








## RESEARCH ARTICLE

# Behaviour test in chronic brain ischemia rats: A bibliometric approach [version 1; peer review: 1 approved with reservations]

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## Abstract

**Background:** Stroke causes severe disability and mortality. Despite the fact that the pathology of acute stroke is well understood, publication on chronic stroke is still limited. Because scarring of glia limits the recovery area of acute stroke and reorganization capacity is reduced, discovering new treatments for chronic stroke poses substantial obstacles. In stroke research, rodent models are commonly utilized, and behavior testing is a crucial tool. To measure stroke outcomes and translating rodent findings to therapeutic trials, selecting relevant behavioral tests that fit the study purpose is critical. Here, we aimed to look at the last decade's publications highlighting behaviour tests on chronic stroke rats. Hopefully, we were able to give more information about the behaviour tests to facilitate the researchers' choice of appropriate test.

**Methods:** By using a bibliometric analysis, we hope to systematically discuss rodent behavior tests in chronic stroke research. Documents were extracted from the Scopus database in April 2022. Excel and VOSviewer 1.6.18 were used to conduct statistical and graphical analysis.

**Results:** Research on "behavioral test in chronic stroke rats" has progressed quickly, although the researchers have yet to collaborate with each other. H. Millani was an active researcher and author who connected numerous researchers, according to documents and citation analysis. "Animals", "brain ischemia", "man", "publication", and "animal experiment" were all common keywords. The majority of the articles were from the United States and China. The Morris Water Maze test and the cylinder test were the most commonly used behavior tests.

## Open Peer Review

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1. **Robert Sinurat** , Medical Faculty of Universitas Kristen, Jakarta, Indonesia

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**Conclusions** Clinical applications and therapeutic effectiveness against stroke could be improved with more collaboration amongst authors. When using a behavior test, researchers need to think about which neurological deficiency is being addressed and whether the test covers long-term evaluation.

### Keywords

Bibliometric analysis, Scopus, Stroke, chronic, behaviour test, rats



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## Introduction

Stroke causes severe disability and mortality. Moreover, stroke is considered the number one cause of disability and independency (Katan and Luft, 2018). Acute and subacute strokes have been targeted with medicines provided within 48 hours after onset, thanks to recent breakthroughs in stroke treatment. Thrombus breakdown using a tissue-type plasminogen activator (*e.g.*, alteplase) within 4.5 hours of stroke onset or mechanical thrombectomy within six hours are two current treatment options. Both of these treatments, however, are only appropriate for a tiny percentage of patients, and not all of them work well (Wardlaw *et al.*, 2014).

Despite the fact that the mechanism of acute stroke is widely recognized, publication on chronic stroke is still limited. Because glial scars mark the location of brain injury and the capacity for reorganization may be substantially reduced, finding new treatments for chronic stroke poses significant challenges. In recent investigations, a paracrine effect has been proposed as a mechanism for improving recovery, implying that when surviving, neurons surrounding the infarction are adequately activated, and have the ability to change function in ways that improve brain function. Replacement of destroyed brain tissue and restoration of missing connections may be necessary for greater improvement and maybe complete recovery. This would necessitate the replacement of neuron, endothelial cells, astrocytes, and supportive cells. Some of these challenges are currently being investigated in animal models, with the expectation of progressing rapidly toward the objective of finding viable treatments for chronic stroke patients (Wechsler *et al.*, 2018).

In stroke research, rodent models are commonly utilized and behavior testing is a crucial tool (Saré *et al.*, 2021). Rodents have various advantages over other species, including quick reproduction, minimal maintenance costs, and more ethical acceptance (Ruan and Yao, 2020). However, rats and humans have quite different neurological behaviors and higher brain processes. Rodents, for example, may only perform tasks that imitate their natural responses, whereas human patients can have their neurological processes tested by answering questions and following directions. This makes determining the outcome of a stroke, particularly in terms of cognitive function and consciousness, problematic.

In measuring stroke outcome and translating rodent findings to therapeutic trials, selecting relevant behavioral tests that fit the study purpose is critical. Although 30-minute temporary middle cerebral artery occlusion (30-min tMCAO) generates consistent infarct in subcortical areas of rats' brains, the behavioral tests such as the rotarod test, adhesive-removal test, or narrow beam test make it difficult to assess the subsequent neurological loss. The development of a quantitative evaluation method would aid in the development of a unique cerebral infarction therapy approach (Wakayama *et al.*, 2007).

Here, we'll look at some of the recent publications that have focused on behavior testing in chronic stroke patients. Hopefully, we were able to provide additional information regarding the behavior test, allowing researchers to select the best test for their needs. A bibliometric analysis was used to examine global collaboration patterns, patterns in institutions and countries, as well as to determine trends in studies.

## Methods

### Data collection

The Scopus database was searched using the terms "behavior test" and "rats", as follows: (ALL ("behaviour test") OR TITLE-ABS-KEY ("behavioural outcomes") AND TITLE-ABS-KEY (rats) OR TITLE-ABS-KEY (rodents) AND TITLE-ABS-KEY ("brain ischemia") AND TITLE-ABS-KEY (chronic) OR TITLE-ABS-KEY ("chronic ischemic stroke")). A total of eighteen papers were collected and analyzed bibliometrically.

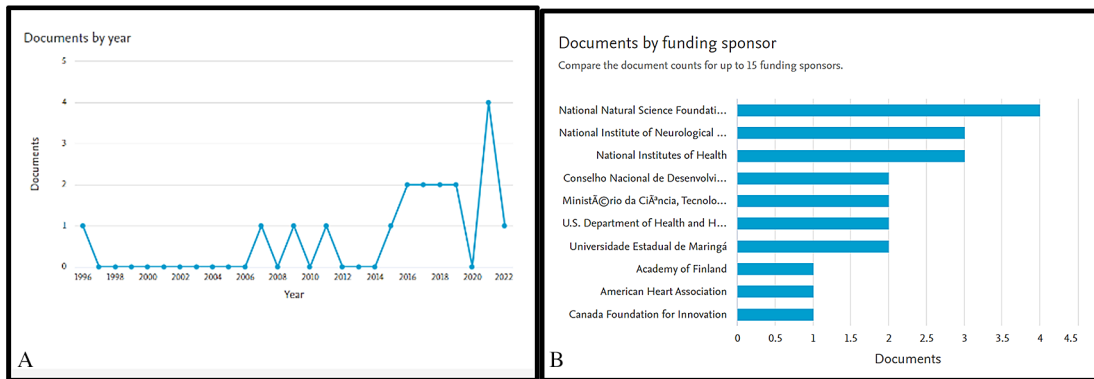
### Data analysis

To begin, Scopus search and retrieval results were used to examine the general information of the literature, which included the publication year, country of origin, organization, journal, and author. Following that, bibliometric and visual analysis were performed using the VOS viewer 1.6.18 software open source (<https://www.vosviewer.com>), including primary author, keyword, collaboration link, citation analysis, and co-citation analysis.

## Results

### Articles published

From 1996 to 2022, the Scopus database contained 18 entries relating to "behaviour test in chronic stroke rats". Three articles were excluded (Macaca article, a Chinese article we were unable to translate, mice-related articles). **Figure 1A** illustrates the annual publication trend. In 1996, there was only one publication, which then gradually increased year after year until it peaked in 2021 (four publications). The study "behaviour test in chronic stroke rats" received funding from 23 different sources. The National Natural Science Foundation of China (frequency: 4), the National Institute of Neurological Disorders and Stroke (frequency: 3), and the National Institutes of Health (frequency: 2) were the top three primary funding sources (frequency: 3) (**Figure 1B**).



**Figure 1.** A. Yearly published articles in the Scopus database between 1996 and 2022. The peak year for publication was 2021. B. The top ten funding sources.

**Table 1.** The publication authors’ country and institutions. The United States, China, and Brazil were the top three countries.

Rank	Organization	Country	Papers	Citations	Connection with others author
1	Department of Neurology, University of Texas - Houston, medical school, Houston, TX, United States	United States	2	62	1
2	Department of Pharmacology and therapeutics, State University of Maringá, av. Colombo, 5790, Maringá, Paraná, cep 87020-900, Brazil	Brazil	1	44	1
3	Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Maastricht University, Universiteitsingel 50, Maastricht, 6229 er, The Netherlands	Netherlands	1	44	1
4	Department of Clinical Neurosciences, University of Edinburgh, Edinburgh, United Kingdom	United Kingdom	1	31	2
5	Department of Neurology, Xijing Hospital, Fourth Military Medical University, no. 17 Changle West Road, Xi’an, 710032, China	China	1	31	2
6	Department of Neurosurgery, Institute of Mini-invasive Neurosurgery and Translational Medicine, Xi’an Central Hospital, no. 185 Houzai Gate of North Street, Xi’an, 710003, China	China	1	31	2
7	Department of Neurosurgery, Xijing Hospital, Fourth Military Medical University, no. 17 Changle West road, Xi’an, 710032, China	China	1	31	2
8	Florey Institute of Neuroscience and Mental Health, Melbourne Brain Centre, Austin campus, Heidelberg, Australia	Australia	1	31	2
9	University of Tasmania, School of Medicine, Faculty of Health, Hobart, Australia	Australia	1	31	2
10	Department of Neurological Surgery, Neuroscience program, University of Miami Miller School of Medicine, Miami, FL, United States	United States	1	29	3

### Origin of country and organization

In the 18 papers on “behaviour test in chronic stroke rats” that have been published so far, 12 nations and 49 organizations were identified. The top three countries/regions were China, the USA, and Brazil (Table 1 and Figure 2). With 99 citations, the USA led the pack, followed by Brazil with 63 and China with 52. With two papers and 62 citations, the Department of Neurology at the University of Texas at Houston Medical School in Houston, Texas, was the most productive (Table 1). There were six organizations that collaborated with each other during the publication and other organizations published by their own resource (Figure 3).

### Published journals

The term “behavior test in chronic brain stroke of rats” was found in 14 journals. Table 2 shows that the top three journals published the same article multiple times. *Behavioural Brain Research* and *Brain Research* were the most popular journals. The JCR partitioning in all of the journals was higher (Q1 and Q2).

### Authors of publications

In “behavior test in chronic stroke rats,” 96 authors contributed to 18 papers. Milani H placed first (63 citations) with two papers, followed by J Aronowski, J. C Grotta, and R Strong (Figure 4A). The study “behaviour test in chronic stroke rats” had Milani H as the lead author. Figure 4B illustrates that collaboration amongst active authors in this subject is still lacking.

### Citations

The circle size denotes the number of occurrences of phrases in the subnetwork of keywords and graph, as shown in Figure 5. The top ten keywords were “animals”, “brain ischemia”, “male”, “article”, “animal experiment”, “animal model”, “rats”, “controlled study”, “animal behaviour”, “animal tissue” (Figure 5A). In the overlaid visualization (Figure 5B), the keywords “animal behaviour” were related to “middle cerebral artery occlusion”, “brain ischemia”,

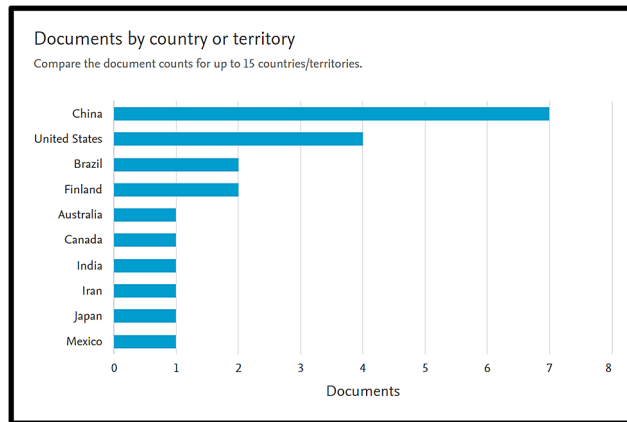


Figure 2. The top 10 countries of the author of publications.

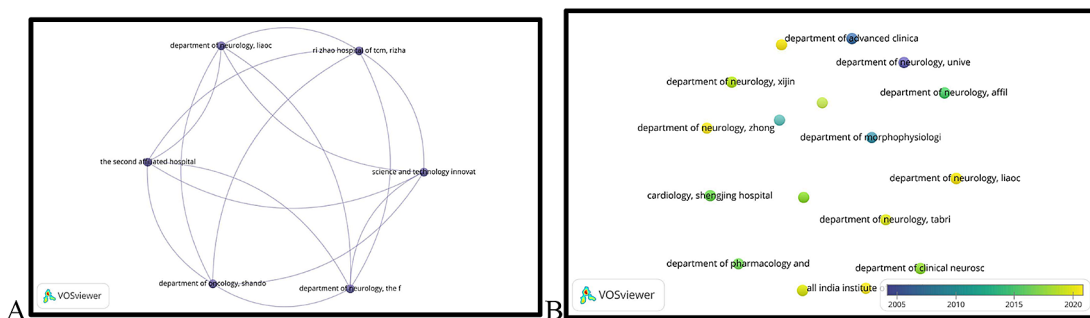
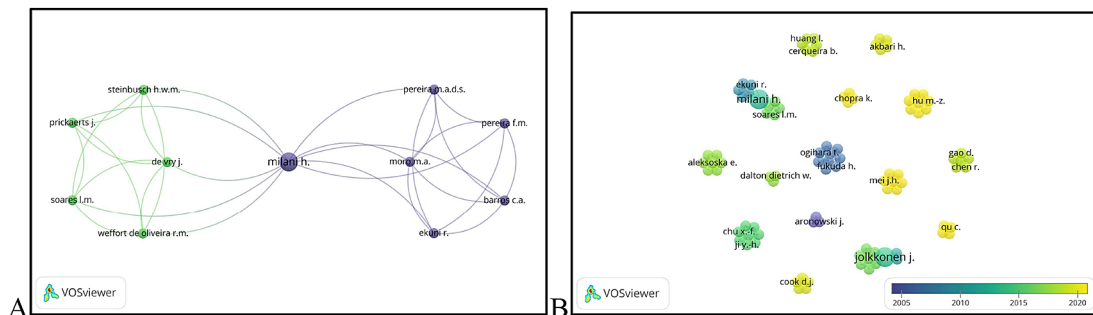


Figure 3. Organizational co-author analysis using the VOSviewer 1.6.18 network visualization. A. Six-organizations connected to each other. B. Other organizations that worked alone for their publication.

**Table 2. The top-ranked journal with the most publications.**

Rank	Published Journals	Number of articles
1	<i>Neuroscience</i>	3
2	<i>Behavioural Brain Research</i>	2
3	<i>Brain Research</i>	2
4	<i>Aging</i>	1
5	<i>Chinese Journal of Tissue Engineering</i>	1
6	<i>Experimental Neurology</i>	1
7	<i>Inflammopharmacology</i>	1
8	<i>International Immunopharmacology</i>	1
9	<i>Journal of Molecular Neuroscience</i>	1
10	<i>Journal of Stroke And Cerebrovasc</i>	1
11	<i>Neural Regeneration Research</i>	1
12	<i>Neurological Research</i>	1
13	<i>Pharmacology Biochemistry And Behavior</i>	1
14	<i>PLOS One</i>	1

**Figure 4. Author co-occurrence analysis.** A. Authors that collaborated in publications. B. Other authors that published independently.

“cognitive function” and “sensorimotor function”. Figure 5C shows the keyword connected with cognitive dysfunction such as “tumor necrosis factor”, “metabolism”, and “inflammation”.

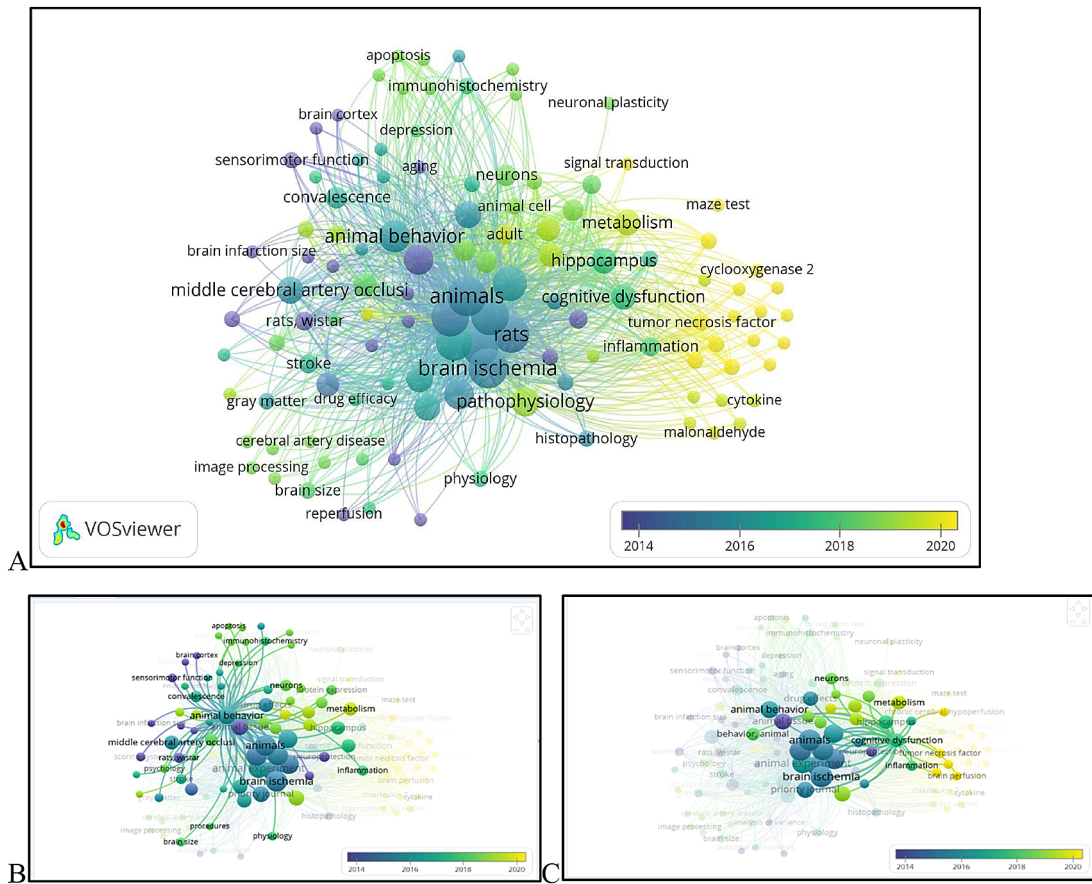
#### Behaviour test applied in the publication

The most used test in the articles was the Morris Water Maze (Dhaliwal *et al.*, 2021; Hei *et al.*, 2018; Yao *et al.*, 2021; Yan *et al.*, 2021) and the second was the cylinder test (Huang *et al.*, 2018; Lipsanen *et al.*, 2011; Loris *et al.*, 2017; Shaafi *et al.*, 2019). Beam walking test (Lipsanen *et al.*, 2011; Wang *et al.*, 2021), forced swim test (FST), elevated zero maze (EZM), open field (OF), and object location test (OLT) (Soares *et al.*, 2016) were also encountered (Table 3).

#### Discussion

Stroke causes long-term impairment that is sometimes accompanied by debilitating deficits, necessitating immediate treatment. Stroke patients commonly experience motor, sensory, and cognitive impairments, but therapeutic options are limited. Functional results in animal models, in addition to histology measurements, have provided vital information into the molecular basis of experimental stroke and future rehabilitation initiatives. Expanding the development of translational medicines necessitates the creation and use of tests that can identify behavioral impairments.

Selecting relevant behavioral measures that meet the study goal is crucial when monitoring stroke outcome and transferring rodent findings into treatment trials. Although a 30-minute tMCAo generates consistent infarct in subcortical area in rats, behavioural tests like the rotarod test, adhesive-removal test, or narrow beam test make measuring the ensuing neurological damage difficult. The development of a new cerebral infarction therapy technique would benefit from the development of a quantitative evaluation method (Wakayama *et al.*, 2007).



**Figure 5. Keywords occurrence.** A. The top ten keywords were “animals”, “brain ischemia”, “male”, “article”, “animal experiment”, “animal model”, “rats”, “controlled study”, “animal behaviour”, “animal tissue”. B. Keyword related animal behaviour. C. Keyword related cognitive function.

**Table 3. Behavior tests used in publications relating to behaviour tests in chronic stroke rats.** The Morris Water Maze (MWM) test was used in the majority of cases, with the cylinder test coming in second.

Number	Title	Behaviour test used	Purpose of the test
1	Dimethyl fumarate improves cognitive deficits in chronic cerebral hypoperfusion rats by alleviating inflammation, oxidative stress, and ferroptosis via NRF2/ARE/NF-κB signal pathway (Yan <i>et al.</i> , 2021)	MWM test	Memory ability
2	EGB761 ameliorates chronic cerebral hypoperfusion-induced cognitive dysfunction and synaptic plasticity impairment (Yao <i>et al.</i> , 2021)	MWM	Short-term spatial memory
3	Saikosaponin A improved depression-like behavior and inhibited hippocampal neuronal apoptosis after cerebral ischemia through p-CREB/BDNF pathway (Wang <i>et al.</i> , 2021)	Open field test, beam-walking test, sucrose preference and forced swimming tests	Sensorimotor impairment
4	Dimethyl fumarate attenuates 2-VO-induced vascular dementia via activating the Nrf2 signaling pathway in rats (Dhaliwal <i>et al.</i> , 2021)	MWM and novel object (NOR) tests.	Cognitive performance

**Table 3.** *Continued*

Number	Title	Behaviour test used	Purpose of the test
5	Early Motor-Behavioral Outcome of Ischemic Stroke with Ketogenic Diet Preconditioning: Interventional Animal Study (Shaafi <i>et al.</i> , 2019)	Adjusting step, beam, and cylinder tests	The rats' motor behaviors
6	HMGB1 Neutralization Attenuates Hippocampal Neuronal Death and Cognitive Impairment in Rats with Chronic Cerebral Hypoperfusion via Suppressing Inflammatory Responses and Oxidative Stress (Hei <i>et al.</i> , 2018)	MWM	Memory and spatial learning ability
7	Chronic oral methylene blue treatment in a rat model of focal cerebral ischemia/reperfusion (Huang <i>et al.</i> , 2018)	Foot-fault test and cylinder test	Sensorimotor impairment
8	The neuroprotective compound P7C3-A20 promotes neurogenesis and improves cognitive function after ischemic stroke (Loris <i>et al.</i> , 2017)	Cylinder and grid-walk task	Sensorimotor impairment
9	Evolution of ischemic damage and behavioural deficit over 6 months after MCAo in the rat: Selecting the optimal outcomes and statistical power for multi-centre preclinical trials (Rewell <i>et al.</i> , 2017)	Adhesive removal test	The persistence of behavioral deficits in rats following an ischemic stroke
10	Rolipram improves cognition, reduces anxiety- and despair-like behaviors and impacts hippocampal neuroplasticity after transient global cerebral ischemia (Soares <i>et al.</i> , 2016)	Elevated zero maze (EZM), open field (OF), object location test (OLT), and forced swim test (FST).	In rodents, the EZM is used to assess anxiety. An OF test was used to assess activity of locomotor and anxiety. The purpose of the OLT was to assess spatial memory performance. The FST was used for testing the efficacy of antidepressant drugs in the lab.
11	Fluoxetine Enhances Neurogenesis in Aged Rats with Cortical Infarcts, but This is not Reflected in a Behavioral Recovery (Sun <i>et al.</i> , 2016)	Tapered/ledged beam-walking Test	Motor impairment
12	Chronic ibuprofen treatment does not affect the secondary pathology in the thalamus or improve behavioral outcome in middle cerebral artery occlusion rats (Lipsanen <i>et al.</i> , 2011)	Limb-placing, tapered ledged beam-walking and cylinder tests	Sensorimotor impairment
13	The cognitive and histopathological effects of chronic 4-vessel occlusion in rats depend on the set of vessels occluded and the age of the animals (Barros <i>et al.</i> , 2009)	Aversive radial maze (AvRM)	Memory ability
14	Quantitative measurement of neurological deficit after mild (30 min) transient middle cerebral artery occlusion in rats (Wakayama <i>et al.</i> , 2007)	Montoya staircase test and methamphetamine-induced rotation, neurological severity score (NSS)	Motor impairment
15	Comparative Dose of Intracarotid Autologous Bone Marrow Mononuclear Therapy in Chronic Ischemic Stroke in Rats (Makkiyah <i>et al.</i> , 2021)	cylinder and a modified neurological severity score NSS test	Motor impairment



Choosing the appropriate behaviour test in chronic stroke research is difficult since rats' brains recover well, and even though infarct pathology still exists, behaviour test findings are comparable to normal rats. This is the component about which researchers should ponder long and hard before beginning their study. It's crucial to use tests that are able to detect the neurological deficits to the injury to the brain and the treatments used. Due to the loss of limb function following a stroke, many tests focus on motor and sensory testing (Lipsanen *et al.*, 2011; Makkiyah *et al.*, 2021; Sun *et al.*, 2016; Wakayama *et al.*, 2007). Because learning and memory problems are frequent after a stroke, cognitive testing is particularly important for determining the full extent of the difficulties (Barros *et al.*, 2009; Dhaliwal *et al.*, 2021; Hei *et al.*, 2018; Yao *et al.*, 2021). As a result, it's critical to have sensitive behavioural approaches for detecting the wide range of deficits that might arise after a stroke. By recording functional improvements over time, behavioral assessments can also be used to measure the efficiency of pharmacological and cell-replacement treatments.

Since 1996, researchers have been using behaviour tests in chronic stroke patients, with a peak occurring in 2021. The literature was dominated by research from countries like the USA and China. In other areas of stroke research, such as the involvement of ferroptosis in stroke, a similar pattern emerged (Chen *et al.*, 2021).

The MWM test, which is the most common test implemented in the literature has some limitations. It may be difficult to distinguish between a merely cognitive deficit and a possible sensorimotor insufficiency in tMCAO rats because of the unilateral ischemia impairment. There was no significant variation in swim speed or path length during the probing session, indicating that ability to swim did not have a role in the cognitive function deficit shown in tMCAO animals. As a result, while the water maze techniques used may provide useful assays for the efficacy of therapeutic interventions targeting the striatum area, other behavioural tests may be more appropriate for measuring rescue area or recovery in injured neocortex areas (Bingham *et al.*, 2012).

Sensorimotor asymmetry is one of the most common signs of stroke, and it can be measured using a variety of behavioural tests, including cylinder test. After a central nervous system injury, the cylinder test was initially used to measure spontaneous forelimb motor performance. It has been used in many publications in research related to behaviour tests in chronic stroke rats (Barros *et al.*, 2009; Huang *et al.*, 2018; Lipsanen *et al.*, 2011; Loris *et al.*, 2017; Makkiyah *et al.*, 2021; Shaafi *et al.*, 2019). The cylinder task has been shown to be objective, simple to use and score, sensitive to chronic issues that other tests overlook, and has strong inter-rater reliability. Furthermore, no prior training is necessary, albeit baseline data is required to assess for pre-operative bias because some animals exhibit independent use of one limb on occasion (Schaar *et al.*, 2010).

### Limitations

Although this is the first bibliometric analysis of "behavior test in chronic stroke rats," it does have some limitations.

To begin with, the retrieval date was 26 April, 2022, but the database is still being updated. There should be more coming articles after that retrieval date. Secondly, the Scopus database's search phrases (ALL ("behavior test") OR TITLE-ABS-KEY ("behavioural outcomes") AND TITLE-ABS-KEY (rats) OR TITLE-ABS-KEY (rodents) AND TITLE-ABS-KEY ("brain ischemia") AND TITLE-ABS-KEY (chronic) OR TITLE-ABS-KEY ("chronic ischemic stroke")) were utilized. There might be some articles that were not included with searching using different keywords. However, because Scopus is the most widely used database for bibliometric research, we feel our study represents the global situation and general trend for bibliometric analysis.

### Conclusions

Clinical applications and therapeutic effectiveness against stroke could be improved with more collaboration amongst authors. When using a behavior test, researchers need to think about which neurological deficiency is being addressed and whether the test covers long-term evaluation.

### Data (and Software) availability

#### Underlying data

Figshare: bibliometric results of behaviour tests of chronic brain rats ischemia.xlsx, <https://doi.org/10.6084/m9.figshare.19911172.v1> (Makkiyah and Susantiningasih, 2022).

Data are available under the terms of the [Creative Commons Attribution 4.0 International license](https://creativecommons.org/licenses/by/4.0/) (CC-BY 4.0).

### Author contributions

Conceptualization: FD, TS, HM. Data collection and analysis: AI, MC. MA-formal analysis. CB, MB, AC, YH, AI, SW, FZ. methodology. Writing—original draft: YS, TR. Writing—review and editing: MST.

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# Open Peer Review

Current Peer Review Status: ?

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Version 1

Reviewer Report 30 August 2022

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**Robert Sinurat**

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The authors analyzed the behavior test in chronic brain ischemic of rat models by a bibliometric approach. The authors have obtained how many articles were published in 1996 - 2022, who and from what country the author was, and how many times each article was cited by another author. The study is interesting, but the authors need to revise the manuscript.

Alteplase and thrombectomy are treatment for ischemic stroke, not for hemorrhagic stroke. The authors cited from an older article about the outcome of the treatment (Wardlaw et al, 2014). It would be better to reveal the outcome of the procedures from more recent articles, such as research reported by Katherin T Mun(2022) title: Fragility index meta analysis of randomized controlled trials shows highly robust evidential strength for benefit of < 3 hours intravenous alteplase<sup>1</sup>.

The purpose of this study is the authors want to add information about the behavior test through bibliometric analysis, but it was not explained in detail what kind of information will be expected to be obtained through the results of this study.

The authors searched the articles from the Scopus database, and the number of articles obtained was eighteen papers. The authors are required to explain why they are limiting the source to only the Scopus database. If the sources were expanded the number of articles that can be analyzed will be raised.

The authors need to enlarge the text in the figures and improve the discussion section by interpreting each point of the results of the bibliometric analysis obtained from this study. It would be nice if the authors could use simpler sentences to make it easier to understand. For examples, the authors maybe can explain why the majority of the articles are from USA and China, why the MWM test was widely used, and how the results of this study helping the researchers to choose the kind of behavior test for their future study.

The authors need to conclude this study according to the results of their bibliometric analysis, and

convey considerations for other prospective researchers on which test is more appropriate to use for research in chronic ischemic stroke rat models.

### References

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**Is the work clearly and accurately presented and does it cite the current literature?**

Partly

**Is the study design appropriate and is the work technically sound?**

Yes

**Are sufficient details of methods and analysis provided to allow replication by others?**

Yes

**If applicable, is the statistical analysis and its interpretation appropriate?**

Partly

**Are all the source data underlying the results available to ensure full reproducibility?**

Yes

**Are the conclusions drawn adequately supported by the results?**

Partly

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Neurosurgery, stem cell for stroke, spinal diseases.

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

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