Investigating techniques of artificial intelligence for the diagnosis of Parkinson's disease with Dopamine SPECT imaging

Journal Club GENOMICS AND DIGITAL HEALTH

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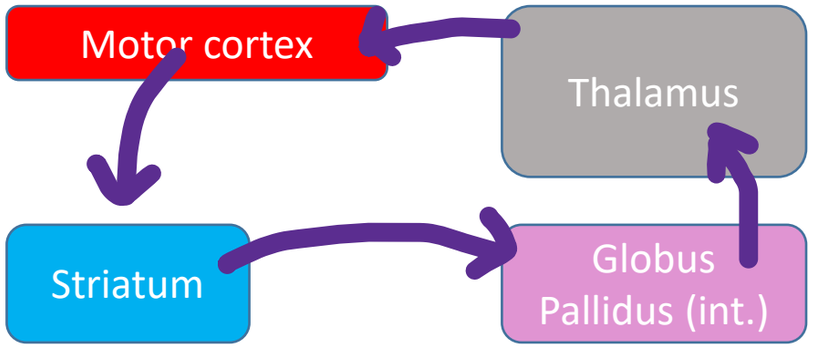
Overview

- Parkinson’s Disease and Dopamine SPECT imaging
- Presentation of Ortiz et al. (2019) paper
- DeepDAT project

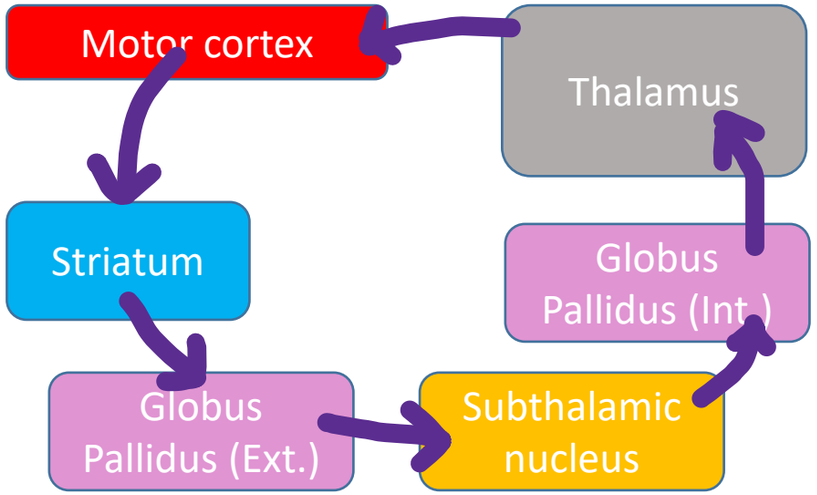
Parkinson’s disease and SPECT imaging

Neural pathways



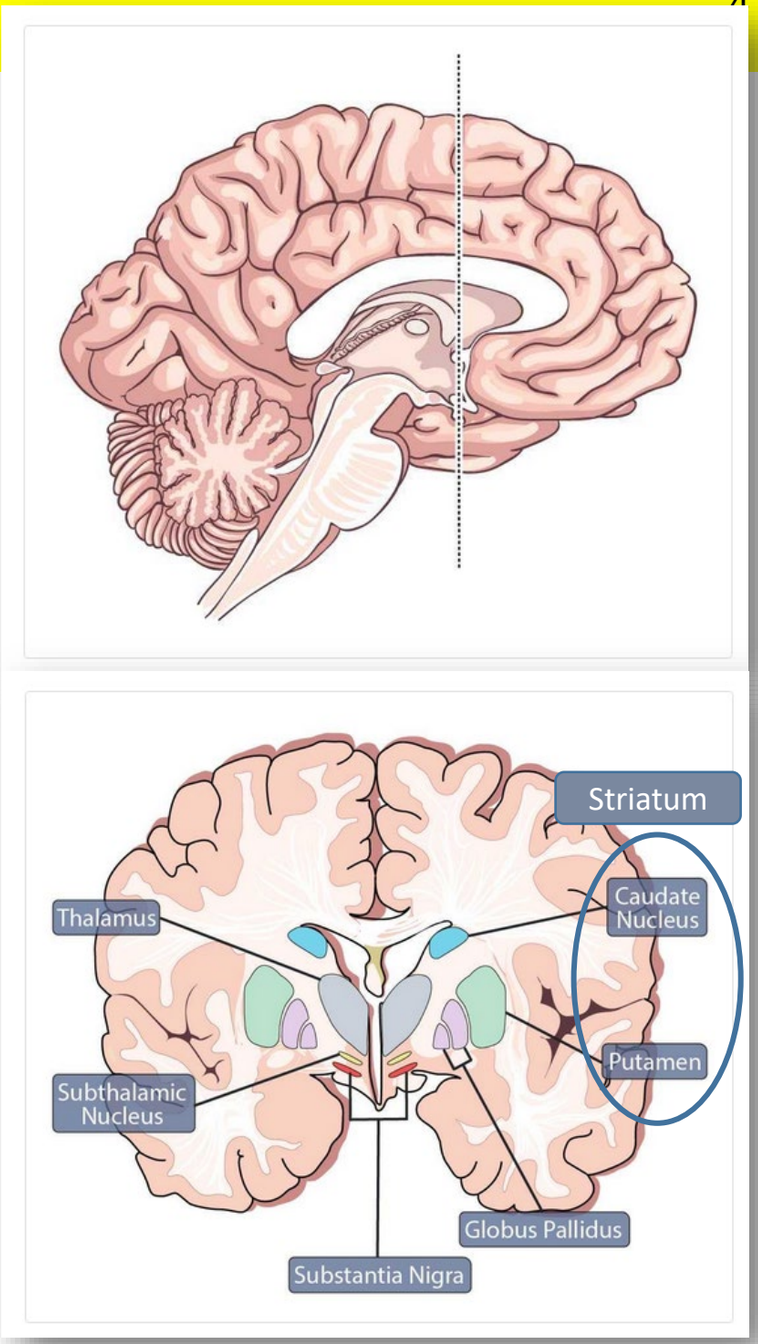
Direct pathway:

- Increases and stimulates motor activity
- Involves Glutamate and GABA neurotransmitters



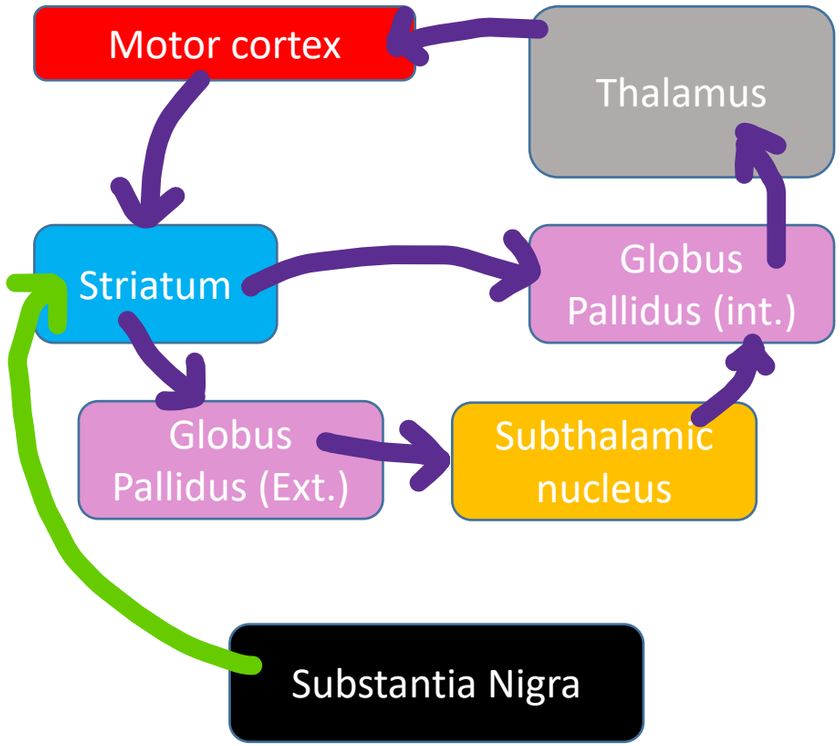
Indirect pathway:

- Decreases motor activity
- Involves Glutamate and GABA neurotransmitters



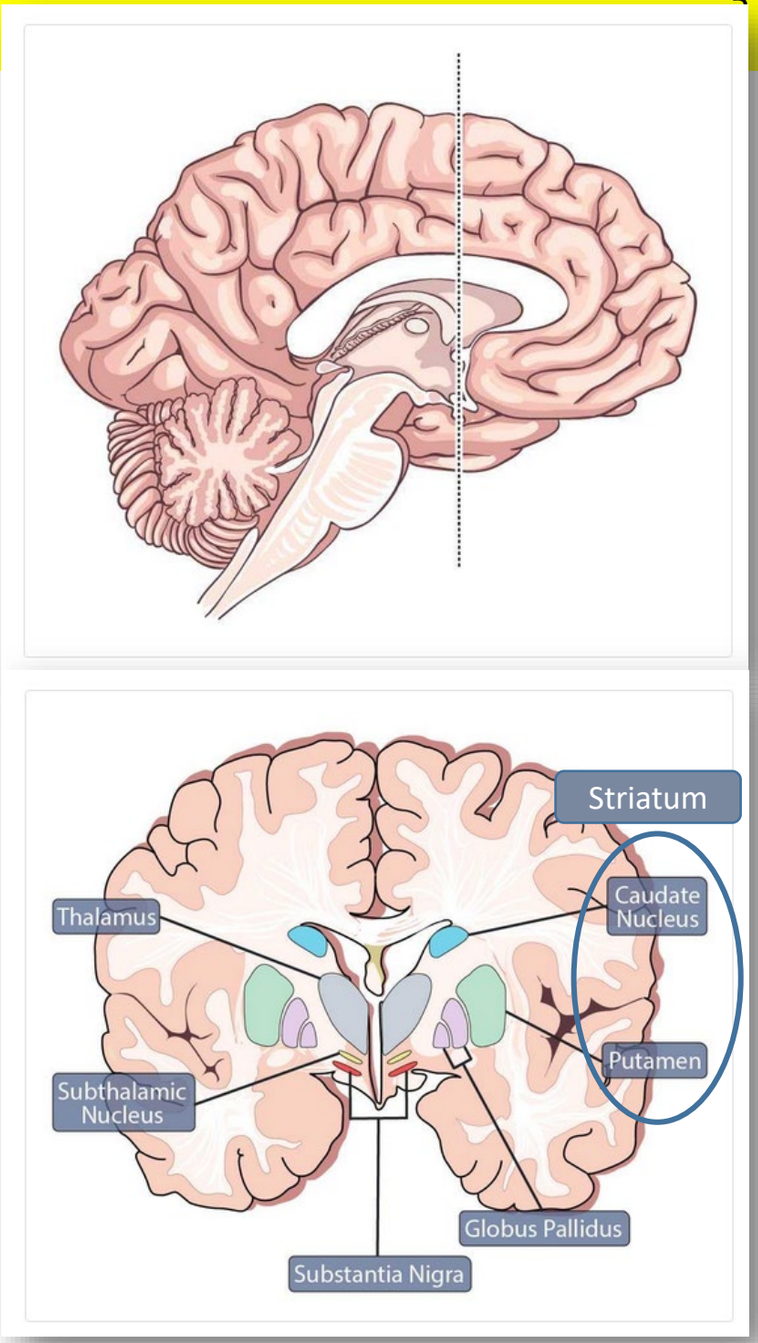
https://miamineurosciencecenter.com/en/conditions/parkinsons-disease/

Neural pathways



Nigrostriatal pathway:

- Modulates direct and indirect pathways
- Involves dopamine neurotransmitter (D1 and D2 receptors)

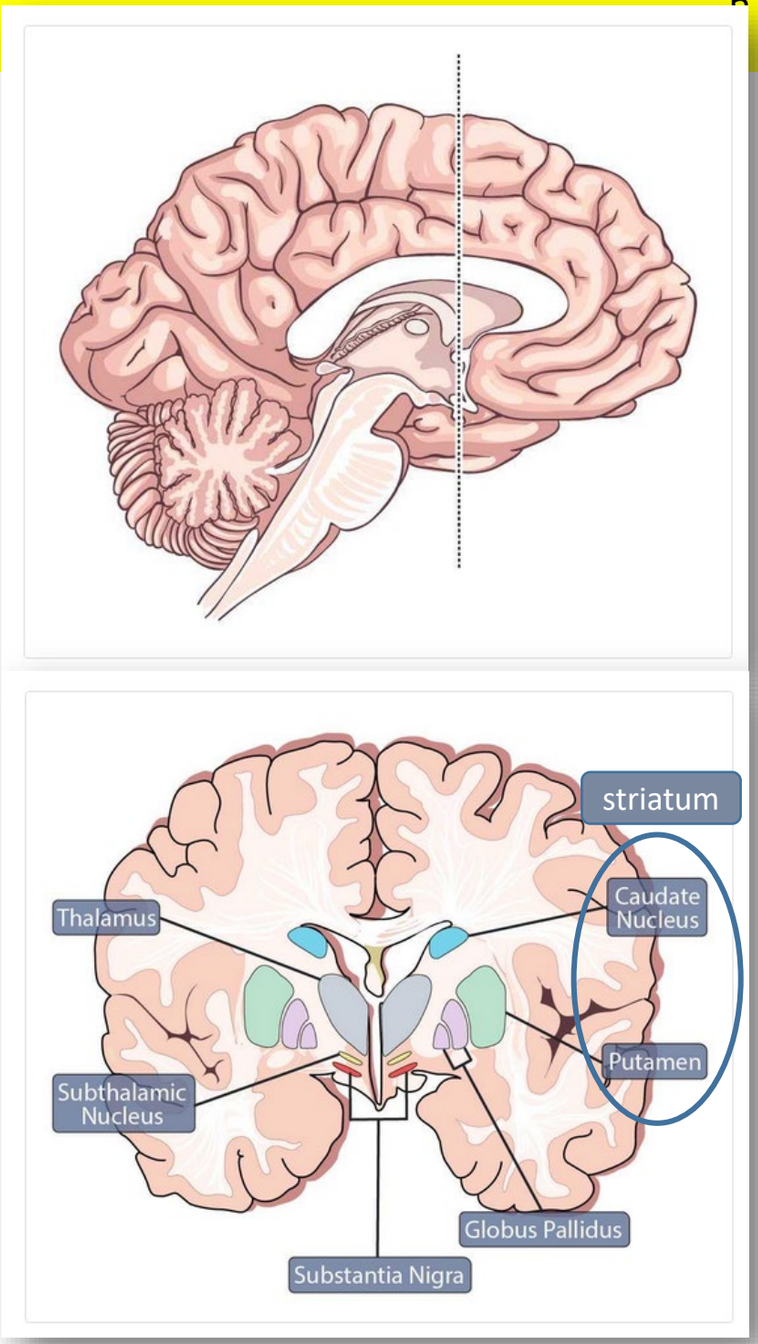


https://miamineurosciencecenter.com/en/conditions/parkinsons-disease/

Parkinson's Disease (PD)

- Progressive loss of dopamine neurons in substantia nigra

→**impact on the nigrostriatal pathway, involved in coordination and facilitation of movement**



https://miamineurosciencecenter.com/en/conditions/parkinsons-disease/

Parkinson’s Disease (PD)

- Symptoms of PD
  - motor symptoms: tremor, rigidity, bradykinesia and akinesia, and posture instability
  - sleep disturbances, mood changes, cognitive impairments
- Exact etiology is unknown, possible causes involve genetics and environment
  - Presence of protein aggregates in dead neurons: Lewy bodies
- 2nd most common neurodegenerative disease affecting 1–2% of the population over 65
- No cure so far, but existence of pharmacological and surgical treatments

Copas, A. N. M., McComish, S. F., Fletcher, J. M., & Caldwell, M. A. (2021). The Pathogenesis of Parkinson's Disease: A Complex Interplay Between Astrocytes, Microglia, and T Lymphocytes?. *Frontiers in Neurology*, *12*.

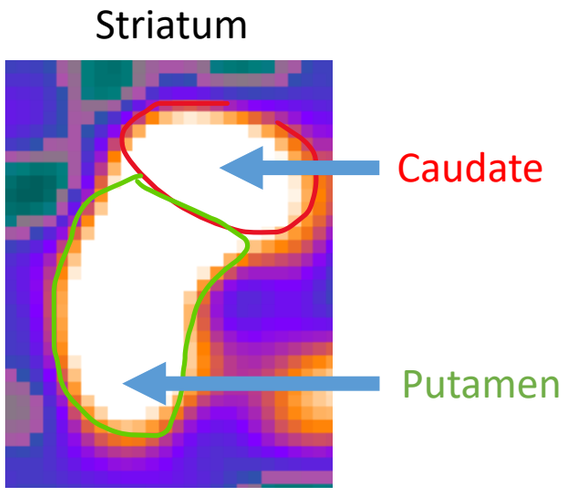
SPECT imaging of PD

- SPECT imaging
  - Injection of radiotracer product composed of Ioflupane and ^{123}I.
  - Ioflupane: strong affinity with a presynaptic transport protein of dopamine (DAT=Dopaminergic Active Transporter)
  - ^{123}I: radioactive substance emitting Gamma radiation detected by SPECT Gamma detectors

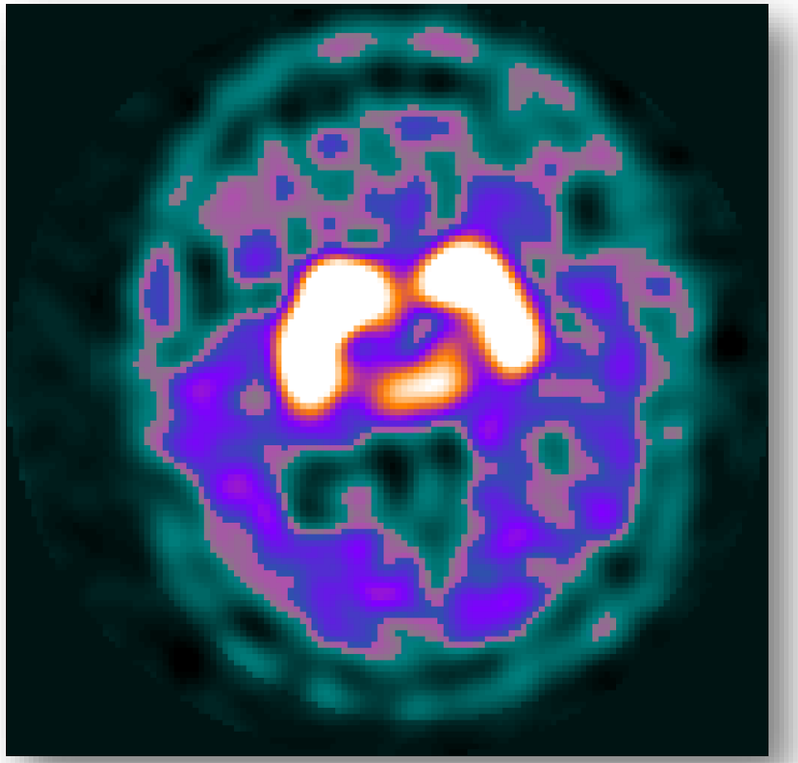
→ Dopamine SPECT imaging
(DaTSCAN = commercial name of the compound)

SPECT-CT
(« GE Healthcare Unveils Discovery NM 630 SPECT | Medgadget », 2011)

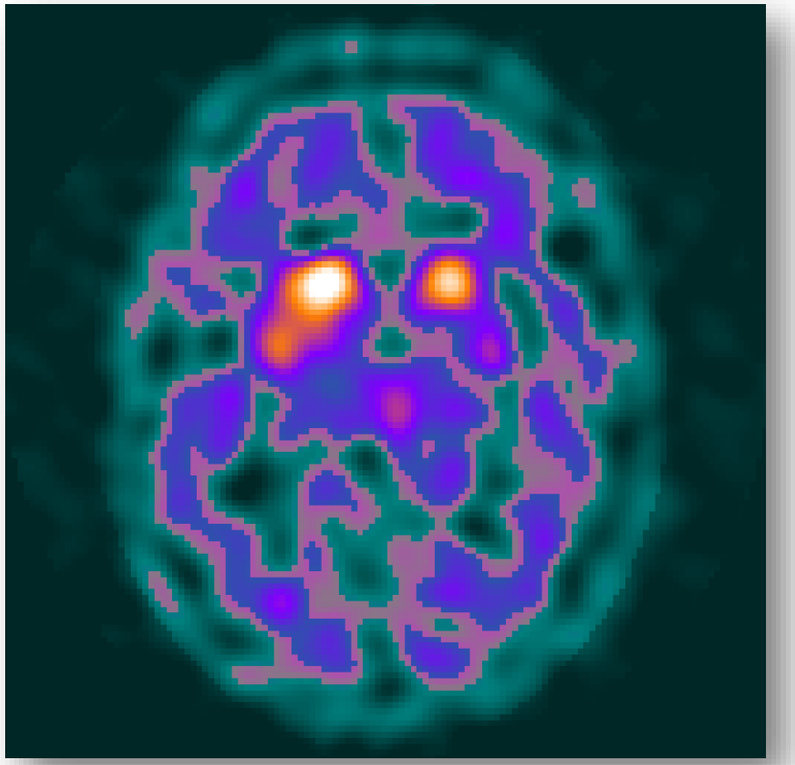
SPECT imaging of PD



Healthy



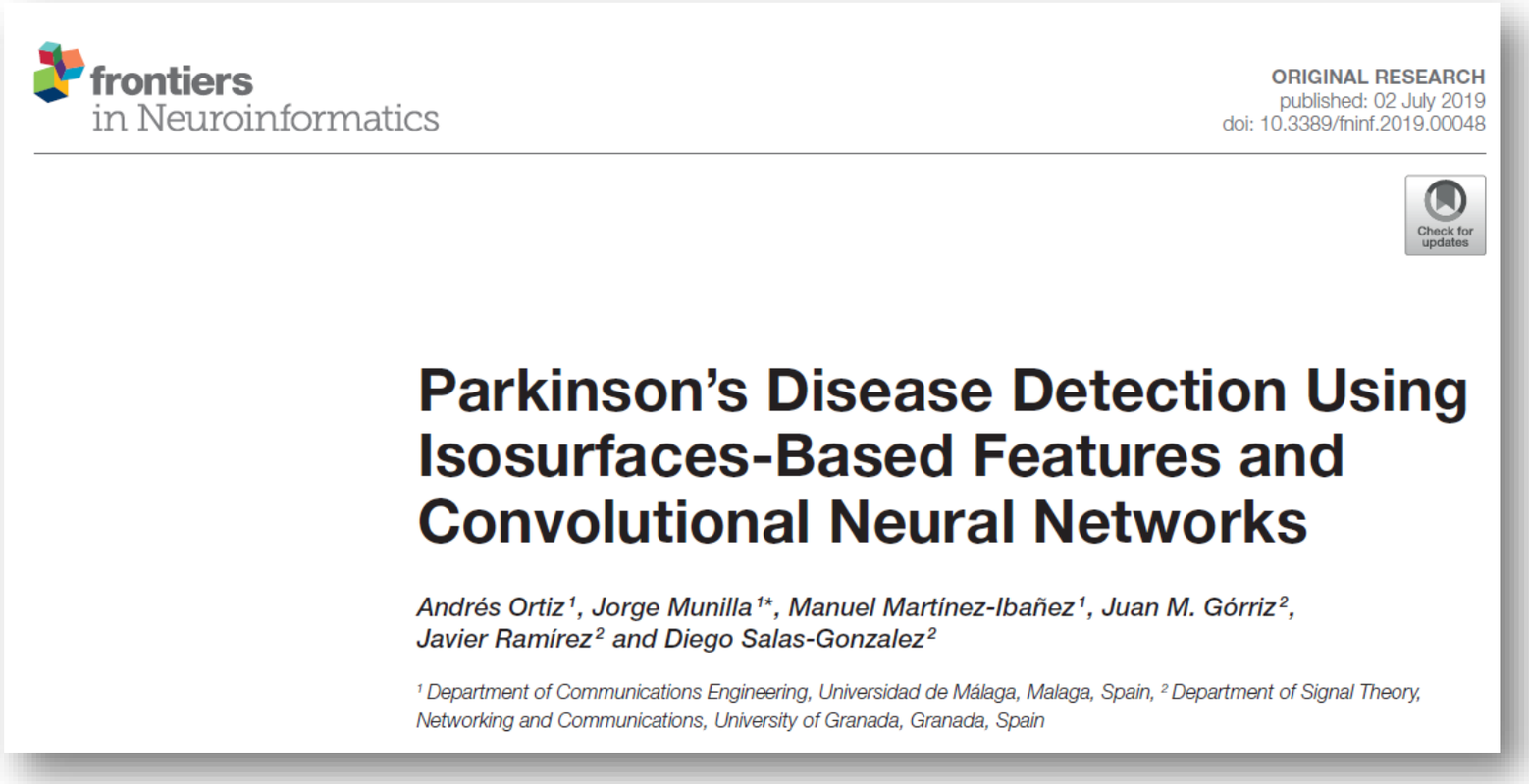
PD



- Visual inspection of dopamine transporter SPECT imaging improves diagnostic confidence
- but depends on readers' level of expertise

→ AI-assisted diagnosis of PD using Dopamine SPECT imaging

Paper presentation



frontiers in Neuroinformatics

ORIGINAL RESEARCH
published: 02 July 2019
doi: 10.3389/fninf.2019.00048

Check for updates

Parkinson's Disease Detection Using Isosurfaces-Based Features and Convolutional Neural Networks

Andrés Ortiz[1], Jorge Munilla[1], Manuel Martínez-Ibañez[1], Juan M. Górriz[2], Javier Ramírez[2] and Diego Salas-Gonzalez[2]*

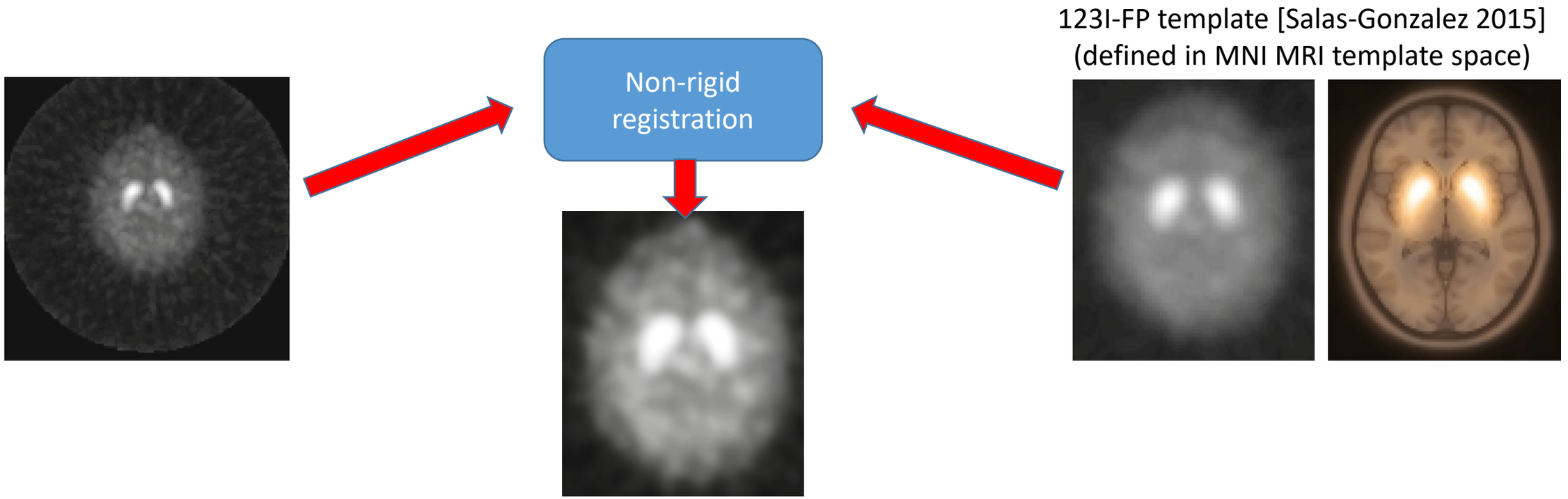
[1] Department of Communications Engineering, Universidad de Málaga, Malaga, Spain, [2] Department of Signal Theory, Networking and Communications, University of Granada, Granada, Spain

Data collection and processing

- Parkinson's Progression Markers Initiative (PPMI) database
  - *N*=269 with 156 PD and 111 normal control (NC) cases

Data collection and processing

- Spatial normalization



Salas-Gonzalez, D., Górriz, J. M., Ramírez, J., Illán, I. A., Padilla, P., Martínez-Murcia, F. J., & Lang, E. W. (2015). Building a FP-CIT SPECT Brain Template Using a Posterization Approach. Neuroinformatics, 13(4), 391–402. doi:10.1007/s12021-015-9262-9

Data collection and processing

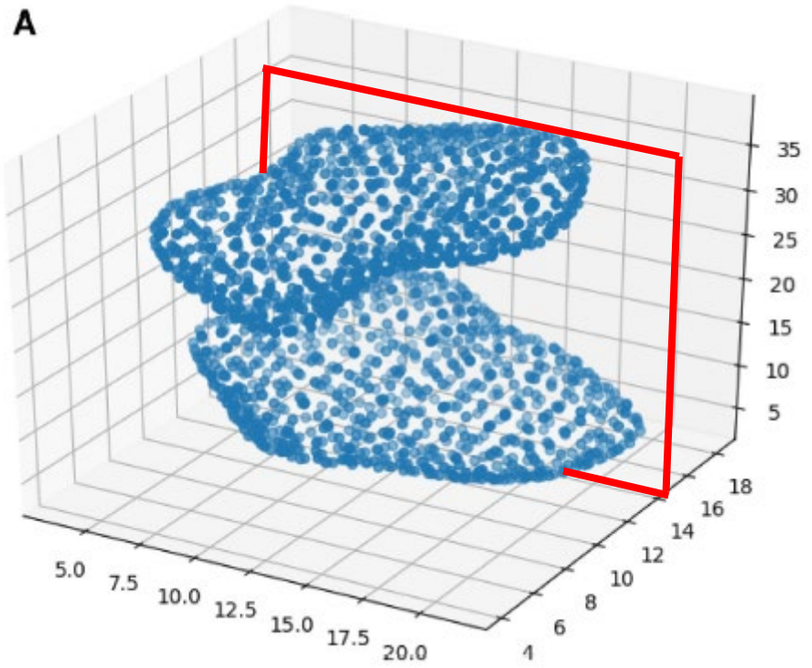
- Intensity normalization

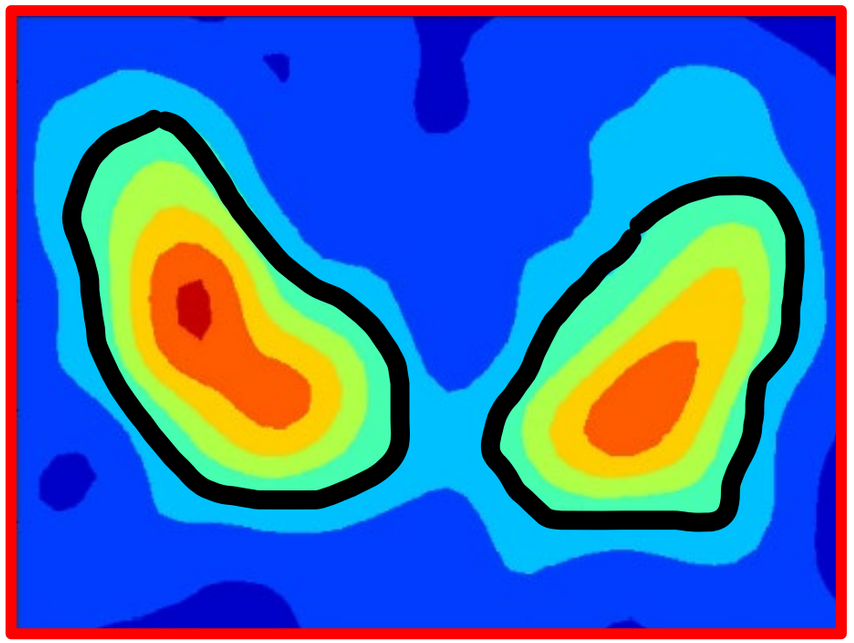
$$\hat{\mathbf{I}}_i = \mathbf{I}_i / I_{n,i}, \rightarrow [0, 1]$$

With $I_{n,i}$ = mean over all voxel intensities including striatum

Data collection and processing

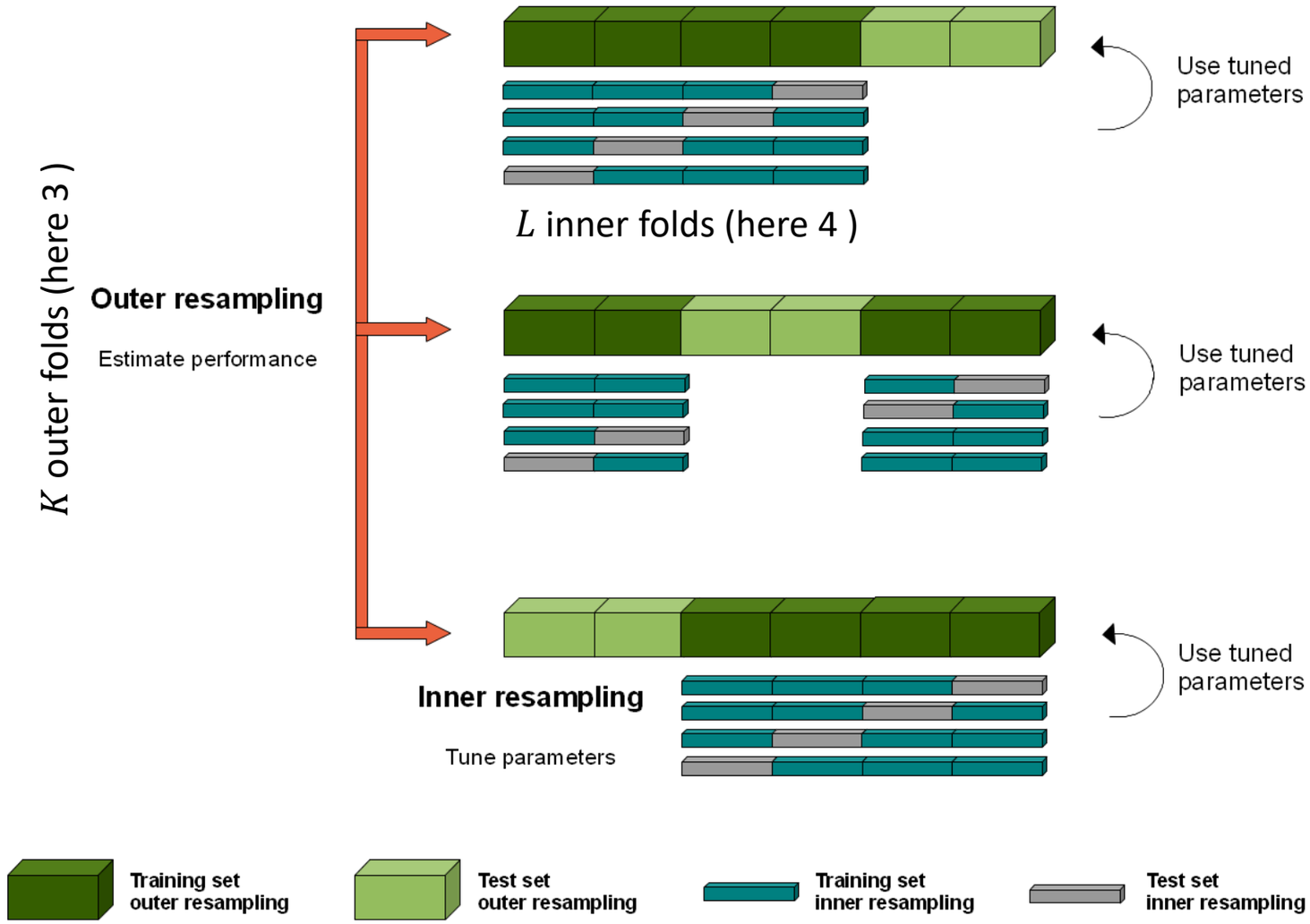
- Manual delineation of striatum region in a constant 29x25x41 subimage
- Isoline computation at threshold $\theta = [0.4, 0.5, 0.6, 0.7, 0.8]$
  - Threshold image by zeroing any intensity < θ





Nested cross-validation

- Stratified folds
- $L = K = 10$
- Metrics averaged over K outer folds
  - Accuracy (Acc)
  - Sensitivity (Se)
  - Specificity (Sp)
  - AUC ROC curve



https://mlr.mlr-org.com/articles/pdf/img/nested_resampling.png

ML architecture

- CNN models
  - LeNet (LeCun et al. 1998)
  - AlexNet (Krizhevsky et al 2012)
- Using single or multiple isoline images as input
- No specific info on training (meta params, loss function, etc.)

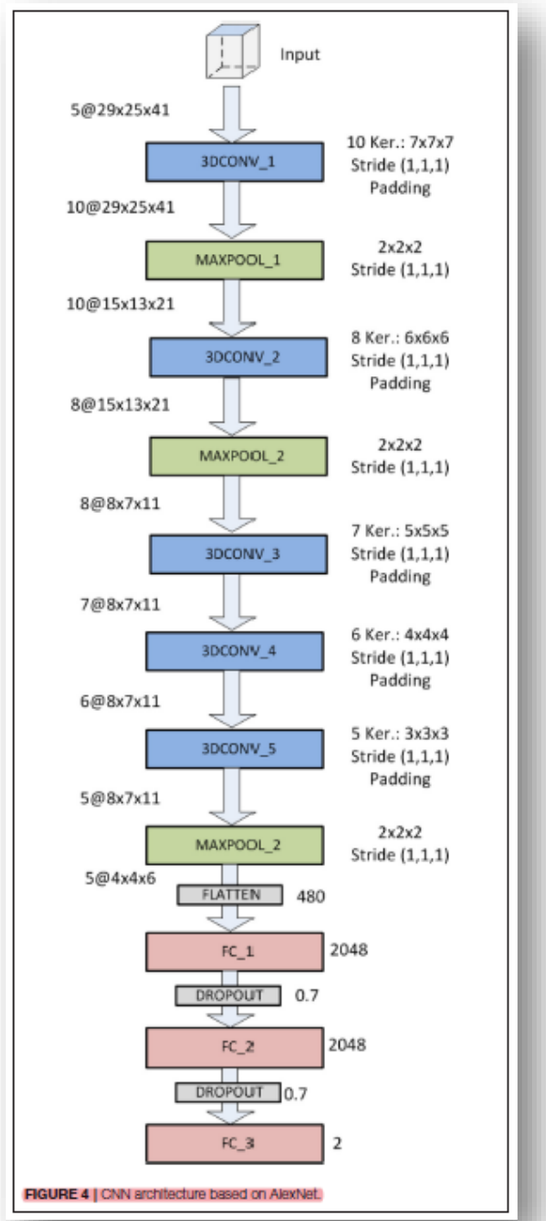


FIGURE 4 | CNN architecture based on AlexNet.

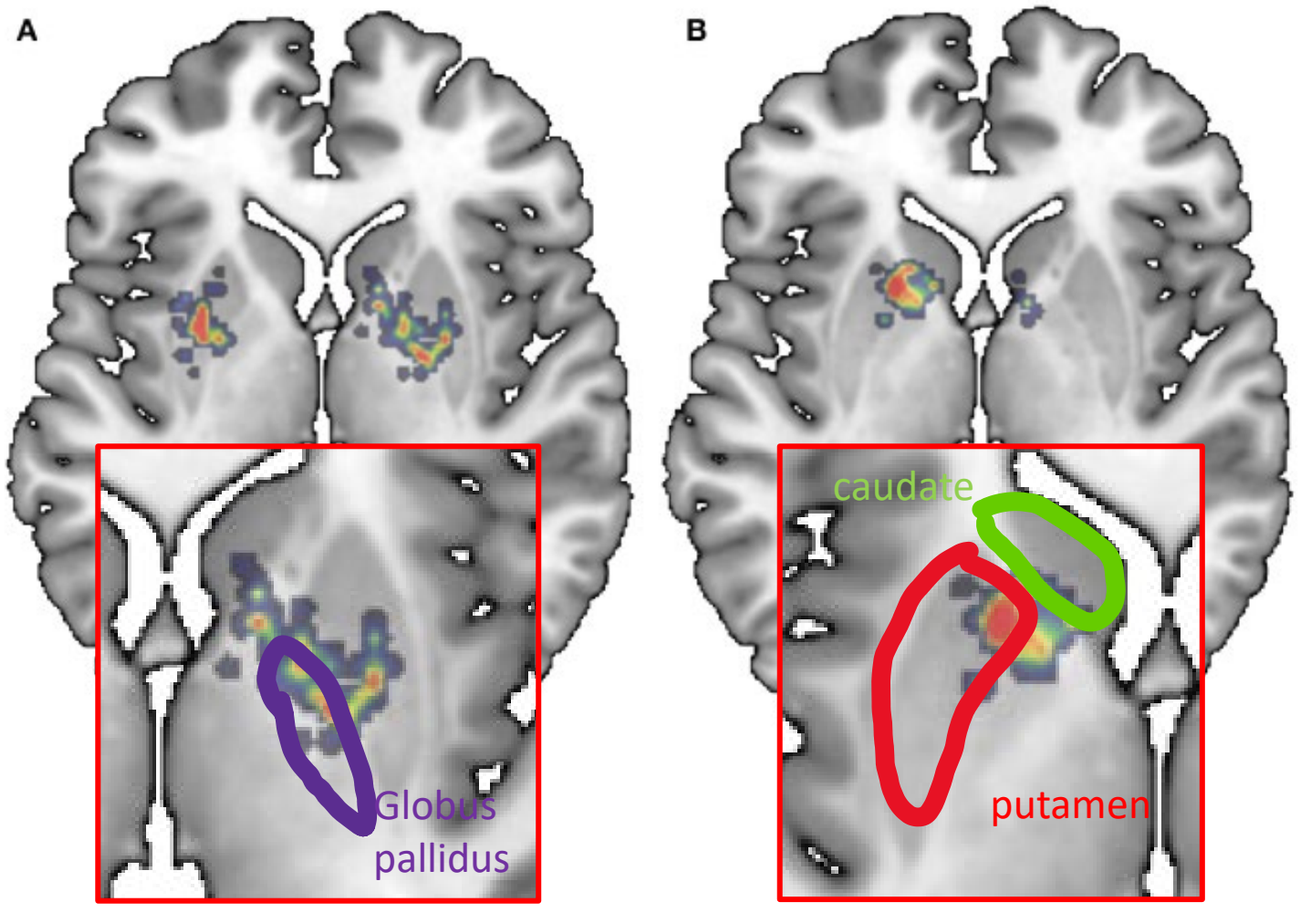
Key results

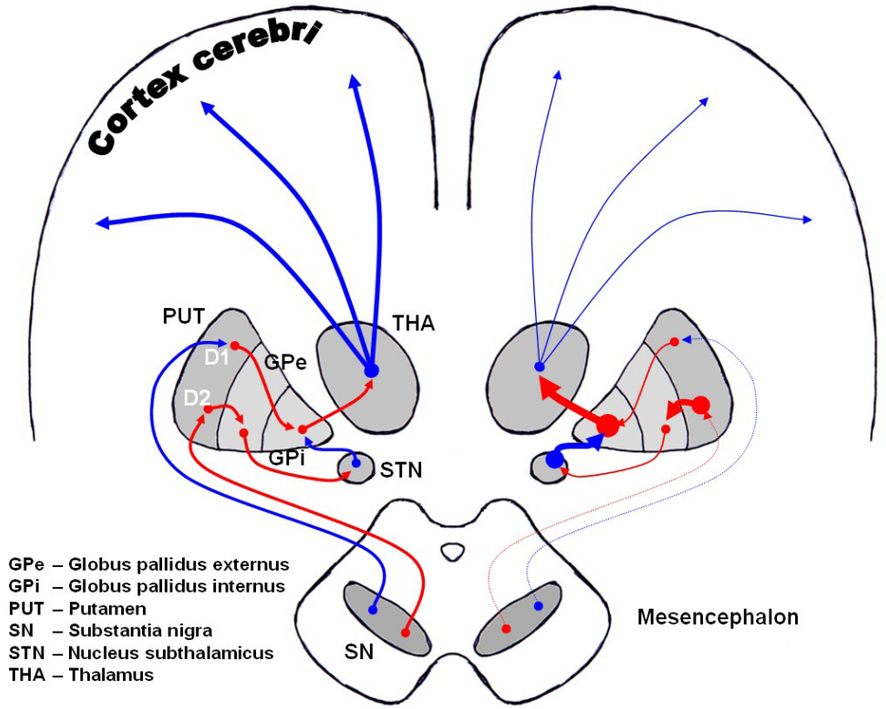
TABLE 2 | Classification results using different methods.

Method	Accuracy	Sensitivity	Specificity	AUC
EMD (Rojas et al., 2013)	0.95	0.95	0.94	0.94
Significance M. (Martínez-Murcia et al., 2014a)	0.92	0.95	0.89	0.90
Brahim et al. (2015)	0.92	0.94	0.91	–
VAF	0.8 ± 0.05	0.72 ± 0.17	0.85 ± 0.14	0.87
PCA	0.87 ± 0.04	0.96 ± 0.03	0.86 ± 0.04	0.9
EfPCA (Ortiz et al., 2018)	0.93 ± 0.05	0.97 ± 0.08	0.88 ± 0.05	0.94
LeNet-based	**0.95 ± 0.03**	**0.94 ± 0.04**	**0.95 ± 0.04**	**0.97**
AlexNet-based	**0.95 ± 0.03**	**0.95 ± 0.05**	**0.95 ± 0.04**	**0.97**

Key results

Saliency maps





https://commons.wikimedia.org/wiki/File:DA-loops_in_PD.jpg

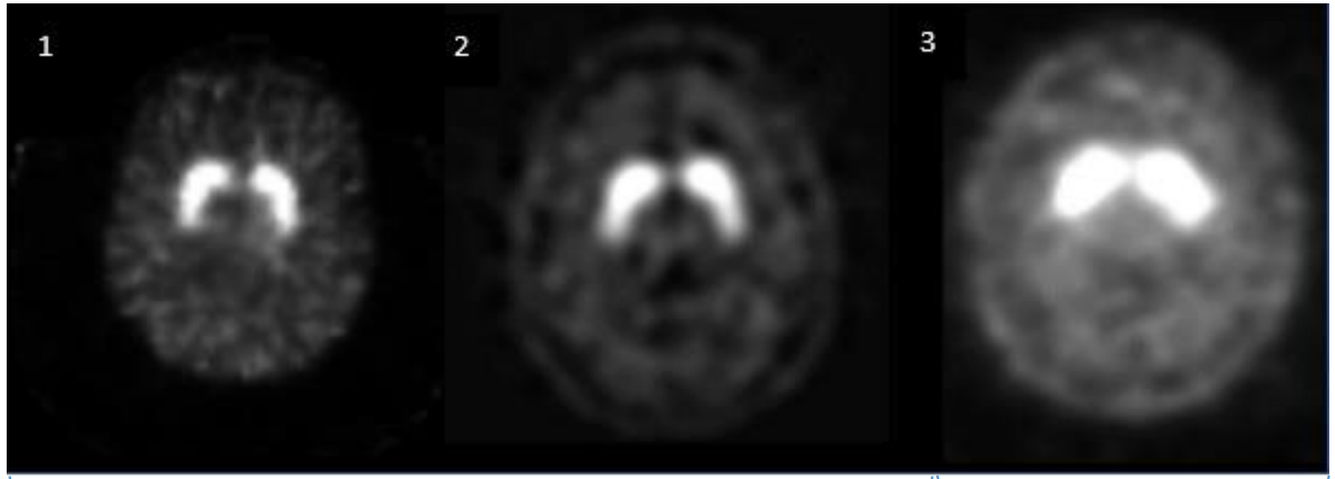
DeepDAT project

DeepDAT project

- Master Thesis (2020-2021): *Adrien Arrigo et Guillaume Favre-Gillioz (2021) L'intelligence artificielle au service de la détection de la maladie de Parkinson à l'Iode-123 Ioflupane en Médecine Nucléaire. Mémoire de Master HES-SO/UNIL Sciences de la santé*
- project funded by the industry in collaboration with HUG (2022):
  - Investigate **DL-based approach** that exploits DaTSCAN SPECT imaging
  - Investigate the inclusion of **additional information** such as image quantitative measurements (e.g., striatal binding ratio), demographic information
  - Support **clinical interpretation by providing AI explainability tools**
  - Evaluate and train the DL approach of **various clinical databases**

Schmid, J., Arrigo, A., Favre-Gillioz, G., Nicastro, N., Garibotto, V. (2022) Investigating data fusion and training strategies of artificial intelligence for the diagnosis of Parkinson's disease with Dopamine SPECT imaging. European Congress of radiology, July 2022.

Datasets

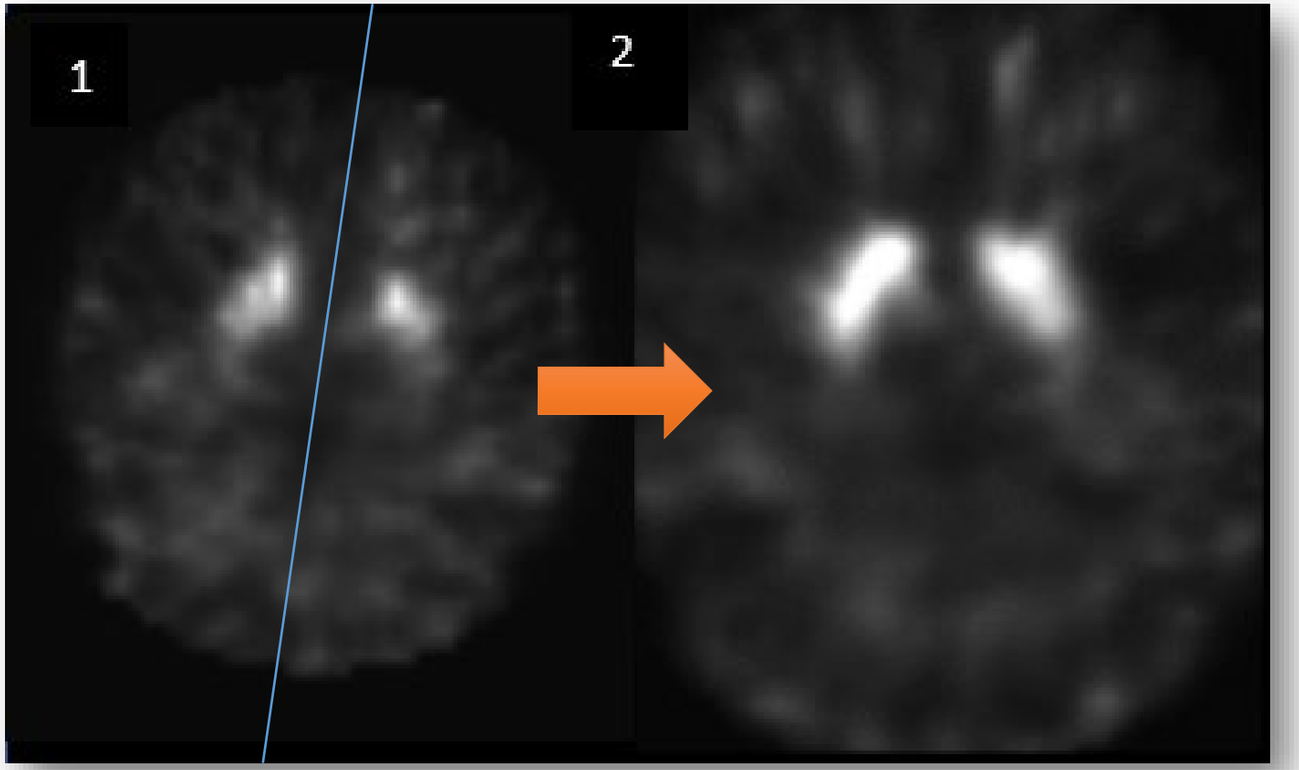


Dataset	#Control	#PD	SNR	Resolution	Contrast	Matrix size
Local dataset 1	72	66	bad	very good	good	128 x 128
Local dataset 2	50	49	excellent	excellent	very good	128 x 128
PPMI	198	466	good	good	good	128 x 128

Data transformation

Spatial normalization

- Affine + non-rigid alignment with reference template defined in MNI space
- SPM 12



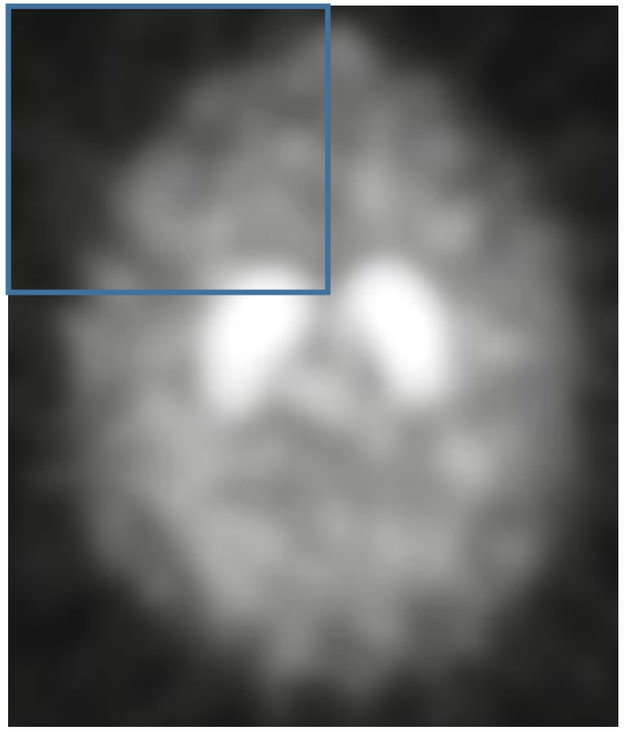
Intensity normalization

Very basic: $\rightarrow [0, 1]$

Optional intensity smoothing

DL architecture and training strategies

- ResNet 3D architecture with 4 levels of strided convolutions and residuals units [He2016]
- Direct use of image with a block-based approach :
  - Do not isolate striatal area
  - Let DL extract relevant image features



[He2016a] K. He et al. Deep residual learning for image recognition. CVPR 2016.
[He2016b] K. He et al. Identity Mappings in Deep Residual Networks. ECCV 2016

DL architecture and training strategies

- Data augmentation
- Data and class balancing techniques: stratified sets and sampling, focal softmax cross entropy loss
- Many training/evaluation strategies, e.g. using some or all datasets, transfer learning from one to another

Results – PPMI dataset

Approach	Acc [%]	Se [%]	Sp [%]	AUC [%]
Ours	95.6	98.6	90	99
Magesh et al. 2015	95.2	97.6	90.9	94
Pianpanit et al. 2017	96.9	96.4	97.9	99
Choi et al. 2017	96	94.2	100	99
Ortiz et al. 2016	95	96	94	95
Ortiz et al. 2019	95	95	95	97
Quan et al. 2019	98.5	99	97.7	99

frontiers in Neuroinformatics

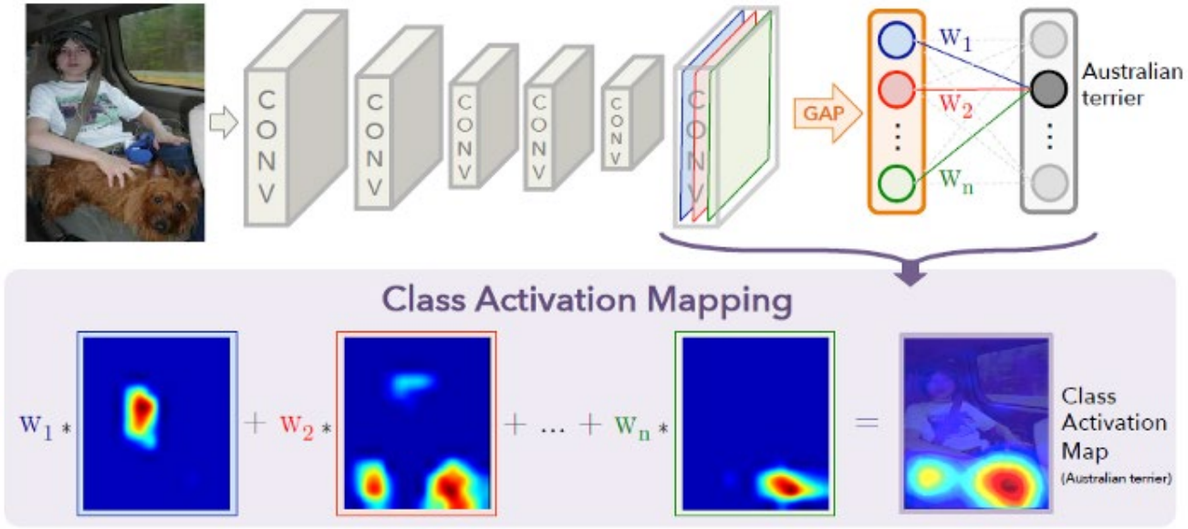
- Trained with PPMI and tested on PPMI data
- PPMI subjects, number of training/test images and prevalence differ among studies.

Magesh et al. (2020). An Explainable Machine Learning Model for Early Detection of Parkinson's Disease using LIME on DaTSCAN Imagery. *Computers in Biology and Medicine*, *126*, 104041. https://doi.org/10.1016/j.compbiomed.2020.104041
Choi et al.. (2017). Refining diagnosis of Parkinson's disease with deep learning-based interpretation of dopamine transporter imaging. *NeuroImage: Clinical*, *16*, 586-594. https://doi.org/10.1016/j.nicl.2017.09.010
Quan et al.. (2019). DaTscan SPECT Image Classification for Parkinson's Disease. *arXiv:1909.04142 [cs, eess, stat]*. http://arxiv.org/abs/1909.04142
Ortiz et al. (2016). Automated Diagnosis of Parkinsonian Syndromes by Deep Sparse Filtering-Based Features. In *Innovation in Medicine and Healthcare 2016* (Vol. 60, p. 249-258). https://doi.org/10.1007/978-3-319-39687-3_24
Pianpanit et al. (2017). Neural network interpretation of the Parkinson's disease diagnosis from SPECT imaging. *arXiv:1908.11199 [cs, eess, stat]*. http://arxiv.org/abs/1908.11199

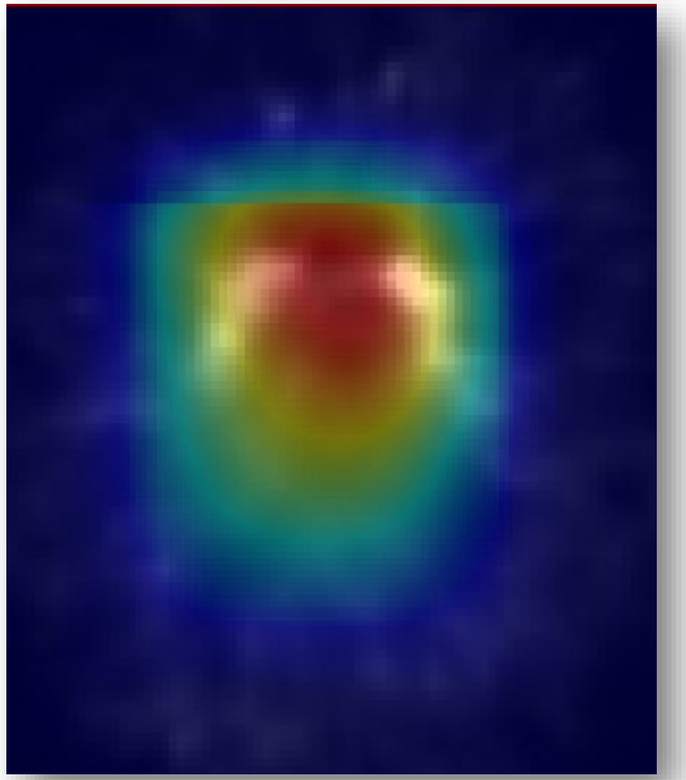
Results – local dataset

Approach	Acc [CI@0.05]	Se	Sp	AUC
Training with dataset 1	82.1 [72.1-92.2]	82.8	81.5	84.5
PPMI → Training with dataset 1 transfer learning	87.5 [78.8-96.2]	82.8	92.6	94

Results – explainability



- Weighted sum of convolution layers used in global average pooling (GAP)
- Use weights of the softmax layer for a given class



Class activation map
(Zhou et al. 2016)

- Network focuses on the striatum area
- CAM resolution too low for fine analysis

Zhou, B., Khosla, A., Lapedriza, A., Oliva, A., & Torralba, A. (2016). Learning deep features for discriminative localization. In *Proceedings of the IEEE conference on computer vision and pattern recognition* (pp. 2921-2929).

Take-home message

- **Inevitable variability** in machinery and protocols in clinical practice!
- **Size matters**: augmentation is positive, training with largest dataset is more effective
- **Normalization matters**: intra- and inter-datasets normalizations yield better results (→ investigate intensity normalization)
- **Focus on information** (→the striatum area, include quantitative measurements)
- **Share knowledge**: Transfer learning promising to exploit other (largest) datasets

Thank you for your attention!

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