Functional, Sensorimotor, and Cognitive Outcomes Following Unilateral MCAO in Rats

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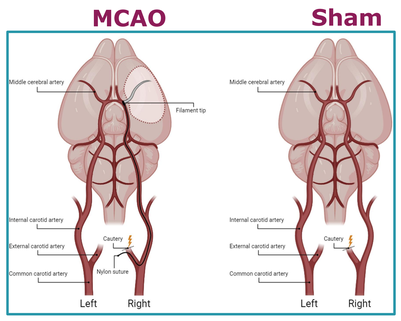
INTRODUCTION

Stroke is a leading cause of death and long-term disability worldwide, with ischemic stroke accounting for approximately 85% of all cases. Despite significant advances in clinical management, effective therapies that promote neuroprotection and functional recovery remain limited, highlighting the need for translationally relevant preclinical models. PsychoGenics has established a middle cerebral artery occlusion (MCAO) model in Sprague Dawley rats that reproduces key pathological and functional features of human ischemic stroke. Transient MCAO followed by reperfusion induces reproducible infarcts within the cortex and striatum, resulting in focal neuronal loss, neuroinflammation, and persistent neurological deficits. Histological assessment of lesion location and extent, combined with longitudinal behavioral evaluation, provides a comprehensive characterization of stroke severity and recovery. Using a battery of clinically relevant outcome measures, including neurological scoring, sensorimotor assessments, and locomotor testing, this model enables evaluation of both acute injury and long-term functional impairment. The MCAO platform therefore provides a robust translational tool for investigating stroke pathophysiology and evaluating novel neuroprotective, restorative, and rehabilitation-based therapeutic strategies.

METHODS

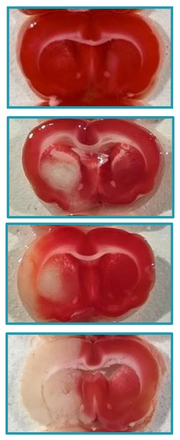
- **Subjects and MCAO Surgeries.**
- Adult male SD rats (300–350 g; Inotiv) underwent transient MCAO induced by a silicone-coated 4-0 nylon monofilament (Doccol Corporation). Filament diameter was selected according to body weight. Occlusion was maintained for 2hrs, followed by reperfusion. Animals recovered from anesthesia during occlusion and were re-anesthetized for filament removal.



- Postoperative care included fluid therapy, thermal support, and nutritional supplementation. Sham animals underwent identical surgical, anesthetic, and postoperative procedures, including vessel dissection and ligation, without filament insertion.
- **Behavioral Assessments.** Neurological score and beam balance were evaluated at 2 hs, 24 hrs, 1 week, and 2 weeks post-MCAO. Sensorimotor asymmetry was assessed using the corner test (1, 2, and 4 weeks) and cylinder test (2 and 4 weeks). Fine motor coordination was evaluated using the horizontal ladder test (2 and 4 weeks). Spatial learning and memory were assessed using the Morris water maze at 5 weeks post-MCAO.
- **Histology and Immunohistochemistry.** TTC staining was performed 24 hours after reperfusion to assess infarct location and acute lesion formation. At 6 weeks post-MCAO, brains were collected, sectioned coronally, and stained with DAPI, NeuN, and GFAP to characterize lesion location and extent, neuronal loss, and astroglial reactivity.
- **Statistics.** Data were analyzed using one- or two-way ANOVA with appropriate post hoc tests. Relationships between behavioral and histological outcomes were evaluated using Pearson correlation analysis.

RESULTS

Stroke extension 24 hours after MCAO using TTC staining



Sham: Neuro-score = 0

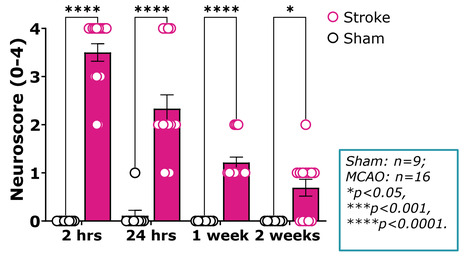
MCAO: Neuro-score 1-2

MCAO: Neuro-score 1-2

MCAO: Neuro-score 3-4

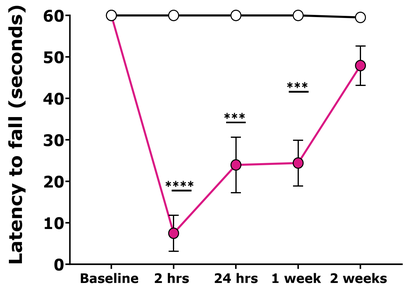
- TTC staining differentiates viable from infarcted tissue based on metabolic activity; living tissue reduces TTC to red formazan, while infarcted tissue appears pale.
- TTC staining performed 24 hours after reperfusion revealed prominent infarcts within the ipsilateral cortex and striatum of MCAO animals, while sham-operated rats showed no evidence of tissue damage.
- MCAO rats exhibited significantly elevated neurological scores, with mild deficits characterized by contralateral circling (scores 1–2) and severe deficits characterized by impaired weight-bearing and barrel rolling (scores 3–4).

Neurological and Balance Deficits Persist from 2 Hours to 2 Weeks Following MCAO



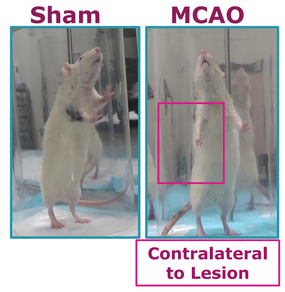
*Sham: n=9; MCAO: n=16 *p<0.05, ***p<0.001, ****p<0.0001.*

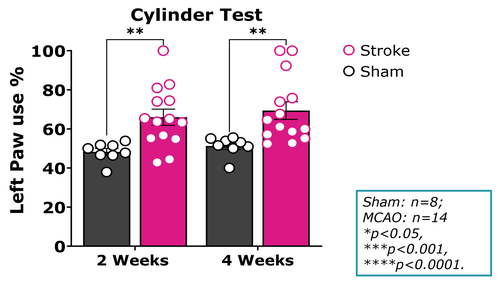
- MCAO rats showed significant increases in Neuroscore, reflecting marked neurological impairment. Peak deficits occurred at the end of occlusion, with impairments persisting up to 2 weeks post-stroke.



- Rats were trained to maintain balance on a narrow beam for at least 1 minute.
- Sham animals retained balance throughout testing, whereas MCAO rats demonstrated pronounced deficits.

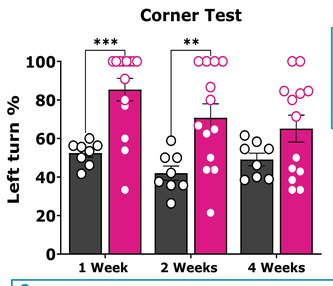
MCAO Results in Sensorimotor Asymmetry (Laterality)





*Sham: n=8; MCAO: n=14 *p<0.05, ***p<0.001, ****p<0.0001.*

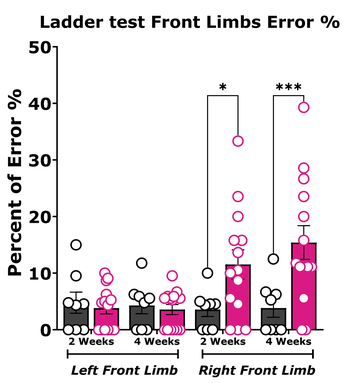
- The cylinder test assesses forelimb use during vertical exploration. MCAO rats favored the forelimb ipsilateral to the lesion, with significant differences at 2 and 4 weeks post-MCAO.



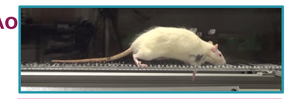
*Sham: n=8; MCAO: n=14 *p<0.05, ***p<0.001, ****p<0.0001 .*

- The corner test evaluates turning bias as rats exit a narrow Plexiglas corner, where a consistent directional preference indicates unilateral sensorimotor and postural deficits. MCAO rats showed a significant turning bias compared with Sham at 1 and 2 weeks post-MCAO, reflecting sensorimotor asymmetry.

Fine Motor Coordination Remains Impaired Following MCAO

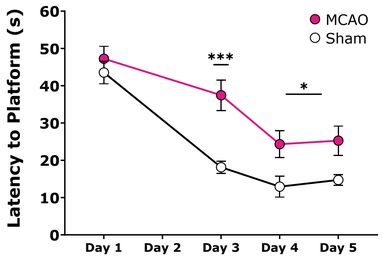


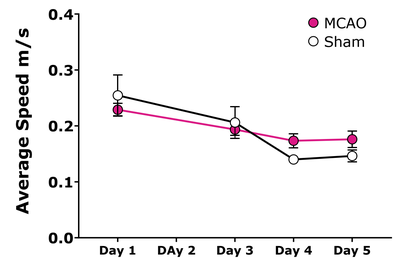
*Sham: n=8; MCAO: n=14 *p<0.05, ***p<0.001, ****p<0.0001.*

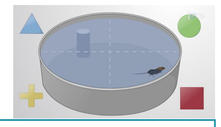


- Fine motor coordination was quantified as the percentage of paw placement errors while crossing a horizontal ladder with irregularly spaced rungs.
- Sham rats exhibited minimal errors, whereas MCAO animals showed a significant increase in paw misplacement errors, particularly in the contralateral (right) forelimb, at 2 and 4 weeks post-stroke.

MCAO increased latency to reach the platform in the Morris water maze test

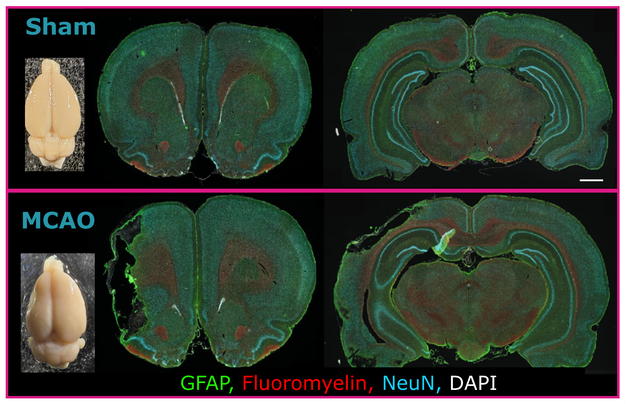


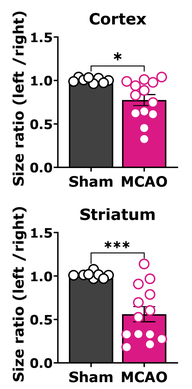




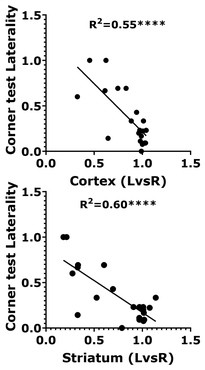
- The Morris water maze (MWM) assesses spatial learning and memory by measuring the ability of rats to learn and recall the location of a hidden escape platform using spatial cues.
- MCAO rats exhibited significantly longer escape latencies during training compared with Sham animals, indicating impaired spatial learning and memory.
- Swim speed did not differ between groups, suggesting that the increased latency was due to cognitive deficits rather than impaired swimming ability.

Histological Changes Following MCAO Correlate with Functional Deficits





- Coronal brain sections were stained with GFAP, FluoroMyelin™, NeuN, and DAPI to evaluate anatomical changes, demyelination, neuronal loss, and lesion extent following MCAO.
- Quantitative analysis of cortical and striatal tissue loss was performed for each animal and correlated with behavioral outcomes.
- Significant correlations were observed between lesion size and multiple functional measures, with the strongest associations identified for the corner test, indicating that greater tissue loss was associated with more severe sensorimotor asymmetry.



SUMMARY

This poster characterizes PsychoGenics' transient MCAO model in Sprague Dawley rats as a translationally relevant platform for ischemic stroke research. Adult male rats underwent 2-hrs filament occlusion followed by reperfusion, with sham controls receiving identical surgery minus filament insertion. The team paired histological readouts (TTC staining at 24 hours; DAPI/NeuN/GFAP at 6 weeks) with a longitudinal behavioral battery covering neurological scoring, beam balance, corner and cylinder tests, horizontal ladder, and the Morris water maze at 5 weeks.
Results demonstrate that MCAO produces reproducible cortical and striatal infarcts alongside persistent, multi-domain functional deficits. Neuroscores peaked immediately post-occlusion and remained elevated for up to two weeks, while sensorimotor asymmetry was detected on the corner and cylinder tests at 1–4 weeks, fine motor coordination deficits was still noted at 4 weeks, and spatial learning was impaired in the Morris water maze at 5 weeks. Histologically, MCAO produced demyelination, neuronal loss, and astroglial reactivity, and quantified cortical and striatal tissue loss correlated with functional deficits, most strongly on the corner test, where greater lesion size predicted more severe sensorimotor asymmetry. Together, the data support MCAO as a robust preclinical model for evaluating neuroprotective, restorative, and rehabilitation-based therapies.