Mount Sinai

Neuropathology
Brain Bank
at Mount Sinai

Computer Vision & Machine Learning in Digital Neuropathology

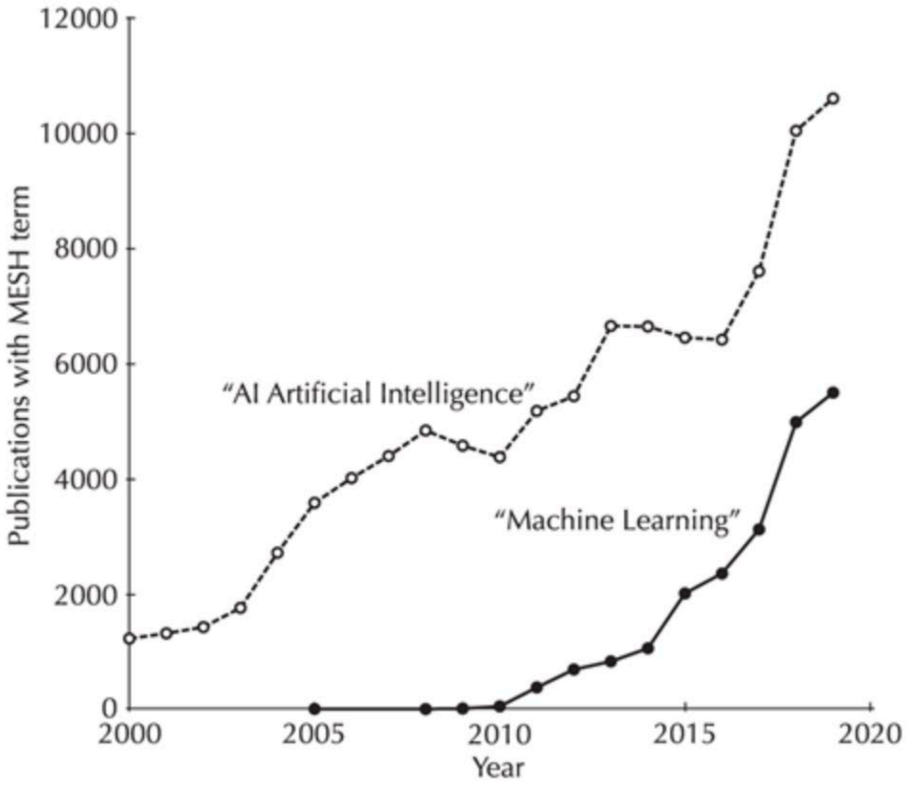
Kurt Farrell, PhD
Assistant Professor, Department of Pathology, Icahn School of Medicine at Mount Sinai

Fall ADRC meeting, Chicago 2022

Outline

- **Overview on AI /machine learning in digital pathology**

- **Current work: machine learning approaches to investigate tau pathology**
  - **Supervised**
  - **Semi-supervised**
  - **Unsupervised**



Harrison et. al. Arch Pathol Lab Med 2021

Types of Machine Learning Models

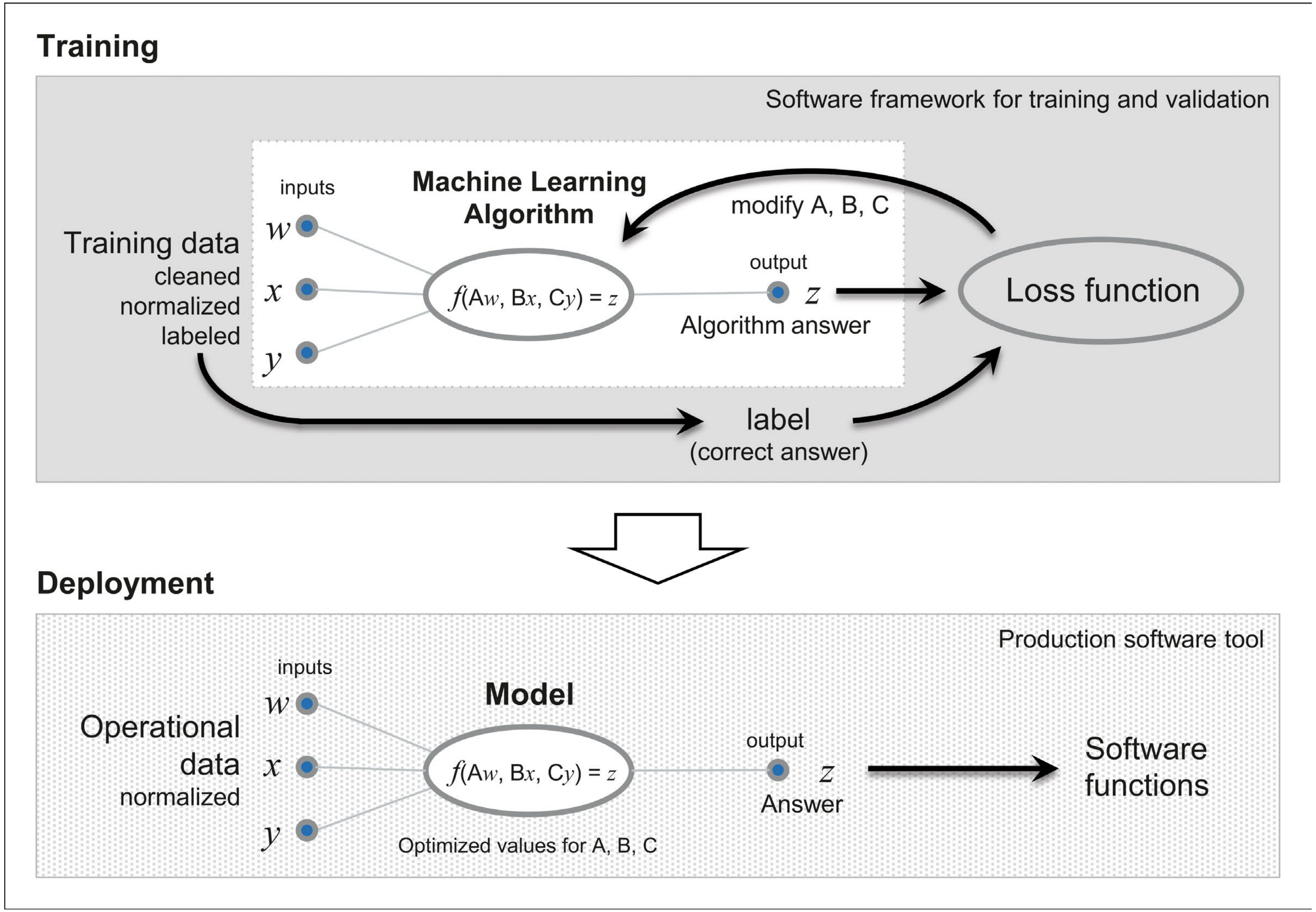
Artificial Intelligence — Software that mimics or models human judgement

- **Expert systems** — Depends on human-curated knowledge base rules
- **Machine learning** — Learns patterns and relationships from data

	Algorithm categories	*Example*
Supervised or unsupervised	**Neural Networks**	Convolutional neural network
Supervised	**Regression methods**	Linear regression
Supervised	**Classification methods**	K-nearest neighbors
Supervised	**Ensemble methods**	Radom forest
Unsupervised	**Clustering methods**	Hierarchical cluster analysis
Unsupervised	**Dimensionality Reduction Methods**	Principal components analysis

Modified from Harrison et. al. Arch Pathol Lab Med 2021

Machine learning fundamentals

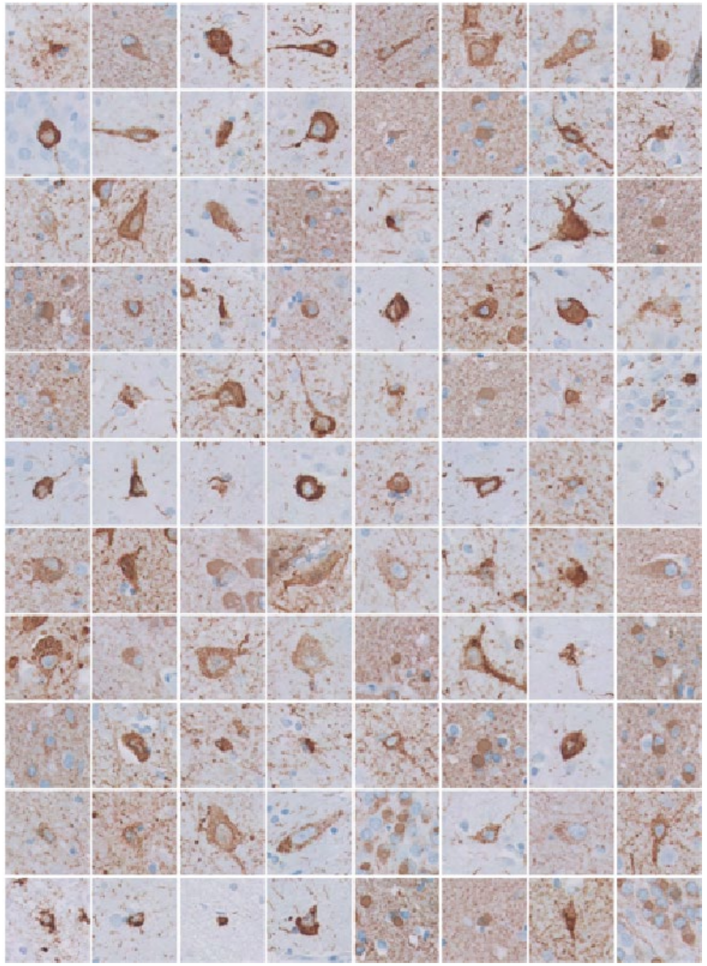


Harrison et. al. Arch Pathol Lab Med 2021

Muffin or chihuahua?

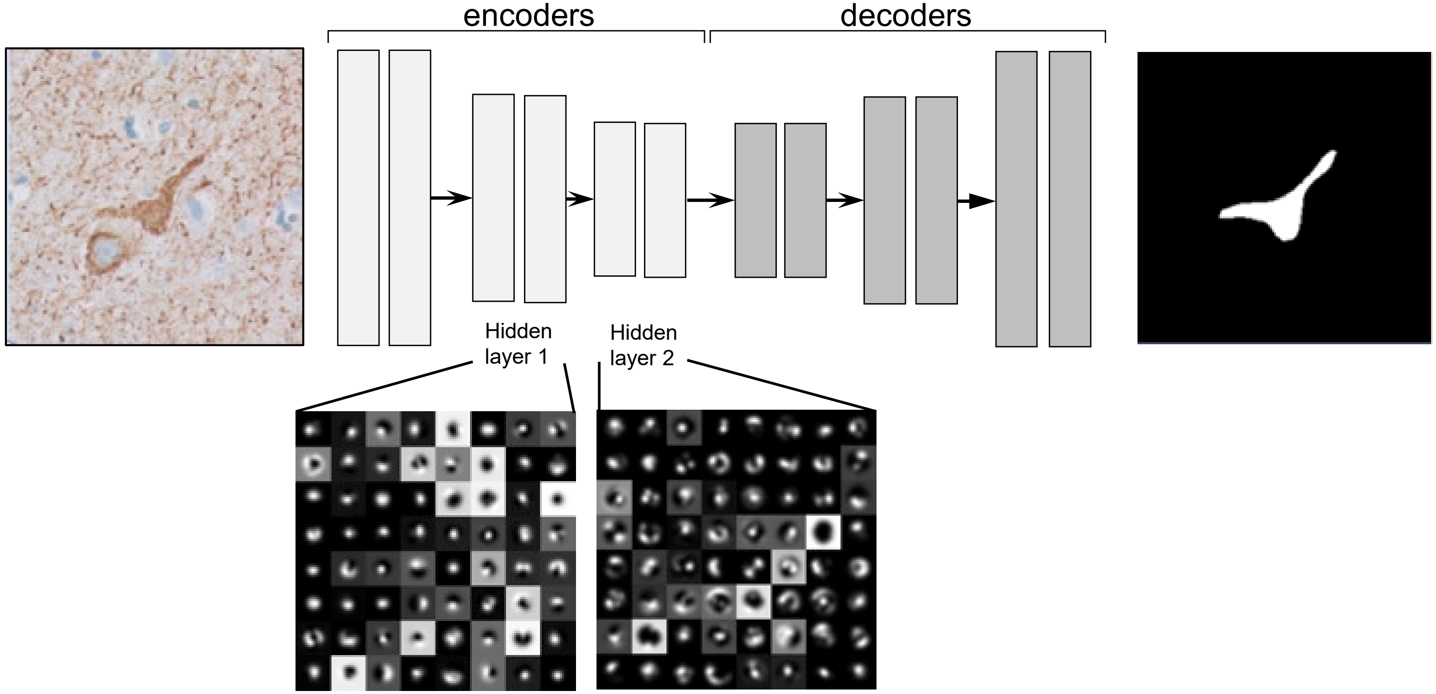
A neural network for NFT detection

a



n=3177 NFT patches

b

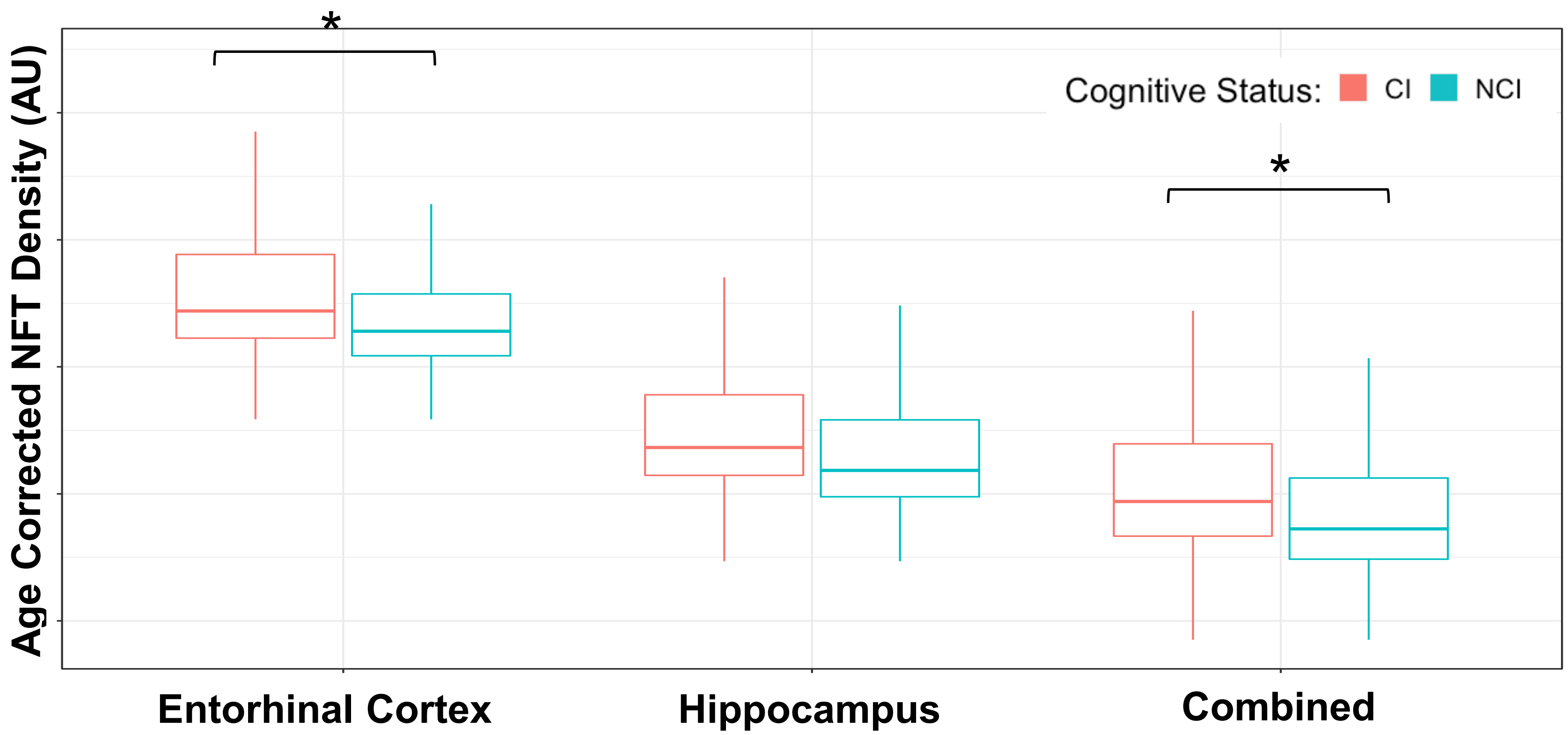


Performance of the fully convolutional neural network for NFT detection

Metrics	Training/Validation	Testing
Recall, TP/(TP+FN), Sensitivity	0.91	0.92
Precision, TP/(TP+FP), PPV	0.80	0.72
F1 score (harmonic mean of precision and recall)	0.85	0.81

Signaevski, Prastawa, Farrell et al., Laboratory Investigations 2019

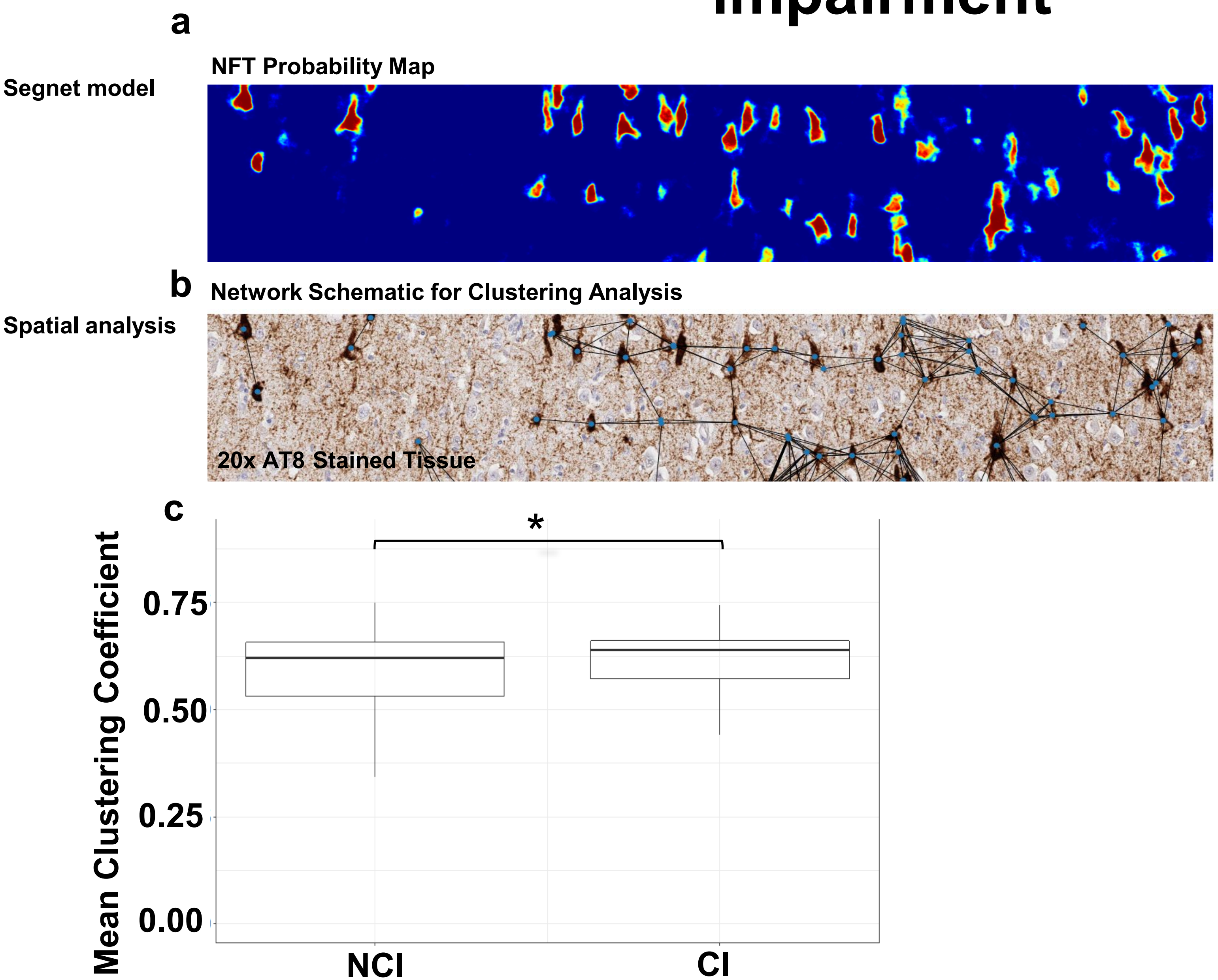
AI quantification of NFT correlates with cognitive status



Odds of being cognitively impaired at death

Measure of Tau Burden	Unadjusted			Age Adjusted		
	OR	**95% CI**	***p value***	**OR**	**95% CI**	***p value***
Braak NFT stage	1.09	0.94 - 1.26	0.2769	0.90	0.77 - 1.05	0.1691
AI-detected NFT density						
Entorhinal Cortex	1.38	1.18 - 1.61	**0.0001**	1.23	1.06 - 1.43	**0.0430**
Hippocampus	1.40	1.20 - 1.64	**0.0001**	1.21	1.04 - 1.41	0.0588
Combined	1.45	1.24 - 1.70	**>0.0001**	1.26	1.08 - 1.47	**0.0415**

NFT spatial clustering is higher in subjects with cognitive impairment



Marx et al, Acta NP Com. (accepted), 2022

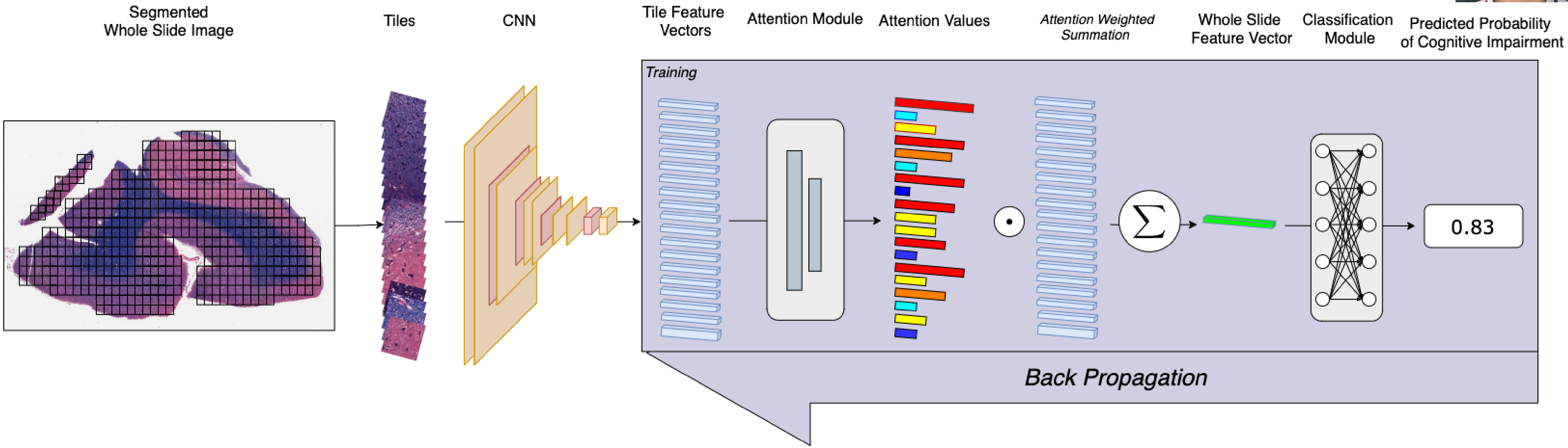
Conclusions

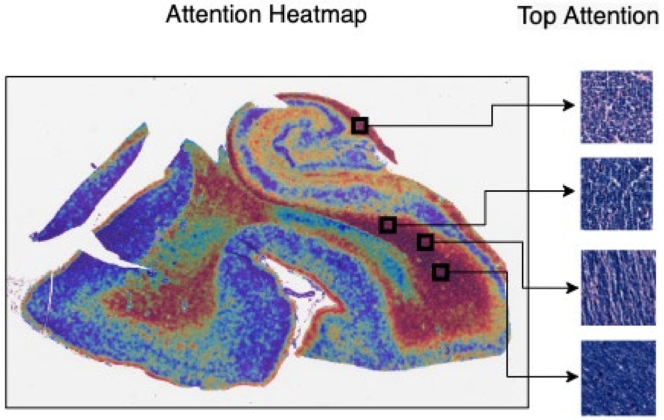
- **A.I. based counting of individual tangles across the medial temporal lobe was the strongest predictor of cognitive impairment when adjusting for age**

- **Despite including PART "possible" subjects (CERAD=1) A.I. based measures were still able to accurately predict cognitive status**

- **Novel graph theory spatial clustering modeling predicted cognitive status**

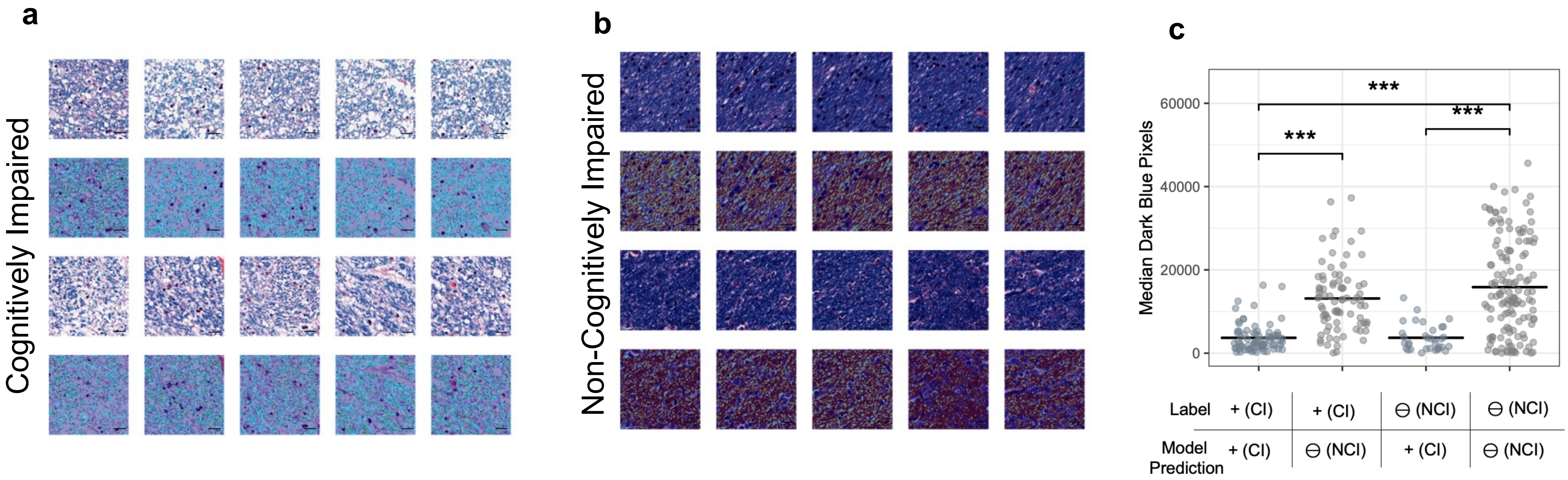
Weakly supervised deep learning pipeline





- Aging cohort whole slide image data
- n = 367 with any clinical evidence of cognitive impairment, n = 349 without

Micro-anatomic focus of model attention reveals changes in white matter



Annotation Heatmaps:

- Red = (+) Dark blue pixels
- Blue = (+) Light blue pixels

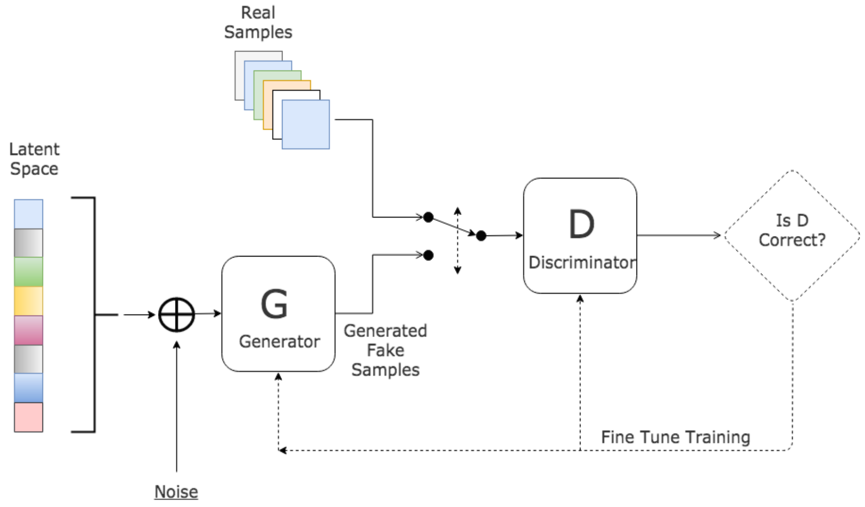
McKenzie et al, Acta NP Com., 2022

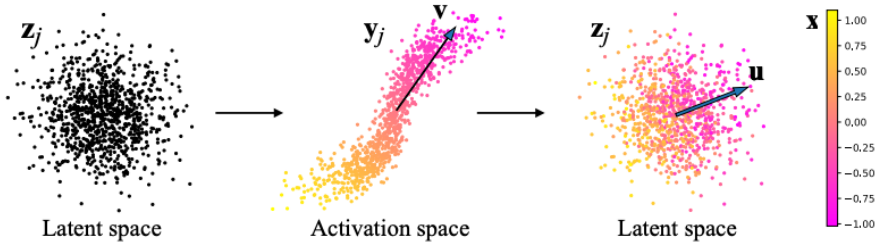
Conclusions

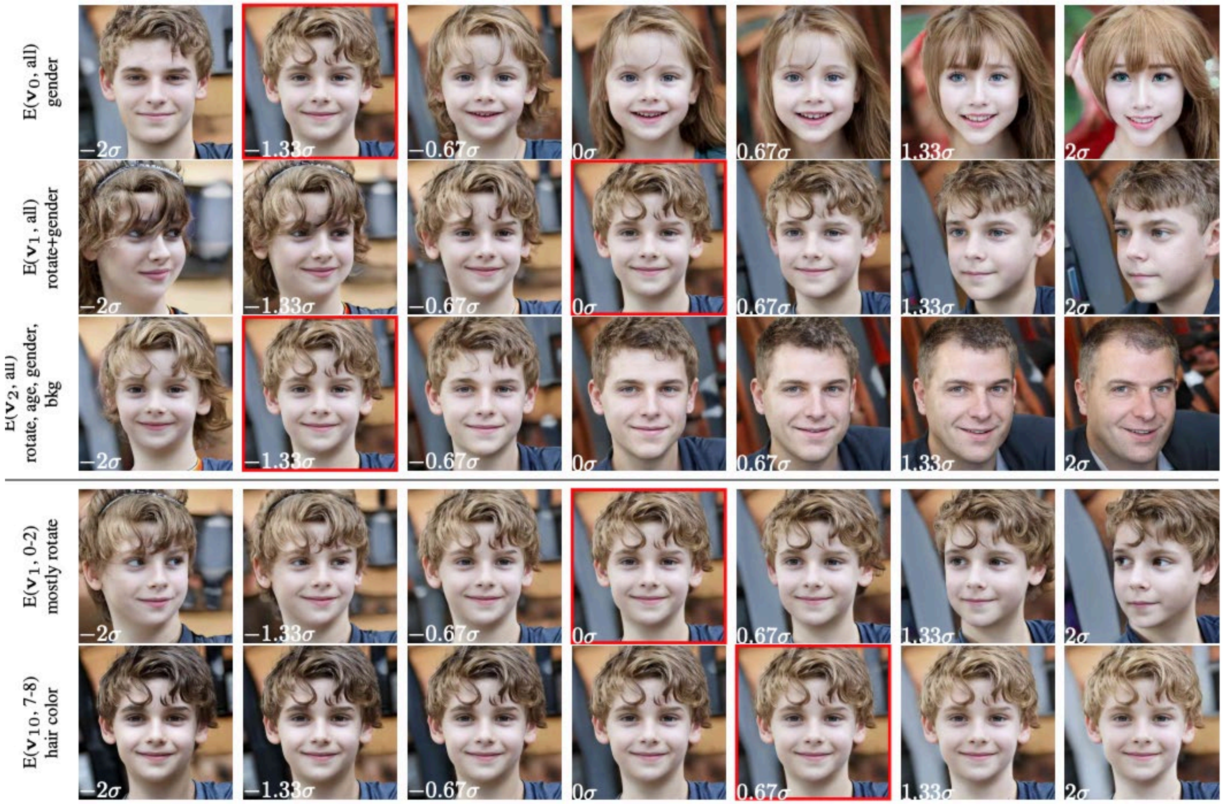
- **Despite noisy labels of cognitive impairment, we found that our trained models performed significantly above chance level at predicting the presence or absence of cognitive impairment.**

- **Interpretation studies showed that on a macroanatomic level, the models had higher attention on white matter than gray matter. And on a microanatomic level, the highest attention tiles showed differences in dark blue staining intensity, suggestive of differences in myelin density.**

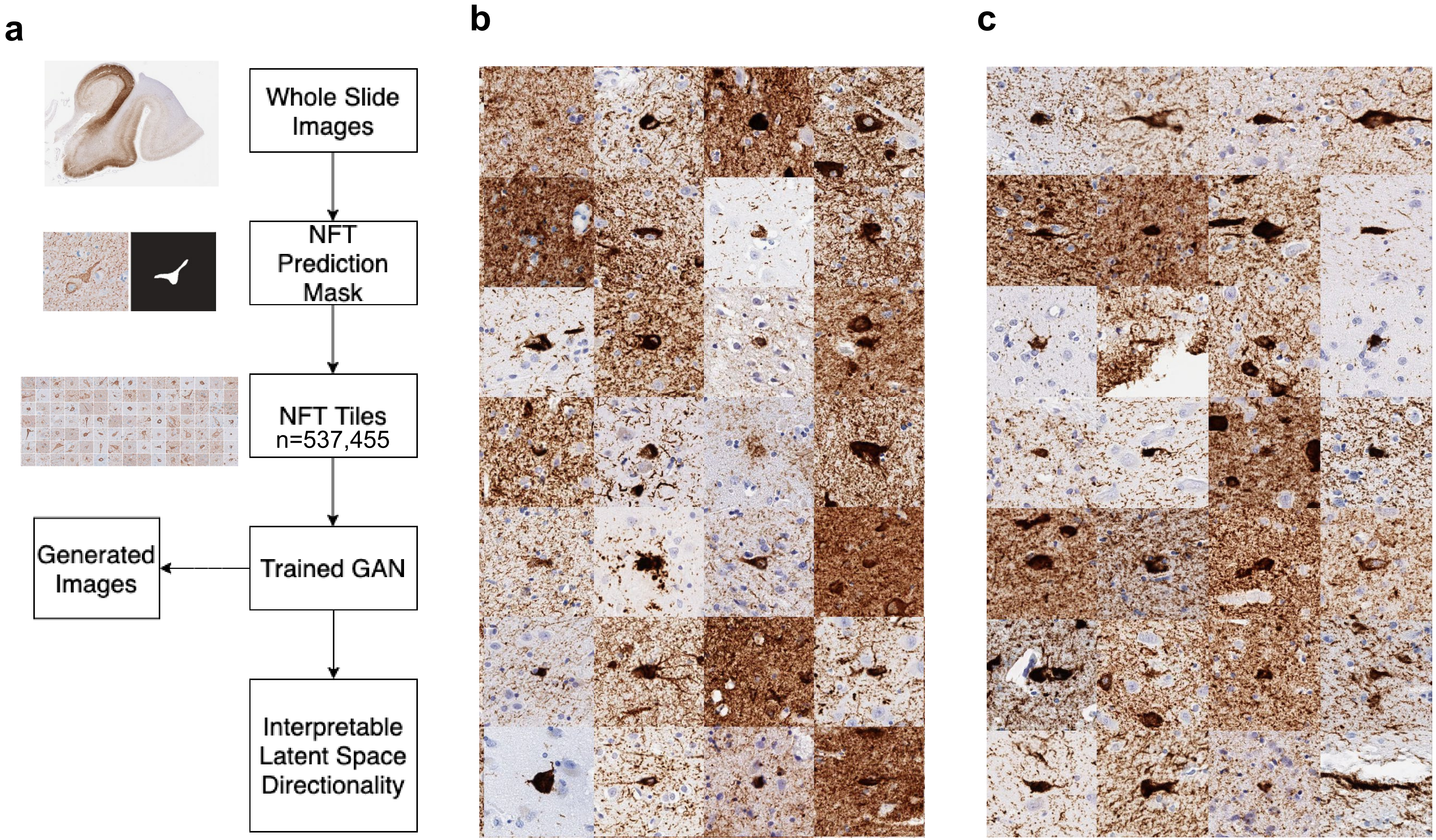
Generative Adversarial Networks: Unsupervised Learning to Analyzing Neurofibrillary Tangle Morphology







Generative adversarial network (stylegan2)



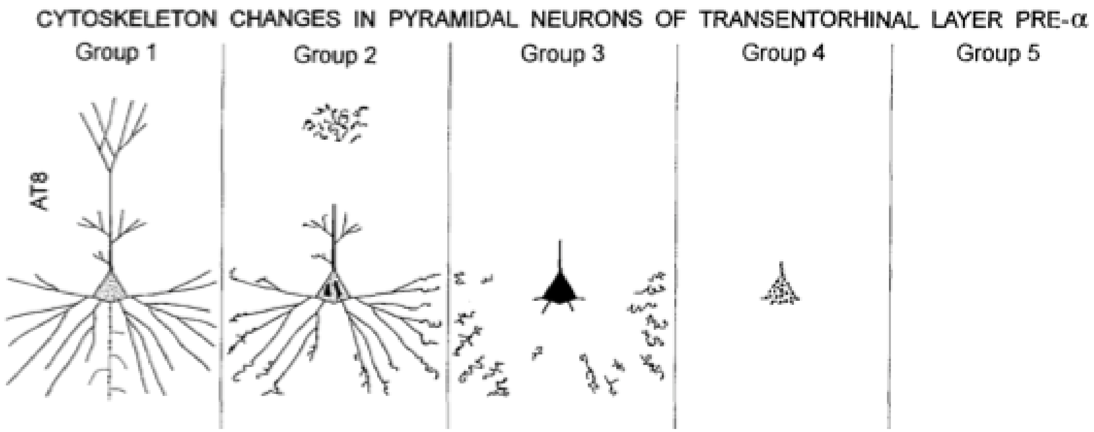
Training data

Synthetic (fake)

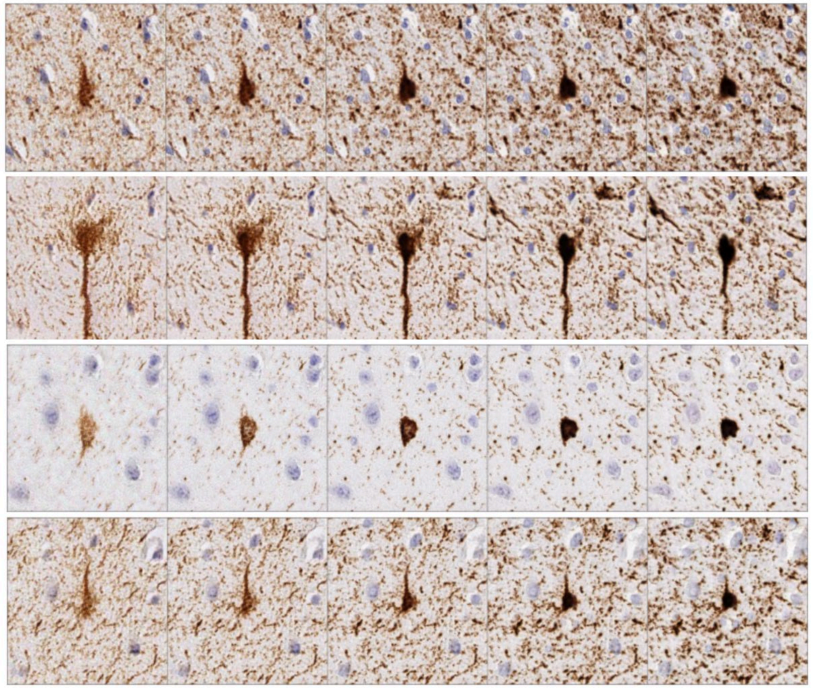
Unpublished

GAN latent space vectors can mimic the progression of neurofibrillary degeneration

Braak NFT cytoskeletal sequence



NFT maturity vector

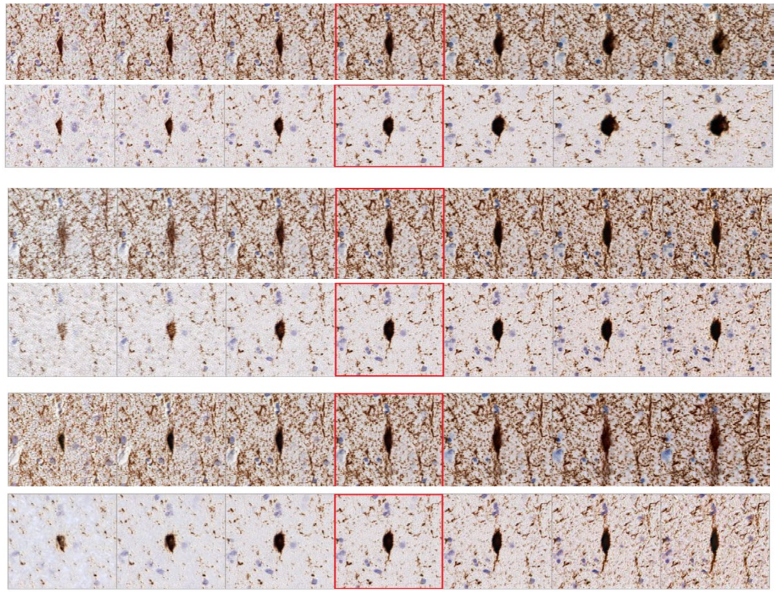


Latent space vectors

Soma size

Inclusion density

Neurite density



Unpublished

Conclusions

- **GANs can be used to generate highly realistic synthetic microscopic pathology data that accurately captures the full breadth of biologic morphology.**

- **GAN latent space contains key morphological features of NFT which recapitulate the process of neurodegeneration and tangle evolution.**

- **GAN-based unsupervised learning is a promising approach to histopathological staging of neurodegenerative disease.**

Mount Sinai

Thank you

The computational Pathology Unit
Andy McKenzie
Gabe Marx
Justin (Jay) Kauffman
Daniel Koenigsberg
Bergan Babrowicz

Crary Laboratory
Soong Kim
Kristen Whitney
Maggie Krassner
Sean Delica

Neuropathology Brain Bank and Research CoRE
Emma Woodoff-Leith
Valeriy Borukhov
Etty Cortes
Ruth Walker
Melissa J. Nirenberg
Alessandra Cervera
Diana Dangoor
Ricky Ditzel
Thomas Christie
Diana Dangoor
Rotating volunteer staff and Interns

UT Southwestern
Charles White III

Mount Sinai
The Hasso Plattner Institute for Digital Health: Thomas Fuchs, Gabriele Campanella
Neuropathology: Jamie Walker, Tim Richardson

CosyPath and the Dept. of Pathology, Molecular & Cell based Medicine
Carlos Cordon-Cardo
Jack Zeineh
Gerardo Fernandez
Marcel Prastawa
Maxim Signaevski

The PART Working Groups

Funding: NIA **(**K01 AG070326, R01 AG062348. R01 AG054008, NIRG-15-363188), NINDS (R01 NS095252), Tau Consortium/Rainwater Foundation, Alexander Saint-Amand Scholar Award, Louis V. Gerstner Jr. Foundation, David Werber foundation

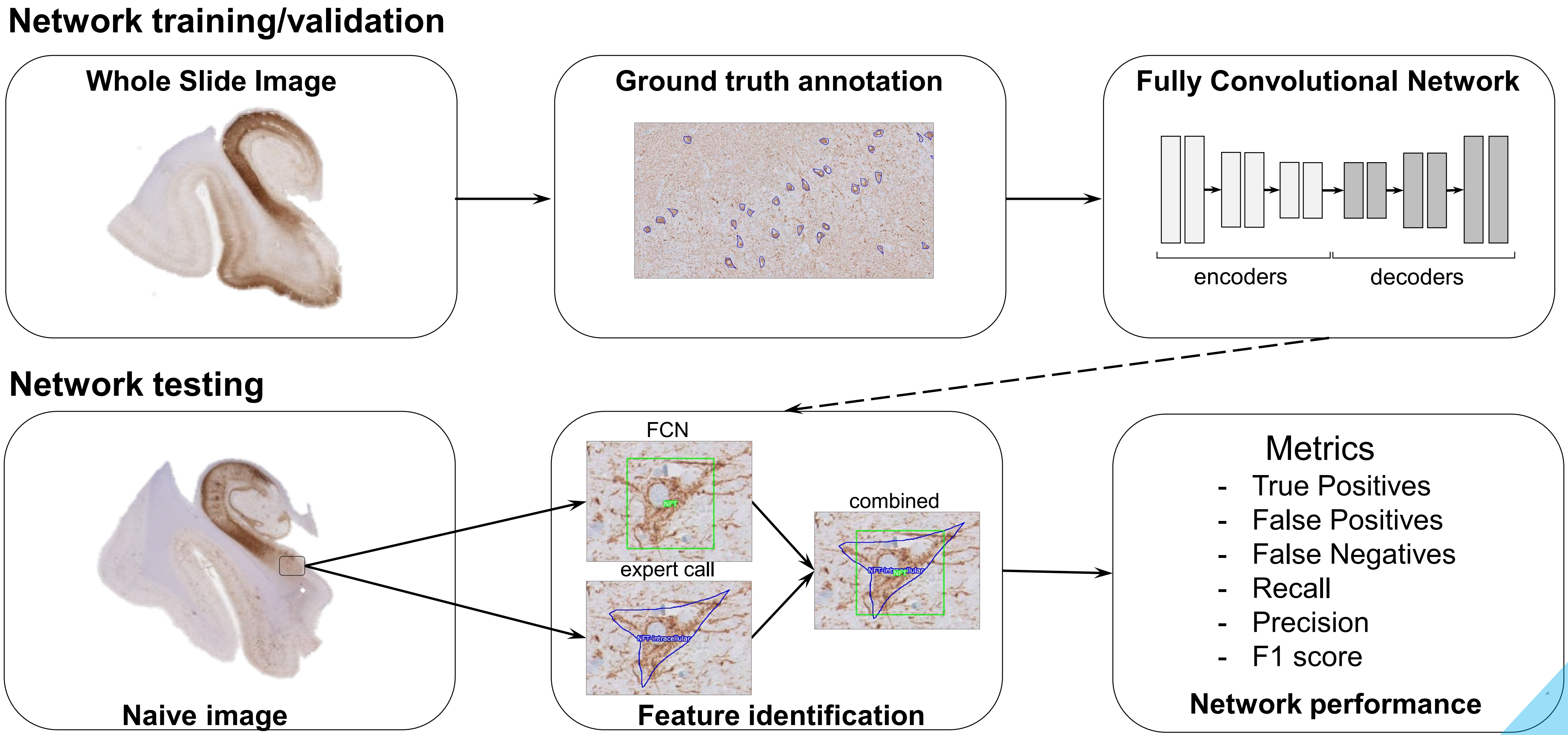
Questions?

ADRC REC Grant

RAINWATER Charitable Foundation

NATIONAL INSTITUTES OF HEALTH

Fully supervised machine learning pipeline



Signaevski, Prastawa, Farrell et al., Laboratory Investigations 2019