Towards an ultra-high resolution 3D neurotransmitter receptor atlas

BIG BRAIN WORKSHOP 2020 | THOMAS FUNCK, PHD

McGill

JÜLICH
Forschungszentrum

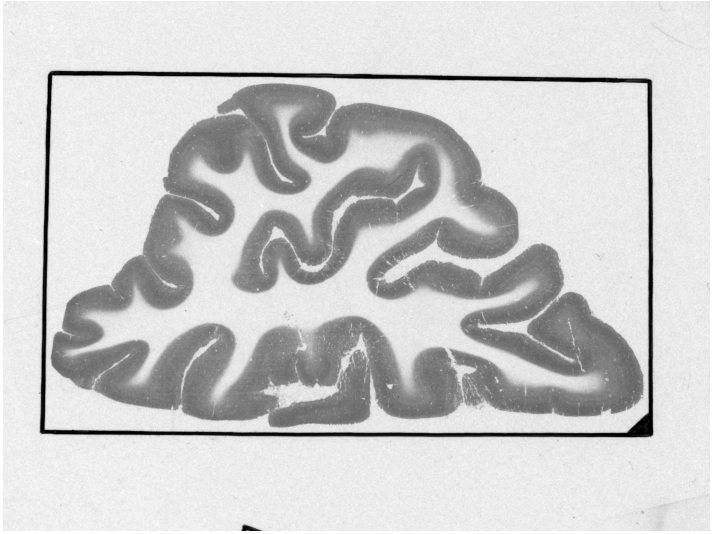
Creating neurotransmitter receptor atlases

- Characterize normal + pathologic receptor distributions
  - Chemoarchitecture of information processing

Creating neurotransmitter receptor atlases

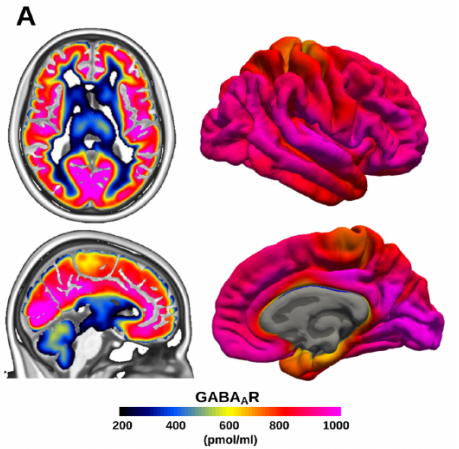
- Characterize normal + pathologic receptor distributions

- Autoradiography
  - + High resolution (0.05mm)
  - + More ligands than PET
  - - Extremely expensive
  - - Only 2D images
  - - Post-mortem

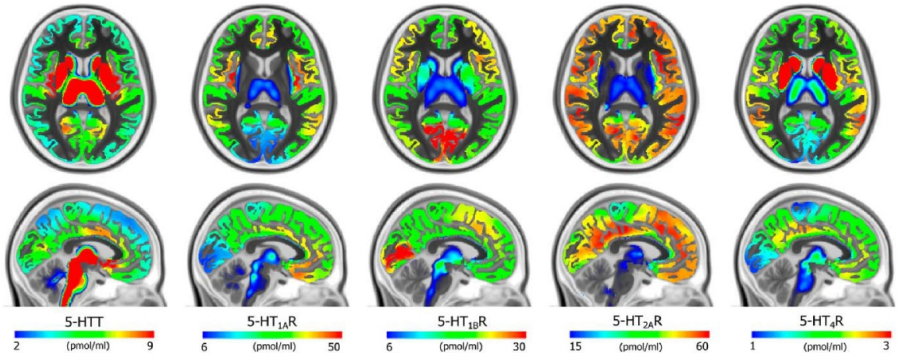


Creating neurotransmitter receptor atlases

- Characterize normal + pathologic receptor distributions
- Autoradiography
- PET
  - + In vivo
  - + Relatively inexpensive → larger data sets
  - - Lower resolution → what is maximum resolution of PET?



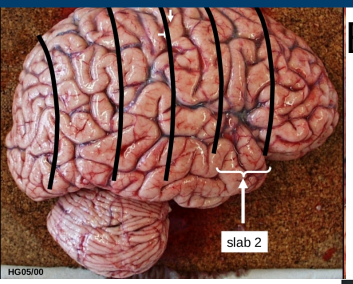
Norgaard, et al. 2020 (preprint)



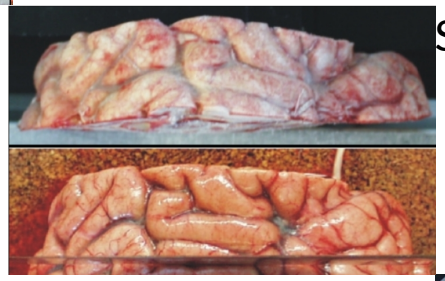
Beliveau, et al. 2017

Reconstructing 3D atlases from 2D autoradiographs

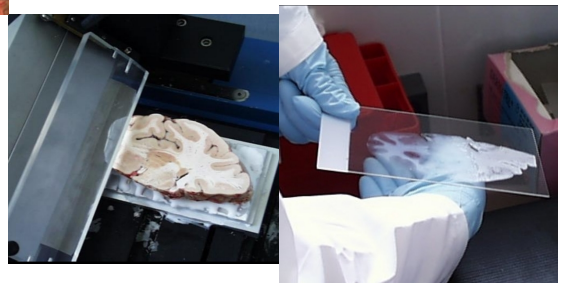
The data



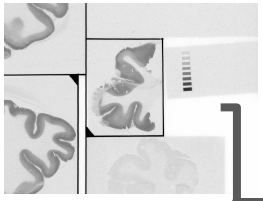
Brain extracted and cut into 2-3cm slabs

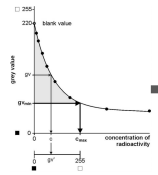


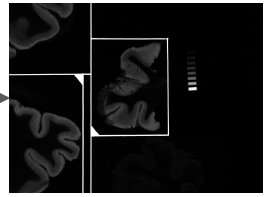
Slabs shock frozen ~-40C



Slabs sectioned and bathed in solution with radioligand







$$C_b = \frac{R}{E \cdot B \cdot W_b \cdot S_a} \cdot \frac{K_D + L}{L}$$

Raw autoradiographs transformed to binding densities

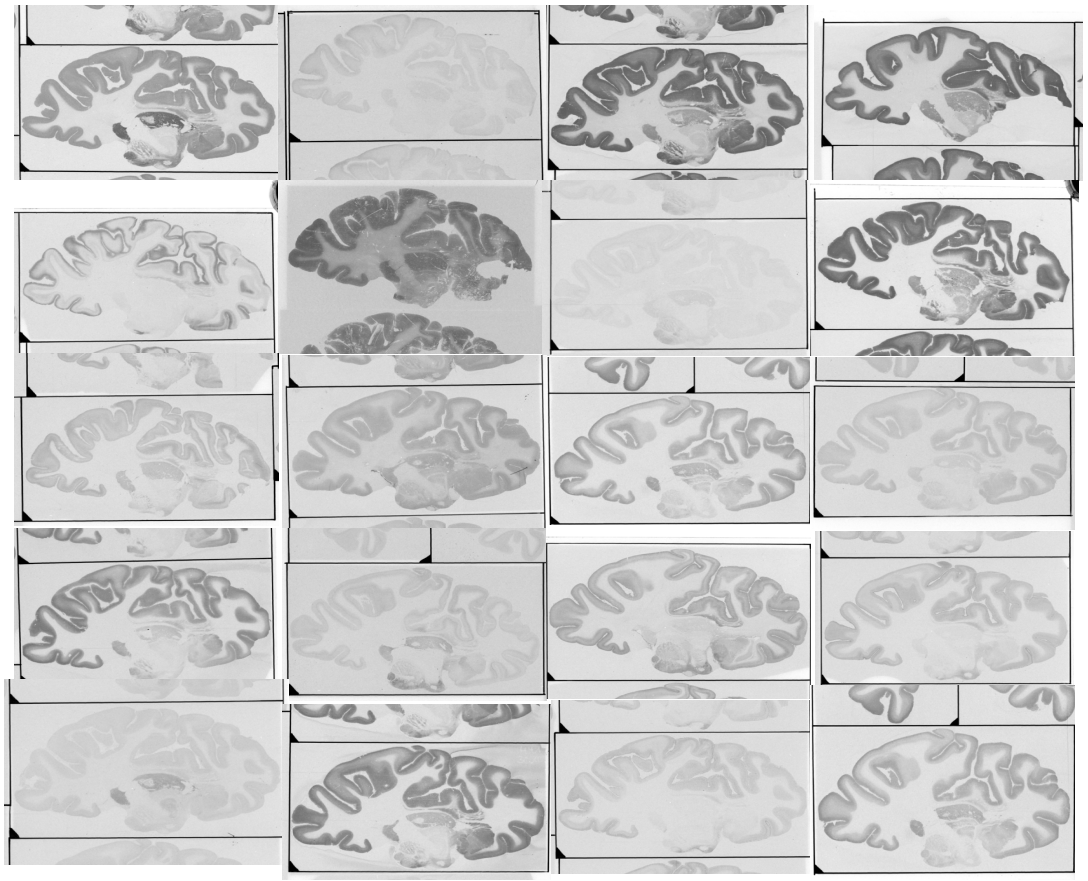
The data

- 3 post-mortem human brains

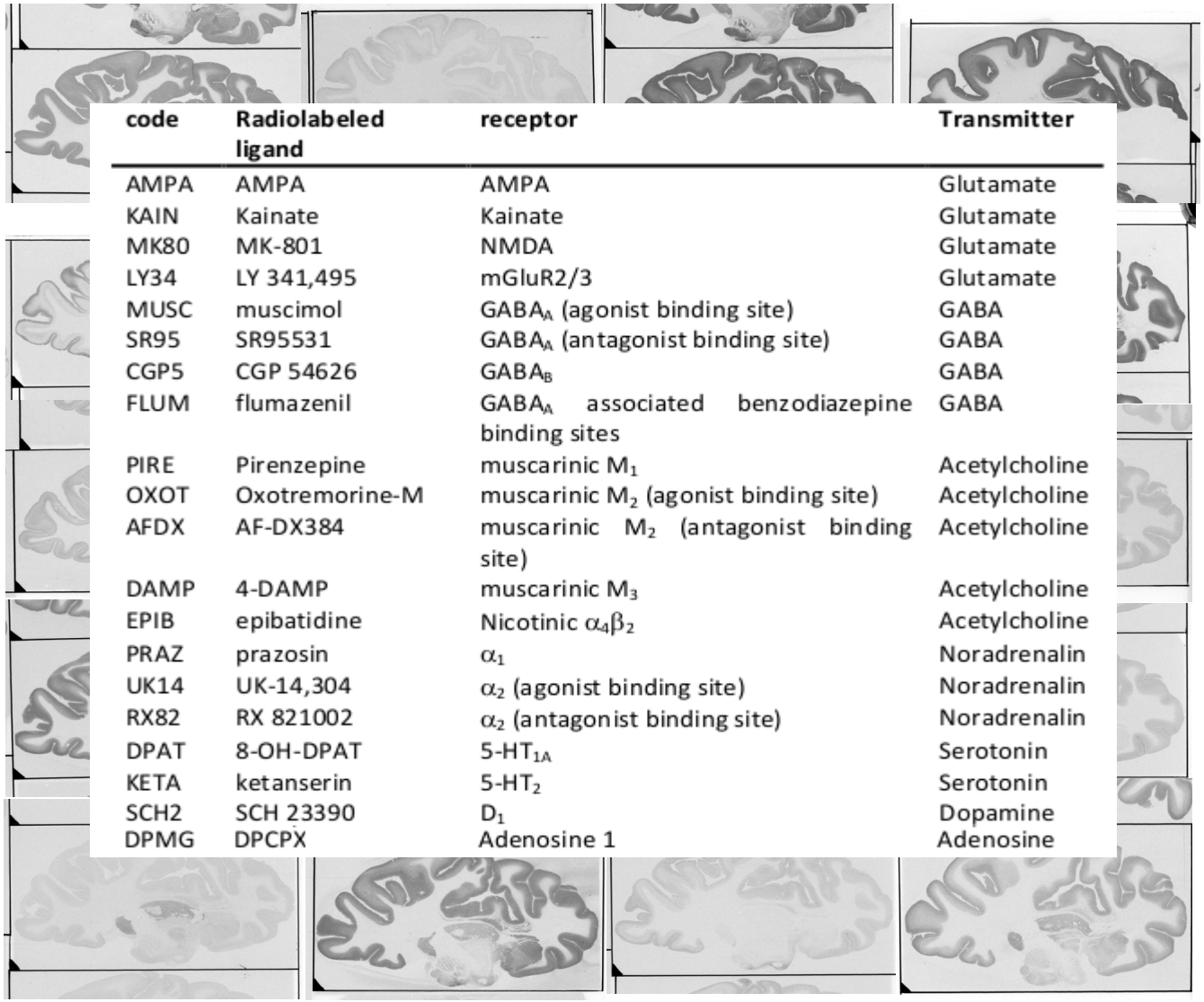
- 20 receptor binding sites
  - visualized with quantitative in vitro receptor autoradiography
  - acquired sequentially → ~400µm+ between particular receptor

Autoradiographs

- 3 post-mortem human brains
- 20 receptor binding sites
  - visualized with quantitative in vitro receptor autoradiography
  - acquired sequentially → ~400µm+ between particular receptor



Autoradiographs

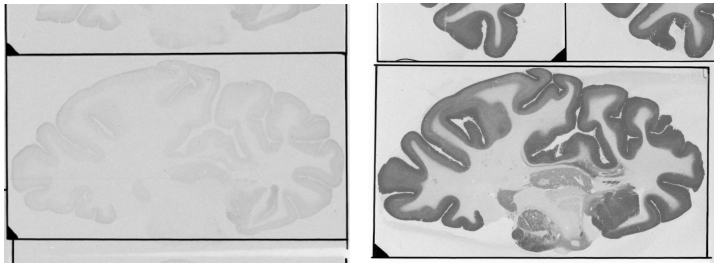


code	Radiolabeled ligand	receptor	Transmitter
AMPA	AMPA	AMPA	Glutamate
KAIN	Kainate	Kainate	Glutamate
MK80	MK-801	NMDA	Glutamate
LY34	LY 341,495	mGluR2/3	Glutamate
MUSC	muscimol	$GABA_A$ (agonist binding site)	GABA
SR95	SR95531	$GABA_A$ (antagonist binding site)	GABA
CGP5	CGP 54626	$GABA_B$	GABA
FLUM	flumazenil	$GABA_A$ associated benzodiazepine binding sites	GABA
PIRE	Pirenzepine	muscarinic M_1	Acetylcholine
OXOT	Oxotremorine-M	muscarinic M_2 (agonist binding site)	Acetylcholine
AFDX	AF-DX384	muscarinic M_2 (antagonist binding site)	Acetylcholine
DAMP	4-DAMP	muscarinic M_3	Acetylcholine
EPIB	epibatidine	Nicotinic $\alpha_4\beta_2$	Acetylcholine
PRAZ	prazosin	α_1	Noradrenalin
UK14	UK-14,304	α_2 (agonist binding site)	Noradrenalin
RX82	RX 821002	α_2 (antagonist binding site)	Noradrenalin
DPAT	8-OH-DPAT	$5\text{-}HT_{1A}$	Serotonin
KETA	ketanserin	$5\text{-}HT_2$	Serotonin
SCH2	SCH 23390	D_1	Dopamine
DPMG	DPCPX	Adenosine 1	Adenosine

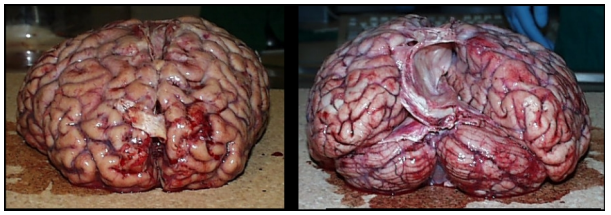
Chart from Nicola Palomero-Gallagher

Challenges to 3D Reconstruction

(I) Autoradiograph intensities

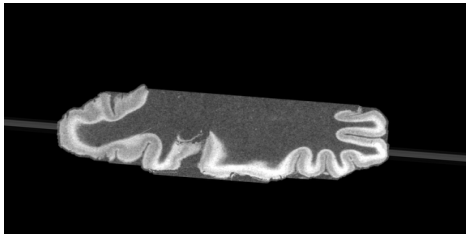


(II) Morphological deformation

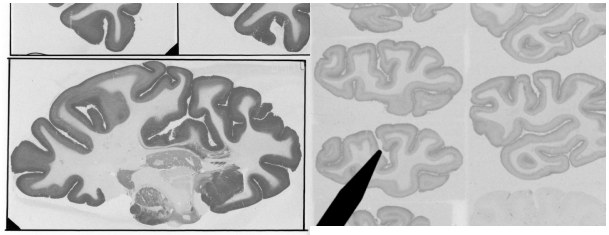


(III) Non-parallel slabs

(IV) Missing / incomplete slices

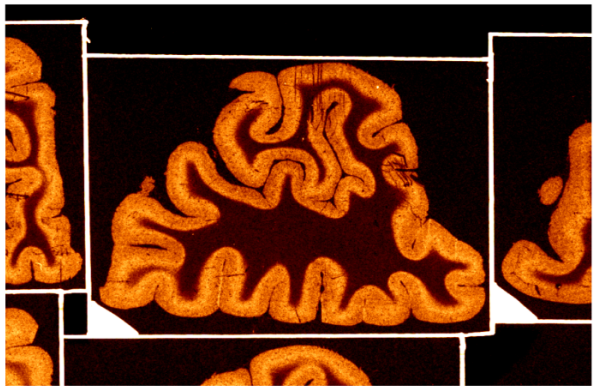


(IV) Autoradiograph slice acquisition



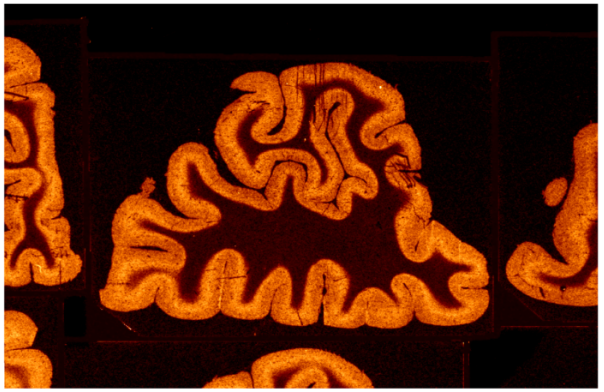
Preprocessing

Initial Image



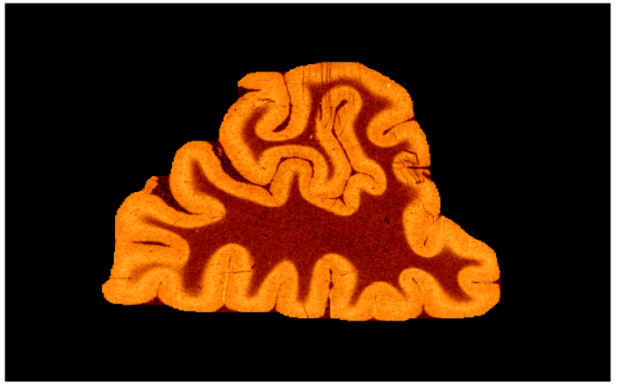
Line Detection

Lines Removed



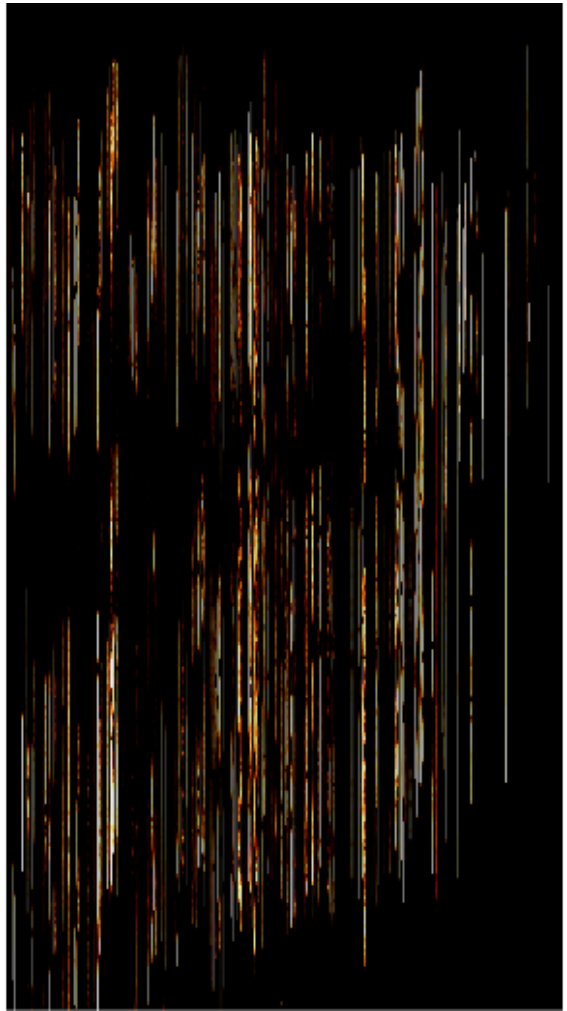
Target Tissue Mask

Cropped Image

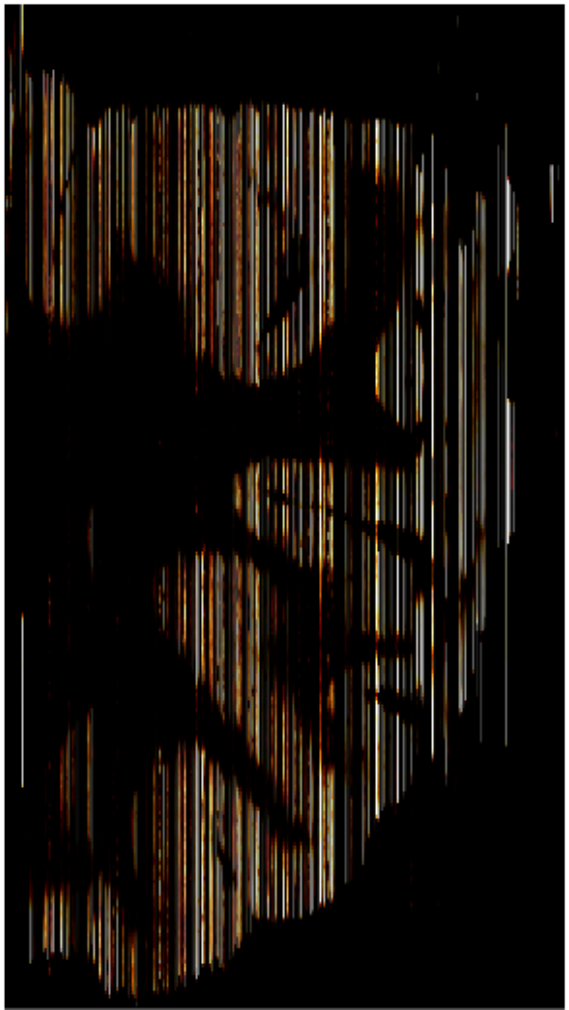


Rigid 2D Autoradiograph Alignment

Iteration 0



Iteration 1

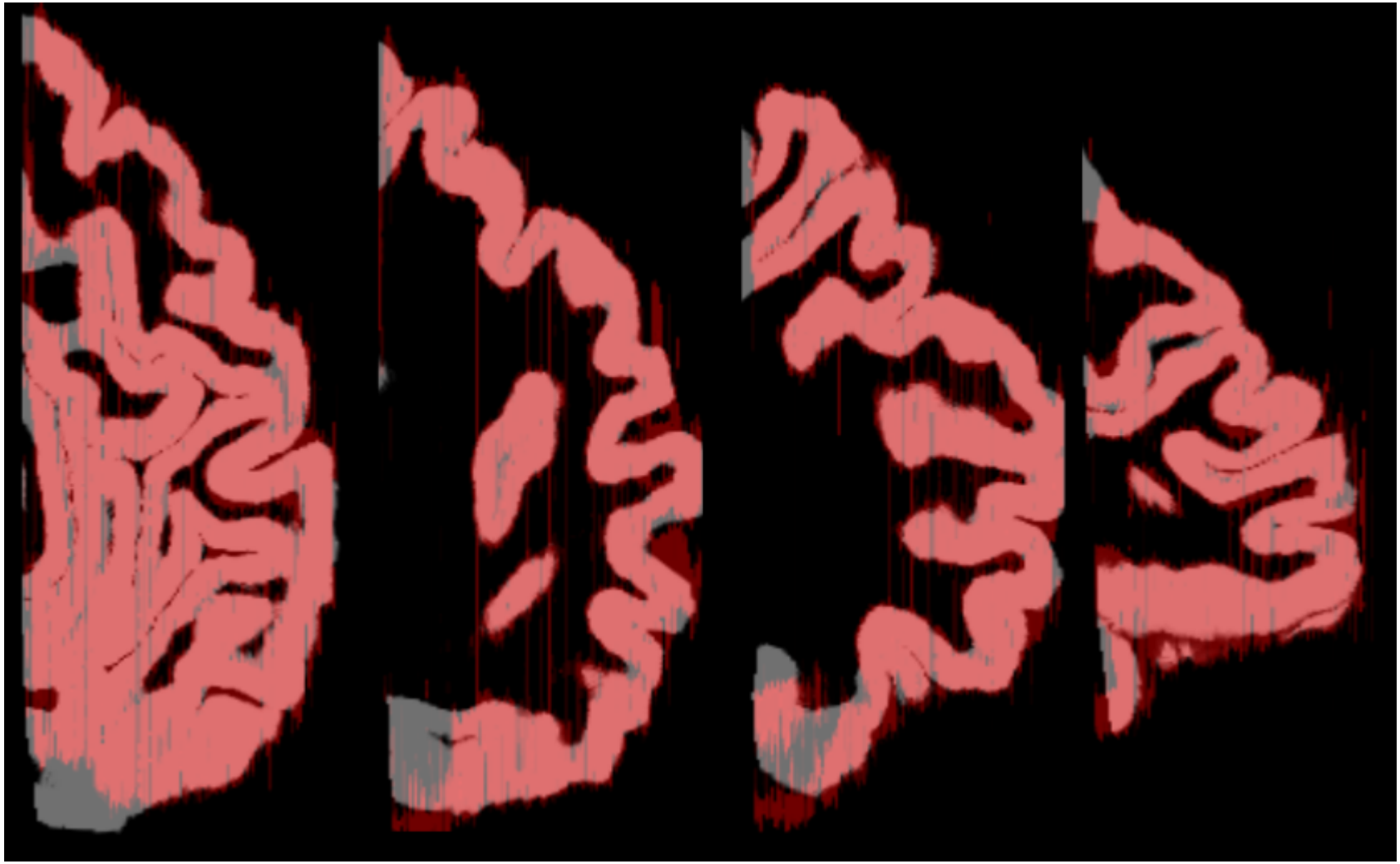


...

Iteration 9

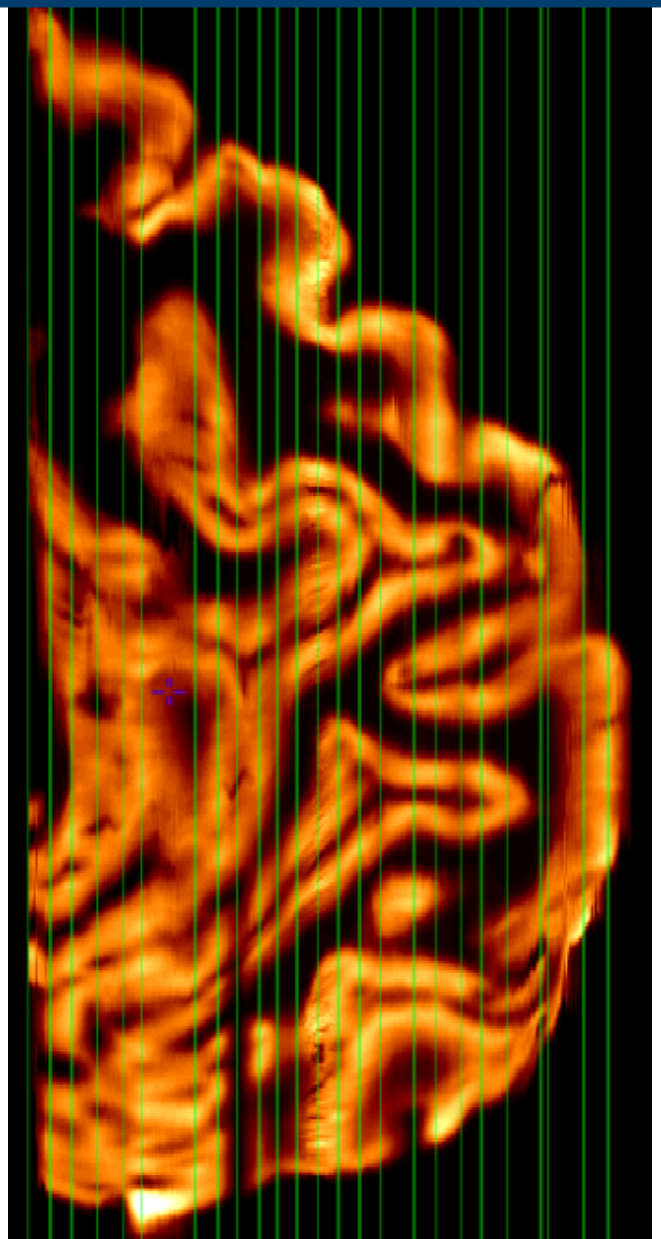
MRI to Autoradiograph Volume Alignment

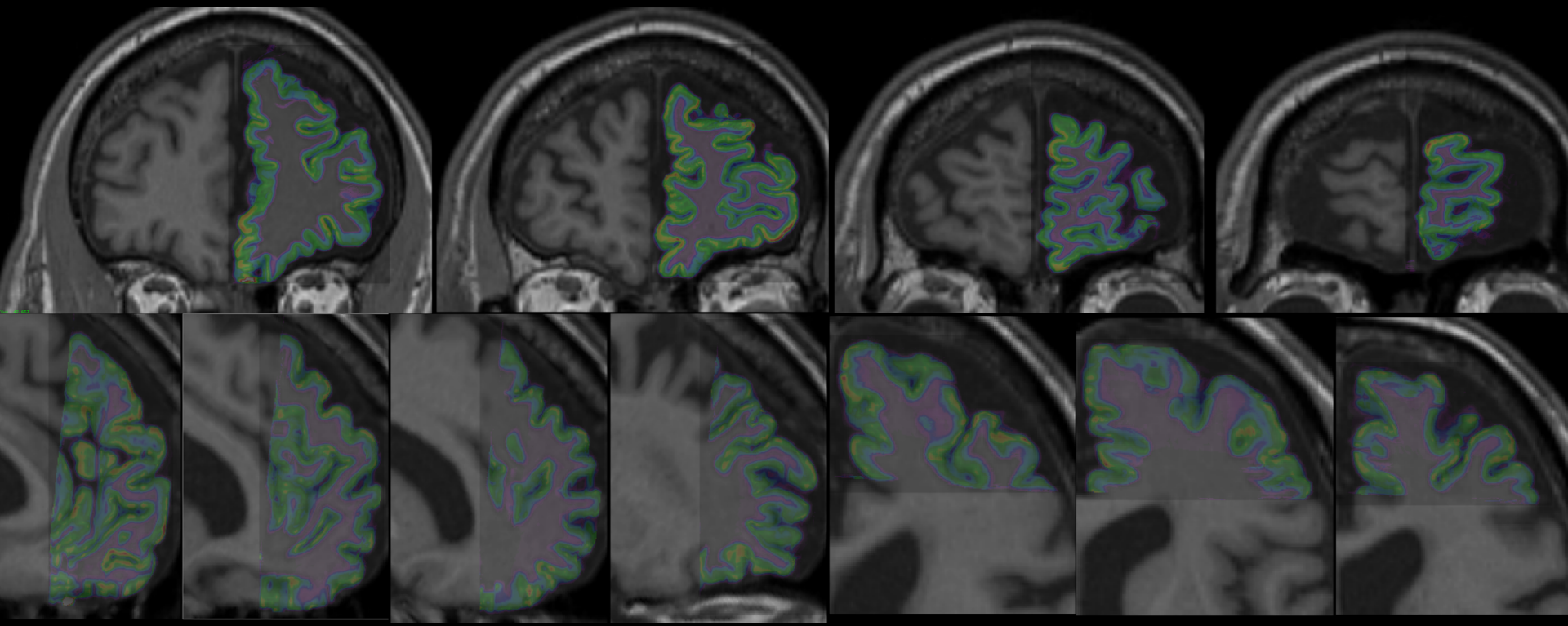
- Grey : Warped MRI GM mask
- Red : Receptor volume GM mask

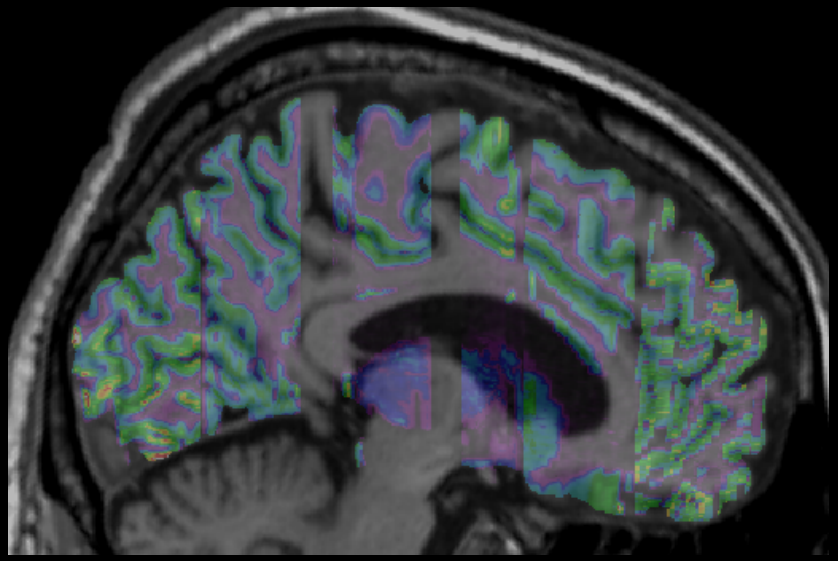
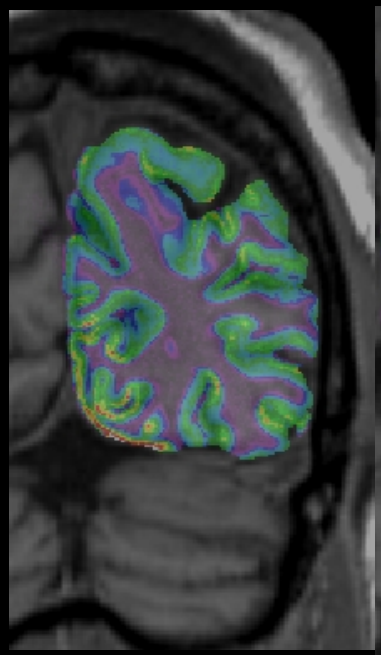
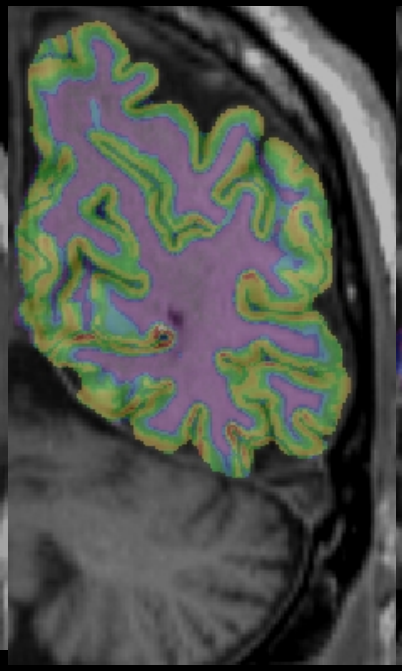
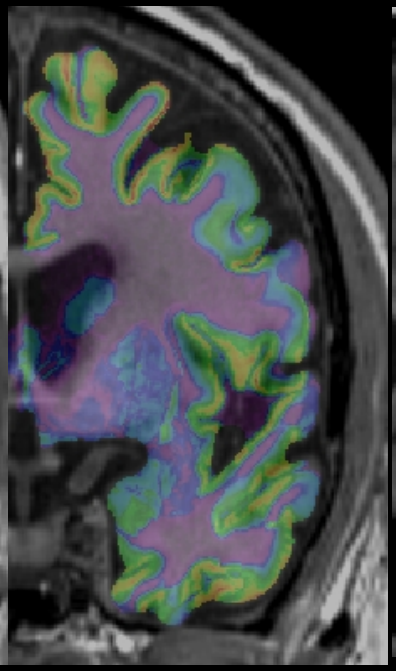
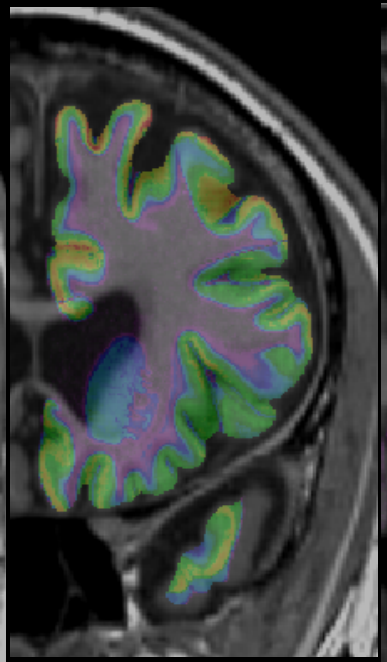
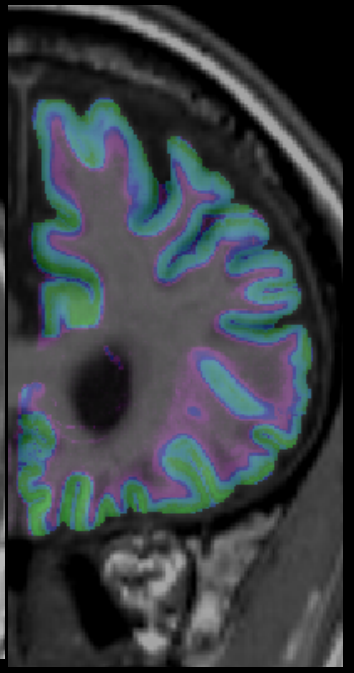


Interpolating missing autoradiographs

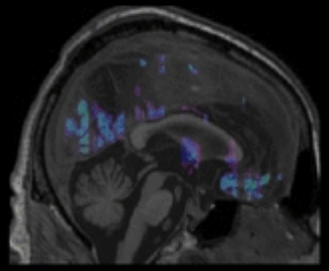
- Morphologically adaptive, distance-weighted interpolation
- Reconstructed GABA-A_{Benz} volume
  - Ligand = Flumazenil
  - Green = acquired autoradiographs



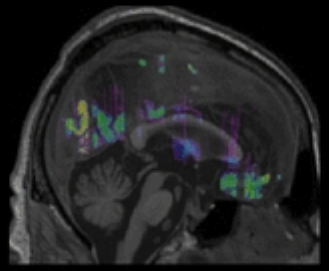


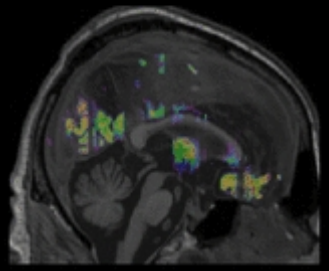
GABAA.Benz.



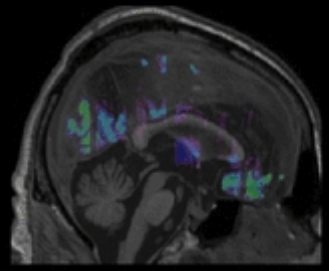
GABAA.Ag.



GABAB

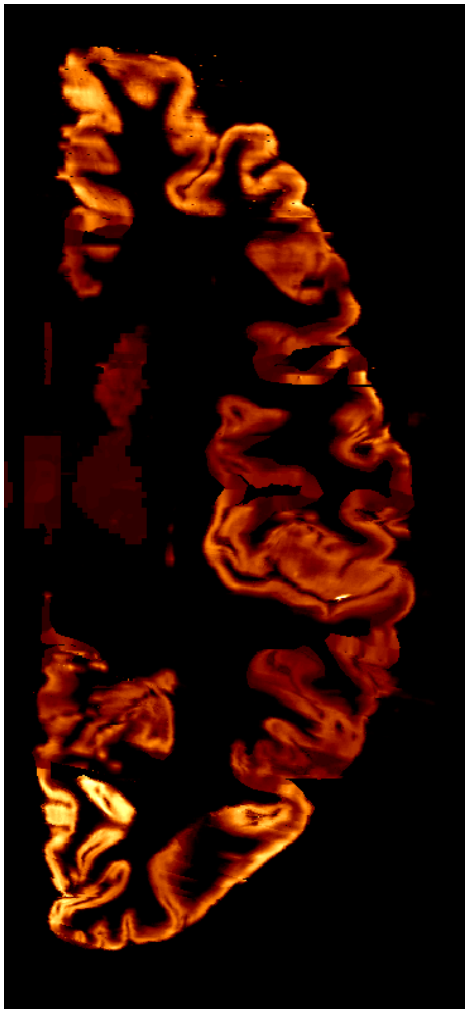


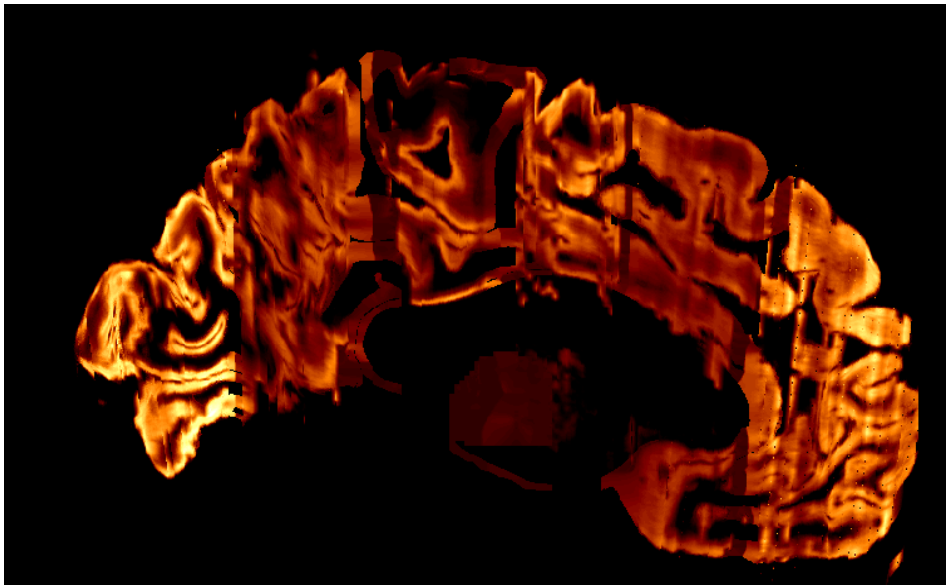
GABAA.Ant.



Interslab Interpolation

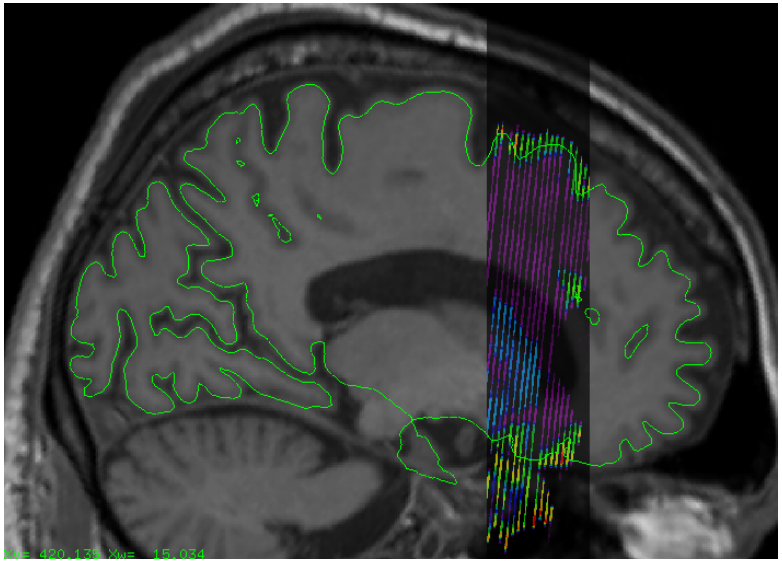
- Volumetric interpolation

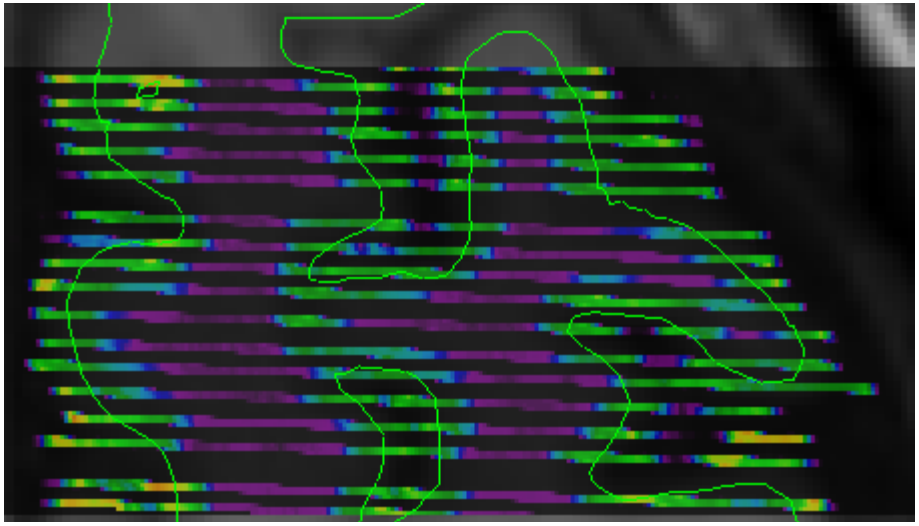


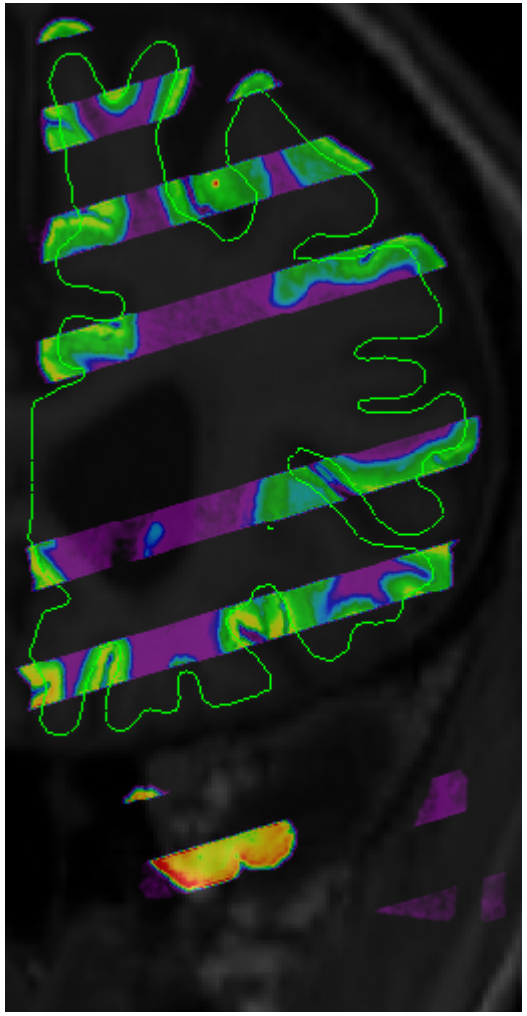


Inter/intra-slab Interpolation

- Surface-based interpolation







Inter/intra-slab Interpolation

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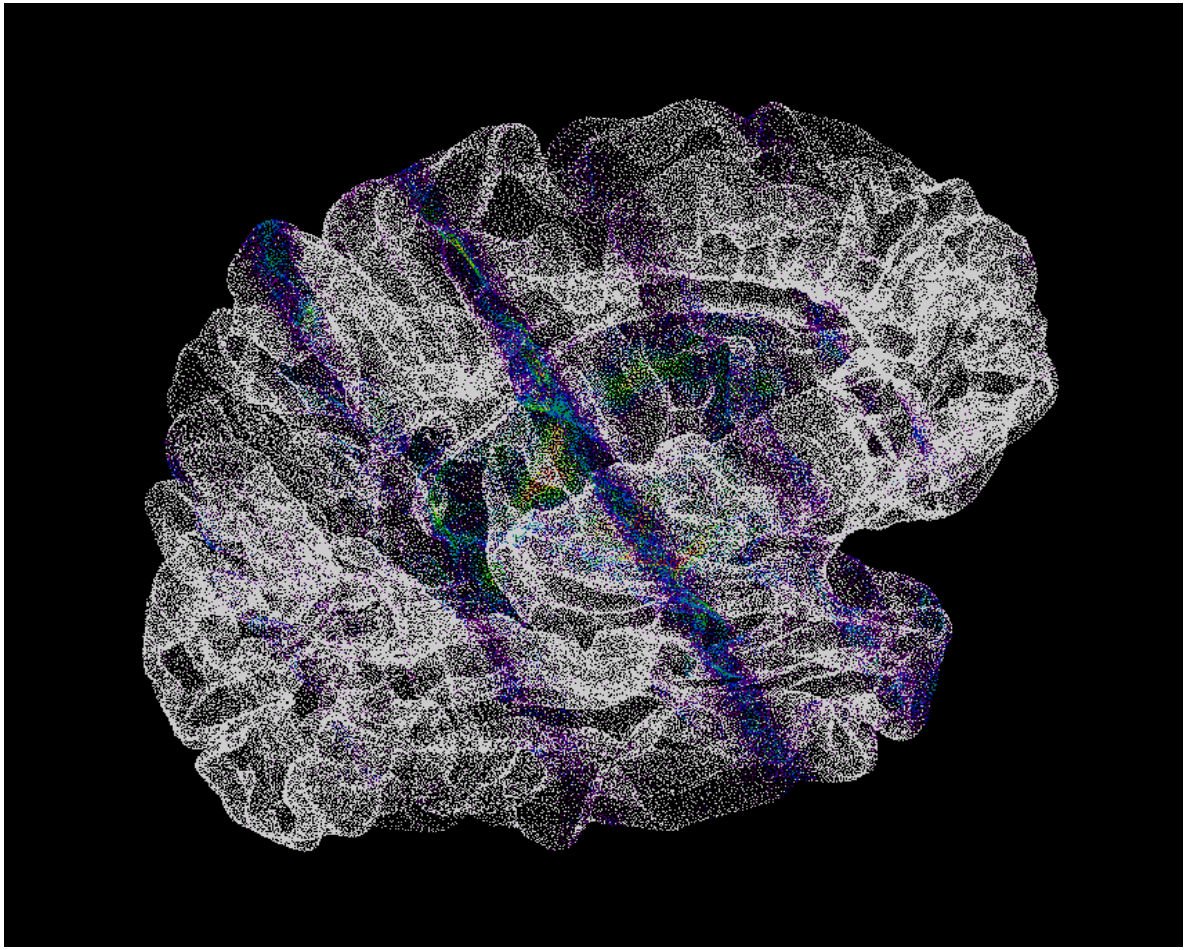


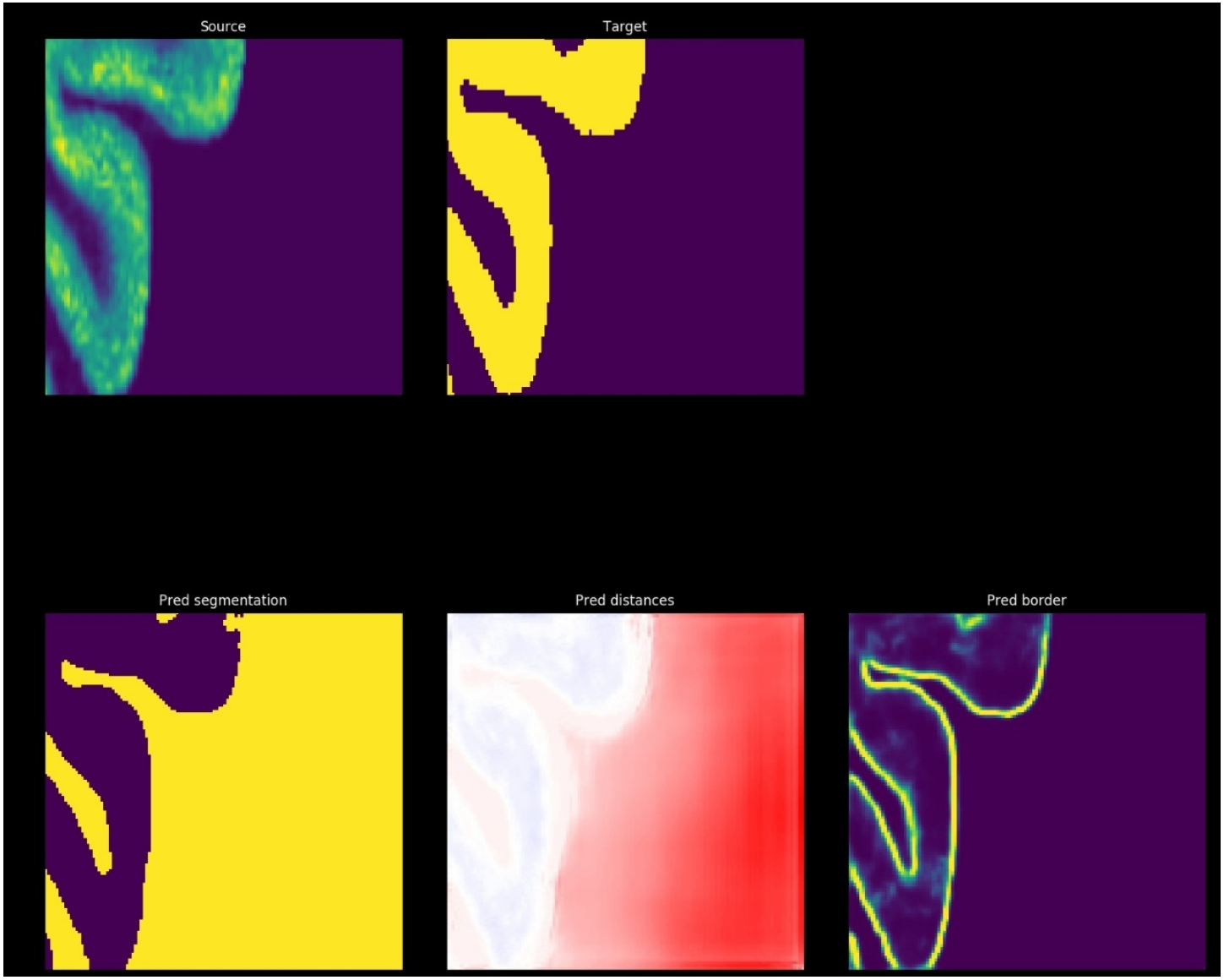
Preprocessing of all autoradiographs

- Semi-automated and manual cropping
- ~18,000 autoradiographs
- 3 brains x 2 hemispheres → ready for reconstruction

GM Segmentation

- Segmentation with deep neural nets
  - Network learns intensity thresholds instead of shapes
- Solution: make learning task harder
  - → nudge network away from simple intensity thresholding
- Learning targets :
  - Prior cortical segmentation
  - Distance map from cortex
  - Cortical border

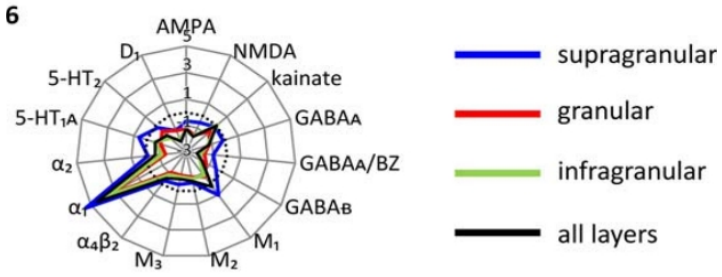
GM Segmentation



Future Perspectives

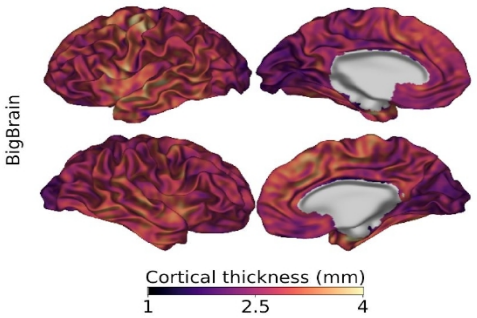
- Multi-modal receptor mapping → novel atlases

3D Receptor Fingerprints



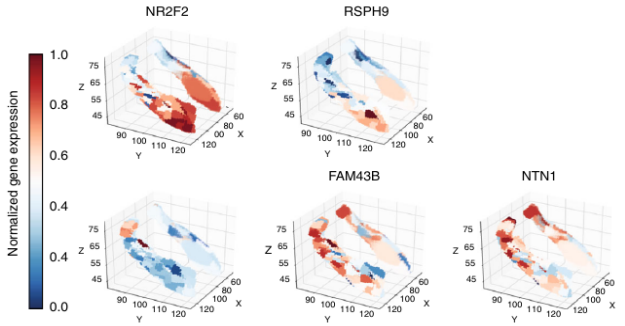
Zilles & Palomero-Gallagher 2017

Gradients



Wagstyl et al 2019

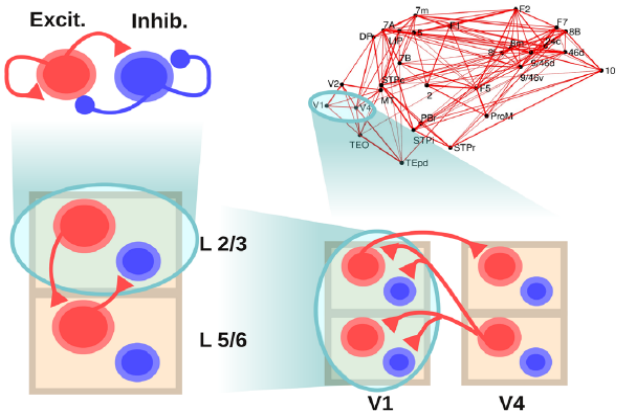
Gene Expression



Vogel et al 2020

- Receptor Targets of DBS
  - Acetylcholine and dopamine (Udapa & Chen, 2015)

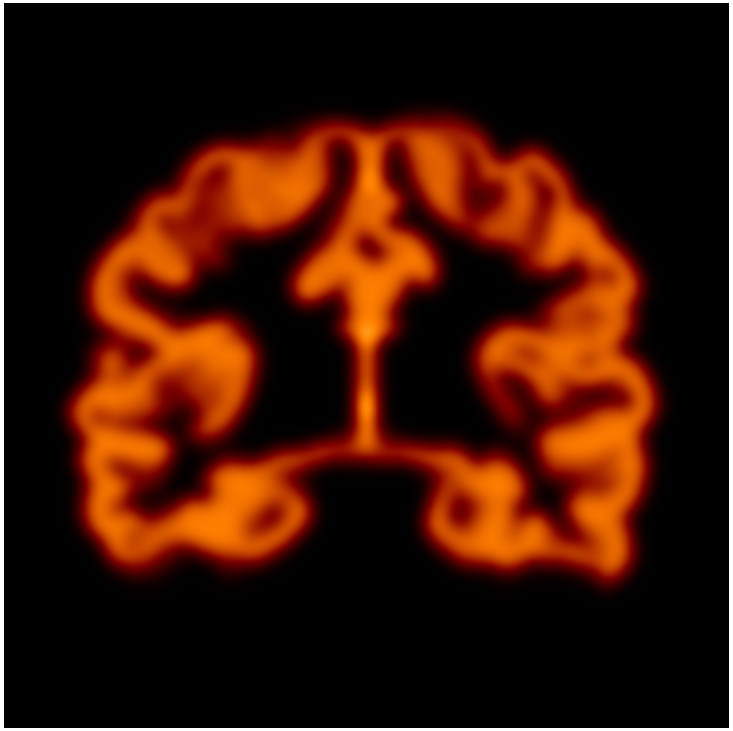
- Computational Modeling
  - HIBALL



Mejias et al 2016

Application: PET simulation and resolution

PET resolution



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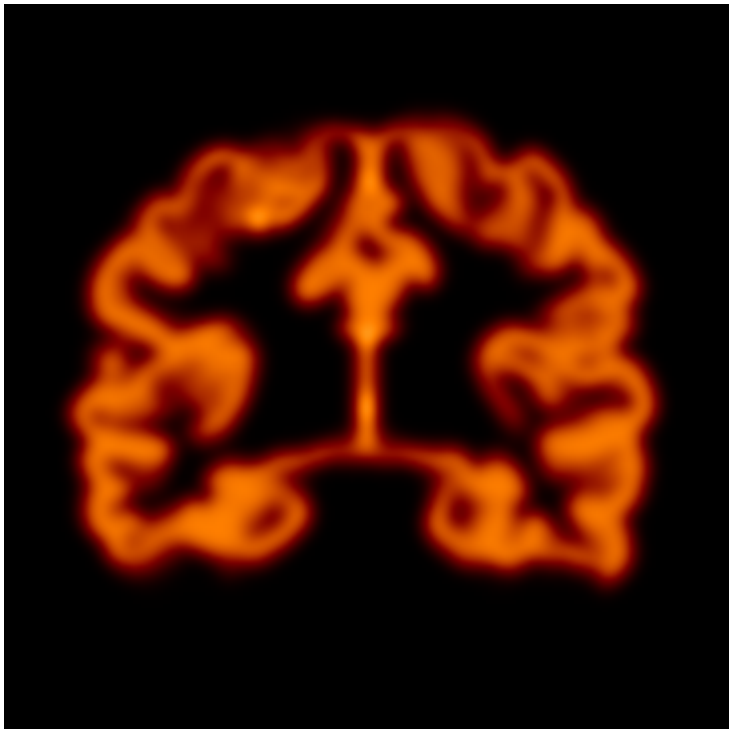
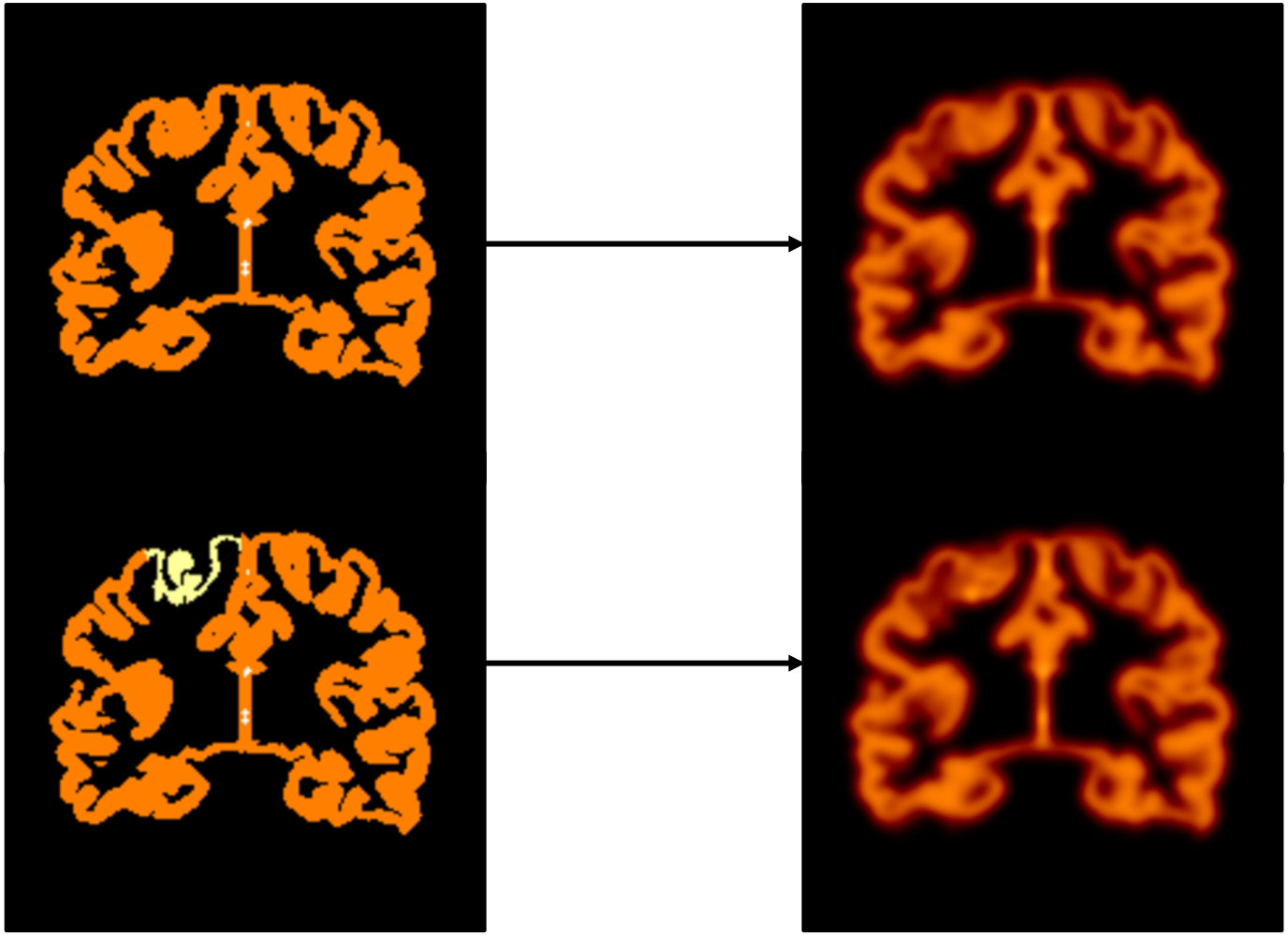
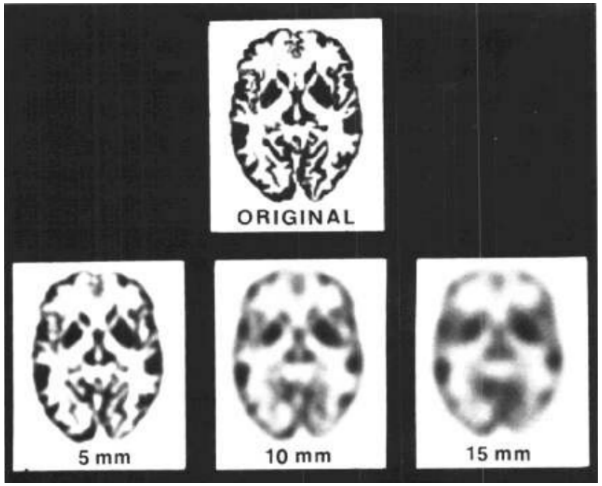


PET resolution

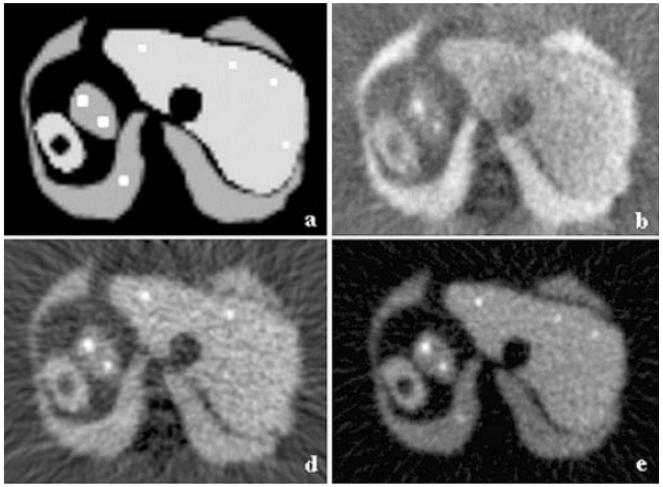


Receptor volumes for PET simulation

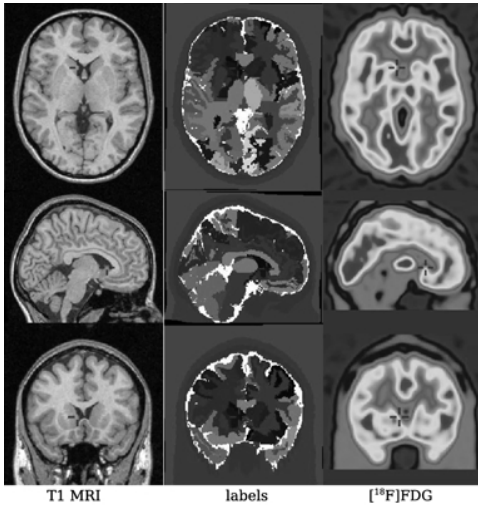
- Previous simulations used large, uniform regions



(Mazziotta, et al 1981)



(Castiglioni, et al 2005)



(Reilhac et al, 2005)

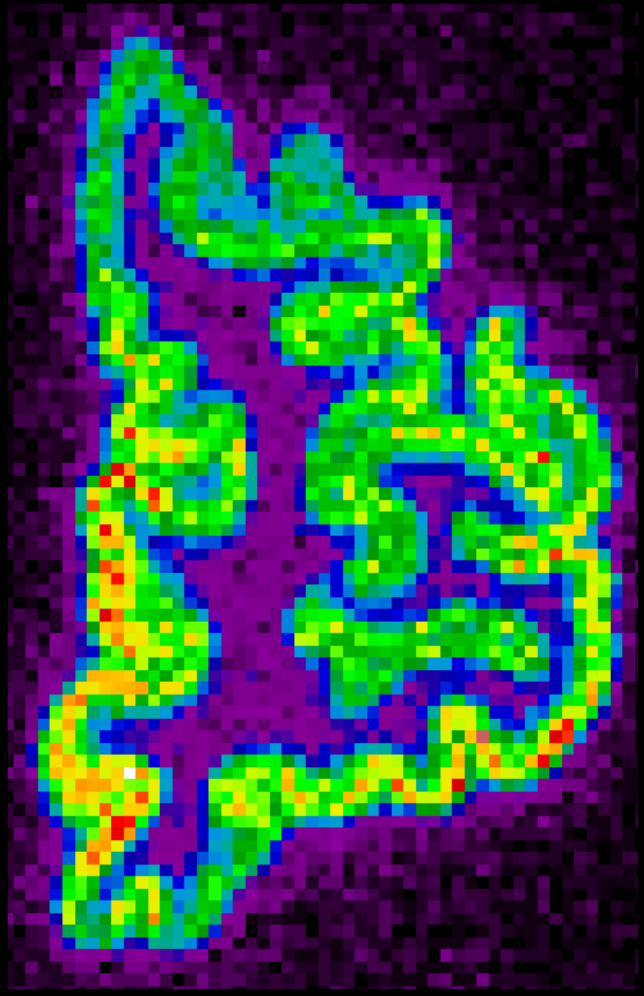
Receptor volumes for PET simulation

- Previous simulations used large, uniform regions
- 3D GABA-A_{Benz} atlas → Ground truth for PET simulation
- PET simulation performed with Gate
  - Digital PET scan simulates most of the physics of acquisition
  - Scanner : Siemens ECAT HRRT (Bataille, et al. 2004)

Example Application : PET Simulation

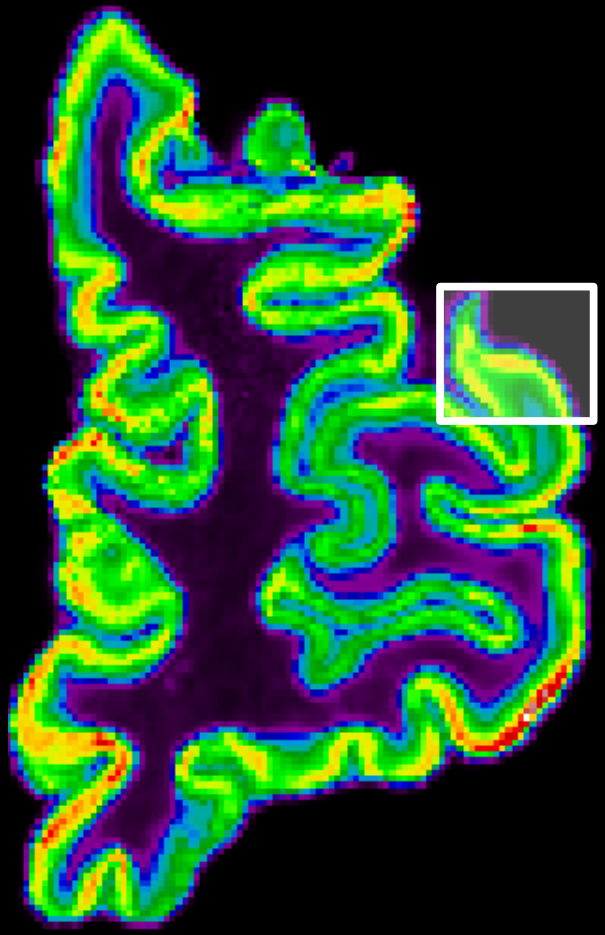
GABA-$A_{Benz.}$ receptor volume

Theoretical Maximum PET Resolution

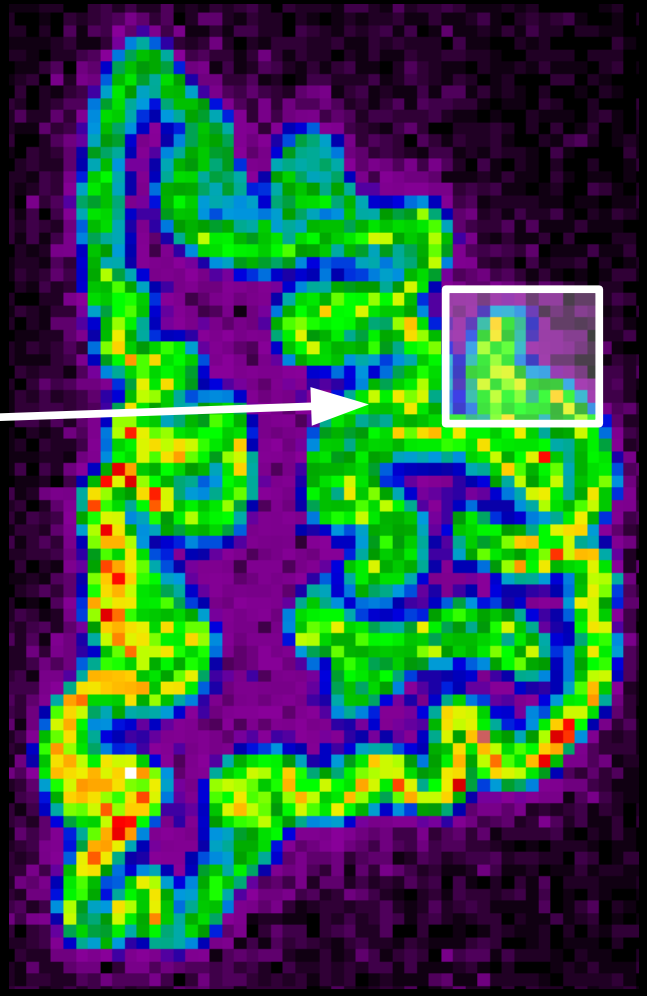


Evaluating PET Resolution

GABA-$A_{Benz.}$ receptor volume



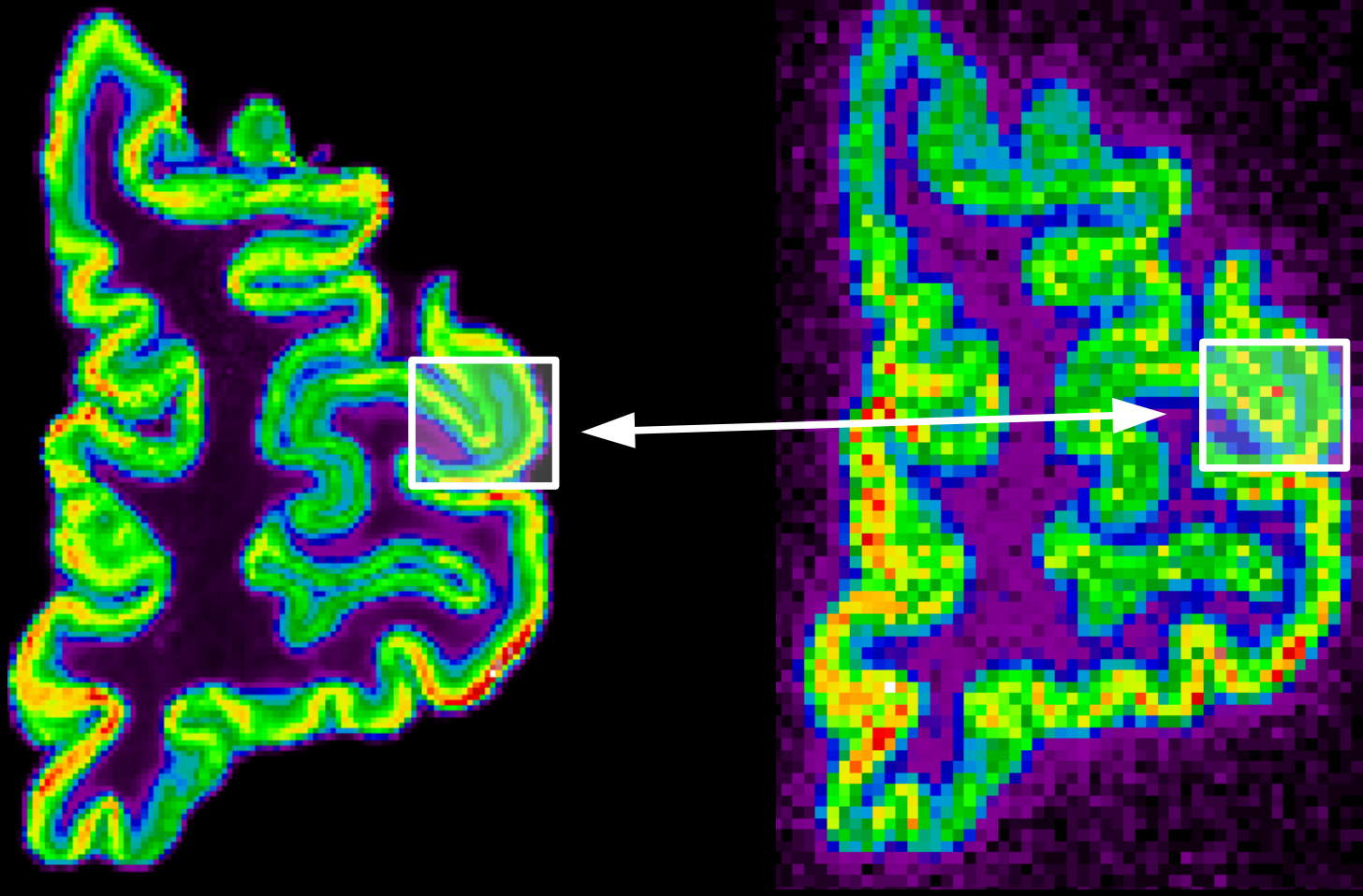
Theoretical Maximum PET Resolution



Evaluating PET Resolution

GABA-$A_{Benz.}$ receptor volume

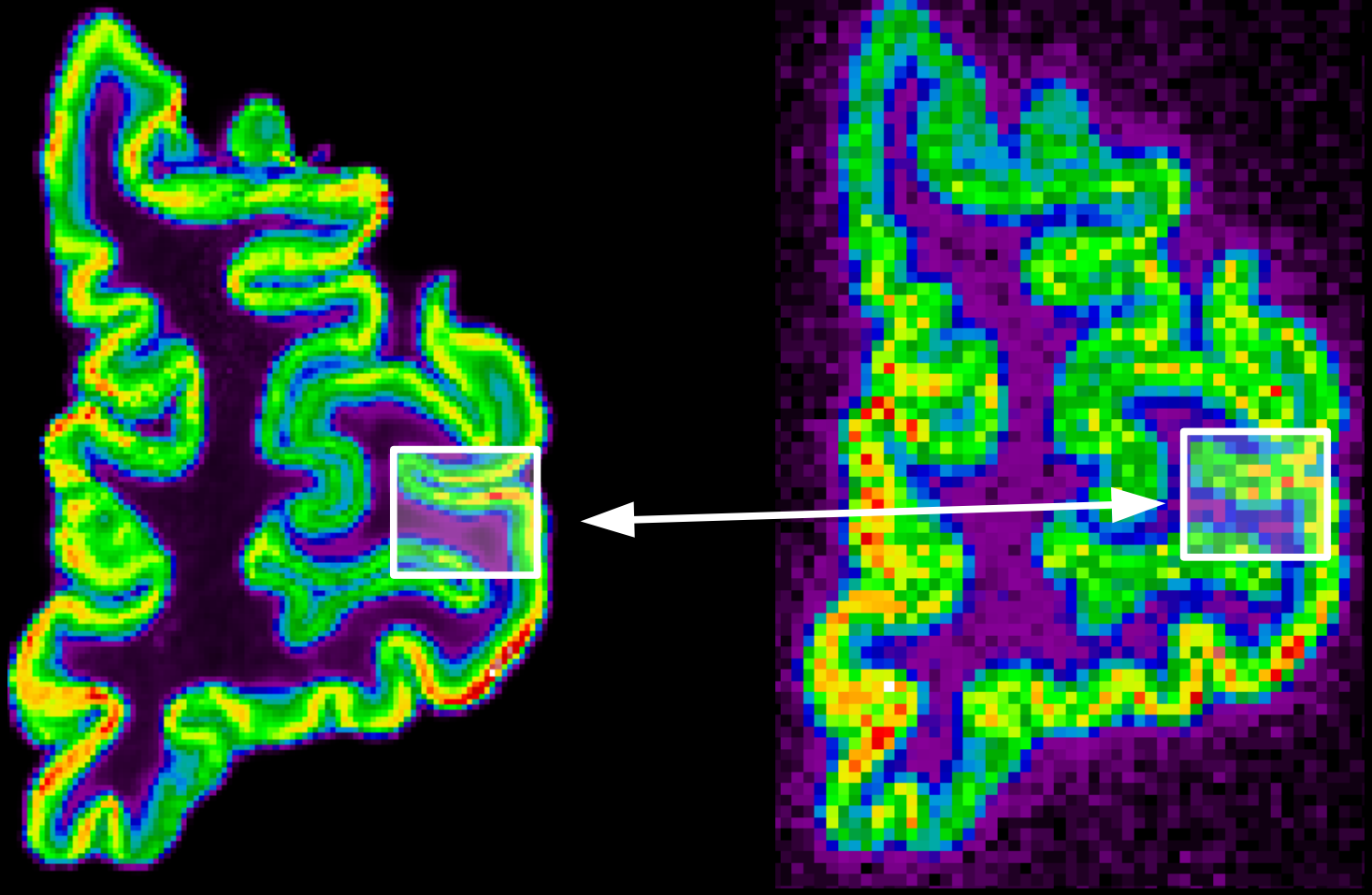
Theoretical Maximum PET Resolution



Evaluating PET Resolution

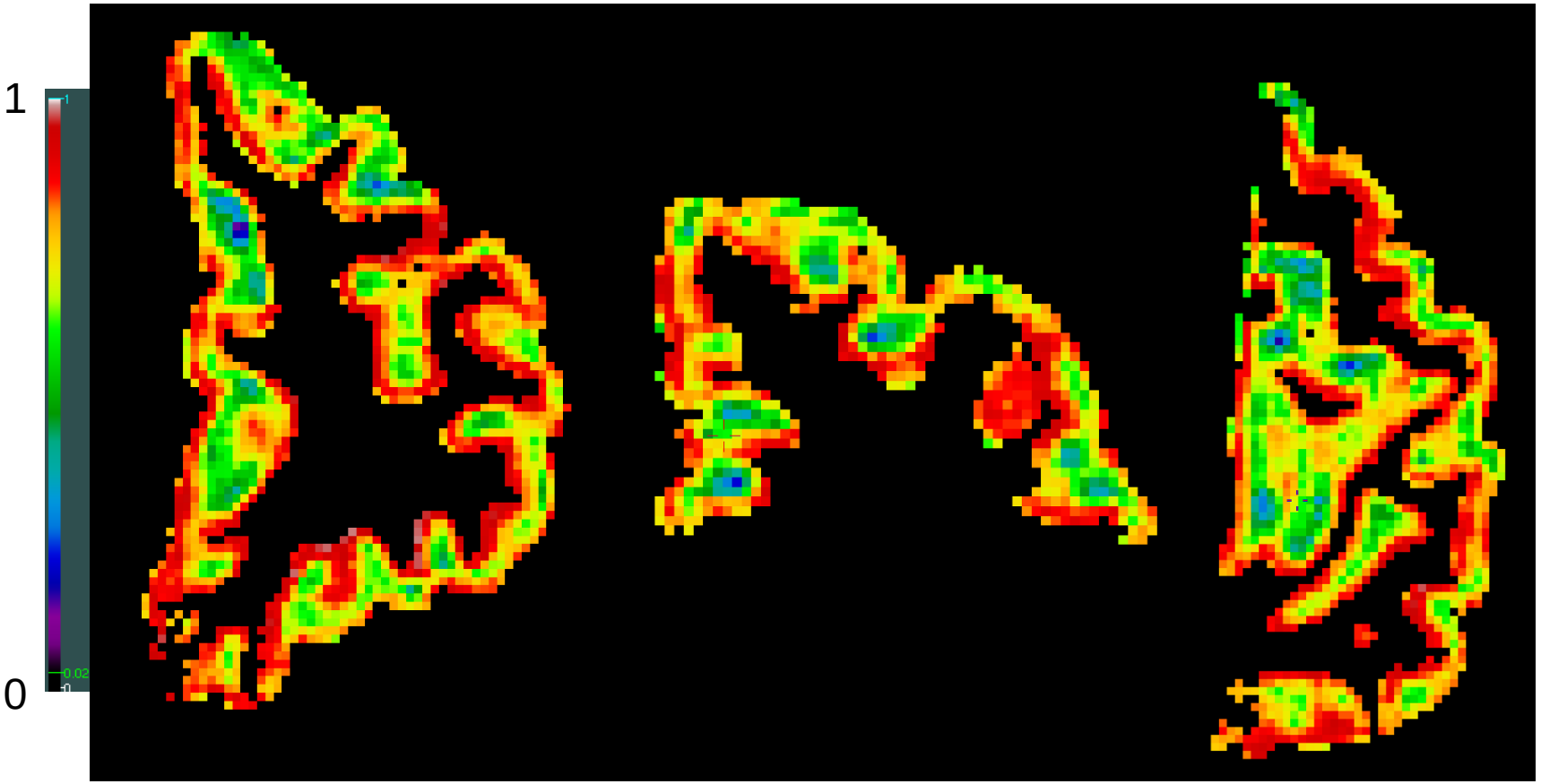
GABA-$A_{Benz.}$ receptor volume

Theoretical Maximum PET Resolution



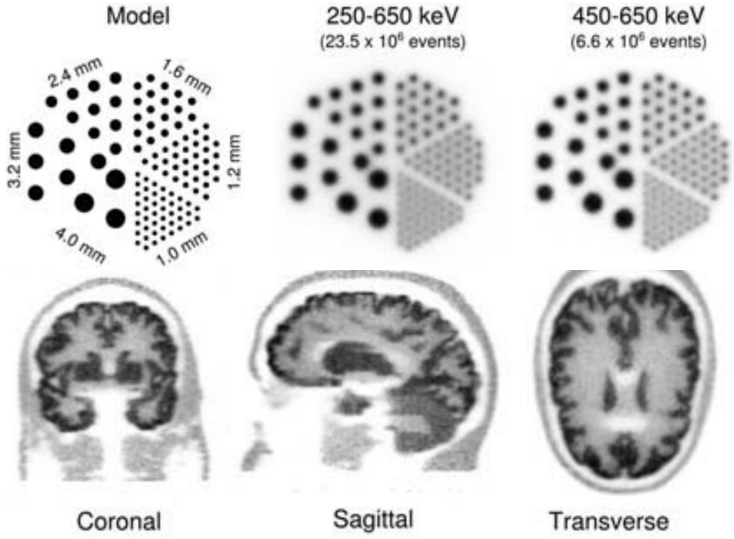
Evaluating PET Resolution

- Local correlation $5mm^3$: 0.71 +/- 0.09
  - Kendall's Tau

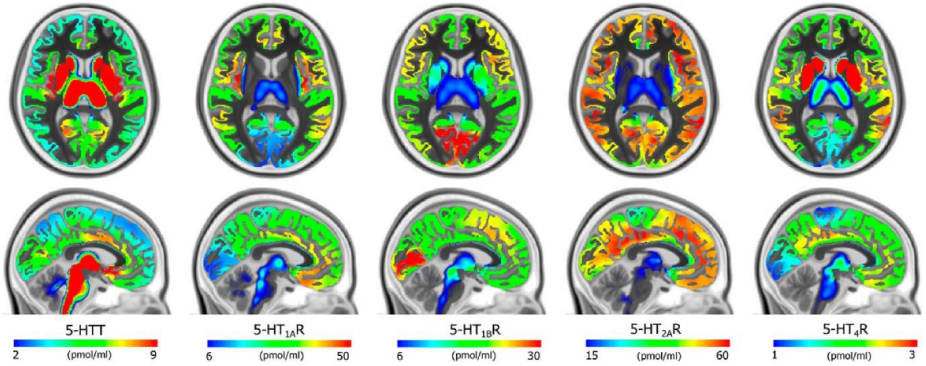


Future Perspectives

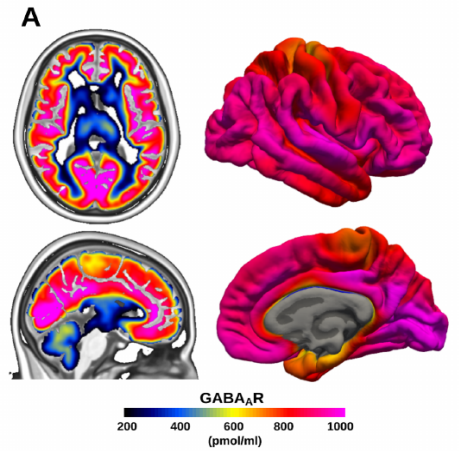
- Sub-millimeter PET Receptor Atlases
  - 1.2mm FWHM PET scanners + PVC (<1mm?) → Laminar PET?



Lecompte, et al. 2019



Beliveau, et al 2017



Norgaard, et al. 2020 (preprint)

Conclusions

- Reconstruction of 3D receptor atlases
  - Proof-of-principle for pipeline → up to 50um
  - 3 brains x 2 hemispheres x 20 receptors

- Realistic PET simulation
  - Simulated PET from gold-standard receptor distribution
  - Evaluate maximum effective PET spatial resolution
  - Validate resolution-enhancement & quantification algorithms

Questions, comments, suggestions : thomas.funck@mail.mcgill.ca

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Interslab Interpolation

- Volumetric interpolation
  1) Dilate mask of receptor slabs
  2) Find border voxels inside MRI GM mask
  3) For each voxel calculate average within 3x3x3 kernel
  4) Add interpolated voxels to receptor slab mask
  5) Step 1