NeUrons ReUnited

Second Periodic Report
22.03.2022

FLAG-ERA

AGENCIA ESTATAL DE INVESTIGACIÓN

NWO
Netherlands Organisation for Scientific Research

HBP
Human Brain Project

Consortium NeuronsReunited

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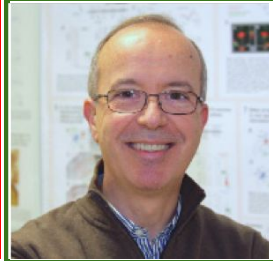

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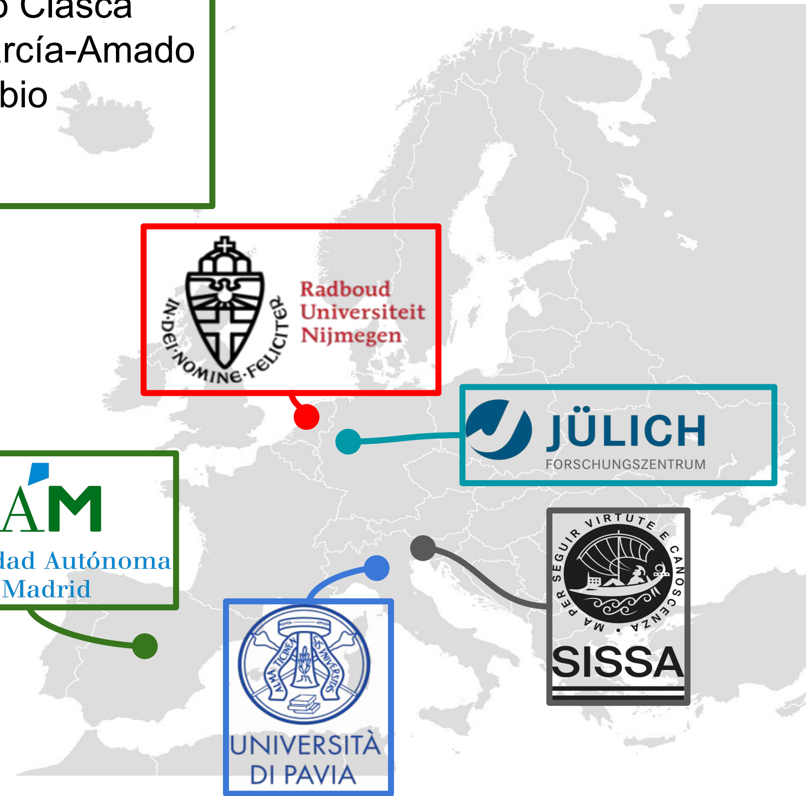

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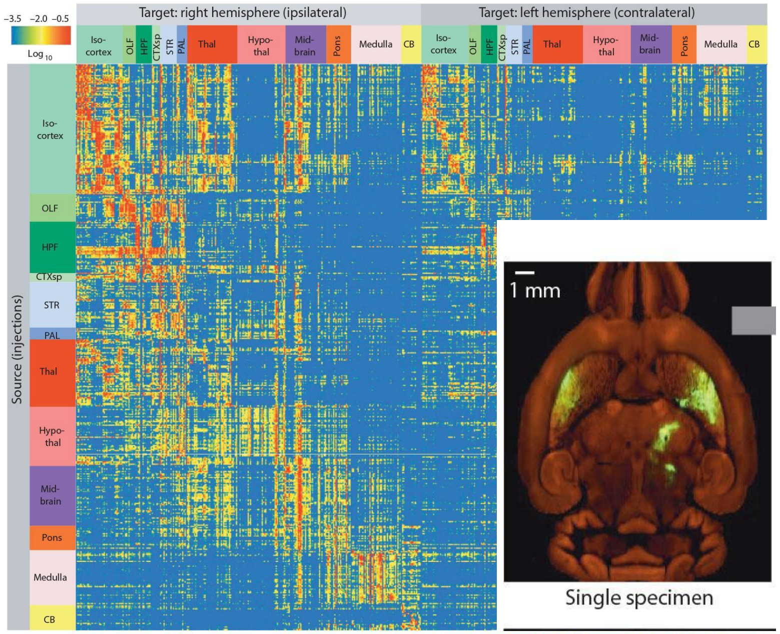
PER SEGUIR VIRTUTE E CANOSCENZA
SISSA

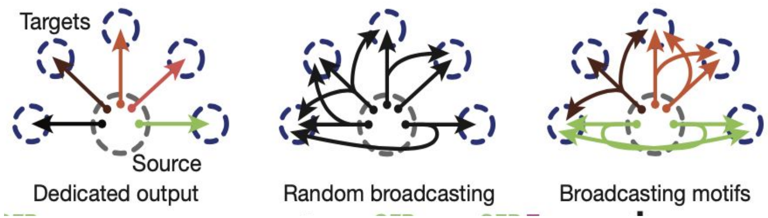
Recently published mesoconnectome is of tremendous importance for experimental and computational neuroscientists alike, but it needs augmentation

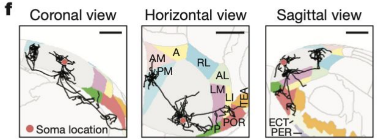
A mesoscale connectome of the mouse brain

Seung Wook Oh[1]*, Julie A. Harris[1]*, Lydia Ng[1]*, Brent Winslow[1], Nicholas Cain[1], Stefan Mihalas[1], Quanxin Wang[1], Chris Lau[1], Leonard Kuan[1], Alex M. Henry[1], Marty T. Mortrud[1], Benjamin Ouellette[1], Thuc Nghi Nguyen[1], Staci A. Sorensen[1], Clifford R. Slaughterbeck[1], Wayne Wakeman[1], Yang Li[1], David Feng[1], Anh Ho[1], Eric Nicholas[1], Karla E. Hirokawa[1], Phillip Bohn[1], Kevin M. Joines[1], Hanchuan Peng[1], Michael J. Hawrylycz[1], John W. Phillips[1], John G. Hohmann[1], Paul Wohnoutka[1], Charles R. Gerfen[2], Christof Koch[1], Amy Bernard[1], Chinh Dang[1], Allan R. Jones[1] & Hongkui Zeng[1]



The logic of single-cell projections from visual cortex



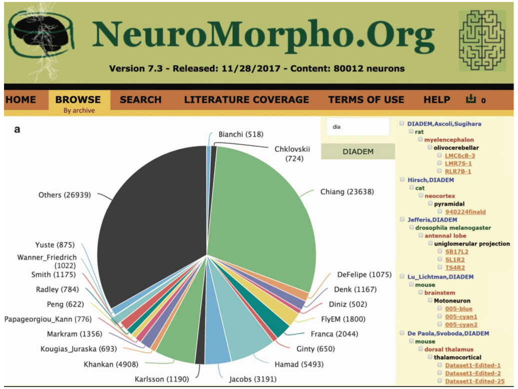


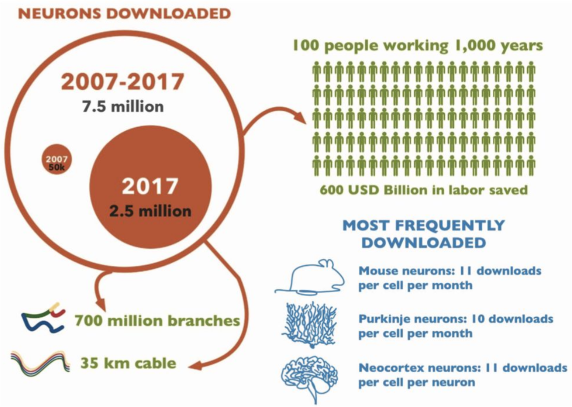
Oh et al 2014; Han et al 2018; Tiesinga & Timonidis 2021

Orphans: Neurons that need a home

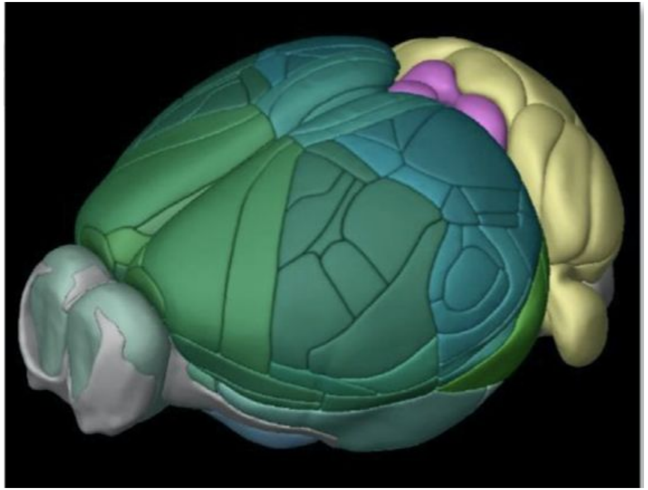
Generate gold standard reconstruction, properly register them, to facilitate "crowd sourcing" neurons and computational studies

An open repository for single-cell reconstructions of the brain forest





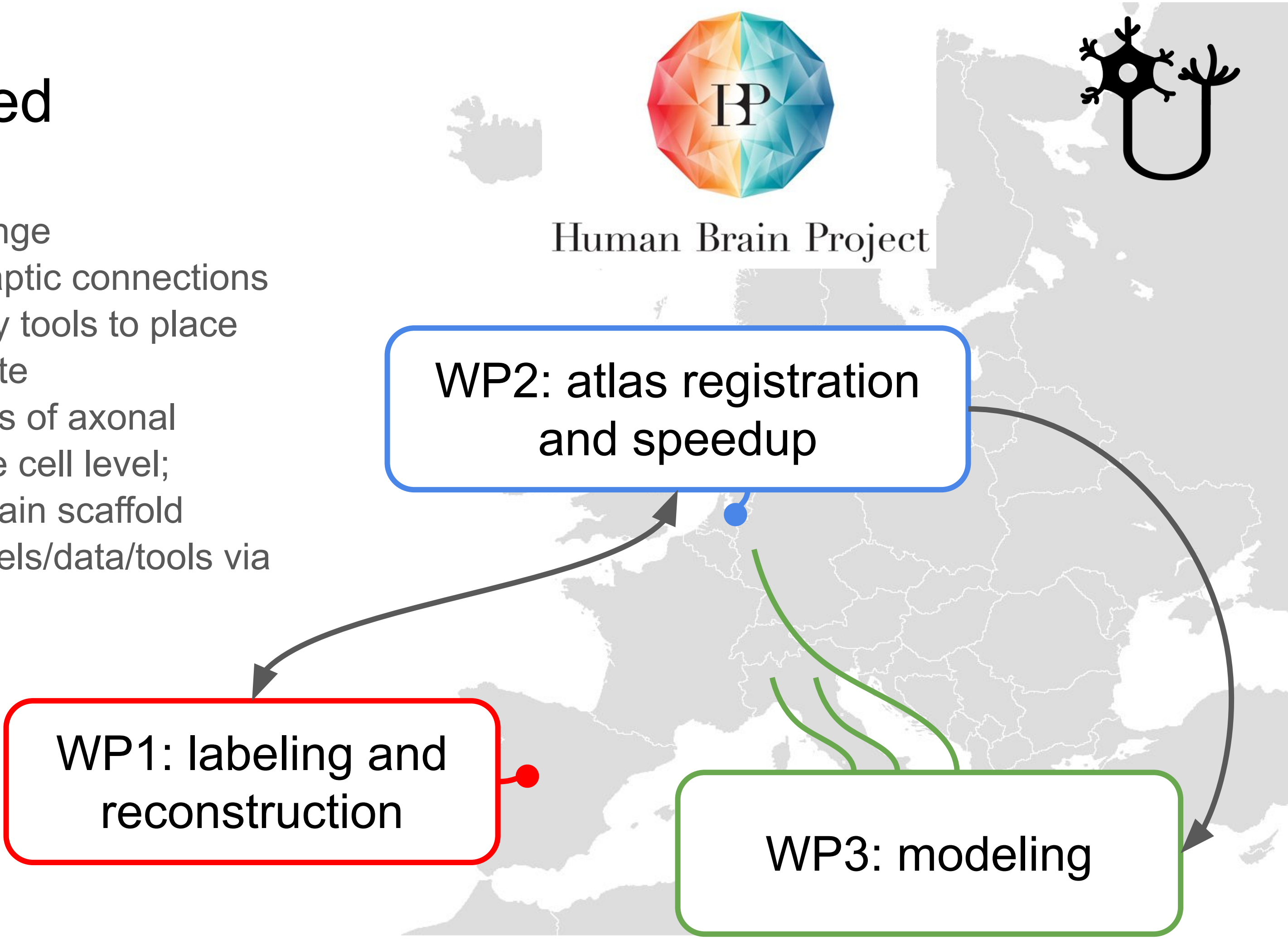
The Allen Mouse Brain Common Coordinate Framework: A 3D Reference Atlas



Wang et al 2020; Akram et al 2018

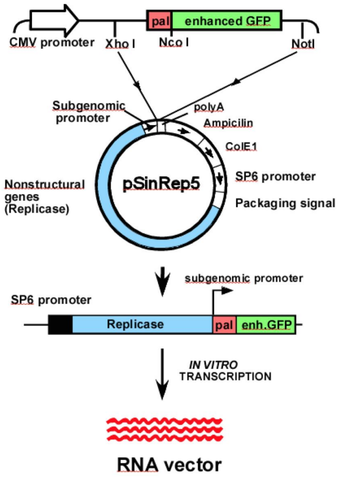
NeuronsReunited

- Reconstruct long-range thalamocortical synaptic connections
- Implement and apply tools to place them in atlas template
- Model consequences of axonal morphology at single cell level; network level and brain scaffold
- Make available models/data/tools via EBRAINS

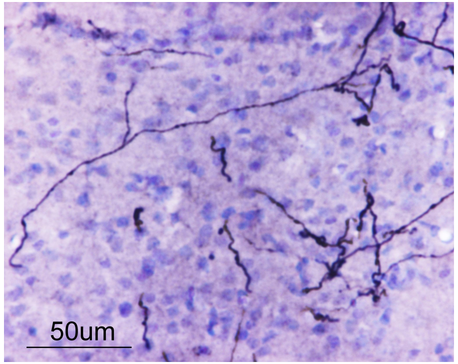


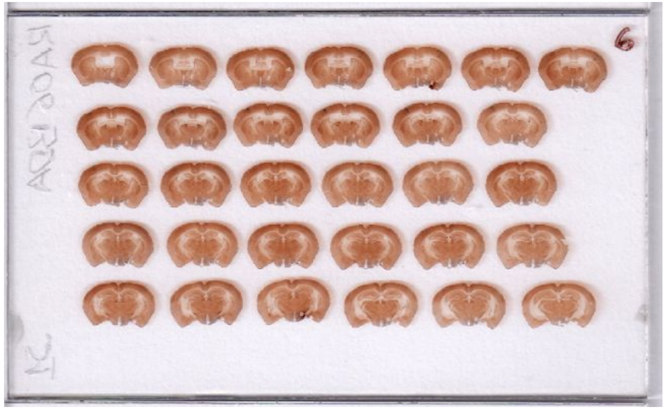
WP1: Single-cell labeling in adult brains

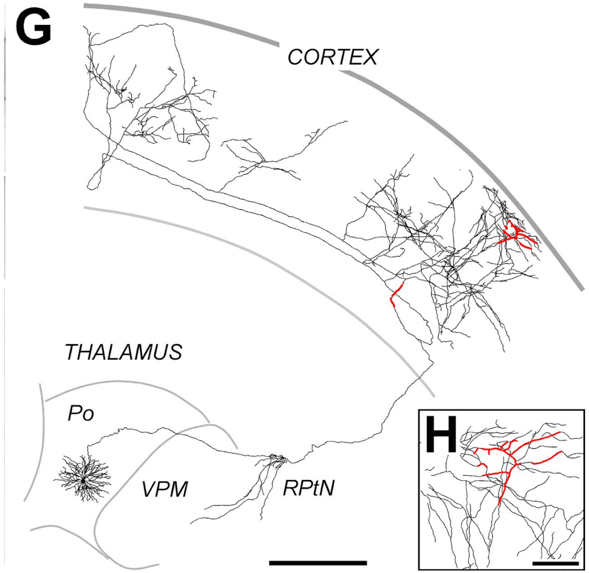
Sindbis Pal-eGFP & RNA electroporation



Furuta et al. *Neuroscience* (2001)

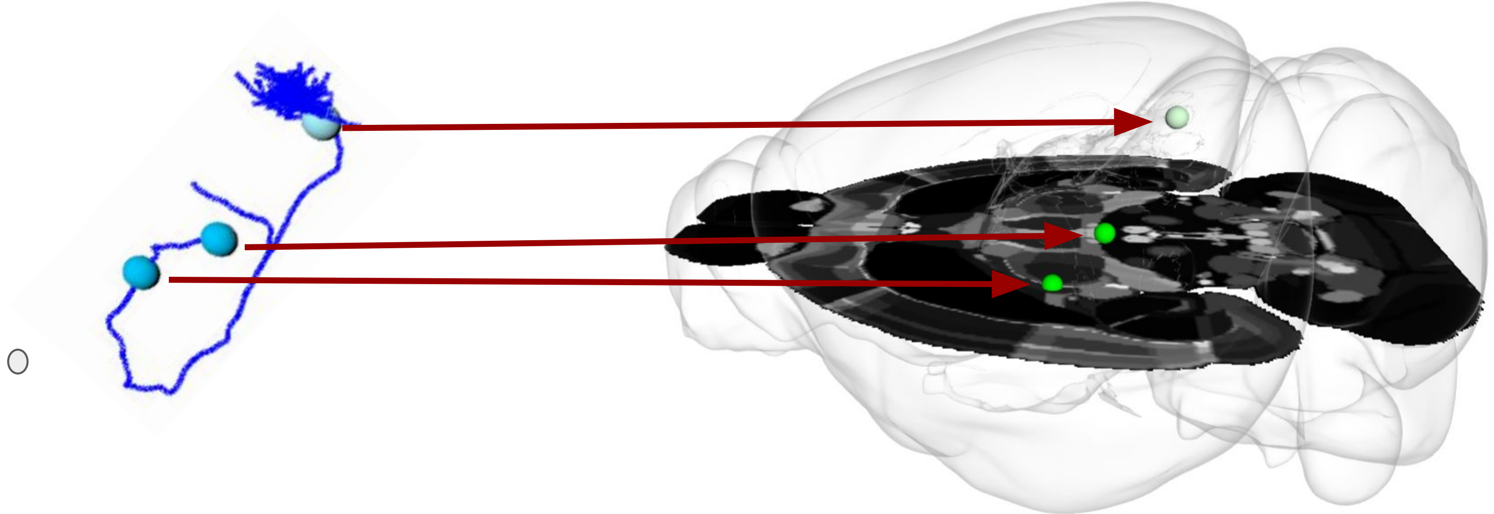






Porrrero et al. *Front. Neurosci.* (2016)

WP2: Neuron alignment based on corresponding points

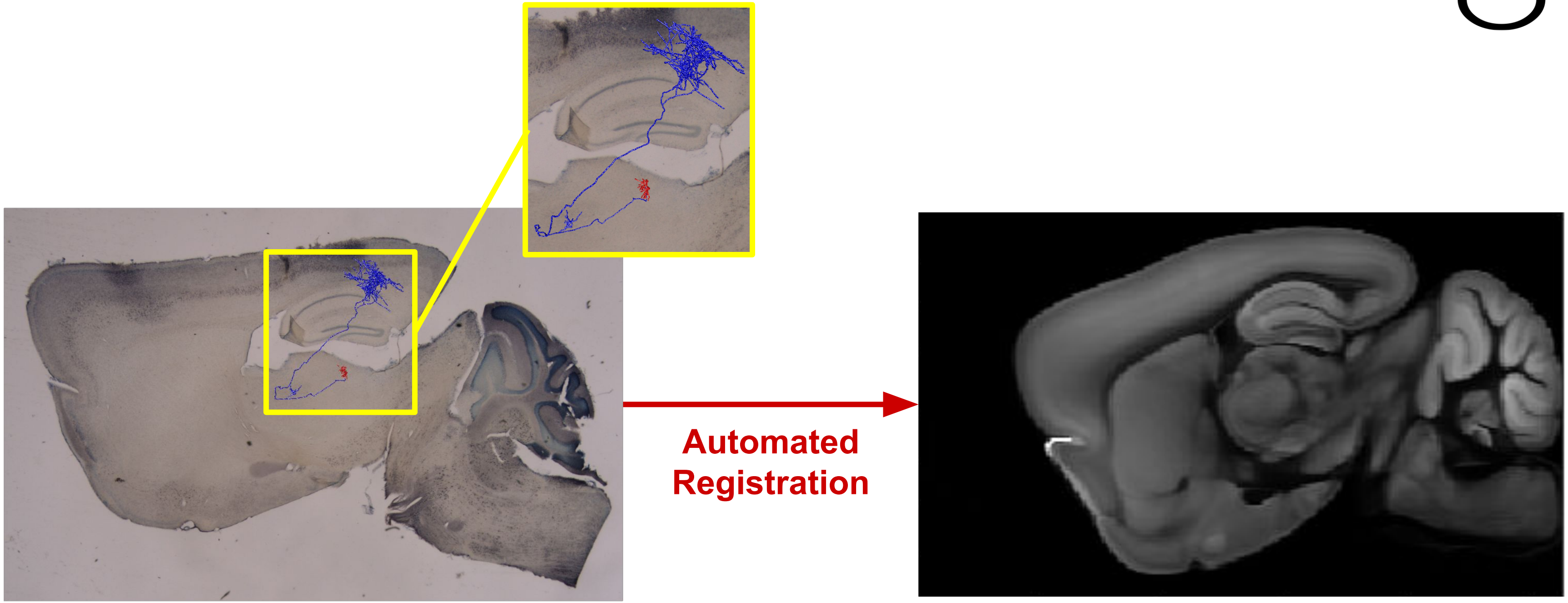


Basic corresponding points registration implemented as **online workflow***.
Placing the points requires expert anatomical knowledge.
Next step:

- Add digital tissue images to the neuron and develop semi-automatic registration pipeline.

*https://neuroinformatics.nl/HBP/morphology-viewer and https://sba-dev.incf.org/composer

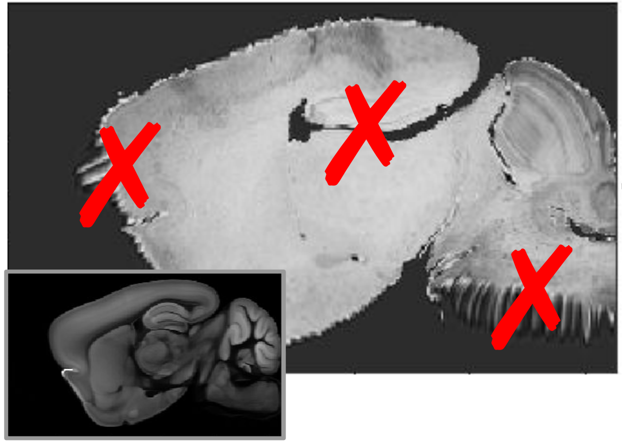
WP2: Improved alignment with tissue images



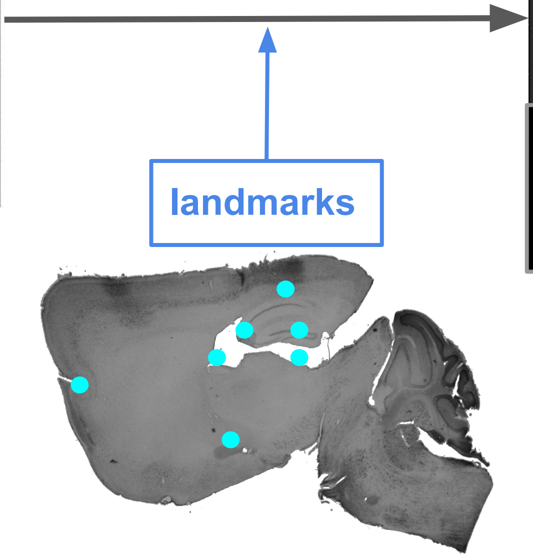
experimental slice

atlas slice

Challenge: dealing with large deformations

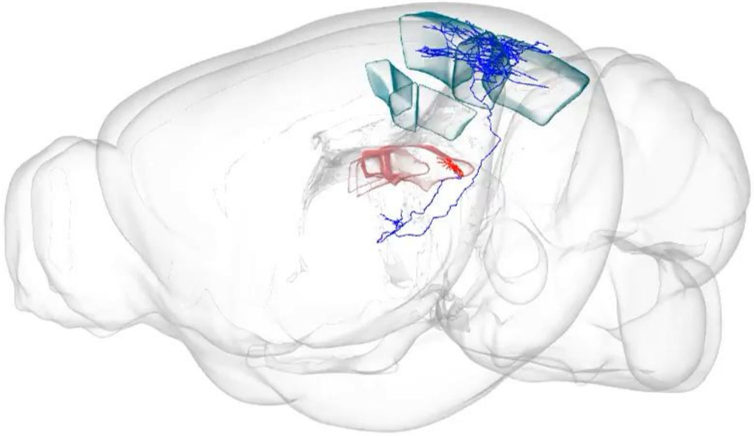


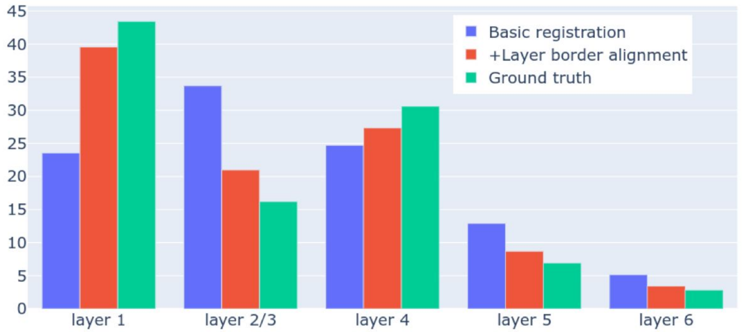
Test 1: Deformable registration, comes with huge artifacts.



Test 2: Deformable registration, including a set of manually inserted landmarks.

End result of the procedure:

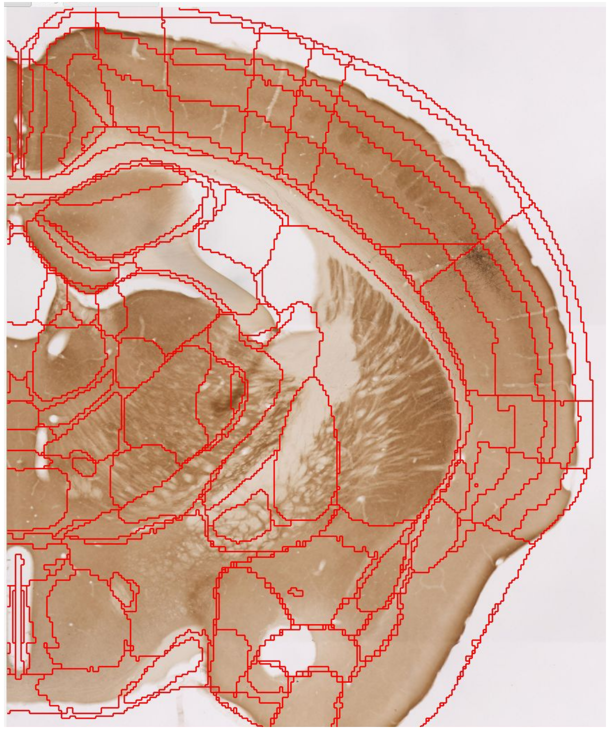




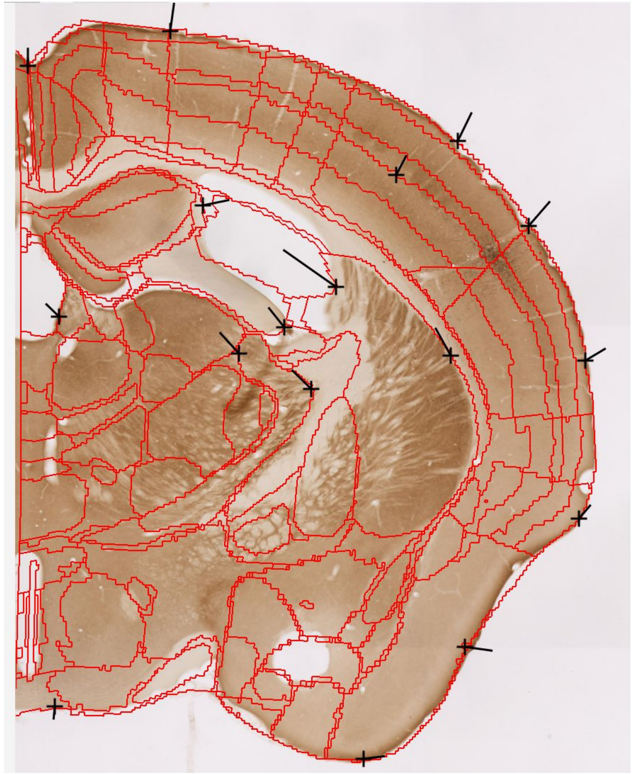
Piastra et al 2022, In preparation

VisuAlign (HBP) presents a user friendly alternative

(after we managed to invert the transformations)



Before

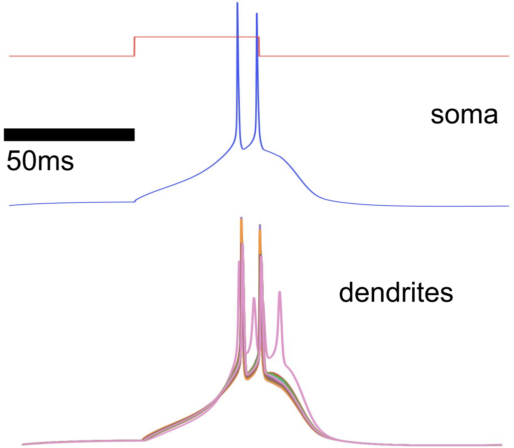


After multiple manual, local deformations *of the atlas*

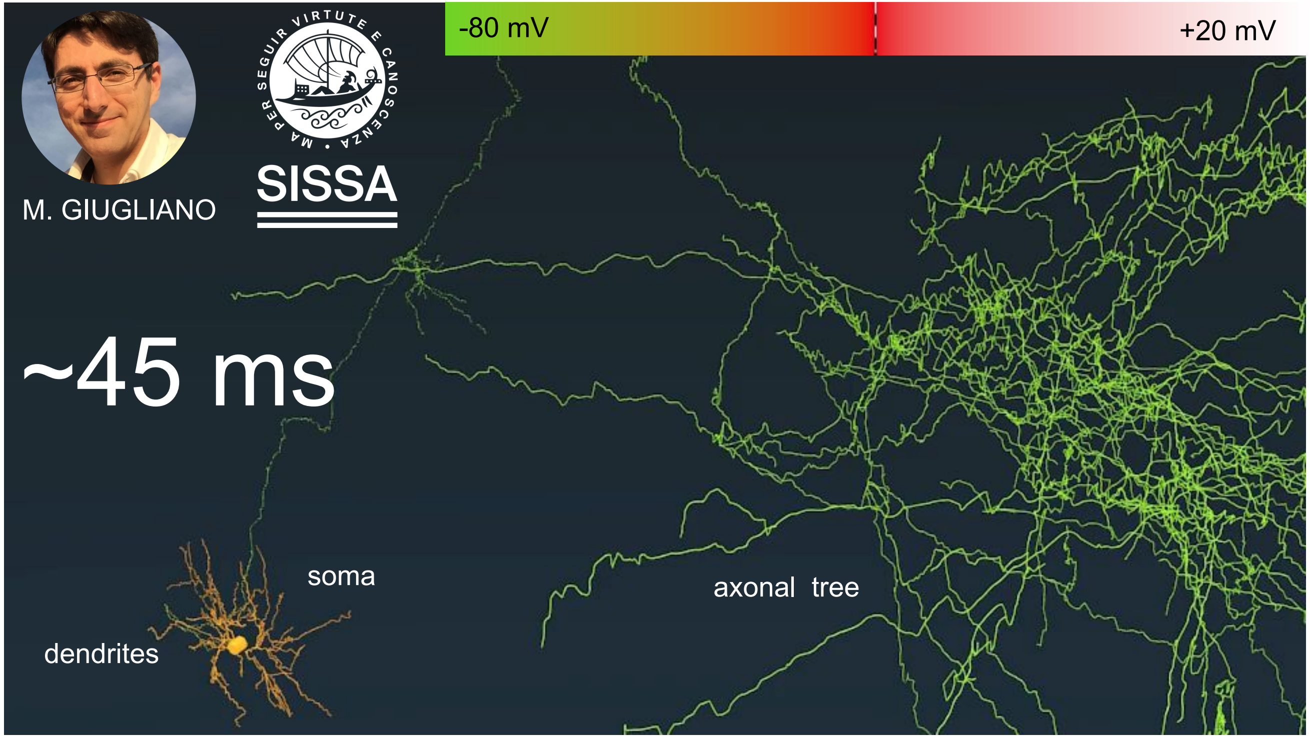
Puchades et al 2019

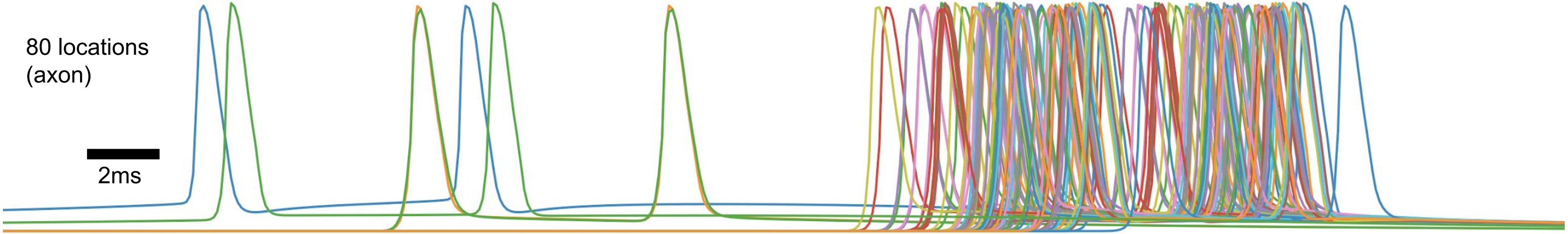
WP3: Modeling

- Part 1: Consequences of realistic axons in multicompartmental models (SISSA)
- Part 2: Adding proper thalamocortical projections to cortex model (Juelich) extract necessary statistics from databases



- SK-type Ca-activated K+ current
- Fast Na+ and K+ currents
- Fast Transient K+ Current IA
- L-current, (high-thr.) Ca++ current
- Ih current





BlenderNEURON by J. Birgiolas, PhD

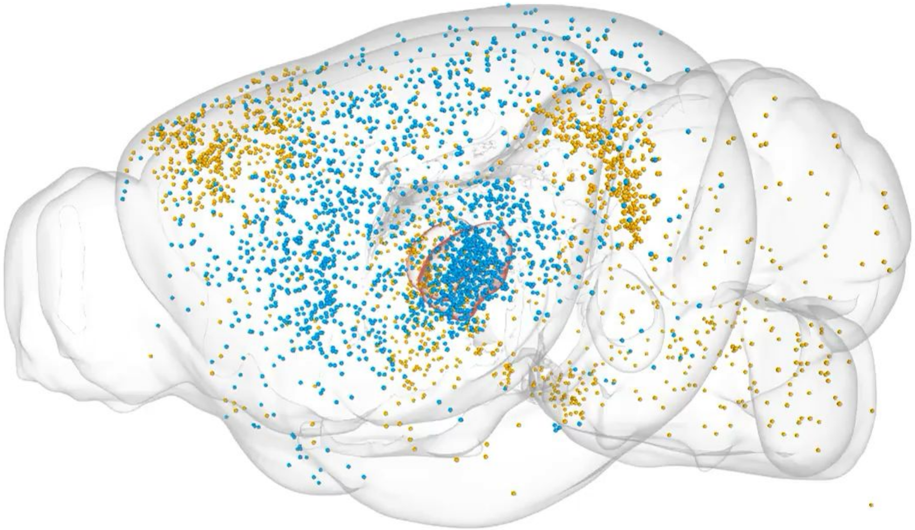
Iavarone *et al.*, 2019, PLoS Comput Biol 15(5): e1006753

Assessing the registration accuracy of neurons from two large repositories-1

1) Mouselight (Janelia Farms) contains 1544 neurons (yellow)

2) Braintell (Southeast Univ. / Allen Inst.) contains 1741 neurons (blue)

3) The most densely sampled area is the VPM thalamic nucleus. It projects primarily to layer IV of somatosensory cortex



Reconstruction of 1,000 Projection Neurons Reveals New Cell Types and Organization of Long-Range Connectivity in the Mouse Brain

Johan Winnubst,[1] Erhan Bas,[1,5] Tiago A. Ferreira,[1] Zhuhao Wu,[2] Michael N. Economo,[1] Patrick Edson,[3] Ben J. Arthur,[1] Christopher Bruns,[1,6] Konrad Rokicki,[1] David Schauder,[1] Donald J. Olbris,[1] Sean D. Murphy,[1] David G. Ackerman,[1] Cameron Arshadi,[1] Perry Baldwin,[1] Regina Blake,[1] Ahmad Elsayed,[1] Mashtura Hasan,[1] Daniel Ramirez,[1] Bruno Dos Santos,[1] Monet Weldon,[1] Amina Zafar,[1] Joshua T. Dudman,[1] Charles R. Gerfen,[4] Adam W. Hantman,[1] Wyatt Korff,[1] Scott M. Sternson,[1] Nelson Spruston,[1] Karel Svoboda,[1] and Jayaram Chandrashekar[1,7,*]

Morphological diversity of single neurons in molecularly defined cell types

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Hanchuan Peng[1,2,15], Peng Xie[2,15], Lijuan Liu[2,3,15], Xiuli Kuang[4], Yimin Wang[2,5], Lei Qu[2,6], Hui Gong[7,8], Shengdian Jiang[2], Anan Li[7,8], Zongcai Ruan[2], Liya Ding[2], Zizhen Yao[1], Chao Chen[4], Mengya Chen[5], Tanya L. Daigle[1], Rachel Dalley[1], Zhangcan Ding[2], Yanjun Duan[2], Aaron Feiner[1], Ping He[5], Chris Hill[1], Karla E. Hirokawa[1,14], Guodong Hong[2,3], Lei Huang[2], Sara Kebede[1], Hsien-Chi Kuo[1], Rachael Larsen[1], Phil Lesnar[1], Longfei Li[6], Qi Li[5], Xiangning Li[7,8], Yaoyao Li[4], Yuanyuan Li[6], An Liu[2,3], Donghuan Lu[9], Stephanie Mok[1], Lydia Ng[1], Thuc Nghi Nguyen[1,14], Qiang Ouyang[2], Jintao Pan[2], Elise Shen[1], Yuanyuan Song[2], Susan M. Sunkin[1], Bosiljka Tasic[1], Matthew B. Veldman[10], Wayne Wakeman[1], Wan Wan[6], Peng Wang[5], Quanxin Wang[1], Tao Wang[6], Yaping Wang[2], Feng Xiong[2], Wei Xiong[4], Wenjie Xu[1], Min Ye[4], Lulu Yin[2], Yang Yu[1], Jia Yuan[2,3], Jing Yuan[7,8], Zhixi Yun[2], Shaoqun Zeng[7], Shichen Zhang[2], Sujun Zhao[2], Zijun Zhao[2], Zhi Zhou[1], Z. Josh Huang[11,12], Luke Esposito[1], Michael J. Hawrylycz[1], Staci A. Sorensen[1], X. William Yang[10], Yefeng Zheng[9], Zhongze Gu[2], Wei Xie[2,3], Christof Koch[1], Qingming Luo[7,13], Julie A. Harris[1,14], Yun Wang[1] & Hongkui Zeng[1]

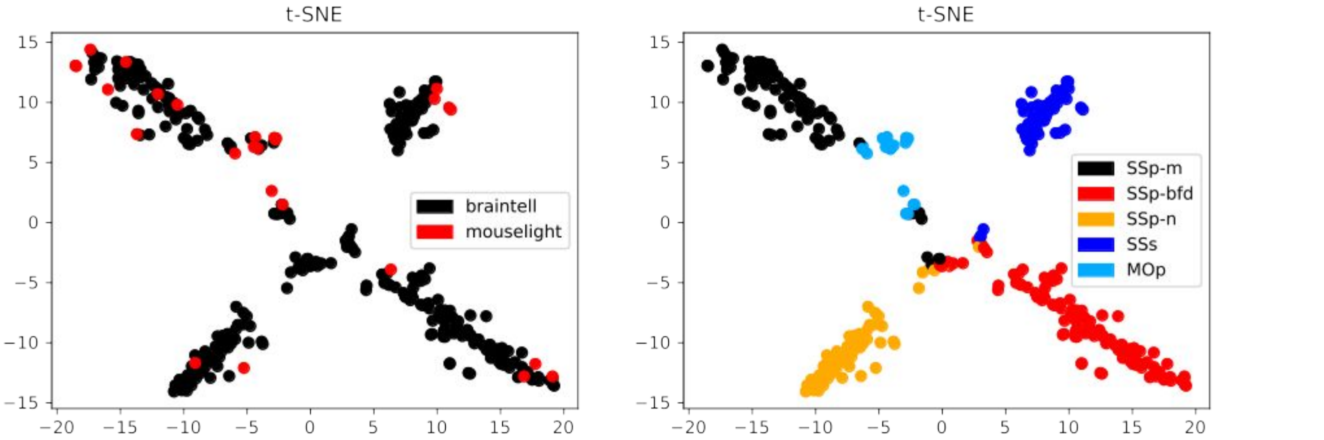
https://neuroinformatics.nl/HBP/neuronsreunited-viewer/

Assessing the registration accuracy of neurons from two large repositories-2

1) For each neuron, the axonal length in 8 pre-defined cortical areas is calculated

2) The 8x300 'feature matrix' is compressed to two dimensions with t-SNE.

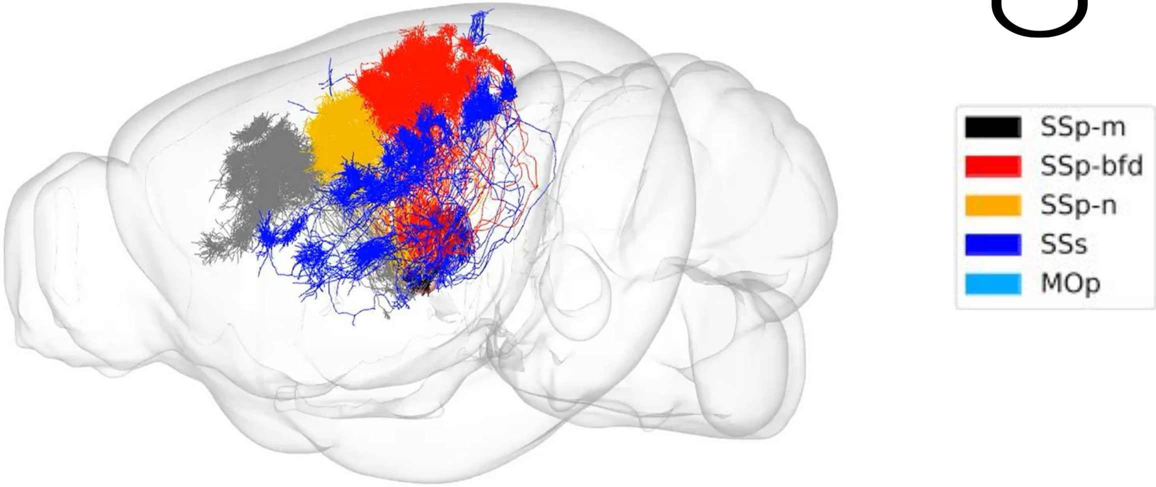
3) There are 5 clusters based on the **dominant projection target**.

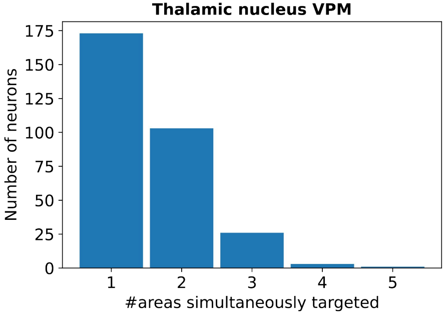


Van der Maten & Hinton (2008)

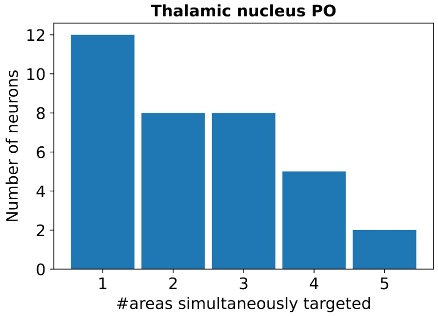
Visualizing the neurons that target a single cortical region

The various somatosensory targets (barrel field, mouth, nose) can be seen to originate in
spatially distinct subareas of VPM.



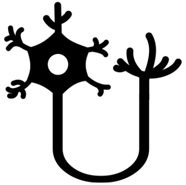


Most VPM neurons have 90% of axonal length in a single cortical region (primary projection neurons that target layer 4).

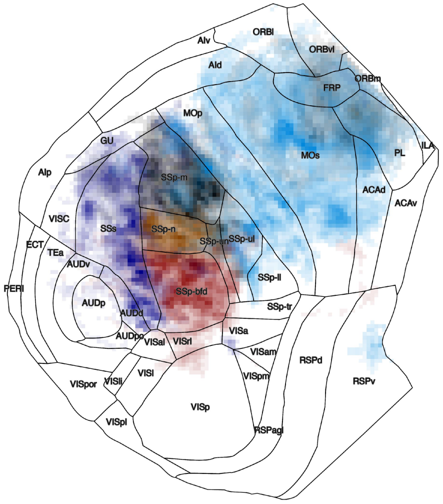


Adjacent nucleus PO typically targets multiple cortical areas.

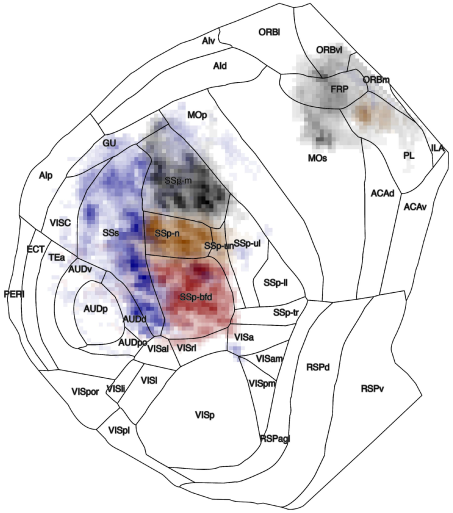
Some ‘VPM neurons’ that target multiple areas might belong to adjacent nuclei: imprecise registration



All neurons



Targeting a single cortical area

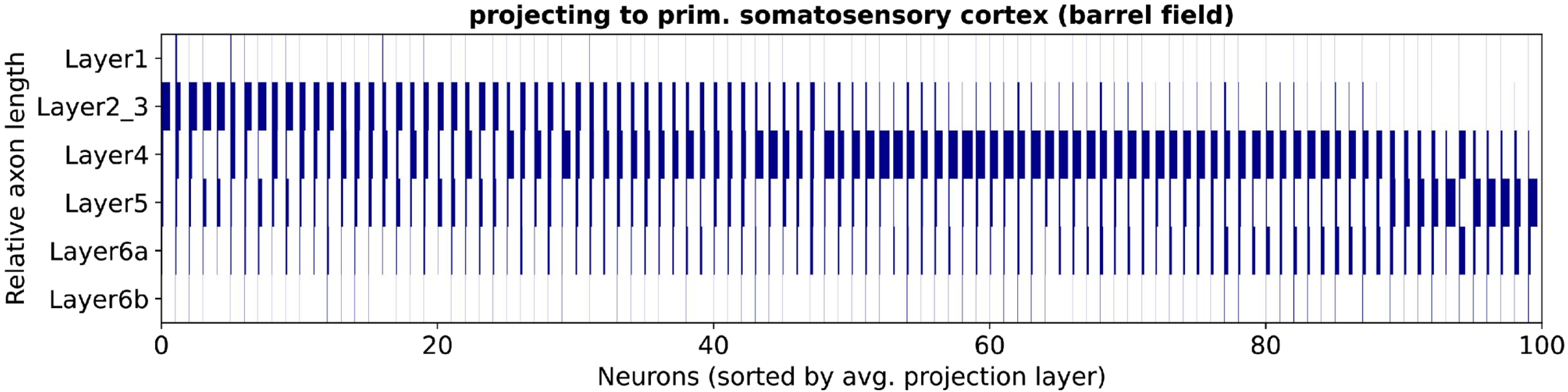


Neurons colored according to dominant target (see legend).

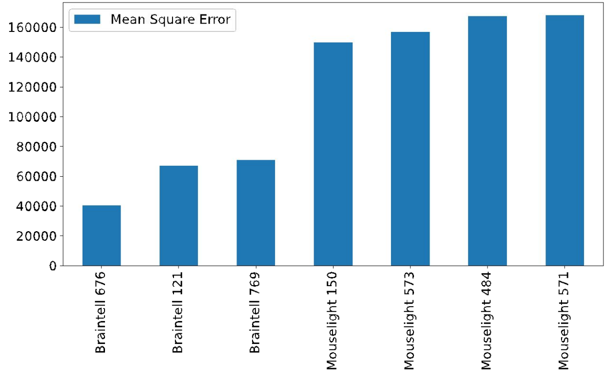
Made with the NeuronsReunited online flatmap service, https://neuroinformatics.nl/HBP/allen-flatmap/.

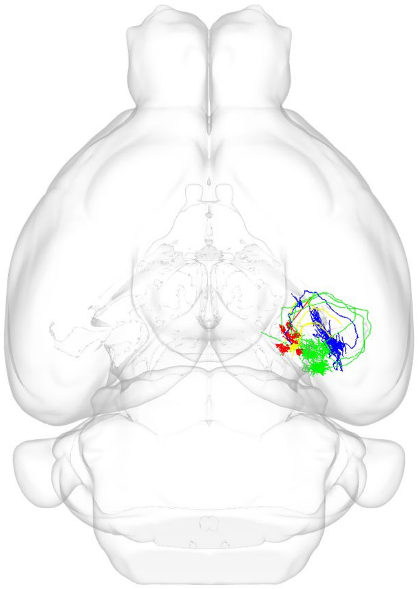
Layer distribution of VPM neurons targeting barrel cortex

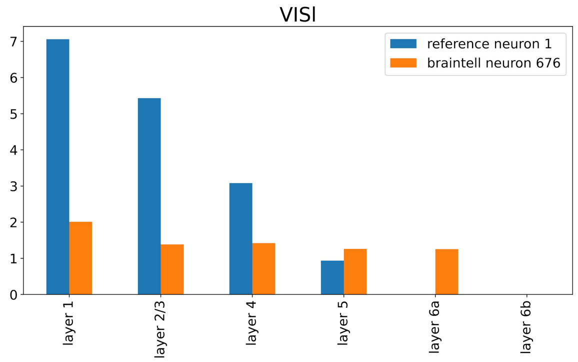
- A clear majority of neurons targets layers 2/3 and 4.

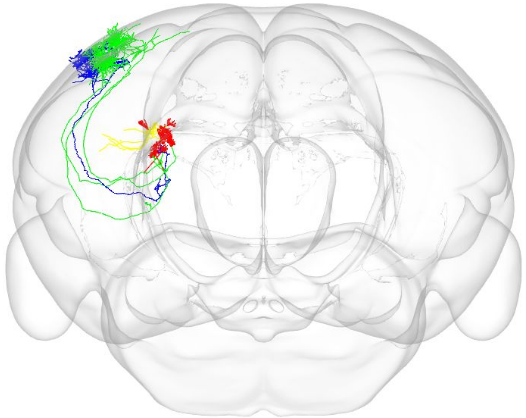


Finding friends with Coherent Point Drift (CPD) and comparing statistics









CPD from Myronenko & Song 2010

Future steps

- Automatic registration pipeline for high quality/undamaged slices based on volume reconstruction
- Thalamocortical model of integration/gain modulation
- Impact of timing variation due axonal branching (oscillations)

Responsible Research and Innovation

- Make available gold-standard, properly registered reconstruction
- Make available tools for other neuroscientists to do the same
- Contribute standards (Brain Addressing System, BIDS)
- Exemplify how to use new data in models

All data, tools & models will be available via EBRAINS as well as other public repositories (Scalable Brain Atlas, GitHub, Donders).