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Comparative Effects of Posterior Versus Total Corpus Callosotomy in a PTZ-Induced Rat Model of Epilepsy

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Abstract

Corpus callosotomy is a palliative surgical procedure for drug-resistant generalized epilepsy that disrupts interhemispheric propagation of epileptic activity. Although total callosotomy (TC) is conventionally performed, posterior callosotomy (PC) may provide comparable seizure control while preserving prefrontal commissural connectivity. Systematic experimental comparisons between the two techniques remain scarce. This study investigated the differential effects of posterior versus total callosotomy in a pentylenetetrazole (PTZ)-induced rat model of epilepsy.

Eleven adult male Wistar rats (500–700 g; 8–9 months) underwent epileptogenesis via the PTZ kindling protocol (37.5 mg/kg, i.p.; seven alternating sessions over four weeks). Seizures were classified using the revised Racine scale (grades 0–6c). After establishing stable baseline seizure profiles, animals were randomly assigned to PC (n = 5) or TC (n = 6). One week postoperatively, a PTZ rechallenge was conducted. Statistical analysis included paired t-tests and Wilcoxon signed-rank tests for within-group comparisons, and independent t-tests or Mann–Whitney U tests for between-group comparisons ($\alpha = 0.05$).

No statistically significant differences were observed in seizure duration between preoperative baseline and postoperative rechallenge in either surgical group across all Racine grade categories (all $p > 0.05$). Likewise, no significant between-group differences were found in postoperative seizure change (PC vs TC; grade 0: $p = 0.403$; grades 1–4: $p = 0.486$; grades 5a–5c: $p = 0.174$; grades 6a–6c: $p = 0.177$). The TC group demonstrated a consistent directional trend toward shorter high-grade seizure duration (grades 5–6), whereas PC showed a directional tendency toward slightly increased high-grade duration, potentially reflecting residual frontal network synchronization via preserved anterior callosal fibers.

These findings indicate that the acute effects of callosotomy are limited in the PTZ model, likely reflecting the diffuse chemically induced nature of ictal discharge and the brief postoperative evaluation window. Future studies employing chronic focal epilepsy models with longer follow-up and electrophysiological verification are warranted to fully characterize the differential effects of each technique.

Introduction

Corpus callosotomy is an established palliative procedure for patients with pharmacoresistant generalized epilepsy, particularly those whose seizures rely on rapid interhemispheric propagation.[1,2] The corpus callosum, the largest commissural white-matter tract in the mammalian brain, plays a central role in synchronizing bilateral cortical activity; disrupting this pathway can attenuate the spread of generalized tonic, atonic, and convulsive seizures.[3–5]

Total callosotomy (TC) remains the conventional surgical option; however, transection of anterior callosal fibers may produce cognitive and behavioral sequelae, including executive dysfunction and personality changes.[4] These concerns have driven interest in more selective approaches that preserve

frontal connectivity while maintaining antiepileptic efficacy. Posterior callosotomy (PC), which preserves the genu and rostral body, has emerged as a potentially safer alternative.[6,7] Clinical series have reported that PC can achieve seizure attenuation comparable to—or exceeding—TC specifically for drop attacks, while minimizing disruption to prefrontal networks.[6,7] Despite these promising data, systematic experimental comparisons between PC and TC remain scarce.

Animal models provide an essential platform for investigating the functional mechanisms of callosal disconnection. The pentylenetetrazole (PTZ) kindling paradigm is widely used to induce generalized seizures by antagonizing $GABA^A$ receptors, producing bilaterally synchronous cortical discharges. Although the PTZ model primarily reflects chemically induced generalized epileptiform activity rather than focal epileptogenesis, it offers a reproducible, well-validated platform for evaluating interventions targeting interhemispheric propagation.[8–10]

This study aimed to compare the acute behavioral effects of posterior versus total callosotomy on seizure duration and severity in a PTZ kindling rat model. We hypothesized that PC would produce seizure attenuation trends comparable to TC while offering the anatomical advantage of preserving frontal commissural fibers.

Materials and Methods

Animals

Eleven adult male Wistar rats (*Rattus norvegicus*; 500–700 g; 8–9 months old) were used. Animals were housed in groups of 2–3 in polyethylene cages lined with wood shavings, under controlled temperature (22 ± 1°C), relative humidity (50–60%), and a 12 h light/dark cycle (lights on 07:00–19:00), with ad libitum access to commercial chow and filtered water. Three animals died prior to surgery (one during a prolonged high-grade seizure; two from intercurrent illness confirmed on necropsy). All experimental procedures complied with national guidelines for animal research (CONCEA) and were approved by the Institutional Animal Ethics Committee (CEUA, PUC-SP; protocol no. 2023/136). This report adheres to the ARRIVE 2.0 guidelines for reporting animal research.

PTZ Kindling Protocol

Epileptogenesis was induced using the pentylenetetrazole (PTZ) kindling-window (win) protocol.[10] Rats received intraperitoneal injections of PTZ (37.5 mg/kg) on alternating days in two blocks: four injections (sessions 1–4), followed by a 22-day drug-free interval, and then three additional injections (sessions 5–7). Each session consisted of a 20-minute behavioral observation period under continuous video recording (n = 7 sessions per animal). Completion of all seven sessions, irrespective of seizure grade attained, was used as the operational criterion for chronic epileptogenesis.

Seizures were classified according to the revised Racine scale[11] (grades 0–6c): grade 0, whisker tremor; grade 1, behavioral arrest; grade 2, facial clonus; grade 3, head bobbing; grade 4, clonic seizure (upright); grade 5a, clonic seizure (supine); grade 5b, tonic–clonic seizure (prone); grade 5c, tonic seizure; grade 6a, clonic seizure (lateral); grade 6b, tonic–clonic seizure (lateral); grade 6c, wild running/jumping.

For the primary analysis, seizure grades were grouped as follows: grade 0 (no convulsion), grades 1–4 (low-grade), grades 5a–5c (high-grade, lying position), and grades 6a–6c (high-grade, severe). For each animal, preoperative baseline values were calculated as the mean cumulative duration (seconds) of each Racine grade category across the seven preoperative sessions. Sessions prematurely interrupted for humane reasons—when animals showed sustained hypoxia (mucosal cyanosis) during prolonged high-grade seizures—were excluded from statistical analyses.

Stereotaxic Surgery

All surgical procedures were performed under aseptic conditions in a stereotaxic frame (Insight Instruments, Brazil). Animals were anesthetized by intraperitoneal injection of ketamine (100 mg/kg), xylazine (10 mg/kg), midazolam (5 mg/kg), and methadone (3 mg/kg), with anesthesia maintained by inhaled isoflurane (1–2%). Local analgesia was achieved with subcutaneous lidocaine (7 mg/kg); postoperative analgesia was administered with meloxicam.[12,13]

Physiological monitoring included assessment of respiratory rate, heart rate, and reflex responses throughout the procedure; body temperature was maintained with a thermal pad.

Following scalp incision, craniotomy, and careful dural opening, the corpus callosum was exposed. Stereotaxic coordinates were determined using the Paxinos and Watson rat brain atlas[14], with bregma as the zero reference. Animals were randomly assigned—on the day of surgery—to one of two groups:

Posterior Corpus Callosotomy (PC; n **= 5)**: A single midline incision with an ophthalmic microsurgical blade (fixed to the stereotaxic arm) targeted the posterior body, isthmus, and splenium, spanning from coordinates AP − 1.56 mm, ML + 0.5 mm, DV + 3.9 mm to AP − 5.2 mm, ML + 0.5 mm, DV + 3.9 mm. A 0.5-mm lateral offset was applied to avoid injury to the superior sagittal sinus.

Total Corpus Callosotomy (TC; n **= 6)**: Two sequential incisions were performed. The anterior incision spanned from AP + 1.1 mm, ML + 0.5 mm, DV + 5.2 mm to AP − 0.8 mm, ML + 0.5 mm, DV + 5.2 mm; the posterior incision extended from AP − 0.8 mm, ML + 0.5 mm, DV + 3.5 mm to AP − 5.2 mm, ML + 0.5 mm, DV + 3.5 mm (same lateral offset). Coordinates followed the Paxinos and Watson atlas.[14,15]

Hemostasis was maintained with gentle saline irrigation. The scalp was closed with interrupted sutures, and animals were monitored until full recovery from anesthesia. Postoperative pain assessment followed published rodent pain behavior guidelines.[13]

Postoperative PTZ Rechallenge

One week after surgery, all animals received a single PTZ injection (37.5 mg/kg, i.p.) to assess postoperative seizure behavior. Seizures were recorded for 20 minutes and classified using the revised Racine scale by an observer blinded to surgical group allocation.

Outcome Measures

Primary outcomes were: (1) cumulative duration (seconds) of each Racine grade category per session; (2) postoperative change from baseline (Δ = postoperative − mean preoperative duration); and (3) between-group differences in Δ.

Statistical Analysis

All analyses were performed with R statistical software (version 4.3.1; R Core Team, Vienna, Austria). Normality of continuous variables was assessed with the Shapiro–Wilk test. Within-group pre- versus postoperative comparisons were performed using paired t-tests (when normality was satisfied) or Wilcoxon signed-rank tests. Between-group comparisons of postoperative change scores (Δ) were performed using independent-samples t-tests or Mann–Whitney U tests as appropriate. Statistical significance was set at $\alpha = 0.05$. Effect sizes and descriptive statistics (mean, standard deviation, 95% CI, quartiles) are reported for all comparisons.

Results

Baseline Equivalence

Descriptive statistics and between-group comparisons of body weight and surgical duration are presented in Table 1. Body weight tended to be higher in the TC group (mean 660.7 ± 103.2 g) than in the PC group (585.0 ± 55.3 g), but this difference did not reach statistical significance (independent t-test, $t(9) = -1.60$, $p = 0.161$). Surgical duration was comparable between groups (PC: 45.4 ± 27.7 min; TC: 40.8 ± 12.3 min; Wilcoxon U, $p = 0.806$). These findings indicate adequate baseline equivalence between groups.

Table 1

Descriptive statistics for body weight (g) and surgical duration (min) by surgical group. p-values: body weight, independent t-test (p = 0.161); surgical duration, Wilcoxon test (p = 0.806). SD, standard deviation; CI, confidence interval; Q, quartile.

Variable / Group	N	Mean	SD	95% CI (LL)	95% CI (UL)	Min	1st Q	Median	3rd Q	Max
Body weight (g)										
Posterior callosotomy	5	585.0	55.3	536.6	633.4	515	564.0	582.0	597.0	667
Total callosotomy	6	660.7	103.2	578.1	743.2	556	574.8	642.5	757.5	775
Surgical duration (min)										
Posterior callosotomy	5	45.4	27.7	21.2	69.6	25	27.0	40.0	42.0	93
Total callosotomy	4	40.8	12.3	28.7	52.8	25	37.0	41.5	45.3	55

Pre- versus Postoperative Seizure Duration: Posterior Callosotomy Group

Within the PC group, paired comparisons revealed no statistically significant differences between mean preoperative baseline and postoperative seizure duration for any Racine grade category (Table 2). Mean postoperative change was − 2.72 s (SD 7.04, p = 0.44) for grade 0; +2.13 s (SD 6.61, p = 0.51) for grades 1–4; +0.30 s (SD 0.42, p = 0.18) for grades 5a–5c; and + 0.29 s (SD 0.51, p = 0.28) for grades 6a–6c. Notably, for high-grade seizures (grades 5–6), positive mean Δ values indicate a directional trend toward longer postoperative duration; however, wide confidence intervals and the small sample size preclude definitive conclusions.

Table 2

Pre- versus postoperative seizure duration change (Δ = postoperative − mean preoperative, in seconds) for the posterior callosotomy group (n = 5), by Racine grade category. p-values from paired t-tests. SD, standard deviation; CI, confidence interval; Q, quartile.

Racine Grade	N	Mean Δ (s)	SD	95% CI (LL)	95% CI (UL)	Min	1st Q	Median	3rd Q	p-value
Grade 0	5	−2.72	7.04	−8.89	3.45	−13.16	−4.77	−2.84	1.90	0.44
Grades 1–4	5	2.13	6.61	−3.66	7.93	−5.03	−1.90	2.40	2.71	0.51
Grades 5a–5c	5	0.30	0.42	−0.07	0.67	−0.23	0.16	0.22	0.45	0.18
Grades 6a–6c	5	0.29	0.51	−0.16	0.73	−0.17	0.00	0.21	0.24	0.28

Pre- versus Postoperative Seizure Duration: Total Callosotomy Group

Within the TC group, no statistically significant pre- versus postoperative differences were observed for any Racine grade category (Table 3). Mean postoperative changes were minimal and showed no consistent directional trend: grade 0, Δ = +0.45 s (SD 3.90, p = 0.79); grades 1–4, Δ = −0.32 s (SD 3.56, p = 0.84); grades 5a–5c, Δ = −0.05 s (SD 0.34, p = 0.75); grades 6a–6c, Δ = −0.09 s (SD 0.16, p = 0.23). Both increases and decreases were observed across individual animals, with no systematic pattern of seizure attenuation.

Table 3

Pre- versus postoperative seizure duration change (Δ = postoperative − mean preoperative, in seconds) for the total callosotomy group (n = 6), by Racine grade category. p-values from paired t-tests. SD, standard deviation; CI, confidence interval; Q, quartile.

Racine Grade	N	Mean Δ (s)	SD	95% CI (LL)	95% CI (UL)	Min	1st Q	Median	3rd Q	p-value
Grade 0	6	0.45	3.90	−2.67	3.58	−3.68	−2.23	−0.28	2.20	0.79
Grades 1–4	6	−0.32	3.56	−3.16	2.53	−6.32	−1.58	0.14	2.23	0.84
Grades 5a–5c	6	−0.05	0.34	−0.31	0.22	−0.43	−0.24	−0.17	0.21	0.75
Grades 6a–6c	6	−0.09	0.16	−0.22	0.04	−0.33	−0.20	−0.03	0.00	0.23

Between-Group Comparison: Posterior versus Total Callosotomy

Direct comparison of postoperative change scores (Δ) between PC and TC groups revealed no statistically significant differences for any Racine grade category (Table 4): grade 0 (p = 0.403), grades 1–4 (p = 0.486), grades 5a–5c (p = 0.174), and grades 6a–6c (p = 0.177). Despite the absence of statistical significance, a notable directional pattern emerged: the TC group demonstrated consistent reductions in high-grade seizure duration across all categories, whereas the PC group showed slight directional increases (grades 5a–5c: PC mean Δ = +0.30 s vs TC mean Δ = −0.05 s; grades 6a–6c: PC mean Δ = +0.29 s vs TC mean Δ = −0.09 s), These directional differences, while not statistically significant, suggest that TC may exert modest acute modulation of high-grade seizure networks, possibly through more complete disruption of callosal propagation pathways, whereas the slight increases observed in the PC group may reflect residual interhemispheric synchronization preserved via anterior callosal fibers.

Table 4

Between-group comparison of postoperative change scores (Δ, in seconds) by Racine grade category. p-values (*) from independent t-tests (Student). SD, standard deviation; CI, confidence interval; Q, quartile.

Racine Grade / Group	N	Mean Δ (s)	SD	95% CI (LL)	95% CI (UL)	Min	1st Q	Median	3rd Q	p-value
Grade 0										
Posterior	5	−2.72	7.04	−8.89	3.45	−13.16	−4.77	−2.84	1.90	0.403*
Total	6	0.45	3.90	−2.67	3.58	−3.68	−2.23	−0.28	2.20	
Grades 1–4										
Posterior	5	2.13	6.61	−3.66	7.93	−5.03	−1.90	2.40	2.71	0.486*
Total	6	−0.32	3.56	−3.16	2.53	−6.32	−1.58	0.14	2.23	
Grades 5a–5c										
Posterior	5	0.30	0.42	−0.07	0.67	−0.23	0.16	0.22	0.45	0.174*
Total	6	−0.05	0.34	−0.31	0.22	−0.43	−0.24	−0.17	0.21	
Grades 6a–6c										
Posterior	5	0.29	0.51	−0.16	0.73	−0.17	0.00	0.21	0.24	0.177*
Total	6	−0.09	0.16	−0.22	0.04	−0.33	−0.20	−0.03	0.00	

Discussion

This pilot study provides an experimental comparison of PC versus TC in a PTZ rat model of generalized epilepsy. The primary finding is that neither technique produced statistically significant acute reductions

in seizure duration across any behavioral grade, as assessed one week postoperatively. The absence of significance likely reflects three converging factors: the acute timeframe of evaluation, the inherent limitations of the PTZ model for detecting the effects of disconnection surgery, and the small sample size imposed by practical constraints.

Regarding the PTZ model, PTZ primarily generates bilaterally synchronous cortical discharges through $GABA^A$ receptor antagonism, without establishing an established focal epileptogenic zone or relying on persistent network reorganization.[8–10] The effects of callosal section in this model may therefore be masked by the diffuse, chemo-convulsive nature of the ictal discharge, which can be propagated via subcortical pathways independent of callosal connectivity. This contrasts with focal cortical or limbic models, in which callosal fibers play a more direct role in seizure generalization.

The one-week postoperative interval likely captured only the acute phase of callosotomy effects. Clinical and experimental evidence indicates that the functional benefits of callosal disconnection may evolve over weeks to months, as cortical network reorganization, synaptic plasticity, and compensatory mechanisms develop.[3,5] Longer-term studies with chronic epilepsy models and repeated behavioral assessments would be better positioned to detect the full temporal profile of each technique.

Despite the lack of statistical significance, a notable pattern emerged: the TC group showed small negative Δ values (reductions) in high-grade seizure categories, whereas the PC group demonstrated positive Δ values (slight increases relative to baseline) for the same grades. This unexpected directionality in the PC group may reflect post-surgical neurological changes, incomplete sectioning at high-grade grades, or random variability amplified by the small sample size. Alternatively, preservation of the genu and anterior body in PC may allow greater residual synchronization of frontal networks, which is particularly relevant for high-grade generalized motor seizures that rely on frontally-driven motor recruitment.

A potential bias in the present study is the unintended weight imbalance between groups: TC animals were, on average, 75 g heavier than PC animals (660.7 g vs 585.0 g), though this difference was not statistically significant ($p = 0.161$). Given that older, heavier rodents may metabolize PTZ differently and may have distinct baseline seizure thresholds, this distribution could have introduced variability in seizure profiles. Future studies should employ formal stratified randomization by body weight.

The present results should be interpreted in the context of the growing clinical literature on PC. A prospective cohort study in Porto Alegre reported a 95% median reduction in monthly drop attacks and complete control in 80% of patients following PC, compared with only 24% in historical controls treated with anterior callosotomy.[6] A separate four-year follow-up series found that 85% of PC-treated patients achieved ≥ 90% reduction in drop attacks.[7] These clinical data, combined with the mechanistic rationale for preserving prefrontal interhemispheric connectivity, support continued investigation of PC as a viable and potentially superior alternative to TC for specific seizure phenotypes.

The main limitations of this study include the small sample size (n = 11 operated; n = 6 excluded during kindling), the acute postoperative evaluation window, the use of a generalized chemo-convulsive model, the absence of electrophysiological or histological verification of callosal sectioning, and the lack of long-term behavioral follow-up. These limitations are inherent to a pilot study conducted under the practical constraints of a novel surgical protocol in an academic setting. No formal a priori power analysis was performed, as this was an exploratory pilot study; the sample size reflects these practical constraints. Regarding histological verification, post-mortem macroscopic inspection of callosal integrity was performed in all cases; formal histological sectioning should be incorporated in subsequent studies. Nonetheless, the data provide a useful methodological foundation and inform the design of adequately powered follow-up studies with chronic epilepsy models and electrophysiological endpoints.

Conclusion

In a PTZ-induced rat model of generalized epilepsy, neither posterior nor total corpus callosotomy produced statistically significant acute reductions in postoperative seizure duration. These findings highlight the limitations of acute chemo-convulsive seizure models for evaluating disconnection surgery and underscore the need for future studies employing chronic or focal epilepsy paradigms with longer postoperative follow-up and electrophysiological assessment. The present results provide preliminary experimental support for posterior corpus callosotomy as a mechanistically plausible and potentially advantageous alternative to total callosotomy in the modulation of generalized seizure propagation, consistent with the growing body of clinical evidence supporting this selective approach.

Declarations

Competing Interests:

The authors declare no competing interests.

Ethical Approval:
All experimental procedures complied with national guidelines for animal research (CONCEA) and were approved by the Institutional Animal Ethics Committee (CEUA, Faculdade de Ciências Médicas e da Saúde, PUC-SP; protocol no. 2023/136). Housing, surgery, analgesia, and euthanasia procedures adhered to the ARRIVE 2.0 guidelines for reporting animal research.

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Author Contribution

Author contributions: VBC: conceptualization, surgeries, data acquisition, writing, statistical support. LM: conceptualization, surgeries, writing, statistical support. LC, FN, FF, WMGF: data collection and methodology. PHPdA: supervision, review, and project administration.

Data Availability

Data Availability StatementThe datasets generated and analyzed during the current study—including raw behavioral seizure recordings, Racine scale classifications, processed datasets, and statistical analysis scripts generated in R—are available from the corresponding author upon reasonable request. Additional statistical outputs are provided in the Supplementary Material.

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Figures

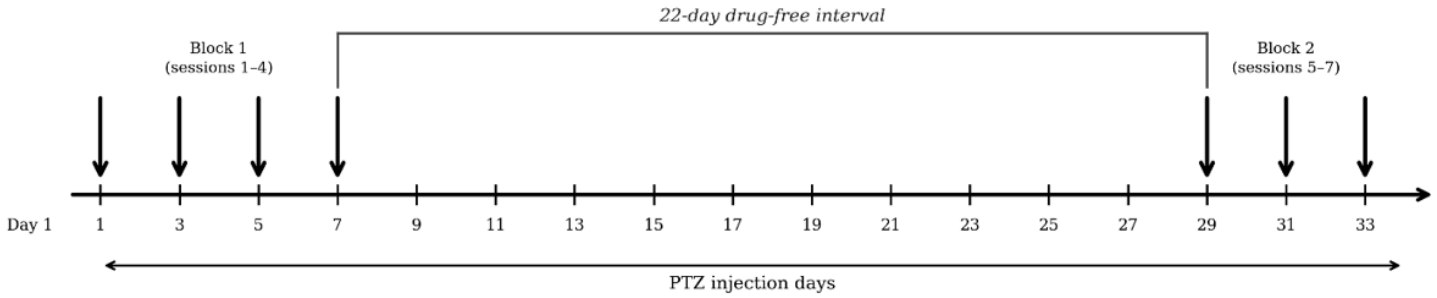


Figure 1

The PTZ win-kindling protocol. Arrows indicate intraperitoneal PTZ injection sessions (37.5 mg/kg). Four injections were administered on alternating days (days 1–7), followed by a 22-day drug-free interval, and then three additional injections (days 29–33). Completion of all seven sessions constituted the criterion for chronic epileptogenesis. Adapted from Shimada and Yamagata (2018).

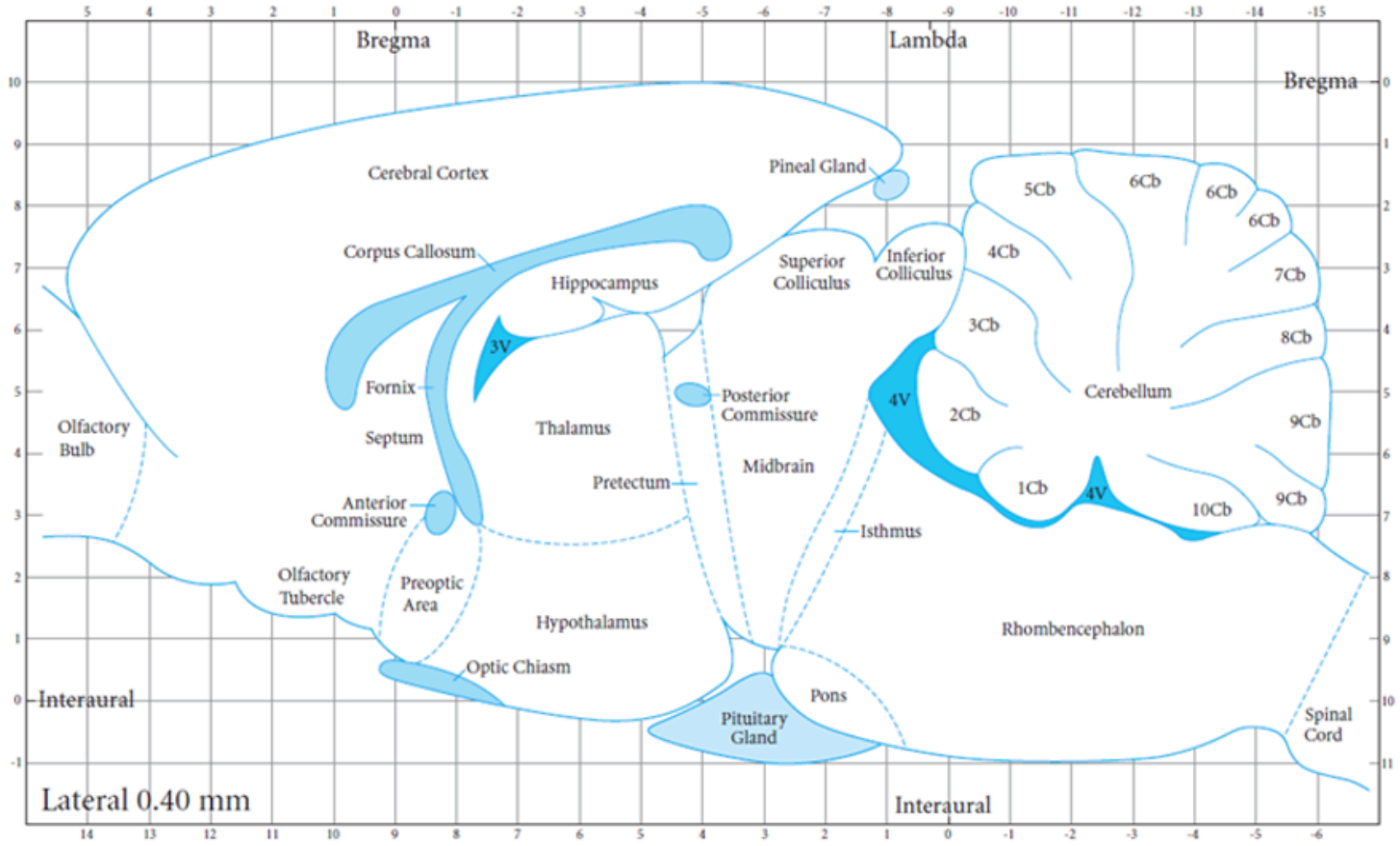


Figure 2

Lateral sagittal section of the rat brain from the Paxinos and Watson atlas (lateral 0.40 mm), illustrating the position of the corpus callosum and key anatomical landmarks used for stereotaxic targeting. Bregma and lambda reference points are indicated. The corpus callosum spans from approximately AP +1.44 mm to AP −5.2 mm relative to bregma. Adapted from Paxinos and Watson (2007); permission to reproduce obtained from the publisher.

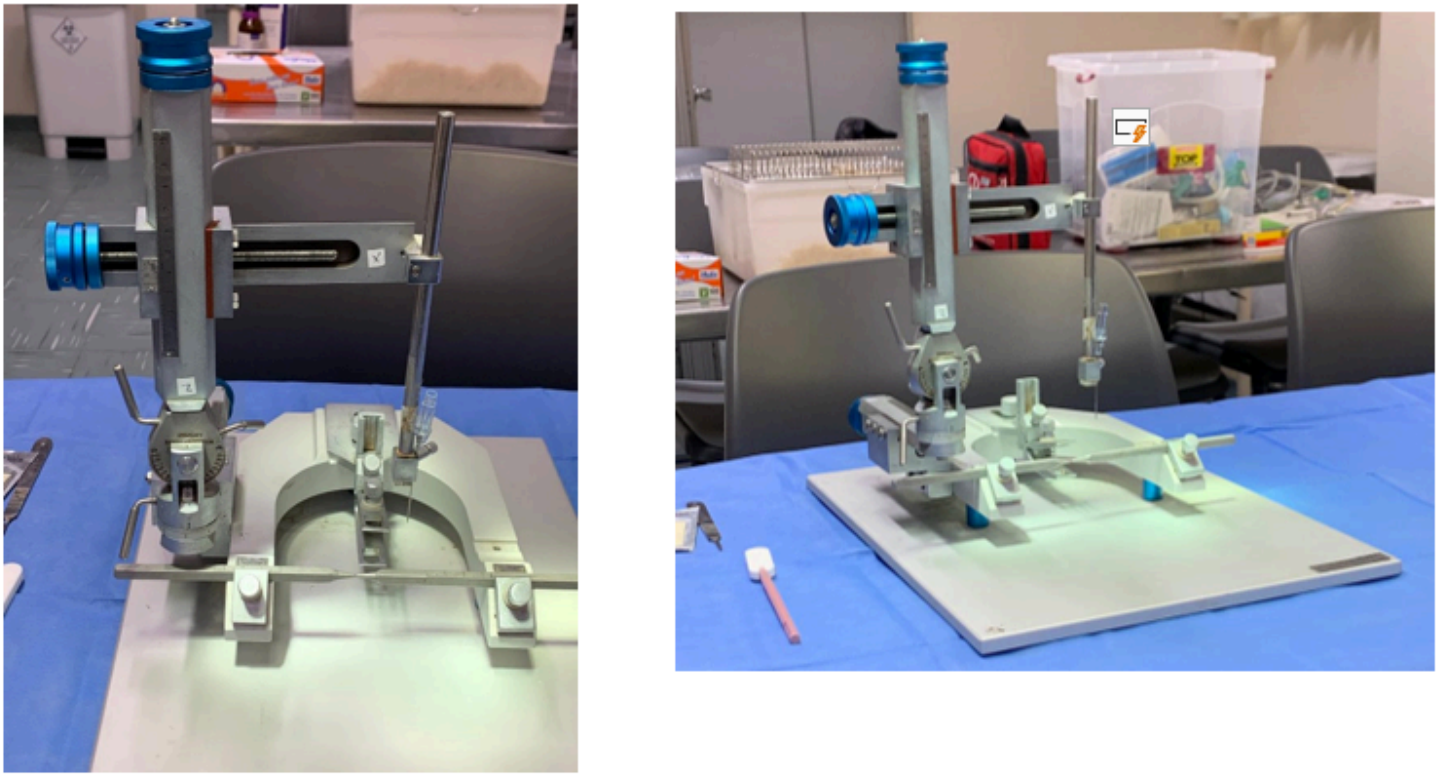


Figure 3

Stereotaxic frame used for all surgical procedures. Left: frontal view showing the rat head-holder and arm for blade placement. Right: lateral view showing the setup on the surgical field. The ophthalmic microsurgical blade was mounted on the stereotaxic arm to perform precise callosal incisions at predetermined coordinates.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- StatisticalReportSupplementary.docx