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Mini review

Where do you measure the Bregma for rodent stereotaxic surgery?

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A R T I C L E I N F O

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A B S T R A C T

The advent of the stereotaxic apparatus developed by Clarke and Horsley revolutionized neuroscience research, enabling precise 3D navigation along the skull mediolateral, anteroposterior, and dorsoventral axes. In rodents, the Bregma is widely used as the origin reference point for the stereotaxic coordinates, but the specific procedure for its measurement varies among different laboratories. Notably, the renowned brain atlas developed by Paxinos and Franklin lacks explicit instructions on the Bregma determination. Recent studies have found discrepancies in skull and brain landmark measurements. This review describes the commonly used brain atlases and highlights the limitations in accurately measuring the stereotaxic coordinates. In addition, we propose alternative and more reliable approaches to measure the Bregma. It is imperative to address the misconceptions about the accuracy of stereotaxic surgeries, as it can significantly impact a substantial portion of neuroscience research.

Introduction

The interest in brain function began centuries before the advance of modern medicine. Greeks associated symptoms like headaches with the presence of intracranial lesions and used craniotomy to heal pain conditions (Nanda et al., 2016). Out of curiosity, Greek mythology tells us that Athena was born out of Zeus' skull after a craniotomy performed to cure a terrible headache (Nanda et al., 2016). Beyond ancient mythologies, Greeks have strongly influenced medicine and science. The studies of Claudius Galen about human physiology and anatomy influenced the work of Leonardo da Vinci and Andreas Vesalius (Tubbs et al., 2018). Aristotle's philosophical views on the substance of the mind and the nature of qualia influenced the development of Rene Descartes' questions about the nature of knowledge (Gawu and Inusah, 2019). Centuries later, the advance of tissue conservation and microscopy techniques allowed physicians to investigate the nervous system in more detail (Narang et al., 2021). Santiago Ramon y Cajal and Camilo Golgi were awarded the Nobel Prize in Physiology or Medicine in 1906 "*in recognition of their work on the structure of the nervous system*" (Nobel Prize in Physiology or Medicine in 1906). It was an important step in visualizing neuron morphology and the organization of the brain.

To improve accuracy in studying the brain, neuroscientists have to look at specific subregions. For example, a significant advance in function neuroanatomy was achieved through the groundbreaking work of Wilder Penfield, an American surgeon and neurophysiologist (Leblanc, 2022). In 1937, Penfield and Edwin Boldrey presented their work about the topological localization of motor and sensory functions in the cerebral cortex (Catani, 2017; Pogliano, 2012). They electrically stimulated different cortical subregions of 163 patients during awakening brain surgery to functionally map the cortex (Penfield and Boldrey, 1937). These brain maps were named by Penfield as *Homunculus* (both motor and sensory) (Catani, 2017). Recently, studies using new technology continue exploring the brain cortex to create more complete and precise topographical maps (Gordon et al., 2023).

In other to better target specific parts of the brain, Dmitry Nikolaevich Zernov, a professor at the Moscow University, presented a new device named encephalometer at the Meeting of the Society of Physics and Medicine in 1889. The encephalometer was an apparatus for anatomical studies and neurosurgical operations on the human brain. Zernov used the idea of a geographical map around the head, which was fixed by a stem named the equator above the sagittal suture, and a movable meridian stem attached to the sagittal plane to measure degrees along the hemispheres. The spatial navigation was calculated using the equator divisions for longitude and the meridian divisions for latitude (Kandel and Schavinsky, 1972).

Years later, in 1906, the first stereotaxic apparatus, with the format we know nowadays, was developed by Victor Horsley and Robert Clarke (Fodstad et al., 1991; Tan and Black, 2002). Their stereotaxic apparatus

Abbreviations: RBSC atlas, Rat Brain in Stereotaxic Coordinates atlas; MBSC atlas, Mouse Brain in Stereotaxic Coordinates atlas; ARA, Allen Reference Atlas; CCF, Allen Mouse Brain Common Coordinate Framework; MRI, Magnetic Resonance Image; PET, Positrons Emission Tomography.

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allowed three-axes navigation in the monkey skull based on the Cartesian system (Al-Rodhan and Kelly, 1992; Clarke and Horsley, 1906; Horsley and Clarke, 1908; Rahman et al., 2009). The first human stereotaxic apparatus was developed around 1918 by Aubrey Mussen (Rahman et al., 2009). However, only in 1947, Ernest Spiegel and collaborators (Spiegel et al., 1947) performed the first human stereotaxic surgery. They used head radiographs to compare landmarks outside and inside the skull (Rahman et al., 2009).

Stereotaxic surgery is one of the most used and important techniques for neuroscience and neurosurgery, allowing scientists and physicians to reach specific brain regions. The principles of skull measures used in stereotaxic surgery has also an important impact on other techniques such as functional Magnetic Resonance Imaging (fMRI) and Positrons Emission Tomography (PET). In addition, new computerization approaches have revolutionized neuroscience and neurosurgery. Current digitalized images for calculations of brain target coordinates and the robotization of surgical procedures just began with the idea of Cartesian 3D navigation through the brain. While the application of stereotaxic surgery is extensively documented in various animal species, its utilization in scientific research is particularly prominent in rodent models.

Rodent stereotaxic surgery and atlases

The small stereotaxic apparatus for rats and mice basically consists of a horizontal base plate, assembly with one or two micromanipulators affixed to the frame, and a holder affixed to the micromanipulators. The holders are used for electrodes, syringes, or cannulas. Two ear bars and one head holder are provided according to each specie to fix the animal head. Nowadays, the head holder may be adapted for an inhalator anesthesia mask. There are several commercially available apparatuses such as the one from Kopf Instruments, RWD Life Science, Harvard Apparatus, World Precision Instruments, and Stoelting Company (Fig. 1).

Like the human stereotaxic, the rodent stereotaxic apparatus uses a 3D cartesian system, with the x, y and z-axis, as the mediolateral, anteroposterior, and dorsoventral axes, respectively. To set axes origin, visible landmarks on rodent skull bones are necessary. The adult mouse skull (Fig. 2A-B), for example, is formed by 26 bones and joints, which are also known as sutures (Marghoub et al., 2019). There are three sutures in the upside view of the skull: the coronal, the sagittal, and the lambdoidal (Fig. 2C). The coronal suture seems like a parabolic curve between the frontal and parietal bones. The sagittal suture divides the skull into two sides by the medial line. The lambdoidal suture looks like the Greek letter Lambda at the posterior part of the skull among both parietal bones and the occipital bone. Overall, the point among both parietal bones and the occipital bone is named Lambda while the crossing point of the coronal and the sagittal sutures is named Bregma. The Lambda is essential for the alignment of the dorsoventral coordinates. The Bregma is the most used origin point of the stereotaxic system in rodents (De Vloo and Nuttin, 2019; Ferry et al., 2014; Paxinos et al., 1980).

In addition to accurately establishing the axes origin, neuroscientists employ well-defined atlases to determine the coordinates corresponding to the brain region of interest. The atlases are constructed from meticulous histology and anatomy studies which established coordinates on brain section planes, namely coronal, sagittal, and horizontal orientations. To determine the coordinates for each structure, the atlases also must identify the origin set of the stereotaxic coordinates, especially the Bregma.

Renowned neuroanatomists George Paxinos and Keith Franklin have developed the most widely used brain atlases for rat and mouse: “The Rat Brain in Stereotaxic Coordinates” (RBSC) atlas in 1980 (Paxinos et al., 1980), and “The Mouse Brain in Stereotaxic Coordinates” (MBSC) atlas in 1997 (Franklin and Paxinos, 1997). Both atlases use Nissil or acetylcholinesterase staining of 40 μm brain slices to indicate structure demarcations. It is important to highlight that craniometric parameters and brain volume can exhibit inter and intra-strain variations by factors such as body size, weight, age and sex (Paxinos et al., 1985).

More recently, other atlases editions were published. For example, Hong Wei Dong, from the Allen Institute, created a 2D atlas (Allen Reference Atlas - ARA) (Dong, 2008). The Allen Mouse Brain Common Coordinate Framework (CCF) 3D reference atlas used a cellular-level resolution. The first version of CCF was created using a conversion of Nissl-based ARA 2D structure annotations to 3D with brain gene expression mapping (Lein et al., 2007). The second version of CCF atlas contains more structure annotations and higher voxels resolution, in addition to introducing brain-wide mesoscale connectivity (Oh et al., 2014). The third version was created in a new 3D reference brain template using multimodal reference datasets (Wang et al., 2020). The author included dataset histology stains, immunohistochemistry, transgene expression, *in situ* hybridization, and anterograde tracer connectivity experiments. In addition, they used 1675 young adult

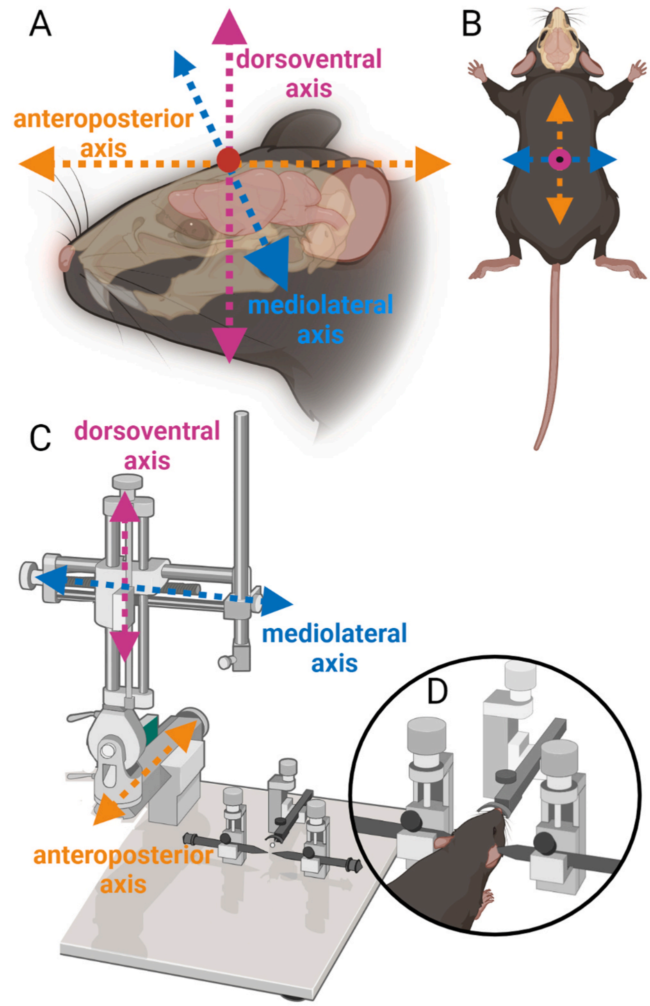

Fig. 1. Mouse skull-body orientation and a rodent stereotaxic apparatus. **(A)** Lateral view of the mouse head, illustrating its orientation in three axes in relation to the skull and brain. **(B)** Dorsal view of the mouse body, highlighting the three axes. **(C)** Illustration of the rodent animal stereotaxic apparatus. **(D)** Detailed view of the mouse head holder and ears bars. Note: All figures in this review employ a consistent color pattern for the three axes: orange represents the anteroposterior axis, pink represents the dorsoventral axis, and blue represents the mediolateral axis.
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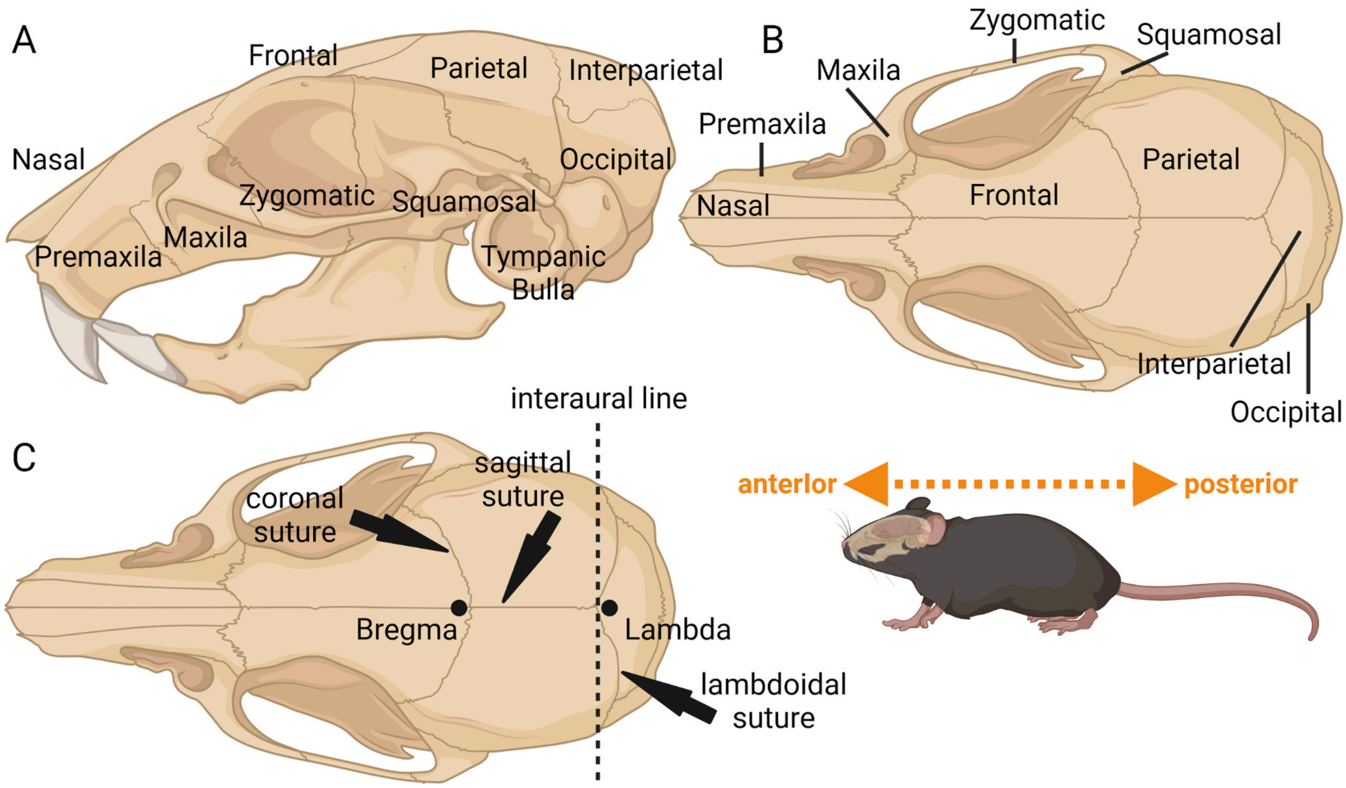

Fig. 2. Anatomical representation of the mouse skull from different perspectives (based on Cook, 1965) **(A)** Lateral view of the mouse skull, highlighting the bones. **(B)** Dorsal view of the mouse skull, highlighting the bones. **(C)** Dorsal view of the rodent skull sutures and landmarks relevant for stereotaxic surgery. Created using BioRender.

mouse brain images to construct 3D spatial templates and the Mouse Brain Connectivity Atlas (Kuan et al., 2015; Lein et al., 2007; Oh et al., 2014; Wang et al., 2020). The Allen Institute Atlases are open access[1]

Stereotaxic coordinates

Despite the advances in the development of new atlases, certain inconsistencies pose challenges for scientists when attempting to compare stereotaxic coordinates across different studies. One of the major concerns lies in the precise determination of the specific point of the skull to measure the Bregma, the origin point to calculate all other coordinates. While researchers use the atlases to determine some coordinates, several labs report pilot studies to improve the precision in targeting the desirable brain region.

The RBSC atlas, for example, describes the Bregma as "…*the point of intersection of the sagittal suture with the curve of best fit along the coronal suture*" (Paxinos and Watson, 2006). The MBSC atlas, on the other hand, does not explain where the Bregma should be measured (Paxinos and Franklin, 2019). Both atlases used the same skull figure showing the Bregma at the crossing point between the coronal and the sagittal sutures which is not compatible with the description mentioned before (Fig. 3A). It is interesting to notice around the neuroscience community that most articles do not mention where exactly they measured the Bregma.

Blasiak et al. (2010) compared the precision of the stereotaxic surgery when the Bregma was measured on the crossing point of the coronal and the sagittal sutures (old Bregma shown by the red dot in Fig. 3B) and the crossing pointing between the sagittal suture with the best-fit parabola on the coronal suture (new Bregma shown by the blue dot in Fig. 3B, as described by Paxinos in the RBSC atlas). The findings revealed that in 44% of the rats, the position of the old Bregma deviated by 0.22 mm or more from the new Bregma. Stereotaxic surgeries conducted using the new Bregma measurement have significantly smaller errors in the anteroposterior and mediolateral axes compared to those performed using the old Bregma measurement.

Resolving these disparities in Bregma's positioning is a nontrivial endeavor. Few scientists have been directly studying better approaches to measure the Bregma. Sergejeva et al. (2015), for example, investigated how skull-based landmarks are aligned to internal brain structures. They used an anatomical *ex vivo* MRI to compare the best-fitting slices from the MBSC atlas to the position of the Bregma, but they did not specify how they set the Bregma. The anteroposterior position of skull-based landmarks Bregma and Lambda varied considerably with respect to the internal brain structure.

The automation of Bregma setting could improve the surgeries, but digital stereotaxic apparatus with camera and software are expensive. To solve this problem, surgeons can manually draw a parabola that best fits the coronal suture (an adaptation from Blasiak et al. (2010)). This adaptation can improve setting the Bregma. In addition, training and standardization of surgery procedures may reduce discrepancies of the Bregma measure among research groups (see the surgery guide provide by Ferry et al. (2014)).

Atlases are not dogmatic representation of brains, but their choice is a crucial step of surgery standardization. Although a neuroscientist can have success with the older Paxinos' atlas or the new Allen Institute's atlases, once the choice has been made, one must remain until the end of the experiment. Chon et al. (2019) investigated MBSC and CCF atlases discrepancies in coordinates and in anatomical borders. They used manual adjustment to initially align the the MBSC atlas on the CCF atlas. Additionally, they used transgenic mouse strains that mark distinct cell

[1] Allen Developing Mouse Brain Atlas available on https://developingmouse.brain-map.org/; Allen Mouse Brain Atlas available on https://mouse.brain-map.org/; Allen Mouse Brain Connectivity Atlas available on https://connectivity.brain-map.org/.

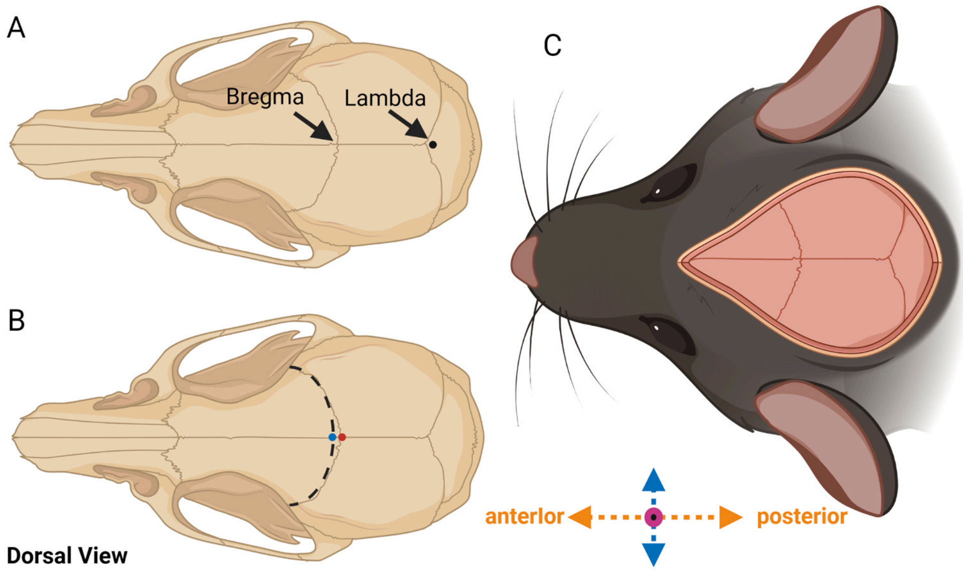

Fig. 3. Dorsal view of the rodent skull diagram with sutures and detailed points of measurement of the Bregma and the Lambda. Bregma and Lambda based on Paxinos and Franklin (2019). Red dot: the Bregma measured on the crossing point between the coronal and the sagittal sutures. Blue dot: the Bregma measured on the crossing pointing between the sagittal suture with the best-fitting parabola on the coronal suture. Based on Blasiak et al. (2010) **(C)** Skull landmarks on surgery view, it is important to note that during the surgery the research will partially see the skull depending on the incision size. Created using BioRender.

populations to refine structure borders. Information from the Mouse Connectome Project (Oh et al., 2014) was used to complete the analysis. The results were used to frame another atlas, available online, on Dr. Yongsoo Kim's Lab website (link to the online atlas: https://kimlab.io/brain-map/atlas/).

The key to surgery success is knowing the technique limitations and performing careful coordinate standardization. Also, it is important to point out that for long-term skull implants, increased caution is required regarding the stereotaxic coordinates due to deformation of brain surface after opening the cranial window (Arefev et al., 2021). In this case, Arefev et al. (2021) suggested a mathematical adjustment of stereotaxic coordinates based on the Bregma and the intersection of blood vessels on brain surface.

Tips for trainees

Surgery techniques are a fundamental step for neuroscientists because it is a routine practice for many experiments. More precise stereotaxic surgeries result in trustworthy data and the use of less animals. Beyond practice, a well design protocol and theorical knowledge about rodent skull anatomy are crucial to better perform stereotaxic surgery. Considering the surgery itself, a very difficult step for beginners is the correct positioning of the animal head on the stereotaxic apparatus. After setting the Bregma, the surgeon has also to pay attention to measure the Lambda coordinates. According to the methodology described on The Mouse Brain in Stereotaxic Coordinates (Franklin and Paxinos, 1997), the Lambda landmark is defined *"as the point of intersection of the best-fit lines passing through the sagittal suture and the left and right portions of the lambdoid suture"*.

To further improve the surgery, researchers could calculate the estimated distance between the Bregma and the Lambda using the distances from interaural line (the line between bilateral ear drums - for reference, see Zhang and Xiong, 2014) (Fig. 4) (Paxinos and Watson, 2006; Paxinos and Franklin, 2019). The result can be used to verify if the landmarks settings and head alignment are correct. However, the interaural line is not simple to identify for beginners.

Finally, the Bregma and the Lambda must be in the same vertical coordinate, measured by the dorsoventral axis. In Fig. 5A, the angle between the axis of the bones and the horizontal axis is highlighted. This angle is important to better align both landmarkers (in general a coordinate difference of less than 0.02 mm in dorsoventral axis is acceptable). This adjustment can be made using the angle manipulator present in the head holder of the stereotaxical apparatus.

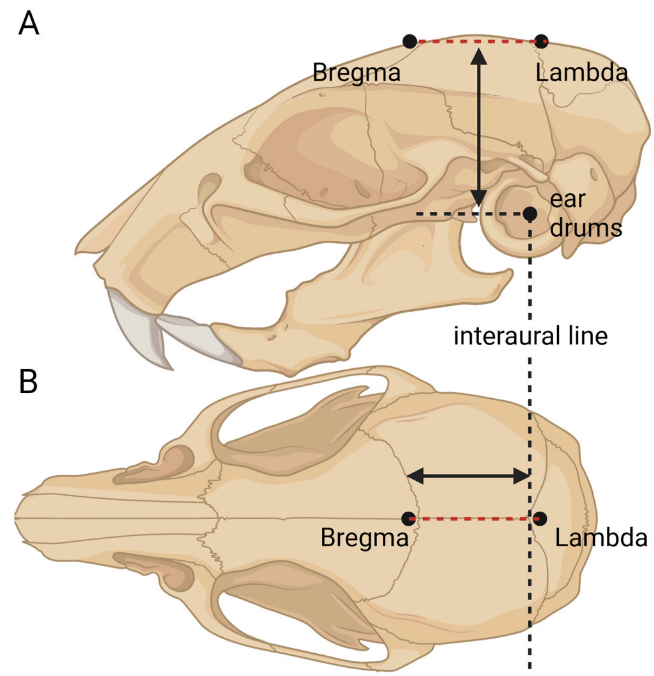

Fig. 4. Craniometric and stereotaxic skull landmarks and measures. According to MBSC, the Bregma is 3.8 (± 0.25) mm rostral and 5.8 (± 0.48) from the interaural line, and the lambda is 0.41 (± 0.26) mm caudal and 5.8 (± 0.48) from the interaural line. **(A)** Lateral view of mouse skull, Bregma and Lambda dorsoventral distances from the intraural line. **(B)** Dorsal view of mouse skull, Bregma and Lambda anteroposterior distances from the intraural line.
Based on Fig. 1 of Paxinos et al. (1985) and adapted for mouse skull. Created using BioRender.

Conclusion

The imprecisions created by the variability in the measure of the Bregma and by the discrepancies in its alignment to the internal brain structures may be an underrated neuroanatomy issue that is crucial for future research. The correct measure of the Bregma will improve rodent stereotaxic surgery. Thus, we believe that cell-type details, connectivity mapping and *in vivo* neural pattern recordings can refine stereotaxic surgery and, consequently, neuroscience development.

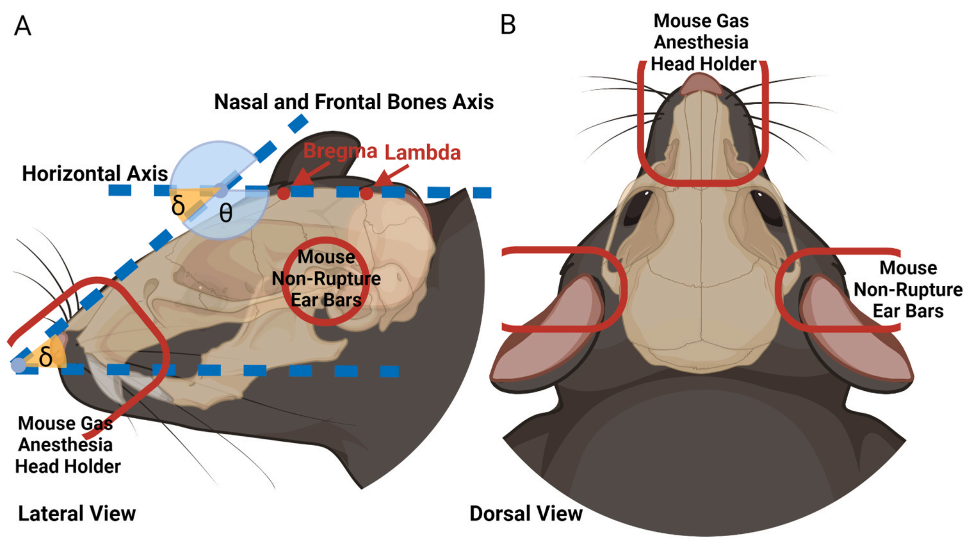

Fig. 5. Mouse head position on stereotaxic apparatus. **(A)** Lateral view of the mouse head. Note that the Bregma and the Lambda are on the same horizontal plane. Nasal and frontal bones are in angle relative to the horizontal plane (δ). The δ and θ are complementary to 180 degrees. The mouse head holder must be in the correct angle with the horizontal plane to coorectly position the mouse head. In red, the approximate position of mouse head holder and ear bars. **(B)** Dorsal view of the mouse head. In red, the approximate position of mouse head holder and ear bars . Created using BioRender.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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