





La science pour la santé _____ From science to health

Machine Learning for Medical Images Processing

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Part II

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Comuter vision: Image classification

ImageNet 14 M images 20000 different object categories 2022 91% accuracy





[Krizhevsky et al 2012]



Explosion ...



Google scolar "(AI OR artificial OR (machine learning) OR (neural network) OR computer OR software) AND ([specific keyword])

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Joshi et al. Electronics 2024



Joshi et al. Electronics 2024



The majority (97%) of FDA approvals was approved through the 510(k)-clearance pathway, relying on the demonstration of substantial equivalence that circumvents the necessity for exhaustive clinical trials (3%).

Joshi et al. Electronics 2024

Automatic segmentation



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CNN in Radiology

• PubMed 2013-18 ("DL" or "CNN") and ("image" or "imaging" or "radiology")



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Clinical Deployment

Table 4 Clinical integration of medical AI at different developmental stages										
	Areas where AI performance is more reliable than that of a human expert	Areas where AI performance is at the expert level	Areas where Al performance is reasonable	Areas where Al performance is not yet good enough	Areas where the nature of the clinician- patient interaction is fundamentally different from that of the AI- patient interaction					
Examples	Serum analyser ^{144,145} ; alert systems (such as drug-drug interaction checkers ^{146,147})	Assessment of certain radiology images (for example, annotation of cardiovascular MRI images ^{57,58} or evaluation of X-ray images for distal radius fracture ¹⁴⁸); dermoscopic melanoma diagnosis ¹⁴⁹ ; fundus photograph evaluation for DR ^{5,7}	ECG reading ¹¹	Surgery; full interaction with patients	Emotional support and rapport					
Potential clinical integrations	Delegate to Al	AI does the majority of the task, clinicians confirm the diagnosis	Al does a portion of the task (such as screening), clinicians confirm the diagnosis	Clinicians lead the clinical evaluations and intervention, Al assists in routine sub-tasks	Clinicians continue to provide the service					

Yu et al Nat Bio Eng 2018



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Challenges



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ML & CNN



[Hosny et al 2018 Nature]

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Life Science applications

Classification/segmentation/detection

Moeskops et al TMI 2016; Rajchl et al MIDL 2018 (*brain tissue*); Dolz et al. Neuroimage 2018 (*brain structures*); Kamnitsas et al MediA 2016 (*brain lesions*)

Kleesiek et al Neuroimage 2016 (brain extraction); Havaei et al MediA 2016 (brain tumors)

Suk et al NeuroImage 2014 (AD/MCI)

Zhao et al MediA 2017; Suk et al NeuroImage 2016; Kin et al Neuroimage 2016 (*functional brain networks*) Ciompi et al Scient Rep 2017 (*lung nodules*); Esteva et al Nature 2017 (*skin cancer*)

Synthetic image generation

Nie et al Miccai 2017 (MR-CT); Liu et al Radiology 2017 (MR-CT); Zhao et al Media 2018 (retinal images)

• Predictive models

Polpin et al Nat Bio Eng 2018 (cardiovascular risk); Miotto et al. Scient Rep 2016 (deepPatient)

Processing

Rajchl et al MIDL 2018 (automatic process for segmentation) denoising, registration (see Litjens Media 2017)

Retrieval

Anavi et al Spie 2016

Brain encoding/decoding models





Classification example

- Training set: train the model
- Validation set: Refine hyperparameters, avoid overfitting
- Test set: new set of data to verify the performances

- 3 hidden layers with 100 nodes
- ReLu
- Softmax output





Architecture example



Implementation

Matlab	<pre>%% NN with 3 HIDDEN LAYER NEURONS nElements = 100; nLayers = 3; inputLayer=imageInputLayer([nFeatures,1,1]); f1=fullyConnectedLayer(nElements); f2=fullyConnectedLayer(nElements); f3=fullyConnectedLayer(nElements); f4=fullyConnectedLayer(nClasses); s1=softmaxLayer(); outputLayer=classificationLayer(); architecture = [inputLayer; f1; f2; f3; f4; s1; outputLayer]; disp(architecture);</pre>					
	<pre>epochs = 250; miniBatchSize = 1024; InitialLearnRate = 0.001; % Training options: Note that we set the validation patience stopping % criterion to the number of epochs. This is a stupid thing to do, but we % want force the training to go to the defined number of epochs so that it % is consistent with Tensorflow and Pytorch options = trainingOptions('adam', 'MaxEpochs', epochs, 'InitialLearnRate', InitialLearnRate, 'MiniBatchSize', miniBatchSize, 'ExecutionEnvironment', 'cpu', 'Plots', 'training-progress', 'ValidationData', {x_val, y_val}, 'ValidationPatience', epochs);</pre>					
	<pre>%% Train tic [net,op] = trainNetwork(x_train,y_train,architecture,options); toc</pre>					

From Knoll Ismrm 2018



Results





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Skin cancer classification

- Dermatologists vs CNN
 - 127.463 biopsy images for training
 - 1942 for validation

Grenoble Alpes

• Inception v3



Skin cancer classification



Glioblastome classification



IDH Status · MUT · WT



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Computational pathology



Original image



manually annotated by an expert

Kidney tissue

Purple: glomerulus; red: sclerotic glomerulus; Dark blue: proximal tubule; orange: distal tubule; Green: atrophic tubule; turquoise: artery or arteriole



using a deep learning algorithm

[van des Laak et all Nat Med 2021]







For brain tissue and structures classification







For brain tissue and structures classification



 $X_i = [T1w_i, FA_i, MD_i, ADi, RDi]$

Y_i=[1,2,3, 4, 5, ...]







Specific considerations in medical domain

- Few training sets
- Few ground truth
- Need of localization not just classification
- Touching objects of the same class to be separated





Brain Lesion Segmentation: CNN example



4 3x3x4 convolutional layers, Relu activation 2D MaxPooling

1 fully connected layer with 16 elements Sigmoid Output

26117 parameters to be estimated

Adapted from Knoll Ismrm 2018





Brain Lesion Segmentation

Kamnitsas et al MedIA 2017



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Transformation Affine





12 paramètres

Insuffisante

Affine = rigide + isométrie (12 paramètres)



[from Cachia workshop Inserm/CNRS anatomie cérébrale 2006]

Nécessité de recalage non-linéaire

$$T = \underset{\forall T}{\operatorname{arg\,min}} \{ Mis(O_c, O_s, T) + \gamma Reg(T) \}$$

Registration toward a common template



[Collins D. et al., *HBM*, 1995.]







Some templates



MNI250 250 subjects Manual registration No cerebellum [Evans et al. 92]



MNI305 350 subjects Automatic registration No cerebellum [Collins et al. 94]



Colin27 1 subject, 27 scans Automatic registration [Holmes et al. 98]



ICBM152 152 subjects Automtic registration T1,T2,PWD, No cortical info [Maziotta et al. 01]



ICBM152 Non linear 152 sujets

[Maziotta et al. 01]



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CNN for tissue segmentation



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Lesion detection in MR brain scans

• 3D CNN for MRI

- Computationally expensive so limitation of the number of layers
- Internal covariate shift > convergence pb



Kamnitsas et al Media 2017



Lesion detection in MR brain scans



Traumatic Brain Injury

9 real cases, 9 centers

Normal values computed on 3 healthy cases for each center



Inter-Raters	DICE 0.60± 0.03	Precisic 0.68±	on ± 0.04	Sensitivity 0.86± (7).04	ICC 0.70
AUTOMATIC	0.59 ± 0.06	0.59 ± 0.07		0.66± ().06	0.70
Stroke (Maier et al 2015)	0.73		0.84	0.69		
Kamitsas et al Media 2017	R, Forest R, Forest+CRF DeepMedic DeepMedic+CRF Ensemble Ensemble+CRF	DSC 51.1(20.0) 54.8(18.5)** 62.3(16.4) 63.0(16.3)** 64.2(16.2) 64.5(16.3)*	Precision 50,1(24,4) 58,6(23,1) 65,3(18,8) 67,7(18,2) 67,7(18,3) 69,8(17,8)	Sensitivity 60,1(15,8) 56,9(17,4) 64,4(16,3) 63,2(16,7) 65,3(16,3) 63,9(16,7)	ASSD 8,29(6,76) 6,71(5,01) 4,24(2,64) 4,02(2,54) 3,88(2,33) 3,72(2,29)	Haussdorf 64,17(15,98) 59,45(15,52) 56,50(15,88) 55,68(15,93) 54,38(15,45) 52,38(16,03)



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Subcortical segmentation



9 structures

Dolz et al Neuroimage 2018



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U-Net approach



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U-Net approach





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freiburg.de/people/ronneber/u-net/

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2x2 Max Pooling







2x2 convolution





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NeuroNet

Rajchl et al MIDL 2018

- 3D Unet structure (DLTK+Tensorflow)
 - 16, 32, 64, 128 feature
 - 1,2,2,2 stride
 - Upsampling: 64, 32, 16
 - Training 5000 T1w, segmented FSL, SPM &MALP-EM

ResNet

Encoder

Multiple

FCN decoder

- Validation 713
- UK-biobank

protocol	fsl_fast	fsl_first	malp_em	malp_em_tissue	spm_tissue
mean	93.1	88.8	85.8	93.2	93.4
std	2.4	4.9	3.1	1.9	4.3
min	73.7	28.8	57.3	75.8	6.2
max	96.5	92.7	89.7	95.9	96.1
time	20 1	min	1 h.	8 CPU	>30 min
			vs 90s		
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SPM12

NeuroNet



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Data hungry systems

- Gather many data
- Artificially increase the number of examples
- Transfert Learning
- Generate synthetic data
- Pooling from many centers
- Anomaly Detection





Gather many data

UK BioBank

How to scan 100.000 people Brain Imaging in UK Biobank

4 scanners, 54 pat/day, 7/7, 5 years 2022 Jv 50000 subjects

Cost: about 10k€ for data import

Miller et al Nat Neurosc <u>Multimodal population brain imaging</u> in the UK Biobank prospective epidemiological study.2016

Modality	Duration	Voxel, Matrix	Key Parameters
T1	4:54	1.0x1.0x1.0 mm 208x256x256	3D MPRAGE, sagittal, R=2, TI/TR=880/2000 ms
T2 FLAIR	5.52	1.05x1.0x1.0 mm	FLAIR, 3D SPACE, sagittal, R=2, PF 7/8, fat sat,
	5.52	192x256x256	TI/TR=1800/5000 ms, elliptical
SWMRI	2.34	0.8x0.8x3.0 mm	3D GRE, axial, R=2, PF 7/8 TE1/TE2/TR=9.4/20/27
SWMRI 2:34 2		256x288x48	ms,
dMDI	7.00	2.0x2.0x2.0 mm	MB=3, R=1, fat sat, b=0(5x + 3x phase-encoding-
UMKI	7.00	104x104x72	reversed), 1000(50x), 2000(50x)
rfMDI	6.10	2.4x2.4x2.4 mm	TE/TP-20/735 ms MR-8 P-1 flip angle 52° fat sat
	0.10	88x88x64	$1 \text{ E}/1 \text{ K} = 3.9/7.33 \text{ Ins, MD} = 0, \text{ K} = 1, \text{ Inp angle } 32^\circ$, lat sat
+fMDI	4.12	2.4x2.4x2.4 mm	Acquisition same as rfMRI. Task is faces/shapes
	4:13	88x88x64	"emotion" task.

R = in-plane acceleration factor, MB = multiband factor, PF=partial Fourier. All non-EPI scans are pre-scan normalized (on-scanner bias-field corrected). Gradient distortion correction is turned off on the scanner and applied in post-processing.

Genome-wide association studies of brain imaging phenotypes in UK Biobank T Eliott et al Nat Neurosc 2018

The UK Biobank imaging enhancement of 100,000 participants: rationale, data collection, management and future directions

Phenotypic and genetic associations of quantitative magnetic susceptibility in UK Biobank brain imaging Wang et al Nat Neurosc 2022 LittleJohns TJ et al Nature Comm 2020

SARS-CoV-2 is associated with changes in brain structure in UK Biobank Douaud et al Nat Neurosc 2022







Ivy Glioblastoma Atlas

Gather many data

Alignment of histologic features, genomic alterations and gene expression patterns



Puchalski et al Science 2018

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ivygap.org

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Segment anything in medical images

A foundation model for medical image segmentation



Ma et al Nat Comm 2024



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Paradigm change

Ivy Gliobastoma atlas

[Puchalski et al Science 2018]

[Lichtman et al; Nat Neuro 2014]

41 patients, 42 tumors, 440 tissue blocks, 270 transcriptomes 11500 annotated H&E images 23000 ISH images (**400 Gb/image**), 400 MRI scans

Data for connectomics (neural networks):

 1mm^3 rat cortex =>2M Gb =2 x10¹⁵=2 Pb=2x10³ TB total cortex 500mm3=>10³PB (1exabyte, 10⁶ TB) Man = 1000xlarger =10³ exabyte (10⁹ TB) (source lichtman et la; Nat Neuro 2014)

Data rate

1mm³ =>800h (33j) 2.5 Tb/h => 45y on one machine

[Miller et al; Nat Neuro 2016]

UK BioBank

100000 subjects (2016-22) 6 MR imaging modalities: tT1w, T2w, swMRI, dMRI, tfMRI, rfMRI 2501 individual measures of brain structure and function (2Gb p.sub) 1100 other non imaging variables about **0.2 PB (200 TB)**

Dermatologists vs CNN

[Esteva et al Nature 2017]

127463 biopsies for training 1942 for validation Inception v3 (GoogleNet, using several replicas on Nvidia Titan X Gpu)



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Effect of training dataset size



Scaling up the training image size to one million can significantly improve the model performance on both internal and external validation sets.

Ma et al Nat Comm 2024



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Generation of artificial examples

Create examples

Introduce morphing operations, symetry, rotation



Train the NN to learn invariance to such elastic deformations



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Automatic pulmonary module management



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Automatic pulmonary module management

Ciompi et al Scient Rep 2017

		DLCST (468 patients)			
	Training nodules	N	Training samples	Validation nodules	Test nodules test _{ALL} /test _{OBS}
Solid	694	8	88,832	232	382/27
Calcified	233	22	82,016	78	58/27
Part-solid	63	80	80,640	21	37/27
Non-solid	152	33	80,256	50	87/27
Perifissural	181	28	81,088	62	48/27
Spiculated	29	167	77,488	10	27/27
Total	1,352	_	490,320	453	639/162





Automatic pulmonary module management

Ciompi et al Scient Rep 2017

	Accuracy	Fsolid	F Calcified	F _{Part-solid}	Fnon-solid	F _{Perifissural}	$F_{Spiculated}$	F _{Not-a-nodule}
O1 vs. Computer (3 scales)	71.5%	60.8%	88.4%	66.7%	86.3%	62.2%	71.4%	_
O2 vs. Computer (3 scales)	66.2%	62.6%	82.4%	47.8%	72.7%	80.0%	56.4%	_
O3 vs. Computer (3 scales)	67.7%	56.8%	85.1%	59.1%	78.3%	75.6%	60.9%	_
O4 vs. Computer (3 scales)	72.8%	64.2%	88.9%	71.7%	80.0%	77.3%	62.7%	_
Average	69.6%	61.1%	86.2%	61.3%	79.3%	73.8%	62.9%	_
O ₁ vs. O ₂	66.0%	52.7%	84.0%	51.3%	79.2%	63.6%	83.3%	50.0%
O ₁ vs. O ₃	71.0%	55.0%	87.0%	66.7%	80.0%	81.5%	74.4%	40.0%
O ₁ vs. O ₄	72.8%	64.8%	90.9%	66.7%	71.7%	75.5%	89.4%	0.0%
O ₂ vs. O ₃	76.5%	74.7%	88.9%	61.5%	81.0%	77.3%	75.7%	66.7%
O2 vs. O4	72.2%	64.4%	88.5%	70.8%	71.1%	79.1%	73.2%	0.0%
O3 vs. O4	79.0%	68.4%	95.8%	71.1%	80.9%	90.6%	79.2%	0.0%
Average	72.9%	63.3%	89.2%	64.7%	77.3%	77.9%	79.2%	26.1%



Ilastik

Interactive training Shallow learning can be trained interactively with immediate feedback Adapting from similar training data







Transfert learning

Transfert learning



Mazurowski et al. JMRI 2018



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Tranfert learning

T. Coudert Master 2021

Dataset	WMH DSC	Sensitivity	Precision	95HD (mm)
9 EpiBrainRad LR=5e-3	0.557 ± 0.203	0.507 ± 0.229	0.703 ± 0.228	21.089 ± 15.469
9 EpiBrainRad LR=1e-5	0.705 ± 0.088	0.869 ± 0.140	0.624 ± 0.144	6.838 ± 4.468
9 EpiBrainRad dropout= 0.3	0.740 ± 0.127	0.719 ± 0.182	0.799 ± 0.112	13.105 ± 17.237
9 EpiBrainRad max epochs set to 150	0.578 ± 0.257	0.578 ± 0.275	0.623 ± 0.258	19.848 ± 24.362

• Few examples : 9 for training / 11 for testing





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Ground truth





Use a pretrained network

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Transfert Learning

T. Coudert Master 2021

Gliomas data from BraTS Challenge¹ dataset 2016 and 2017



	Dataset distribution	WMH DSC	Sensitivity	Precision	95HD (mm)
without	200 BraTS + 9 EpiBrainRad into one training	0.836 ± 0.075	0.879 ± 0.106	0.803 ± 0.073	10.246 ± 12.439
with	200 BraTS pre-trained model, transferred on 9 EpiBrainRad	0.858 ± 0.064	0.890 ± 0.104	0.835 ± 0.057	2.806 ± 3.523

test set of 11 images with **13% of variability with a neurologist segmentation** on this 11 images





Ground Truth Without TL With TL

Clear benefit of transfer learning, <u>best</u> <u>results with exactly the same amount of</u> <u>input images</u>

¹ B. H. Menze et al. **The multimodal brain tumor image segmentation benchmark (brats)**. IEEE Transactions on Medical Imaging, 34(10):1993–2024, 2015.













Image Generation PJ Lartaud PhD 2022







Results



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Image Generation PJ Lartaud PhD 2022



Training with artificial data ...









Producing new data

Synthetic data

• Generative Adversarial Networks (GAN): produces output undistinguable from "real" images.



Goodfellow et al 2014 arXiv:1406.2661



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Generative Adversarial Network





GAN:



Role of GAN in HealthCare



Generative Adversarial Network

Liu et al Radiology 2017



Generative Adversarial Network

To generate realistic synthetic images

A cascade of GANs



Image Harmonization - I

Pooling data



Cakowsky et al 2022 AIM



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Image Harmonization - II







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Image Harmonization - III





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Variational Auto-encoder: Anomalies detection



Parkinson

Input	U-Net	sAE	SVAE	dVAE
	Si the	A. A.	A. M.	No.

	U-Net	sAE	sVAE	dVAE
	0-mer	artis	anne	umu
Subcortical structures/Brainstern	0.70	0.76	0.77	0.70
Frontal lobe	0.56	0.58	0.56	0.59
Parietal lobe	0.45	0.62	0.62	0.62
Temporal lobe	0.59	0.67	0.72	0.69
Occipital lobe	0.35	0.43	0.41	0.43
White matter	0.62	0.80	0.78	0.76
Insular/Cingulate cortex	0.70	0.68	0.76	0.68
Ventricles	0.68	0.53	0.50	0.52
Red Nucleus	0.51	0.69	0.64	0.58
Substantia Nigra	0.61	0.73	0.72	0.66
Subthalamic Nucleus	0.67	0.69	0.66	0.50
Caudate	0.60	0.57	0.53	0.62
Putamen	0.46	0.62	0.61	0.60
Globus Pattidus external	0.54	0.56	0.58	0.60
Globus Patlidus internal	0.54	0.64	0.67	0.64
Thalamus	0.67	0.65	0.73	0.68
Superior Colliculus	0.66	0.45	0.54	0.52
Inferior Colliculus	0.55	0.40	0.42	0.43

Table 4. ROC AUC contemplating the eight regions (top) and the ten subcortical structures (bottom)

Kmetzsch et al 2019







Beyond CNN

• Limitations

- No model of long spatial dependencies (limit by kernel)
- Fixed weights at the inference time
- Tranformers

Alpes

- To manage
- VisioTranf



An example



DeepLabv3++

(Azad et al 2023 arXiv)



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Unsupervised Learning



CheXzero training with chest X-ray image report а

> Grenoble Alpes

On cheXpert test





Data pipeline for ML



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Specific ethical considerations - I

- Data collection and respect private for life
- GPRD, securisation



Rajpurkar et al 2022 Nat Med



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Specific ethical considerations - II

- Data collection and respect private for life
- GPRD, securisation



Rajpurkar et al 2022 Nat Med

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Cross-silo federated learning for healthcare



Zhang et al Nat Bio Eng 2022





Specific architectures

For Storage and ML algorithms execution / comparison

- Lesion load estimation is crucial for therapy adaptation
- Manual deliniation too variable and time-consumming
- How to obtain a fair comparison of automatic segmentation?





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MS-SEG



FLAIR from center 01



FLAIR from center 03



FLAIR from center 07



FLAIR from center 08









- 53 Ground truth
- MRI from three different centers: Bordeaux, Lyon, Rennes
- Acquisitions from 4 different scanners Siemens Verio 3T (01) – Rennes – 10 cases GE Discovery 3T (03) – Bordeaux – 8 cases Siemens Aera 1.5T (07) – Lyon – 10 cases Philips Ingenia 3T (08) – Lyon – 10 cases

MRI following the OFSEP protocol

- 3D T1, FLAIR, axial DP and T2
- 13 challengers (4 CNN)
- 7 expert manual delineation per case => Ground Truth





Process ...



8**3**

Results



Results







Conclusion

• Results still far from experts

- Mainly on images with low lesion load
- All methods sensitive to image quality (center 03)

[Commonwick et al Scient Reports 2018]



