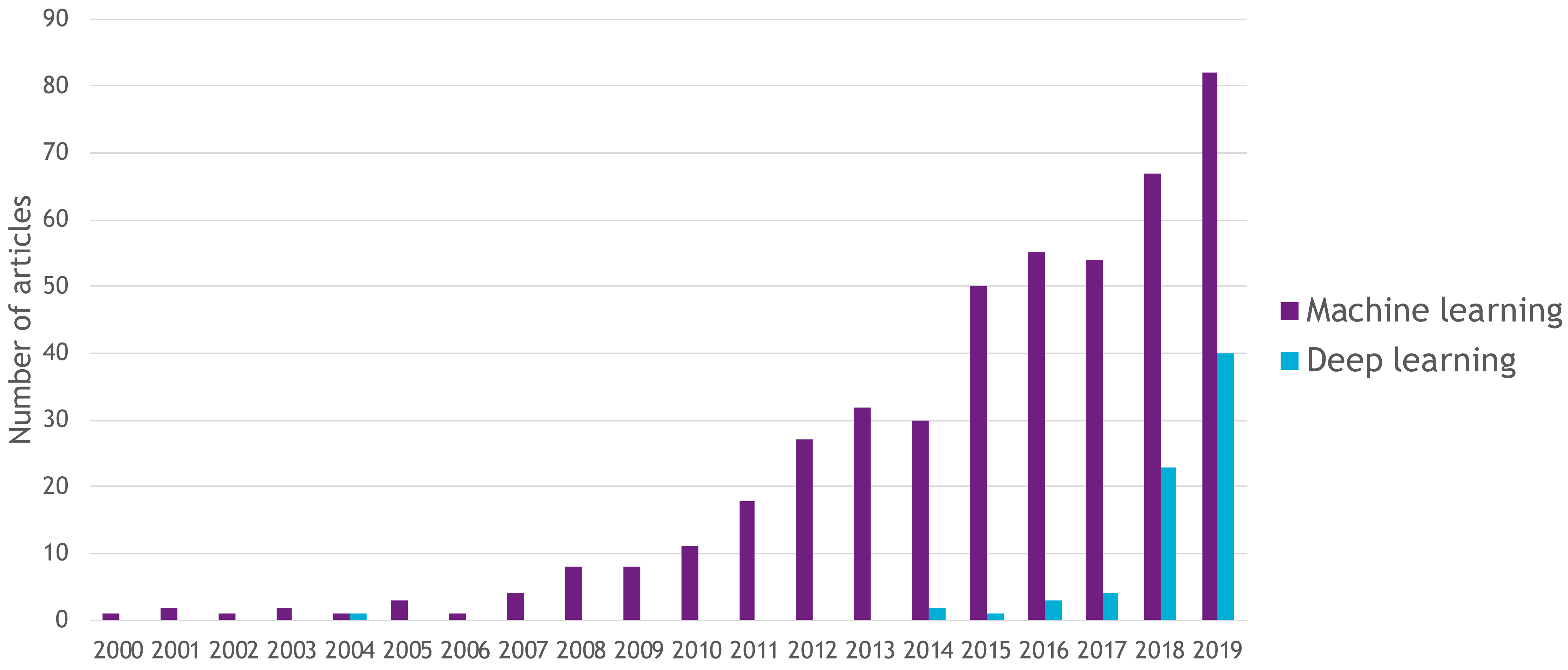
- **Classification**
  - Controls vs AD patients
  - Stable vs progressive mild cognitive impairment (MCI)
- **Regression**
  - Time of onset
  - Future clinical score



Klöppel et al., NeuroImage, 2008; Davatzikos et al, Neurobiology of Aging, 2008; Zhang et al, NeuroImage, 2011; Cuingnet et al, NeuroImage, 2011

ML/DL for Alzheimer's diagnosis & prognosis

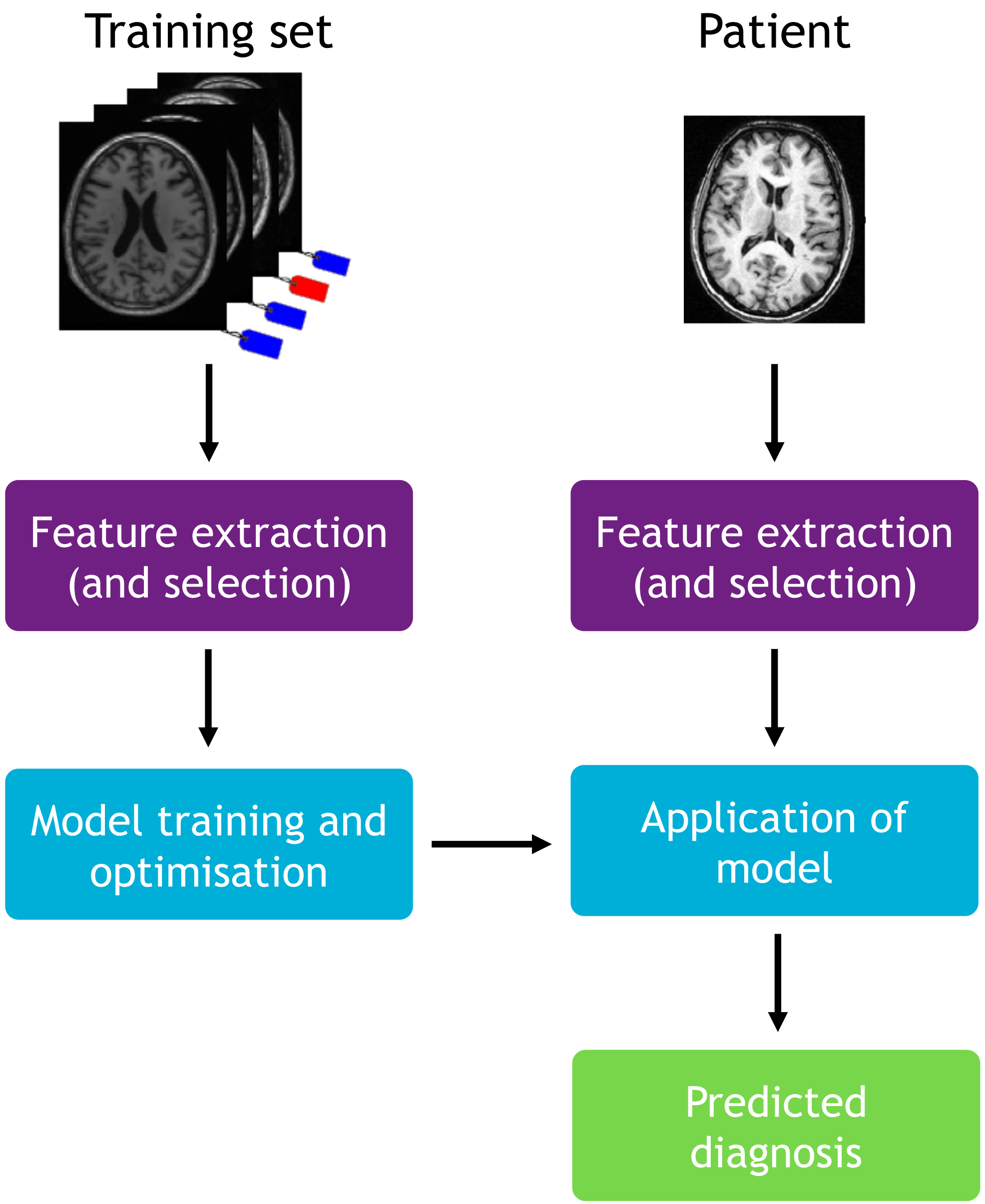
A very active field of research



ML/DL for Alzheimer's diagnosis & prognosis

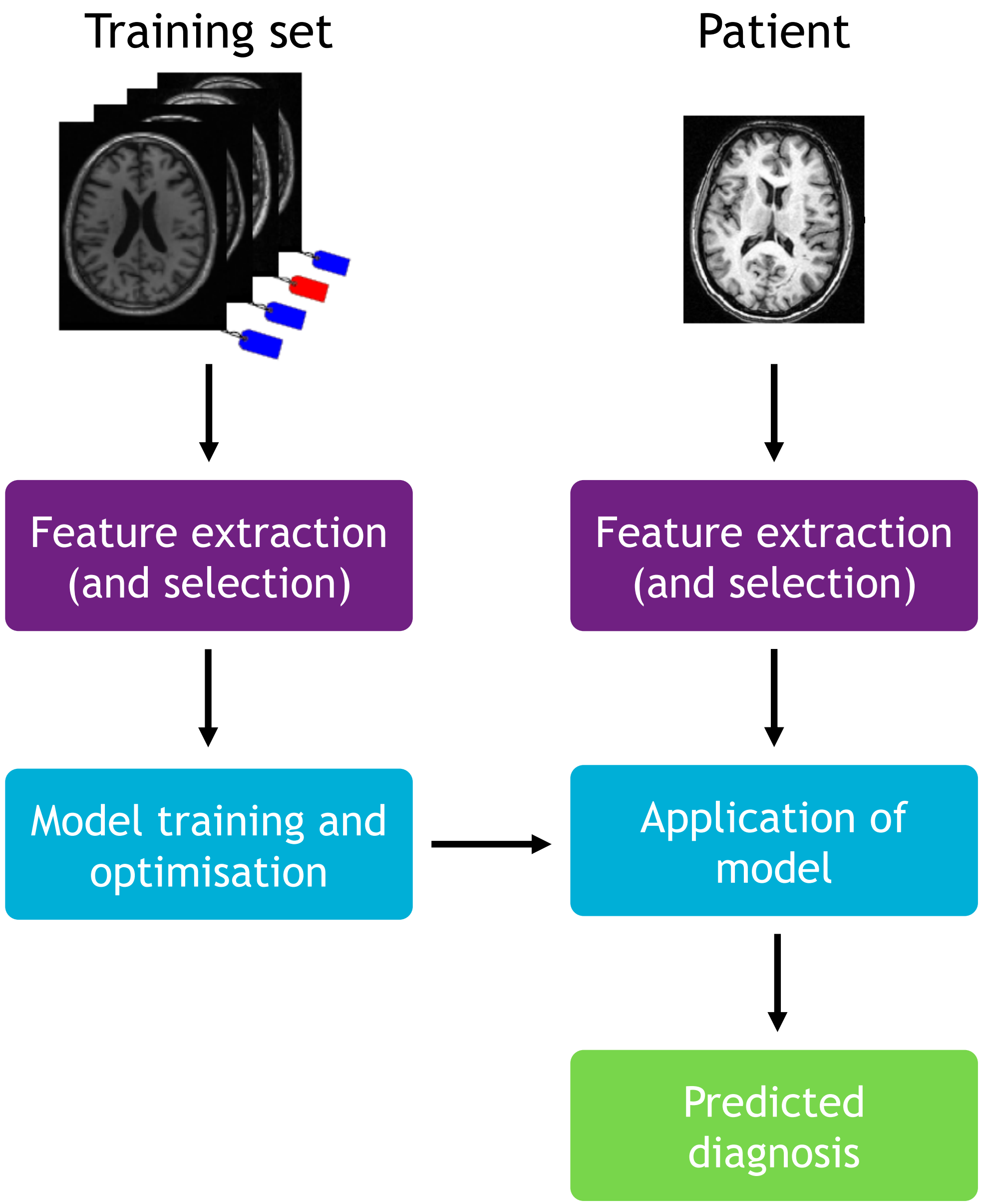
Elements that might differ between AD classification studies

- Training and test sets
- Imaging modality/ies
- Image preprocessing pipelines
- Features extracted
- Classification algorithms
- Cross-validation procedures
- Reported evaluation metrics



Clinical pattern recognition

- Where to find data?
- How to organise data?
- How to preprocess and extract features from images?
- Which classifiers can be selected?
- Which cross-validation strategy can be implemented?
- Which tasks may be of interest?
- What is the influence of these choices on the classification performance?



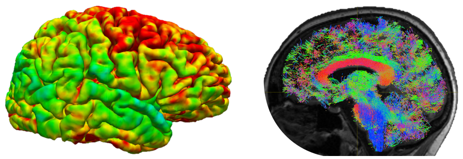
Software platform for clinical neuroimaging studies

Modalities

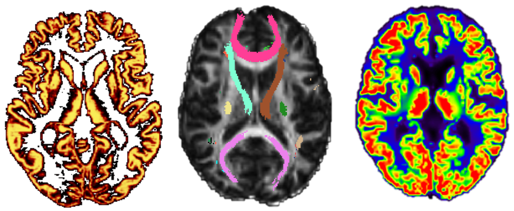
- Anatomical MRI
- Diffusion MRI
- PET

→

Preprocessing and Feature extraction



FreeSurfer, FSL, SPM,
MRtrix3, PETPVC, ANTS



→

Morphometric and statistical models

Machine learning / Deep learning

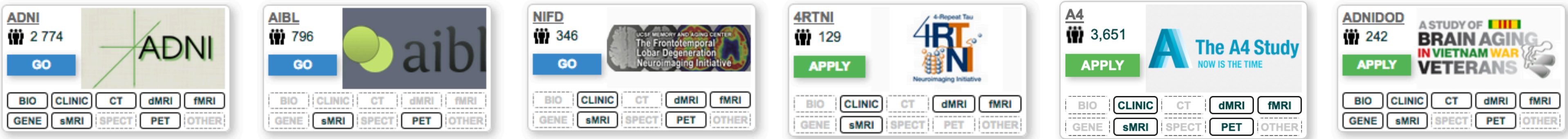
scikit learn
PyTorch

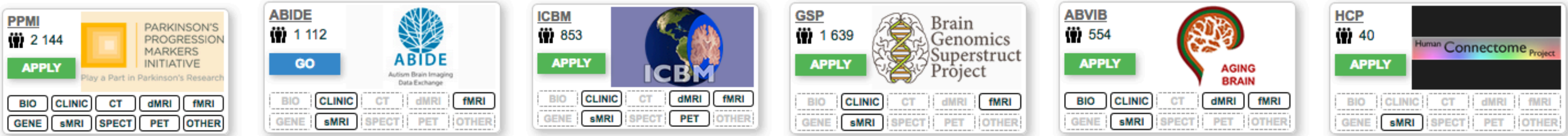
Standardized data structures: BIDS & CAPS

Finding data

Public datasets

- **Dementia**
  - Image and Data Archive (https://ida.loni.usc.edu)



  - Open Access Series of Imaging Studies (www.oasis-brains.org)
- **Other conditions**
  - 

  - BraTS (http://braintumorsegmentation.org)
  - IXI (https://brain-development.org/ixi-dataset)
  - etc.

Data organisation and curation


```
094_S_4089
...
|— Accelerated_SAG_IR-SPGR
|— AV45_Coreg,_Avg,_Standardized_Image_and_Voxel_Size
...
|— Average_DC
|— Axial_DTI
|— Axial_FLAIR
|— Axial_T2_Star
|— Calibration_Scan
|— Coreg,_Avg,_Standardized_Image_and_Voxel_Size
...
|— Eddy_current_corrected_image
|— EPI_current_corrected_image
|— Fractional_Ansio.
|— HarP_135_final_release_2015
|— HHP_6_DOF_AC-PC_registered_MPRAGE
|— MT1__GradWarp__N3m
|— Sag_IR-SPGR
|   |— 2011-06-29_14_37_16.0
|   |— 2011-10-18_12_15_56.0
|   |   └— S125692
|   |       |— ADNI_094_S_4089_MR_Sag_IR-SPGR__br_raw_20111019095510271_80_S125692_I261478.dcm
|   |       |— ADNI_094_S_4089_MR_Sag_IR-SPGR__br_raw_20111019095512256_62_S125692_I261478.dcm
|   |       |— ...
|   |— 2011-12-14_15_53_24.0
|   |— 2012-08-15_14_00_36.0
|   └— 2013-09-25_14_14_23.0
|— Sag_IR-SPGR_REPEAT
|— Spatially_Normalized,_Masked_and_N3_corrected_T1_image
└— T2-weighted_trace
```

```
sub-ADNI094S4089
|— ses-M00
|   |— anat
|   |   └— sub-ADNI094S4089_ses-M00_T1w.nii.gz
|   └— dwi
|       |— sub-ADNI094S4089_ses-M00_acq-axial_dwi.bval
|       |— sub-ADNI094S4089_ses-M00_acq-axial_dwi.bvec
|       └— sub-ADNI094S4089_ses-M00_acq-axial_dwi.nii.gz
|   |— pet
|   |   |— sub-ADNI094S4089_ses-M00_task-rest_acq-av45_pet.nii.gz
|   |   └— sub-ADNI094S4089_ses-M00_task-rest_acq-fdg_pet.nii.gz
|   └— sub-ADNI094S4089_ses-M00_scans.tsv
|— ses-M03
|— ses-M12
└— ses-M24
```

BIDS
BRAIN IMAGING DATA STRUCTURE

http://bids.neuroimaging.io
Gorgolewski et al., Nature Scientific Data, 2016

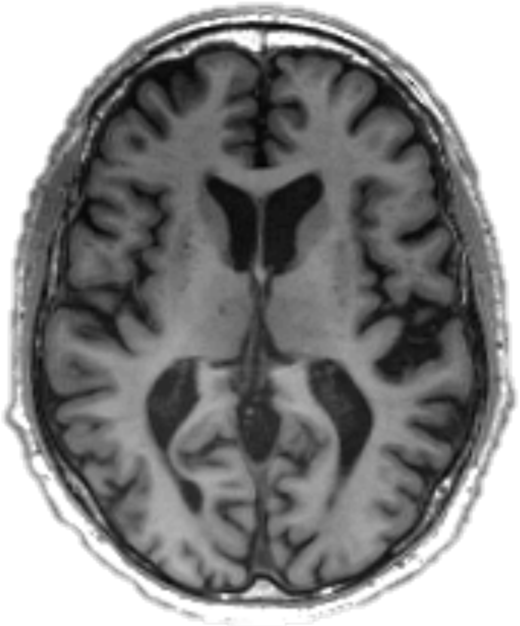
Data organisation and curation with Clinica

Converters available for:

- ADNI (Alzheimer's Disease Neuroimaging initiative)
- AIBL (Australian Imaging Biomarker & Lifestyle Flagship Study of Ageing)
- OASIS (Alzheimer's Disease and age-related dementia)
- NIFD (Neuroimaging in Frontotemporal Dementia)
- + internal studies to which we collaborate

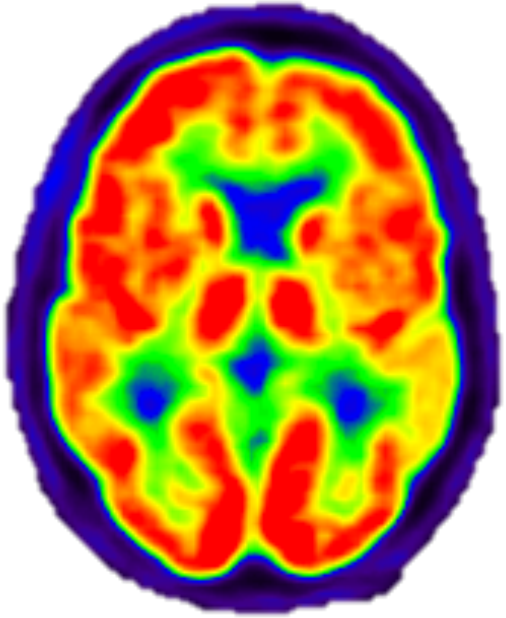
Imaging modalities

Example from the ADNI dataset:



Anatomical MRI
Atrophy

Diffusion MRI
White matter alterations



FDG PET
Hypometabolism

Amyloid PET
Protein aggregates

Image preprocessing

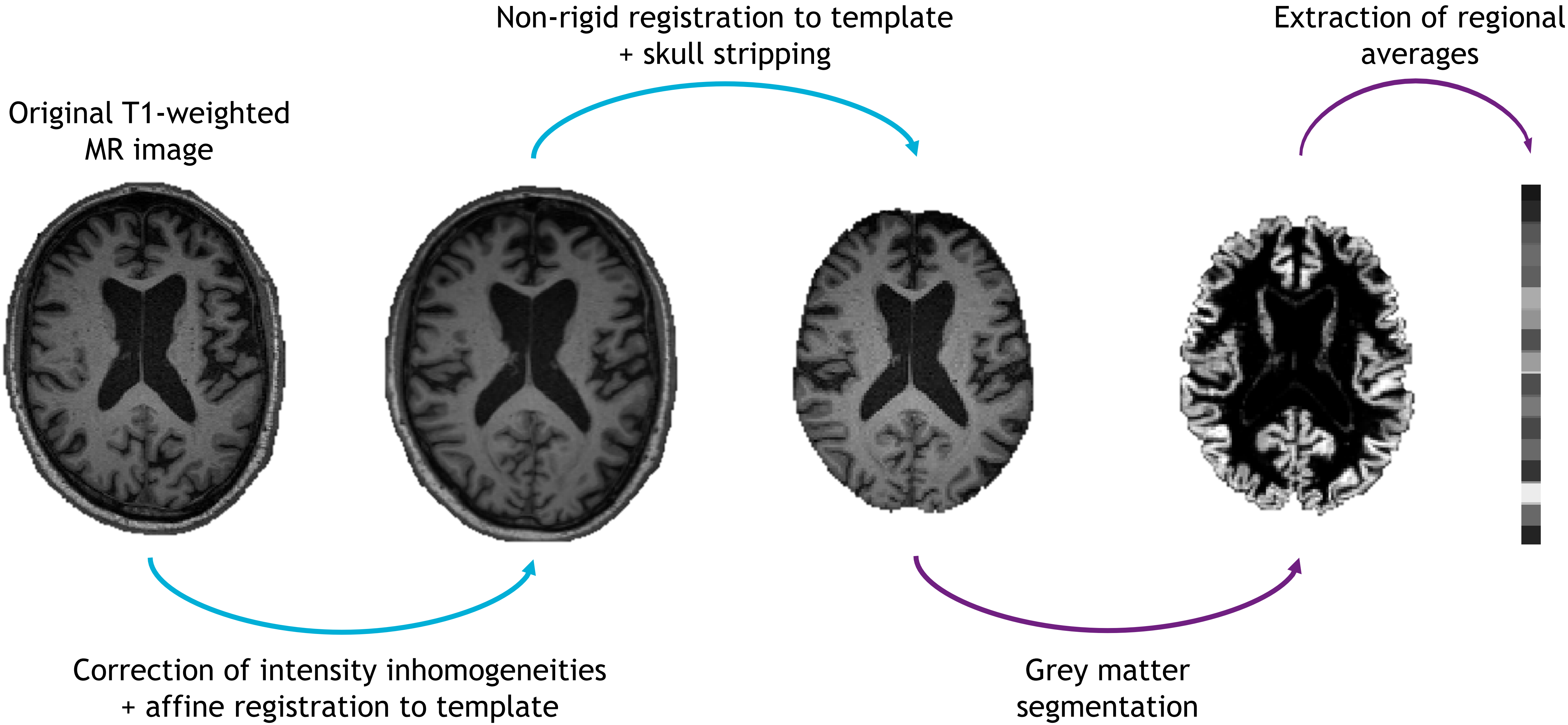


Image preprocessing

Statistical Parametric Mapping (SPM)

- www.fil.ion.ucl.ac.uk/spm
- **Modalities:** Structural and functional MRI, PET, SPECT, EEG, MEG
- **Features:** preprocessing, modelling, statistical inference, voxel-based morphometry, connectivity analysis

Frackowiak, Friston, Frith, Dolan, and Mazziotta, editors. Human Brain Function. Academic Press USA, 1997

FreeSurfer

- https://surfer.nmr.mgh.harvard.edu
- **Modalities:** Structural, functional, diffusion MRI
- **Features:** skullstripping, registration, cortical surface reconstruction, segmentation, longitudinal processing, fMRI analysis, tractography

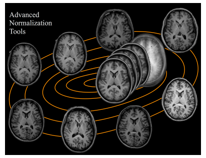
Fischl, NeuroImage, 2012

FMRIB Software Library (FSL)

- https://fsl.fmrib.ox.ac.uk
- **Modalities:** Structural, functional, diffusion MRI
- **Features:** brain extraction, segmentation, registration, tractography, longitudinal analysis, statistical analysis

Jenkinson et al., NeuroImage, 2012

Advanced Normalization Tools (ANTs)



- http://stnava.github.io/ANTs
- **Modalities:** Structural, functional, diffusion MRI, PET
- **Features:** bias field correction, registration, segmentation, cortical thickness estimation

Avants et al., Frontiers in Neuroinformatics, 2014

Clinica image (pre)processing pipelines

Anatomical MRI (T1-weighted)

- **t1-linear** Bias field correction and affine registration to standard space using ANTs
- **t1-volume** Tissue segmentation, spatial normalization and parcellation using SPM
- **t1-freesurfer** Cortical surface extraction, spatial normalization and parcellation using FreeSurfer

Diffusion MRI (DWI)

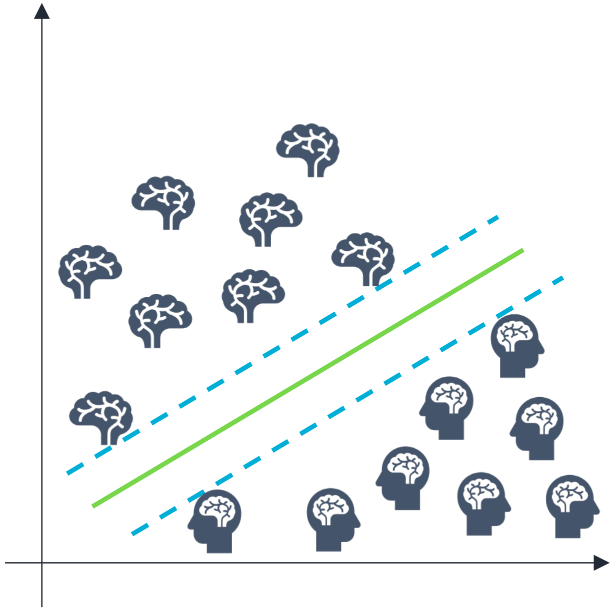
- **dwi-preprocessing-*** Correction of head motion, magnetic susceptibility, eddy current and bias field induced distortions
- **dwi-dti** Extraction of DTI-based measures and spatial normalization
- **dwi-connectome** Computation of fiber orientation distributions, tractogram and connectome

Positron emission tomography (PET)

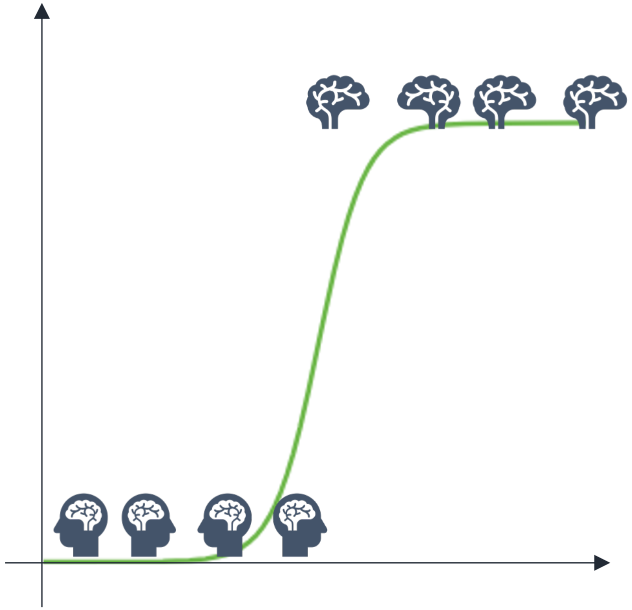
- **pet-volume** Registration to T1w MRI, intensity normalization, partial volume correction and spatial normalization
- **pet-surface** Registration to T1w MRI, intensity normalization, partial volume correction, projection of the PET signal onto the subject’s cortical surface and spatial normalization

Classifiers

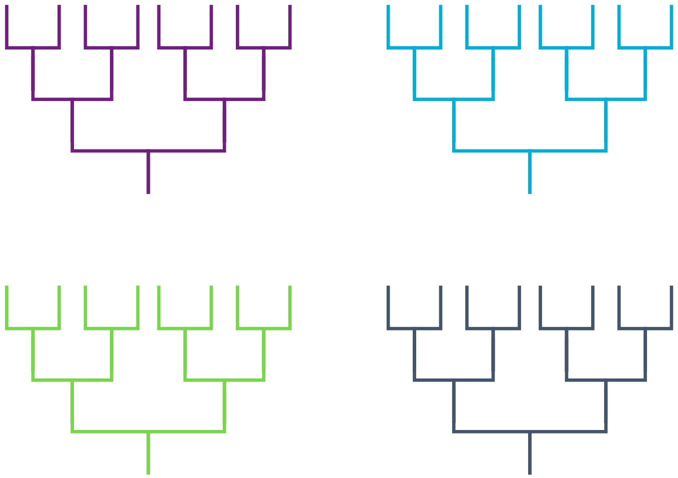
Linear SVM



$\ell 2$ logistic regression



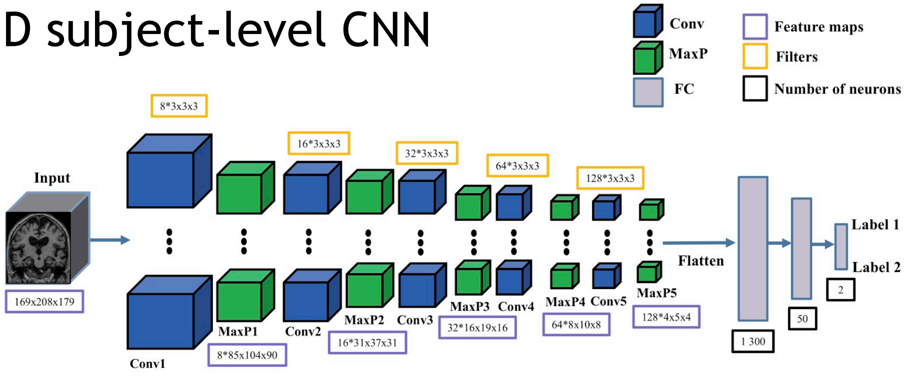
Random forest



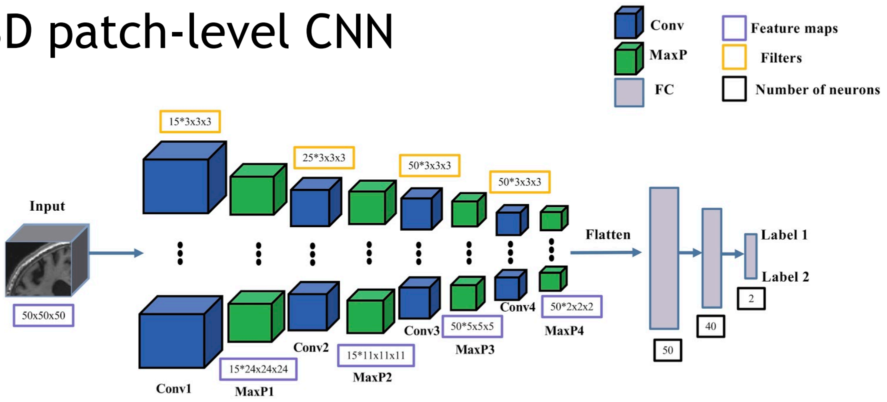
Pedregosa et al., JMLR, 2011; Samper-González et al., NeuroImage, 2018

Convolutional neural networks

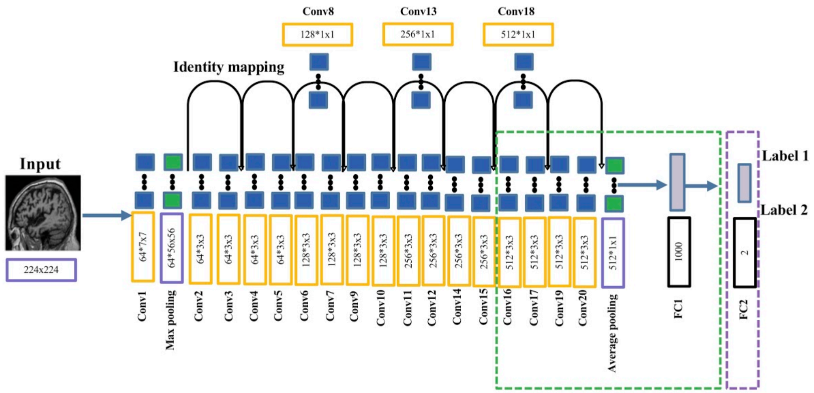
3D subject-level CNN



3D patch-level CNN



2D slice-level CNN

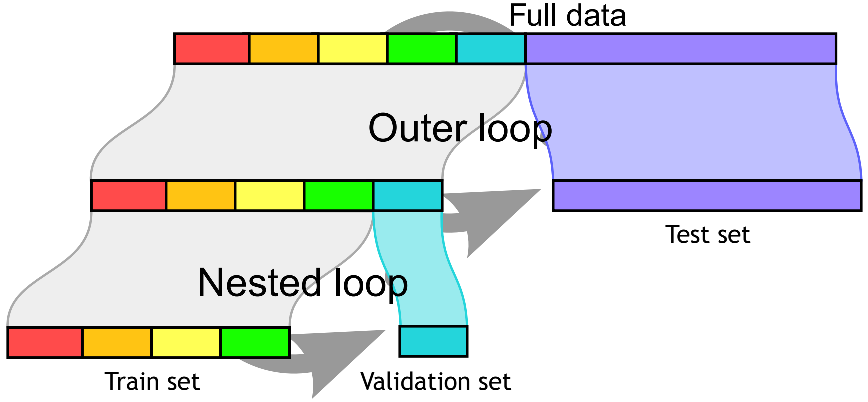


Wen, Thibeau-Sutre et al., Medical Image Analysis, 2020

Cross-validation procedures

Nested cross-validation

- Outer loop
- Nested loop



Adapted from Varoquaux et al., NeuroImage, 2017

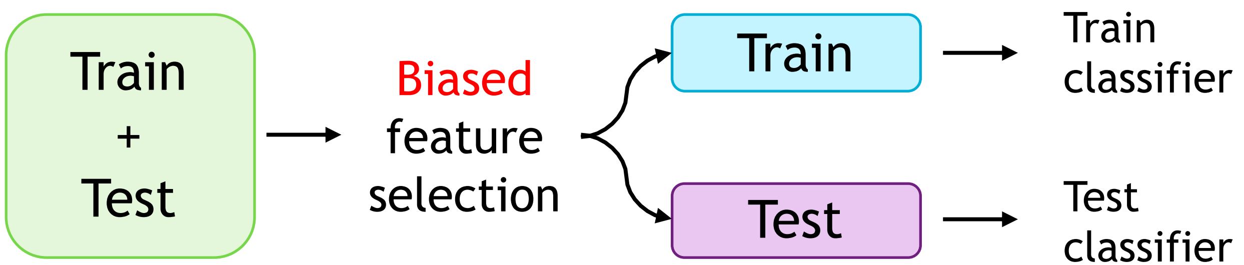
(Repeated) k-fold

Repeated hold-out

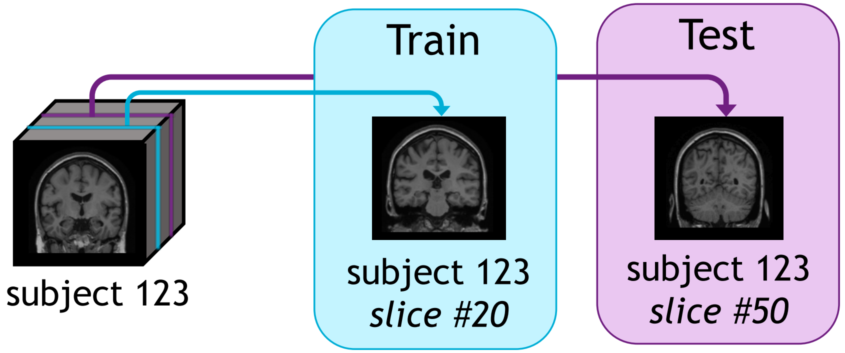
Samper-González et al., NeuroImage, 2018

Main causes of data leakage in DL scenarios

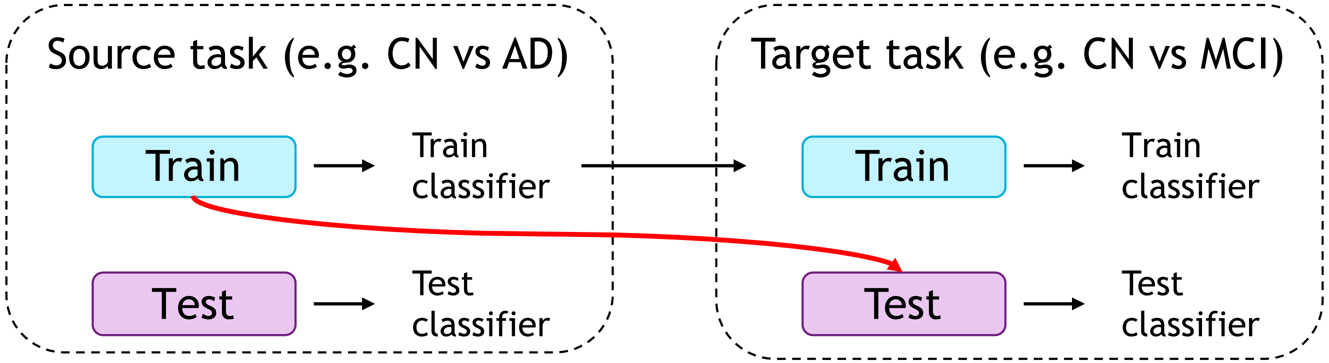
- Late split



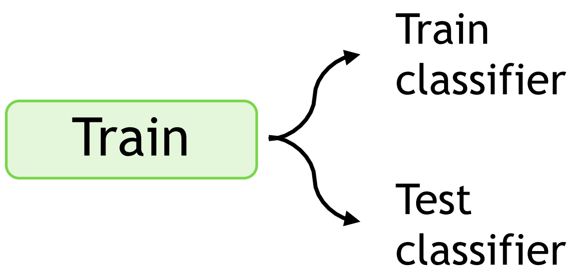
- Biased within-subject split



- Biased transfer learning



- No independent test set



Wen, Thibeau-Sutre et al., Medical Image Analysis, 2020

Task selection

ADNI dataset

	N	Age	Gender	MMSE	CDR
CN	282	74. 3 ± 5.9 [56.2, 89.0]	147 M / 135 F	29.0 ± 1.2 [24, 30]	0: 281; 0.5: 1
MCI	640	72.7 ± 7.5 [55.0, 91.4]	378 M / 262 F	27.8 ± 1.8 [23, 30]	0: 1; 0.5: 638; 1:1
AD	237	74.9 ± 7.8 [55.1, 90.3]	137 M / 100 F	23.2 ± 2.1 [18, 27]	0.5: 99; 1: 137; 2: 1
AD	237	74.9 ± 7.8 [55.1, 90.3]	137 M / 100 F	23.2 ± 2.1 [18, 27]	0.5: 99; 1: 137; 2: 1

Values are presented as mean ± SD [range].
M: male, F: female, MMSE: mini-mental state examination, CDR: global clinical dementia rating

- **Tasks selected:**
  - CN vs AD clinical diagnosis classification tasks
  - sMCI vs pMCI “predictive” task of the evolution

Samper-González et al., NeuroImage, 2018

Machine learning for AD classification

Inputs

Feature types:
- Voxels
- Regions

↓

Classifier

- Linear SVM
- L2 Logistic regression
- Random forest

↓

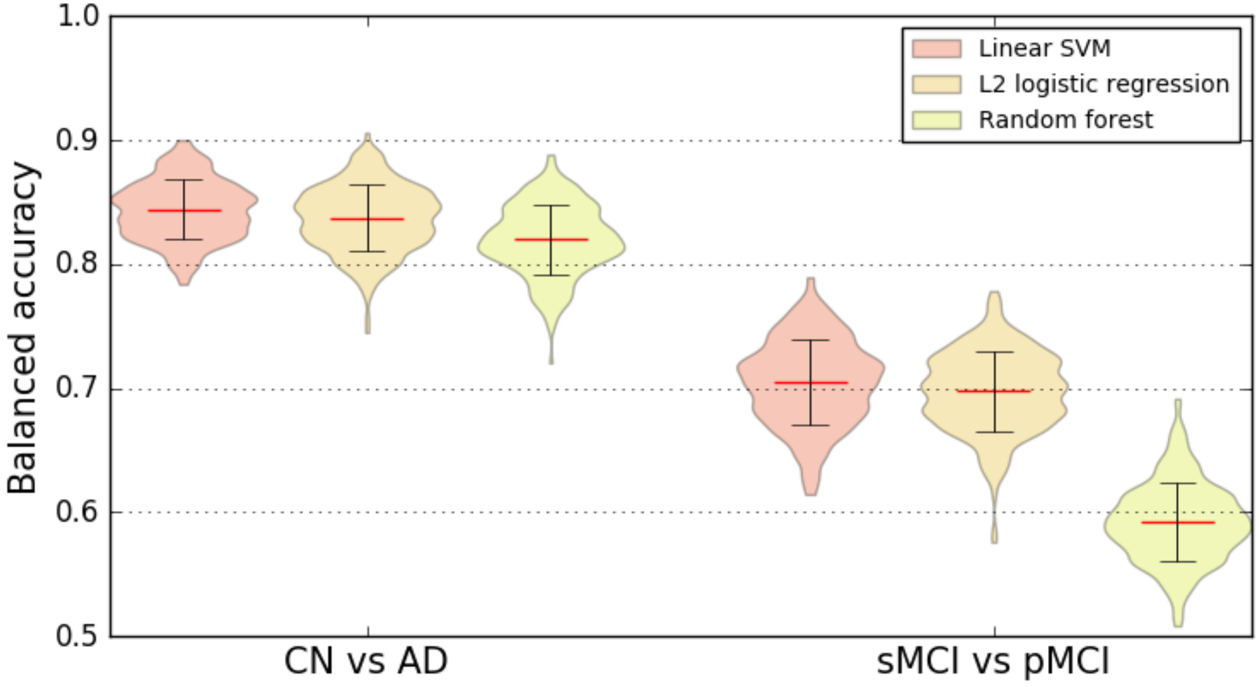
CV

- K-fold
- Repeated k-fold
- Repeated hold-out

Samper-González et al., NeuroImage, 2018;
https://gitlab.icm-institute.org/aramislab/AD-ML

Machine learning for AD classification

Influence of the classifier



- Linear SVM and logistic regression with L2 regularization: similar balanced accuracies
- Random forest: consistently lower balanced accuracy

Machine learning for AD classification

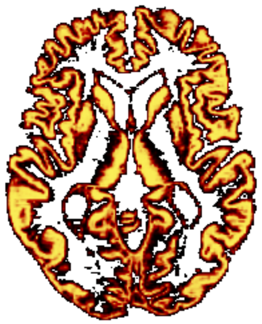
Influence of the type of features

	Linear SVM	
	Voxel-based	Region-based
CN vs AD	87% ± 2.6%	84% ± 2.4%
sMCI vs pMCI	66% ± 4.0%	70% ± 3.4%

Balanced accuracy — Values are presented as mean ± SD.

➢ No systematic effect

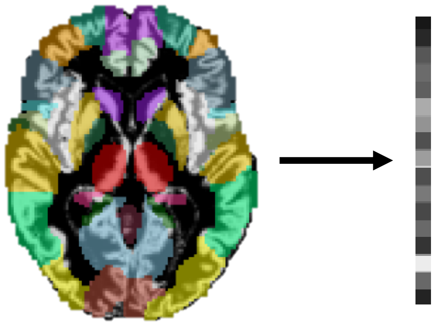
- Voxel-based features



$x \in \mathbb{R}^p$

where p is the number of voxels

- Region-based features



$x \in \mathbb{R}^p$

where p is the number of regions

Machine learning for AD classification

Generalisation across datasets

- Task: CN vs AD
- Subsets of equal size for each dataset (CN: 70, AD: 70)

Testing dataset	Training dataset	Voxel-based	Region-based
ADNI	ADNI	85% ± 4.8%	81% ± 6.0%
AIBL	AIBL	86% ± 4.8%	85% ± 5.8%
	ADNI	86%	87%
OASIS	OASIS	67% ± 6.3%	64% ± 7.2%
	ADNI	67%	70%

Balanced accuracy — Values are presented as mean ± SD.

➢ The classifiers trained on ADNI data generalise well

Deep learning for AD classification

Inputs

Preprocessing types:
- Minimal
- Extensive

↓

Classifier

- 3D subject-level CNN
- 3D patch-level CNN
- 2D slice-level CNN

↓

CV

- K-fold

Wen, Thibeau-Sutre et al., Medical Image Analysis, 2020;
https://gitlab.icm-institute.org/aramislab/AD-DL; https://zenodo.org/record/3491003

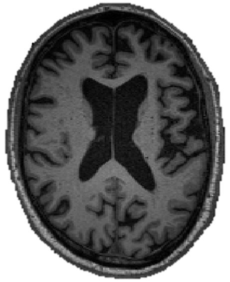
Deep learning for AD classification

Influence of the type of preprocessing

	3D subject-level CNN	
	Minimal	**Extensive**
CN vs AD	85% ± 4%	86% ± 6%

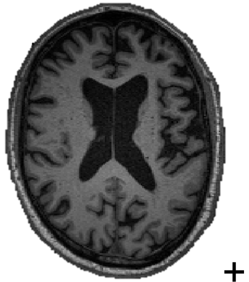
Balanced accuracy on the validation set
Values are presented as mean ± SD.

- Minimal preprocessing



Bias field correction
+ affine registration

- Extensive preprocessing



Bias field correction
+ non-rigid registration
+ skull stripping

➢ No systematic effect

Deep learning for AD classification

Influence of the type of network architecture

	3D subject-level	3D patch-level	3D patch-level (hippocampi only)	2D slice-level
CN vs AD	85%	86%	85%	74%
sMCI vs pMCI	73%	70%	74%	-

Balanced accuracy on the test set — Values are presented as mean ± SD.

- 3D subject-level and 3D patch-level approaches: similar balanced accuracies
- 2D-slice approach: consistently lower balanced accuracy

Deep learning for AD classification

Generalisation across datasets

- Training: ADNI

	3D subject-level		
	ADNI	**AIBL**	**OASIS**
CN vs AD	85%	86%	68%
sMCI vs pMCI	73%	50%	-

Balanced accuracy on the test set –
Values are presented as mean ± SD.

➢ **The models trained on ADNI data do not always generalise well**

Deep/machine learning for AD classification

Comparison deep learning / machine learning

- Training: ADNI

	3D subject-level			Linear SVM		
	ADNI	AIBL	OASIS	ADNI	AIBL	OASIS
CN vs AD	85%	86%	68%	87%	87%	71%
sMCI vs pMCI	73%	50%	-	76%	68%	-

Balanced accuracy on the test set — Values are presented as mean ± SD.

➢ Machine learning at least as good as deep learning

Reproducible evaluation of AD classification

Evaluation of machine learning and deep learning approaches in Alzheimer's disease

- **More reproducible**
  - Data sharing
  - Storing of data using community standards
  - Fully automatic data manipulation
  - Code sharing
- **More objective**
  - Baseline approaches against which new methods can easily be compared
  - Rigorous validation
    - Large number of repeated random split to extensively assess the performance variability
    - Reporting of full distribution of metrics
    - Adequate nested CV for hyperparameter tuning

Varoquaux et al., NeuroImage, 2017;
Samper-González et al., NeuroImage, 2018; Wen, Thibeau-Sutre et al., Medical Image Analysis, 2020

Reproducible evaluation of AD classification with Clinica

- Clinica
  - www.clinica.run
  - Preprint: https://hal.inria.fr/hal-02308126
- Reproducible evaluation of AD classification
  - Machine learning
    - https://github.com/aramis-lab/AD-ML
    - Samper-González et al., NeuroImage, 2018
    - Wen et al., Neuroinformatics, 2020
  - Deep learning
    - https://gitlab.icm-institute.org/aramislab/AD-DL
    - https://zenodo.org/record/3491003
    - Wen, Thibeau-Sutre et al., Medical Image Analysis, 2020

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Thank you!

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Jorge Samper-Gonzalez
Elina Thibeau--Sutre
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Software platform for clinical neuroimaging studies

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