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Jumping dimensions: Integration of multimodal imaging into a unified brain atlas space

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Background & Aim

Understanding the complex structure and function of the mammalian brain requires advanced methodologies capable of integrating diverse imaging modalities into a unified reference space. Recent advancements in 3D imaging, particularly light-sheet fluorescence microscopy (LSFM), have revolutionized the examination of intact biological specimens. However, integrating LSFM data with other modalities like MRI, histology, and spatial transcriptomics remains a significant challenge.

Aim: To develop an innovative pipeline that unifies multimodal imaging data within standardized brain atlases. This integration facilitates comprehensive analysis across different scales and data types, enhancing our understanding of neurobiology and accelerating drug discovery for CNS disorders.

Conclusion

We have developed a methodology for integrating multimodal imaging data into a unified brain atlas space. By combining our LSFM-derived 3D atlas with data from 2D and 3D immunohistochemistry, precision injections, and mapping with public gene expression maps we achieve precise alignment and analysis across modalities. This integrated approach enables detailed exploration of brain structure, connectivity, function, and molecular profiles.

Impact:
- **Research advancement:** Provides a powerful toolbox for neuroscience research, enabling comprehensive analysis that surpasses the limitations of individual data streams.
- **Drug discovery acceleration:** Enhances the ability to understand disease mechanisms and identify therapeutic targets, addressing urgent needs in CNS disorder research.

Future directions: Expand on an online platform to enable researchers to explore the different modality data aiding them in their drug discovery efforts.

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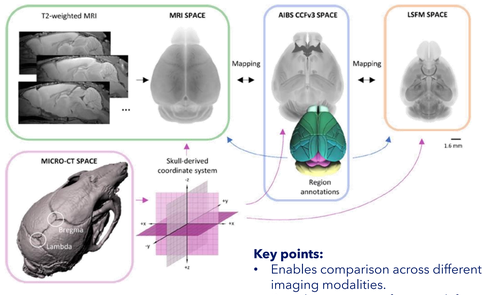
1 Digital brain atlases

Cross-modality mapping

Perens, Johanna, et al. "Multimodal 3D Mouse Brain Atlas Framework with the Skull-Derived Coordinate System." *Neuroinformatics* 21.2 (2023): 269-286.

Wang, Quanxin, et al. "The Allen mouse brain common coordinate framework: a 3D reference atlas." *Cell* 181.4 (2020): 936-953.

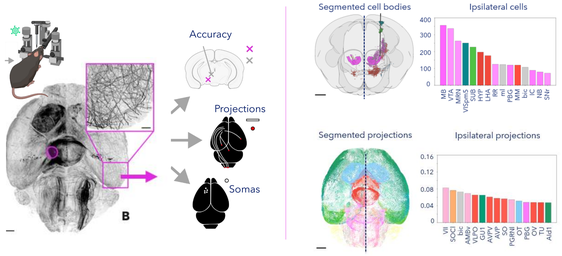


Key points:
- Enables comparison across different imaging modalities.
- Provides a common framework for anatomical annotations.
- Facilitates collaborative research by standardizing data formats.

2 Brain connectivity

Viral tracing experiments

Friedmann, Drew, et al. "Mapping mesoscale axonal projections in the mouse brain using a 3D convolutional network." *Proceedings of the National Academy of Sciences* 117.20 (2020): 11068-11075.



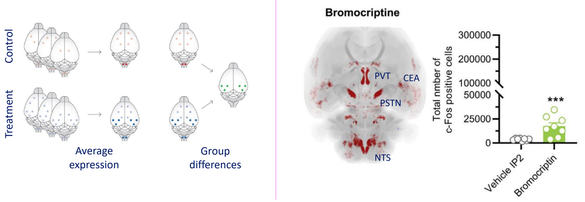
Using our unified atlas space, we performed viral tracing experiments to map neural pathways and connectivity within the mouse brain. The data from viral tracing are precisely registered into the atlas, allowing for detailed analysis of neural circuits and their relationships to anatomical regions.

Highlights:
- Enables exploration of neural pathways.
- Augments brain activity datasets to understand primary vs secondary activation

3 Brain activation

Change in expression levels of the immediate early gene c-Fos

Hansen, Henrik H., et al. "Whole-brain activation signatures of weight-lowering drugs." *Molecular metabolism* 47 (2021): 101171.



We investigated brain activation patterns following Bromocriptine dosing. The activation data are mapped onto the unified brain atlas, providing spatial context to functional changes.

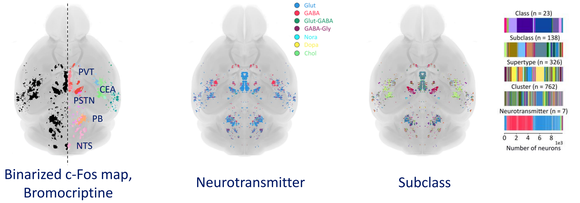
Significance:
- Supports the study of drug effects on brain activity.
- General activation marker allowing comparison across drug types and physiological states.

4 Gene expression

Combining changes in c-Fos levels with gene expression maps

Yao, Zizhen, et al. "A high-resolution transcriptomic and spatial atlas of cell types in the whole mouse brain." *Nature* 624.7991 (2023): 317-332.

Zhang, Meng, et al. "Molecularly defined and spatially resolved cell atlas of the whole mouse brain." *Nature* 624.7991 (2023): 343-354.

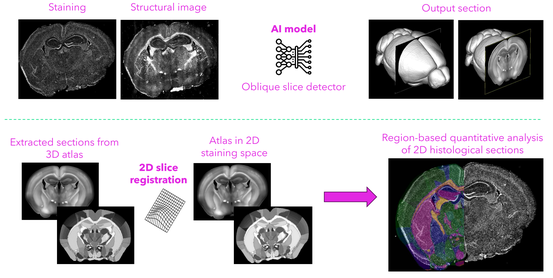


We combined c-Fos activation data with high-resolution single-cell transcriptomic and spatial atlas maps. This allows for exploration of region-specific gene expression patterns within the functional context of brain activation.

Advantages:
- Link between brain activation and receptor expression.
- Detailed molecular profiling within anatomical and functional regions.
- Enhanced understanding of molecular mechanisms underlying brain function.
- Identification of cell-type-specific responses.

5 2D-to-3D atlas mapping

Integrating 2D histology with 3D atlases



We developed a novel approach to integrate 2D histological slices into our 3D brain atlas. By employing deep learning models, including CycleGAN for style transfer and a ResNeXt-based model for spatial transformations, we align stained histological images with LSFM data. This process enriches the 2D images with 3D spatial context and incorporates detailed cellular information into the 3D atlas.

6 Explore in Neuropedia

Digital platform under development to browse brain maps

https://www.neuropedia.dk