# An Atlas of the Human Hypothalamus at Ultra-High Resolution using the BigBrain

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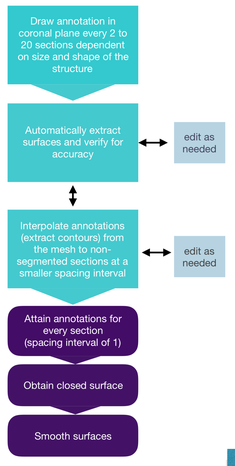
## BACKGROUND

- The hypothalamus is a sexually dimorphic brain structure recognized as a key region for contributing to sex differences in health and disease.
- Yet research using *in vivo* magnetic resonance imaging (MRI) of the human hypothalamus is scarce because of difficulties associated with discrimination of its nuclei and boundaries due to its small size, and because of intermingled gray and white matter within it.
- Here, we segmented the hypothalamus and key surrounding white matter structures on BigBrain, a digital reconstruction of the post-mortem brain of a 65 year-old man with no known neurological conditions (Amunts et al., 2013).
- BigBrain permits detailed observations of anatomical structures due to its ultra-high resolution and contrast.
- We created a 3D atlas of the hypothalamus.
- We aim to use this atlas as a template for segmentation of the hypothalamus with *in vivo* MRI.

## METHODS

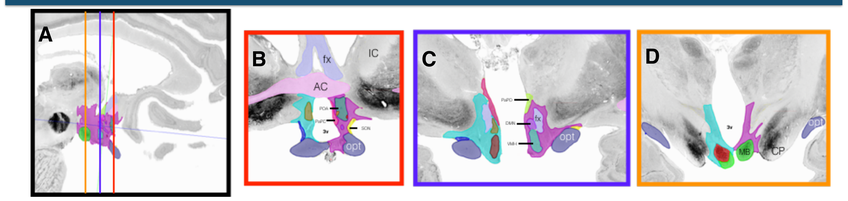
- Hypothalamus segmentation was performed on BigBrain (Amunts et al. 2013) (2015 release).
- Annotation and visualization software: Atelier 3D (A3D) (Borgeat et al., 2007).
- The annotations were performed volumetrically on voxels at 20µm isotropic resolution.
- Identification of hypothalamic nuclei and boundaries were based on the Mai atlas (Mai et al., 2015) referring to the original histological publications.
- The intensity thresholding and color maps feature in A3D facilitated visualization of hypothalamic substructures and boundaries.
- For each structure, the following **workflow** was used

**Workflow**




- Finally, these surfaces were smoothed based on normalized curvature operators (Desbrun et al., 2009; Kroon, 2019), but anistropically, with increased smoothing along the sectioning direction to dampen residual misalignments in BigBrain.
- This algorithm retains the individual structure of the surfaces, by preserving the area on the surface and the volume inside the object, and has a threshold to avoid moving too far from the demarcated points (Omidyaganeh, 2019).

## BigBrain Atlas Segmentation

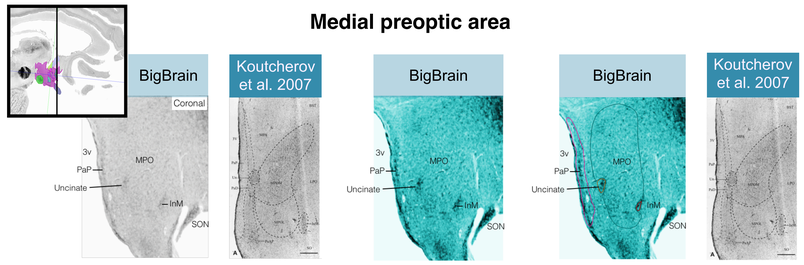



**Segmentation of hypothalamic regions, nuclei and select white matter stuctures on the BigBrain using Atelier 3D segmentation and visualization software**. **A.** Sagittal view of cross sections from anterior to posterior within the hypothalamus. **B-D.** Coronal views of anterior (red box), tuberal (purple box), and mamillary (orange box) hypothalamic regions, respectively.
3v: third ventricle; AC: anterior commissure; CP: cerebral peduncle; DMN: dorsomedial nucleus; fx: fornix; IC: internal capsule; MB: mamillary body; opt: optic tract; PaPC: paraventricular nucleus-parvocellular region; PaPO: paraventricular nucleus-posterior region; POA: preoptic nucleus; SON: supraoptic nucleus; VMH: ventromedial hypothalamic nucleus.

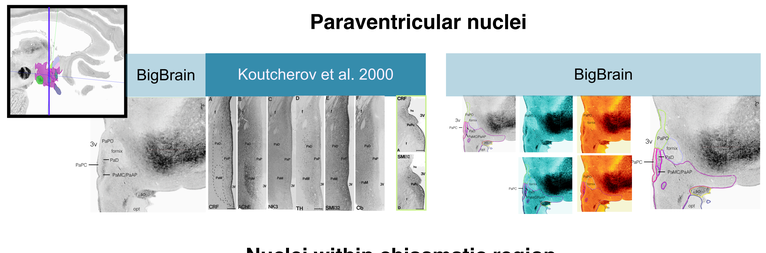
## METHODS

Examples of BigBrain comparisons with histological publications, and use of color maps (e.g. blue teal x-ray; hot metal) in A3D for visualization of substructures within the preoptic area (top) and tuberal region (middle and bottom)

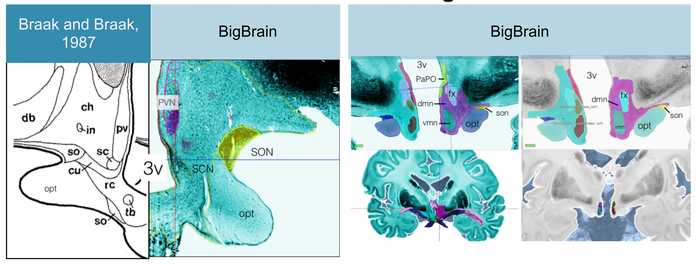
**Medial preoptic area**



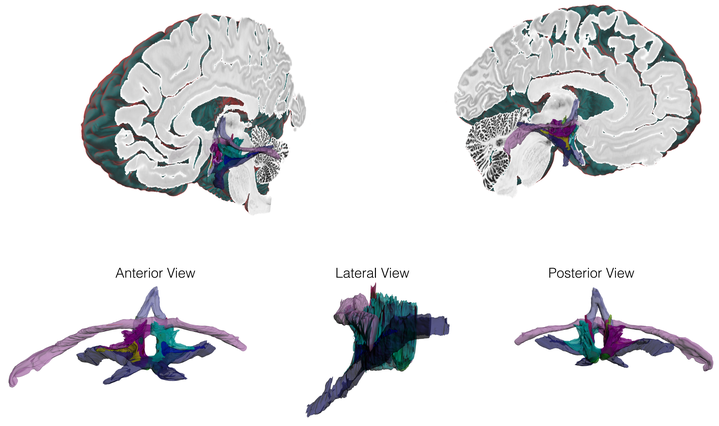

**Paraventricular nuclei**



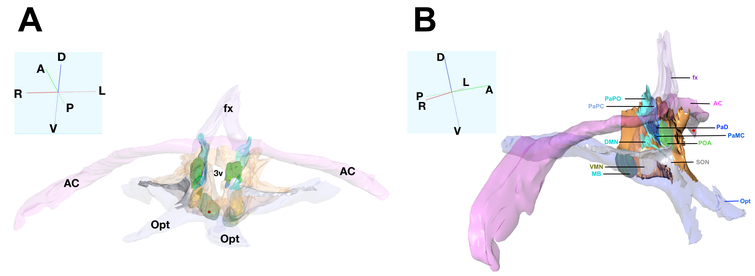

**Nuclei within chiasmatic region**




## 3D Visualization of segmented hypothalamic and white matter structures on BigBrain




## RESULTS




**Three dimensional reconstruction of the hypothalamus and key surrounding white matter structures on BigBrain.** Smoothed surfaces were visualized in BrainBrowser (Sherif et al., 2015). **A**. Front view of hypothalamus with segmented nuclei and surrounding major white matter tracts after surface smoothing. Structures were rendered opaque to show organization of nuclei. **B**. Sagittal view of hypothalamus displaying surrounding major white matter tracts and many of the segmented nuclei of the right hypothalamus. Solid orange color represents left hypothalamus. 3v: third ventricle; AC: Anterior commissure; DMN: dorsomedial nucleus; fx: fornix; MB: mamillary body; PaPC: paraventricular nucleus-parvocellular region; PaPO: paraventricular nucleus-posterior region; PaD: paraventricular nucleus dorsal region; PaMC: paraventricular nucleus magnocellular region; POA: preoptic nucleus; SON: supraoptic nucleus; opt: optic tract; VMN: ventromedial nucleus. Orientation is shown in the blue legends, dorsal (D), ventral (V), right (R), left (L), anterior (A), posterior (P).

## CONCLUSIONS AND FUTURE DIRECTIONS

- This is the first 3D atlas of the human hypothalamus at ultra-high resolution. The segmentation itself will be released as open-source.
- Future applications include

  1) mapping it to MNI space and using it as a template in the analysis of an *in vivo* MRI dataset to determine the influence of parental factors on the child's neuroendocrine development;

  2) using it as a validation tool for our novel *in vivo* manual segmentation protocol of the hypothalamus from high resolution structural MRI images (Jones et al. *submitted*).
- This atlas represents an important step in furthering our understanding of the human hypothalamus as a critical determinant in mental and physical health, especially with regard to sex differences.

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