Brain atrophy: towards clinical application

Marco Battaglini

UNIVERSITÀ DI SIENA 1240

Department of Medicine, Surgery and Neuroscience

University of Siena, Italy

Disclosure

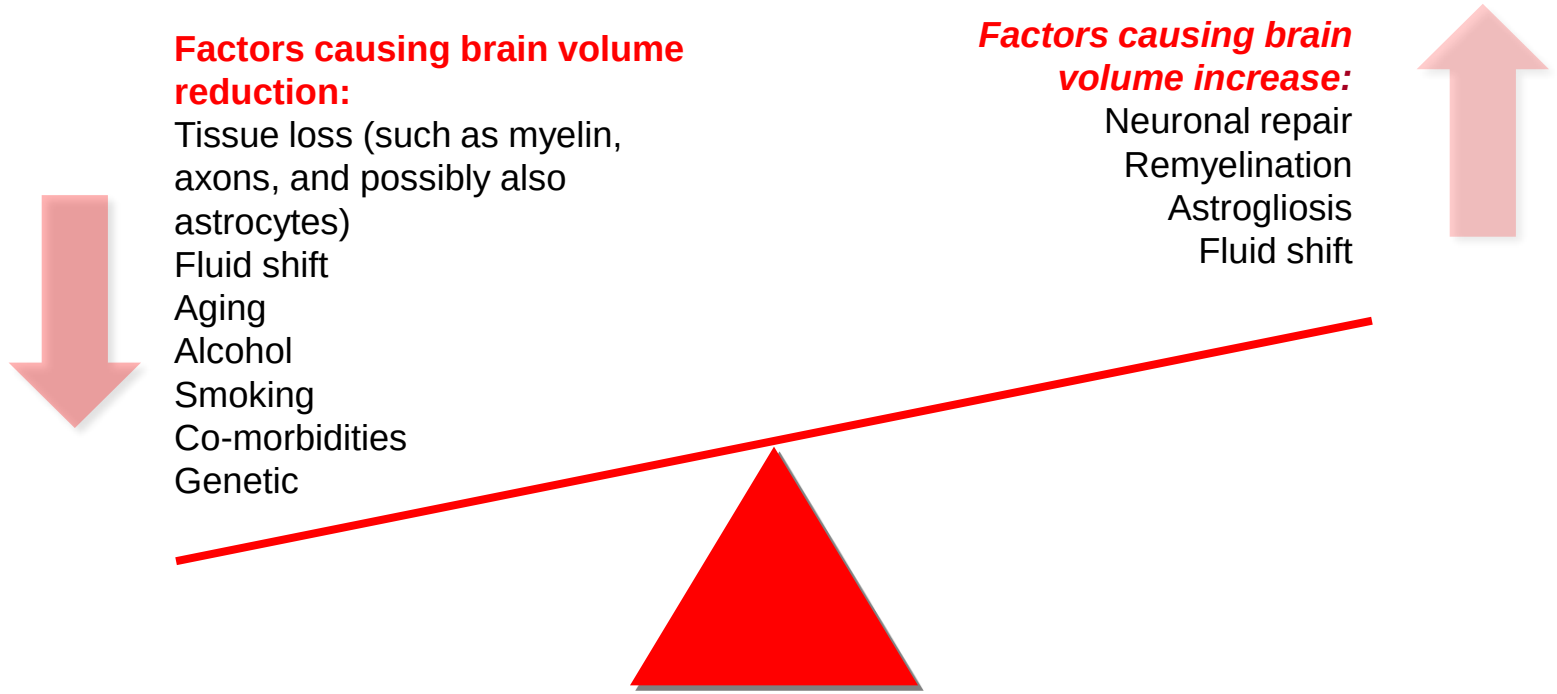
CEO of Siena Imaging

Atrophy: a definition

Atrophy (from Ancient Greek ἀτροφία *atrophia*, "a wasting away", from ἀ- *a-*, "not" and τροφή *trophē*, "food") is the partial or complete wasting away of a part of the body. Causes of atrophy include mutations (which can destroy the gene to build up the organ), poor nourishment, poor circulation, loss of hormonal support, loss of nerve supply to the target organ, excessive amount of apoptosis of cells, and disuse or lack of exercise or disease intrinsic to the tissue itself.

Cerebral Atrophy depends on an excessive amount of apoptosis of cells?

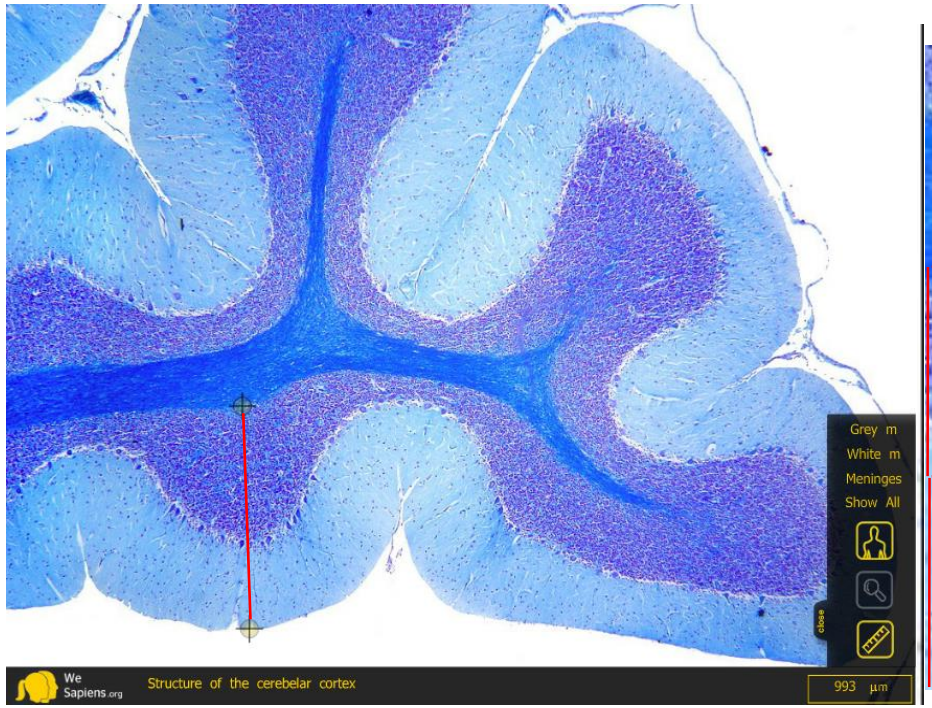
Biological confounding factors

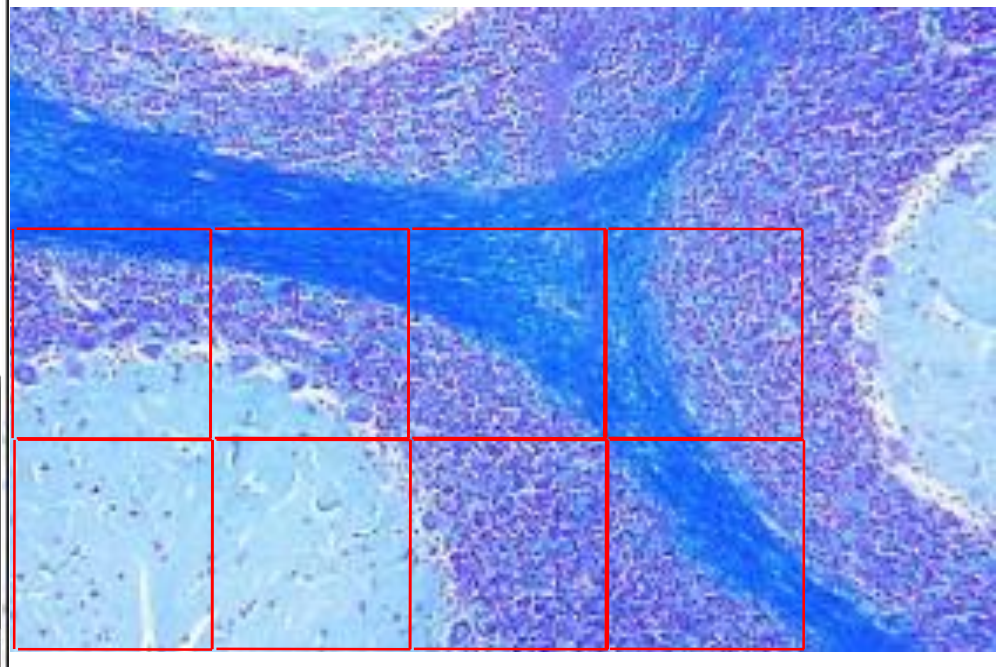


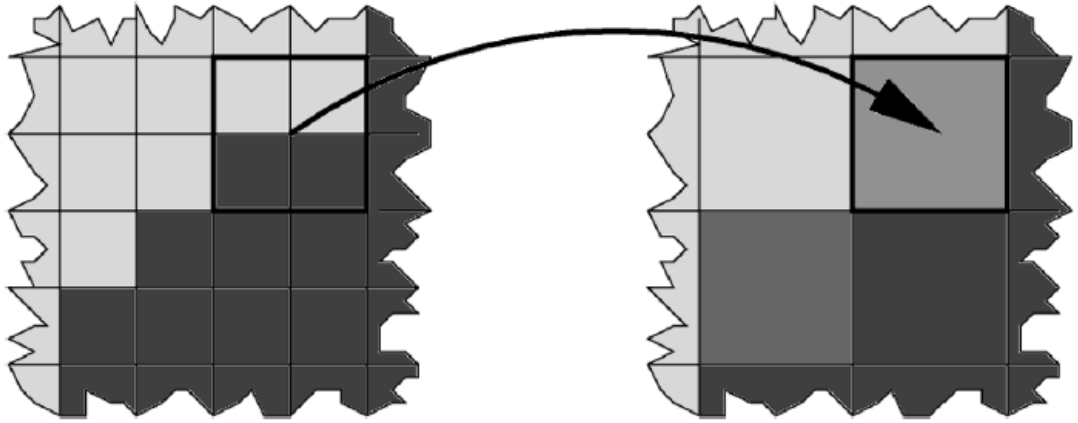
Issues with Data Interpretation

Cerebral Atrophy depends on an excessive amount of apoptosis of cells?

Technical confounding factors







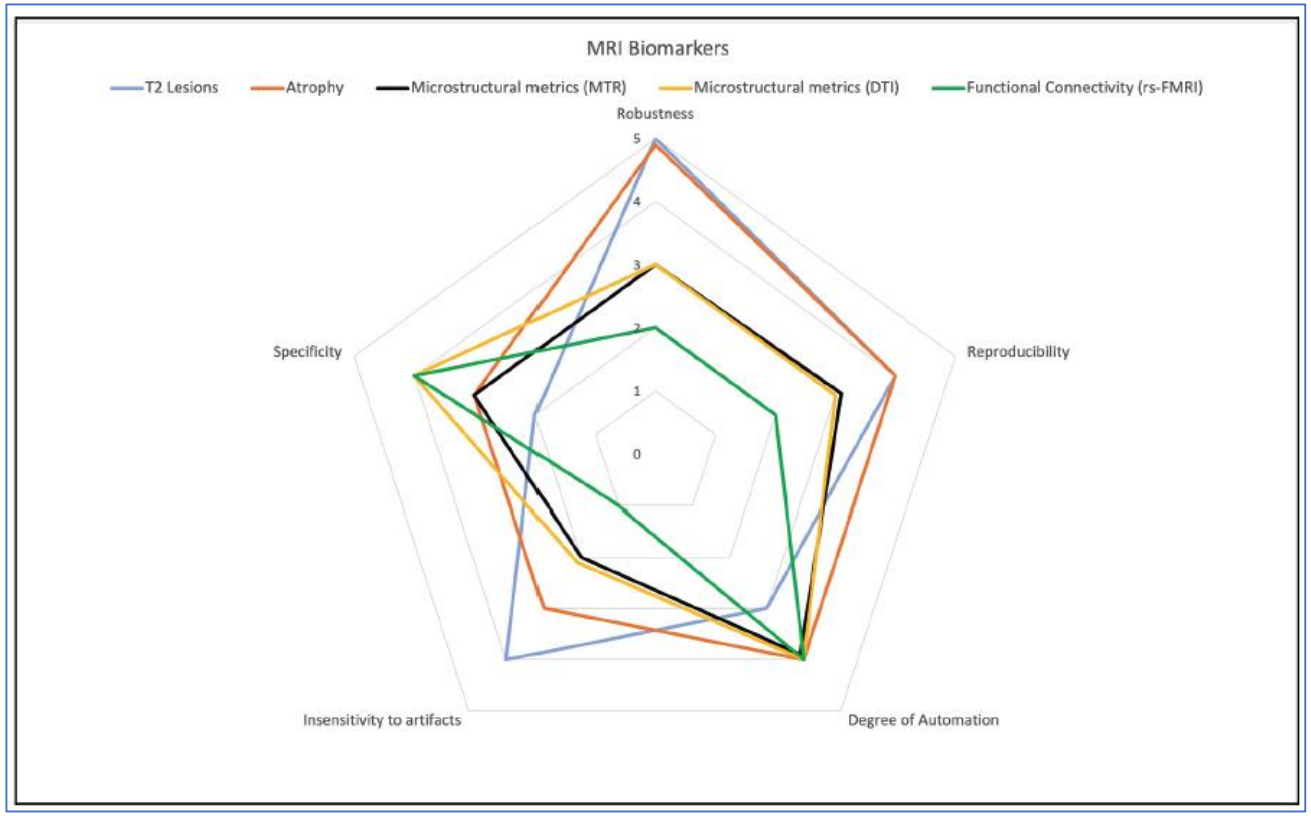
Technical confounding factors

	Cross-sectional			Longitudinal		
	GM	WM	Brain	GM	WM	Brain
FS	679 cm^3	662 cm^3	1341 cm^3	-0.21%	+0.33%	+0.26%
SPM	840 cm^3	609 cm^3	1449 cm^3	-0.026%	-0.001%	-
FSL	675 cm^3	795 cm^3	1471 cm^3	-0.56%	-0.21%	-0.37% - Sienax -0.16% - Siena
….						

Same MRI, different software, different results!

Why do we aim to integrate atrophy in clinical practice?

MAGNIMS recommendations for harmonization of MRI data in MS multicenter studies



Highest:

a. Robustness
b. Degree of Automation
c. Reproducibility

High Insensitivity to the artifacts

Medium/Low Specificity

De Stefano, et al. NeuroImage: Clinical, 2022

how can atrophy measures be incorporated into clinical applications for MS?

Question to be addressed: how far is the atrophy measurement of a patient from physiological condition?

This means to answer to these additional questions:

a. Solution should to provide results for MR images acquired under different condition 

b. Solution should to be “optimized” for different tasks (cross-sectional/longitudinal; different compartment) 

c. Solution should to address bureaucratical/technical issues related to the privacy of data (GDPR) 

d. Solution should to be easy to use and informative (tailored diseases-related reports) 

how can atrophy measures be incorporated into clinical applications for MS?

Question to be addressed: how far is the atrophy measurement of a patient from physiological condition?

This means to answer to these additional questions:

a. Solution should to provide results for MR images acquired under different condition

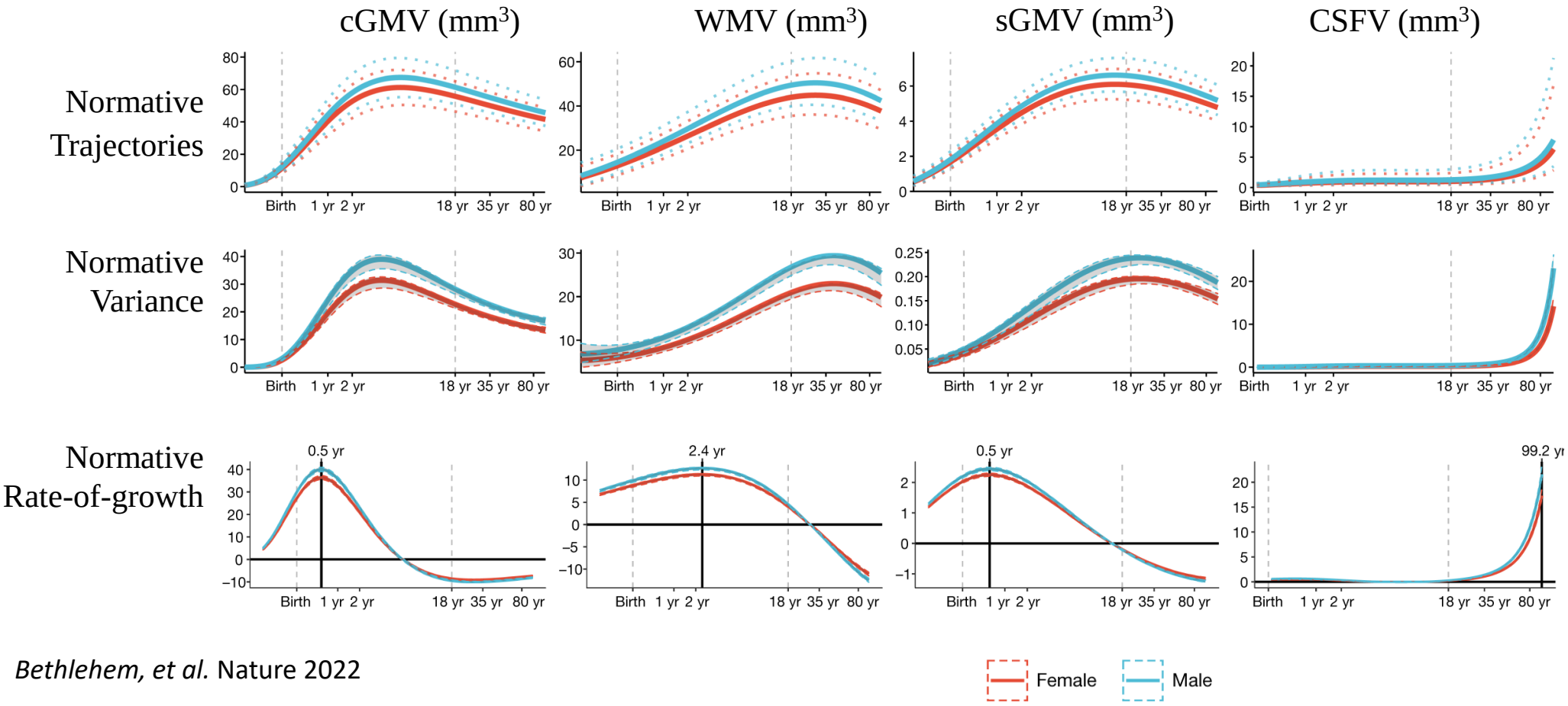
b. Solution should to be “optimized” for different tasks (cross-sectional/longitudinal; different compartment)

c. Solution should to address bureaucratical/technical issues related to the privacy of data (GDPR)

d. Solution should to be easy to use and informative (tailored diseases-related reports)

How to bring measures of atrophy into the practical clinic in MS?

Brain charts from 123k MRI scans (http://www.brainchart.io/)



Covariates used:
Age and gender

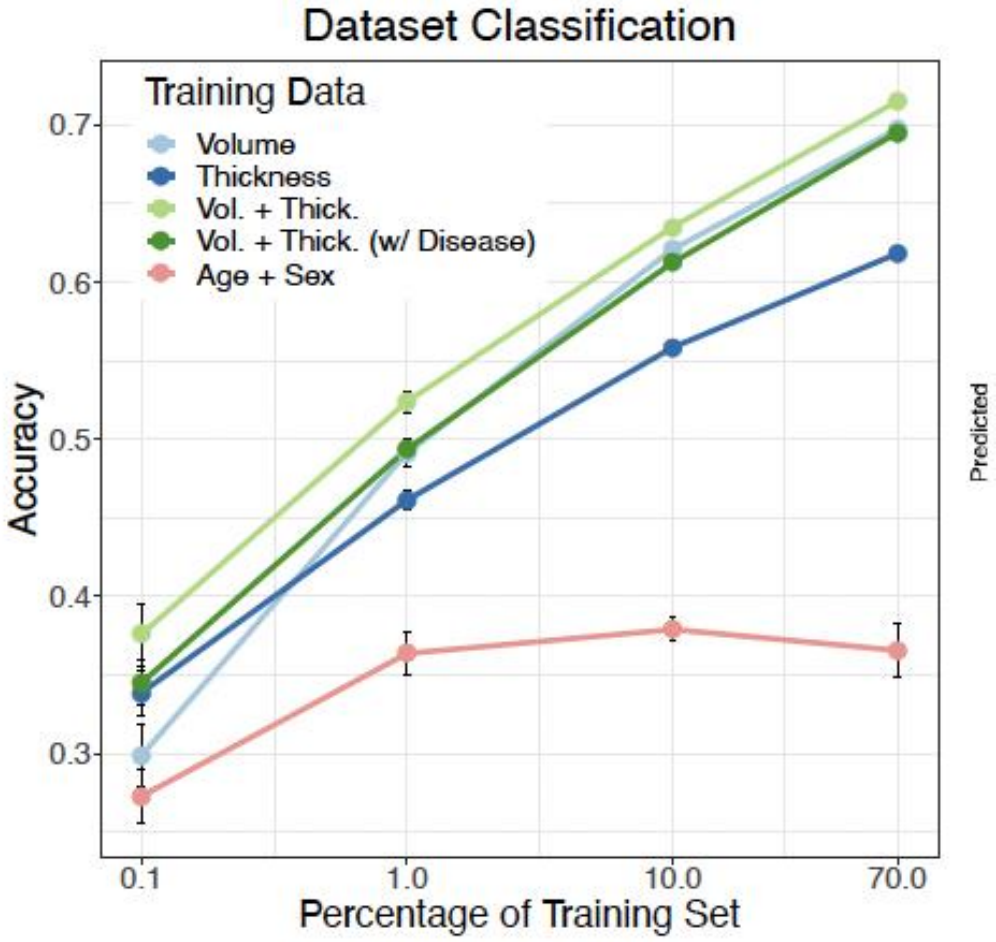
Method used:
FreeSurfer

Is it possible to use it in clinical practice?

Answer: **NO**

Bethlehem, et al. Nature 2022

How to bring measures of atrophy into the practical clinic in MS?



Wachinger et al, Med. Imag. Anal. 2021

Name That Dataset

Population: 15251 HV

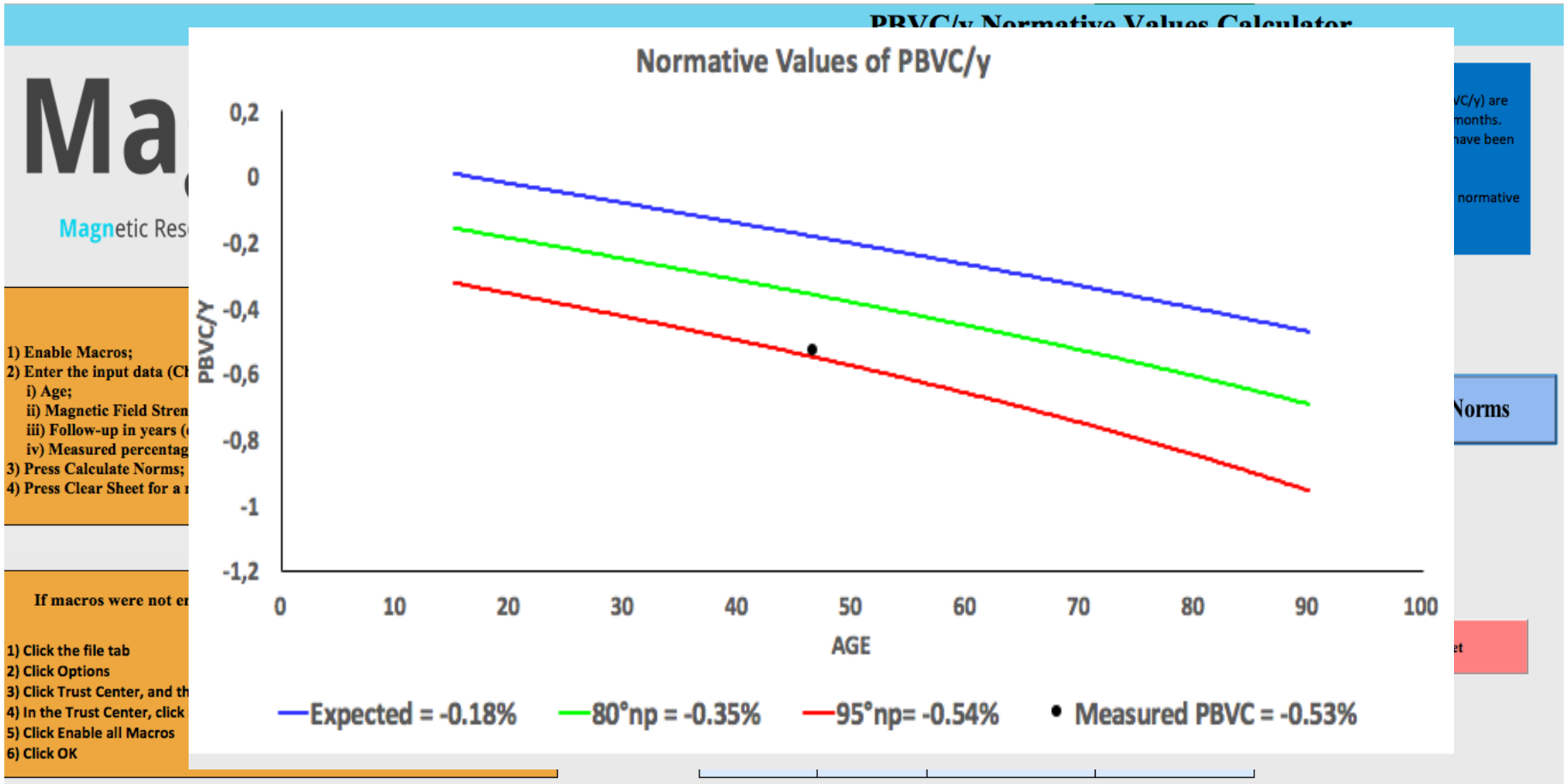
MRI analysis: 55 volume and 70 cortical thickness measures obtained using FreeSurfer. (thus for each subject a total of 125 atrophy measures were labelled)

Statistical analysis: Random Forest trained on different subsample dataset (varying from 10-70% of the whole dataset) to learn, from the atrophy measures, the database from which the measures were coming from.

Results: ~ 70% of accuracy in rightly classifying the database

"*The lesson learned from this experiment is that even when working with image-derived values that represent physical measures (volume, thickness), substantial bias in datasets remains….*"

How to bring measures of atrophy into the practical clinic in MS?



Possible solution: to provide **norms stratified** for **confounding factors** such as Magnetic Field Strength and Vendor partially **reflecting different protocol acquisition**

Battaglini et al, Neurobiology of Ageing, 2019

how can atrophy measures be incorporated into clinical applications for MS?

Question to be addressed: how far is the atrophy measurement of a patient from physiological condition?

This means to answer to these additional questions:

a. Solution should to provide results for MR images acquired under different condition

b. Solution should to be “optimized” for different tasks (cross-sectional/longitudinal; different compartment)

c. Solution should to address bureaucratical/technical issues related to the privacy of data (GDPR)

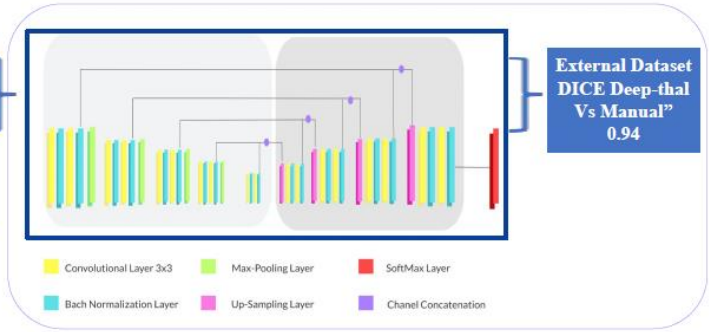
d. Solution should to be easy to use and informative (tailored diseases-related reports)

How to bring measures of atrophy into the practical clinic in MS?

Population

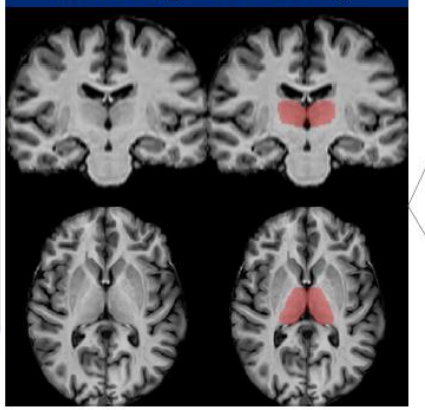
Population	Number	Segmentation
Deep –Thal	628 Healthy Subjects (Training)	Manual
	158 Healthy Subjects (Validation)	Manual
	82 (External dataset)	Manual/Deep-thal
Normative Data	10910 Healthy Subjects	Deep-thal
Multiple sclerosis patients	147 RRMS	Deep-thal

Deep-thal



External Dataset DICE Deep-thal Vs Manual" 0.94

Thalamic Segmentation Example



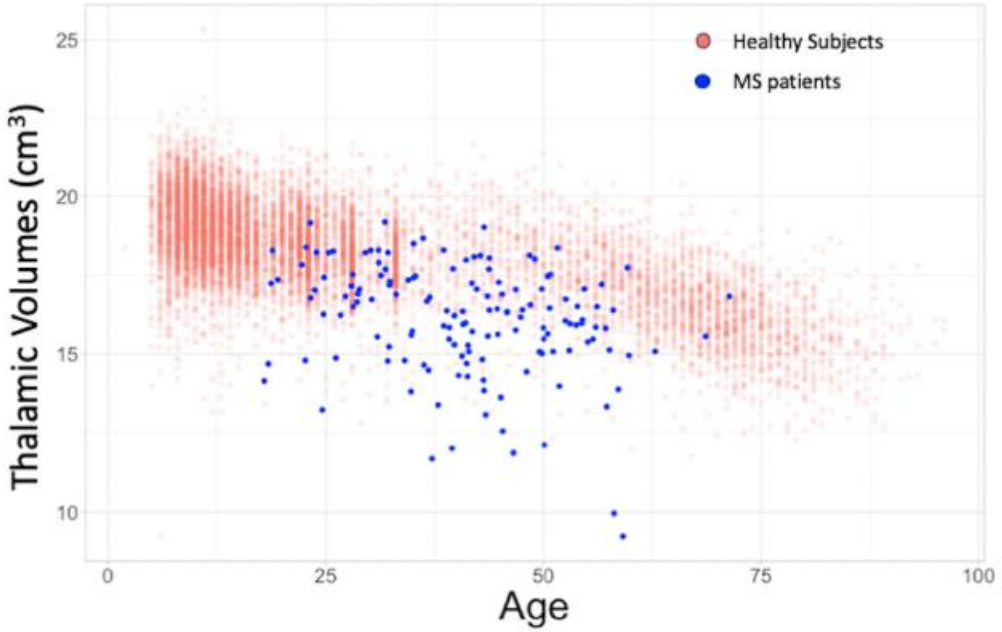
Statistical Analysis

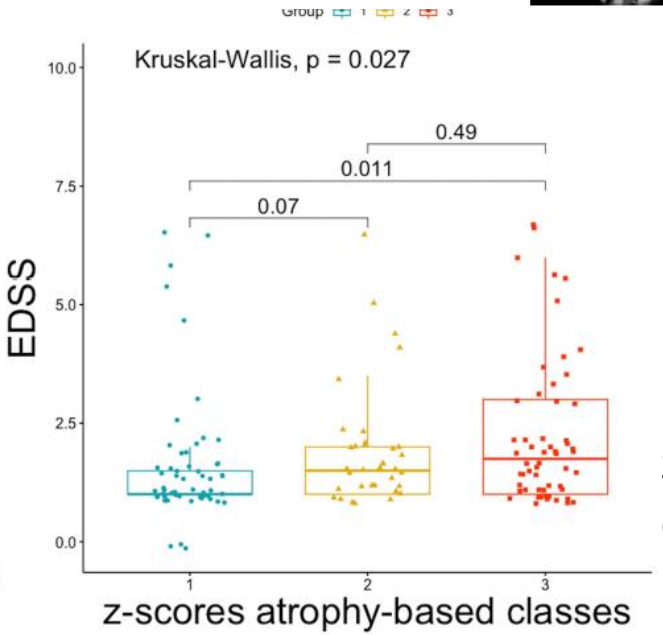
Thalamic Volume Segmentation of Normative population

Regressions

Thalamic Volume Segmentation of MS populations

Z-scores of MS patients





Big available dataset for training the DL solution guarantees generalizability

Big available dataset for evaluating the norms guarantees the accuracy

Selection of covariates reflecting different MR setting guarantees the reproducibility

Battaglini et al, P618, ECTRIMS23

how can atrophy measures be incorporated into clinical applications for MS?

Question to be addressed: how far is the atrophy measurement of a patient from physiological condition?

This means to answer to these additional questions:

a. Solution should to provide results for MR images acquired under different condition

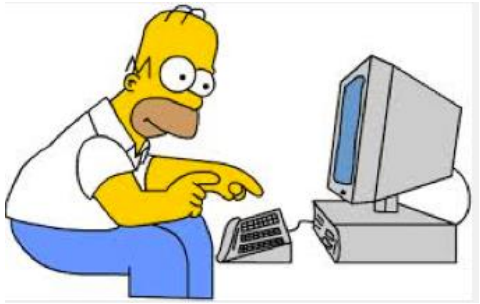
b. Solution should to be “optimized” for different tasks (cross-sectional/longitudinal; different compartment)

c. Solution should to address bureaucratical/technical issues related to the privacy of data (GDPR)

d. Solution should to be easy to use and informative (tailored diseases-related reports)

How to bring measures of atrophy into the practical clinic in MS?

How to manage personal data contained into the Dicom files?

Scan Acquisition	Post-Proc	Analysis Output	Storage
			
Dicom files	Post-Proc in house	Analysis	Organized data collection

Workflow in a laboratory analysing MR images

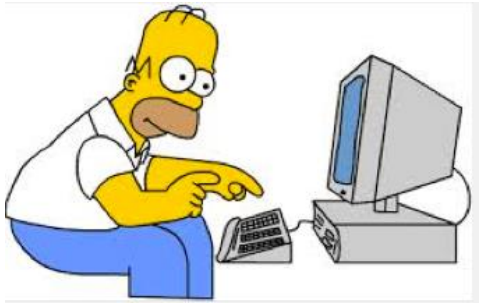
How to bring measures of atrophy into the practical clinic in MS?

How to manage personal data contained into the Dicom files?

Scan Acquisition

Dicom files

Post-Proc



Post-Proc in house

Analysis Output

Analysis

Storage

Organized data collection

Pros: in-house created pipelines able to optimize available software for the MR images of the center

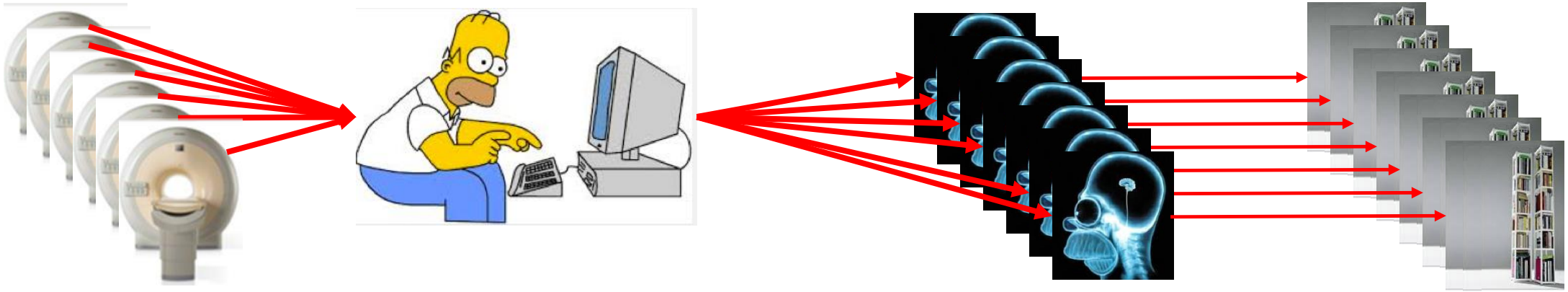
Cons: a. Lack of generalizability of the results: same pipelines could provide different results on different database

b. Difficulties to find, an train, skilled person in post-processing

c. Difficulties to have the calculation power to fully exploit the new artificial intelligence (AI) solutions

How to bring measures of atrophy into the practical clinic in MS?

How to manage personal data contained into the Dicom files?



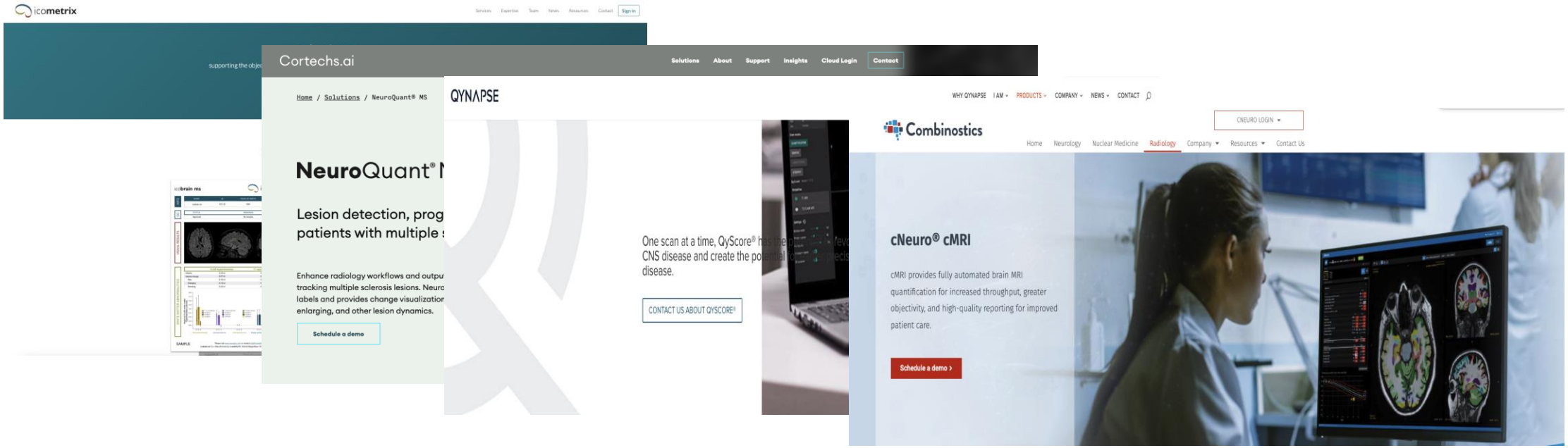
Other possibility: centralized analysis performed by using same pipeline (with integration of AI solutions); distribution of the results and (eventual) storage of data in cloud center-specific.

Pros: a. generalizability of results: usually these solutions has been tested on several different databases
b. Costs saved for neurology and neuroradiologists (a skilled person is rare to find and expensive)
c. Fully exploitation of new AI-based solutions (due to analyses usually performed in cloud)

Cons: a. Results are a kind of "black box" → MDs obtain reports with few insights about the goodness of the analysis.
b. Strong legal caveats on the use of sensitive data contained in the DICOM
c. These solutions are usually provided by companies without disease-specific clinical background

How to bring measures of atrophy into the practical clinic in MS?

How to manage personal data contained into the Dicom files?



Different options, different level of expertise or different level of experience on MS disease

how can atrophy measures be incorporated into clinical applications for MS?

Question to be addressed: how far is the atrophy measurement of a patient from physiological condition?

This means to answer to these additional questions:

a. Solution should to provide results for MR images acquired under different condition

b. Solution should to be “optimized” for different tasks (cross-sectional/longitudinal; different compartment)

c. Solution should to address bureaucratical/technical issues related to the privacy of data (GDPR)

d. Solution should to be easy to use and informative (tailored diseases-related reports)

How to bring measures of atrophy into the practical clinic in MS?

Reports: what they contains and…

- Automated lesion and brain segmentation enable efficient processing.
  - Increased sensitivity, accuracy and reproducibility.[1]
- There is a clinical need for implementation.
- Rise in (commercial) quantitative radiological reporting tools.[2]
  - 10 identified CE/FDA approved companies.
- Little research has focused on clinicians as end-users.
- Lack of systematic identified and synthesized user requirements.

Review | Open Access | Published: 04 November 2022

Commercial volumetric MRI reporting tools in multiple sclerosis: a systematic review of the evidence

Zoe Mendelsohn, Hugh G. Pemberton, James Gray, Olivia Goodkin, Ferran Prados Carrasco, Michael Scheel, Jawed Nawabi & Frederik Barkhof

Neuroradiology **65**, 5–24 (2023) | Cite this article

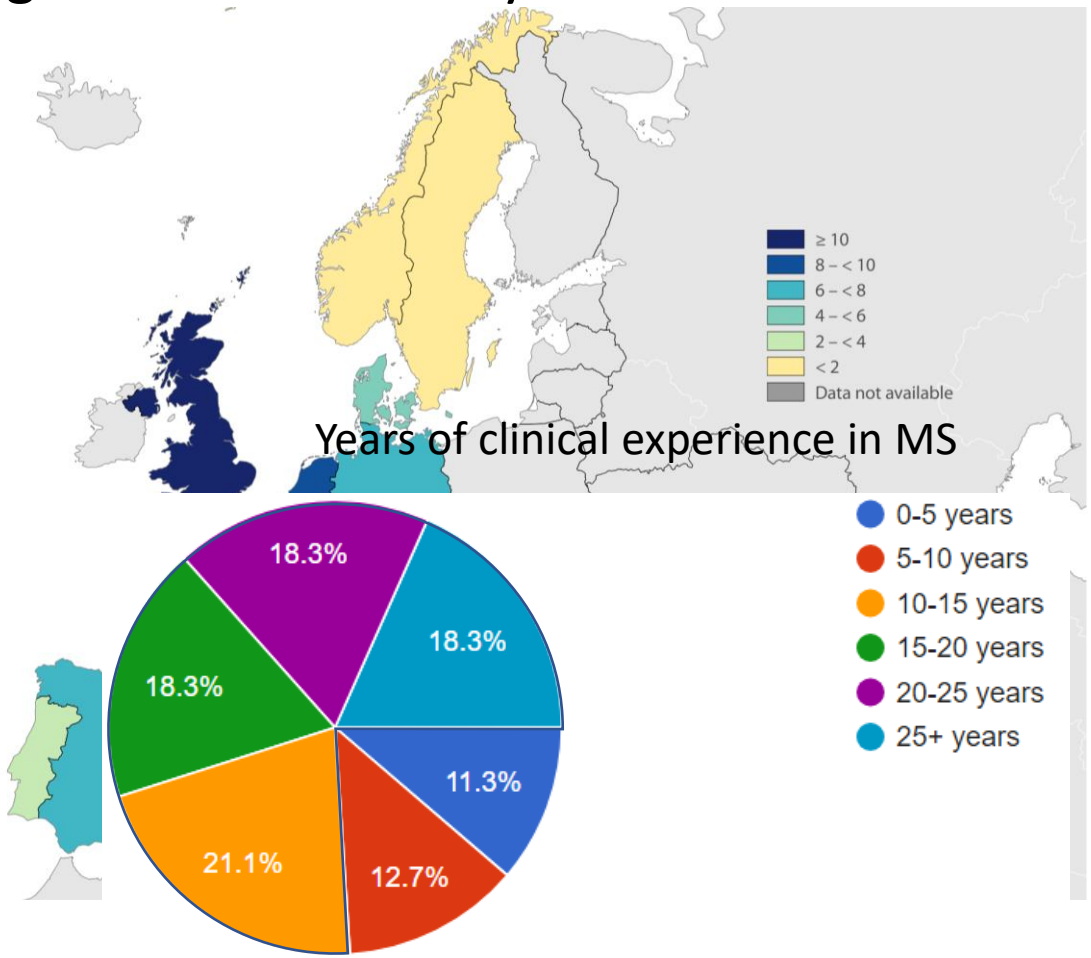
2705 Accesses | **13** Altmetric | Metrics

Kindly provided by *D.R. van Nederpelt, F. Barkhof*

How to bring measures of atrophy into the practical clinic in MS?

it is something that do MDs really care?

- 69 responses
- Final effort to include additional countries
- 50/50% neurologist/(neuro)radiologists
- 76% has ≥ 10 years of clinical experience in MS
- 93% academic hospitals + specialized MS clinicians

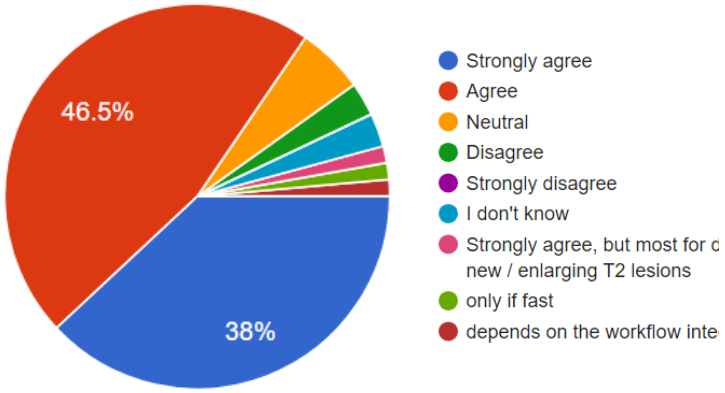


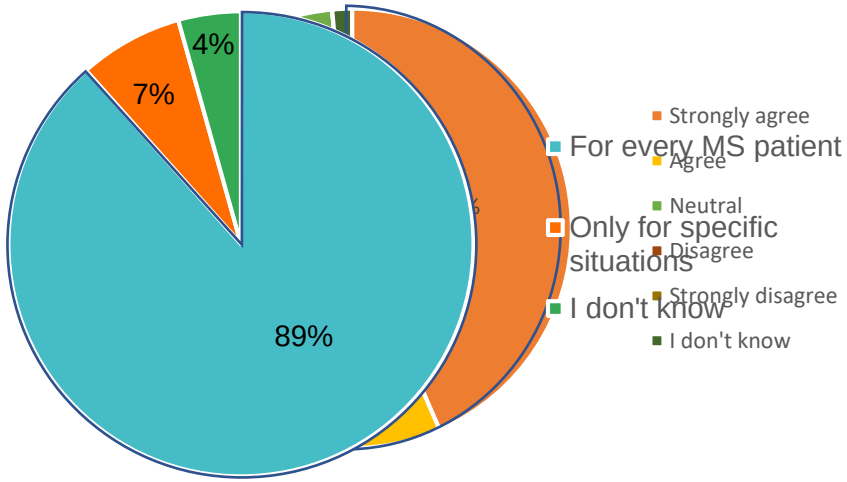
Kindly provided by *D.R. van Nederpelt, F. Barkhof*

How to bring measures of atrophy into the practical clinic in MS?

it is something that do MDs really care?

- 90% agrees that lesion segmentation would aid radiological reporting
- 86% agrees that Qreports can improve the quality of care in MS, 13% is neutral
- 89% would use the Qreport for every pwMS





Kindly provided by *D.R. van Nederpelt, F. Barkhof*

How to bring measures of atrophy into the practical clinic in MS?

it is something that do MDs really care?

Cross-sectional	Diagnosis	Prognosis	Monitoring
Absolute T2 lesion count	✓	?	*N.A.*
Gd+ lesion count	✓	?	*N.A.*
Total brain volume	*N.A.*	✓	✓
Longitudinal	**Diagnosis**	**Prognosis**	**Monitoring**
Absolute T2 lesion count (new)	?	?	✓
Gd+ lesion count (new)	?	?	✓
Absolute T2 lesion volume (change)	?	?	✓
Total brain volume (change)	*N.A.*	✓	✓

- Comments suggested additional topics to include:
  - Spinal cord imaging?
    - Lesions
    - atrophy
  - Optic nerve?
  - Choroid plexus?
  - PRL/CVS
  - SWI/QSM?
  - PIRA?
  - T1/T2 ratio?
  - Ethnicity?
  - Current Qreport landscape?

Kindly provided by *D.R. van Nederpelt, F. Barkhof*

Conclusions (I)

- **Atrophy measures lack specificity** as various competitive biological mechanisms contribute to changes in volumetric assessment. It is essential to consider these factors in the interpretation.

- **Atrophy measures** are **software dependent**: different software provide different volumes estimation, thus MDs need to compare volumes with references obtained with the same software (and possibly the same setting of options)

- **Pathological deviations** from norms must be **adjusted** using covariates **accounting for various acquisition settings** (such as MR Vendor or magnetic field strengths). Without this correction, distinguishing between differences attributable to the disease and those resulting from acquisition variations becomes challenging. **Age and gender alone as covariates are not sufficient!!**

- Medical doctors should be aware of the diverse algorithms employed in assessing atrophy measures. The paramount consideration should be the **generalizability** of the solution, emphasizing its applicability across different scenarios and patient populations.

Conclusions (II)

Despite all these issues:

- **Atrophy measures** are the most **robust**, **insensitive to artifacts** among all the MRI biomarkers

- An **enormous amount** of freely available **MRI data** and the **availability** of new **approaches** based on AI and **reduction** in **elaboration costs** made available the possibility of obtaining accurate, disease-tailored reports obtained by centralized –and standardize- pipeline of analysis

- MDs need to actively contribute to test the validity of these reports and suggests those information that really care!

Thanks!