Dealing with confounders in ML analyses of multicentric datasets: a case study from MRI

CompMat2022

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Autism Spectrum Disorders (ASD)

[DSM-5, American Psychiatric Association. Diagnostic and statistical manual of mental disorders (5th ed.). Washington, DC. (2013)]

- Autism spectrum disorders (ASD) are a heterogeneous category of neurodevelopmental conditions characterized by a different level of symptom severity in two core domains
  - impairments in social communication and interaction
  - restricted repetitive behaviors

- ASD prevalence:
  - median prevalence of **1 out of 161** individuals worldwide data
    [Elsabbagh, M. et al. Global prevalence of autism and other pervasive developmental disorders. Autism Res. 5, 160–179 (2012)]
  - approximately **1 out of 54** children in the **U.S.**, according to 2016 data
    [Centers for Disease Control and Prevention (CDC), 2020]
  - about **1 out of 87** children aged 7–9 years in Italy
    [Narzisi A. et al. Prevalence of Autism Spectrum Disorder in a large Italian catchment area: A school-based population study within the ASDEU project. Epidemiol. Psychiatr. Sci. 2018, 29.]

The search for biomarkers for ASD

- ASD diagnosis is almost entirely based on behavioral observation
- To identify a neuroimaging-based **biomarker** for ASD may be useful for:

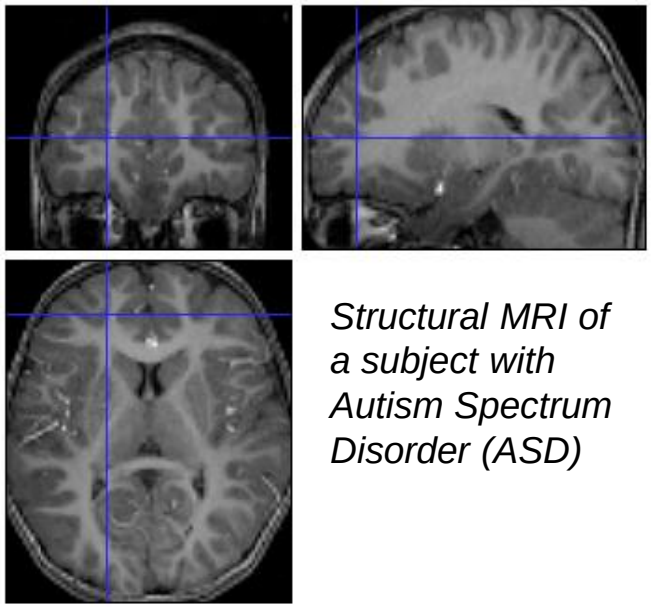
Early diagnosis → Early treatments

Subjects' stratification → Personalized treatments

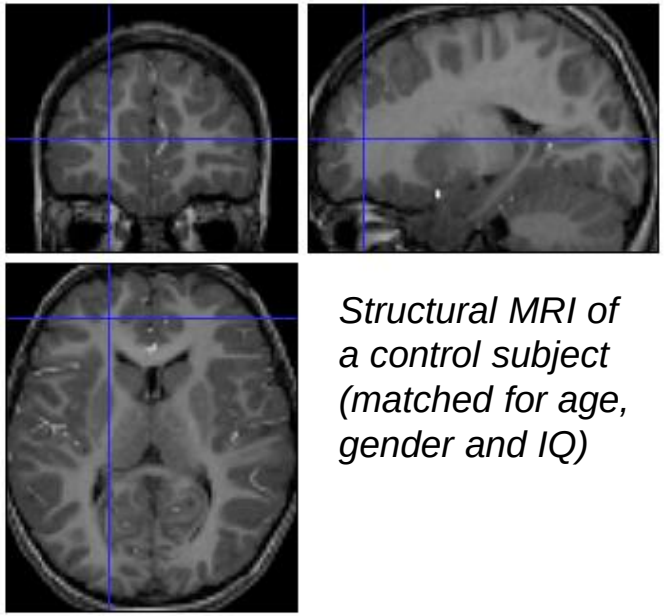
Better outcome for individuals with ASD

- A unique ASD biomarker is not supported by current data

ASD + neuroimaging (MRI)



Structural MRI of a subject with Autism Spectrum Disorder (ASD)



Structural MRI of a control subject (matched for age, gender and IQ)

No appreciable difference between the two images can be identified
Can *machine-learning* analysis of MRI data help in ASD characterization?

ML studies on MRI for ASD: why?

- The main aim is not the ASD/CTR discrimination
  - ASD diagnosis doesn't require MRI
  - At present, there is no interest in CAD systems in ASD

- Understanding the pathology
  - Investigation of possible role of structural/functional features in ASD
    - Areas of reduced/enlarged volume or thickness
    - Modifications in brain connectivity
- Definition of a biomarker
  - The identification of a biomarker may help to broaden the diagnosis to non-cooperative subjects

One of our studies on this topic

Ricerca in collaborazione con

IRCCS FONDAZIONE STELLA MARIS

INFN

Gray Matter Alterations in Young Children with Autism Spectrum Disorders: Comparing Morphometry at the Voxel and Regional Level

J Neuroimaging. 2015 Nov-Dec;25(6):866-74

Ilaria Gori*, Alessia Giuliano*, Filippo Muratori, Irene Saviozzi, Piernicola Oliva, Raffaella Tancredi, Angela Cosenza, Michela Tosetti, Sara Calderoni, Alessandra Retico

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ABSTRACT

BACKGROUND AND PURPOSE: Sophisticated algorithms to infer disease diagnosis, pathology progression and patient outcome are increasingly being developed to analyze brain MRI data. They have been successfully implemented in a variety of diseases and are currently investigated in the field of neuropsychiatric disorders, including autism spectrum disorder (ASD). We aim to test the ability to predict ASD from subtle morphological changes in structural magnetic resonance imaging (sMRI).

METHODS: The analysis of sMRI of a cohort of male ASD children and controls matched for age and nonverbal intelligence quotient (NVIQ) has been carried out with two widely used preprocessing software packages (SPM and Freesurfer) to extract brain morphometric information at different spatial scales. Then, support vector machines have been implemented to classify the brain features and to localize which brain regions contribute most to the ASD-control separation.

RESULTS: The features extracted from the gray matter subregions provide the best classification performance, reaching an area under the receiver operating characteristic curve (AUC) of 74%. This value is enhanced to 80% when considering only subjects with NVIQ over 70.

CONCLUSIONS: Despite the subtle impact of ASD on brain morphology and a limited cohort size, results from sMRI-based classifiers suggest a consistent network of altered brain regions.

Keywords: Autism spectrum disorders, magnetic resonance imaging, machine learning, support vector machines, feature extraction, classification.

41 subjects: 21 male ASD children + 20 matched controls.
Results: regional features are more informative than global and voxel wise measures, yielding to an

AUC = 74%

(AUC = 80% for NVIQ >70)

Moving toward big data

The **ABIDE** initiative

NITRC Neuroimaging Tools & Resources Collaboratory

http://fcon_1000.projects.nitrc.org/indi/abide

Autism Brain Imaging Data Exchange (ABIDE)

Two data collections have been released: ABIDE-I and ABIDE-II

rs-fMRI, structural MRI, and phenotypic information are stored and shared publicly

2226 subjects			
1060 ASDs		1166 TDCs	
907 M	153 F	879 M	287 F
Age at Scan 5 – 64 years			
40 different acquisition sites			

Announcing Manuscripts

Di Martino, A. et al., **The autism brain imaging data exchange: towards a large-scale evaluation of the intrinsic brain architecture in autism.**
Mol Psychiatry. 2014 Jun;19(6):659-67.

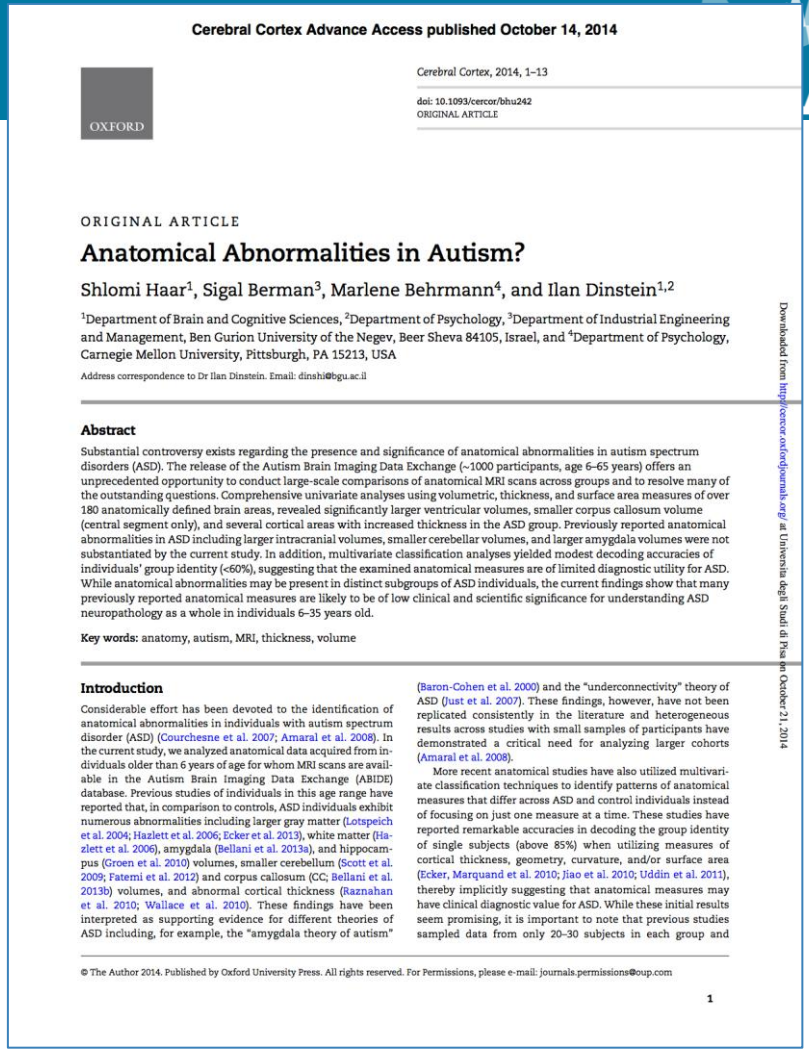
Di Martino, A. et al., **Enhancing studies of the connectome in autism using the autism brain imaging data exchange II.**
Sci Data. 2017 March 14; 4:170010.

ML analysis of ABIDE structural MRI

- 590 participants from ABIDE-I:
  males 6–35 years old

- Univariate analyses of volume, thickness and surface area of over 180 anatomically brain areas led to disappointing results:
  - Previously reported anatomical abnormalities in ASD including larger intracranial volumes, smaller cerebellar volumes, and larger amygdala volumes were NOT SUBSTANTIATED by the current study

- **Multivariate classification analyses led to ASD vs. control discrimination accuracy ≤ 60 %**



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OXFORD

Cerebral Cortex, 2014, 1–13

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ORIGINAL ARTICLE

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Anatomical Abnormalities in Autism?

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Abstract

Substantial controversy exists regarding the presence and significance of anatomical abnormalities in autism spectrum disorders (ASD). The release of the Autism Brain Imaging Data Exchange (~1000 participants, age 6–65 years) offers an unprecedented opportunity to conduct large-scale comparisons of anatomical MRI scans across groups and to resolve many of the outstanding questions. Comprehensive univariate analyses using volumetric, thickness, and surface area measures of over 180 anatomically defined brain areas, revealed significantly larger ventricular volumes, smaller corpus callosum volume (central segment only), and several cortical areas with increased thickness in the ASD group. Previously reported anatomical abnormalities in ASD including larger intracranial volumes, smaller cerebellar volumes, and larger amygdala volumes were not substantiated by the current study. In addition, multivariate classification analyses yielded modest decoding accuracies of individuals' group identity (<60%), suggesting that the examined anatomical measures are of limited diagnostic utility for ASD. While anatomical abnormalities may be present in distinct subgroups of ASD individuals, the current findings show that many previously reported anatomical measures are likely to be of low clinical and scientific significance for understanding ASD neuropathology as a whole in individuals 6–35 years old.

Key words: anatomy, autism, MRI, thickness, volume

Introduction

Considerable effort has been devoted to the identification of anatomical abnormalities in individuals with autism spectrum disorder (ASD) (Courchesne et al. 2007; Amaral et al. 2008). In the current study, we analyzed anatomical data acquired from individuals older than 6 years of age for whom MRI scans are available in the Autism Brain Imaging Data Exchange (ABIDE) database. Previous studies of individuals in this age range have reported that, in comparison to controls, ASD individuals exhibit numerous abnormalities including larger gray matter (Lotspeich et al. 2004; Hazlett et al. 2006; Ecker et al. 2013), white matter (Hazlett et al. 2006), amygdala (Bellani et al. 2013a), and hippocampus (Groen et al. 2010) volumes, smaller cerebellum (Scott et al. 2009; Fatemi et al. 2012) and corpus callosum (CC; Bellani et al. 2013b) volumes, and abnormal cortical thickness (Raznahan et al. 2010; Wallace et al. 2010). These findings have been interpreted as supporting evidence for different theories of ASD including, for example, the "amygdala theory of autism" (Baron-Cohen et al. 2000) and the "underconnectivity" theory of ASD (Just et al. 2007). These findings, however, have not been replicated consistently in the literature and heterogeneous results across studies with small samples of participants have demonstrated a critical need for analyzing larger cohorts (Amaral et al. 2008).

More recent anatomical studies have also utilized multivariate classification techniques to identify patterns of anatomical measures that differ across ASD and control individuals instead of focusing on just one measure at a time. These studies have reported remarkable accuracies in decoding the group identity of single subjects (above 85%) when utilizing measures of cortical thickness, geometry, curvature, and/or surface area (Ecker, Marquand et al. 2010; Jiao et al. 2010; Uddin et al. 2011), thereby implicitly suggesting that anatomical measures may have clinical diagnostic value for ASD. While these initial results seem promising, it is important to note that previous studies sampled data from only 20–30 subjects in each group and

How to interpret these results?

- Small sample studies tend to overestimate case-control discrimination

- ML studies on small samples can suffer from ***overfitting***
  - many free parameters in the model and a few examples for training
  - The model adapts completely to training data
  - performance on test set is significantly worse: the model does not generalize
- On the other hand, studies on large multicentric samples can be affected by :
  - Data quality issues
  - Confounder effects in the analysis, related to the site of origin of the data

Problems of multicentric data sets

The data collected from different sites/acquisition systems contain local "fingerprints", which can hide information of interest.

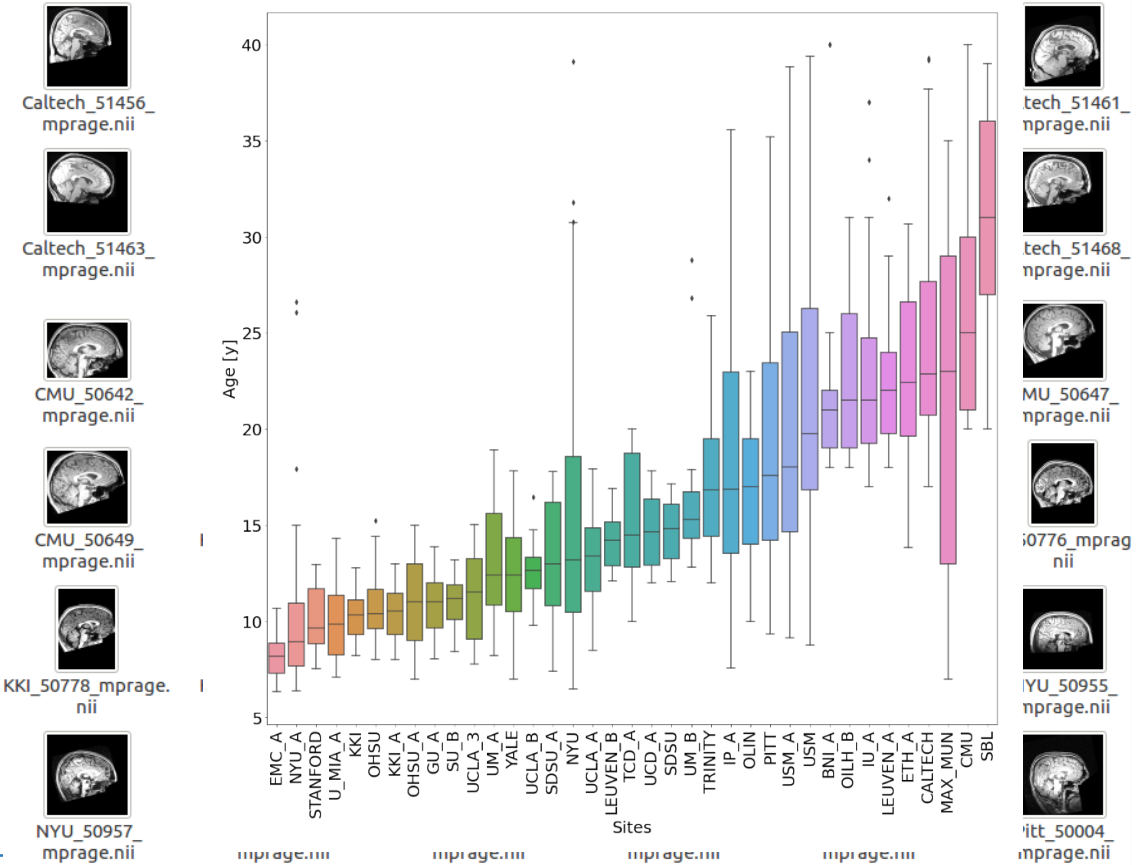
This problem is similar to the handling of **systematic errors** in Physics experiments.

Autism Brain Imaging Data Exchange

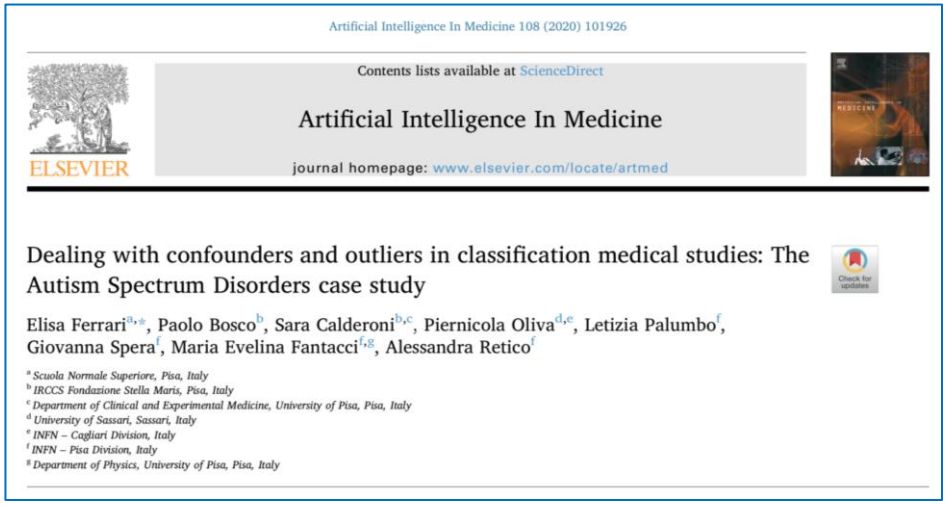
ABIDE

NITRC NeuroImaging Tools & Resources Collaboratory

http://fcon_1000.projects.nitrc.org/indi/abide



A possible approach to confounders and outliers



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Dealing with confounders and outliers in classification medical studies: The Autism Spectrum Disorders case study

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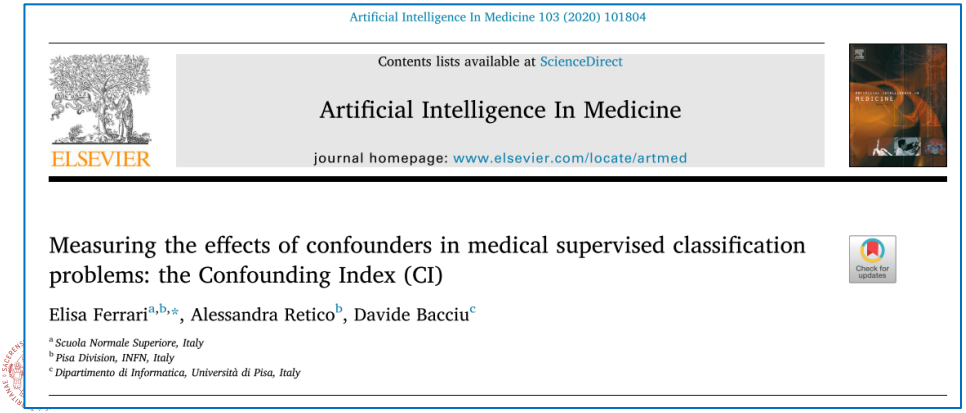

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Measuring the effects of confounders in medical supervised classification problems: the Confounding Index (CI)

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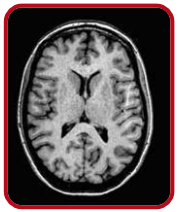
- Define a method for developing two-class classifiers that:
  - is not sensitive to confounding parameters
  - shows generalizable performance on other samples
- The proposed approach:
  - A method for identifying outliers based on Neural Network (NN): **Replicator NN (RNN)**
  - A method for identifying confounding parameters for an ML classifier: the **Confounding Index (CI)**
- Classification of ASD vs. CTR:
  - A classifier is trained on a dataset that is not affected by confounding parameters
  - The identified classification pattern is also valid for the rest of the sample.

Extraction of physical parameters from imaging data

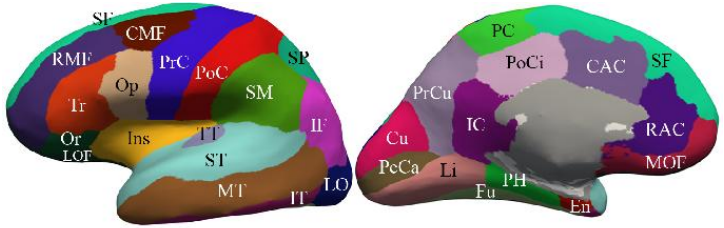
3D image processing



Brain measurements/feature

- Global volumes
- Local volumes of brain regions
- Cortical thicknesses
- Surfaces
- …

- Cortical features: volumes, thicknesses, curvatures, etc. of each brain parcel;
- Subcortical features: volumes of subcortical structures

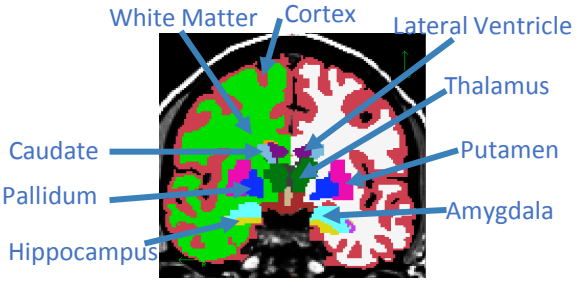


Region (gyrus)	Abb.
Caudal anterior cingulate	CAC
Caudal middle frontal	CMF
Cuneus	Cu
Entorhinal	En
Fusiform	Fu
Inferior parietal	IP
Inferior temporal	IT
Isthmus cingulate	IC
Lateral occipital	LO
Lateral orbitofrontal	LOF
Lingual	Li

Region (gyrus)	Abb.
Medial orbitofrontal	MOF
Middle temporal	MT
Parahippocampal	PH
Paracentral	PC
Pars opercularis	Op
Pars orbitalis	Or
Pars triangularis	Tr
Pericalcarine	PeCa
Postcentral	PoC
Posterior cingulate	PoCi

Region (gyrus)	Abb.
Precentral	PrC
Precuneus	PrCu
Rostral anterior cingulate	RAC
Rostral middle frontal	RMF
Superior frontal	SF
Superior parietal	SP
Superior temporal	ST
Supramarginal	SM
Transverse temporal	TT
Insula	Ins

http://freesurfer.net



Feature normalization

- To reduce inter-individual variation due to head size and inter-image differences caused by voxel-scaling variations, the data of each subject have been normalized to global quantities of the same subject:
  - volumetric features are divided by the Estimated Total Intracranial Volume (eTIV), i.e. the Freesufer measure of the intracranial volume;
  - cortical surfaces are divided by the area of the total white matter
  - cortical thicknesses are divided by the mean cortical thickness across the entire brain.

- After “self-normalization”, z-score is applied to bring all features in the same range.

$$z = \frac{x - \mu}{\sigma}$$

μ = Mean
σ = Standard Deviation

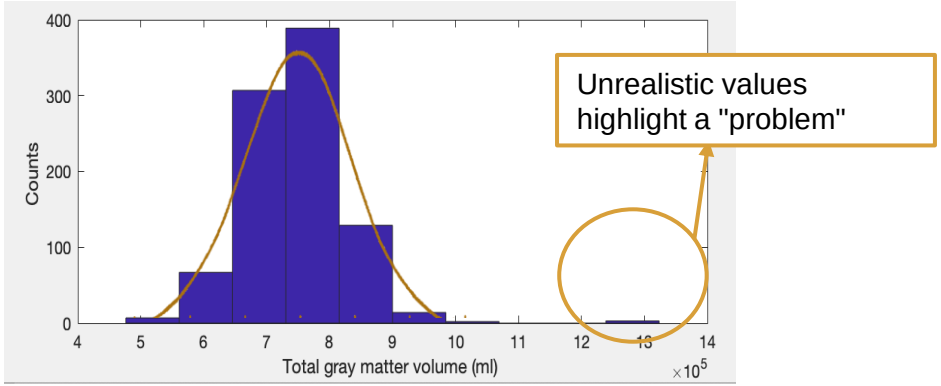
Search for outlier in feature distributions

Outliers of a distribution are:

- observations that differ significantly from other available observations

Possible approaches in outlier definition:

- Distance from the mean of the distribution, in terms of s.d. (for normal distributions)
- Median and interquartile distance can be used
- …



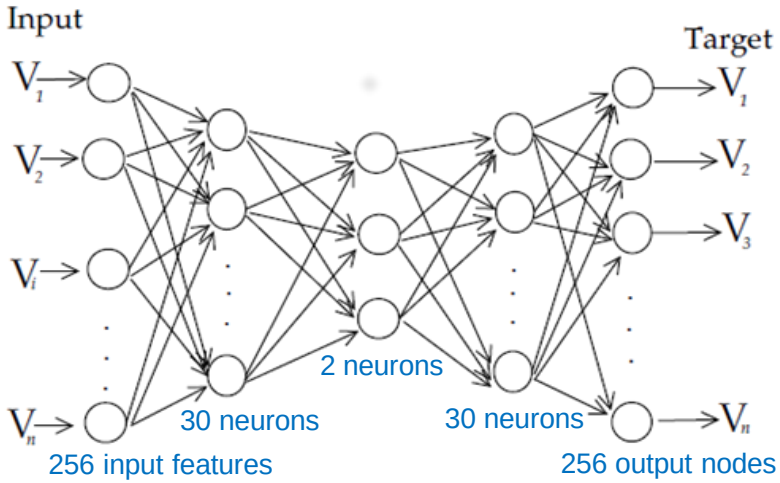
Once the outliers have been identified, it is possible :

- Check the subject with the outlier and possibly remove it from the sample
- If a feature is particularly affected by outlier, consider to remove the feature from the analysis

But: outliers not due to errors, can indicate something new!!!

Replicator Neural Network (RNN) for outlier identification

- We used an RNN to identify outliers in feature distributions
- No hypothesis is required on shape of their distributions



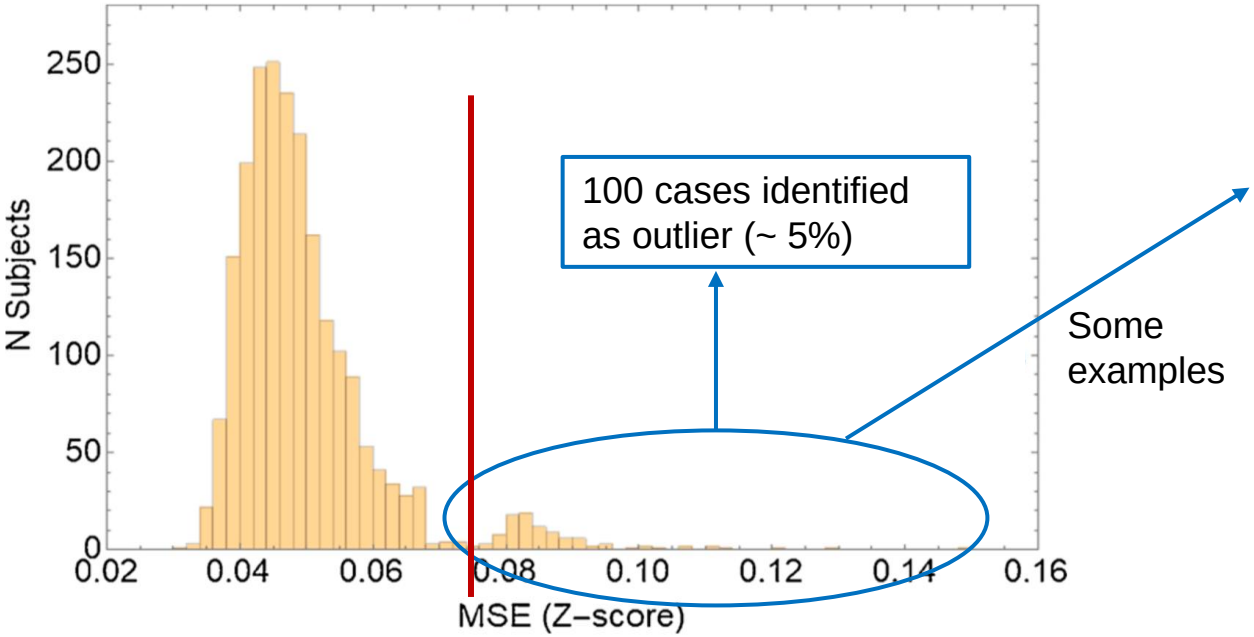
Hawkins S, He H, Williams G, Baxter R. Outlier detection using replicator neural networks. International conference on data warehousing and knowledge discovery 2002:170–80.

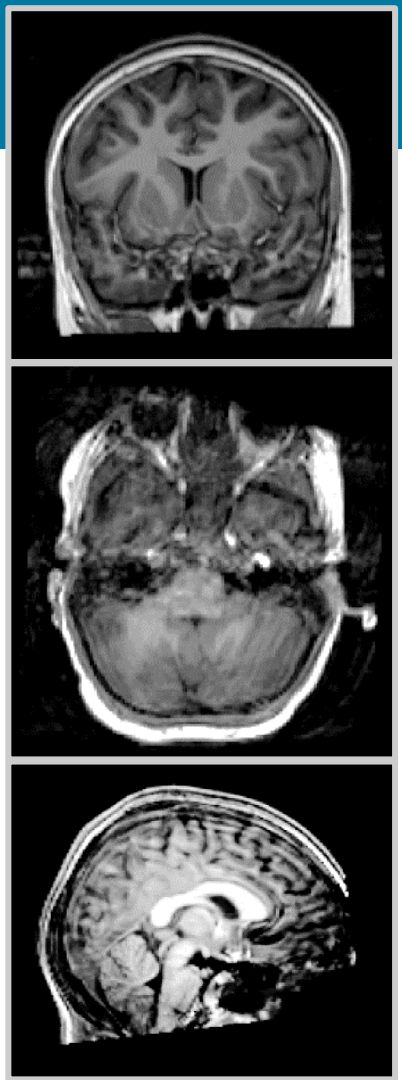
Ferrari E, Bosco P, Calderoni S, Oliva P, Palumbo L, Spera G, Fantacci ME, Retico A, Dealing with confounders and outliers in classification medical studies: the Autism Spectrum Disorders case study, Artif Intell Med 2020, 108,, 101926. doi: 10.1016/j.artmed.2020.101926

- The RNN is trained to reproduce the input, after having compressed it into a smaller number of parameters.
- It will therefore not be able to accurately reproduce extreme cases
- The outliers will hence present a larger reconstruction error, measured in terms of Mean Squared Error (MSE) between input and output

Analysis of the outliers

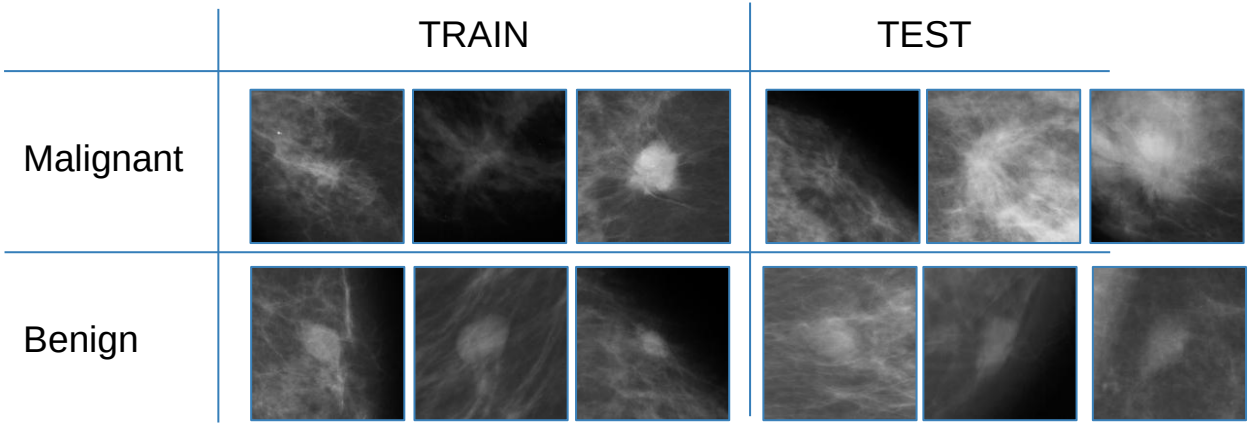
- Analysis of MSE distributions
- Identification of a cut-off





Confounding factors in a classification problem

- A **confounding variable** is an extra variable in principle irrelevant to a classification problem, but which can affect the outcome if not properly taken into account
- For example:



Suppose we can discriminate the two classes with ***AUC ~ 85%***

Confounding factors in a classification problem

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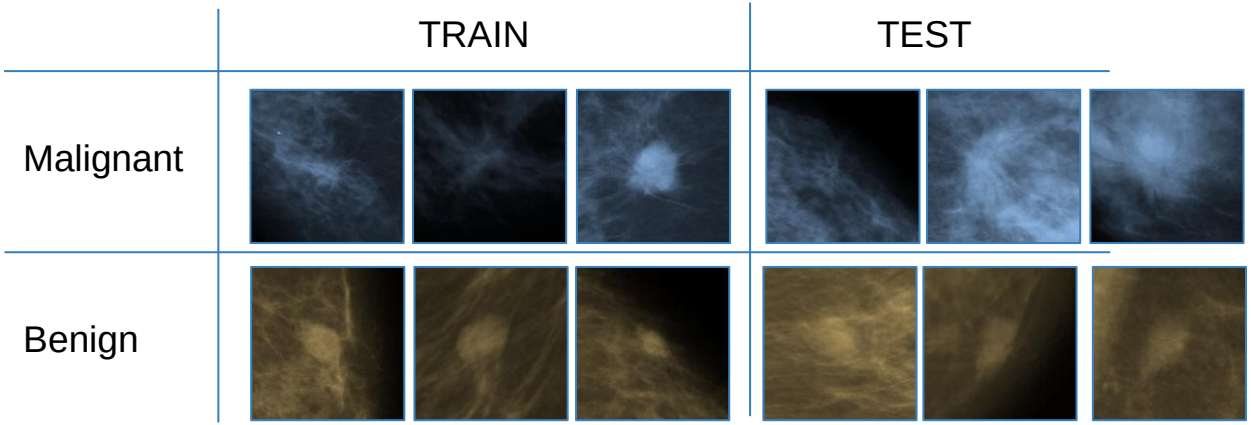
- For example:



Does a good discrimination performance between cases and controls ensure that the classifier is exploiting the right information?

Confounding factors in a classification problem

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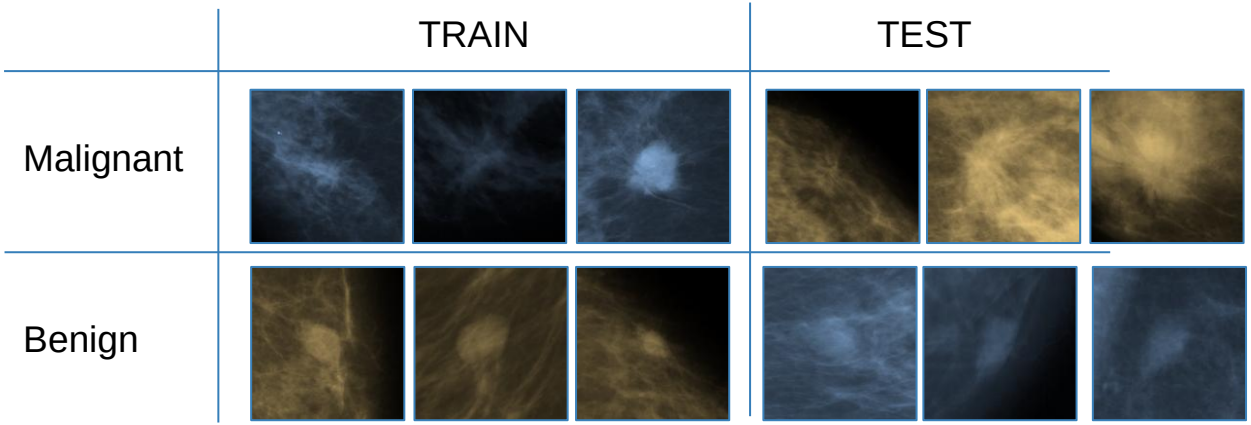
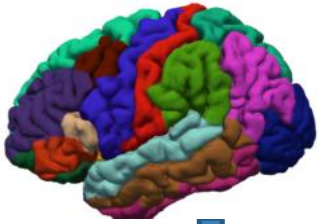
- For example:

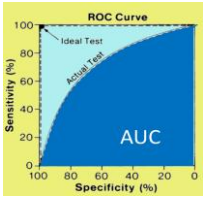


What happens instead if the confounding effect affects the diagnosis on the TEST dataset in the opposite way?
→ AUC decreases!

Dependence on the acquisition site for MRI data and features

http://freesurfer.net





- Analysis only on ABIDE control subjects (CTR)
- Binary classification

  $Site_i$ vs. $Site_j$

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AUC values obtained in two-class discrimination

	NYU ABIDE1	NYU-1 ABIDE2	NYU-2 ABIDE2	OHSU ABIDE1	OHSU ABIDE2	USM ABIDE1	USM ABIDE2	UM-1 ABIDE1	UM-2 ABIDE1
NYU ABIDE1	-	0.78	0.89	0.99	1.00	0.99	1.00	0.99	0.98
NYU-1 ABIDE2		-	0.70	0.99	1.00	1.00	1.00	0.99	0.98
NYU-2 ABIDE2			-	1.00	0.98	0.99	0.99	1.00	1.00
OHSU ABIDE1				-	0.63	0.97	0.96	1.00	1.00
OHSU ABIDE2					-	0.99	0.96	0.98	0.98
USM ABIDE1						-	0.75	0.99	0.99
USM ABIDE2							-	0.97	0.97
UM-1 ABIDE1								-	0.96
UM-2 ABIDE1									-

How can we quantify and manage the confounding effect of the acquisition site?

How to identify confounding factors in ML?

- Machine learning (ML) models trained on features extracted from brain MRI (e.g. those calculated with FreeSurfer) are strongly influenced by the confounding effect introduced by the acquisition site.
- Furthermore, in a typical case-control classification, other confounding variables must be considered (e.g. age, sex).

We used the **Confounding Index (CI)** to quantify the impact of confounding factors with respect to two-class ML classification tasks

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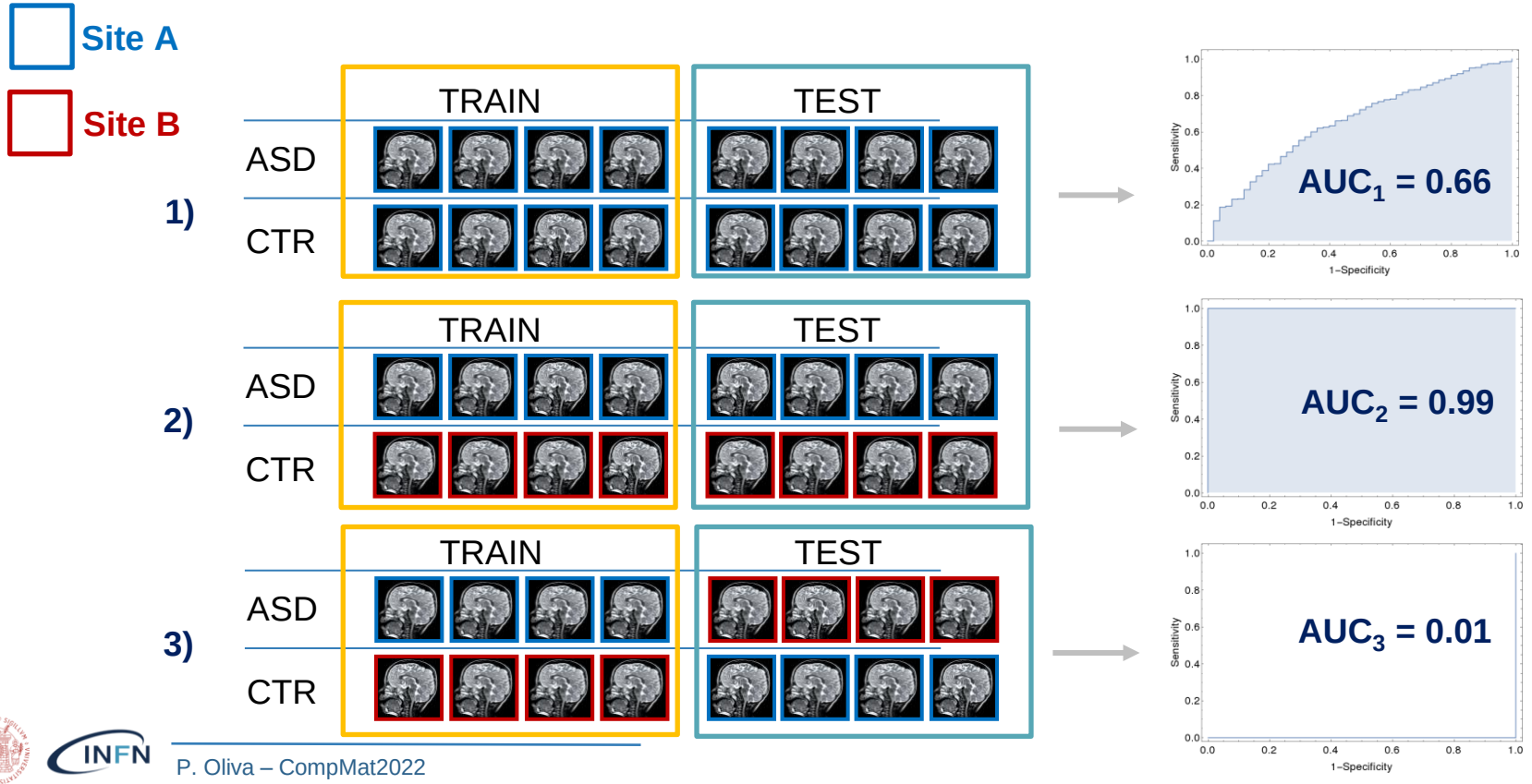
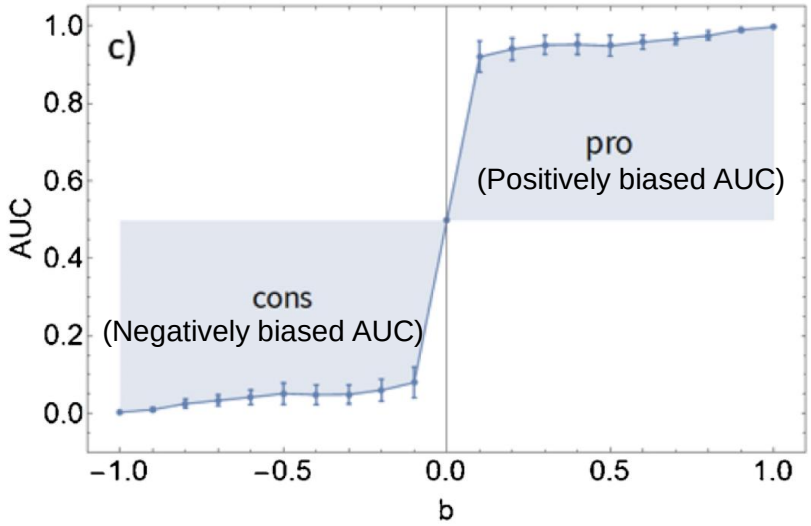
Evaluating confounding effect of a variable

An ML classifier can be trained **3 times,** changing the composition of Train and Test sets



Confounding Index (CI)

- The CI is based on measuring the variation of the AUC obtained using different engineered biases during training and thus depends on how the confounder and the class labels affect the input features.
- The CI ranges from 0 to 1 and allows:
  - to **test the effect of a confounding variable** on a specific binary classifier;
  - to **rank variables** with respect to their confounding effect;
  - to evaluate the effectiveness of a normalization procedure and assess the robustness of a training algorithm against confounding effects.



CI = Area_pro – Area_cons

Tested on sex, age, intelligence quotient (IQ), and acquisition site

Testing for CI in ABIDE

- Sex and acquisition modality (AM) have significant confounding effects on a classification analysis between ASD and CTR

Acquisition Modality (Site)

Variable			Non-normalized Data		Normalized Data	
			CI	Error	*CI*	Error
Handedness			0.01	0.06	0.02	0.06
Sex			0.43	0.03	0.23	0.04
AM	$\neq$ scanners and protocols	NYU-I vs KKI_{8ch}-II	0.54	0.02	0.62	0.03
		NYU-I vs UM_1-I	0.63	0.02	0.70	0.02
	= scanners and protocols	NYU-I vs NYU_1-II	0.32	0.04	0.39	0.03
		UM_1-I vs UM_2-I	0.29	0.02	0.35	0.02

The normalization procedure does not mitigate the site effect

The sex, age and acquisition site parameters should be taken into account in the ML analysis, for example by accurately matching for them the ASD and CTR samples

Classification ASD vs. CTR

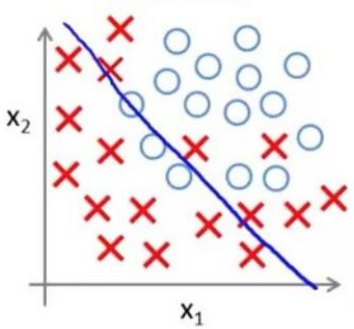
- It is not trivial to generate a completely balanced sample with respect to all those variables, especially with modest sized databases
- We focused on the most populated site (NYU-I), obtaining a sample of **116 subjects**, ASD-CTR age-paired (within 2.5 yrs, only males, age < 30 years)

- Classification scheme: **hold-out**

  75% of data in train, 25% in test
- Binary classificator: **logistic regression**
- Classification performance ASD vs CTR:

  AUC= 0.82 ± 0.11 (CV on train set)

  AUC= 0.79 (on independent test set)



$h_\theta(x) = g(\theta_0 + \theta_1 x_1 + \theta_2 x_2)$

(g = sigmoid function)

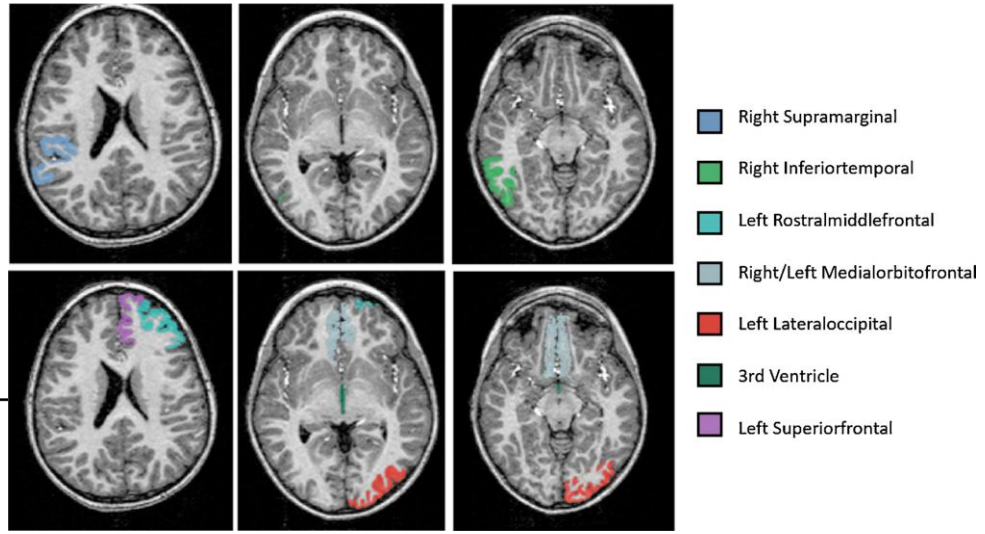
Correct generalization of the model on data from the same acquisition site

Classification pattern

- We identified the most relevant features in the classification process (permutation test), thanks to the interpretability of the model

Feature	Measurement	Increased (+) or decreased (−) in ASDs with respect to TDCs
rh_supramarginal	ThickAvg	−
rh_MeanThickness		−
lh_MeanThickness		+
rh_medialorbitofrontal	MeanCurv	+
lh_medialorbitofrontal	ThickAvg	+
lh_lateraloccipital	ThickAvg	+
lh_rostralmiddlefrontal	MeanCurv	+
rh_inferiortemporal	SurfArea	−
lh_superiorfrontal	MeanCurv	+
lh_lateraloccipital	GrayVol	+
3rd-Ventricle	Volume_mm3	+

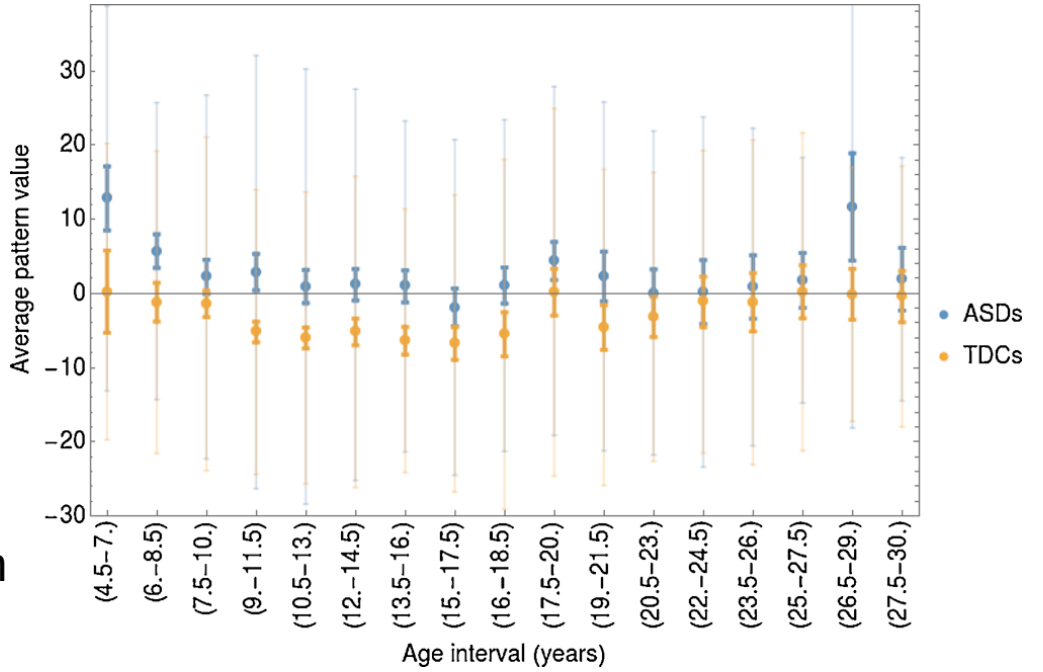
Alterations in thicknesses /volumes belonging to the fronto-temporal network confirm the results of previous studies



Generalizability test on the whole ABIDE sample

On all the male of ABIDE (in the same age range selected for NYU: 1460 subjects, 40 sites):

- it is not possible to correctly distinguish ASD from CTR on the whole sample
- but it occurs that, in subgroups of subjects with a maximum age difference of 2.5 years, the average value of the discrimination pattern in ASD subjects is always higher than that of CTRs



Harmonization methods in MRI

- MRI data suffer from technical between-scanner (namely between-site) variations.
- Another possible approach in dealing with site dependence is to **harmonize the features**, employing ComBat-GAM: a batch-effect correction tool aimed to reduce inter-site variability while preserving variations due to other biologically-relevant covariates[1].
- For site i, subject j, region k:

Harmonized feature | Original feature | covariates model | Site effect | Scale effect

$$Y^*_{ijk} = (Y_{ijk} - f_k(x_{ij}, z_{ij}, w_{ij}) - g^*_{ik}) / d^*_{ik} + f_k(x_{ij}, z_{ij}, w_{ij})$$

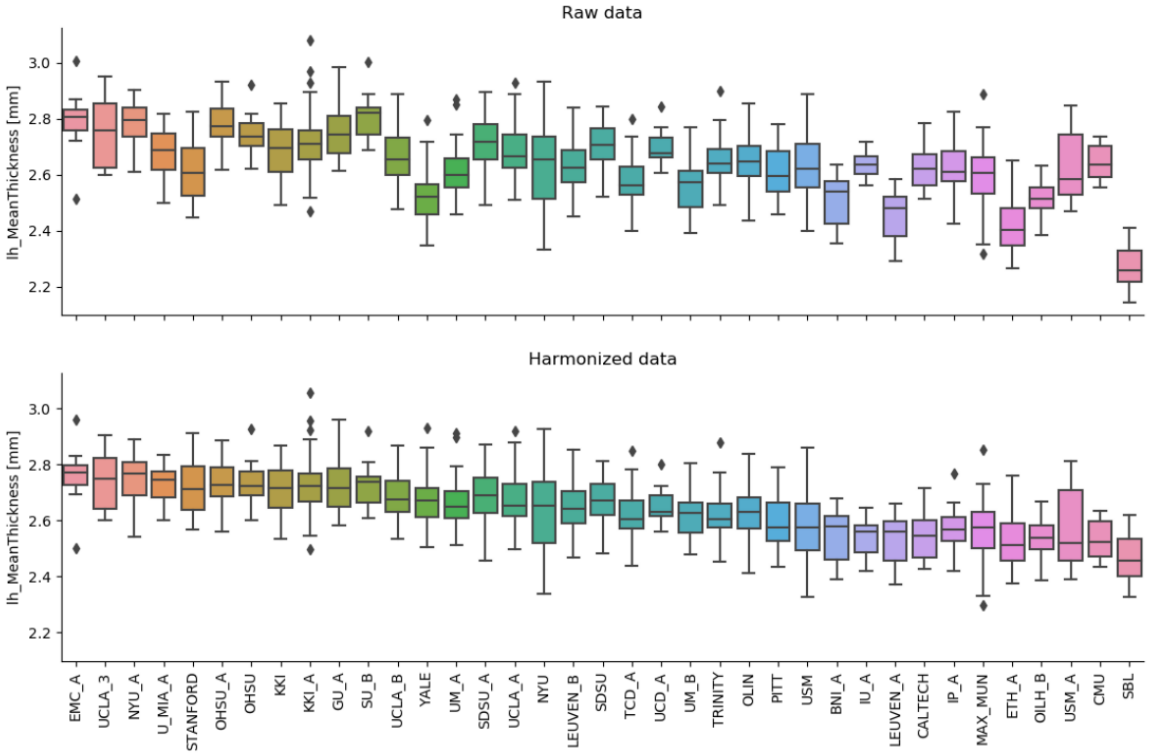
[1]) Pomponio, R., et al., (2020). "Harmonization of large MRI datasets for the analysis of brain imaging patterns throughout the lifespan", Neuroimage 208, 116450

Effect of the harmonization process

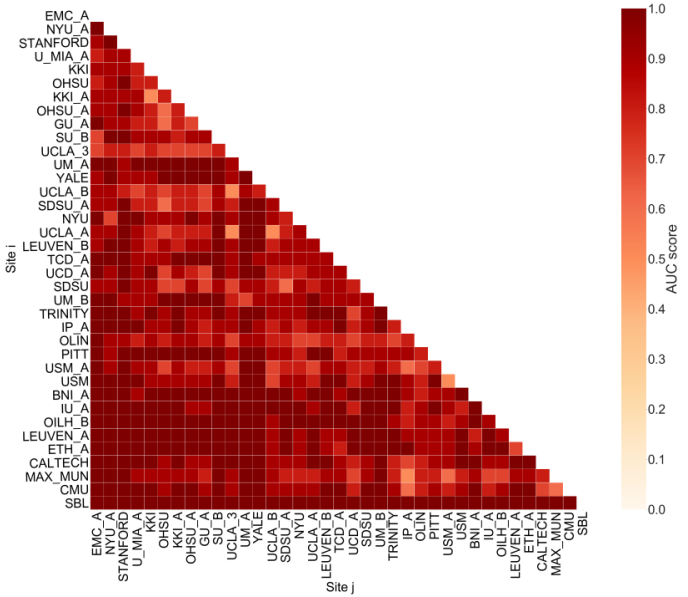
Effect of the harmonization process on an example feature, the left hemisphere cortical thickness, is shown.

The box plots show of the distributions of the feature, grouped by site, ordered by increasing median age.

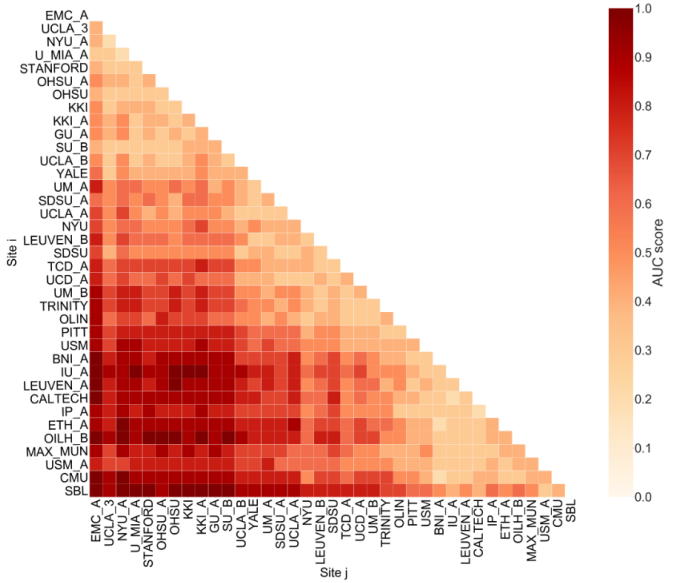
The presence of inter-site biases which is visible on raw data (top panel) is canceled by the harmonization process while preserving the expected age trend of the feature (bottom).



Effect of the harmonization process



Heatmap obtained on non-harmonized data.

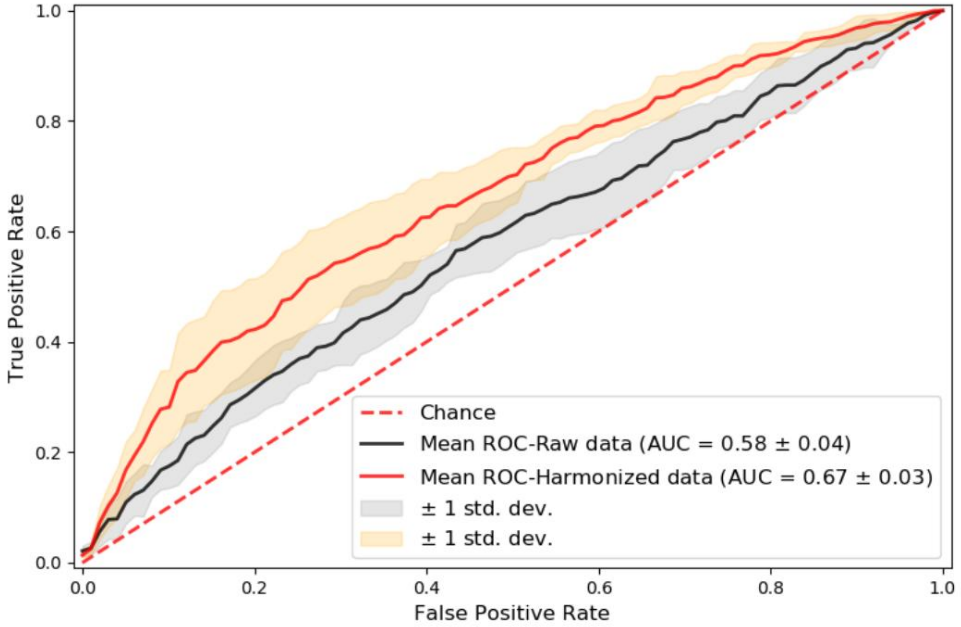


Heatmap obtained on harmonized data

Case/control classification scores

- Classifier:
  - Random Forest
  - 5-fold cross-validation
  - Balanced training set for each site

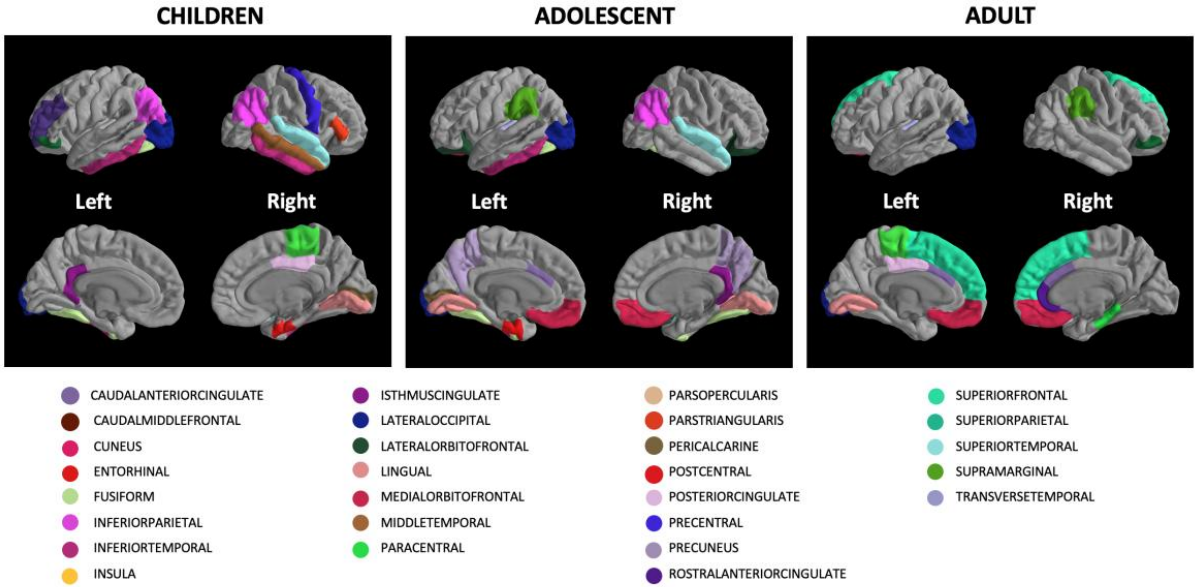
Subgroups	AUC	
	Raw data	Harmonized data
Children	0.52 ± 0.09	0.62 ± 0.02
Adolescents	0.47 ± 0.07	0.65 ± 0.03
Adults	0.62 ± 0.07	0.69 ± 0.06



Feature Importance

The feature importance was evaluated by feature permutation

The most discriminative features are mainly from the frontal, parietal and temporal regions.



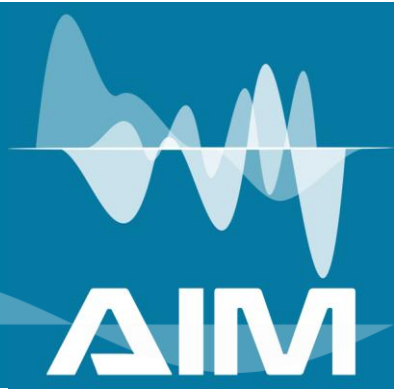
Saponaro S., Giuliano A. , Bellotti R., Lombardi A., Tangaro S., Oliva P., Calderoni S., Retico A., Multi-site harmonization of MRI data uncovers machine-learning discrimination capability in barely separable populations: an example from the ABIDE dataset, Neuroimage: Clinical, under review

Conclusions

- ML techniques can be used not only to classify and make predictions, but also as a tool to **study a certain clinical condition**

- In implementing ML techniques, attention must be paid:
  - to quality and size of the data aim of the study
  - to possible confounding factors/biases that could alter the model training
  - the generalizability of the results obtained

Thank you!



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