Unraveling Brain Weaknesses in Learning Disorders Combining Multimodal Imaging and Machine Learning

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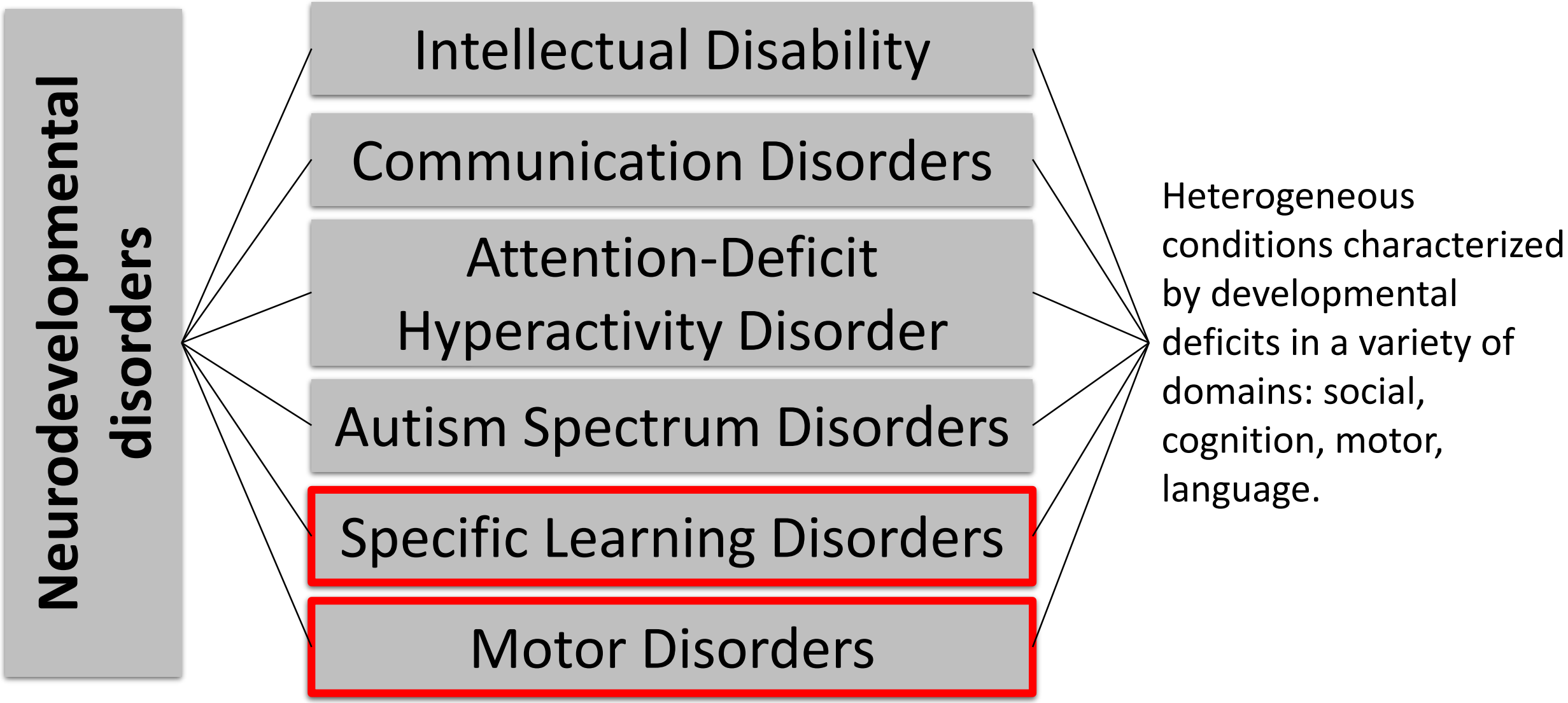
The general picture

► **DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, fifth edition 2013)**



The general picture

► **DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, fifth edition 2013)**

Specific Learning Disorders

- with impairment in reading, or

<u>Developmental Dyslexia (DD)</u>

- with impairment in writing
- With impairment in mathematics

Accuracy and speed when reading significantly low

Tests
ODEDYS, Alouette …
Prevalence
3-12%

Motor Disorders

- **<u>Developmental Coordination Disorder (DCD)</u>**
- Stereotypic Movement Disorder
- Tic Disorders

Motor coordination problems

Tests
M-ABC …
Prevalence
2-7%

The general picture

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COMORBIDITY : 30-50%

Motor Disorders

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- Stereotypic Movement Disorder
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Motor coordination problems

Tests
M-ABC …
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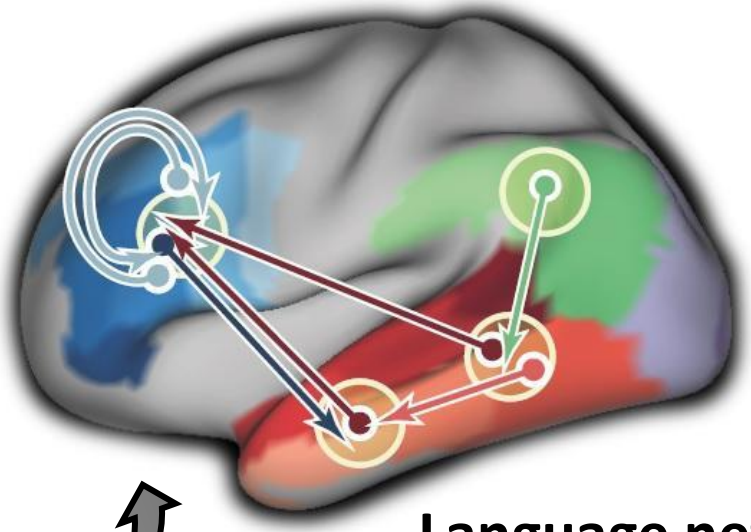
The general picture

► **Major Explanatory Theories**

Developmental Dyslexia



Language network

Schoffelen et al. *PNAS* 2017

- Phonological Theory

  impairment in the representation, storage and/or retrieval of speech sounds, then affecting grapheme-phoneme correspondences

- Cerebellar Theory

  cerebellum is dysfunctional, affecting articulation (then deficient phonological representations) and capacity to automatize (affecting grapheme-phoneme correspondences)

Ramus et al. *Brain* 2003 ; Nicolson et al. *Trends Neurosci* 2001

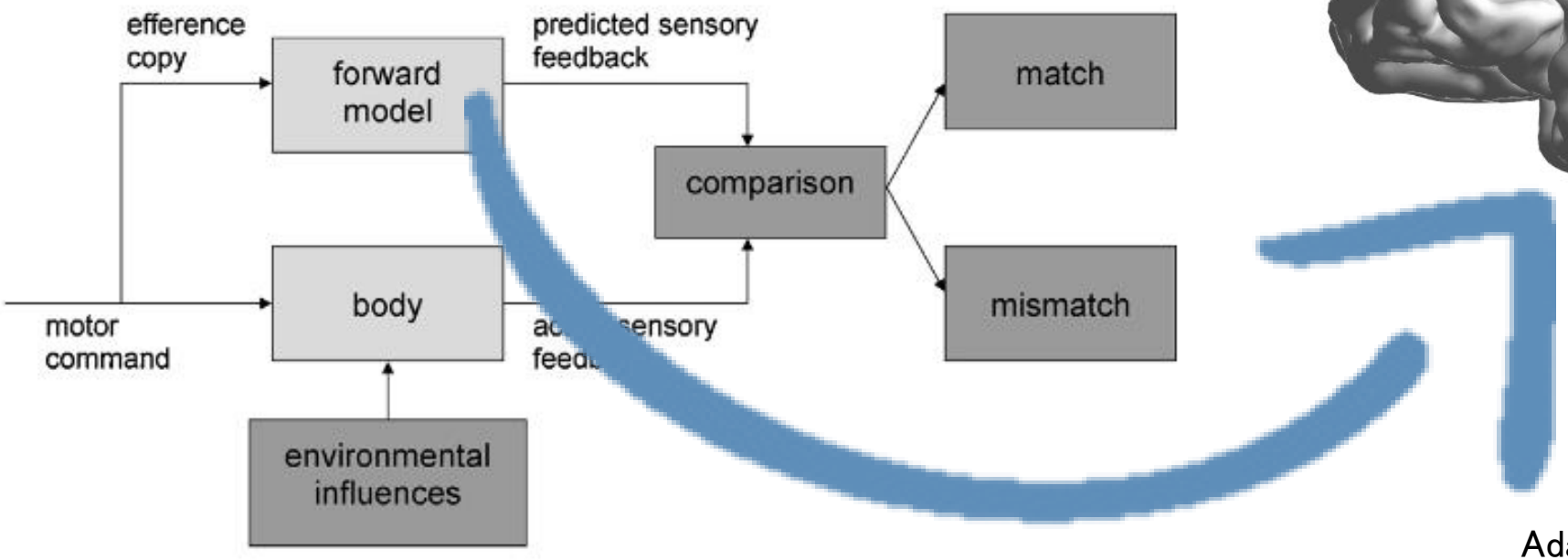
The general picture

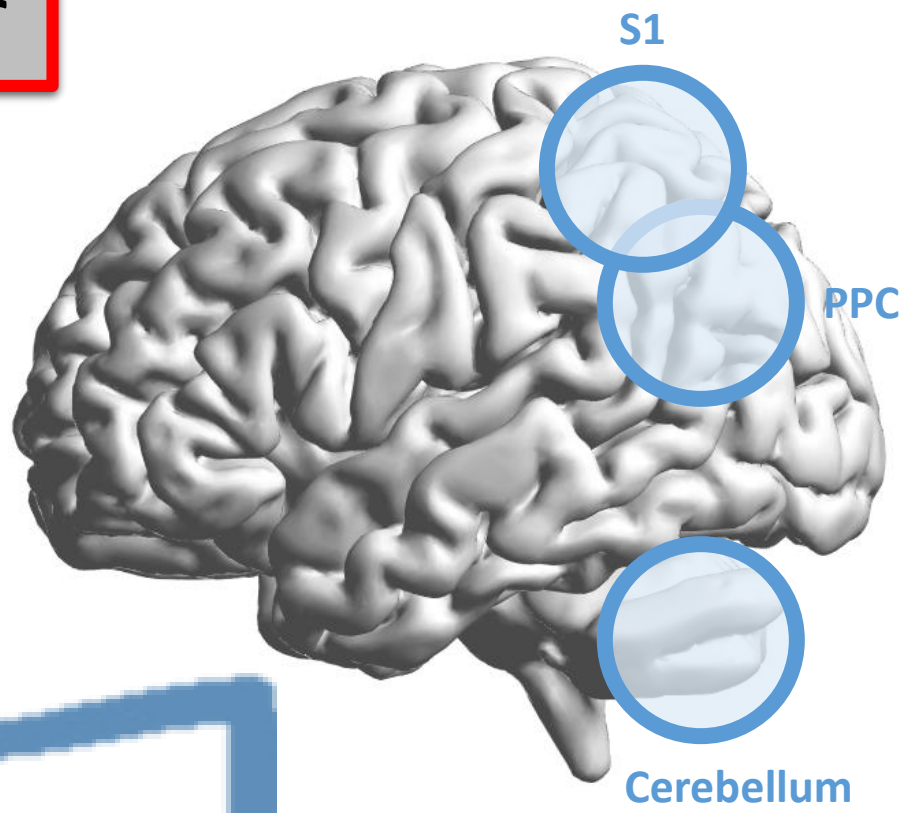
► **Major Explanatory Theories**

Developmental Coordination Disorder

- Internal Modeling Deficit Theory

  difficulty representing predictive models of action





Adams et al. *Neurosci Biobehav Rev* 2014

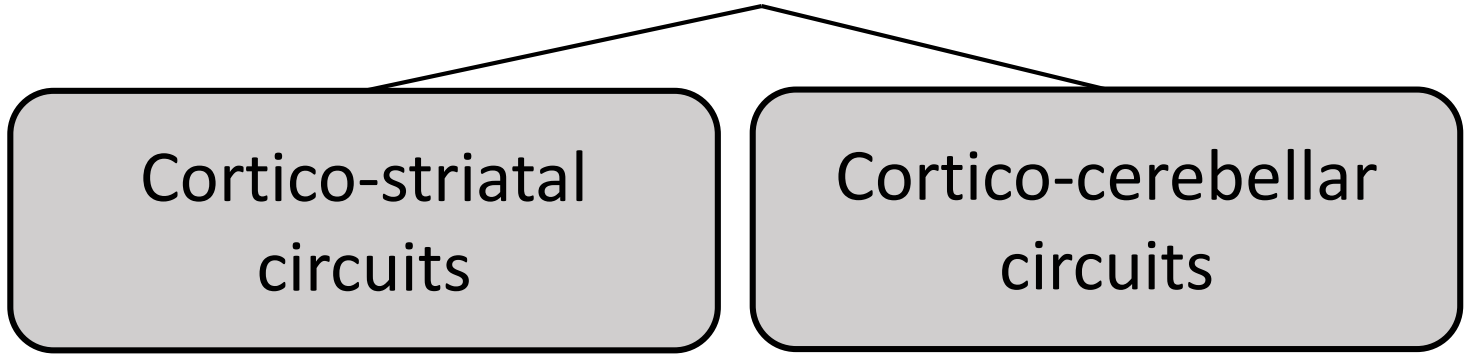
The general picture

► **Major Explanatory Theories**

Developmental Dyslexia & Developmental Coordination Disorder

- Procedural Learning Deficit Theory

impairments of the procedural learning system, which subserves the learning of new, and the control of established, sensorimotor and cognitive skills, rules and habits



Nicolson & Fawcett et al. *Trends Neurosci* 2007

The general picture

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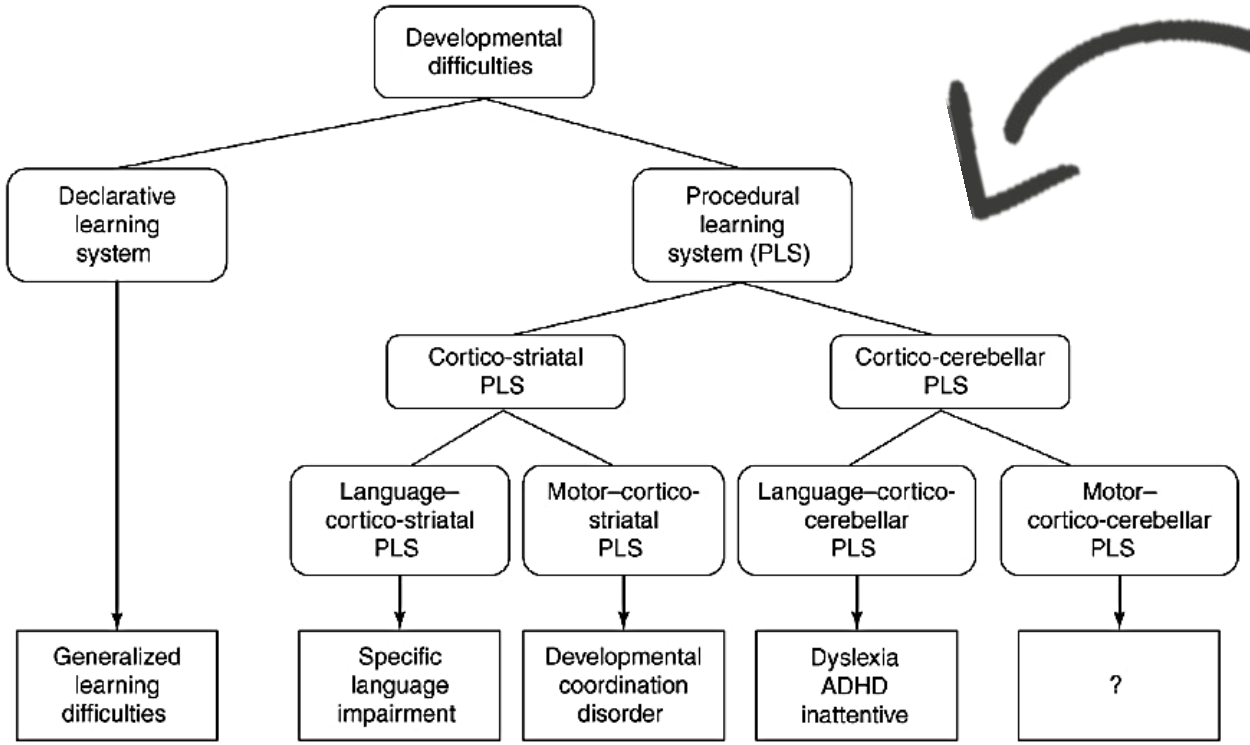


Neural System Topography for Learning Disorders

Nicolson & Fawcett et al. *Trends Neurosci* 2007

The general picture

► **Major Explanatory Theories**

Developmental Dyslexia & Developmental Coordination Disorder

- Procedural Learning Deficit Theory

  - *would explain deficits in a range of motor and perceptual skills in DCD children as well as secondary motor symptoms in DD children*
  - *may also explain difficulties in DD children to acquire rule-based procedures that govern language ('the mental grammar'), including aspects of phonology*

Nicolson & Fawcett et al. ***Trends Neurosci*** 2007

The general picture

► **A number of issues**

Developmental Dyslexia & Developmental Coordination Disorder

- difficult to validate or invalidate these hypotheses for a number of reasons:

disorders often studied independently

neuroimaging standards not always respected

multimodal brain imaging data poorly exploited

varying diagnostic/exclusion criteria (overlap between DD and DCD)

small sample size

…

The DYSTAC-MAP Project

Aix-Marseille Université (LNC, PSYCLE, CHU Timone-Enfants) | Université de Toulouse (ToNIC, CHU de Toulouse-Enfants)

TYP children	DD children	DCD children	COM children	NF1 children
n=42	n=45	n=20	n=29	n=38

[8-12 yo.]

Siemens Magnetom Skyra 3.0 T MRI scanner, 32-channel head coil

Rs-fMRI (EPI sequence, 3mm iso.)

T1-weighted (MPRAGE, 1mm iso)

Philips Achieva dStream 3.0 T MRI scanner, 32-channel head coil

Diffusion-weighted (2 mm iso, 34 dir.)

Fluid attenuated inversion recovery

+ neuropsychological (memory, attention …) and motor control assessment

GM/WM volumes, correlation (local, global, seed-to-voxels…), fALFF, FA, MD, …

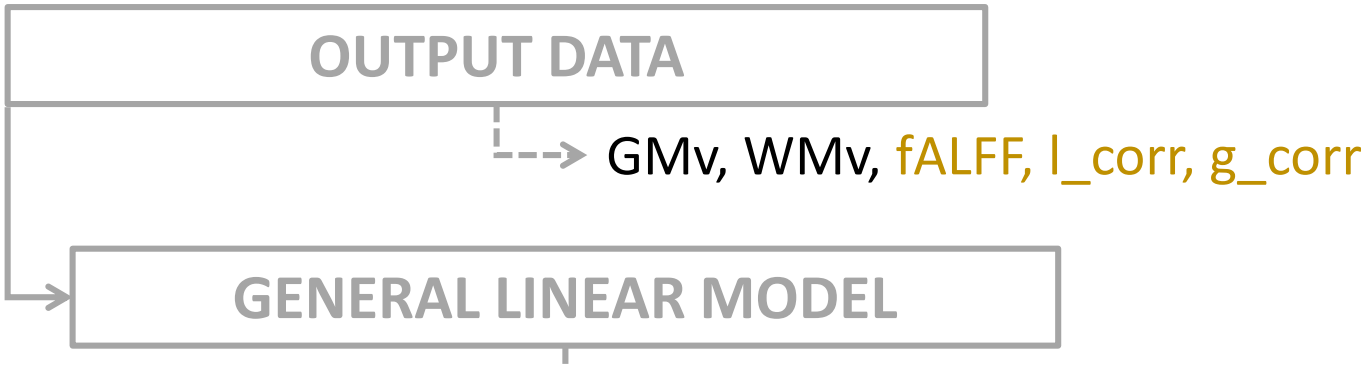
Univariate (GLM) and multivariate (SVM, MKL) modeling

Discriminating between learning disorders by means of multimodal MRI and multivariate analyses

INPUT DATA	PROCESSING	OUTPUT DATA
T1w MRI images	• sample-specific tissue probability maps (Cerebr-o-Matic toolbox) • spatial normalization and segmentation in grey matter, white matter and cerebrospinal fluid (CAT toolbox)	• GM/WM volumes corrected for total intracranial volume
rs-fMRI images	• realignment & unwarp, slice-timing correction, spatial normalization, outliers detection, smoothing (SPM & ART toolboxes) • aCompCor denoising (CONN toolbox)	• fraction of amplitude of low frequency fluctuations (fALFF) -> local activity at rest • local correlation -> local coherence • global correlation -> network centrality

Nemmi, Cignetti et al. *in progress*

Discriminating between learning disorders by means of multimodal MRI and multivariate analyses



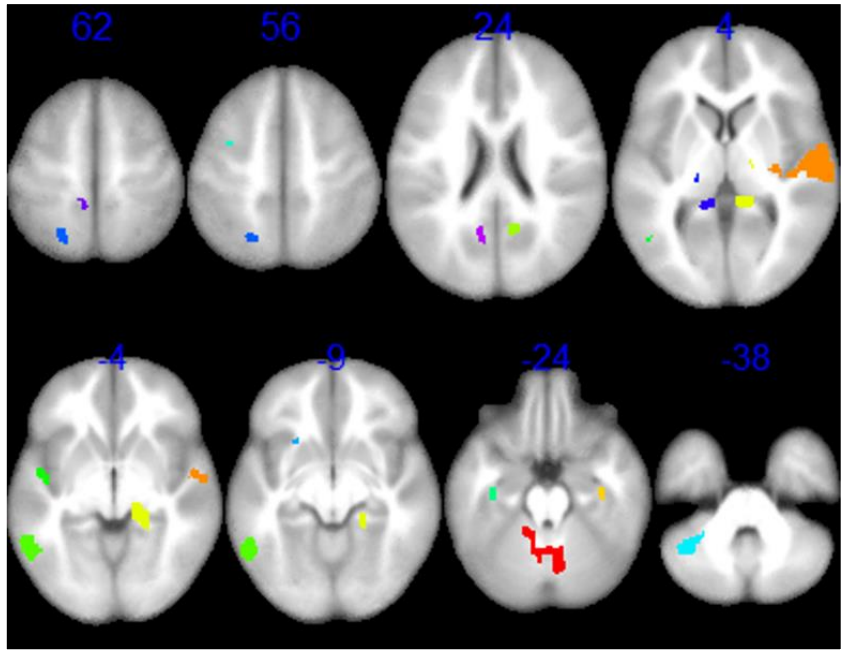
Contrast treatment: at least one pathological group different from the typically developing group (TIV, sex, centre of acquisition and age as nuisance variables) -> a set of "pathological areas" (feature selection)

Nemmi, Cignetti et al. *in progress*

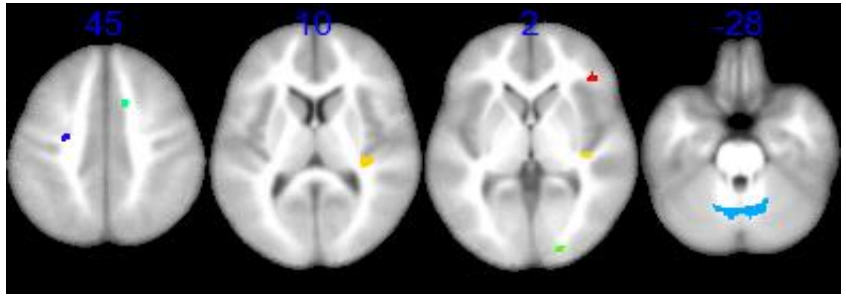
Discriminating between learning disorders by means of multimodal MRI and multivariate analyses

► GLM

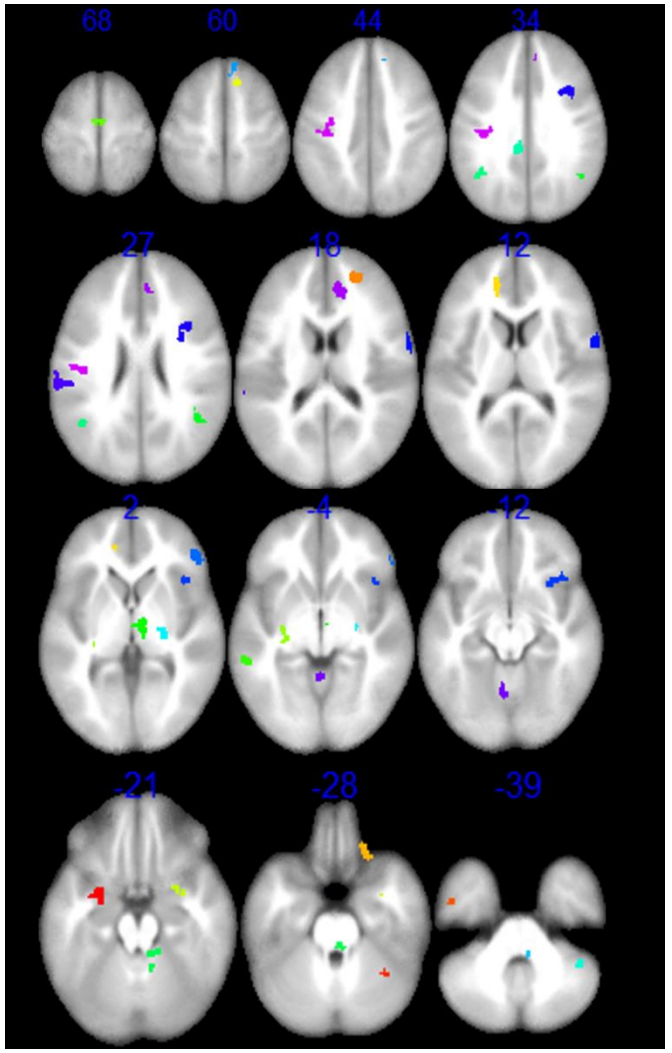
GMv



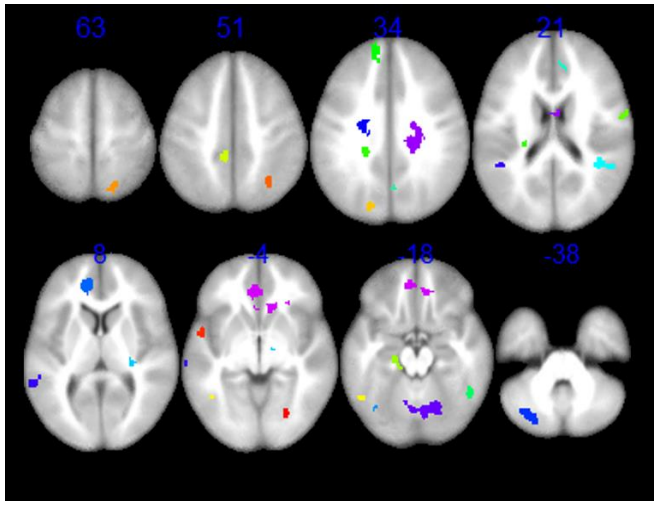
WMv



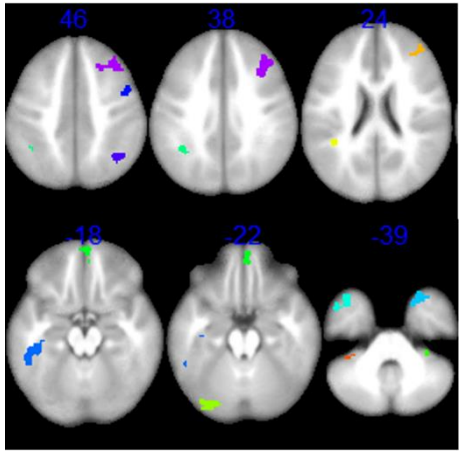
fALFF



l_corr

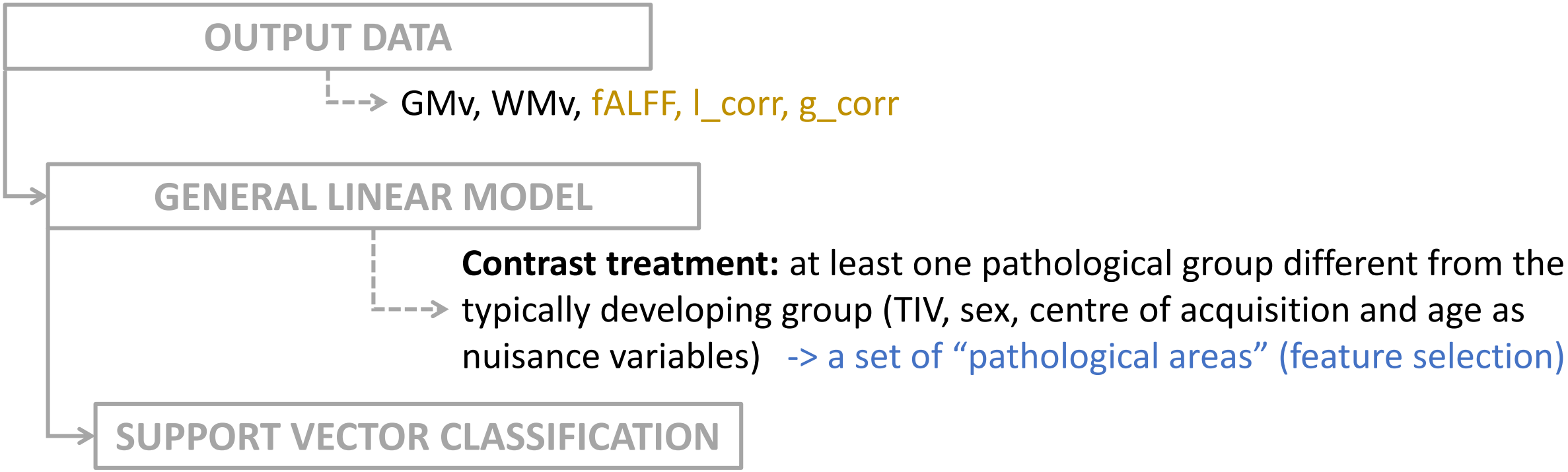


g_corr



Nemmi, Cignetti et al. *in progress*

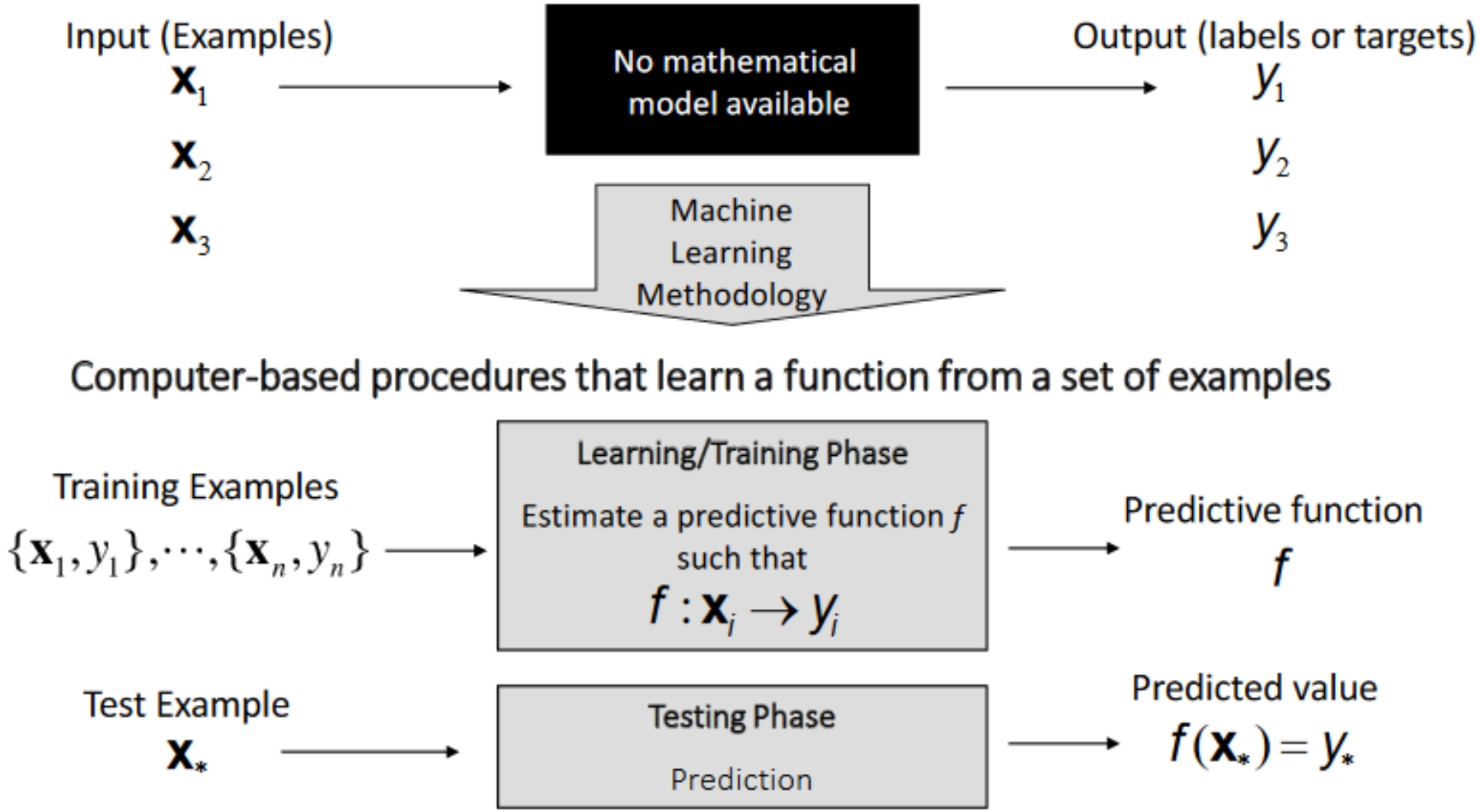
Discriminating between learning disorders by means of multimodal MRI and multivariate analyses



Nemmi, Cignetti et al. *in progress*

Discriminating between learning disorders by means of multimodal MRI and multivariate analyses

► **Machine learning framework**



Discriminating between learning disorders by means of multimodal MRI and multivariate analyses

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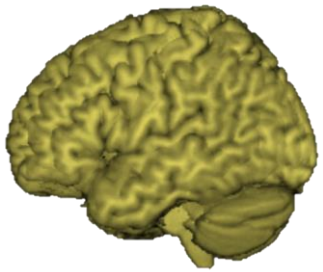


Feature Vector

$\mathbf{x}_i$ is a vector of size dx1 where d is the number of voxels

Input (Examples)

$\mathbf{x}_1$

$\mathbf{x}_2$

$\mathbf{x}_3$

No mathematical model available

Output (labels or targets)

y_1

y_2

y_3

Machine Learning Methodology

Computer-based procedures that learn a function from a set of examples

Training Examples

$\{\mathbf{x}_1, y_1\}, \cdots, \{\mathbf{x}_n, y_n\}$

Learning/Training Phase

Estimate a predictive function f such that

$f : \mathbf{x}_i \rightarrow y_i$

Predictive function

f

Test Example

$\mathbf{x}_*$

Testing Phase

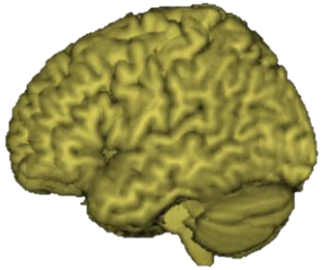
Prediction

Predicted value

$f(\mathbf{x}_*) = y_*$

Discriminating between learning disorders by means of multimodal MRI and multivariate analyses

► Machine learning framework



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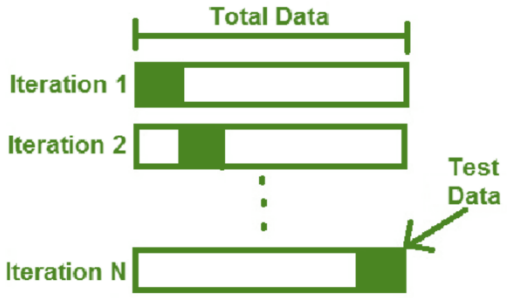
Cross-validation



Discriminating between learning disorders by means of multimodal MRI and multivariate analyses

► **Support Vector Machine**

Find the optimal hyperplane separating the data, that is the one which presents the largest margin

$$f(x_i) = \langle w, x_i \rangle + b$$
$$\langle w, x_i \rangle + b = 0$$

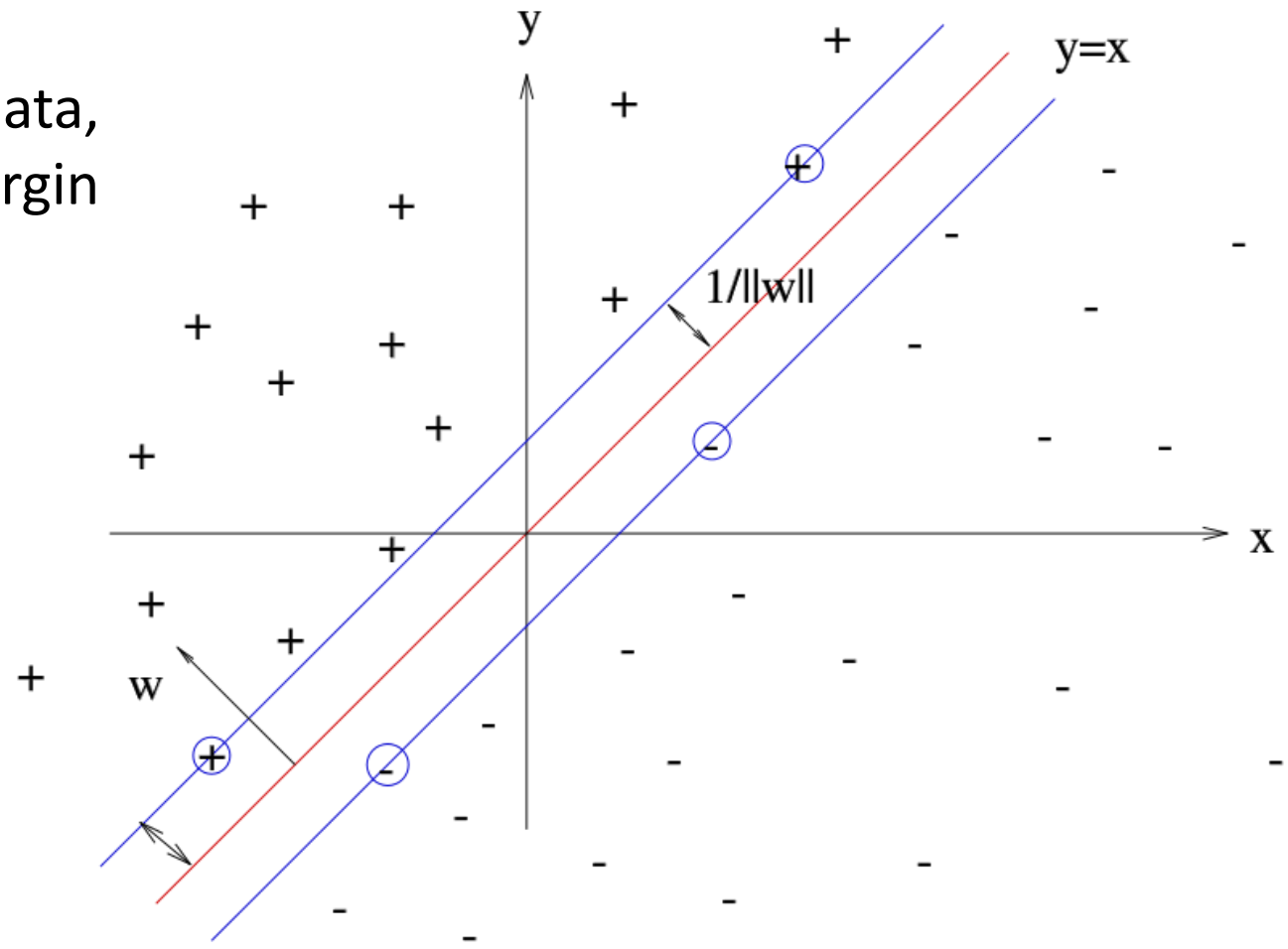
How? by solving the optimization problem

$$\begin{cases} min_w \frac{1}{2} \|w\|^2 \\ \langle w, x_i \rangle + b \geq 1 \end{cases}$$

Primal formulation

$$f(x_i) = \sum_{i=1}^{n} \alpha_i K(x, x_i) + b$$

Dual formulation



Discriminating between learning disorders by means of multimodal MRI and multivariate analyses

OUTPUT DATA

→ GMv, WMv, fALFF, l_corr, g_corr

GENERAL LINEAR MODEL

Contrast treatment: at least one pathological group different from the typically developing group (TIV, sex, centre of acquisition and age as nuisance variables) -> a set of "pathological areas" (feature selection)

SUPPORT VECTOR CLASSIFICATION

sklearn.svm.LinearSVC: multiclass (one vs all), stratified 10-fold cross-validation, 10 repetitions -> 100 folds

sklearn.feature_selection.SelectFromModel: selects only the 'most important' features (clusters) and then fits again

balanced accuracy (average of sensitivity and specificity)

1000 permutations of the training labels

Nemmi, Cignetti et al. *in progress*

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balanced accuracy (the average of sensitivity and specificity)
1000 permutations of the training labels

GENERALIZED LEAST SQUARES MODEL

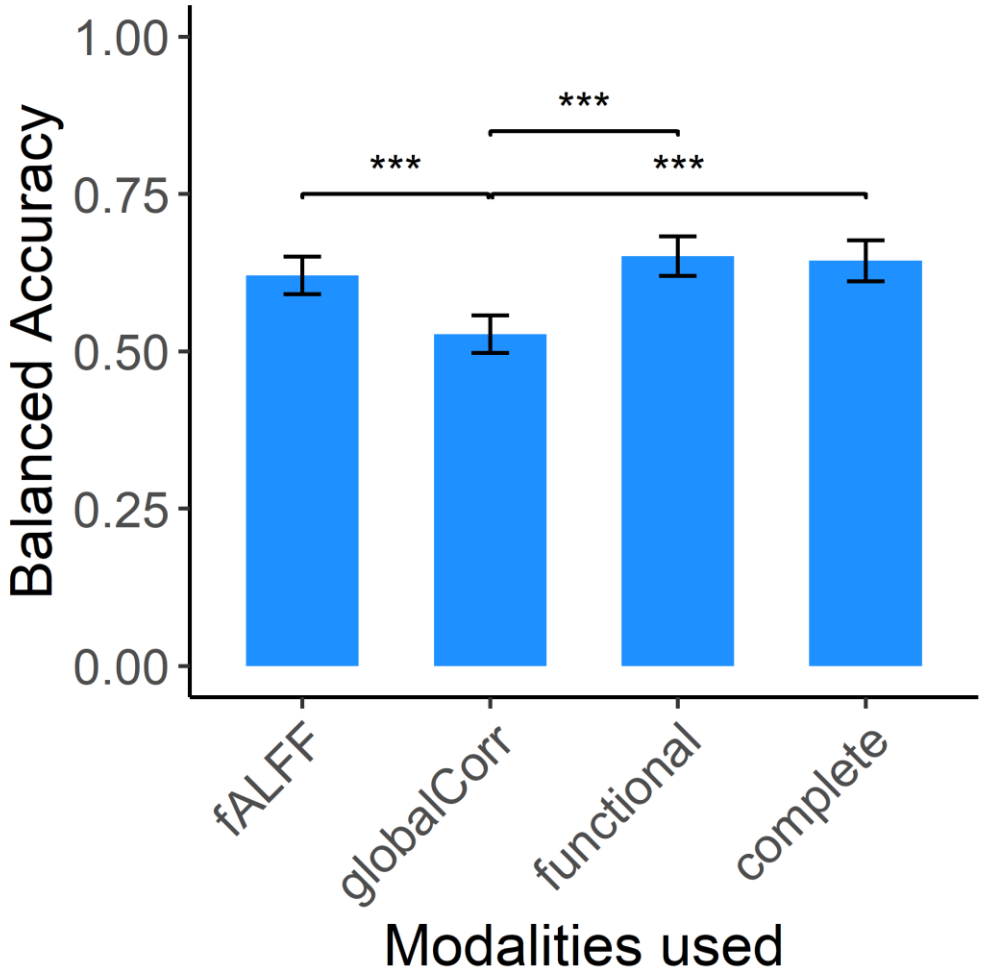
if model significant
for clusters selected more
than 66 times out of 100

R-package 'nlme': assessed group (DD, DCD, COM), cluster, and group x cluster interaction effects

Nemmi, Cignetti et al. *in progress*

Discriminating between learning disorders by means of multimodal MRI and multivariate analyses

► **SVM**



All functional indices, either combined or not, led to a performance significantly different from chance level, while structural indices did not

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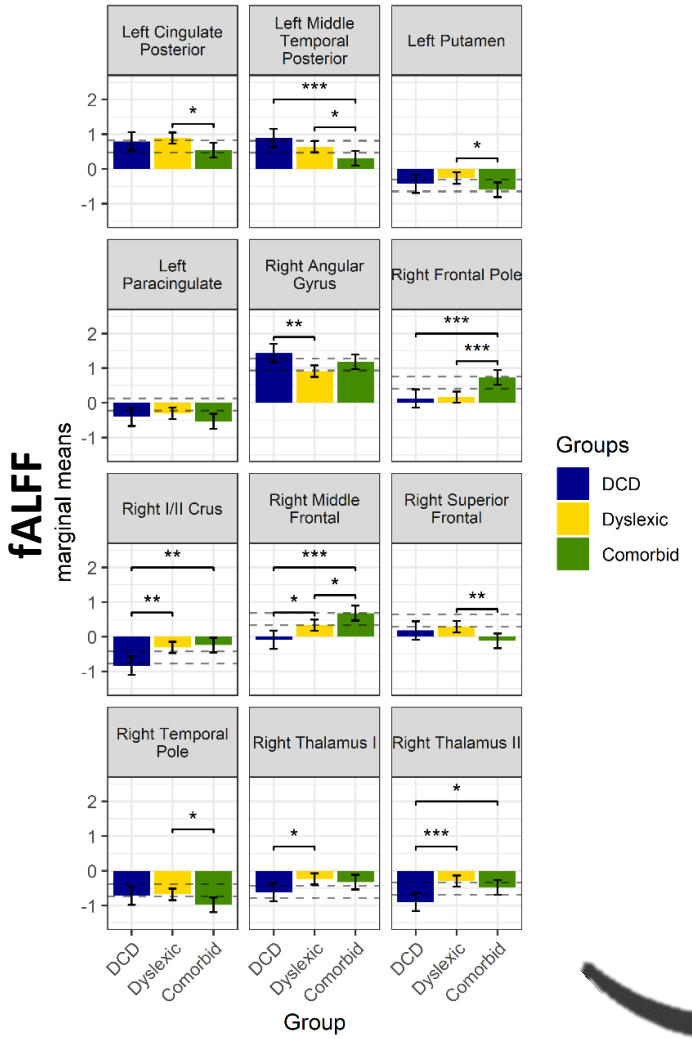
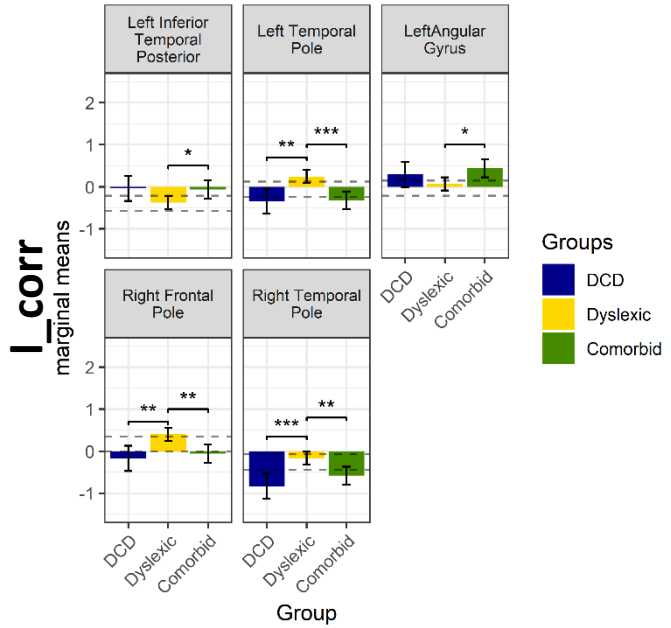
Discriminating between learning disorders by means of multimodal MRI and multivariate analyses

► **GLS**



DD are different from DCD and COM wrt connectivity

COM are different from DD and DCD wrt activity



Nemmi, Cignetti et al. *in progress*

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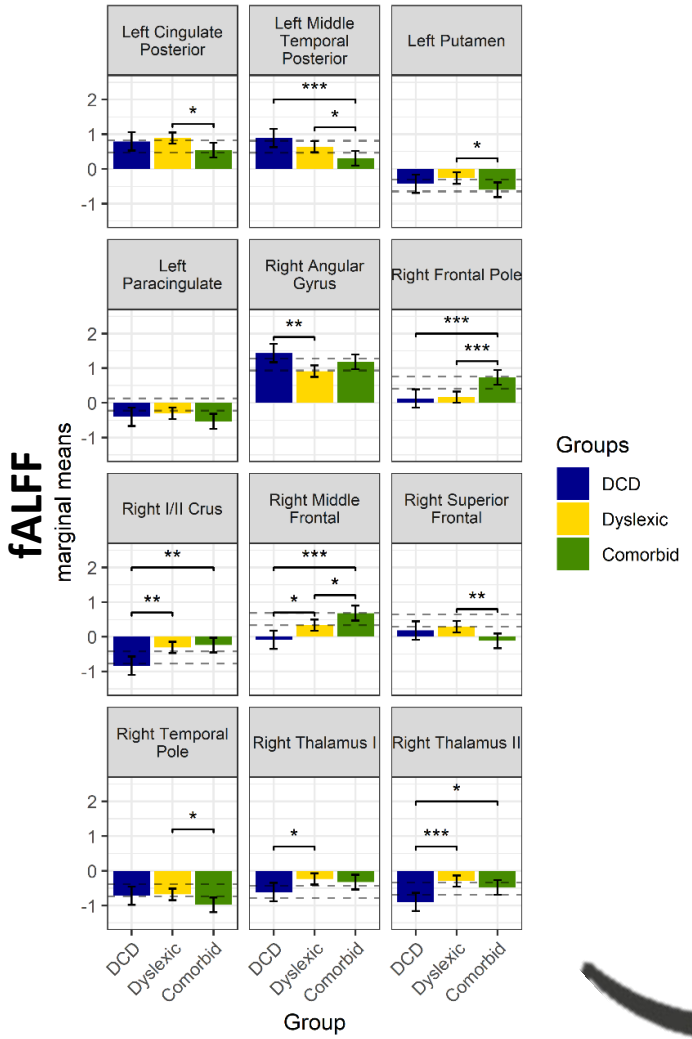
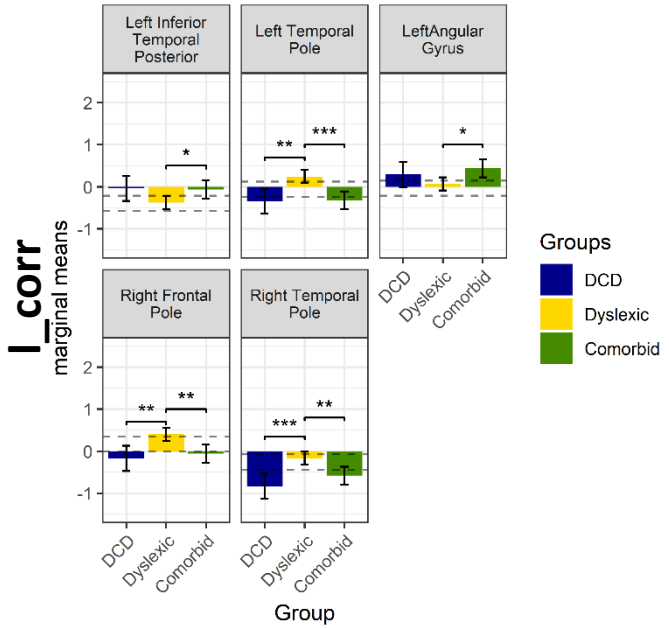
- **GLS**



DD are dif[illegible]t from DCD and [illegible]ivity

Patterns not limited to striatum and cerebellum

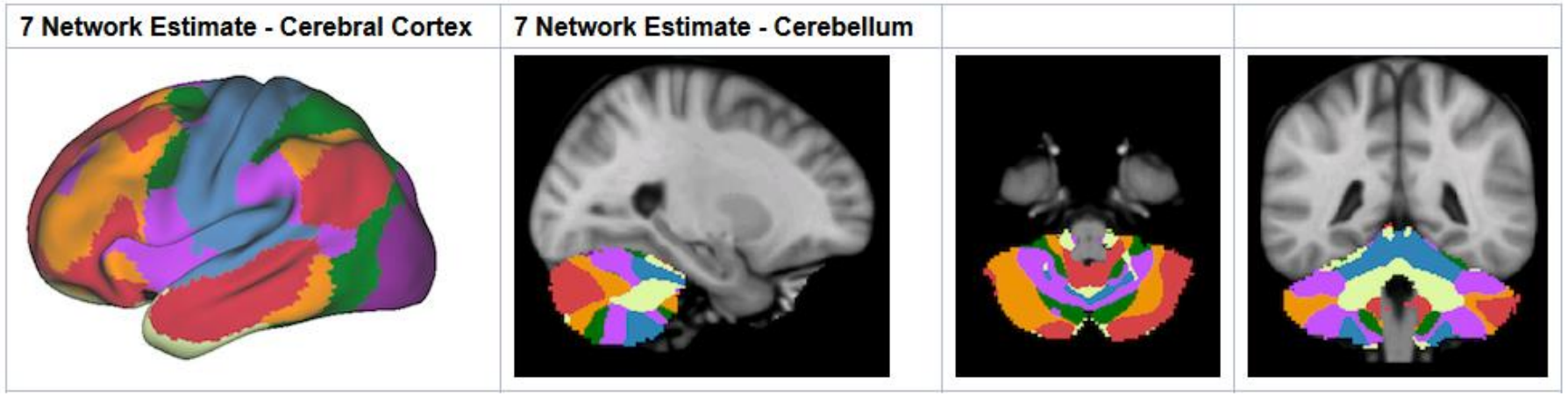
COM[illegible]rom DD and [illegible]ctivity



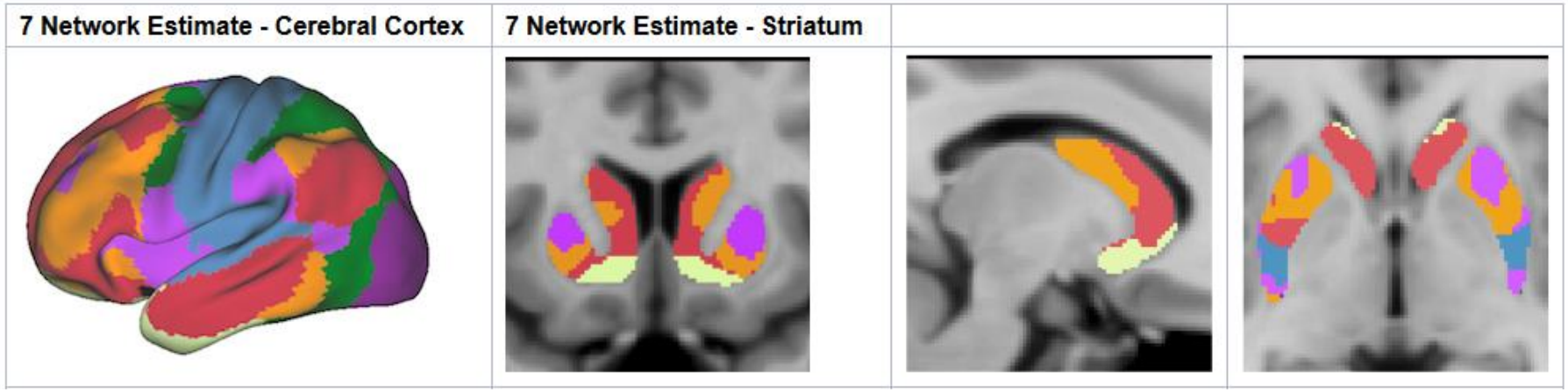
Nemmi, Cignetti et al. *in progress*

Discriminating between learning disorders through cortico-subcortical functional circuits

► Cerebellar Parcellation Estimated by Intrinsic Functional Connectivity



► Striatal Parcellation Estimated by Intrinsic Functional Connectivity



Winner-takes-all algorithm that associated each voxel in the cerebellum and striatum with a cortical network

Yeo et al. ***J Neurophysiol** 2011 ;* Buckner et al. ***J Neurophysiol** 2011 ;* Choi et al. ***J Neurophysiol** 2012*

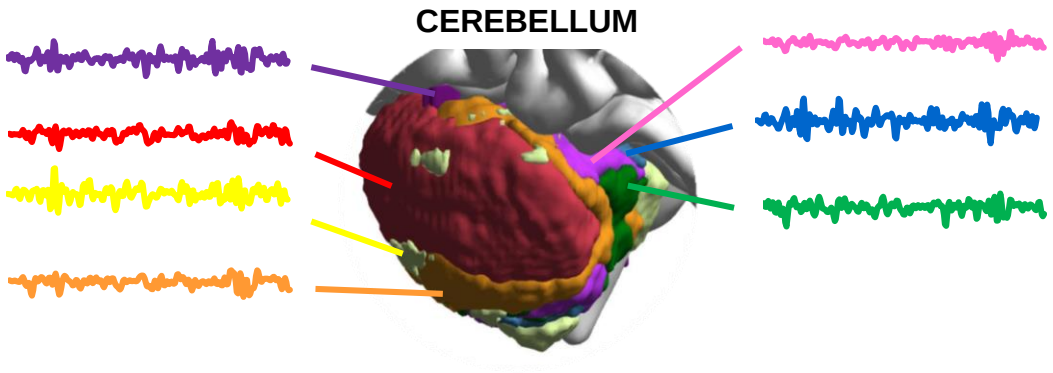
Discriminating between learning disorders through cortico-subcortical functional circuits

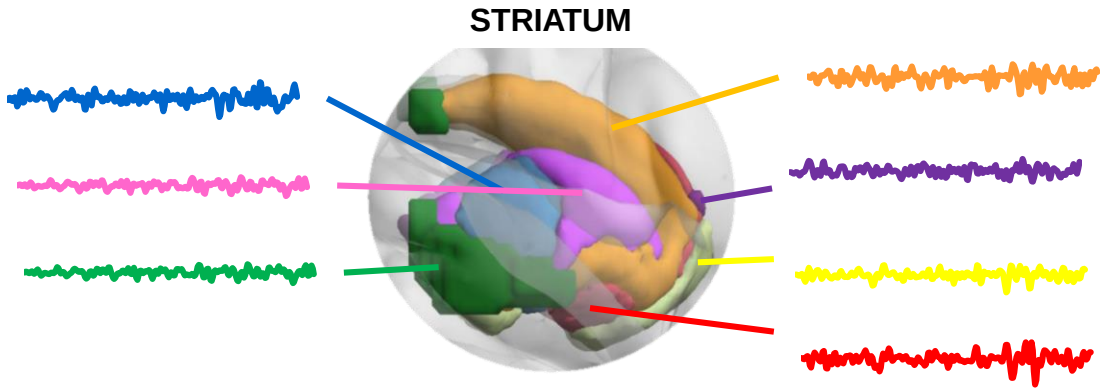
► DATA PROCESSING

▪ **Pre-processing**: 1/ realignment & unwarp, 2/ slice-timing correction, 3/ direct normalization to functional MNI space, 4/ detection of functional outliers (motion threshold > 0.9 mm ; global signal z-value threshold > 5), 5/ smoothing (8-mm kernel)

▪ **Denoising**: aCompCor (5 PCAs for WM and CSF each), confound regression (12 realignment parameters and outliers), detrending, band-pass filtering (.008-.09 Hz)

▪ **Seed-based approach**: functional connectivity (correlation) between seeds and every location in the brain



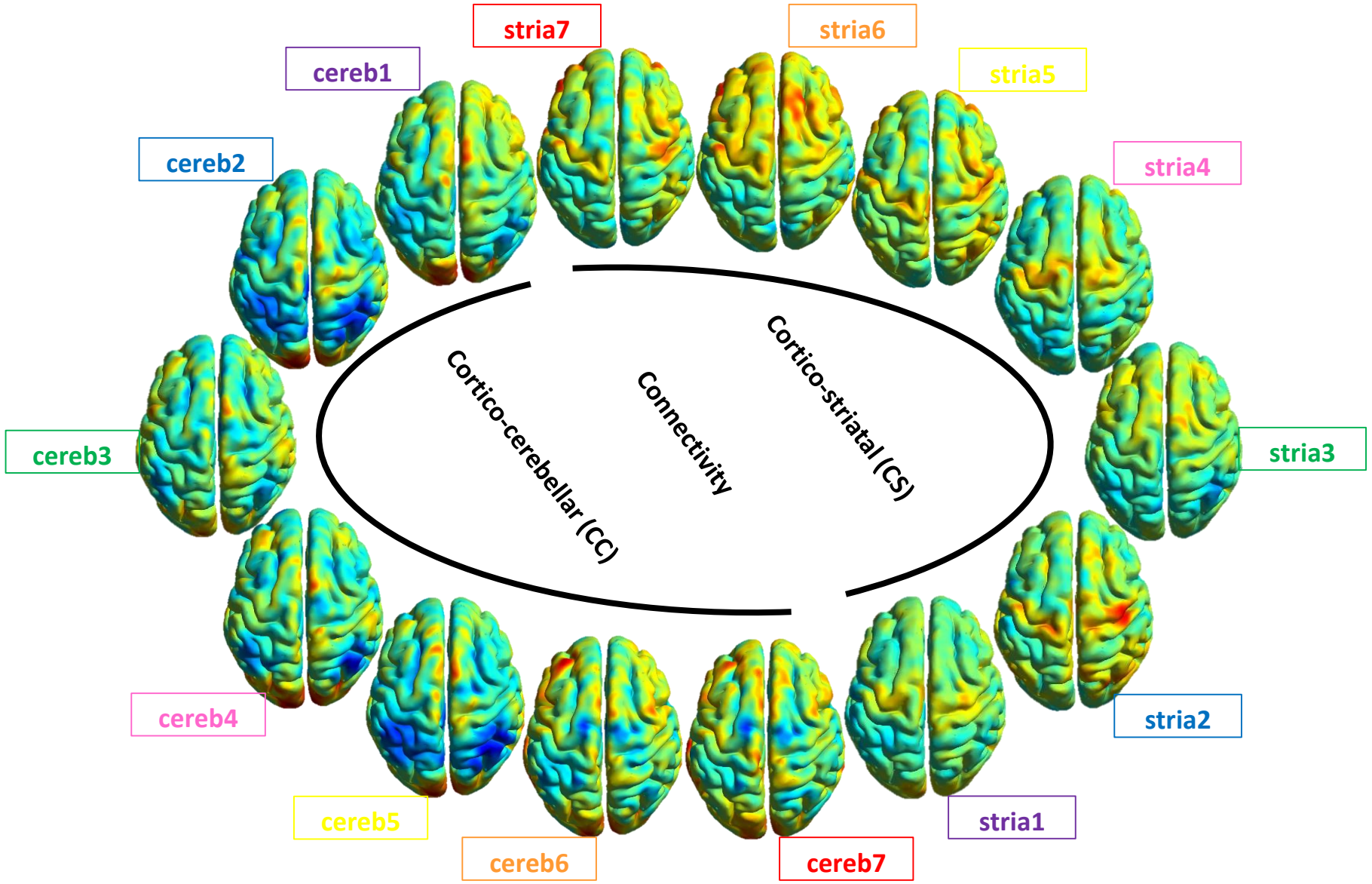


Cignetti et al. *submitted* ***eLife***

Discriminating between learning disorders through cortico-subcortical functional circuits

▶ DATA PROCESSING

14 connectivity maps per subject



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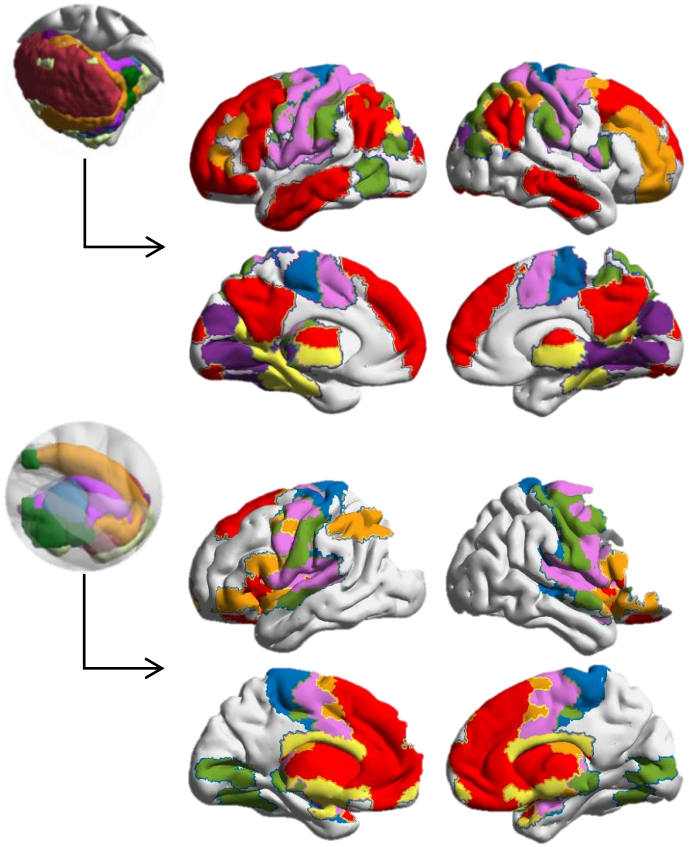
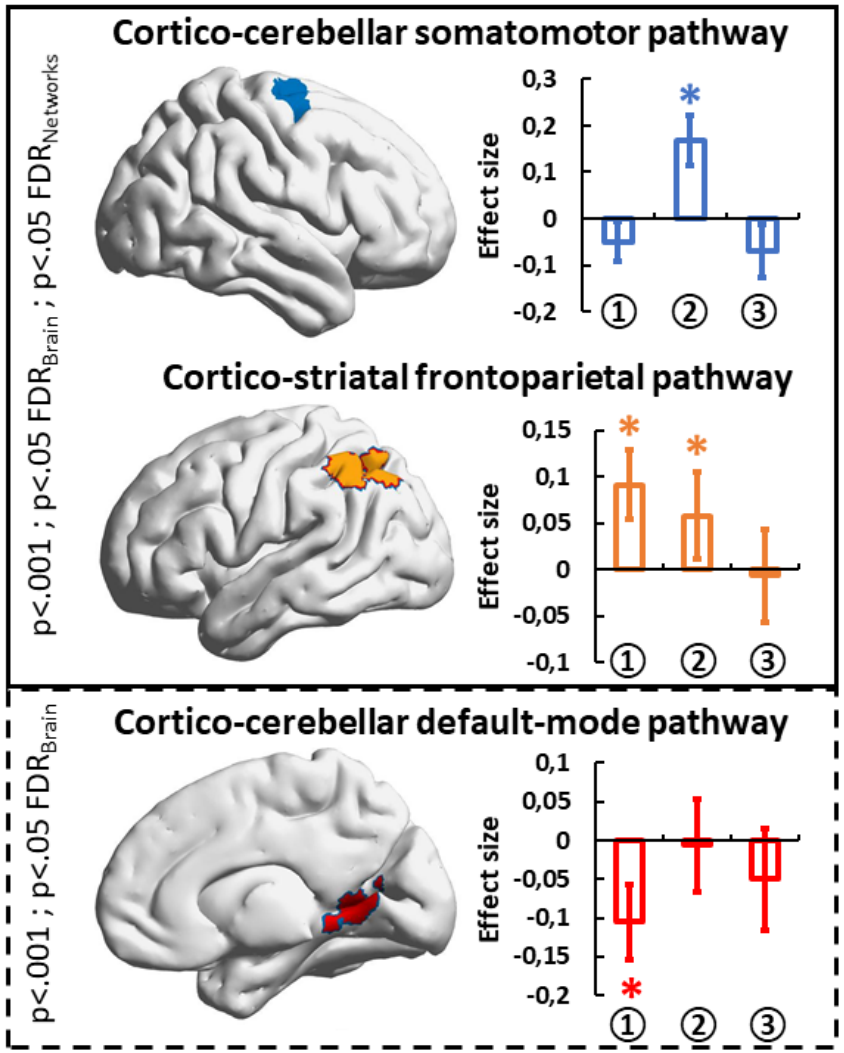
► Univariate_GLM



Better segregation of cortico-cerebellar networks than cortico-striatal networks

ANOVA F-test

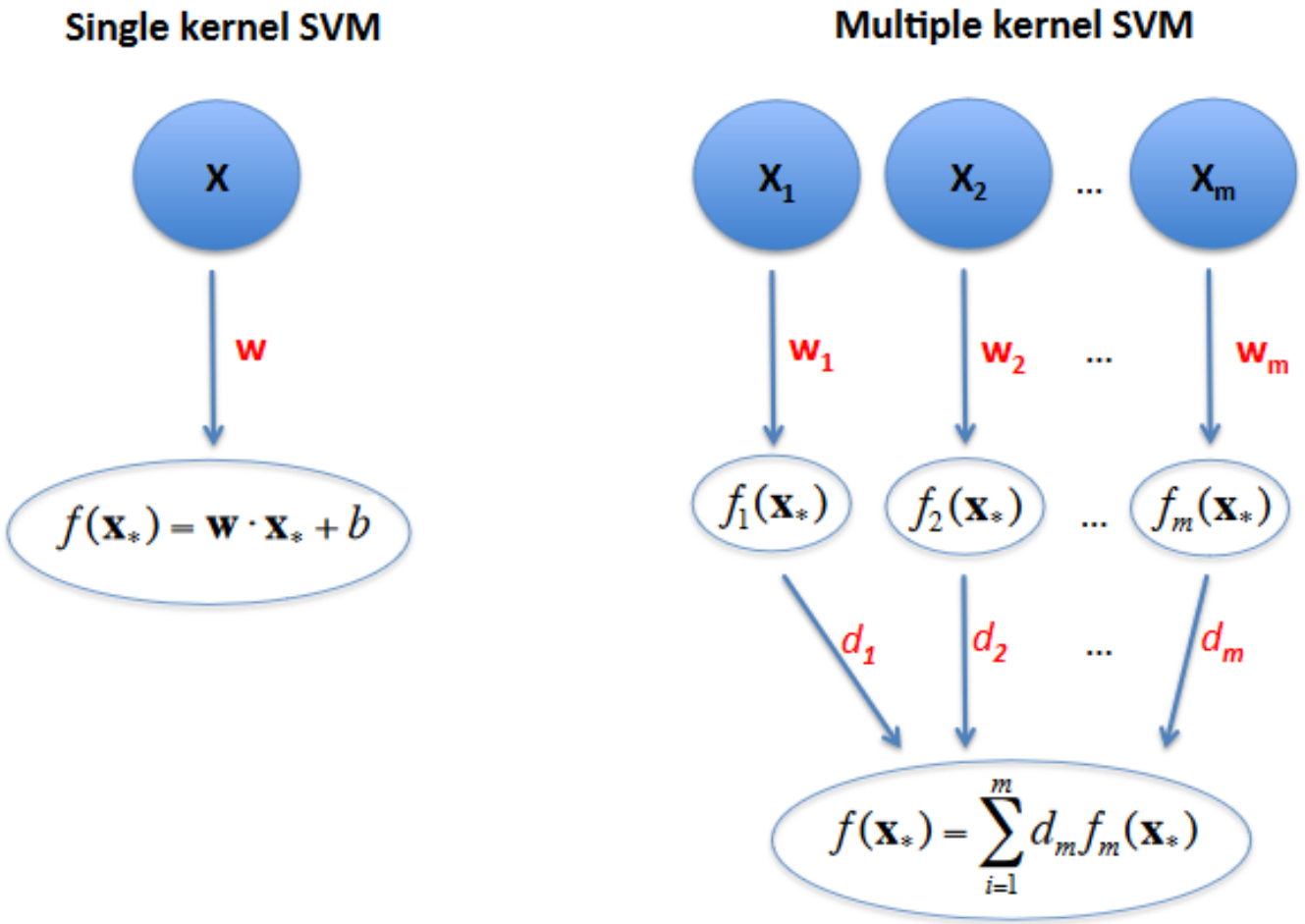
$$\begin{matrix}①\\②\\③\end{matrix}\begin{bmatrix}-1 & 1 & 0 & 0 & 0 & 0\\ 0 & -1 & 1 & 0 & 0 & 0\\ 0 & 0 & -1 & 1 & 0 & 0\end{bmatrix}\begin{bmatrix}\beta_{TYP}\\ \beta_{DD}\\ \beta_{DCD}\\ \beta_{COM}\\ \beta_{AGE}\\ \beta_{GCOR}\end{bmatrix} = 0$$



Cignetti et al. *submitted* ***eLife***

Discriminating between learning disorders through cortico-subcortical functional circuits

► **Multivariate_Multiple kernel learning (MKL)**



Includes subset of features, and enables evaluating which features have predictive information

Only some kernels have non-null contribution d_m to the final decision function (sparse solution)

Schrouff et al. ***Neuroinform*** *2013, 2018*

Discriminating between learning disorders through cortico-subcortical functional circuits

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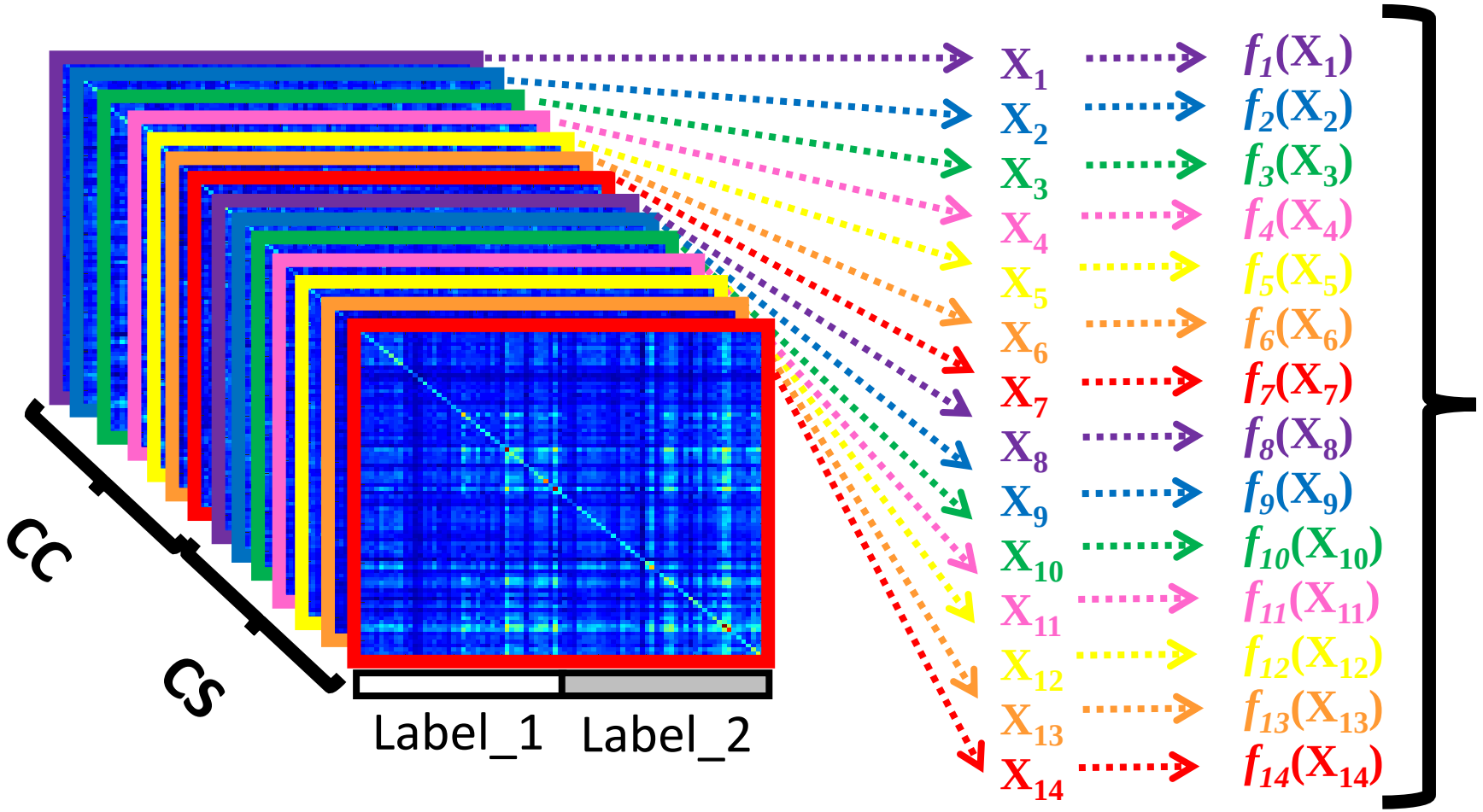


$$f(X) = \sum_{m=1}^{M=14} d_m f_m(X_m)$$

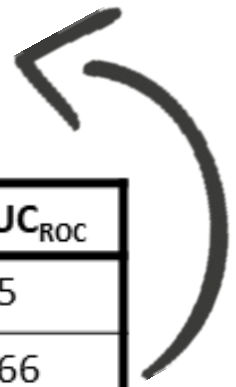
with $\sum_{m=1}^{M=14} d_m = 1, d_m \geq 0$

Cignetti et al. *submitted* ***eLife***

Discriminating between learning disorders through cortico-subcortical functional circuits

► **Multivariate_Multiple kernel learning (MKL)**

4-class problem (TYP, DD, DCD, COM) into 6 (4(4-1)/2)) binary learning problems
► class binarization one vs. one



Model MKL	Balanced Accuracy (%)	True Positives / Total Positives	True Negatives / Total Negatives	AUC_{ROC}
[TYP] vs. [DD]	46.43 (p=0.72)	19/42	20/42	0.5
[TYP] vs. [DCD]	62.50 (p = 0.12)	13/20	12/20	0.66
[TYP] vs. [COM]	68.97 (p = 0.01)	21/29	19/29	0.67
[DD] vs. [DCD]	50 (p=0.53)	11/20	9/20	0.51
[DD] vs. [COM]	51.72 (p=0.44)	14/29	14/29	0.49
[DCD] vs. [COM]	50 (p=0.54)	10/20	10/20	0.48
[TYP] vs. [DCD-COM]	64.29 (p = 0.02)	28/42	26/42	0.70
[TYP] vs. [DD-COM]	52.38 (p=0.41)	24/42	20/42	0.58

Distinction between TYP and COM that remains unchanged when mixing COM with DCD only

→ **BRAIN ABNORMALITIES AS A RESULT OF DCD PHENOTYPE**

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Discriminating between learning disorders through cortico-subcortical functional circuits

► Multivariate_Multiple kernel learning (MKL)

Model MKL [TYP] vs. [DCD-COM]			Model MKL [TYP] vs. [COM]		
ROI#	d_m contribution (%)	Expected Ranking	ROI#	d_m contribution (%)	Expected Ranking
cereb7	32.2299	13.9286	cereb7	48.5085	14
cereb4	25.2479	12.9762	cereb4	17.4247	12.2308
stria6	20.5977	12	stria6	14.9683	12.0385
cereb2	15.3609	11.0714	cereb1	8.6784	10.3846
cereb3	4.9949	9.6905	stria7	6.7463	10.2308
cereb6	1.0060	3.6905	cereb3	2.9550	5.7692
stria4	0.3156	2.3571	stria4	0.4655	1.8846
stria7	0.1627	1.6190	cereb2	0.2533	0.7308
stria5	0.0844	0.4048	cereb5	0	0
cereb1	0	0	cereb6	0	0
cereb5	0	0	stria1	0	0
stria1	0	0	stria2	0	0
stria2	0	0	stria3	0	0
stria3	0	0	stria5	0	0

Kernels that contributed the most to the decision function included default-mode and sensorimotor cortico-cerebellar and frontoparietal cortico-striatal iFC maps

Cignetti et al. *submitted* ***eLife***

Discriminating between learning disorders through cortico-subcortical functional circuits

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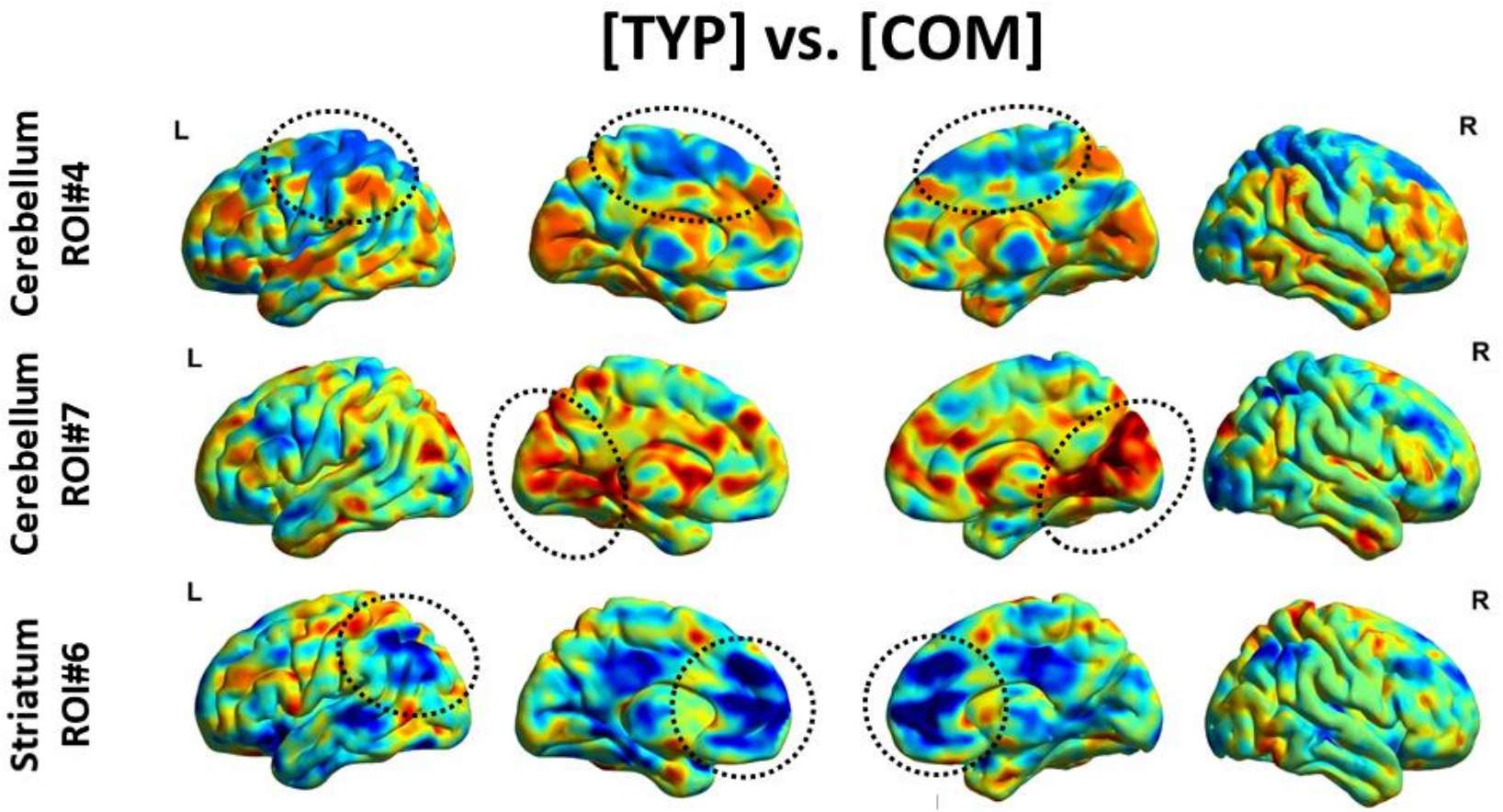

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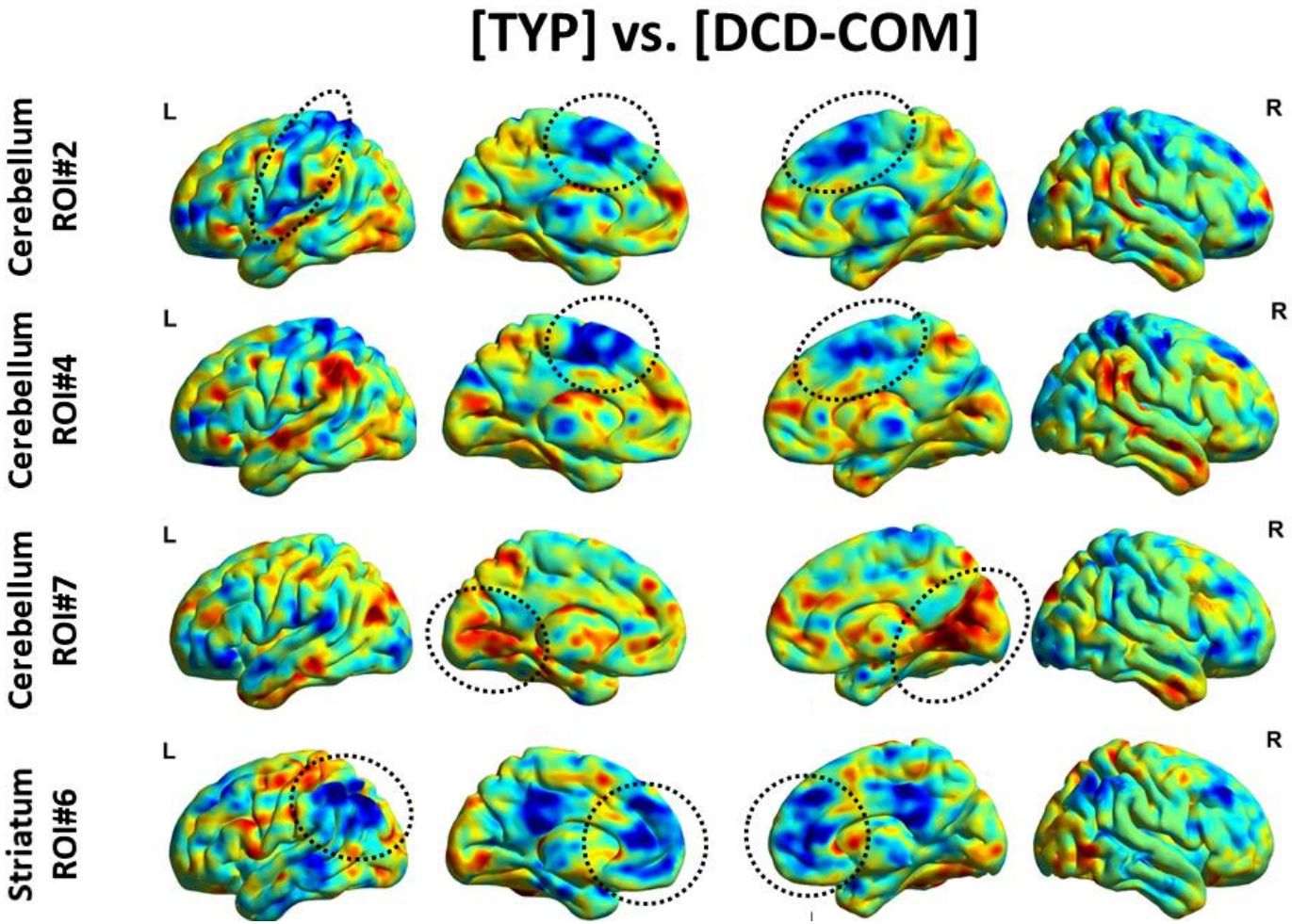
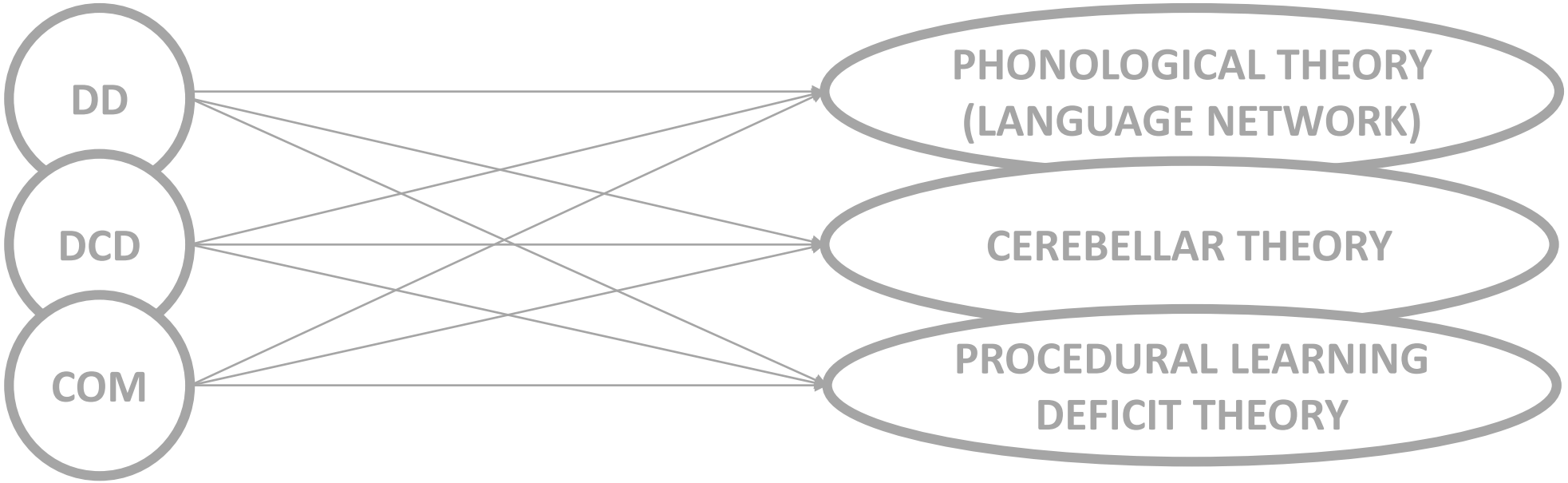


Kernels that contributed the most to the decision function included default-mode and sensorimotor cortico-cerebellar and frontoparietal cortico-striatal iFC maps

Cignetti et al. *submitted* ***eLife***

To sum up …

- Abnormalities in function but not in structure in DD and/or DCD learning disorders
  - Complex pattern of altered activity/connectivity including temporal, parietal, frontal, cerebellar and striatal regions



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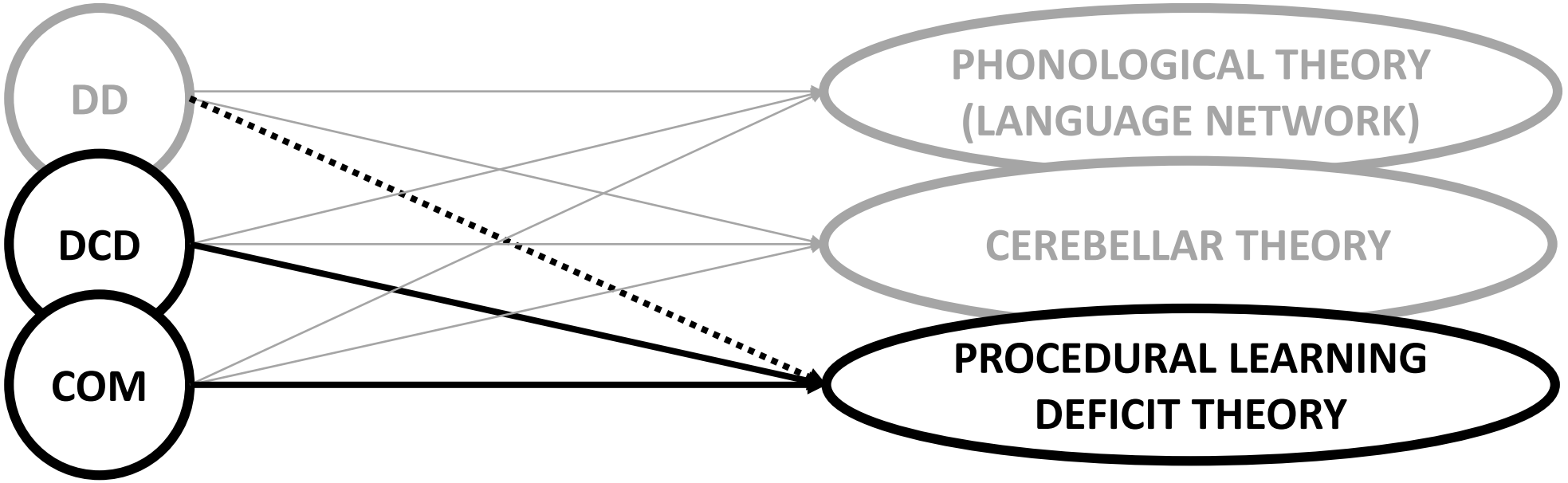
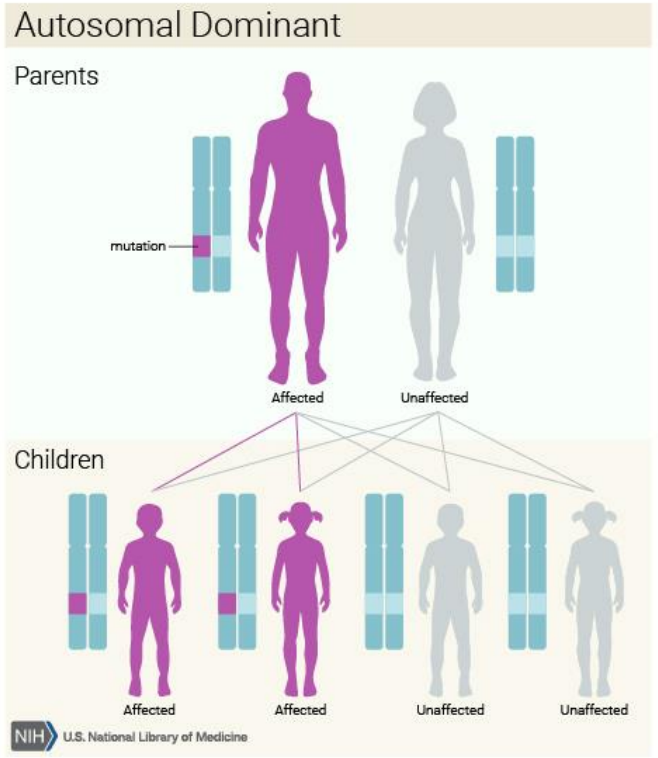


  - A subset of functional cortico-striatal (frontoparietal) and cortico-cerebellar (somatomotor, default-mode) circuits impaired mainly in DCD

Discriminating between NF1 and TYP children by means of multimodal MRI and multivariate analyses

Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic disorder. It is one of the most common genetic disorder, with a prevalence of 1 in 3500



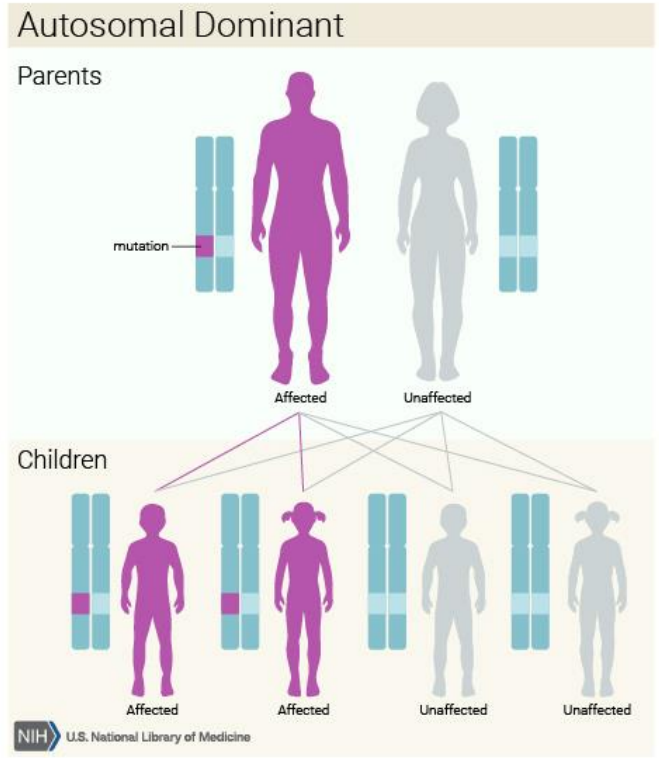
Nemmi, Cignetti et al. *Hum Brain Mapp 2018*

Discriminating between NF1 and TYP children by means of multimodal MRI and multivariate analyses

Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic disorder. It is one of the most common genetic disorder, with a prevalence of 1 in 3500

due to the mutation of a gene (neurofibromin 1) on chromosome 17

dysregulates the production of the protein neurofibromin, which is a tumor suppressor (prevent cells from growing and dividing too rapidly or in an uncontrolled way)



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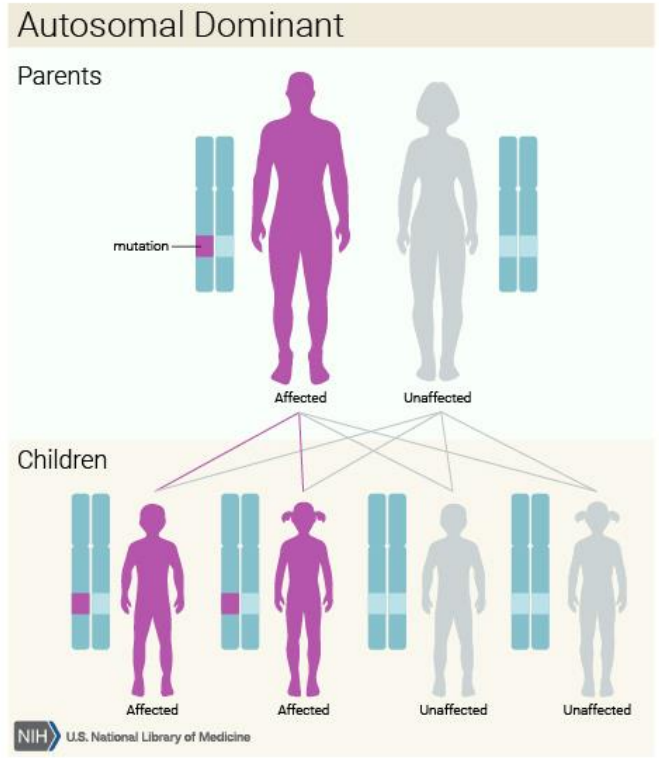
due to the mutation of a gene (neurofibromin 1) on chromosome 17

dysregulates the production of the protein neurofibromin, which is implicated in synaptic plasticity and thus memory and learning



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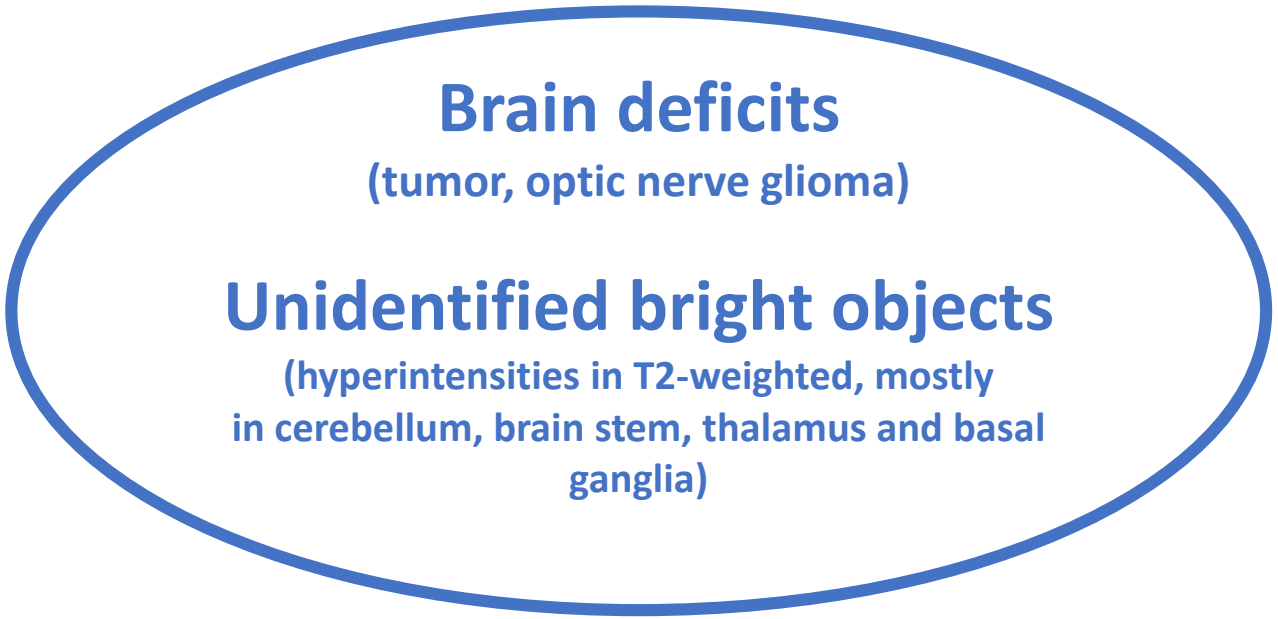

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Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic disorder. It is one of the most common genetic disorder, with a prevalence of 1 in 3500

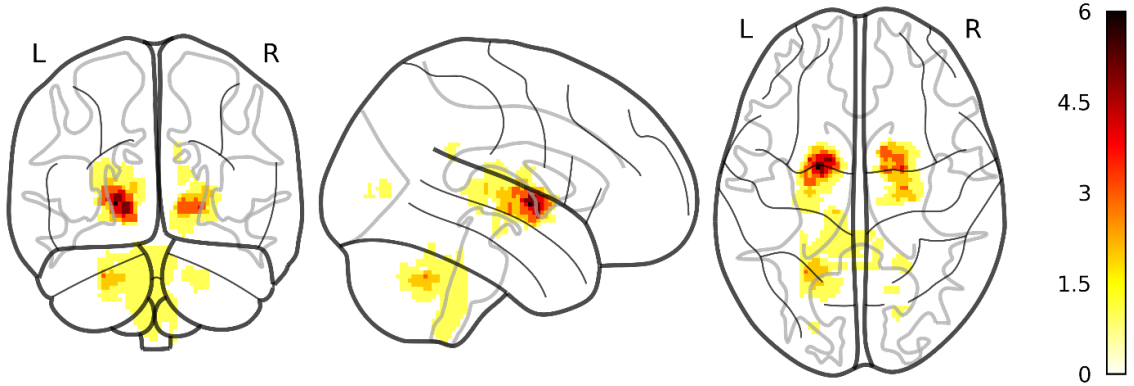
Brain deficits

(tumor, optic nerve glioma)

Unidentified bright objects

(hyperintensities in T2-weighted, mostly in cerebellum, brain stem, thalamus and basal ganglia)

18 out of 38 NF1 children included in the study



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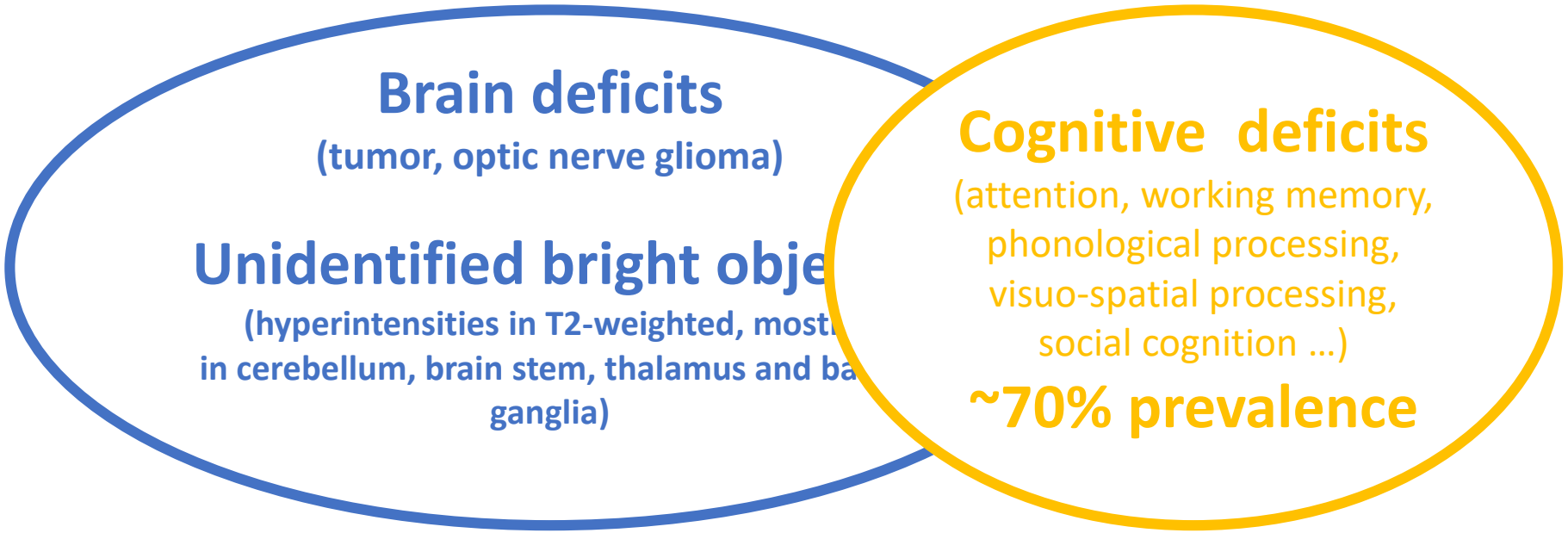

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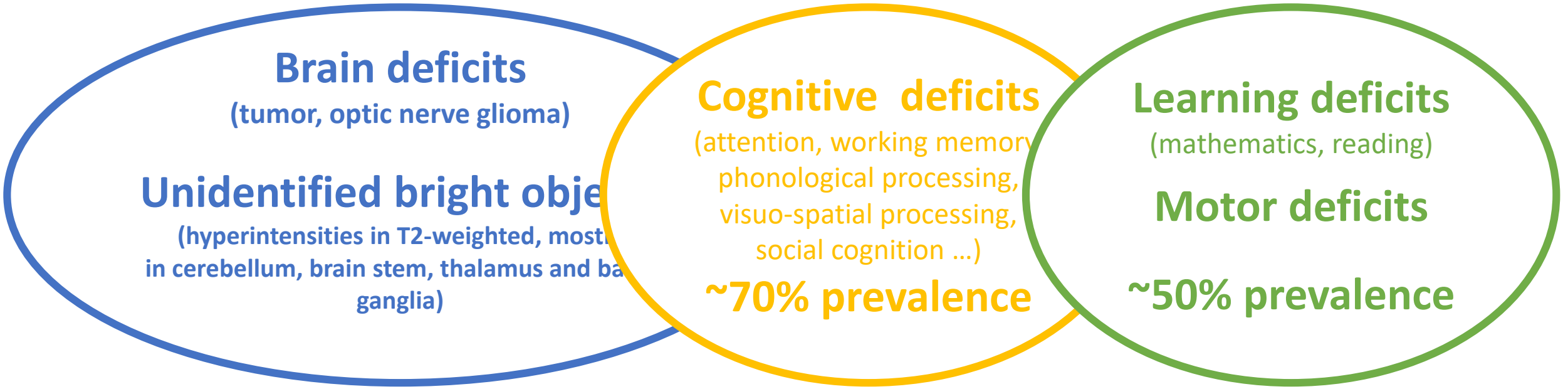

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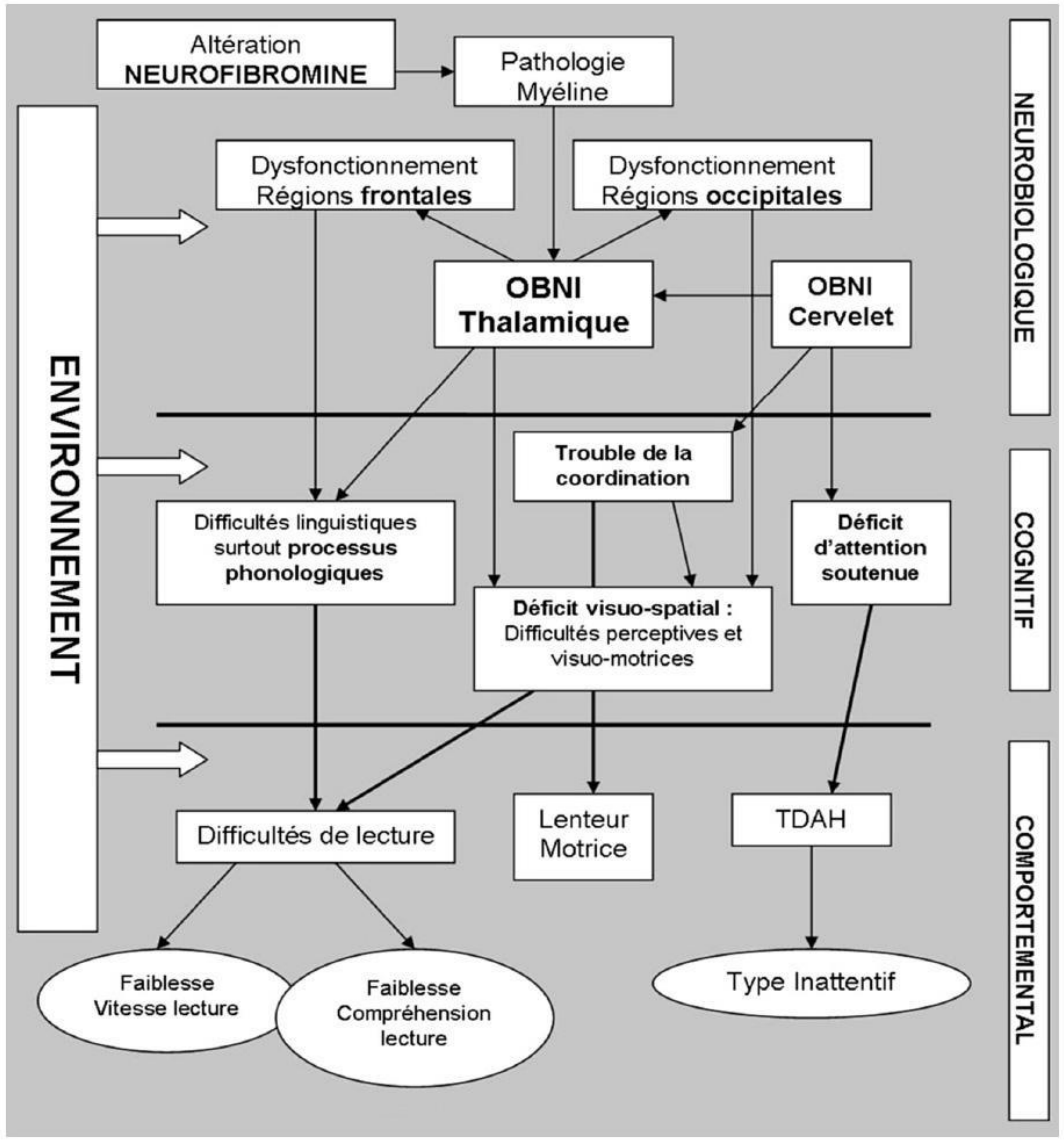
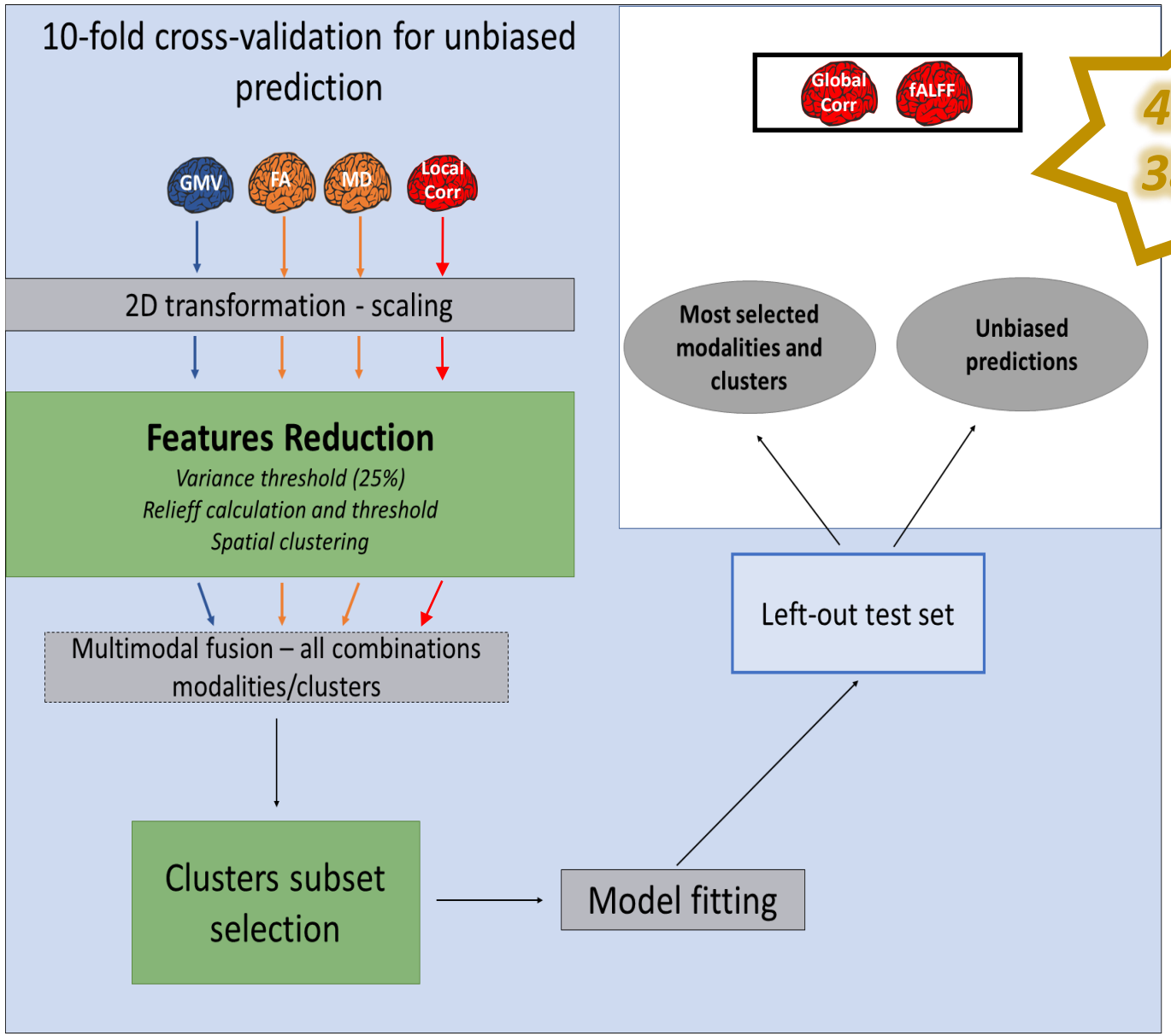


Hypothetical links between the different levels of description

Hachon et al. *Brain Dev 2011*

Discriminating between NF1 and TYP children by means of multimodal MRI and multivariate analyses



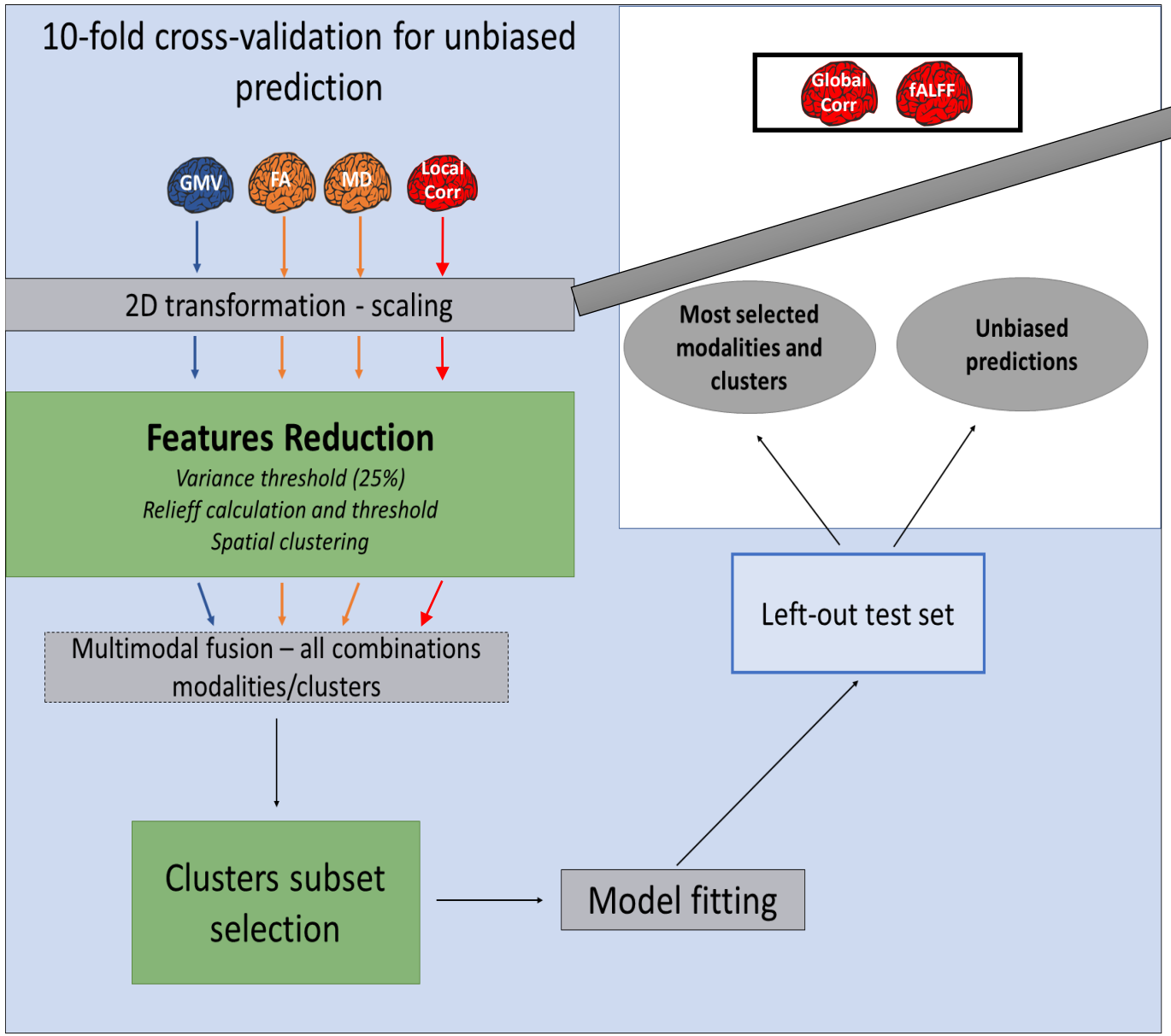
42 TYP
38 NF1

GitHub

https://github.com/fnemmi-tonic/multimodal_MRI_pipeline_classification

Nemmi, Cignetti et al. *Hum Brain Mapp 2018*

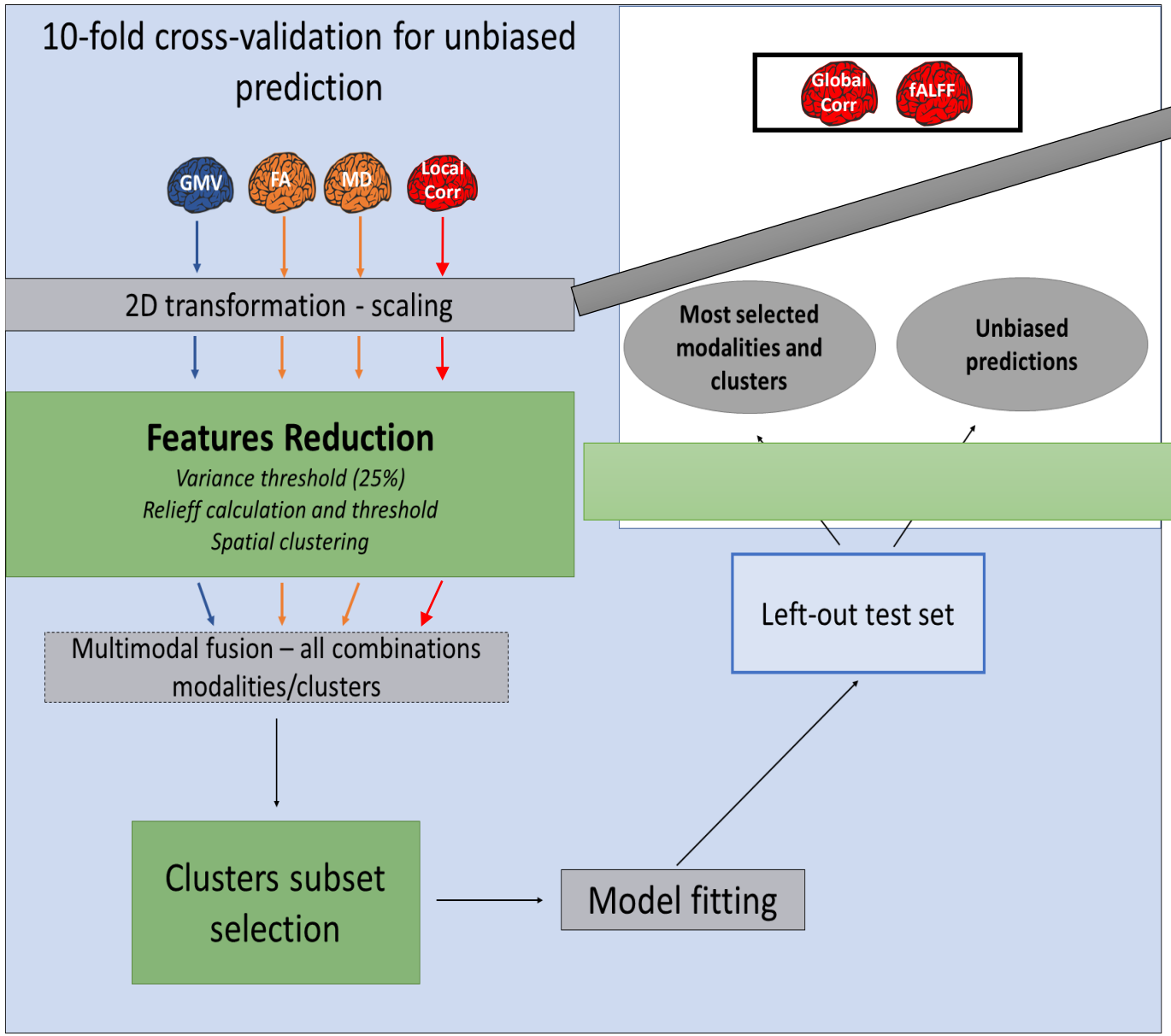
Discriminating between NF1 and TYP children by means of multimodal MRI and multivariate analyses



2D matrix with subjects × voxels dimensions

Nemmi, Cignetti et al. *Hum Brain Mapp 2018*

Discriminating between NF1 and TYP children by means of multimodal MRI and multivariate analyses



2D matrix with subjects × voxels dimensions

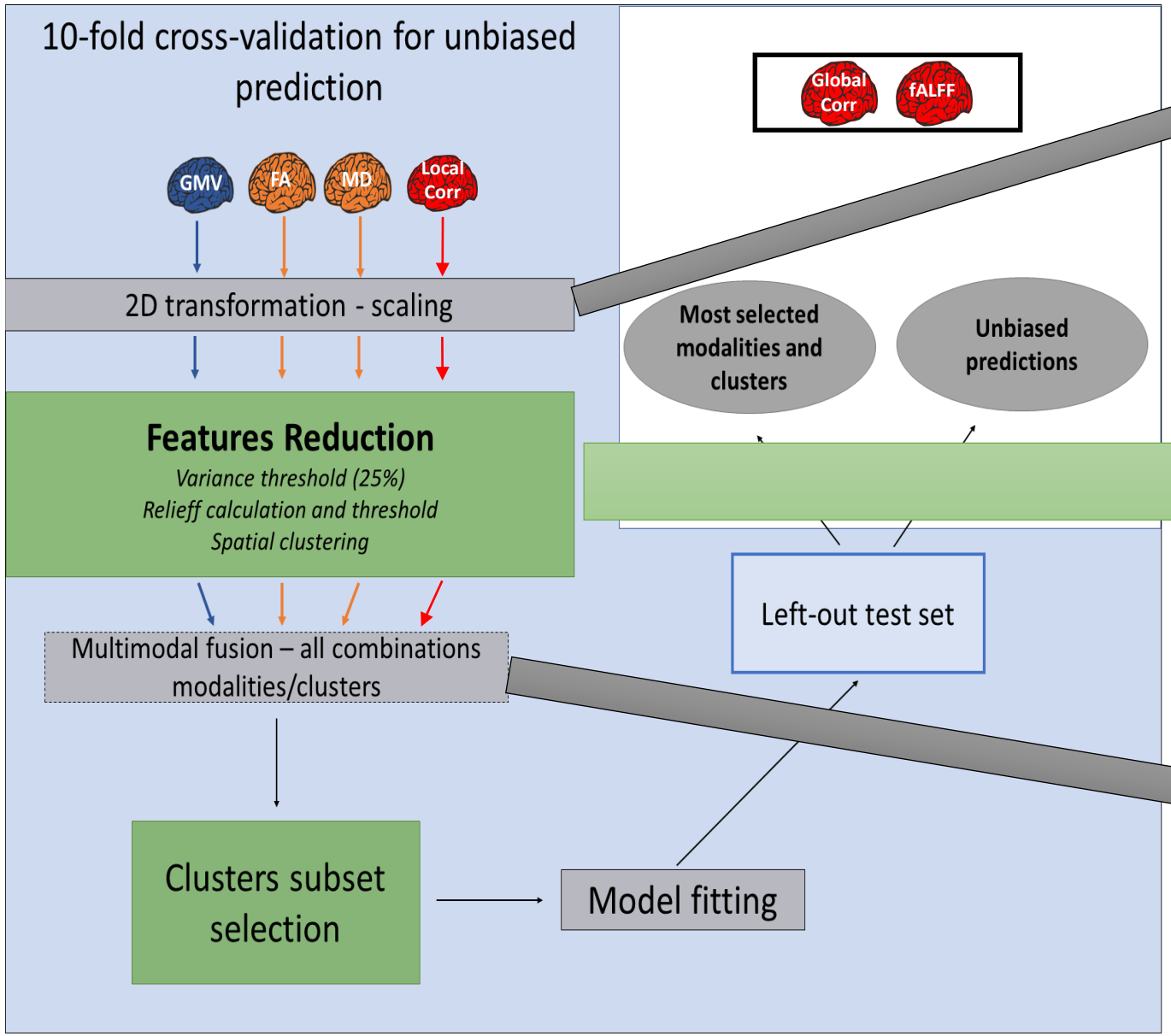
Variance thresholding: Elimination of the 25% of features with the lowest variance between subjects

Relieff: Select the most relevant features calculating the distance of the intra and interclass cases in feature space (elimination if distance intraclass ≈ distance interclass)

Spatial clustering: contiguous voxels were assigned the same cluster

Nemmi, Cignetti et al. *Hum Brain Mapp 2018*

Discriminating between NF1 and TYP children by means of multimodal MRI and multivariate analyses



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Merging of modalities

Nemmi, Cignetti et al. *Hum Brain Mapp 2018*

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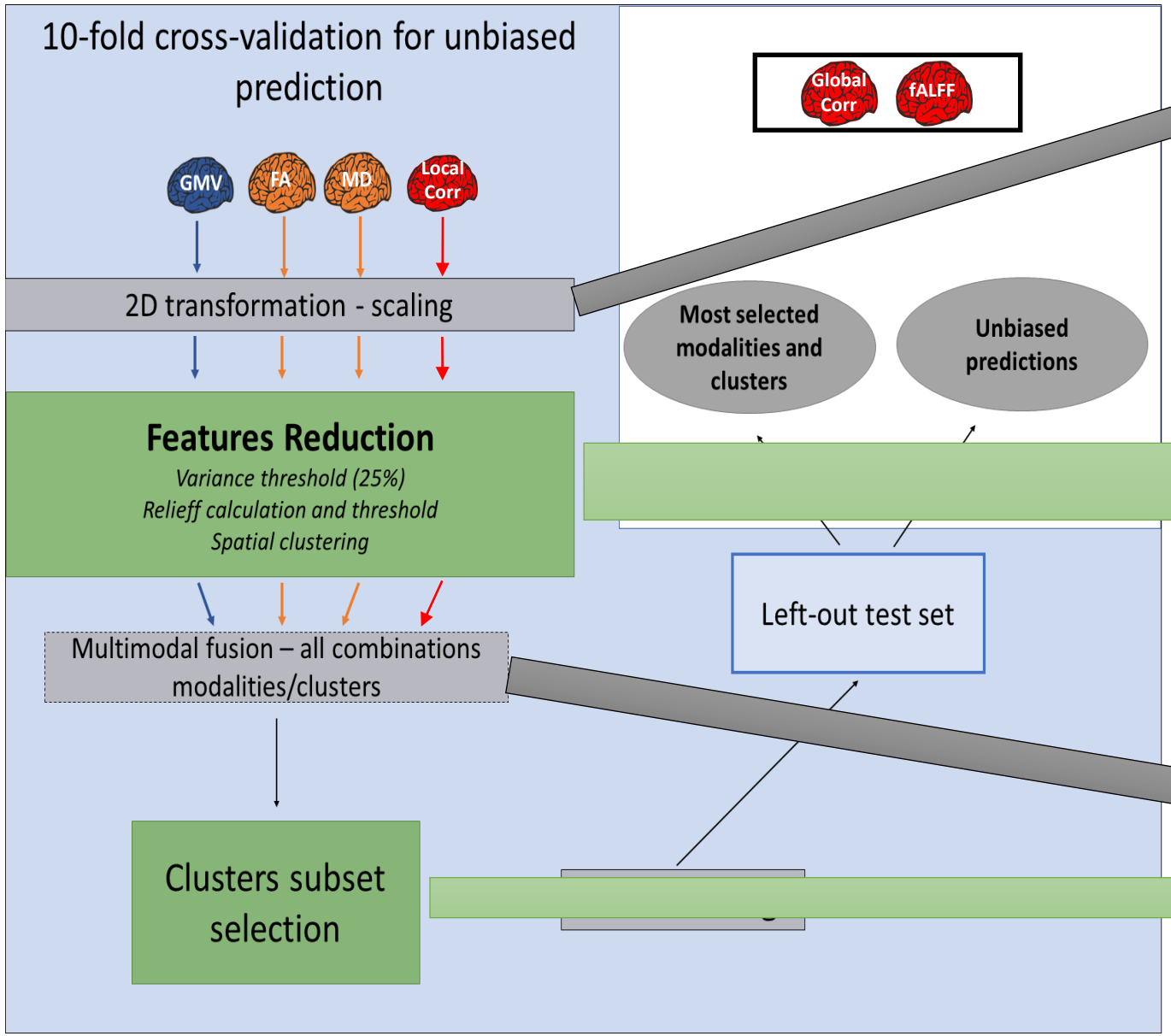

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Merging of modalities

Subset selection based on correlation

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Discriminating between NF1 and TYP children by means of multimodal MRI and multivariate analyses

55 (±2) subjects out of 80

Acc. = 0.69
95%CI [0.66–0.70]

Spec. = 0.78
95%CI [0.72–0.80]

Sens. = 0.61
95%CI [0.57–0.65]

p values = .0001–.05, median = 0.01

65 (±2) subjects out of 80

Acc. = 0.82
95%CI [0.80–0.84]

Spec. = 0.88
95%CI [0.86–0.90]

Sens. = 0.75
95%CI [0.73–0.77]

p values = .00001–.00001, median = 0.00001

69 (±1) subjects out of 80

Acc. = 0.86
95%CI [0.85–0.87]

Spec. = 0.89
95%CI [0.87–0.90]

Sens. = 0.83
95%CI [0.80–0.86]

p values = .00001–.00001, median = .00001

52 (±3) subjects out of 80

Acc. = 0.64
95%CI [0.62–0.67]

Spec. = 0.68
95%CI [0.64–0.72]

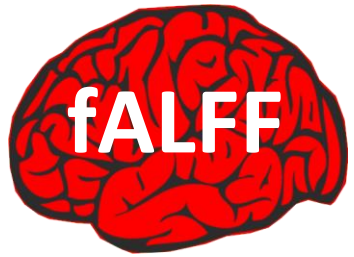
Sens. = 0.61
95%CI [0.55–0.65]

p values = .001–.2, median = 0.03

50 (±4) subjects out of 80

Acc. = 0.63
95%CI [0.59–0.65]

p values = .01–.3, median = 0.1



45 (±2) subjects out of 80

Acc. = 0.56
95%CI [0.54–0.58]

p values = .05–.7, median = 0.3

Nemmi, Cignetti et al. *Hum Brain Mapp 2018*

Discriminating between NF1 and TYP children by means of multimodal MRI and multivariate analyses

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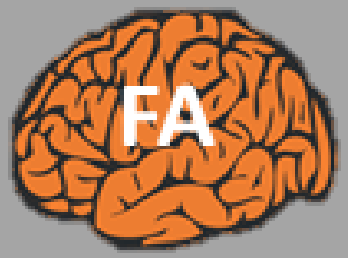

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Sens. = 0.83
95%CI [0.80–0.86]

p values = .00001–.00001, median = .00001

STRUCTURAL MODEL

68 (±2) subjects out of 80

Acc. = 0.84
95%CI [0.82–0.86]

Spec. = 0.87
95%CI [0.85–0.89]

Sens. = 0.82
95%CI [0.77–0.86]

p values = .00001–.0001, median = 0.00001

Nemmi, Cignetti et al. *Hum Brain Mapp 2018*

Discriminating between NF1 and TYP children by means of multimodal MRI and multivariate analyses

55 (±2) subjects out of 80

Acc. = 0.69
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Sens. = 0.61
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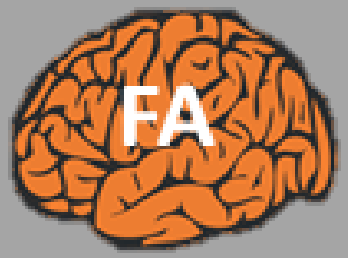

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p values = .00001–.00001, median = .00001

52 (±3) subjects out of 80

Acc. = 0.64
95%CI [0.62–0.67]

Spec. = 0.68
95%CI [0.64–0.72]

Sens. = 0.61
95%CI [0.55–0.65]

p values = .001–.2, median = 0.03

COMPLETE MODEL

65 (±3) subjects out of 80

Acc. = 0.81
95%CI [0.79–0.84]

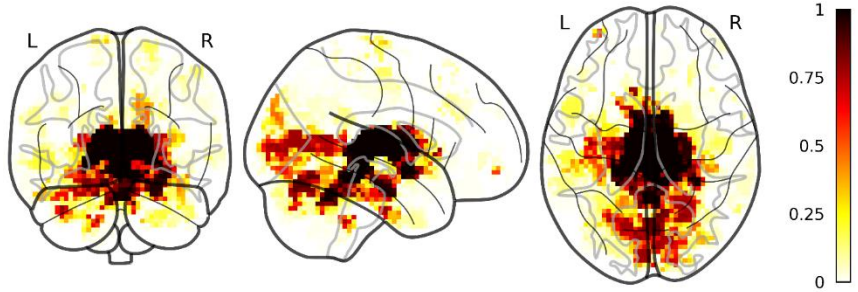
Spec. = 0.85
95%CI [0.81–0.88]

Sens. = 0.77
95%CI [0.75–0.80]

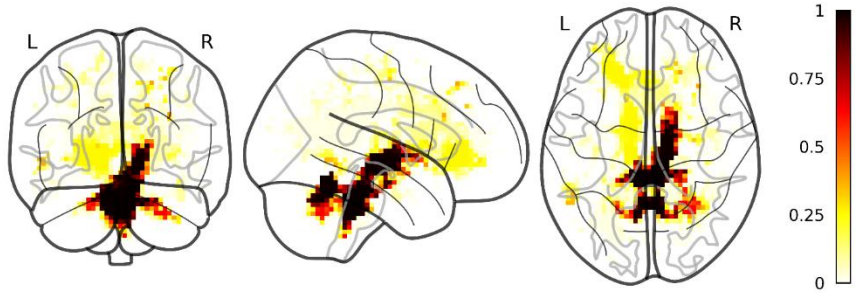
p values .00001–.00001, median = 0.00001

Nemmi, Cignetti et al. *Hum Brain Mapp 2018*

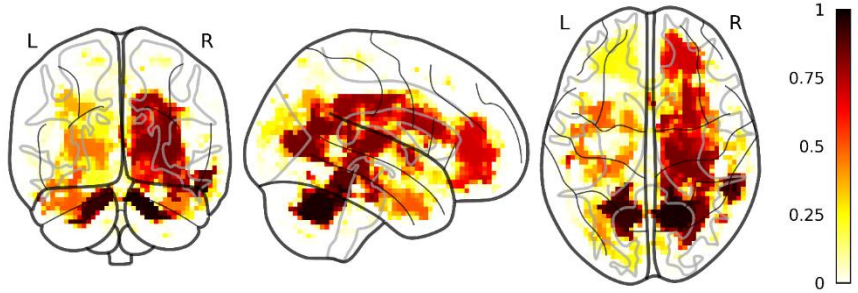
Discriminating between NF1 and TYP children by means of multimodal MRI and multivariate analyses



Abnormalities (higher or lower GMV) in the subcortical nuclei and the medial occipital lobe



Abnormalities (lower FA) in the cerebellum and brainstem



Abnormalities (higher MD) predominantly in the right hemisphere, extending both in the white and the gray matter

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Discriminating between NF1 and TYP children by means of multimodal MRI and multivariate analyses

- The MRI signature of NF1 brain pathology is a combination of gray and white matter abnormalities

  ↘ Diffuse microstructural abnormalities, possibly related to variations in the barriers that restrict the motion of water, such as cell membranes

  ↘ Neural substrates of motor and learning deficits different in NF1 (structure) and learning disorders (function) ; NF1 cannot serve as a 'genetic model' of learning disorders

Nemmi, Cignetti et al. *Hum Brain Mapp 2018*

Teams/People

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Nadine GIRARD, MD/Ph.D

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