Integrating In-Vivo, Ex-Vivo MRI and Histology in Patients Undergoing Epilepsy Surgery

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Western

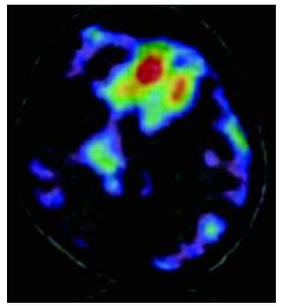
robarts IMAGING

Drug-resistant epilepsy and surgical treatment

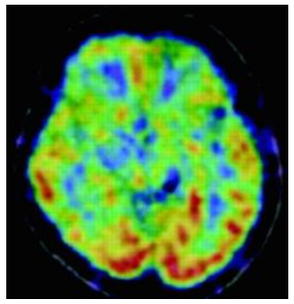
- 1 in 3 have drug-resistant epilepsy and require surgical treatment

Assessment

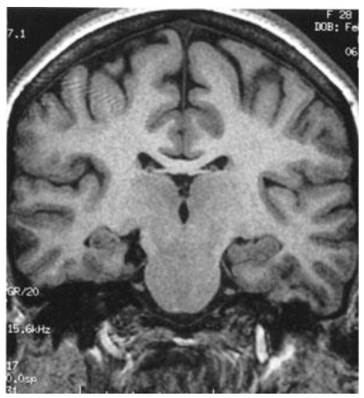
EEG with video monitoring

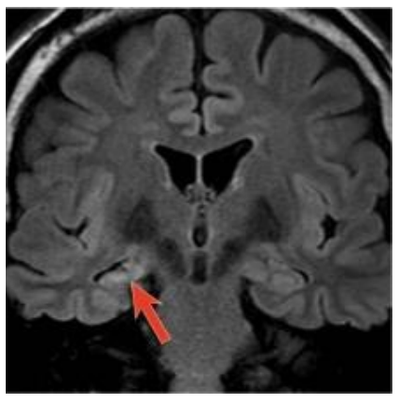


SPECT



PET

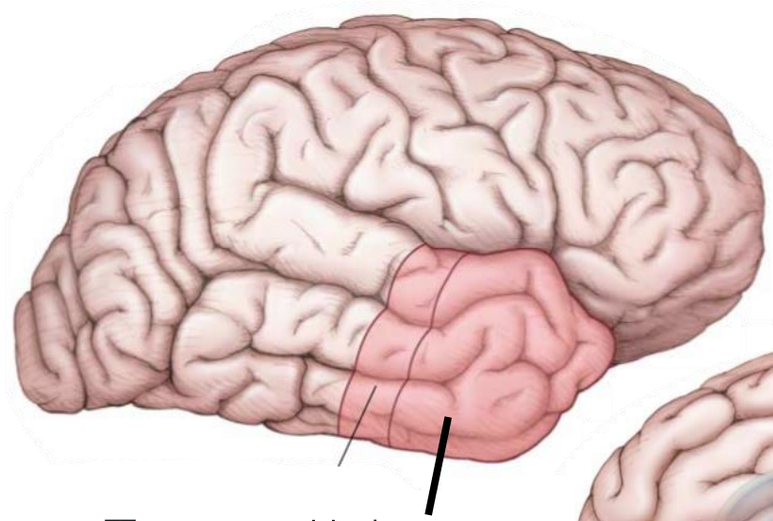


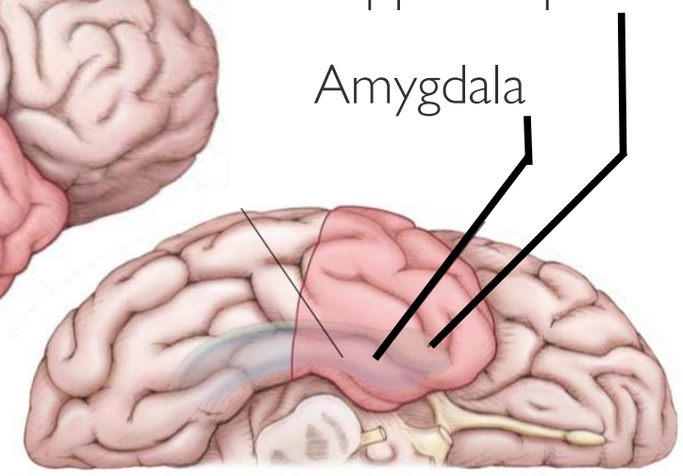


T1-weighted and T2-weighted MRI

Surgery

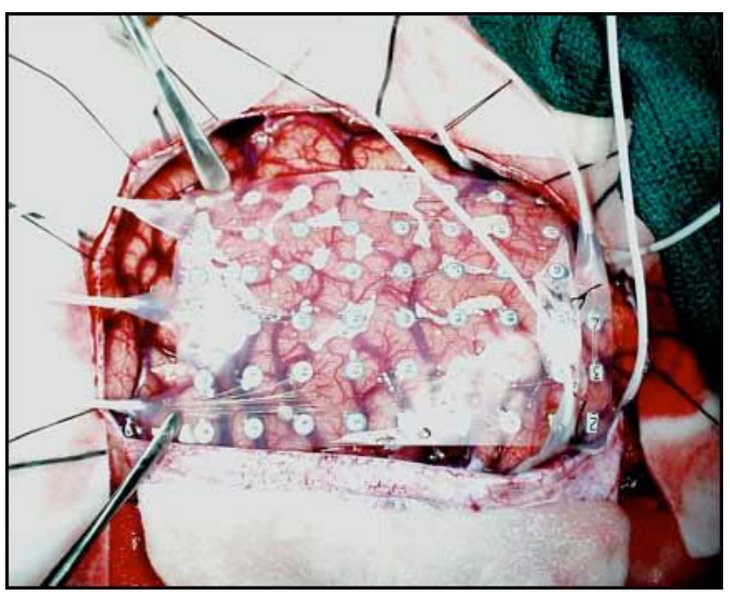
e.g.: anterior temporal lobectomy





If localization is wrong, surgery may not treat seizures

- MRI shows no lesion in up to 30% of cases *
- Drawbacks of other localization modalities
  - Seizure semiology, electrophysiology (EEG)



Sub-dural grid electrodes

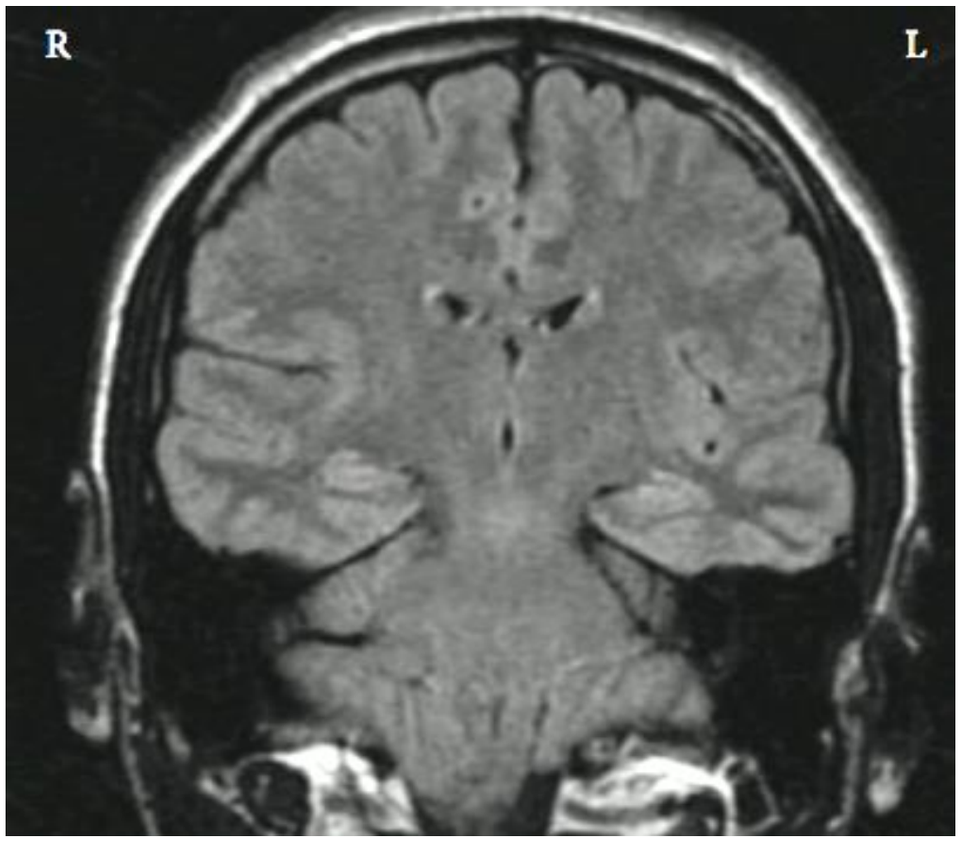
Depth electrodes

* Bernasconi A1, Bernasconi N, Bernhardt BC, Schrader D.. Advances in MRI for 'cryptogenic' epilepsies. Nat Rev Neurol. 2011 Feb;7(2):99-108. doi: 10.1038/nrneurol.2010.199.

Non-lesional MRI and cortical dysplasia

Intracranial EEG

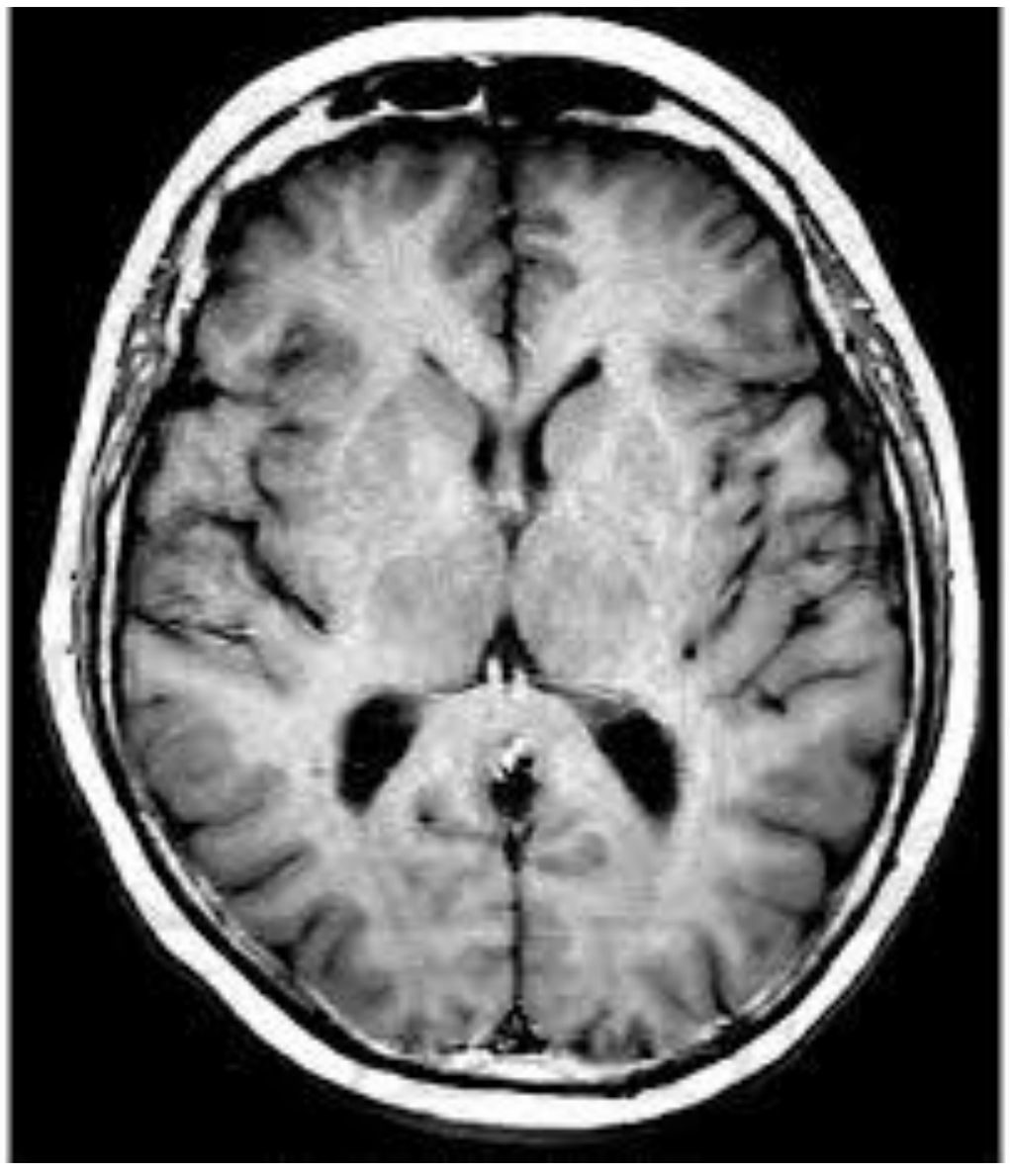
Resective Surgery



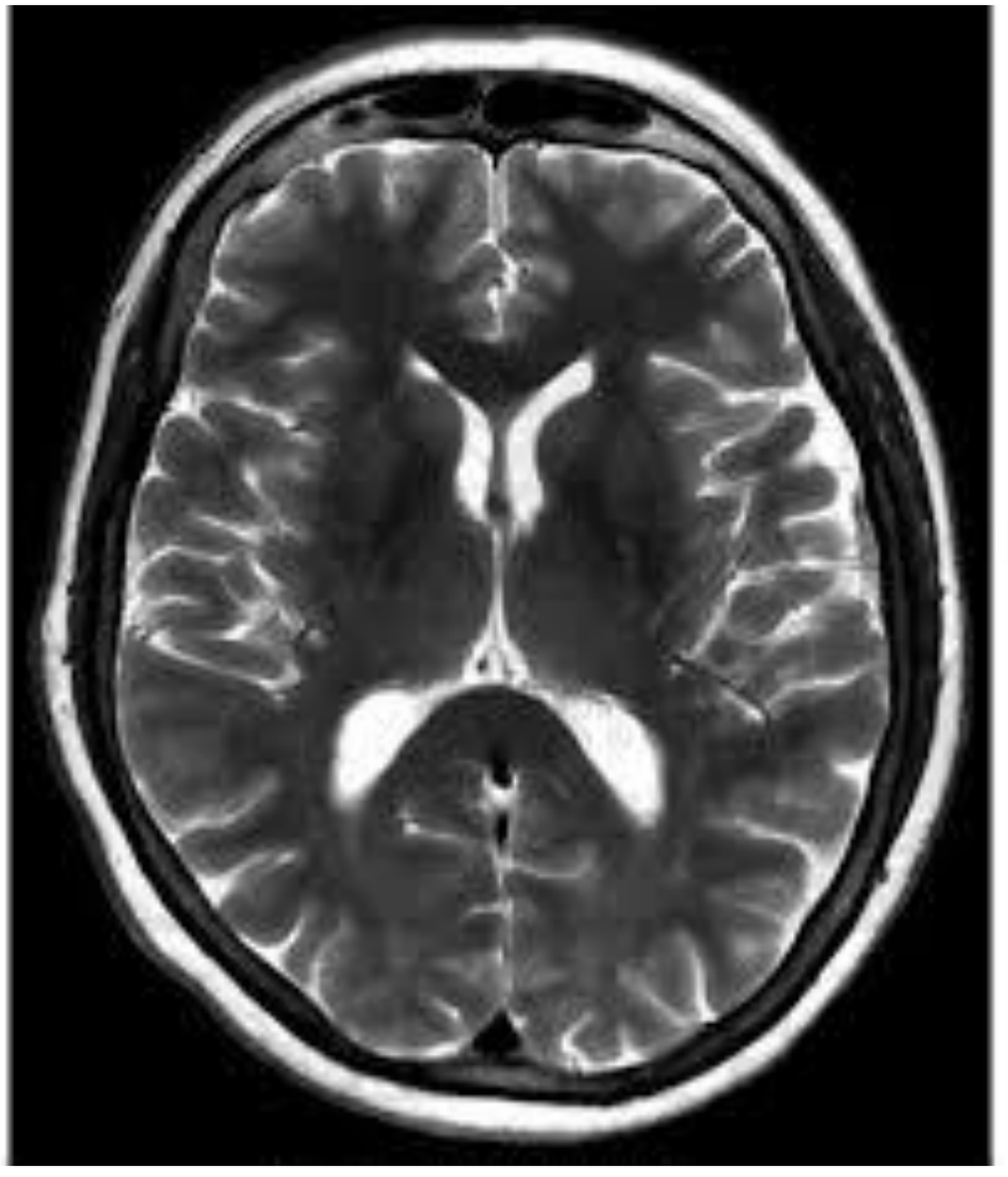
No lesion on MRI

Positive Pathology (Focal cortical dysplasia)

Traditional “qualitative” MRI

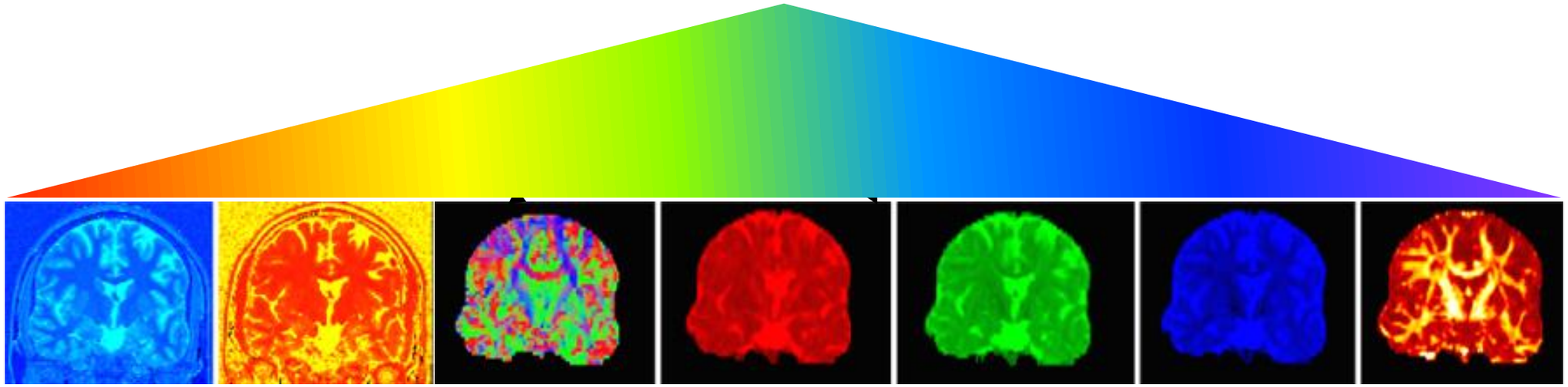


T1-weighted MRI



T2-weighted MRI

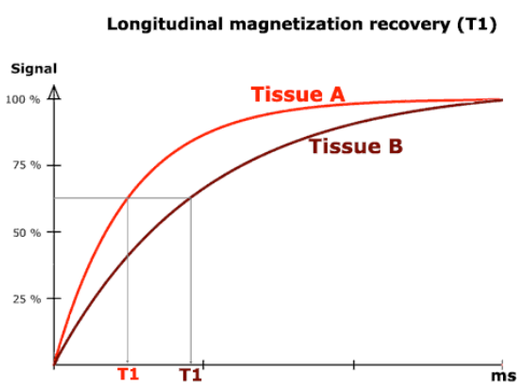
The quantitative imaging revolution

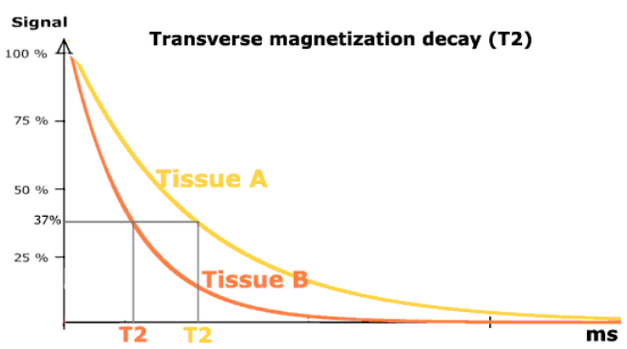


… … …

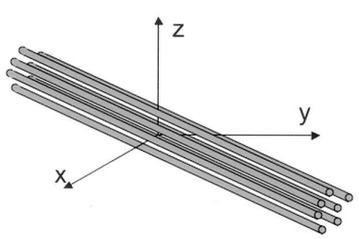
T_1 T_2 T_1-w v_1 λ_1 T_2-w λ_2 λ_3 FA

Quantitative Relaxometry (DESPOT)

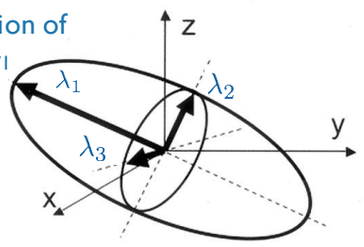




Diffusion tensor imaging

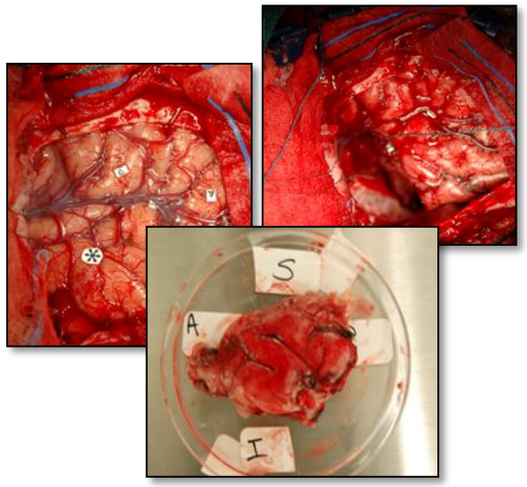


Principal direction of diffusion: v_1

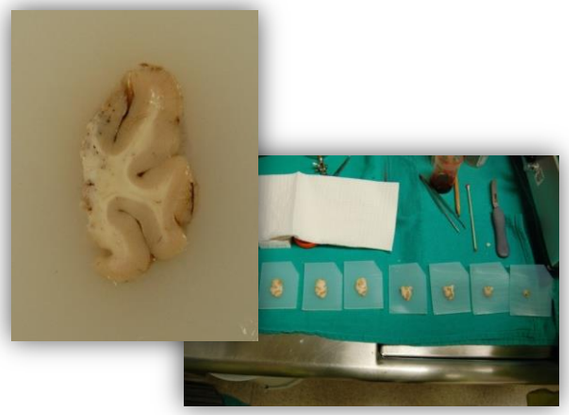


Our epilepsy imaging study: quantitative imaging + histology

Quantitative MRI



Epilepsy Surgery



Histological processing

Histology

Training Images

Training Labels

Pathology Prediction Machine

Goubran M, Crukley C, de Ribaupierre S, Peters TM, Khan AR. Image registration of ex-vivo MRI to sparsely sectioned histology of hippocampal and neocortical temporal lobe specimens. NeuroImage, 83: 770-781, 2013.

Goubran M, de Ribaupierre S, Hammond, RR, Currie C, Burneo JG, Parrent AG, Peters TM, Khan AR. Registration of in-vivo to ex-vivo MRI of surgically resected specimens: A pipeline for histology to in-vivo registration. Journal of Neuroscience Methods. 241 (15) 2015

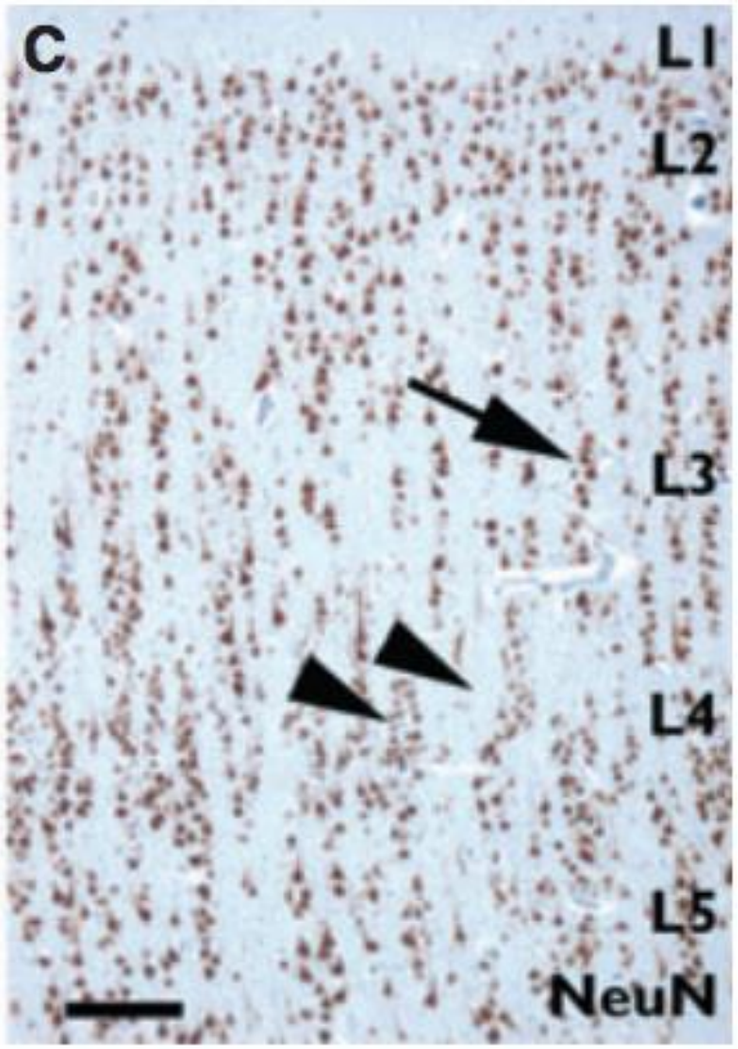
Quantitative MRI can predict neuronal markers

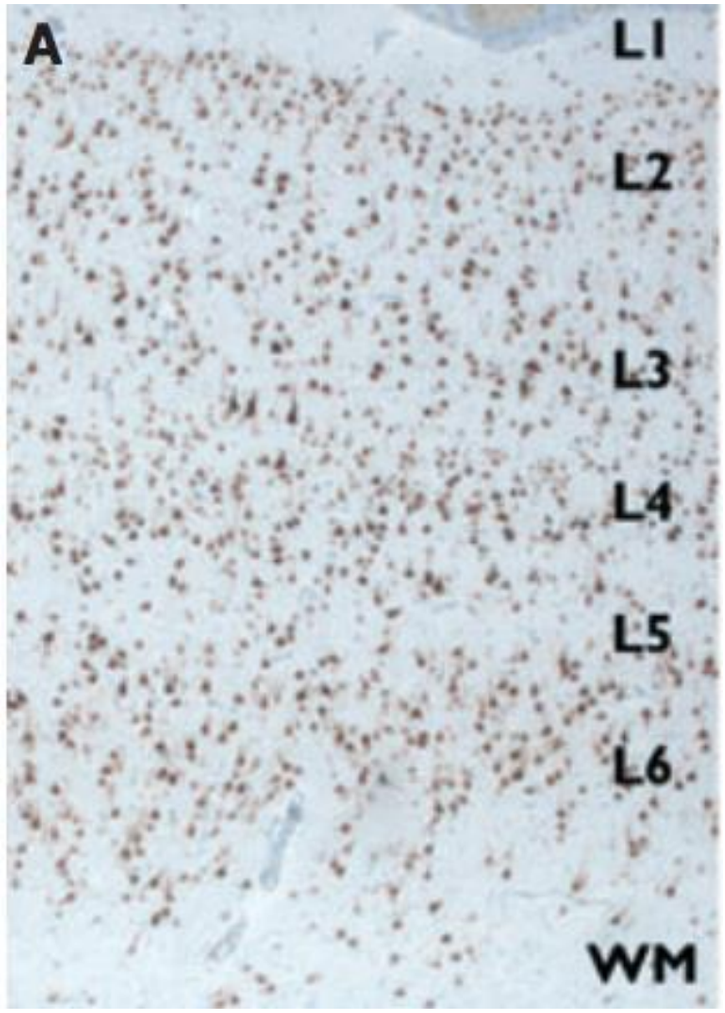
- Combining relaxometry (T_1) and diffusion (FA) can predict neuronal density measurements *

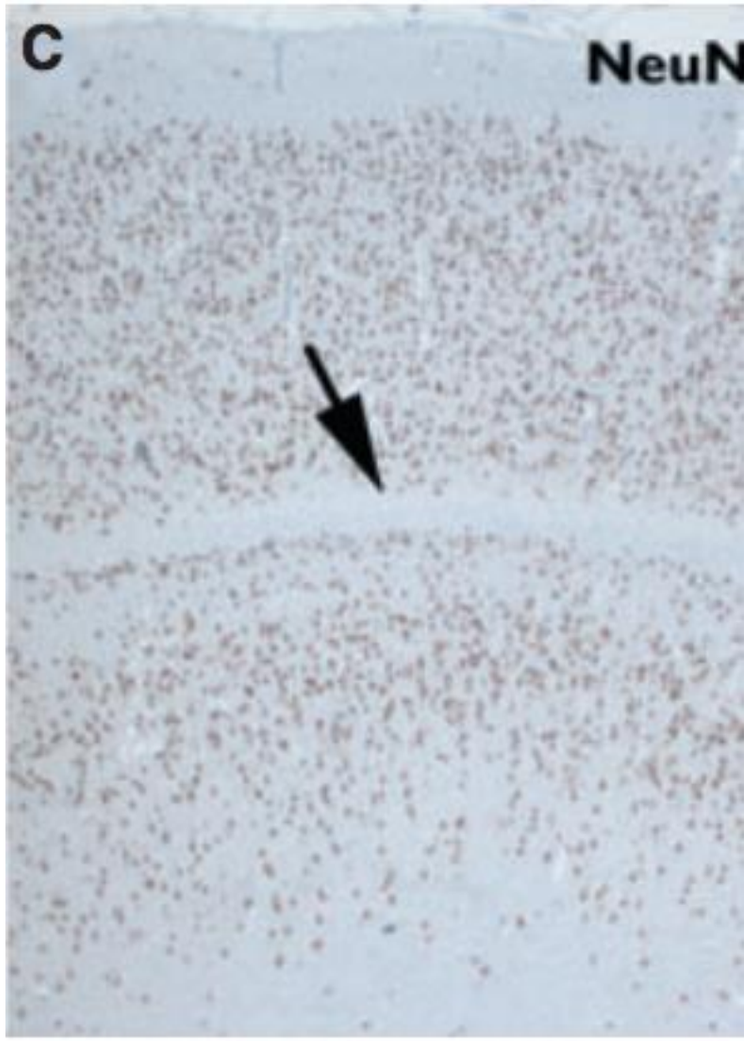
Can we find a MRI signature for focal cortical dysplasia?

* Goubran M, Hammond RR, de Ribaupierre S, Burneo JG, Mirsattari S, Steven D, Parrent AG, Peters TM, Khan AR. Magnetic Resonance Imaging and Histology Correlation in the Neocortex in Temporal Lobe Epilepsy. Annals of Neurology, Volume 77, Issue 2, pages 237–250, February 2015.

Focal cortical dysplasia (FCD)



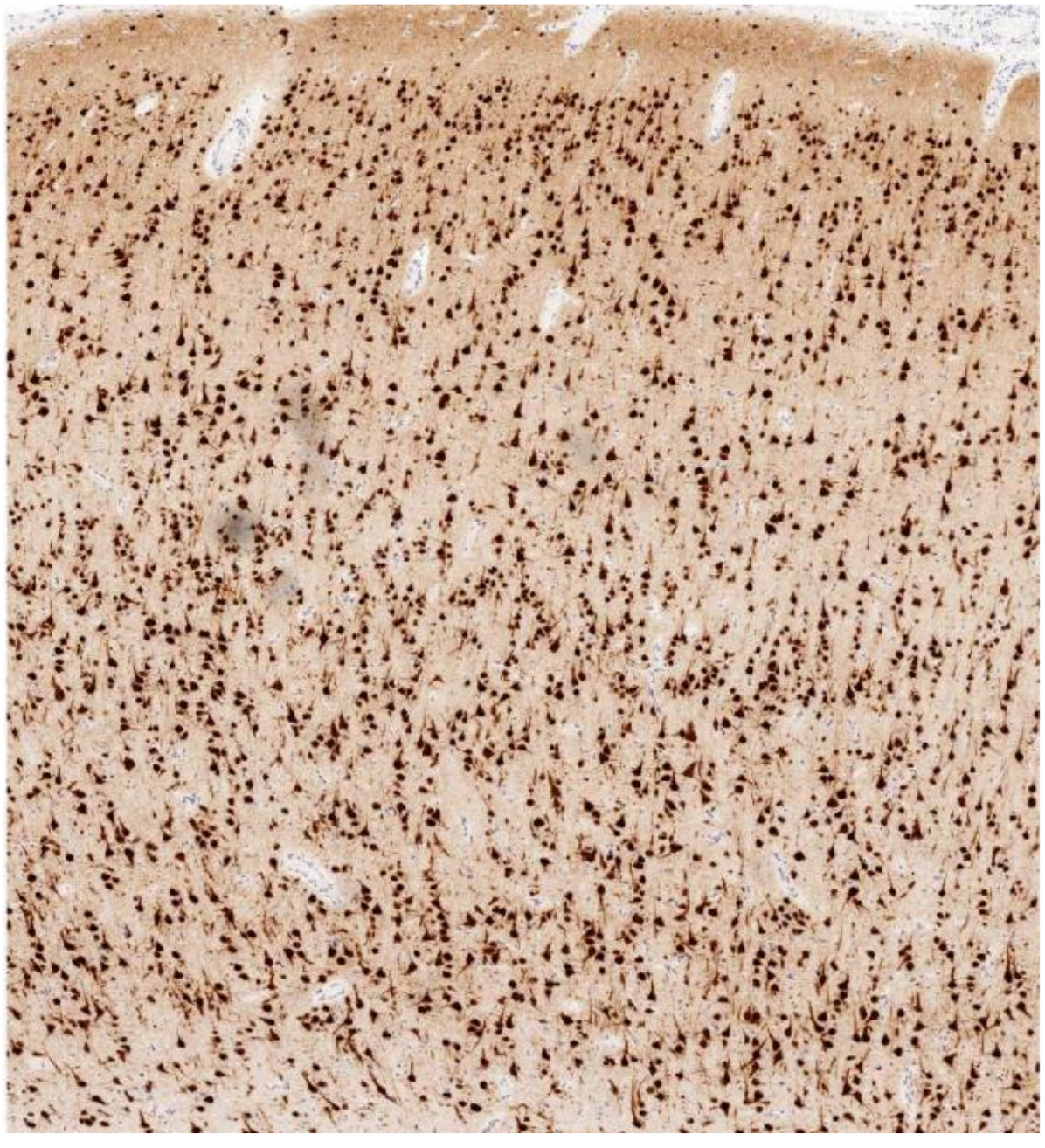




* Blümcke, Ingmar et al. "The Clinico-Pathological Spectrum of Focal Cortical Dysplasias: A Consensus Classification Proposed by an *ad Hoc* Task Force of the ILAE Diagnostic Methods Commission." *Epilepsia* 52.1 (2011): 158–174. *PMC*. Web. 21 Sept. 2017.

Histology of FCD Type I

Normal Cortex



Layer 1

Layer 2

Layer 3

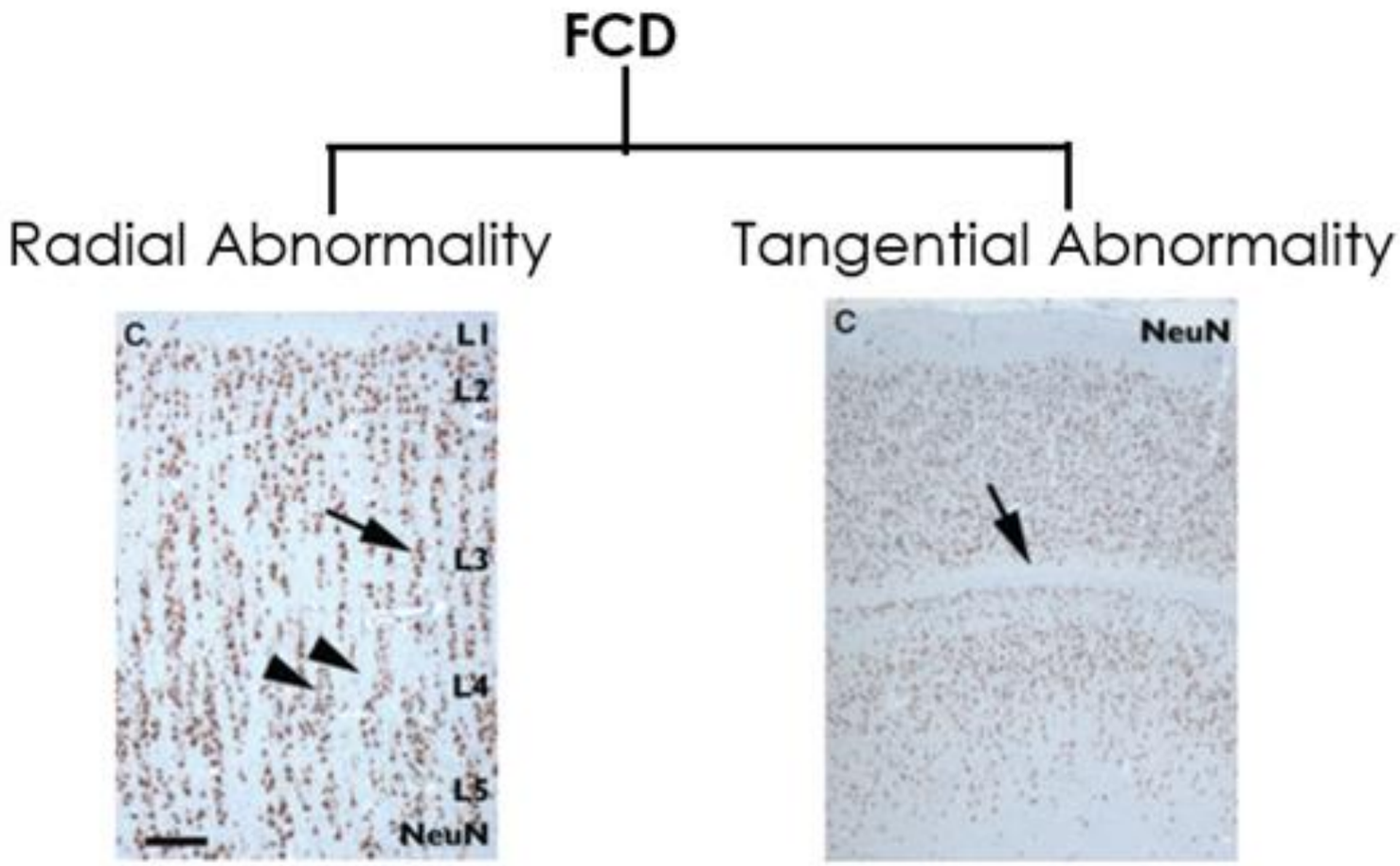
Layer 4

Layer 5

Layer 6

Histology of FCD Type I

- Defect in the formation of the cerebral cortex during intra-uterine development
- Caused by genetic mutation or environmental insults



* Blümcke, Ingmar et al. "The Clinico-Pathological Spectrum of Focal Cortical Dysplasias: A Consensus Classification Proposed by an *ad Hoc* Task Force of the ILAE Diagnostic Methods Commission." *Epilepsia* 52.1 (2011): 158–174. *PMC*. Web. 21 Sept. 2017.

Facilitating MRI Correlation

Table 2. Interobserver agreement in the first, second, and third evaluation rounds per FCD types (κ values)

Round	FCD Ia	FCD Ib	FCD Ic	FCD IIa	FCD IIb	FCD IIIa	FCD IIIb	FCD IIIc	FCD IIId	No FCD	Mean
1	0.4821	0.3877	0.1319	1.0000	1.0000	0.8316	0.4869	0.7685	0.6062	0.3746	0.6360
2	0.7084	0.4287	−0.004[a]	1.0000	0.9565	0.7862	0.5113	0.6435	0.5465	0.4164	0.6532
3T	0.3252	0.1917	0.1509	0.4239	0.8045	0.5822	0.4407	0.6109	0.1800	0.2409	0.4060
3A	0.4220	0.4323	0.3438	0.5252	0.7828	0.7195	0.6101	0.7023	0.2951	0.2606	0.5056
3B	0.3185	0.1071	0.1608	0.4311	0.8555	0.5063	0.4451	0.5981	0.0517	0.2586	0.3884
3C	0.3763	0.0778	0.2137	0.3307	0.7136	0.4911	0.2171	0.4718	0.1955	0.1270	0.3265

3T, [illegible] 21 neuropathologists; 3A, neuropathologists with level A access to >40 epilepsy surgery cases/year; 3B, neuropathologists reviewing 10–40 cases/year; 3C, neuropathologists seeing <10 cases/year.

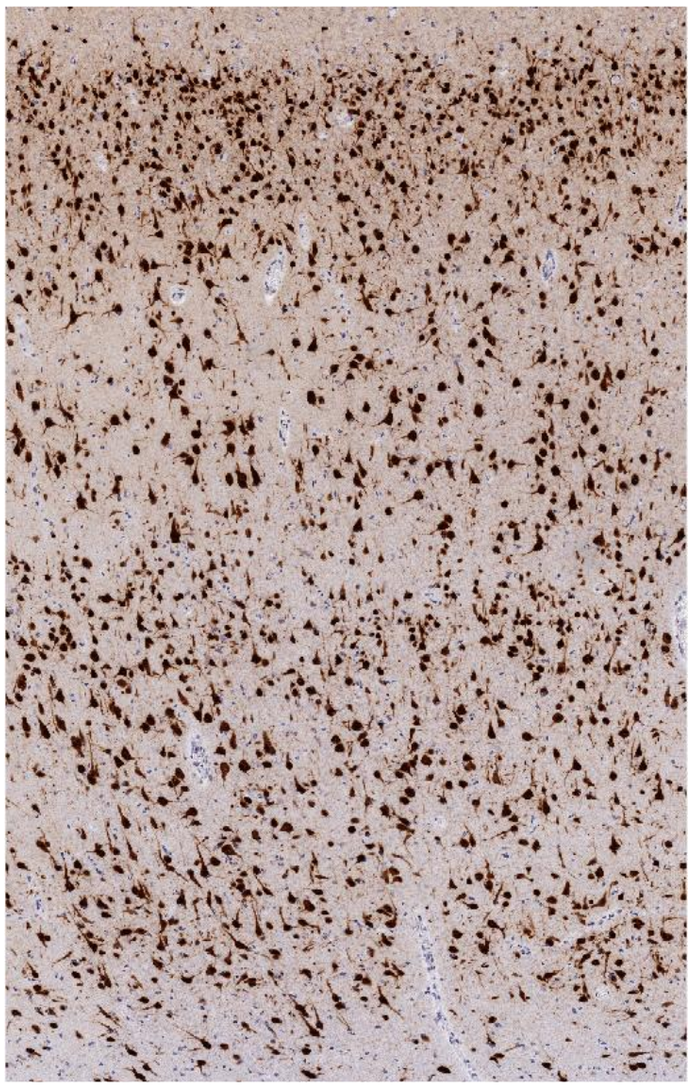
Kappa values were scored as follows: <0.2, poor agreement; 0.2–<0.4, fair agreement (yellow boxes); 0.4–<0.6, moderate agreement (purple boxes); 0.6–<0.8, good agreement (green boxes); 0.8–1.0, very good agreement (blue boxes).

[a]Kappa values can be negative in rare situations indicating that the observers agreed less than expected by chance.

* Coras, R et al. (2012), Good interobserver and intraobserver agreement in the evaluation of the new ILAE classification of focal cortical dysplasias. Epilepsia, 53: 1341–1348.

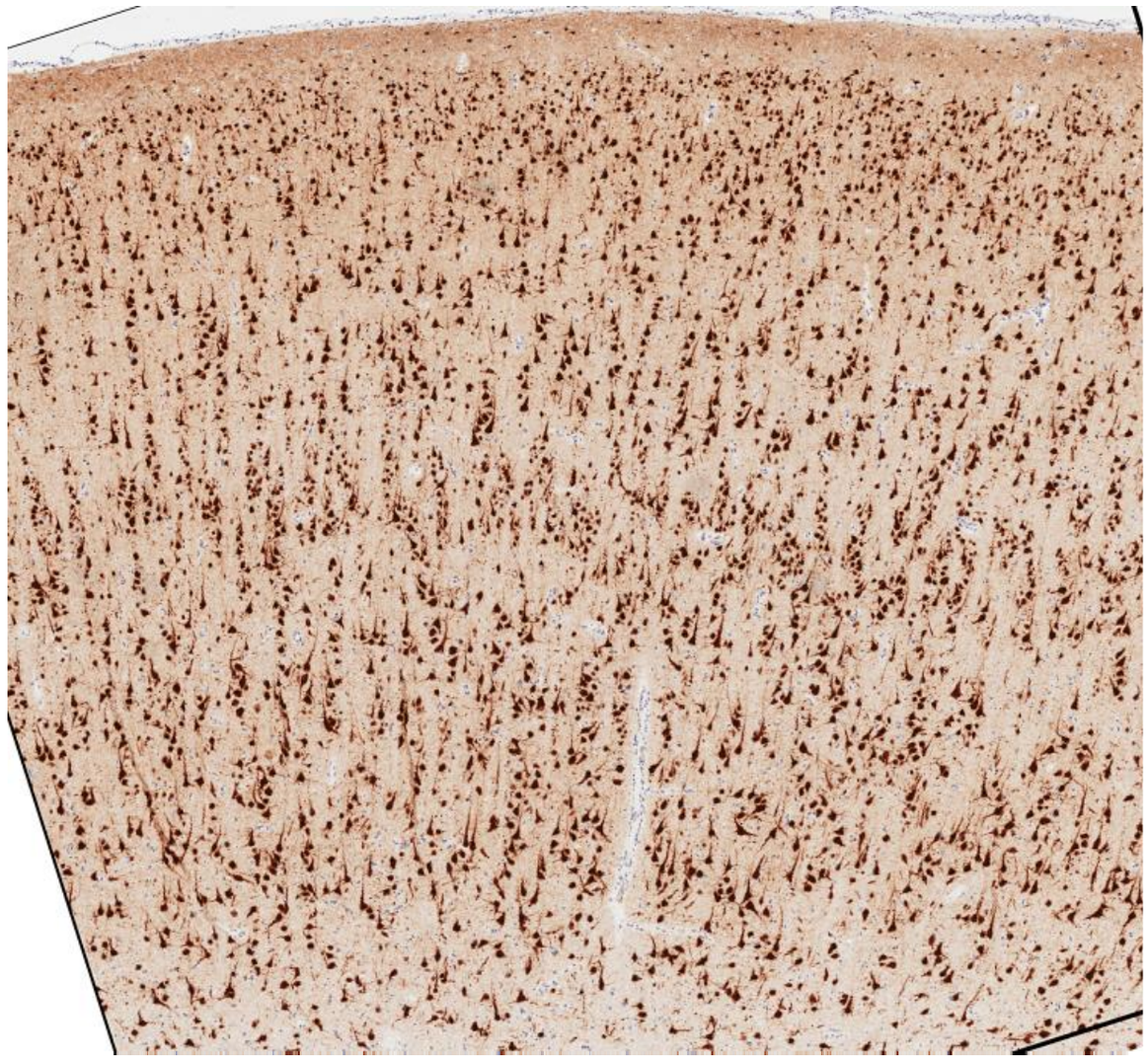
Quantifying radial abnormalities

Normal Cortex



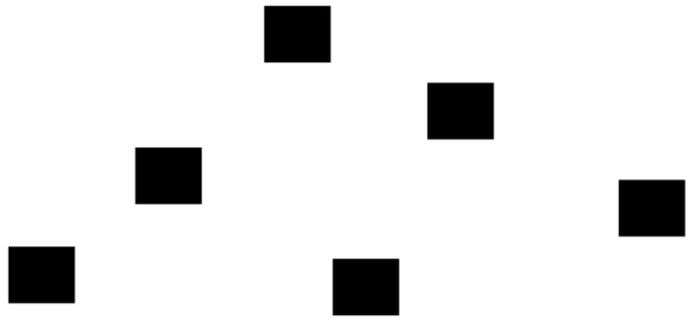
VS

Radial Abnormality

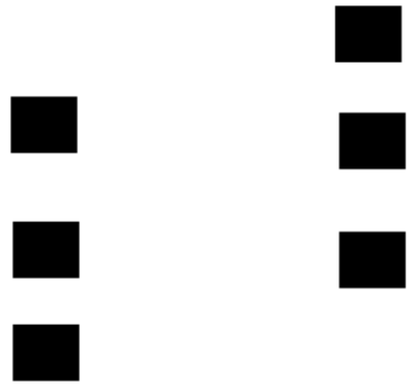


Spatial Analysis

Normal

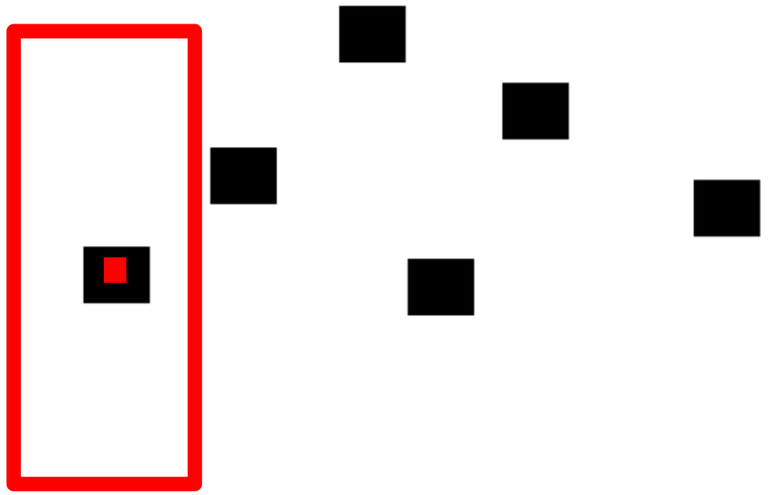


Radial Abnormality

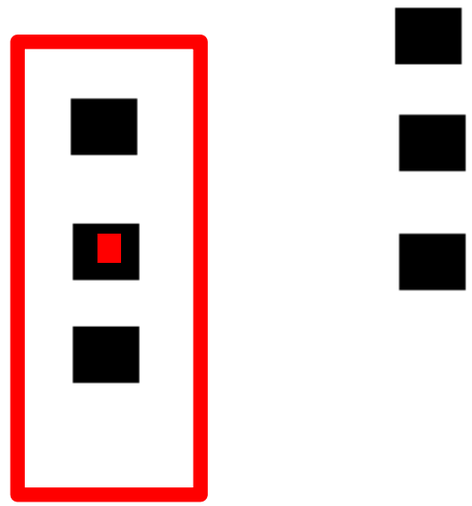


Spatial Analysis

Normal

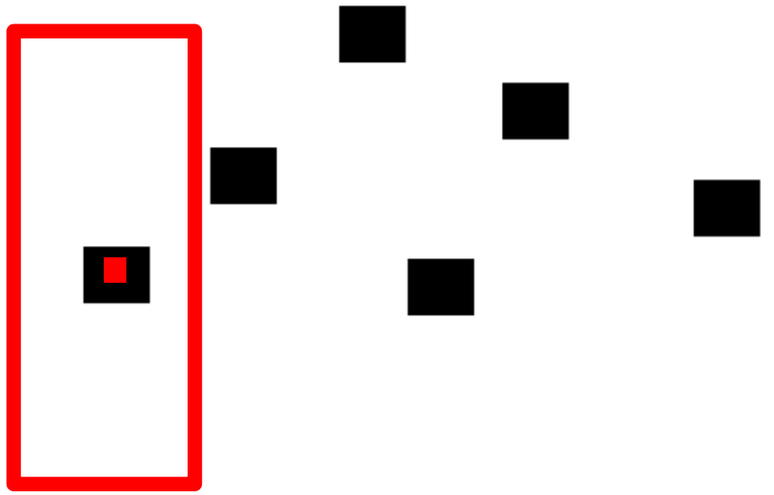


Radial Abnormality



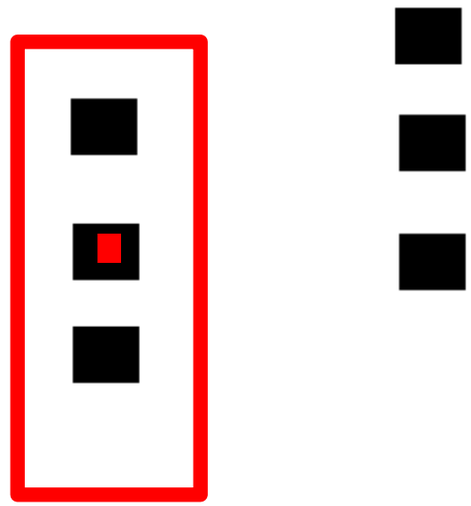
Spatial Analysis

Normal



Number of Neighbours in VERTICAL Direction: **0**

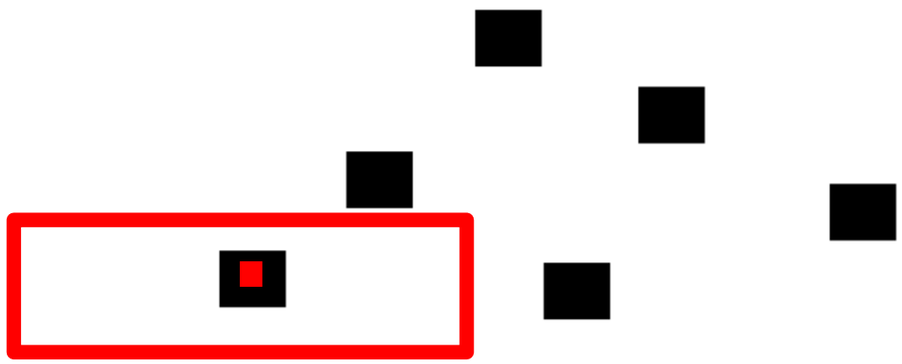
Radial Abnormality



Number of Neighbours in VERTICAL Direction: **2**

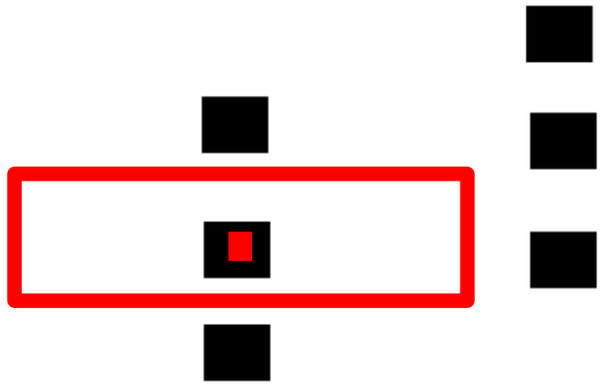
Spatial Analysis

Normal



Number of Neighbours in HORIZONTAL Direction: **0**

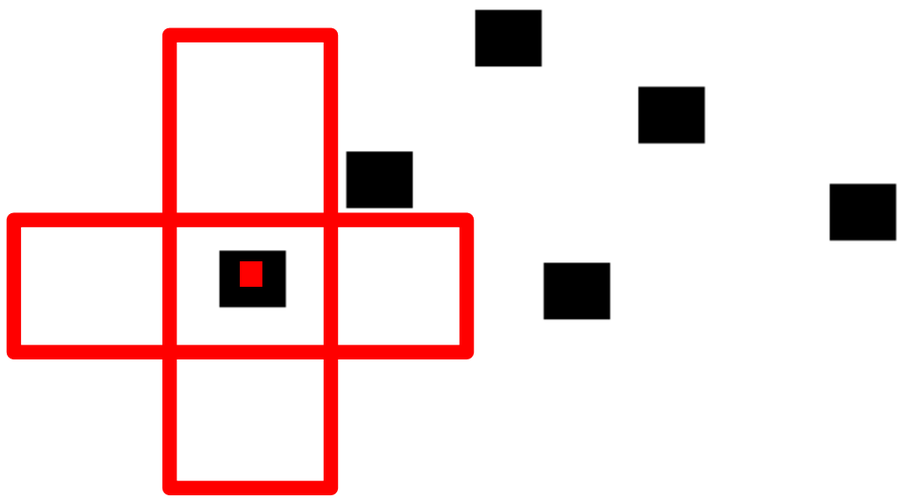
Radial Abnormality



Number of Neighbours in HORIZONTAL Direction: **0**

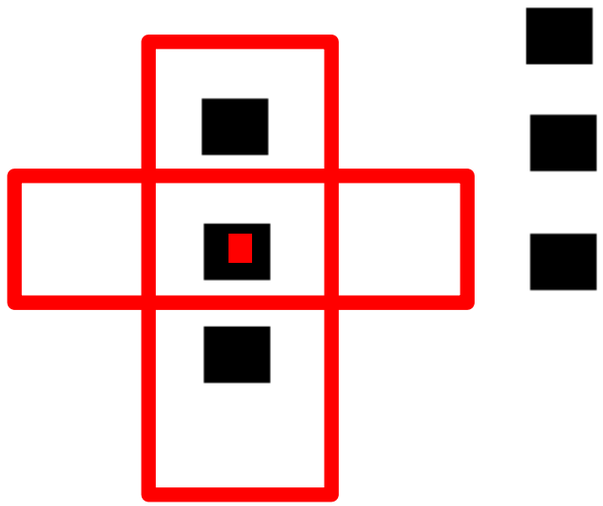
Spatial Analysis

Normal



K-score: 0

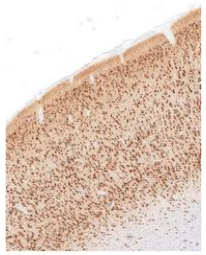
Radial Abnormality

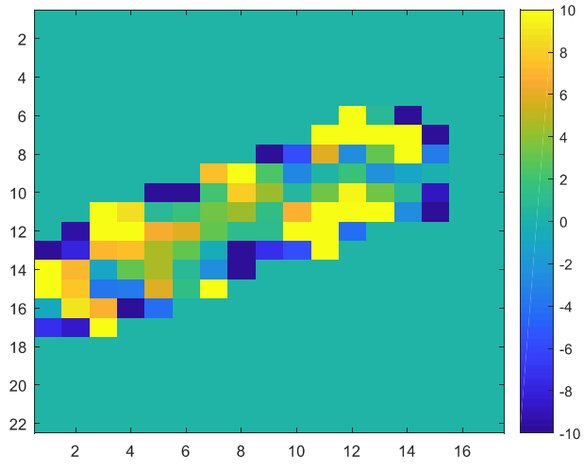


K-score: 2

Results of Radial Abnormality Quantification

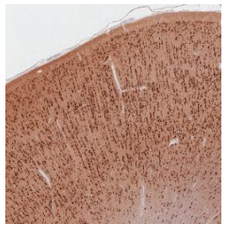
Normal

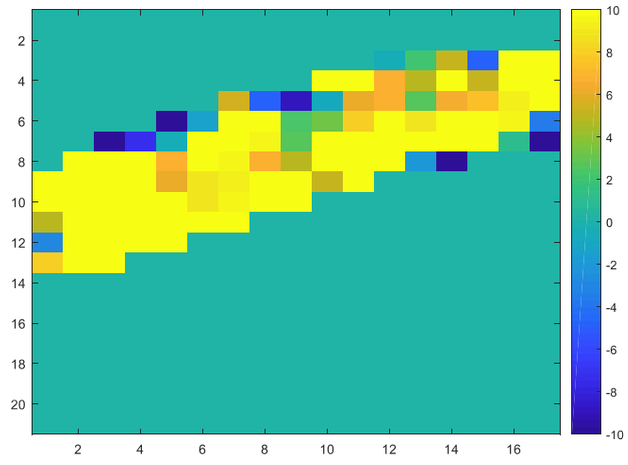




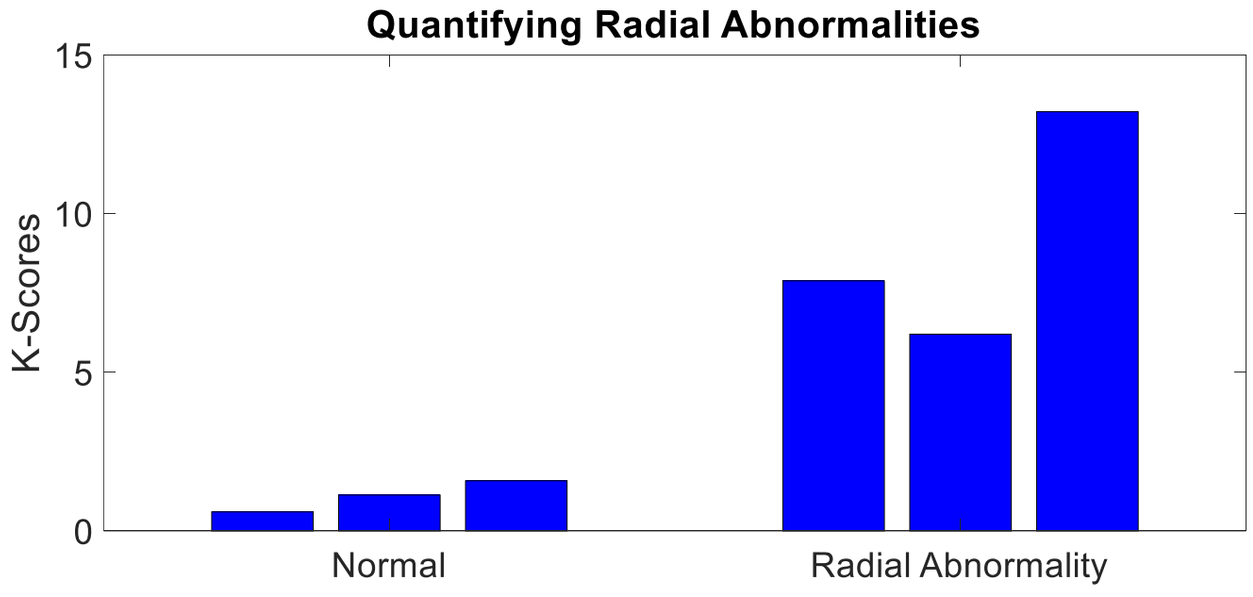
Average K-Score: 1

Radial Abnormality



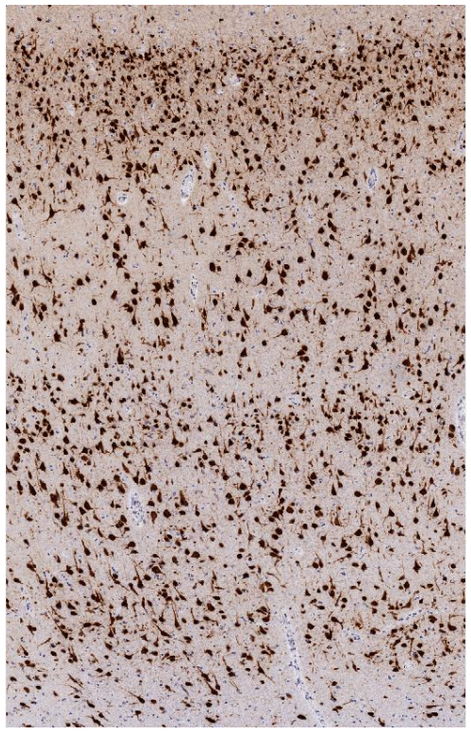


Average K-Score: 13



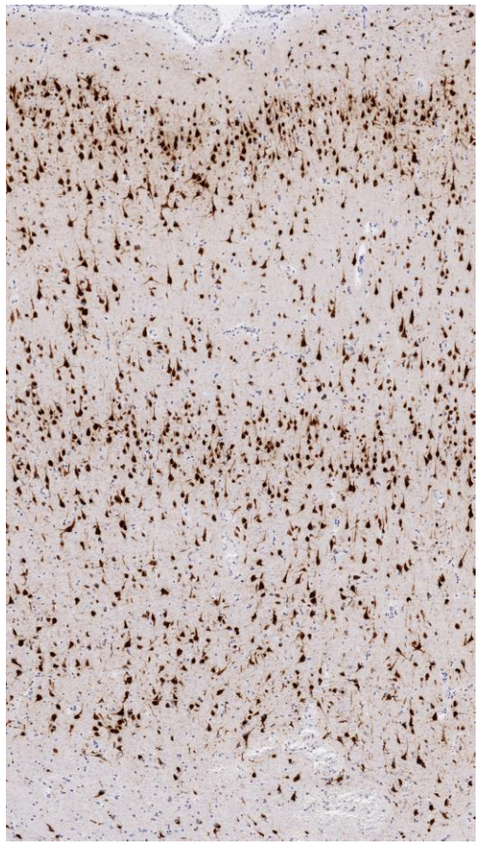
Quantifying Tangential Abnormalities

Normal

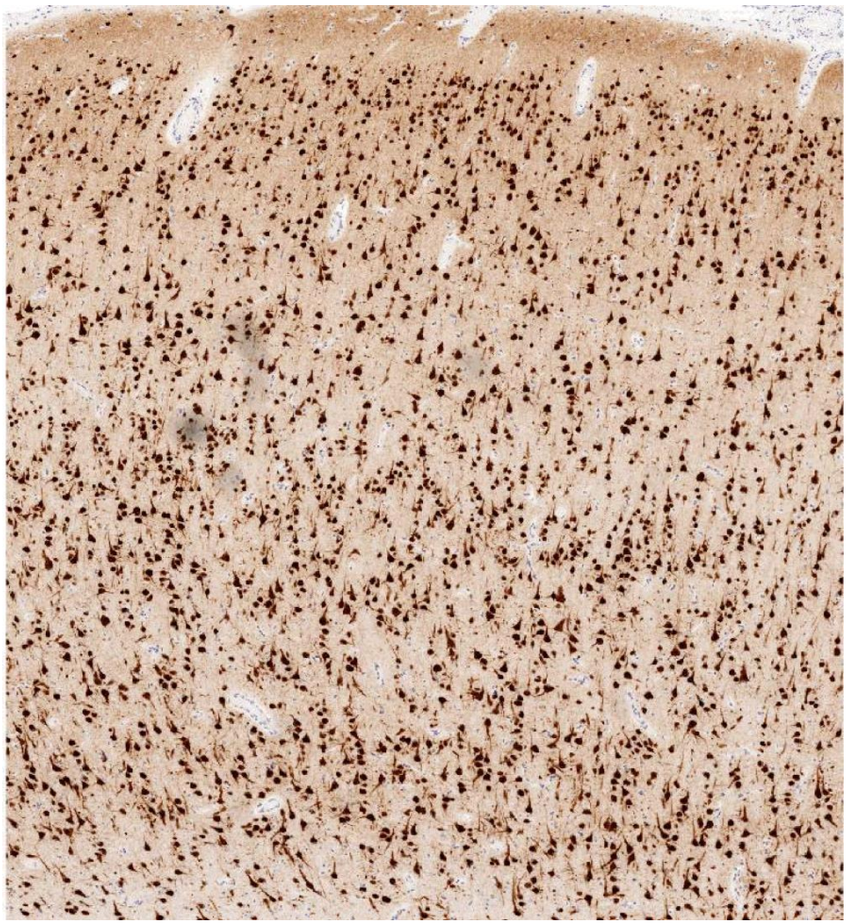


VS

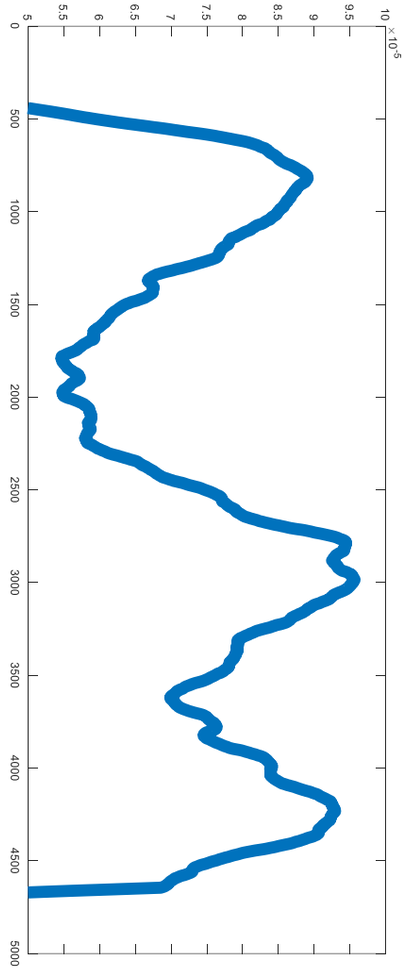
Tangential Abnormality



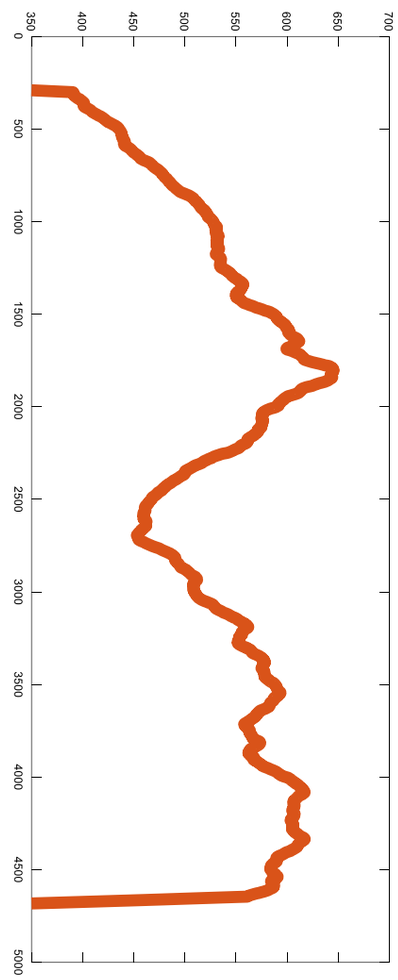
Cortical Profiles



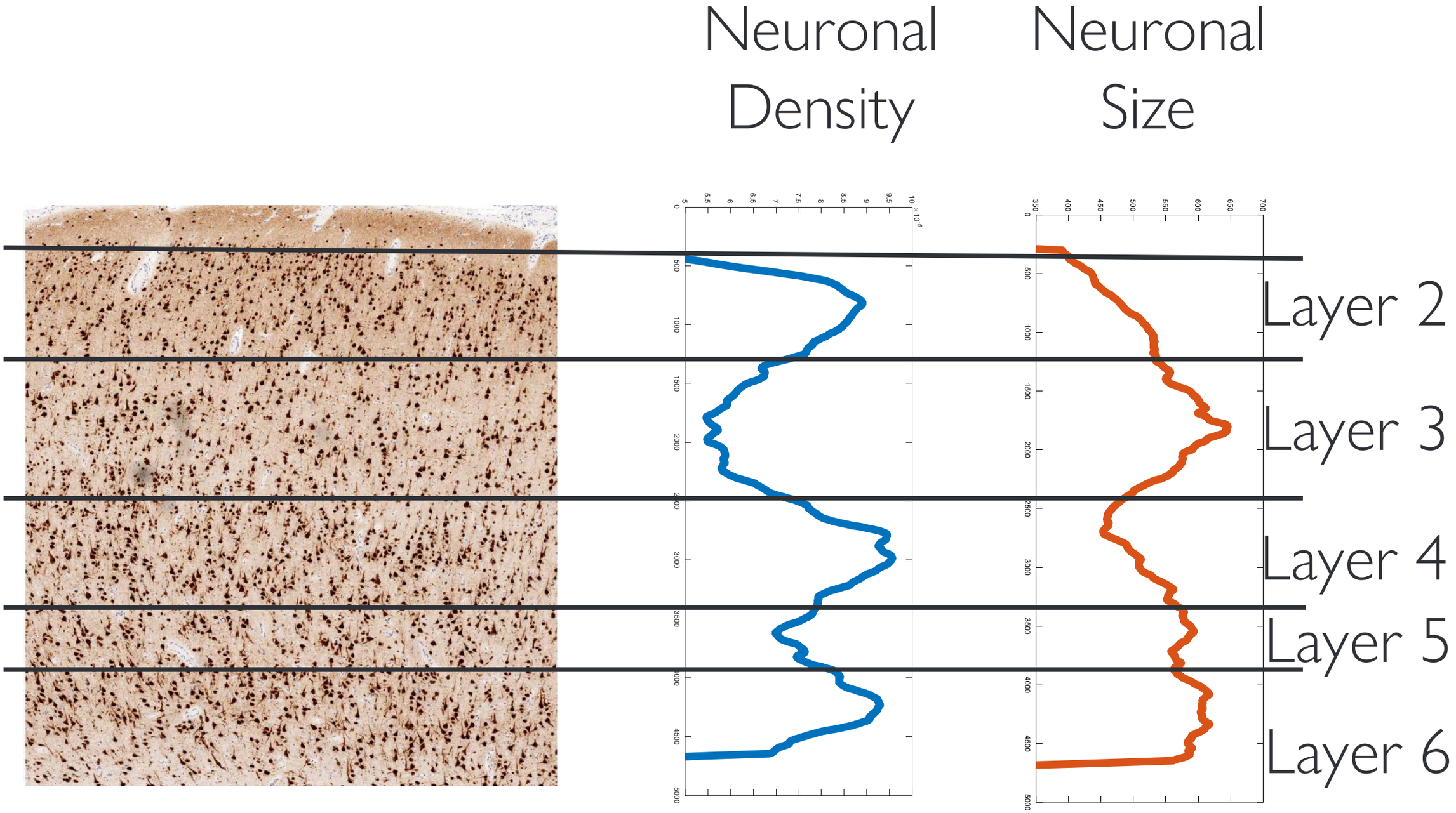
Neuronal Density



Neuronal Size

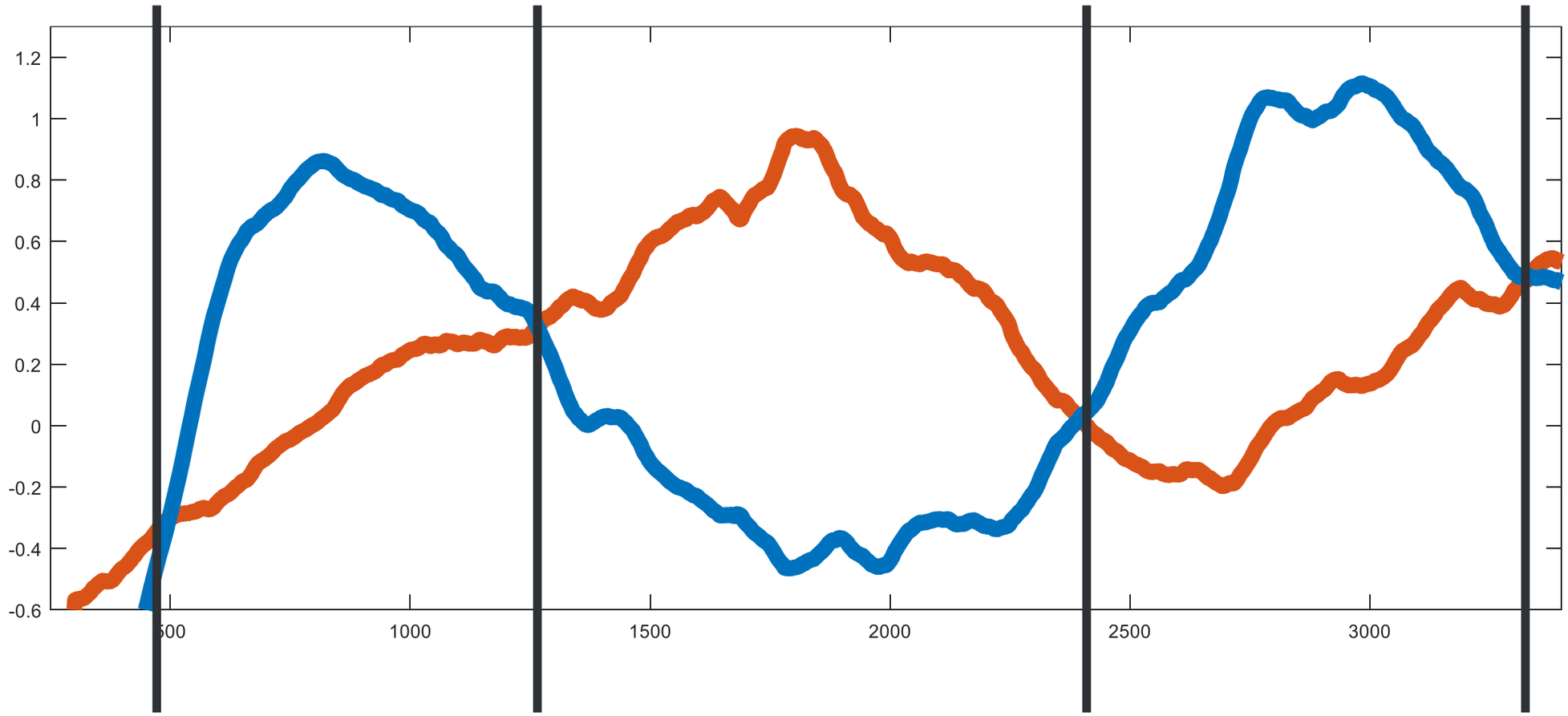


Cortical Profiles



Cortical Profiles

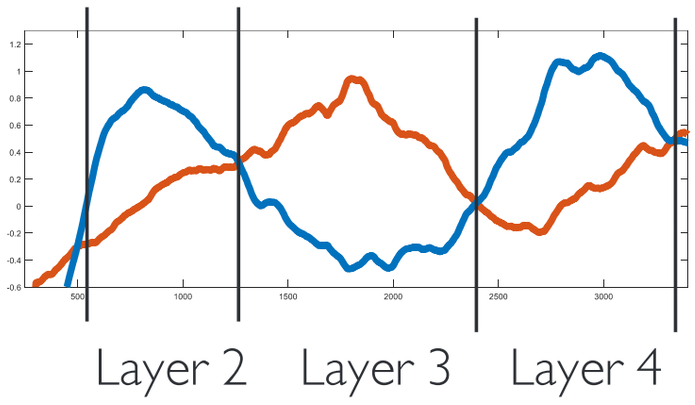
Neuronal Size and Density Profile



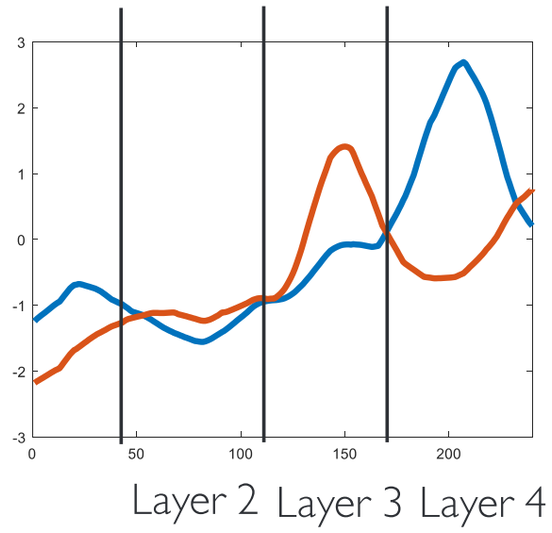
Layer 2 Layer 3 Layer 4

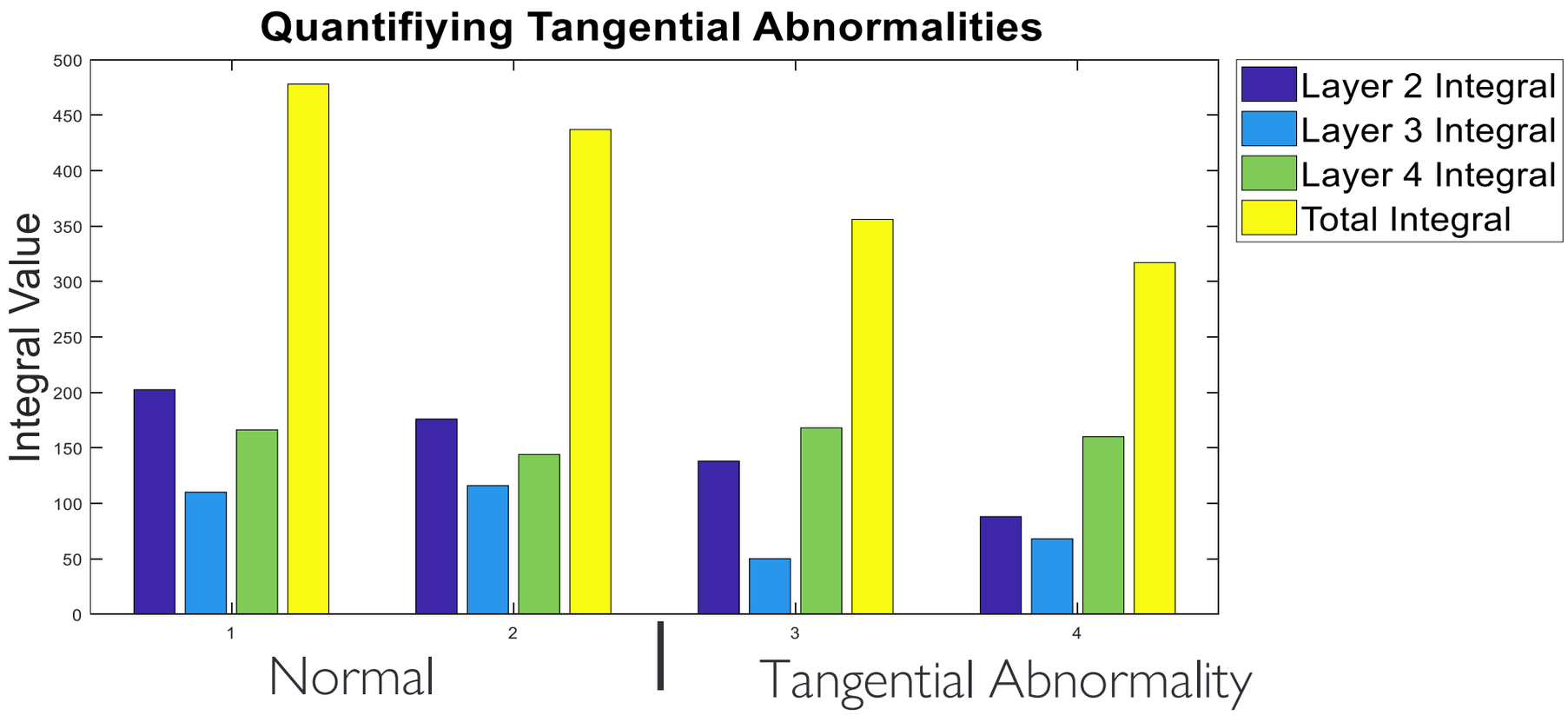
Results of Tangential Abnormality Quantification

Normal



Tangential Abnormality





Predicting surgical outcomes

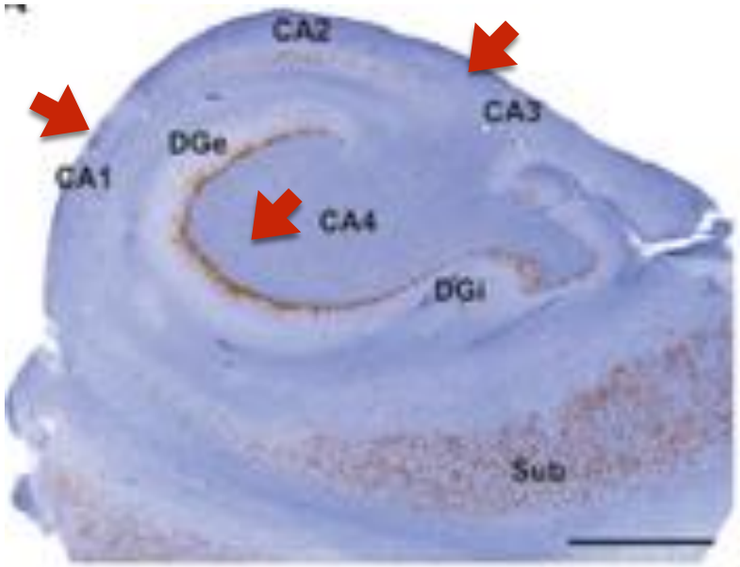
- Even if localization is successful, seizures recur in 30% of cases *
- Long-term outcomes are worse, recent estimates at 50% seizure-free at 10 years †
- We cannot predict which patients will have poor outcomes

* S. Wiebe et al. "A randomized, controlled trial of surgery for temporal-lobe epilepsy," The New England Journal of Medicine, vol. 345 (5) pp 311-318, 2001

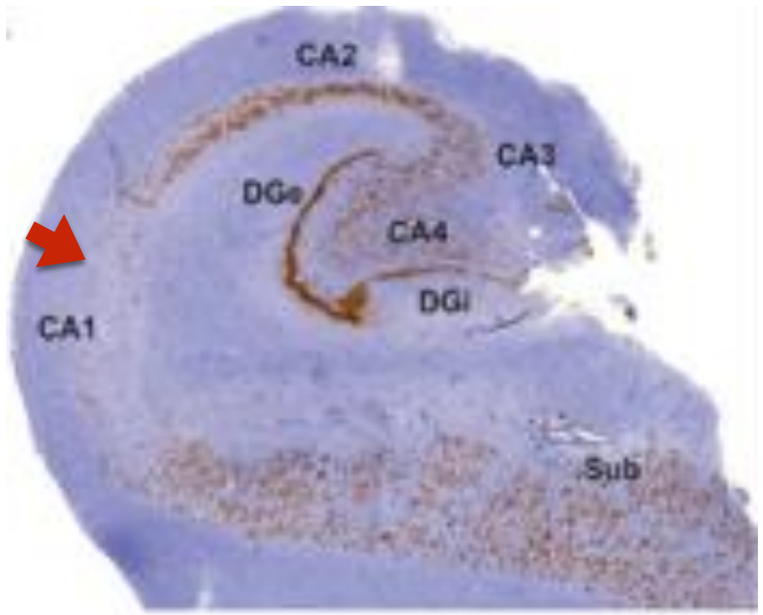
† de Tisi et al. " The long-term outcome of adult epilepsy surgery, patterns of seizure remission, and relapse: a cohort study" Lancet, 2011

Hippocampal pathology in epilepsy

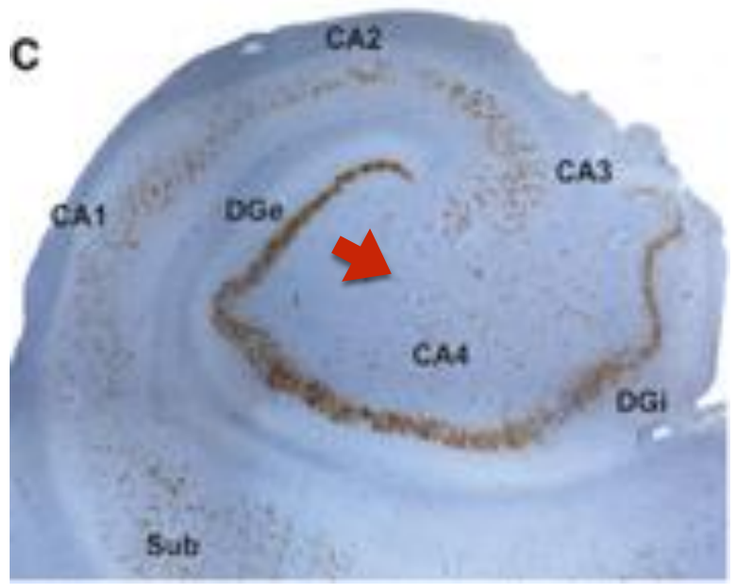
- Severe neuronal loss in the hippocampus



Classical hippocampal sclerosis



CA1-predominant subtype



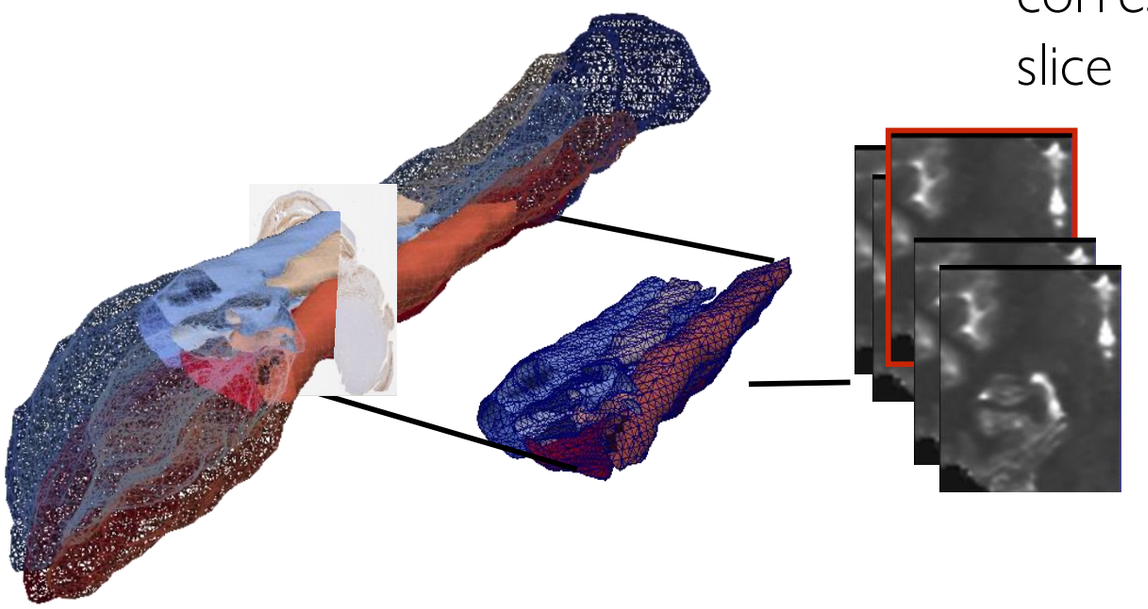
CA4-predominant subtype

Different sub-types have different surgical outcomes

† Thom et al. Reliability of patterns of hippocampal sclerosis as predictors of postsurgical outcome. Epilepsia 2010

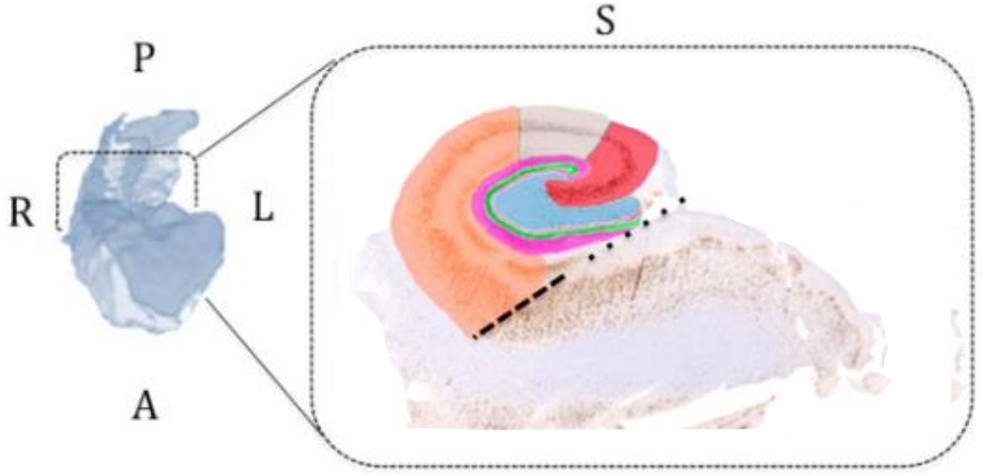
* Na et al. Long-term seizure outcome for international consensus classification of hippocampal sclerosis: A survival analysis. Seizure 2015

Can we quantify subfield integrity *in vivo*?

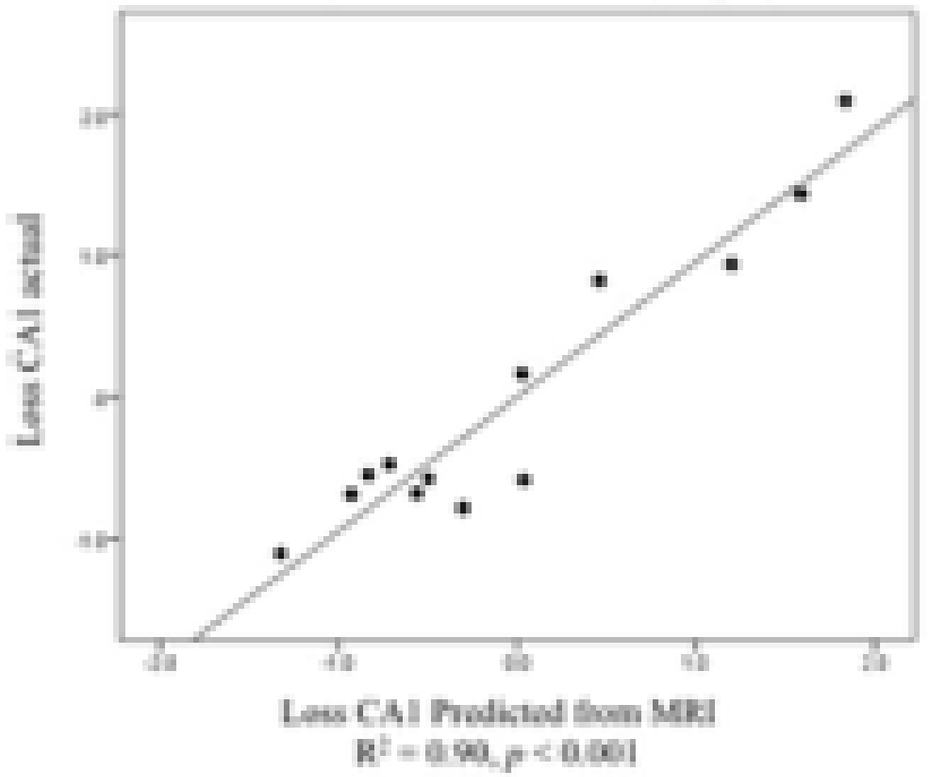


corresponding MRI slice

Histology



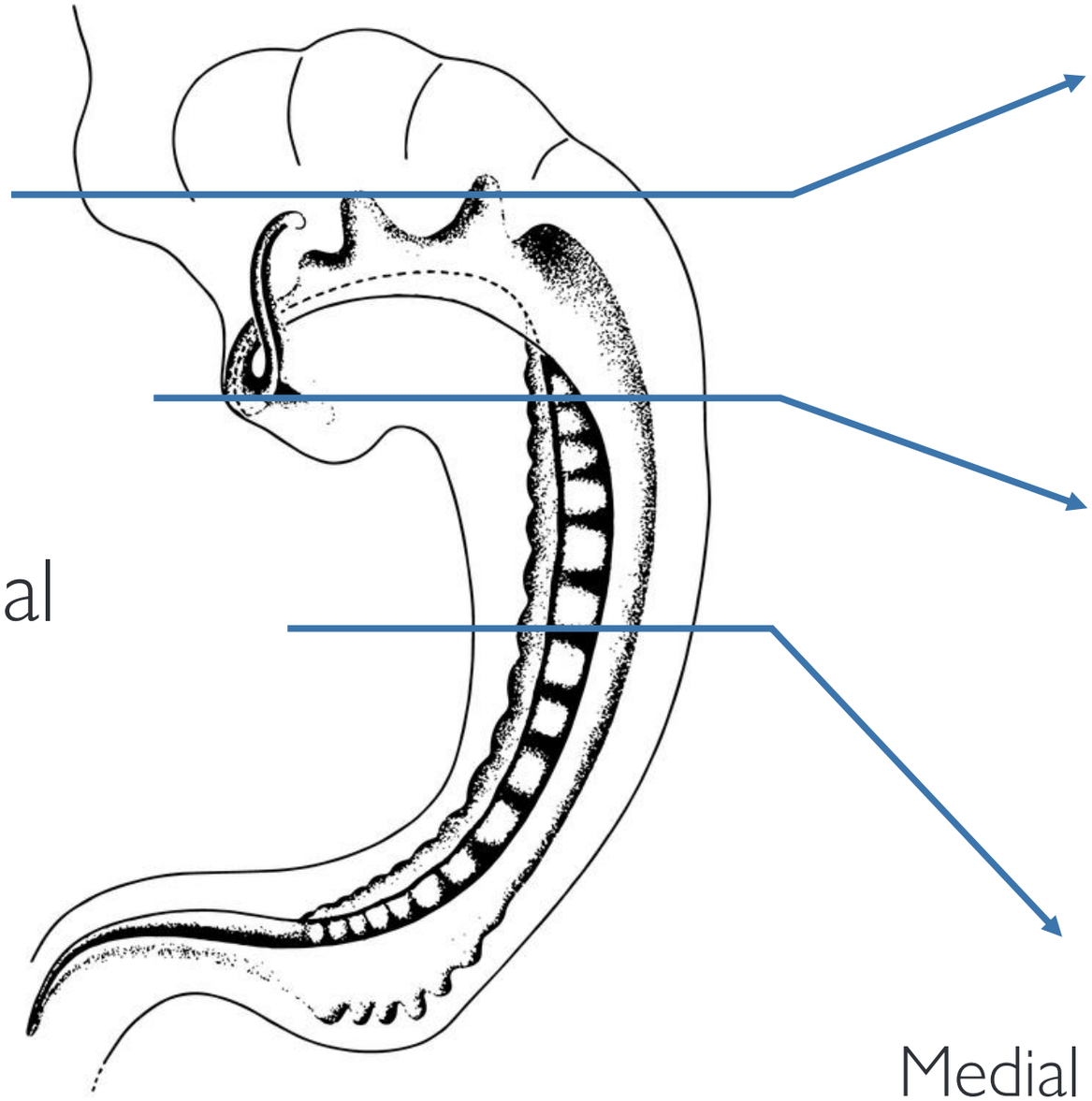
Accurate prediction of neuronal loss by combined volumetric and quantitative MRI markers



Goubran M, Bernhardt BC, Cantor-Rivera D, Lau JC, Blinston C, Hammond RH, de Ribaupierre S, Burneo JG, Mirsattari S, Steven DA, Parrent AG, Bernasconi A, Bernasconi N, Peters TM, Khan AR. In vivo MRI signatures of hippocampal subfield pathology in intractable epilepsy. Human Brain Mapping, 37(3) pp1103-1119, Mar 2016.

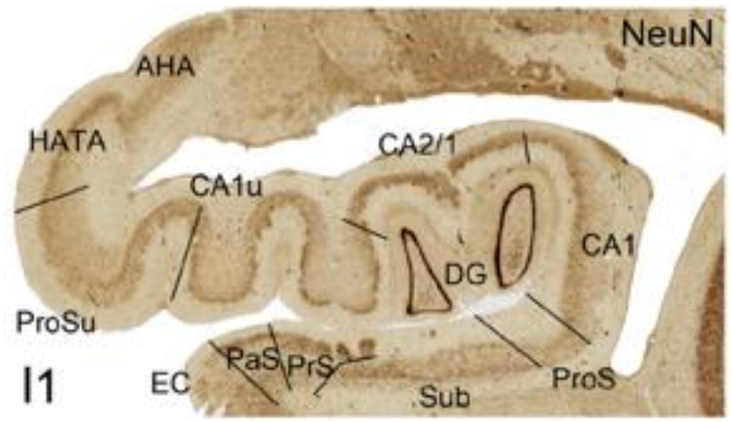
Labelling is challenging due to folding of the hippocampus

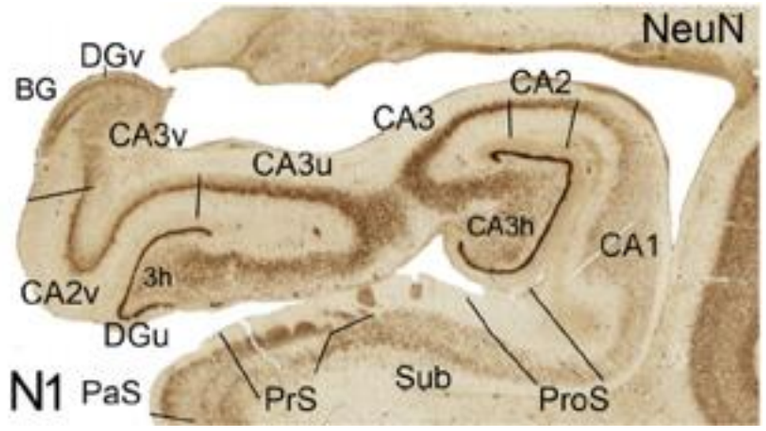
Anterior



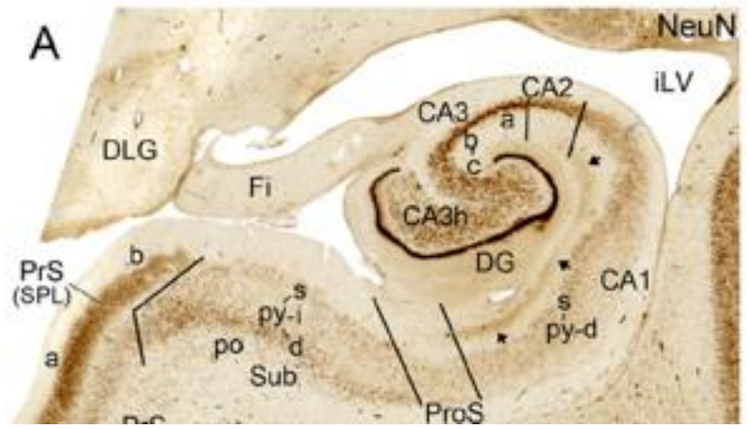
Medial

Posterior





Medial

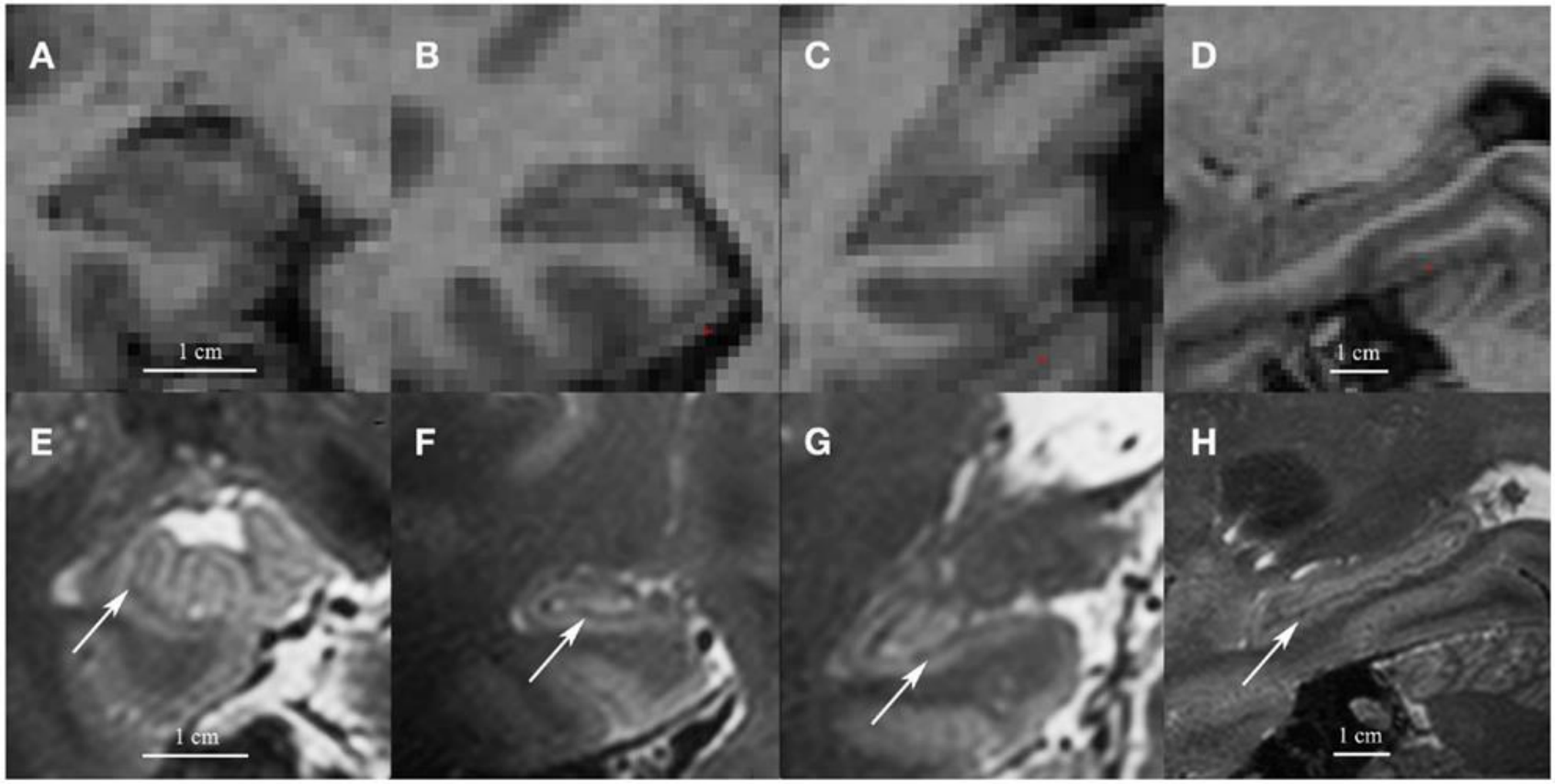


Lateral

Ultra-high field 7T MRI can reveal internal structure

3T

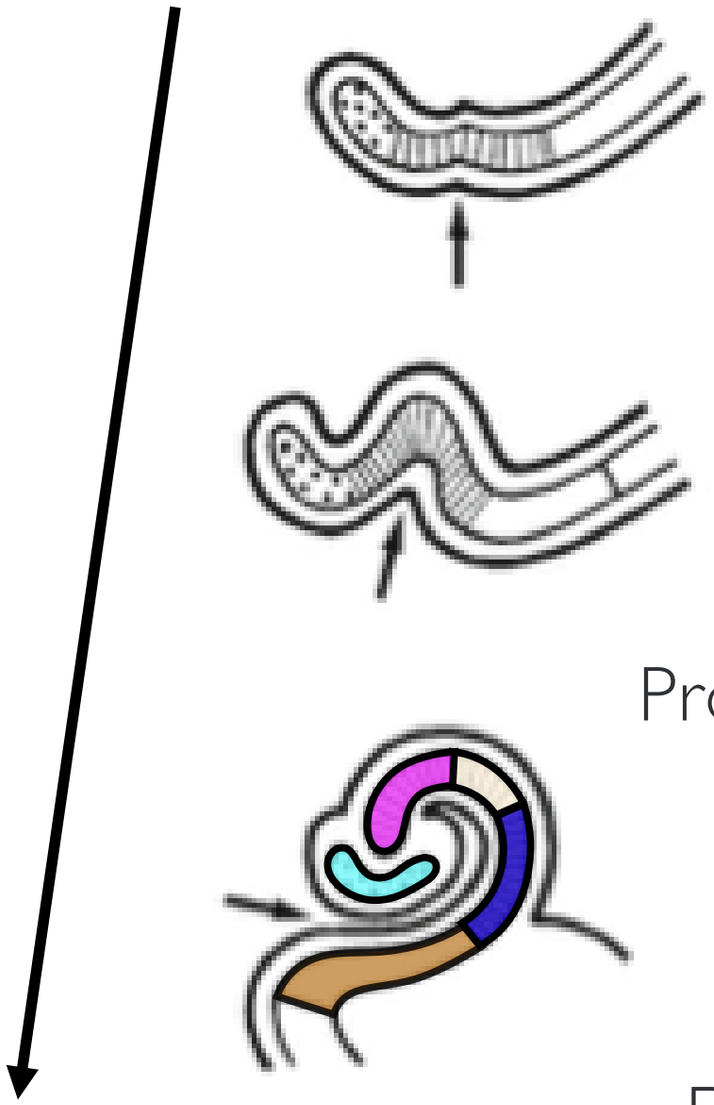
7T



Wisse et al. A critical appraisal of the hippocampal subfield segmentation package in FreeSurfer. Front. Aging Neurosci., 25 September 2014

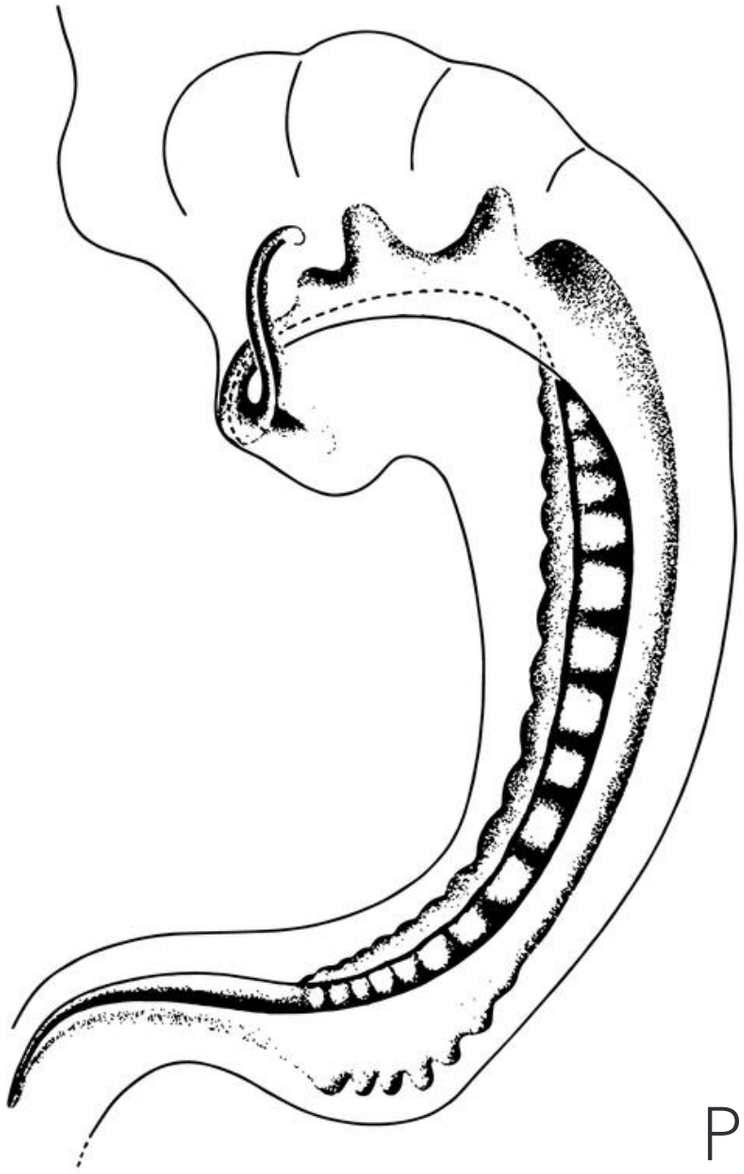
Unfolding the hippocampus

Development



Proximal

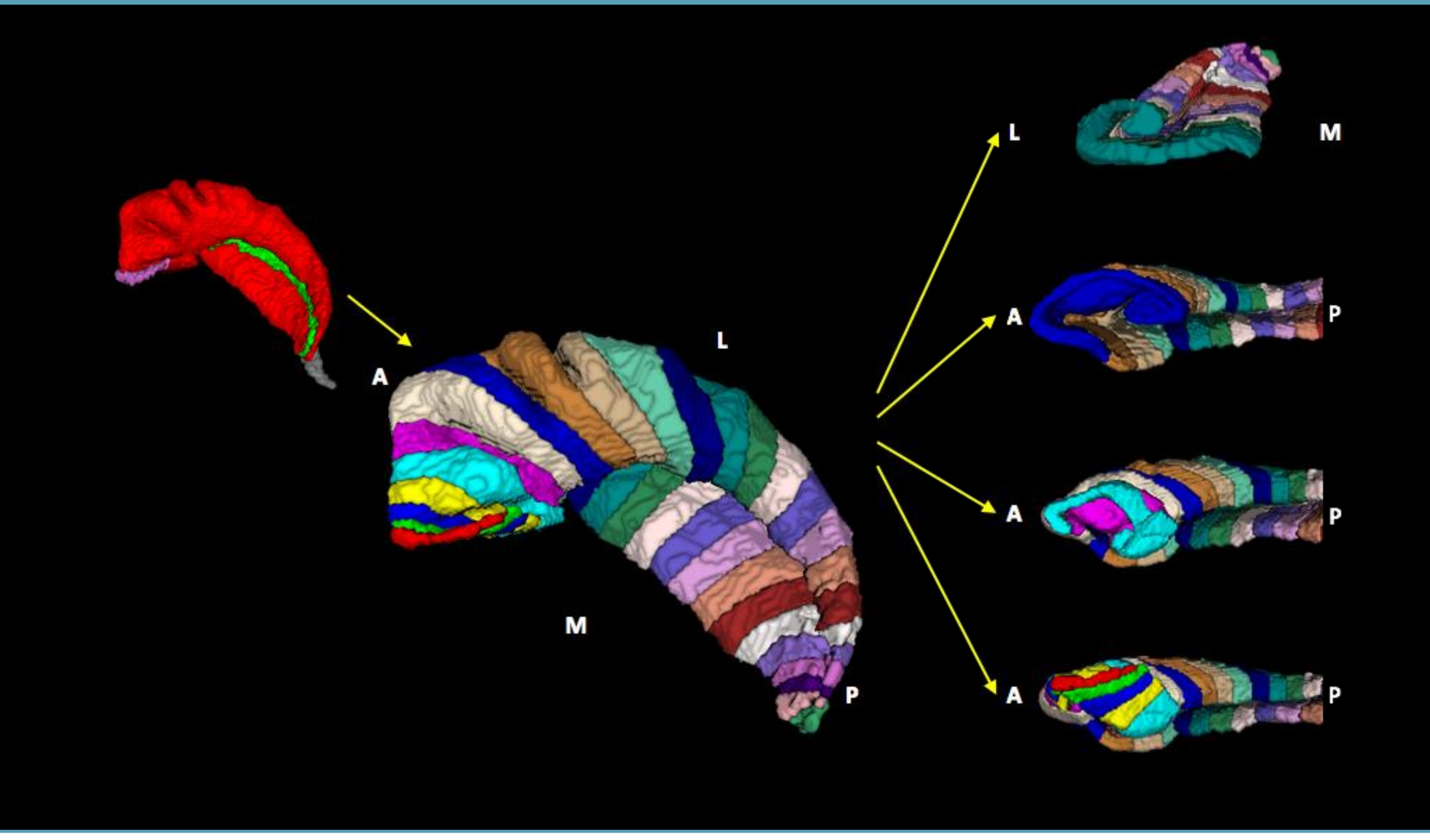
Distal



Anterior

Posterior

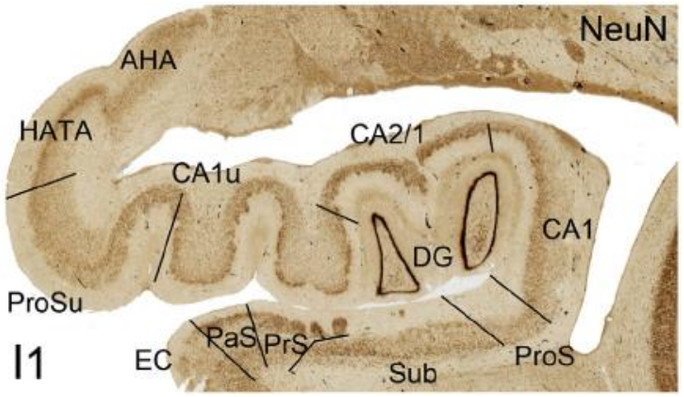
Anterior-posterior mapping

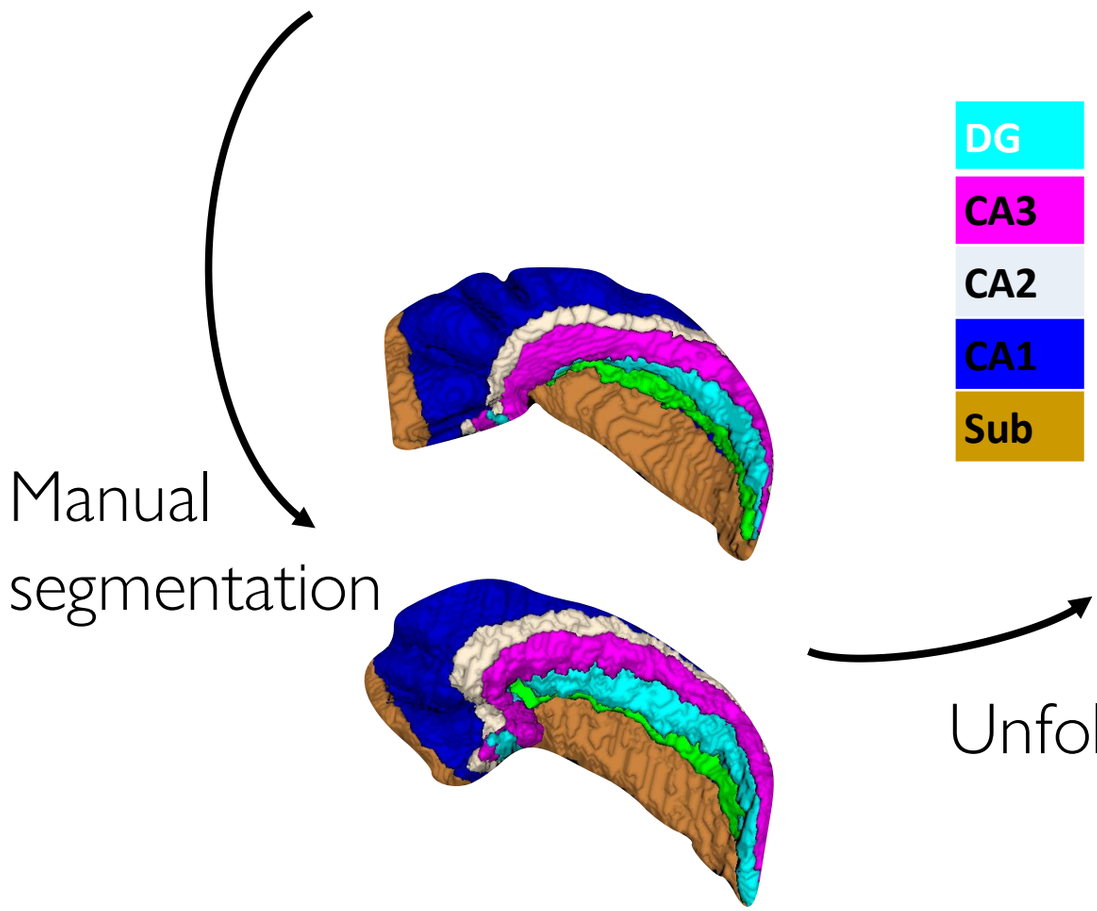


DeKraker, Ferko, Khan & Köhler. Oral presentation at SfN 2016.

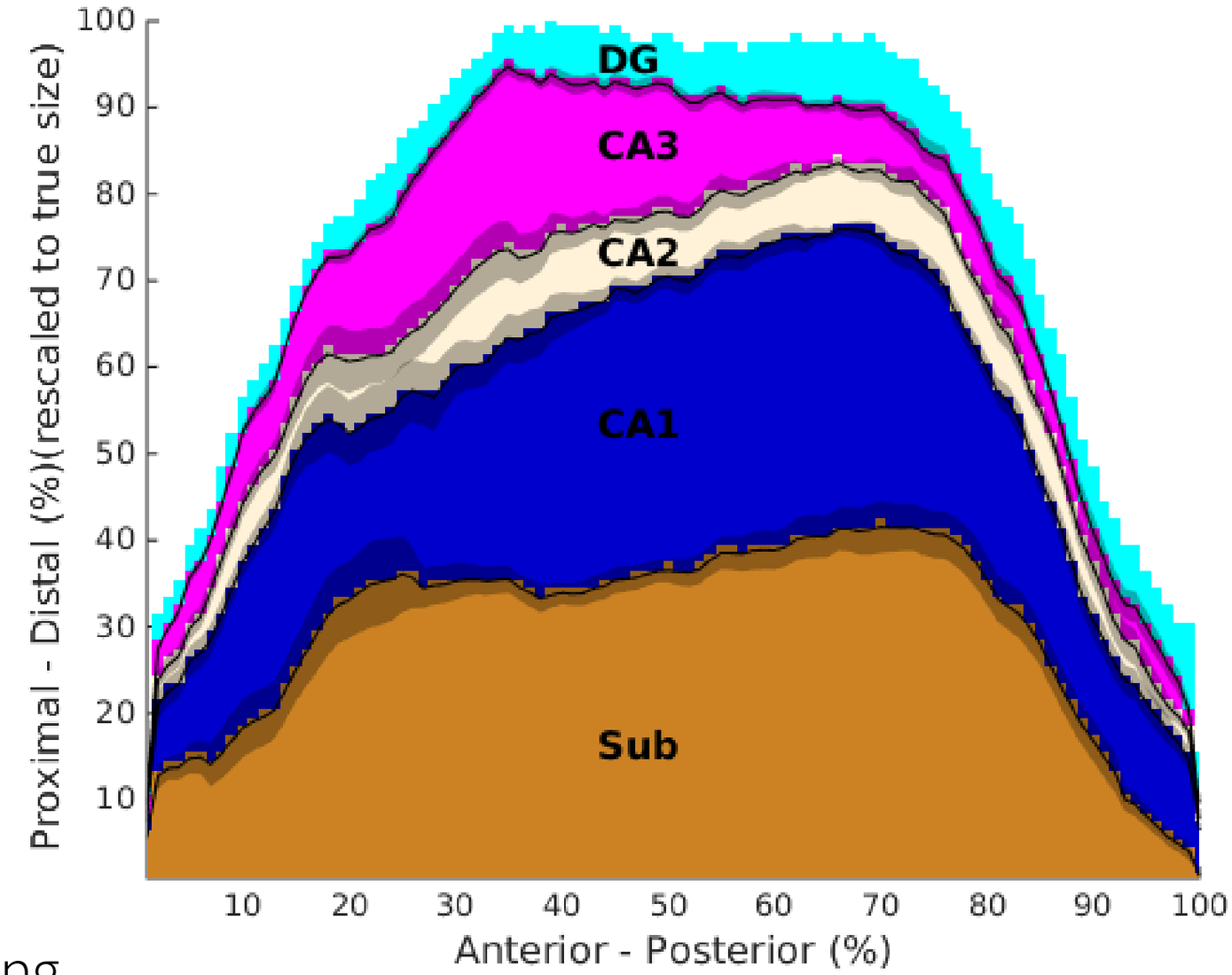
Subfields in unfolded coordinate space

Histology-derived Parcellation (Ding et al. 2015)





Subfield atlas in unfolded space

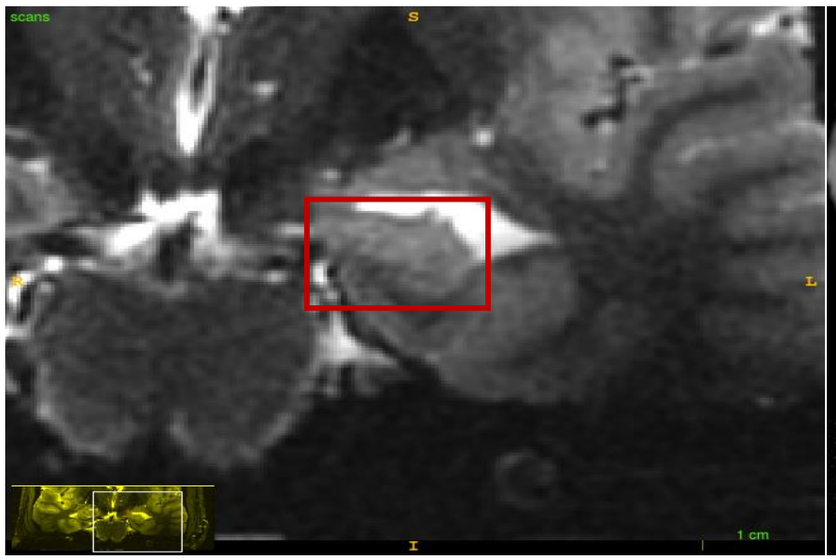


DeKraker, …Khan. Unfolding the hippocampus: an intrinsic coordinate system for subfield segmentations and quantitative mapping. Revision submitted to NeuroImage. *bioRxiv pre-print online.*

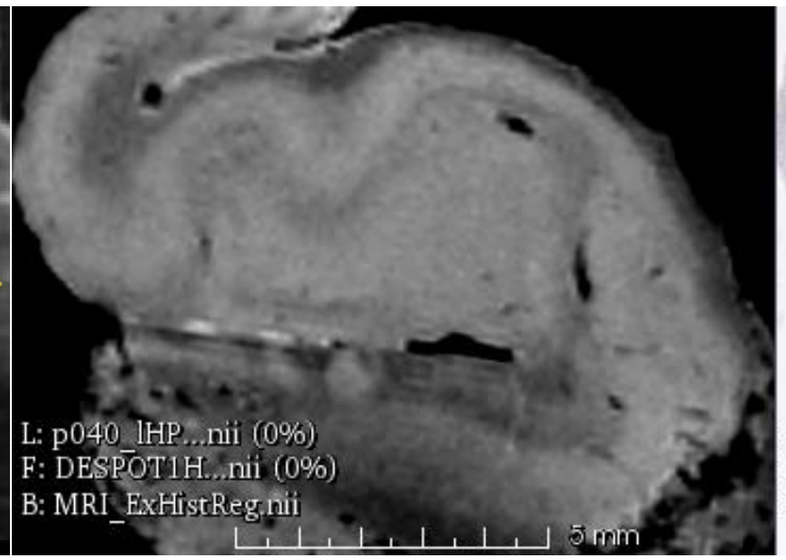
Histological validation

- Single case with pre-op high-resolution 7T MRI

7T presurgical

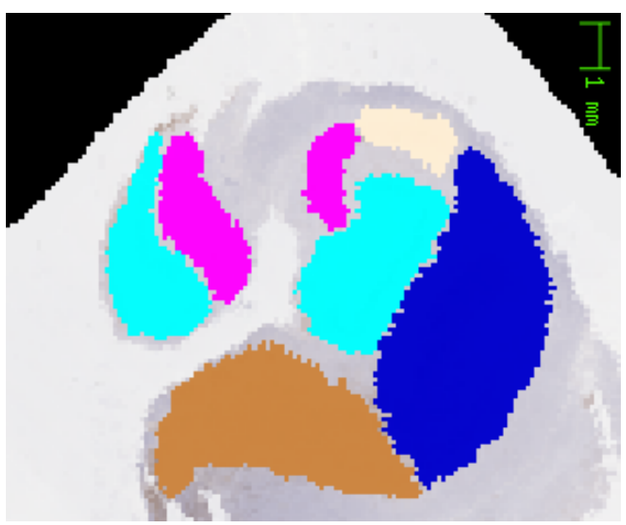


9.4T resected

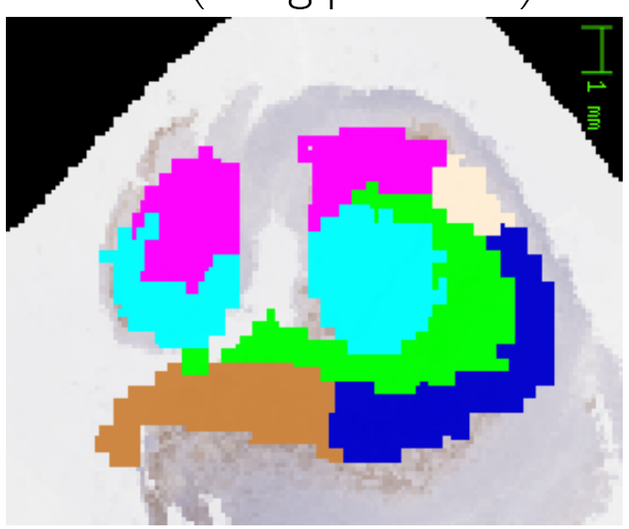


Histology (NeuN)

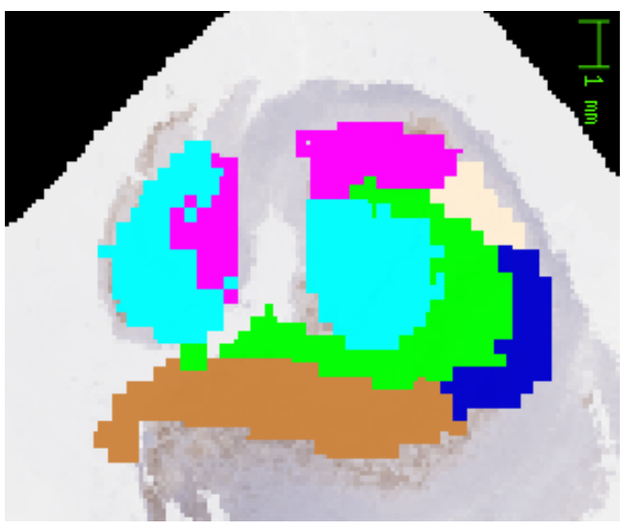
Ground truth



Manual (Ding protocol)

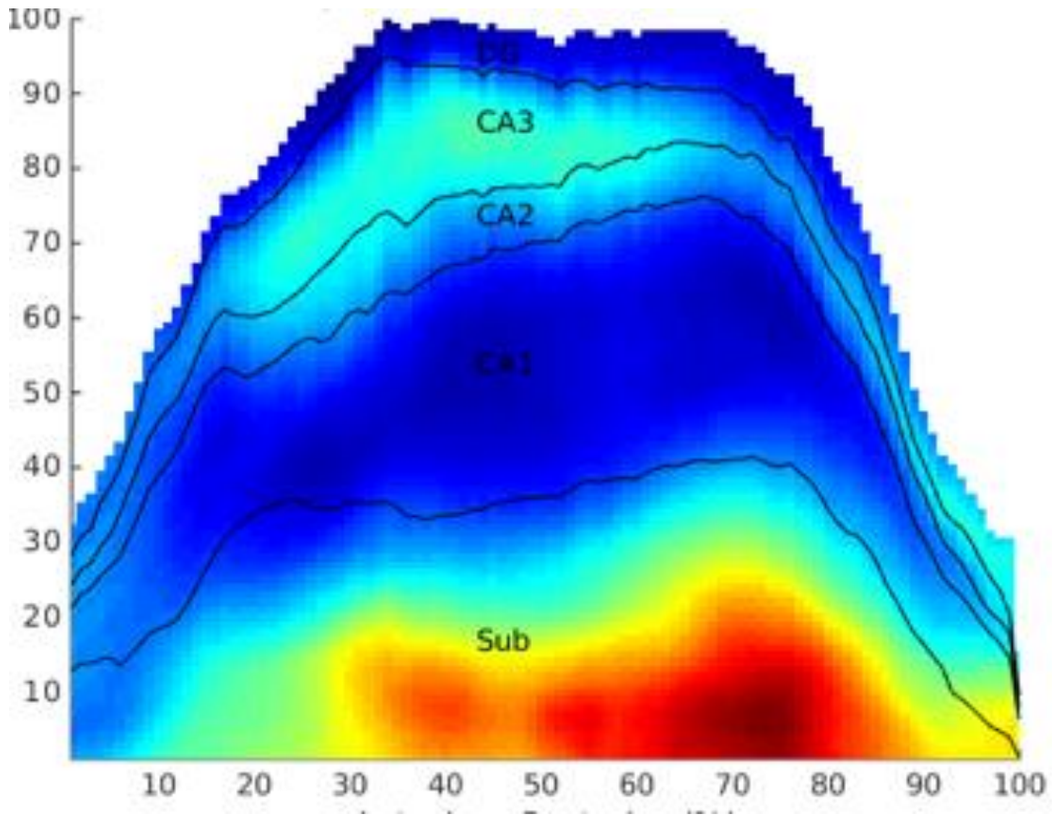


Unfolded atlas

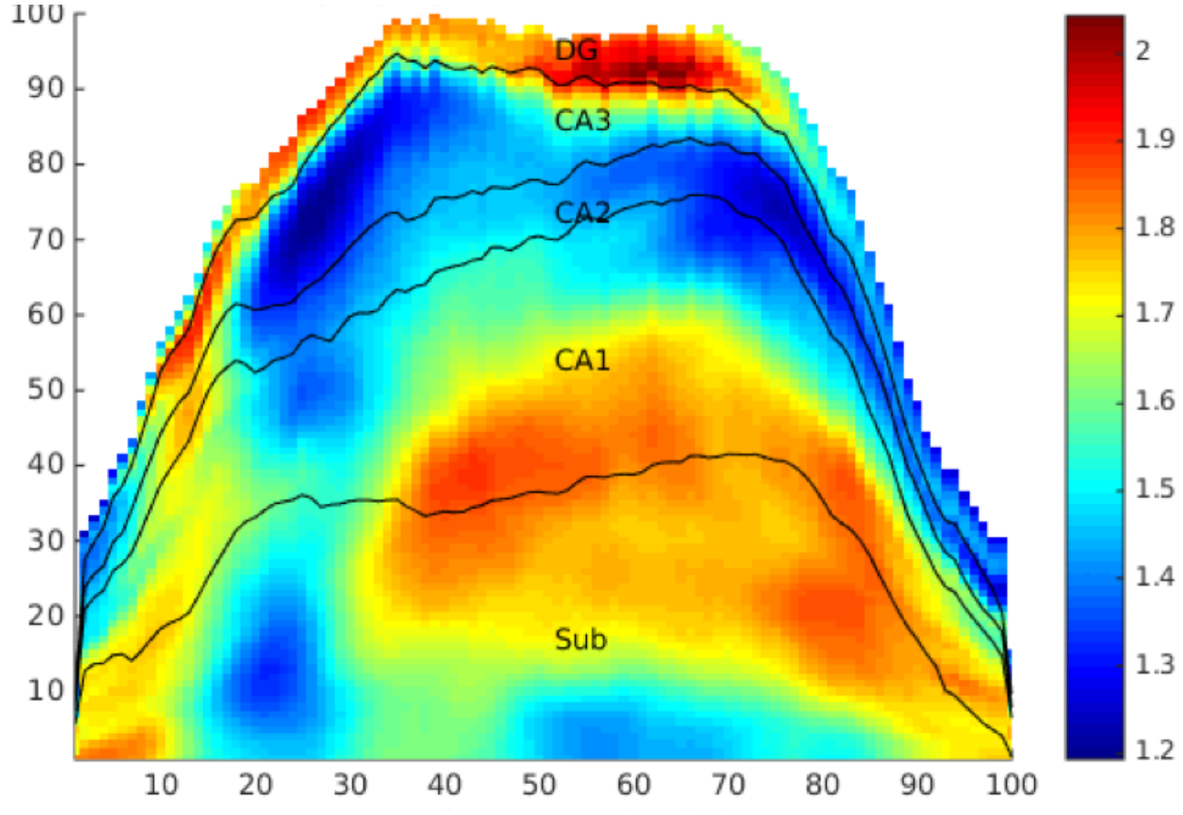


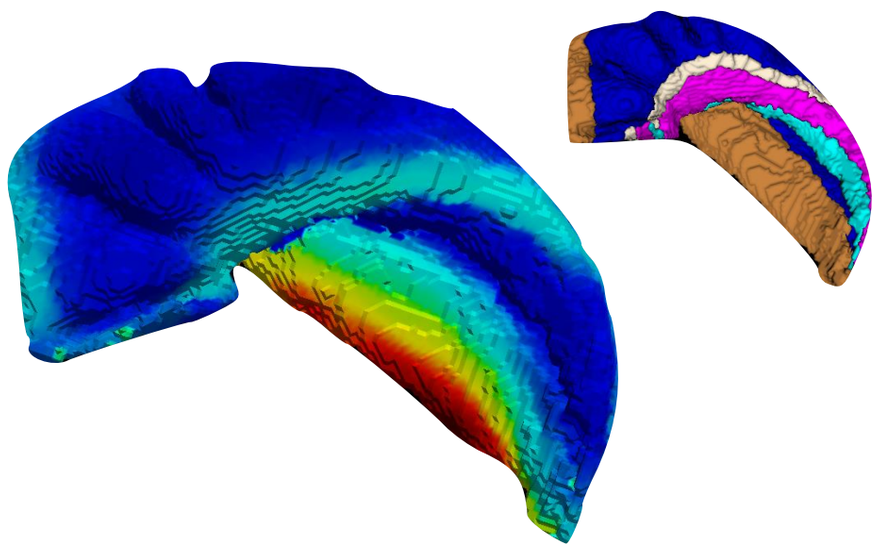
Quantitative mapping in standardized coordinate system

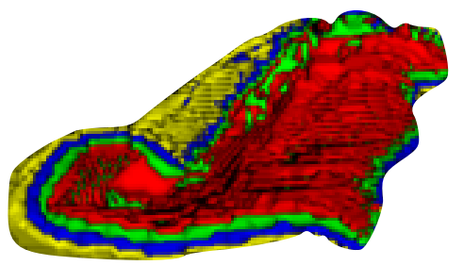
Group Average Myelin Map



Group Average Thickness







DeKraker, Ferko, Lau, Köhler, Khan. Accepted for oral presentation. ISMRM 2017.

Take home

- Quantitative MRI can be a reliable marker for histological properties
- Seizure localization can be a challenge in epilepsy, especially FCD Type I
    - Quantifying cortical architecture may facilitate the discovery of imaging markers
- It is difficult to predict surgical outcome in epilepsy
    - Techniques to segment hippocampal subfields may help better predict seizure outcome