

Photothrombotic lesion in left medial prefrontal cortex in adult rats: a suitable model for the study of post-stroke depression?

Lesión fototrombótica en la corteza prefrontal medial izquierda en ratas adultas: ¿un modelo para el estudio de la depresión posictus?

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Abstract

Objective: Stroke is a leading cause of death and disability worldwide, often resulting in post-stroke depression (PSD), a common neuropsychiatric consequence affecting survivors' quality of life. This study aimed to determine whether the photothrombotic lesion technique is a suitable model for studying PSD. **Methods:** The photothrombotic lesion method could effectively induce a depression-like phenotype in rats, facilitating the study of PSD without causing significant motor deficits. An ischemic lesion was induced in the left medial prefrontal cortex of 43 male Wistar rats. Depression-like behavior was assessed using the sucrose preference test and the forced swim test (FST) at 14- and 30-days post-stroke (DPS), respectively. The beam walking test (BWT) was used to evaluate motor function at 30 DPS. **Results:** Stroke rats showed reduced sucrose preference at 14 DPS, indicating anhedonia. However, no significant differences were observed in the FST or BWT at 30 days. **Conclusions:** The photothrombotic lesion model showed potential for studying PSD, but the behavioral results were inconclusive. Future research should include depression biomarkers to better assess the model's validity.

Keywords: Photothrombotic lesion. Post-stroke depression. Ischemic stroke.

Resumen

Objetivo: Evaluar si la técnica de lesión fototrombótica es un modelo adecuado para investigar la depresión posictus. **Métodos:** Se propuso que la lesión fototrombótica podría inducir un fenotipo depresivo en ratas sin causar déficits motores significativos. Se indujo una lesión isquémica en la corteza prefrontal medial izquierda de 43 ratas Wistar machos. Se evaluó el comportamiento depresivo con la prueba de preferencia por la sacarosa y la prueba de nado forzado a los 14 y 30 días posictus, respectivamente. La función motora se evaluó con la prueba de caminar sobre la viga a los 30 días. **Resultados:** Las ratas con ictus mostraron una menor preferencia por la sacarosa a los 14 días, lo que sugiere anhedonia. No se encontraron diferencias significativas en la prueba de nado forzado ni en la de caminar sobre la viga a los 30 días. **Conclusiones:** La técnica de lesión fototrombótica tiene potencial para estudiar la depresión posictus, pero los resultados conductuales fueron inconclusos. Se sugiere incluir biomarcadores de depresión en futuros estudios para evaluar mejor el modelo.

Palabras clave: Lesión fototrombótica. Depresión posictus. Ictus isquémico.

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Introduction

Stroke is a clinical syndrome of vascular origin characterized by the sudden onset of focal neurological signs.¹ It represents a significant public health issue globally, as it is one of the leading causes of death and disability.² Stroke survivors often experience a decline in their quality of life due to various sequelae, with depression being the most common neuropsychiatric consequence.³

Post-stroke depression is diagnosed in approximately more than one-third of all stroke survivors,^{4,5} and it is considered the main predictor of poor functional outcome.³ Among the multiple factors underlying post-stroke depression, several studies have explored the relationship between the location of the stroke lesion and the development of this sequelae. Their results suggest that stroke lesions in the left cerebral hemisphere as well as in frontal regions lead to depression.^{3,6} To study post-stroke depression in animal models, the left medial prefrontal cortex has also been suggested as a region of interest.⁷

Even though the middle cerebral artery occlusion model in combination with chronic mild stress is considered a valid pre-clinical model for the study of post-stroke depression,⁸ it has been observed that this model can produce motor deficits that interfere with the evaluation of depression-like behavior.⁷ Taking that into consideration, this study hypothesized that the photothrombotic lesion technique could be a useful model for the study of post-stroke depression. Knowing that it facilitates the behavioral study of ischemic stroke consequences in specific anatomical-functional regions⁹ since it allows inducing focal lesions in the cortical¹⁰ or subcortical¹¹ brain area of interest.

To induce a stroke, this technique involves administering a photosensitive dye (such as Rose Bengal), followed by illuminating the brain through the skull. The dye, activated by the light, generates singlet oxygen and superoxide. This results in endothelial injury and platelet activation and aggregation, ultimately leading to ischemic cell death and the formation of a cortical ischemic lesion.¹¹

Methods

An experimental study using independent groups was conducted between August and December 2023. The animals were treated in accordance with the specifications for the production, care, and use of

laboratory animals (NOM-062-ZOO-1999), and the research protocol approved by the Internal Committee for the Care and Use of Laboratory Animals of the National Institute of Neurology and Neurosurgery Manuel Velasco Suárez (88/18) was followed.

The sample size was determined based on previously published studies employing similar methodologies to ensure methodological consistency and comparability of results.^{12,13} This study adhered to the ARRIVE guidelines to enhance transparency and reproducibility in animal research. All efforts were made to minimize the number of animals used while maintaining statistical rigor and ensuring reliable outcomes. In terms of study design, a negative control was implemented by comparing sham surgery with stroke surgery, enabling the identification of differences attributable to the photothrombotic lesion. To maintain data integrity, rats that developed otitis post-surgery were excluded based on predefined exclusion criteria. Randomization was conducted using a computer-based random order generator to assign each rat to either the sham or stroke group.

A timeline of the experimental design is provided in figure 1, summarizing the key steps: habituation, baseline, and evaluation phases for the forced swim test (FST), as well as the timing for the sucrose preference test (SPT) and beam walking test (BWT). This figure aims to facilitate understanding of the protocol and clarify the methodological approach.

Forty-three male Wistar rats (weighing 220-390 g) were used in this study. The rats were randomly divided into two groups: the sham group ($n = 20$) and the stroke group ($n = 23$). They were primarily pair-housed in standard acrylic cages under a 12-h light-dark cycle, with *ad libitum* access to food and water. However, during the SPT, they were temporarily housed individually.

Rats were anesthetized with a combination of ketamine (90 mg/kg) and xylazine (8.5 mg/kg) prior to stereotaxic surgery. A trephine was made on the skull to target the left medial prefrontal cortex at the following coordinates in reference to the bregma:¹⁴ AP = +3.2, LM = +1.6. Subsequently, a 0.5 mL/kg dosage of a previously prepared 15 mg/mL Rose Bengal and saline solution was administered intravenously to the stroke group. A 0.5 mL/kg dose of saline solution was used for the sham group. The administration was allowed to diffuse into the bloodstream for 5 min.^{15,16} A fiber-optic bundle of a cold light source (KL 1500 LCD, Schott, Germany) with a 3 mm aperture was placed over the trephine for 20 min (Fig. 2). Post-surgery, a hemostatic sponge was placed at the

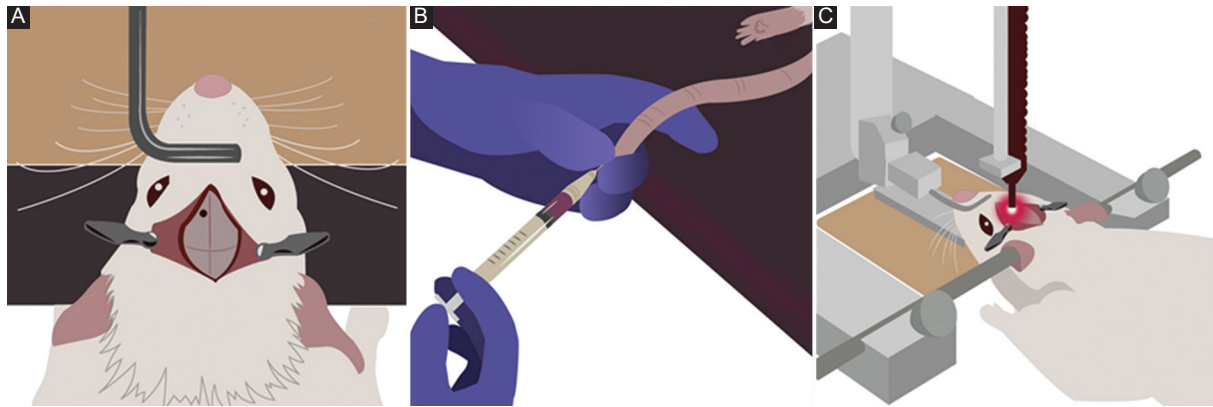


Figure 1. Photothrombotic lesion procedure. **A:** rats were anesthetized with a combination of ketamine (90 mg/kg) and xylazine (8.5 mg/kg) prior to stereotaxic surgery. A trephine was made on the skull to target the left medial prefrontal cortex. **B:** rose Bengal (or saline solution for the sham group) was administered intravenously. **C:** a cold light source was placed over the trephine for 20 min.

trephine site, and the wound was sutured. The rats were given a subcutaneous dose of tramadol and saline solution for pain management. The animals' temperature was regulated throughout all the procedures using a thermal pad.

Depression-like behavior was evaluated at 14 days post-stroke (14 DPS) using a SPT protocol adapted from the one established by De la Tremblaye et al.,¹⁷ and at 30 DPS (30 DPS) using the FST protocol described by Yankelevitch-Yahav et al.¹⁸

Given the high prevalence of motor deficits after an ischemic stroke,¹⁹ the BWT was conducted to minimize potential biases while evaluating FST performance. Rats were trained to cross the beam for 5 days prior to establishing the baseline. Motor performance was assessed at 30 DPS using the scores described by Ramos-Languren et al. (Fig. 2).²⁰

IBM Statistical Package for the Social Sciences Statistics ver. 29.0 (IBM Co., Armonk, NY, USA) was used for statistical analysis. The results obtained in the behavioral tests were analyzed with the Mann-Whitney U test and expressed as the mean $\pm$ standard error of the mean. In all cases, the level of significance was set at $p < 0.05$.

Results

Of the 45 Wistar rats initially enrolled in the study, two died prior to group allocation due to unrelated complications, leaving a final sample of 43 animals divided into two groups: 20 sham and 23 stroke. Over the course of the experimental protocol, an additional five rats (two from the sham group and three from the stroke group) were lost due to post-surgical

complications or humane euthanasia criteria. Consequently, the final sample size for statistical analyses comprised 18 stroke and 17 sham rats, reflecting survival rates of 78.26% and 85%, respectively.

Mortality and survival analysis

The mortality rates observed in both groups deviated from previous studies using similar methodologies, where 100% survival was reported. The increased mortality in the sham group (15%) and the stroke group (21.7%) highlights potential complications related to surgical stress or individual variability rather than the lesion itself (Fig. 3).

Behavioral tests

SPT

At 14 days post-surgery, stroke rats exhibited a significant reduction in sucrose consumption compared to sham rats ($U = 90$, $p = 0.023$), indicating anhedonia-like behavior. Stroke rats consumed an average of $67.3 \pm 5.1\%$ sucrose solution, whereas sham rats consumed $81.4 \pm 3.8\%$ (Fig. 4). This result aligns with previous findings suggesting an early onset of depression-like behaviors in photothrombotic models.

FST

Immobility times were measured at 30 DPS to evaluate depression-like behavior. However, no significant differences were observed between the groups ($U = 107$, $p = 0.289$). Stroke rats displayed an average

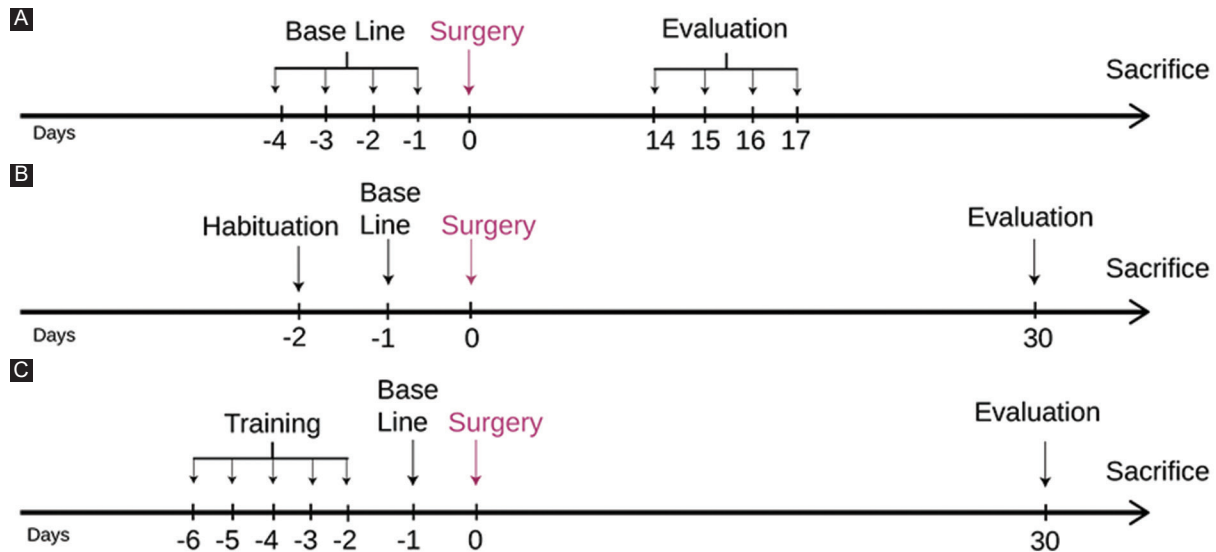


Figure 2. Experimental timeline: (A) Arrows indicate days on which the sucrose preference test, (B) forced swim test, (C) and beam walking test were conducted.

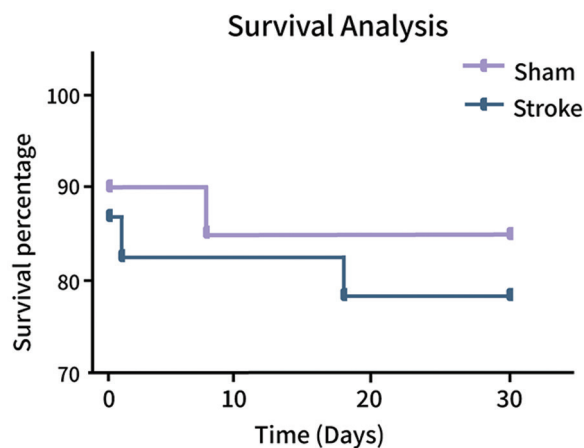


Figure 3. Percentage of survival along the experimental procedure. Comparison between sham and stroke groups.

immobility duration of 168.7 ± 12.5 s, compared to 160.3 ± 10.2 s in sham rats. This lack of significance suggests that the depressive-like phenotype observed in the SPT may not be robustly reflected in this behavioral test, potentially due to methodological factors or the timing of evaluation (Fig. 5).

BWT

To rule out motor impairments as a confounding factor for the FST, motor performance was assessed

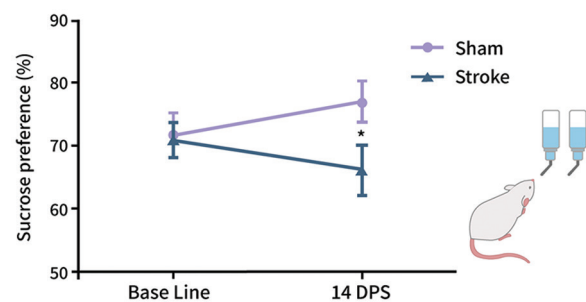


Figure 4. Sucrose preference test analysis. It was observed that there was a decrease in sucrose preference in photothrombotic lesioned rats, suggesting anhedonia. Mann-Whitney's U (* $p = 0.023$).

at 30 days post-surgery. No significant differences in beam traversal times were found between groups ($U = 130$, $p = 0.825$). Stroke rats required an average of 7.3 ± 0.6 s to traverse the beam, whereas sham rats took 7.1 ± 0.5 s (Fig. 6). This result supports the hypothesis that the photothrombotic lesion did not induce substantial motor deficits, allowing a more targeted assessment of depression-like behaviors.

Discussion

Regarding the need to develop new pre-clinical models for post-stroke depression research, this study tested the usefulness of the photothrombotic lesion technique. To evaluate whether an ischemic stroke

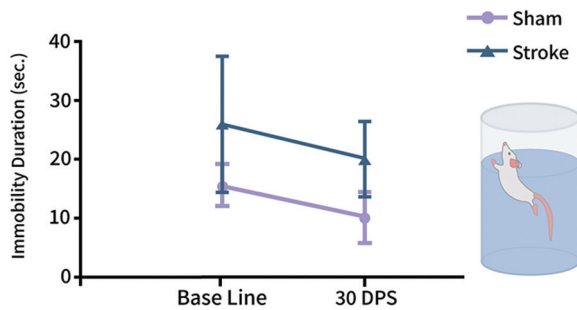


Figure 5. Forced swim test. No significant differences were observed in immobility duration, suggesting no changes in motor performance.

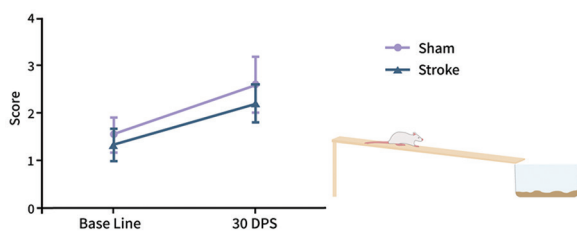


Figure 6. Beam walking test. No significant differences were found in beam walking test scores, showing the absence of motor effects of the photothrombotic lesion.

induced by photothrombosis promoted the development of a depression-like phenotype in rats, the SPT and the FST were used. In addition, the BWT was employed to rule out any potential biases in the FST results due to post-stroke motor alterations.

Although one of the major drawbacks of the photothrombotic technique is the limited or absent ischemic penumbra, this model was selected for its significant advantages, such as the ability to target a specific cortical brain region for the ischemic lesion, its simplicity of execution, minimally invasive nature, and low mortality rate.²¹

Regarding the survival rate, while previous studies have reported a 100% survival rate for the animals using this technique,²² our study observed a lower survival rate (78.26%) in stroke-induced rats. However, it is important to highlight that the strokes were induced in different brain regions, which may account for the variation. Therefore, in this study, the higher mortality observed in the sham group (15%) compared to previous reports may be attributed to surgical stress or individual variability. Importantly, all post-surgical care, housing conditions, and testing protocols were identical for both groups, reducing the likelihood of methodological bias.

As for the behavioral assessment, the differences found in the SPT between groups 2 weeks after surgery are consistent with previously reported findings.^{17,23} Conversely, the results obtained in the FST differ from previous studies, which showed an increased immobility time between weeks 3 and 5 post-stroke.^{23,24}

Post-stroke depression is not only the most common neuropsychiatric sequel but also a major factor in poor functional and cognitive recovery in survivors.³ Therefore, it is crucial to conduct research that enhances our understanding of this condition to reduce the sequelae and complications for the patients²⁵ and develop new and more specific treatments.²⁶ Although still under development,²⁷ pre-clinical models play a significant role in achieving these goals.^{4,25,28}

Rodents are often the primary choice for animal models in cerebrovascular disease research;^{10,23} however, it is crucial to recognize that they are not merely miniature versions of humans.²⁹ This distinction is significant because stroke lesions in humans are confined to the white matter, whereas rodent studies on white matter are limited due to its reduced volume.³⁰ Moreover, within the study of depression, some subjective and complex aspects experienced by humans, such as low self-esteem or suicidal ideation, cannot be modeled in rodents.²⁹

Regarding the behavioral assessment, it is important to note that although the SPT is considered the best method to evaluate anhedonia in rodents, its lack of standardized equipment makes it difficult to control water loss, potentially affecting experimental results.³¹ Conversely, repeated exposure to the FST can lead to inaccurate results.²⁹ In this project, animals underwent the test on three occasions to adhere to the established protocol, which may explain the lack of significant differences between groups.

Although the photothrombotic lesion technique allows for the induction of a focal stroke, no technique was employed to evaluate the volume of the infarction. Given that the peri-infarct cortex is connected to other brain regions,¹¹ Nissl staining could be a valuable tool for enhancing future studies. It is also essential to consider that while many studies associate left hemisphere lesions with post-stroke depression,³ there are also reports linking right hemisphere lesions to PSD.^{6,7} Therefore, it may be important to induce lesions in the right hemisphere and compare the resulting behavioral outcomes with those observed in this study. Furthermore, future research should evaluate the

similarities and differences between male and female rodents, as well as among young and old rodents and different strains.²⁸ This approach will help determine whether these factors influence the characteristics of infarction and/or the development of post-stroke depression. Since motor deficits in the early days post-lesion were not assessed in this study, future research could incorporate longitudinal motor evaluations to provide a more comprehensive understanding of functional recovery.

Regarding the behavioral assessment, it would be beneficial to evaluate depression-like behavior using the SPT at multiple time points to ascertain its onset and duration. Previous studies have demonstrated a decreased sucrose preference 1 week³²⁻³⁴ and 28 days^{34,35} after implementing the post-stroke depression model.

Given the inconclusive results from behavioral tests, it is recommended that future studies evaluate additional parameters associated with depression-like behavior following a stroke. These include body weight,^{17,35} food intake,¹⁷ and various depression biomarkers such as inflammatory cytokines,³⁶ corticosterone levels,¹⁷ hypothalamic-pituitary-adrenal axis hormones,³⁷ and brain-derived neurotrophic factor levels.^{27,33,35,36,38}

Several limitations of this study must be acknowledged. The higher mortality observed in the sham group raises concerns about potential surgical stress or individual variability. In addition, the lack of early motor assessments limits the understanding of initial recovery patterns. Although the photothrombotic lesion technique offers precise targeting, it presents challenges such as a narrow ischemic penumbra and variability in infarct size, which may affect its translational value. Another limitation is the lack of a formal sample size calculation based on Festing's criteria. While the sample size was selected based on previously published studies with similar methodologies to ensure comparability and methodological consistency, future research should incorporate a priori power analyses to optimize the number of animals used while maintaining statistical robustness and ethical considerations. Standard behavioral tests, such as the SPT and FST, may not fully capture the complexity of depression-like behavior, highlighting the need for complementary biochemical and histological evaluations. Addressing these limitations in future research will enhance the utility and validity of this pre-clinical model.

Conclusions

The high incidence of post-stroke depression highlights the need to conduct research aimed at mitigating its impact on survivors' quality of life. Although pre-clinical studies are essential for this purpose, the limitations of current models make it crucial to explore new alternatives. This study proposed that the photothrombotic lesion technique could be a promising method for investigating post-stroke depression due to its various advantages. However, because the results from behavioral tests were not sufficiently conclusive, it is recommended that future research incorporate additional complementary techniques, such as depression biomarkers, to better determine the presence of a depression-like behavioral phenotype following a photothrombotic stroke.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of human subjects and animals. The authors declare that the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the World Medical Association and the Declaration of Helsinki. The procedures were authorized by the Institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. This study does not involve personal patient data, medical records, or biological samples, and does not require ethical approval. SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

References

1. Arauz A, Ruiz-Franco A. Enfermedad vascular cerebral. *Rev Facult Med*. 2012;55:11-21.
2. GBD 2019 Stroke Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global burden of disease study 2019. *Lancet Neurol*. 2021;20:795-820.
3. Espárrago-Llorca G, Castilla-Guerra L, Fernández-Moreno M, Ruiz-Doblado S, Jiménez-Hernández M. Depresión post ictus: una actualización. *Neurología*. 2012;30:23-31.
4. Kronenberg G, Gertz K, Heinz A, Endres M. Of mice and men: modelling post-stroke depression experimentally. *Br J Pharmacol*. 2014;171:4673-89.
5. Wei N, Yong W, Li X, Zhou Y, Deng M, Zhu H, et al. Post-stroke depression and lesion location: a systematic review. *J Neurol*. 2015;262:81-90.
6. Santos M, Kövari E, Gold G, Bozikas V, Hof P, Bouras C, et al. The neuroanatomical model of post-stroke depression: towards a change of focus? *J Neurol Sci*. 2009;283:158-62.
7. Vahid-Ansari F, Lagace D, Albert P. Persistent post-stroke depression in mice following unilateral medial prefrontal cortical stroke. *Transl Psychiatry*. 2016;6:1-11.
8. Wang SH, Zhang ZJ, Guo YJ, Zhou H, Teng GJ, Chen BA. Anhedonia and activity deficits in rats: impact of post-stroke depression. *J Psychopharmacol*. 2009;23:295-304.
9. Watson B, Dietrich W, Busto R, Wachtel M, Ginsberg M. Induction of reproducible brain infarction by photochemically initiated thrombosis. *Ann Neurol*. 1985;17:497-504.
10. Prieto-Arribas R, Moreno-Gutierrez A, Simal-Hernández P, Pascual-Garvi J, Matías-Guio J, Roda J, et al. Modelos experimentales de isquemia cerebral. *Rev Neurol*. 2008;47:414-26.
11. Sommer C. Ischemic stroke: experimental models and reality. *Acta Neuropathol*. 2017;133:245-61.
12. Festing M. On determining sample size in experiments involving laboratory animals. *Lab Anim*. 2018;52:341-50.
13. Harris J, Yeh H, Choi I, Lee P, Berman N, Swerdlow R, et al. Altered neurochemical profile after traumatic brain injury: H-1-MRS biomarkers of pathological mechanisms. *J Cerebral Blood Flow Metab*. 2012;32:2122-34.
14. Paxinos G, Watson C. *The Rat Brain in Stereotaxic Coordinates*. 7th ed. Amsterdam: Elsevier; 2013.
15. Hong M, Kim M, Kim T, Park S, Kim M, Park Y, et al. Treadmill exercise improves motor function and short-term memory by enhancing synaptic plasticity and neurogenesis in photothrombotic stroke mice. *Int Neurol*. 2020;24:S28-38.
16. Weber R, Grönnert L, Mulders G, Maurer M, Tackenberg C, Schwab M, et al. Characterization of the blood brain barrier disruption in the photothrombotic stroke model. *Front Physiol*. 2020;11:1-10.
17. De la Tremblay PB, Linares NN, Schock S, Plamondon H. Activation of CRHR1 receptors regulates social and depressive-like behaviors and expression of BDNF and TrkB in mesocorticolimbic regions following global cerebral ischemia. *Exp Neurol*. 2016;284:84-97.
18. Yankelevitch-Yahav R, Franko M, Huly A, Doron R. The forced swim test as a model of depressive-like behavior. *J Vis Exp*. 2015;97:52587.
19. Fluri F, Malzahn U, Homola GA, Schuhmann MK, Kleinschnitz C, Volkmann J. Stimulation of the mesencephalic locomotor region for gait recovery after stroke. *Ann Neurol*. 2017;82:828-40.
20. Ramos-Languren LE, Avila-Luna A, García-Díaz G, Rodríguez-Labrada R, Vázquez-Mojena Y, Parra-Cid C, et al. Glutamate, glutamine, GABA and oxidative products in the pons following cortical injury and their role in motor functional recovery. *Neurochem Res*. 2021;46:3179-89.
21. Uzdensky A. Photothrombotic stroke as a model of ischemic stroke. *Transl Stroke Res*. 2017;9:437-51.
22. Labat-Gest V, Tomasi S. Photothrombotic ischemia: a minimally invasive and reproducible photochemical cortical lesion model for mouse stroke studies. *J Vis Exp*. 2013;76:1-6.
23. Balkaya MG, Trueman RC, Boltze J, Corbett D, Jolkonen J. Behavioral outcome measures to improve experimental stroke research. *Behav Brain Res*. 2018;352:161-71.
24. Tian H, Li X, Tang Q, Zhang W, Li Q, Sun X, et al. Yi-nao-jie-yu prescription exerts a positive effect on neurogenesis by regulating notch signals in the hippocampus of post-stroke depression rats. *Front Psychiatry*. 2018;9:483.
25. Wu C, Zhang J, Chen Y. Study on the behavioral changes of a post-stroke depression rat model. *Exp Ther Med*. 2015;10:159-63.
26. Robinson RG, Jorge RE. Post-stroke depression: a review. *Am J Psychiatry*. 2016;173(3):221-31.
27. Boyko M, Kutz R, Gruenbaum BF, Cohen H, Kozlovsky N, Gruenbaum SE, et al. The influence of aging on poststroke depression using a rat model via middle cerebral artery occlusion. *Cogn Affect Behav Neurosci*. 2013;13:847-59.
28. Schaar KL, Brennen MM, Savitz SI. Functional assessments in the rodent stroke model. *Exp Transl Stroke Med*. 2010;2:13.
29. Cryan JF, Holmes A. The ascent of mouse: advances in modelling human depression and anxiety. *Nat Rev Drug Discov*. 2005;4:775-90.
30. Kolb B, Teskey G, Gibb R. Factors influencing cerebral plasticity in the normal and injured brain. *Front Hum Neurosci*. 2010;204:1-10.
31. Shi X, Bai H, Wang J, Wang J, Huang L, He M, et al. Behavioral assessment of sensory, motor, emotion, and cognition in rodent models of intracerebral hemorrhage. *Front Neurol*. 2021;12:1-17.
32. Shao B, Zhou YL, Wang H, Lin YS. The role of calcitonin gene-related peptide in post-stroke depression in chronic mild stress-treated ischemic rats. *Physiol Behav*. 2015;139:224-30.
33. Su Q, Cheng Y, Jin K, Cheng J, Lin Y, Lin Z, et al. Estrogen therapy increases BDNF expression and improves post-stroke depression in ovariectomy-treated rats. *Exp Ther Med*. 2016;12:1843-8.
34. Pei CD, Zhang LL, Fei PG, Gu SN, Li WQ, Mu JL, et al. Upregulation of aryl hydrocarbon receptor nuclear translocator 2 in the hippocampus of post-stroke depression rats. *Biomed Rep*. 2019;11:51-8.
35. Zhang Z, Wu L, Song J, Li W. Correlations between cognitive impairment and brain-derived neurotrophic factor expression in the hippocampus of post-stroke depression rats. *Mol Med Rep*. 2012;6:889-93.
36. Carboni L. Peripheral biomarkers in animal models of major depressive disorder. *Dis Markers*. 2013;35:33-41.
37. Stepanichev M, Dygalo N, Grigoryan G, Shishkina G, Gulyaeva N. Rodent models of depression: neurotrophic and neuroinflammatory biomarkers. *BioMed Res Int*. 2014;932757:1-20.
38. Madinier A, Bertrand N, Rodier M, Quiríé A, Mossiat C, Prigent-Tessier A, et al. Ipsilateral versus contralateral spontaneous post-stroke neuroplastic changes: involvement of BDNF? *Neuroscience*. 2013;231:169-81.