

Towards an ultra-high resolution 3D neurotransmitter receptor atlas

BIG BRAIN WORKSHOP 2020 | THOMAS FUNCK, PHD



#### 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  $\rightarrow$  larger data sets
- Lower resolution  $\rightarrow$  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



Raw autoradiographs transformed to binding densities



# The data

- 3 post-mortem human brains
- 20 receptor binding sites
  - visualized with quantitative in vitro receptor autoradiography
  - $^{\circ}$  acquired sequentially  $\rightarrow ~400\mu$ m+ between particular receptor



# Autoradiographs

- 3 post-mortem human brains
- 20 receptor binding sites
  - visualized with quantitative in vitro receptor autoradiography
  - acquired sequentially  $\rightarrow ~400 \mu$ m+ between particular receptor



# Autoradiographs

	RAR	200 A 1902	A BRA	100000				
	code	Radiolabeled	receptor	Transmitter				
Sa		ligand						
	AMPA	AMPA	AMPA	Glutamate				
	KAIN	Kainate	Kainate	Glutamate				
	MK80	MK-801	NMDA	Glutamate				
	LY34	LY 341,495	mGluR2/3	Glutamate				
210	MUSC	muscimol	GABA <sub>A</sub> (agonist binding site)	GABA				
RR	SR95	SR95531	GABA <sub>A</sub> (antagonist binding site)	GABA				
	CGP5	CGP 54626	GABA <sub>B</sub>	GABA				
	FLUM	flumazenil	GABA <sub>A</sub> associated benzodiazepine binding sites	GABA				
	PIRE	Pirenzepine	muscarinic M1	Acetylcholine				
AC	OXOT	Oxotremorine-M	muscarinic M <sub>2</sub> (agonist binding site)	Acetylcholine				
en	AFDX	AF-DX384	muscarinic $M_2$ (antagonist binding site)	Acetylcholine				
	DAMP	4-DAMP	muscarinic M <sub>3</sub>	Acetylcholine				
-06	EPIB	epibatidine	Nicotinic $\alpha_4\beta_2$	Acetylcholine				
	PRAZ	prazosin	α1	Noradrenalin				
	UK14	UK-14,304	$\alpha_2$ (agonist binding site)	Noradrenalin				
73	RX82	RX 821002	$\alpha_2$ (antagonist binding site)	Noradrenalin				
Crr	DPAT	8-OH-DPAT	5-HT1A	Serotonin				
	KETA	ketanserin	5-HT <sub>2</sub>	Serotonin				
	SCH2	SCH 23390	D1	Dopamine				
	DPMG	DPCPX	Adenosine 1	Adenosine				
22		250						

#### 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



#### Target Tissue Mask Cropped Image



### Rigid 2D Autoradiograph Alignment



#### 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<sub>Benz</sub> volume
  - Ligand = Flumazenil
  - Green = acquired autoradiographs







#### GABAA.Benz.











GABAA.Ant.



#### Interslab Interpolation

#### • Volumetric interpolation





#### Inter/intra-slab Interpolation

#### • Surface-based interpolation







#### Inter/intra-slab Interpolation

• Surface-based interpolation



#### Preprocessing of all autoradiographs

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

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rx82#	#pire#	#cgp5#	#kain#	#sch2#	#sch2#	#cgp5#	#dpat#	#cgp5#	#damp	#kain#	#cgp5#	#uk14	#oxot#	#sr95#	#praz#	#ampa	#keta#	#ampa	#rx82#	#mk80	. #flum#
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mpa#	#afdx#	#kain#	#dpmg	#keta#	#cgp5#	#keta#	#dpat#	lum#60	#afdx#	#cgp5#	#mk80	#sr95#	#cgp5#	#sch2#	#epib#	#sch2#	#musc	#ly34#	#pire#	#afdx#	. #oxot#
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kain#	#pire#	#uk14	#keta#	#sch2#	#mk80	#rx82#	#dpmg	#musc	#flum#	#ly34#	#dpmg	#praz#	#cgp5#	#kain#	#keta#	#musc	#sr95#	#damp	#epib#	#flum#	. #dpat#
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R2s5#R	MR3s3#L	MR2s1#L	MR1s5#R	MR2s2#L	MR3S5#R	MR1s6#L	MR3s2#R	MR3s5#L	MR1s1#L	MR2s5#R	MR3S3#L	MR1s1#R	MR1s6#L	MR3s4#R	MR3s5#L	MR3s3#R	MR3s2#R	MR3s1#R	MR3s3#L	MR1s3#L	MR1s6#L
dpat#	#ardx#	#ampa	#oxot#	#ly34#	#dpmg	#keta#	#musc	#cgp5#	#sr95#	#ly34#	#praz#	#uk14	#musc	#mk80	#musc	#flum#	#dpat#	#epib#	#afdx#	#afdx#	. #oxot#
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R1s1#L	MR1s3#R	MR1s6#L	MR2S3#L	MR2s3#R	MR1s1#R	MR3s4#R	MR2s1#L	R1s5#L#	MR3s2#R	MR2S4#R	MR3S4#L	MR1s2#R	MR3S1#R	MR1s2#L	MR3s5#R	MR1s1#R	MR3S1#R	MR3s5#L	MR2s3#R	MR2s4#L	MR153#L
praz#	#mk80	#SF95#	#opac#	#ГХ82#	#rx82#	#mk80	#\$195#	ampa#	#0X0C#	#scn2#	#kain#	#rx82#	#pire#	#UK14	#keta#	#Iy34#	#ampa	#keta#	#opat#	#arox#	. #0X0C#
V#HG#	OK#ha#	RF#ha#	OH#ha#	RE#ha#	OL#ha#	PD#ha#	RU#ha#	Ro#HG#	RV#HG#	OW#HG#	RU#ha#	RS#HG#	OO#ha#	OJ#HG#	RO#ha#	OW#HG#	OL#ha#	OF#HG#	OF#HG#	RO#HG#	RR#HG#
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R1s4#L	MR1s1#R #epib#	MR2s4#L #cap5#	MR2S2#L	MR2s5#R #keta#	MR1s3#L #damp	MR2s1#R #flum#	MR2s1#R #dpat#	MR2s4#L	MR3S4#L #ampa	MR2s5#R #musc	MR2S5#R #cap5#	MR2s5#L	MR3s5#R #afdx#	MR3s3#L #cap5#	MR1S3#L #praz#	MR3s4#R #ampa	MR2s5#L #lv34#	MR3S4#L #mk80	MR2s1#L #dpat#	MR2s1#L #cap5#	MR151#R
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### **GM** Segmentation

- Segmentation with deep neural nets
  - Network learns intensity thresholds instead of shapes
- Solution: make learning task harder
  - $\rightarrow$  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  $\rightarrow$  novel atlases



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



#### Application: PET simulation and resolution

### PET resolution





### **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<sub>Benz</sub> atlas  $\rightarrow$  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<sub>Benz.</sub> receptor volume



#### **Theoretical Maximum PET Resolution**







![](_page_32_Figure_1.jpeg)

- Local correlation 5mm<sup>3</sup>: 0.71 +/- 0.09
  - Kendall's Tau

![](_page_33_Figure_3.jpeg)

**Future Perspectives** 

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

![](_page_34_Figure_3.jpeg)

#### Conclusions

- Reconstruction of 3D receptor atlases
  - Proof-of-principle for pipeline  $\rightarrow$  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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![](_page_36_Picture_6.jpeg)

Jewish General Hospital Lady Davis Institute for Medical Research

![](_page_36_Picture_8.jpeg)

![](_page_36_Picture_9.jpeg)

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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

![](_page_37_Picture_7.jpeg)