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High-Resolution 3D Mapping of the Human Hypothalamus: Towards a Comprehensive Cytoarchitectonic Atlas

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The hypothalamus is a brain structure that plays a central role in maintaining homeostasis and regulating various physiological and behavioural processes. It encompasses distinct nuclei with diverse microstructure, connectivity, molecular structure and functions, including circadian rhythm regulation, sleep-wake cycles, appetite control, stress response, and thermoregulation. Dysfunctions of the hypothalamus have been reported in the context of cluster headaches, obesity, addictive behaviour, aggressive disorders, anxiety disorders, sleep disorders, eating disorders, hypertension, and epilepsy. Despite its importance, the structural organization and precise boundaries of the hypothalamus, as well as the functional differentiation of its nuclei, are still not fully understood. Currently, there are no maps available, which inform neuroimaging studies about the microstructural segregation of the hypothalamus in 3D space. Existing maps of the hypothalamus lack the necessary spatial resolution and morphological detail to provide a comprehensive understanding of this complex region. Therefore, in our project we aim to develop a high-resolution 3D map of the human hypothalamus in order to determine its microstructure and localization in the stereotaxic space.

To create a high-resolution 3D reconstruction of the hypothalamus in the BigBrain models, its nuclei were delineated on a subsample of the high-resolution digitized histological sections of the BigBrain datasets (Amunts et al., 2013). To make delineations on every remaining section a deep-learning based brain mapping tool was applied (Schiffer et al., 2021). The model was trained on manual expert annotations on every 15th section in the BigBrain 1 to predict the delineations of the hypothalamus on every remaining sections. The automatically generated maps were re-evaluated to exclude incorrectly delineated sections. The delineations will then be converted into a 3D reconstructed BigBrain space with the use of non-linear registration of the high-resolution digital section (Amunts et al., 2020). Therefore, the resulting map visualized the complex shape of the hypothalamus and its 19 nuclei with high anatomical details.

The hypothalamus is divided into different zones, both in the mediolateral and rostrocaudal directions. Mediolaterally, there are three zones: the periventricular zone next to the third ventricle, the medial zone, and the lateral zone mainly occupied by the lateral hypothalamic area. Rostrocaudally, there are four zones: the preoptic zone bordering the lamina terminalis, the anterior zone, the tuberal zone above the infundibulum, and the mammillary zone.

In the preoptic zone, we identified several nuclei, including the periventricular hypothalamic nucleus, medial preoptic nucleus, median preoptic nucleus, uncinate nucleus, and intermediate hypothalamic nucleus. In the anterior hypothalamic area we distinguished the suprachiasmatic nucleus, paraventricular hypothalamic nucleus, anterior part of the periventricular nucleus, and supraoptic nucleus. The tuberal hypothalamic region contains the ventromedial hypothalamic nucleus, dorsomedial hypothalamic nucleus, arcuate nucleus, and tuberal part of the periventricular nucleus. Lastly, in the mammillary region we identified the medial and lateral mammillary nuclei, supramammillary nucleus, tuberomammillary nucleus, and lateral tuberal nucleus. These histology-based maps in 3D provide detailed anatomical information of a complex region of the hypothalamus and serve as a spatial and structural reference for diagnostic, prognostic and therapeutic neuroimaging studies of the healthy human brain and those of patients.

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