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# Practical Performance of Hippocampal Tissue Resection in Rats in Pharmacomolecular Research

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## ABSTRACT

**AIM:** To explain how to resect hippocampal tissue in rats used as live mammalian subjects for the resection of fresh cerebral tissue in laboratories.

**MATERIAL and METHODS:** Adult male Wistar-Albino rats (n=50) were used for this purpose.

**RESULTS:** The average bodyweight of the rats was 316.4 ± 11.71 g, and the average weight of the resected hippocampal tissues was 1.01 ± 0.03 g; however, there were no statistically significant differences between the body weights and the hippocampal tissue weights ($p>0.05$). The hippocampal tissues to be used in the study were excised practically by preserving the original anatomical configuration without injury to the tissue.

**CONCLUSION:** This paper elucidates a simple, step-by-step methodology for performance in the laboratory in order to improve the standardization of hippocampal tissue dissection.

**KEYWORDS:** Dissection, Brain, Cerebellum, Cortex, Hippocampus, Wistar-Albino, Rat

## INTRODUCTION

The hippocampus is the brain region that is most often studied via clinical and laboratory research in more than 156,000 studies in the PUBMED electronic database of US National Library of Medicine National Institutes of Health. The two major reasons for this high number of studies is the observation of a considerable number of activities associated with verbal and visual memory functions in the hippocampus and the search for a cure for the treatment of pathological conditions related to the visual and verbal memory-related functions associated with hippocampal lesions (19).

Furthermore, there are also studies investigating spatial learning and navigation, affect, neural circuitry (2), the Papez circuit (13), and the relationship between the endocrine function and the hippocampus (15).

Experimental studies on hippocampal tissue also comprise the large number of studies conducted either due to the need to investigate several other diseases, such as medial temporal lobe epilepsy (3), or the increase in the average life span of humans, causing a growing number of patients with neurodegenerative diseases, including Alzheimer's disease, Parkinson disease, Huntington disease, and amyotrophic lateral sclerosis, thus creating a public health issue (26).

Research on hippocampal tissue has become increasingly popular. The hippocampus is a layer of gray matter extending along the temporal horn of the lateral ventricle. This tissue, also called the archicortex, is phlyogenetically one of the oldest regions of the brain. The hippocampus looks like the letter "C" in coronal brain sections and is called the "hippocampus" because of its resemblance to a seahorse. It has also been referred to as "*Cornu Ammonis*", as it looks like the outer face of a horn (9,11). *Cornu Ammonis*, one of the given names to the hippocampus, is abbreviated as "CA" using the initial letters. Based on differences in its cellular structure, the hippocampus can be divided into different regions: CA1, CA2, CA3, and CA4 (Figure 1).

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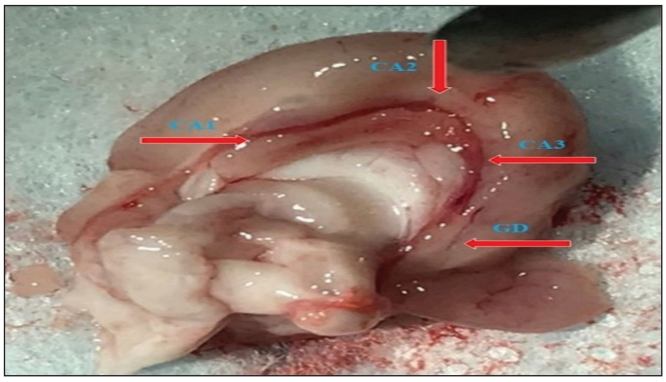


**Figure 1:** The outermost layer of the hippocampus towards the ventricular surface is the alveus. Then, the CA1, CA2, and CA3 regions follow. The innermost region is CA4. CA1 is close to the subiculum and CA4 is close to the dentate gyrus. The hippocampal sulcus lies between the hippocampus and the entorhinal cortex. **TH:** Temporal horn, **CA:** Cornu Ammonis.

Of these regions of the hippocampus, CA1 is the one closest to the subiculum, and CA4 is the one closest to the dentate gyrus. Neurons of the hippocampal CA1 region are essential for spatial learning and memory. CA1 region neurons receive information from the entorhinal cortex or the CA3 region and process this information. An intact connectivity between CA3 and CA1, CA2, and CA3 is absolutely necessary for reference memory. Moreover, the CA3 region is connected to the CA1 region through the Schaffer collateral fibers, and CA1 output projections extend to the subiculum, entorhinal cortex, and prefrontal cortex. CA1 receives input from two locations: primarily CA3 and somewhat from the entorhinal cortex. The CA1 region acts as a flaw detector and detects incompatibility between the cortical information and information from CA3 and the entorhinal cortex. The number of cells in CA1 and CA3 is small prior to adolescence but increases gradually (20). This shows that spatial learning and memory improve during adolescence (20).

Connections in the CA3 region of the hippocampus are especially reported to be important in the formation of hippocampal episodic memory (22). In neurodegenerative diseases such as Alzheimer's, a reduction in the number of pyramidal cells has been discovered in the CA1, CA2, and CA3 regions. In experimental studies that account for the vast majority of pharmaceutical research on the hippocampus, rodents are commonly used as subjects, and rats are particularly used in such experimental designs on live mammal subjects (5).

*In vitro* studies investigating drug metabolism and toxicity profiles use tissue specimens obtained from live mammal subjects. Data from studies using such tissues is then used for predicting what can occur in human diseases and/or how to treat patients. The accuracy of these predictions as well as the extrapolations of findings obtained from human or animal *in vitro* systems to *in vivo* outcomes depend on the tissue quality used in the experiment (6). In experimental studies where tissues are analyzed or where primary cell cultures derived from tissues are established, methods of obtaining tissue samples are critical (6). Therefore, this study aimed to surgically elucidate how to resect hippocampal tissue from rats.

## MATERIAL and METHODS

During the experiments, 50 Wistar-Albino male rats at 10 weeks of age, and weighing 300-320 g were used. These subjects were provided access to standard pellet feeds and water until they were sacrificed. All subjects were kept in cages and exposed to 12:12 hours light-dark (LD) cycles. The number of experimental animals was kept to a minimum.

### Ethical Approval

This study was conducted after obtaining approval from the Istanbul Medipol University Local Ethics Committee for Animals (Permission of Live Mammal Usage for Experiments; 13/03/2019; No. 38828770-604.01.01-E.10835). The experiments were carried out in the MEDITAM/IMU-HAYDEK laboratory (Istanbul Medipol University). Interventions on live mammal subjects were carried out in compliance with the 9th and 17th articles of the "Animals Protection Law" No. 5199 dated June 24, 2004; the Ministry of Food, Agriculture, and Livestock's "Regulation on Welfare and Protection of Animals Used for Experimental and Other Scientific Purposes", published in the Official Gazette on December 13, 2011 with the number 28141; the Ministry of Environment and Forestry's "Regulation on Working Procedures and Principles of Animal Experimental Ethics Committees", published in the Official Gazette on July 6, 2006 with the number 26220; and the "IMU-HAYDEK directive", developed based on these abovementioned regulations.

### Surgical Resection of the Hippocampal Tissue

The inhalational anesthetic agent, *Isoflurane-USP 100ml®*, was administered to the subjects in all study groups prior to the decapitation. The anesthetized study rats were sacrificed using a rodent decapitator with stainless steel blades (Decapitator Catalogue no.: 25303059999990000651400001) to allow for the easy and clear-cut separation of the rat's head from the body at the craniocervical junction (Figure 2).

Throughout the entire procedure, the interventions were carried out under a CL 6000 LED® light device (Figure 3). The heads of the live mammal subjects extracted by means of the decapitator under isoflurane anesthesia were taken to the site at which the procedure would be performed (Figure 4).

### Separation of Hippocampal Tissues by Surgical Dissection

In order to expose the osseous tissue of the cranium, the skin and the subcutaneous tissue covering the skull were incised on the midline from the occipital region to the frontal region using a number 15 scalpel. Then, using a surgical forceps and dissecting scissors, the skin, subcutaneous tissue, and periosteum were laterally and anteriorly dissected from the osseous tissue. The dissected tissues were turned over from the frontal region on both orbits and the nasal bone using forceps. The osseous tissues were exposed anatomically.

The frontal, parietal, interparietal, and occipital bones, as well as the sagittal and lambdoid crests, were anatomically identified and exposed.

Using iris scissors and preserving the cerebral tissue, the osseous tissue was incised as parallel lines in the caudocranial direction, extending bilaterally from the interparietal bone to the frontal bone along the caudolateral border of the interparietal bone, which also forms the caudal part of the sagittal crest.

Meticulous maneuvers were performed in order to not damage the brain tissue or meningeal structures. The frontal bone was incised anteriorly in the cranium by attempting to pass along the arbitrary line extending in the midline between the superior borders of both orbital cavities. The olfactory bulb was exposed, and the frontal, parietal, and interparietal bone tissues covering the dorsal surface of the cerebral tissue were excised.

The osseous structures surrounding the dorsal surface of the brain tissue were reflected off in the shape of a cap, and these bone tissues were excised. Due to the protective function of the meningeal structures extending between the cerebral tissue and the cranium and covering the cerebral tissue, attention was paid to avoid damaging the meningeal structures to limit injuries to the cerebral tissue during the dissection.

The brain tissue was carefully dissected from the meninges circumferentially surrounding the cerebral tissue. Then, the dissection of the cerebral tissue was initiated toward the bases of the temporal bone laterally and the frontal bone anteriorly. Using a curved narrow-pattern forceps in the closed position and mini dissectors in order to preserve the cortical surfaces, the cerebral tissue was dissected bilaterally at the bases of the temporal bones laterally and the bases of the frontal bones anteriorly.

Then, the dissector was slid to the base of the cerebral tissue, and the cerebral tissue and midbrain structures were shifted superiorly. The vascular structures and cranial nerves of the cerebral tissue at the skull base were separated from the cerebral tissue. In the frontal region, the mini dissector was slid under the anterior olfactory bulb, and the brain was slowly counterbalanced superiorly.

The optic nerve and the olfactory nerve were incised, and the cerebral tissue was completely dissected from adjacent osseous structures and resected without injury. The excised cerebral tissue was immediately transferred onto drapes with a frosted plate underneath (Figure 5).

In order to facilitate the anatomical orientation, the ventral surface of the brain tissue was placed facing the frosted plate with the dorsal surface kept in the superior position, and, in the craniocaudal direction, the cerebellum was positioned posteriorly, and the frontal lobe was positioned anteriorly.

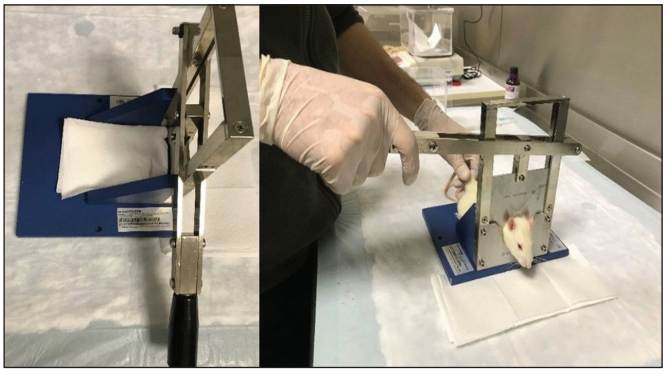

**Figure 2:** The decapitation procedure applied to the live mammal subjects under anesthesia.

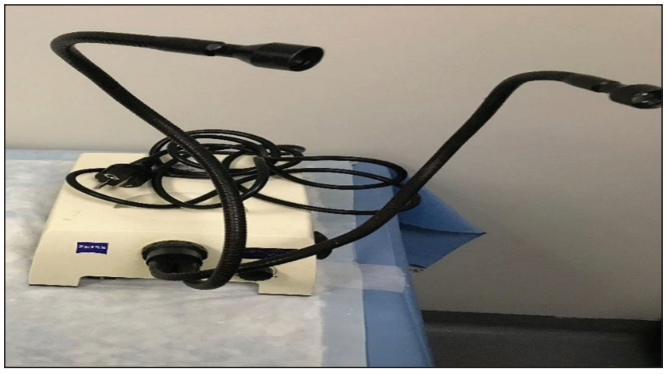

**Figure 3:** The LED light device used during the operation.

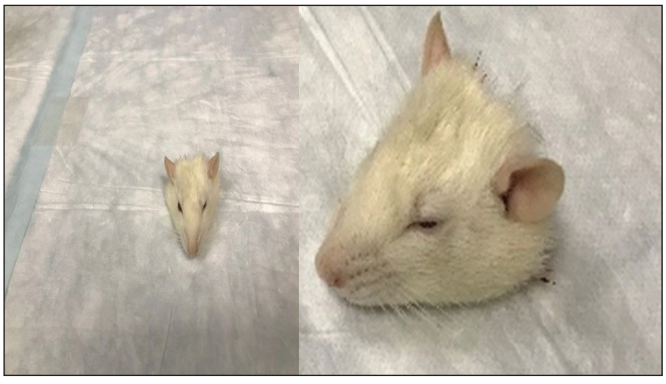

**Figure 4:** Photograph of the decapitated rat head obtained using the decapitator at the site of the procedure.

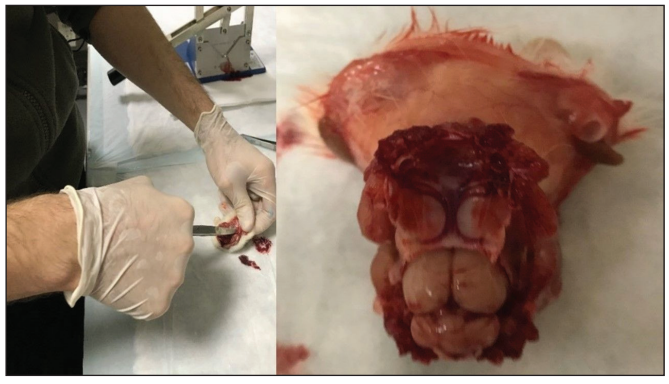

**Figure 5:** Superior view of the intracranial cerebral tissue on the drape with a frosted plate underneath after anteriorly turning over the skin and the subcutaneous tissue covering the rat cranium and removing the osseous structures covering the cerebral tissue.

Using a dissector, the cerebellum, pons, and medulla were slightly dissected from the cerebral cortices. These tissues were then incised and removed from both cerebral cortices using a number 15 scalpel (Figure 6).

The ventral surface of the cerebral cortices was placed to face the frosted plate on the site of the procedure. Then, the incision was performed by means of a number 15 scalpel along the longitudinal cerebral fissure and the interhemispheric sulcus to include the corpus callosum and midbrain structures on the midline. Thus, the two cerebral hemispheres were separated from each other.

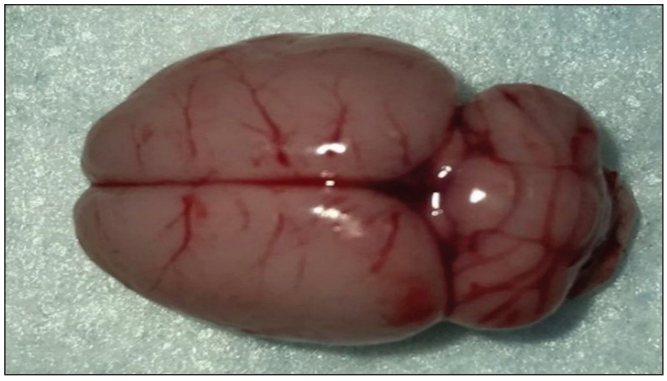

**Figure 6:** Superior view of the cerebral cortex, cerebellum, pons, and medulla in the excised brain tissue.

In order to facilitate the manipulation of the tissue, a 0.5 mm-incision parallel to the surface was made by means of a number 15 scalpel in the anterior-posterior direction on the frontal lobes of both hemispheres, and the tissues were removed from the environment. Of the two cerebral hemispheres, the left hemisphere was first turned over the incised frontal surface. Then, the midbrain tissues were held by means of the forceps and dissected from the cerebral cortical tissue with a scalpel. To reach the hippocampus tissue, located posteriorly to the third ventricle, superiorly to the thalamus, and inferiorly to the corpus callosum, first, the bright white and crescent-shaped corpus callosum was identified (Figure 7A-D).

First, the left cerebral hemisphere was placed on the drape with its cortical surface facing the frosted plate again. With a number 15 scalpel and dissectors, the hippocampus tissue, located inferiorly to the cortical tissue and corpus callosum, was dissected from the tissue, which was fixed from the frontal region using a small curved forceps. In order to expedite and facilitate the dissection process, incisions were made from the medial to the lateral-posterior direction in the posterior part of the cortex. Therefore, access to the hippocampal tissue was facilitated. The pinkish color of the hippocampus tissue in comparison to other cerebral tissue was an auxiliary parameter to guide the dissection. The same procedures were repeated for the right cerebral hemisphere. Thus, the hippocampal tissues on both sides were obtained. The excised hippocampus tissues were re-examined to check for the presence of cerebral cortical structures in the obtained

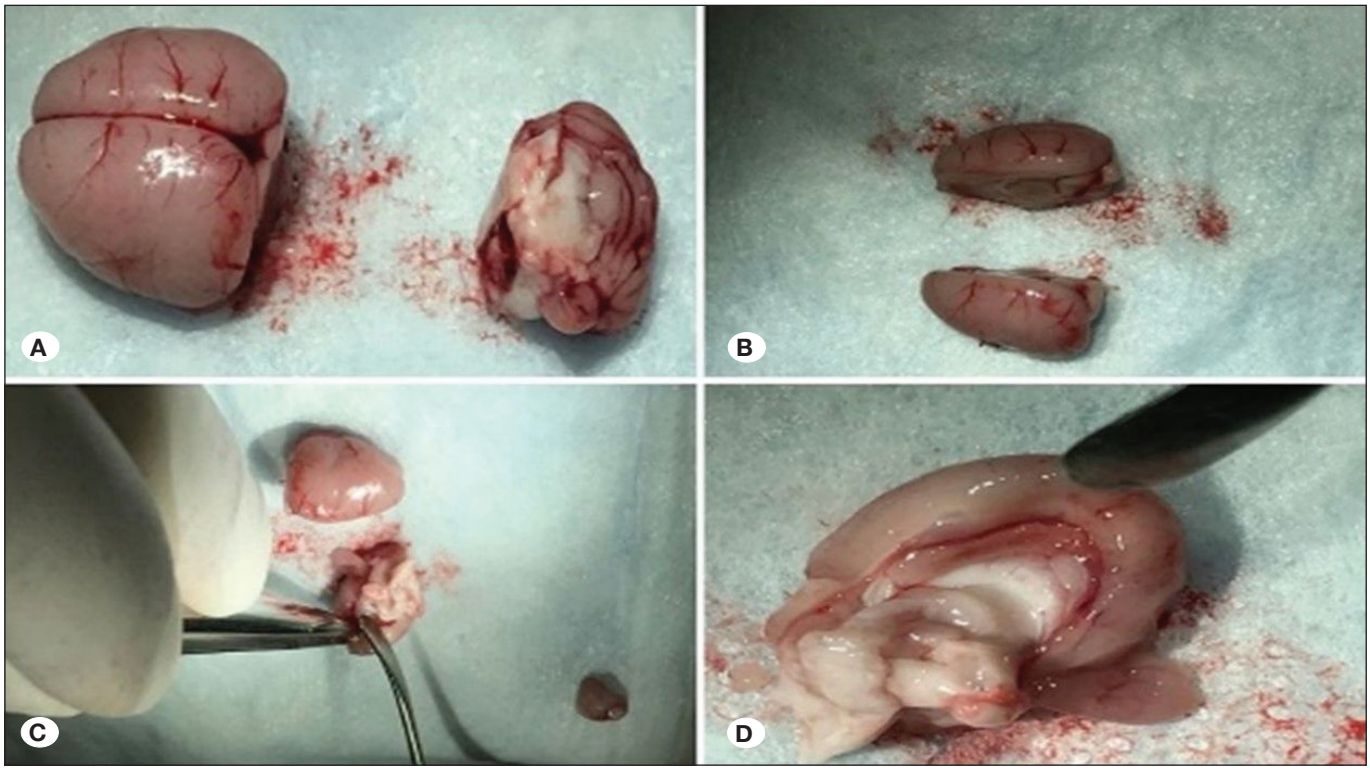


**Figure 7: A)** Separation of the cerebellum and medulla from the cerebral hemisphere; **B)** separation of the two hemispheres by incising on the midline along the longitudinal cerebral fissure and interhemispheric sulcus; **C)** dissection of the middle brain tissues from the right cerebral hemisphere; **D)** exposure of the right hippocampal tissue.

specimens. Hippocampal specimens featuring incomplete removal of the cerebral tissue were immediately dissected, and the cerebral tissues were removed using a smaller forceps. Then, the hippocampal tissue samples were placed into the tubes (Figure 8).

### Statistical Analyses

The body weights of the subjects and the weights of the hippocampal tissues were evaluated using the Minitab program version 16. The data was presented as mean ± standard deviation. The One-Way Variance Analysis (ANOVA) and Post-Hoc Tukey Honestly Significant Difference tests were used for the evaluation of the data and to test the differences between the groups. The alpha significance value was accepted as 0.05.

## RESULTS

The average bodyweight of the rats was 316.4 ± 11.71 grams, and the average weight of the resected hippocampal tissues was 1.01 ± 0.03 grams. However, there were no statistically significant differences between the body weights and the hippocampal tissue weights ($p>0.05$).

In this study, the hippocampal tissues of live mammal subjects were dissected from adjacent cranial and cerebral structures. This way, the hippocampal tissues to be used in the study were excised practically by preserving the original anatomical configuration without injury.

## DISCUSSION

The complexity of the structure of the hippocampus, as well as its close relationship and major connectivity with many regions in the brain, complicate fully elucidating the hippocampal functions as well as clarifying any associated pathologies associated. Therefore, research aiming to identify the functions of only the hippocampus or its role in complex functions has gained popularity (3,9,11,26).

Hippocampal tissues are extensively used for investigating both short- and long-term memory as well as spatial learning and navigation, affect, and neurodegenerative diseases (4).

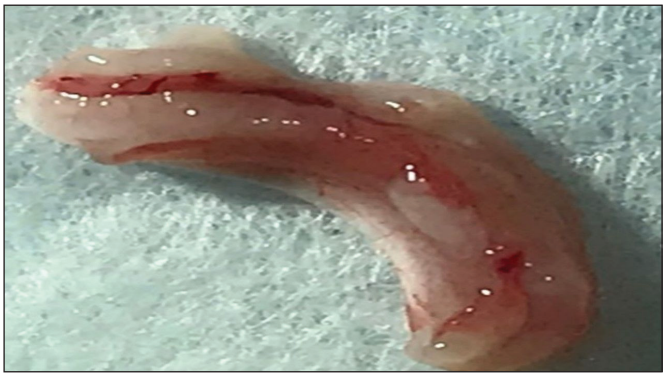

**Figure 8:** Macroscopic image of the resected hippocampus tissue.

Most of these studies comprise *in vivo* experimental research to perform histopathological examinations or conduct experiments on hippocampal cell cultures or commercial cell lines of isolated RNA or extracted proteins obtained in vitro and/or from hippocampal tissues. In these experiments, hippocampal tissues obtained especially from rats were used (12,23). Moreover, dissection of the brain tissue is an important step in the sample preparation process for proteomic studies (18). Therefore, in this study, the aim was to surgically explain how to prepare tissue samples by resecting the hippocampal tissue of Wistar-Albino male rats.

Heffner et al. described a method for the rapid dissection of 17 areas in the rat brain. The authors reported that coronal sections can be dissected from tissue blocks of fresh non-frozen brain tissue (8). They underlined that this method is applicable to pharmacological and behavioral studies that require a large number of brain dissections in short periods of time.

In another study on 38 male Sprague–Dawley rats), the authors sacrificed the subjects via decapitation under anesthesia, which was achieved by the administration of metophane gas. The authors reported that they quickly resected the brain tissue of the rats and dissected the hippocampus; however, this study also does not provide a detailed surgical description (21).

In the present study, isoflurane-USP inhalational anesthesia was administered to 50 adult male Wistar-Albino rats, and these rats were sacrificed using a rodent decapitator.

A review of high-evidence level studies reported in the literature over the last five years revealed that no studies have clearly described how to resect the hippocampal tissue in studies on adult male Sprague–Dawley rats yet (17).

In a study testing the effects of pterostilbene, as an active agent with antidepressant properties and promoting neurogenesis in the hippocampal tissue of adult rats (24), male Sprague-Dawley rats were used. However, in the methodology section, no detailed explanations of the surgical procedures applied to the hippocampal tissues were provided other than reports that the brain tissues of the rats were dissected, rinsed, cut into pieces of 1 $mm^3$, and transferred to a DMEM/F12 medium (24).

In a study assessing diet-induced changes in peptides from the hippocampus, hypothalamus, and striatum aiming to reveal the interactions of neuropeptides across different anatomical regions of the brain (25), adult male Sprague-Dawley rats were used. This study used a total of 24 rats and resected four different brain regions of these rats; however; it only reported that the rats were sacrificed via decapitation under isoflurane anesthesia, and the brain tissues of the rats were removed within a time interval of less than 90 seconds. No surgical details were provided as to how the different tissues of the brain were resected (25).

In a study investigating isotropic fractionation as a tool for quantitative analysis to investigate central nervous system diseases (16), the use of Sprague-Dawley male rats was

reported again. However, it was observed that no dissection methodologies or surgical methods were specified. Moreover, another study on E18 pregnant Sprague–Dawley female rats also did not explain any surgical methods used for the hippocampal tissue dissection (10).

Spijker et al. reported that, of the specialized dissection instruments, it is necessary to use a forceps, standard razor blade, scalpel handle (3–12 cm), tissue puncher, and metal expeller (18). Also, they emphasized the importance of using a straight forceps with larger surface areas without injuring the brain tissue. Spijker et al. also mention that, due to the risk of injury to the adjacent tissues (18), such as the amygdala and ventral tegmental area (VTA), care should be exercised when a tissue puncher is used.

In the present study, a scalpel handle, number 15 scalpel blades, surgical micro-scissors, surgical forceps, surgical fine scissors, and surgical microdissectors were used as the surgical dissection instruments in dissecting the tissues obtained from the live mammals in order to minimize tissue damage and achieve the excision of the hippocampus in its original anatomical configuration.

Moreover, one study using a diabetes mellitus-induced rat model and another evaluating the effects of cilostazol on hippocampal memory and oxidative stress also did not provide any information as to how the hippocampal tissues were resected (14). In another study that investigated the effects of tramadol administration on hippocampal cell apoptosis, learning, and memory and investigated the neuroprotective effects of crocin in adult rats (1), no surgical procedures were described as to how to dissect hippocampal tissues (1).

The hippocampus is a component of the limbic system and one of the most important areas of the brain due to its role in learning and spatial memory. Thus, it is important to understand how to dissect the hippocampus, upon which the pathophysiology of various neurodegenerative diseases, such as Alzheimer's disease, is investigated.

In this study, the hippocampal tissues of live mammal subjects were dissected from adjacent cranial and cerebral structures. The hippocampal tissues used in the study were excised practically by preserving the original anatomical configuration without injury (7).

In the literature, many molecular studies on the hippocampus have not adequately described how to dissect hippocampal tissues in detail; however; this study described how to practically dissect hippocampal tissues of the brains of Wistar-Albino male rats without damaging their brain tissue and meningeal structures while also providing details of the surgical procedures. Therefore, we believe this paper will contribute to the literature.

## CONCLUSION

In this present study, the practical and accurate methods of dissecting the hippocampal tissue of rats were described. The hippocampus is usually the focus of research aiming to clarify the etiology and physiopathology of many neurodegenerative diseases, primarily including dementia and Alzheimer's disease. The results of this research will pave the way for further scientific studies on the hippocampus as well as help clarify the hippocampal functions in the near future.

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