

# A test for detecting long-term sensorimotor dysfunction in the mouse after focal cerebral ischemia

Li Zhang<sup>a</sup>, Timothy Schallert<sup>b</sup>, Zheng Gang Zhang<sup>a</sup>, Quan Jiang<sup>a</sup>, Polly Arniago<sup>a</sup>,  
Qingjiang Li<sup>a</sup>, Mei Lu<sup>c</sup>, Michael Chopp<sup>a,d,\*</sup>

<sup>a</sup> Department of Neurology, Henry Ford Hospital, 2799 West Grand Boulevard, Detroit, MI 48202, USA

<sup>b</sup> Department of Psychology, Neurosurgery and Center for Human Growth and Development, University of Michigan, Ann Arbor MI 48109-0406, USA

<sup>c</sup> Department of Biostatistics and Research Epidemiology, Henry Ford Health Sciences Center, Detroit, MI 48202, USA

<sup>d</sup> Oakland University, Department of Physics, Rochester, MI 48309, USA

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## Abstract

The mouse is an excellent model for investigations of stroke and neural injury. However, there is a paucity of long term functional outcome measurements for the mouse. We, therefore, developed a sensorimotor functional test (corner test) and applied this test to a model of focal cerebral ischemia in the mouse. Male C57/6J mice ( $n = 20$ ) were subjected to embolic middle cerebral artery (MCA) occlusion. Reduction of cerebral blood flow (CBF) was measured by perfusion weighted MRI at 1 h after ischemia. The corner test, which is sensitive to chronic sensorimotor and postural symmetries, a general neurological test battery, and a foot fault test were performed between 2 and 90 days after ischemia. Infarct volume was measured at 90 days after ischemia. Multivariable analysis revealed that the corner test was highly predictive for infarct volume measured at 90 days after stroke, with  $R^2$  values ranging from 0.73 to 0.93. The foot-fault test and neurological score did not detect chronic behavioral impairments. A significant ( $P < 0.001$ ) correlation between the infarct volume and the corner test was detected at 90 days after mild focal cerebral ischemia, whereas, there was no correlation between the infarct volume and neurological score or foot-fault. The data demonstrate that the corner test is a sensitive and objective test, which can be applied to evaluate long term functional outcome after stroke in the mouse. © 2002 Elsevier Science B.V. All rights reserved.

**Keywords:** Embolic; Focal; Cerebral ischemia; Sensorimotor function; Cerebral blood flow; Mouse; Infarct volume

## 1. Introduction

Functional tests have been employed to assess neurological outcome following stroke in rats, with modest success in linking ischemic injury volume and location to behavior (Schallert et al., 2000; Bland et al., 2000; Aronowski et al., 1996; Borlongan et al., 1995). In contrast to the rat for which there are abundant data on functional outcome, there is a scarcity of literature in the mouse. Genetically manipulated mice are very useful for investigating the pathophysiological consequences of stroke (Kinouchi et al., 1991; Chan, 2001). Improved assessment of function in the mouse

subjected to stroke would potentially be beneficial for research on therapeutic interventions, particularly if infarction volume and location can be linked chronically with function in the same test. One problem with mice, unlike rats, has been that ischemic injuries are often fatal when severe enough and encroach extensively enough on forebrain structures associated with sensorimotor asymmetries. For this reason, we designed a single test that might detect a combination of mild to moderate focal ischemia induced symmetries, including sensory to the vibrissae, forelimb use, hindlimb use and postural motor function.

In the present study, we describe this test, a corner test, which was modified for mice from a narrow alley test used acutely to examine forebrain injury to cortex or striatum (Schallert et al., 1982, 1983; Teitelbaum et al., 1983; Barth et al., 1990). We applied this test to a mouse

\* Corresponding author. Tel.: +1-313-916-3936; fax: +1-313-916-1318

E-mail address: [chopp@neuro.hfh.edu](mailto:chopp@neuro.hfh.edu) (M. Chopp).

model of unilateral focal embolic cerebral ischemia. The effectiveness of this sensorimotor functional test was compared with that of a foot-fault test (Hernandez and Schallert, 1988) and a four point standard neurological functional test (Longa et al., 1989) for over a period of 90 days after the ischemic insult. Functional profiles were correlated with the ischemic lesion volume to ascertain the relationship between function and pathological changes over the time course of the study.

## 2. Materials and methods

All experimental procedures have been approved by the Care of Experimental Animals Committee of Henry Ford Hospital.

### 2.1. General preparation

Male C57/6J mice ( $n = 20$ ) weighing 24–30 g were employed in the present study. Mice were anesthetized with 3.5% halothane and maintained with 1.0% halothane in 70% N<sub>2</sub>O and 30% of O<sub>2</sub> using a face mask. Rectal temperature was maintained at 37 °C throughout the surgical procedure by means of a feed-back-regulated water heating system.

#### 2.1.1. Animal model

The middle cerebral artery (MCA) was occluded by placement of an embolus at the origin of the right MCA (Zhang et al., 1997). To generate different volumes of ischemic lesions, two different lengths (8 and 15 mm) of a single intact fibrin-riched clot with a 0.025 mm diameter were placed at the origin of the MCA via a 150 mm length of modified PE-50 catheter. Briefly, under the operating microscope (Carl Zeiss, Inc., Thornwood, NY, USA) the right common carotid arteries (CCA), the right external carotid artery (ECA) and the internal carotid artery (ICA) were isolated via a midline incision. A modified PE-50 catheter with a 0.15–0.18 mm outer diameter filled with a single clot, which was attached to a 100- $\mu$ l Hamilton syringe filled with 0.9% saline, was introduced into the ECA lumen through a small puncture. The tip of the catheter was advanced from the ECA into the lumen of ICA approximately 8 mm to reach the origin of the MCA. The clot in the catheter was injected into the ICA along with 2–3:1 of 0.9% saline. The catheter was withdrawn from the right ECA 5 min after injection.

### 2.2. MRI measurements

To confirm reduction of cerebral blood flow (CBF), perfusion weighted MRI was performed on ischemic mice 1 h after MCA occlusion using a 7.0 T magnet (Magnex Scientific, Abingdon, U.K.) equipped with

actively shielded gradients and a SMIS (Surrey, UK) console (Jiang et al., 1994). This technique is based on the selective inversion of blood water protons at the level of the carotid arteries prior to <sup>1</sup>H MRI measurement in the brain (Jiang et al., 1994). Two images were obtained for perfusion measurement with parameters: repetition time (TR) = 1.055 s; echo time (TE) = 30 ms, 64 × 64 image matrix, 2 mm slice thickness, and a 40 mm field of view (FOV). The duration of the inversion pulse was 1 s and 0.3 kHz in amplitude. CBF maps were calculated according to previous report (Jiang et al., 1994). The numbers of pixels with CBF below 50 ml/100 g-min normalized to the total numbers of pixels in the ipsilateral hemisphere were calculated and data are presented as percent area containing 50% reduction of CBF to the area of the ipsilateral hemisphere (Jiang et al., 1994).

### 2.3. Behavioral testing

Behavioral tests were carried out 2, 7, 14, 30, 60, and 90 days after MCA occlusion.

- 1) Corner test: in the home cage, a mouse was placed between two boards each with dimension of 30 × 20 × 1 cm<sup>3</sup>. The edges of the two boards were attached at a 30° angle with a small opening along the joint between the two boards to encourage entry into the corner. The mouse was placed between the two angled boards facing the corner and half way to the corner. When entering deep into the corner both sides of the vibrissae are stimulated together. The mouse then rears forward and upward, then turns back to face the open end. The non-ischemic mouse turns either left or right, but the ischemic mouse preferentially turns toward the non-impaired, ipsilateral (right) side. The turns in one versus the other direction were recorded from ten trials for each test. Turning movements that were not part of a rearing movement were not scored.
- 2) Neurological score: a four point neurological score was employed (Longa et al., 1989): 0 = no deficit, 1 = failure to extend the left forepaw fully, 2 = circling to the left, 3 = no spontaneous walking with a depressed level of consciousness.
- 3) Foot-fault test: mice were tested for placement dysfunctions of forelimbs with the modified foot-fault test (Hernandez and Schallert, 1988). Mice were placed on elevated hexagonal grids of different sizes. Mice placed their paws on the wire while moving along the grid. With each weight-bearing step, the paw may fall or slip between the wire. This was recorded as a foot fault. The total number of steps (movement of each forelimb) that the mouse used to cross the grid was counted, and the total

number of foot faults for each forelimb were recorded.

#### 2.4. Measurements of the infarct volume

The animals were anesthetized with ketamine (44 mg/kg) and xylazine (13 mg/kg) and were sacrificed at 90 days after MCA occlusion. Each mouse was transcardially perfused with heparinized saline followed by 10% formalin. The brain was removed from the skull and was cut into seven coronal blocks, each with 1 mm thickness. The brain tissue was processed, embedded, and 6  $\mu\text{m}$  thick paraffin sections from each block were cut and stained with hematoxylin and eosin (H&E) for measurements of the ischemic lesion volume. The ischemic lesion volume was measured using a Global Lab Image analysis program (Data Translation, Marlboro, MA). The area of the both hemispheres and the area containing the ischemic neuronal damage ( $\text{mm}^2$ ) were calculated by tracing the area on the computer screen. The lesion volume ( $\text{mm}^3$ ) was determined by multiplying the appropriate area by the section interval thickness (Chen et al., 1992). To reduce errors associated with processing of tissue for histological analysis, the ischemic volume is presented as the percentage of infarct volume of the contralateral hemisphere (indirect volume calculation) (Lin et al., 1993).

Measurements of CBF, behavioral tests and infarct volume were performed by personnel blinded to the experimental design.

#### 2.5. Statistical analysis

To validate ischemia deficits and sensitivities of behavior tests, we compared behavior test scores and CBF 1 h after MCA occlusion between the ischemia and the sham operated mice using two-sample *t*-test. We also compared behavior test scores collected before and after ischemia using a paired *t*-test based on ischemia group.

To investigate the predictive ability of early behavior tests on 3 month infarct volume for mice with MCA occlusion, we conducted a multivariable regression model on a log scale (Lu et al., 2001), given the ill-behaved infarct volume. Adjusted  $R^2$  (predictive ability), in a range from 0 to 1.0, was calculated for each behavior test.  $R^2$  with a value of 1.0 (or close to 1) indicates 100% predictive ability. The higher the adjusted  $R^2$ , the better the predictive model becomes; adjusted  $R^2 > 0.90$  indicates an excellent predictive ability. Spearman correlation coefficients were calculated among data collected at 90 days with *P*-value for testing significant correlation between measurements compared with no correlation at all.

### 3. Results

#### 3.1. CBF

Reduction of CBF in the ipsilateral hemisphere was detected in all ischemic mice at 1 h after MCA occlusion, but not in the sham operated mice (Fig. 1A). The area encompassing the reduction of CBF appears to depend on the length of the embolus. Reduction of CBF was observed in the ipsilateral cortex and subcortex supplied by the right MCA in mice subjected to MCA occlusion with a long (15 mm) embolus (Fig. 1B), while mice with a short (8 mm) embolus exhibited reduction of CBF only in the ipsilateral subcortex (Fig. 1C). Quantitative analysis revealed that mice subjected to MCA occlusion with a long ( $n = 6$ ) and a short ( $n = 10$ ) embolus had  $77 \pm 7.5$  and  $34 \pm 14.4\%$ , respectively, of the ipsilateral hemisphere with 50% reduction in CBF at 1 h after MCA occlusion.

#### 3.2. Infarct volume

Sham operated animals did not show any evidence of lesion at 90 days after surgery. Six mice with large area reduction of CBF ( $77 \pm 7.5\%$ ) died during 4–5 days after MCA occlusion and had ischemic lesion volumes of  $33 \pm 5\%$  of the contralateral hemisphere. These mice were excluded from the statistical analysis. The remaining mice with  $34 \pm 14.4\%$  of CBF reduction survived for 90 days after MCA occlusion and had infarct volumes of  $7 \pm 5\%$ .

#### 3.3. Corner test

Sham operated mice and mice tested prior to MCA occlusion did not show behavioral asymmetries on the corner test, i.e. they made approximately the same number of turns toward either side during the experimental period (the right turn  $5.3 \pm 0.25$  and the left turn  $4.7 \pm 0.25$ ). However, animals subjected to the right MCA occlusion showed a significant ( $P < 0.05$ ) increase in the right turns compared with sham animals 2–90 days after MCA occlusion (Figs. 2 and 3A). Mice that died 4–5 days after MCA occlusion exhibited the worst corner test score (the right turn,  $10 \pm 0$ ) 2 days after ischemia.

#### 3.4. Neurological deficit scores

During first 30 days after ischemia, mice exhibited significantly ( $P < 0.05$ ) elevated neurological deficit scores compared with scores obtained from pre-ischemia and from sham operated mice. However, differences of neurological scores between the post-ischemia values and pre-ischemia values were not significant at 60–90 days after MCA occlusion (Fig. 3B).

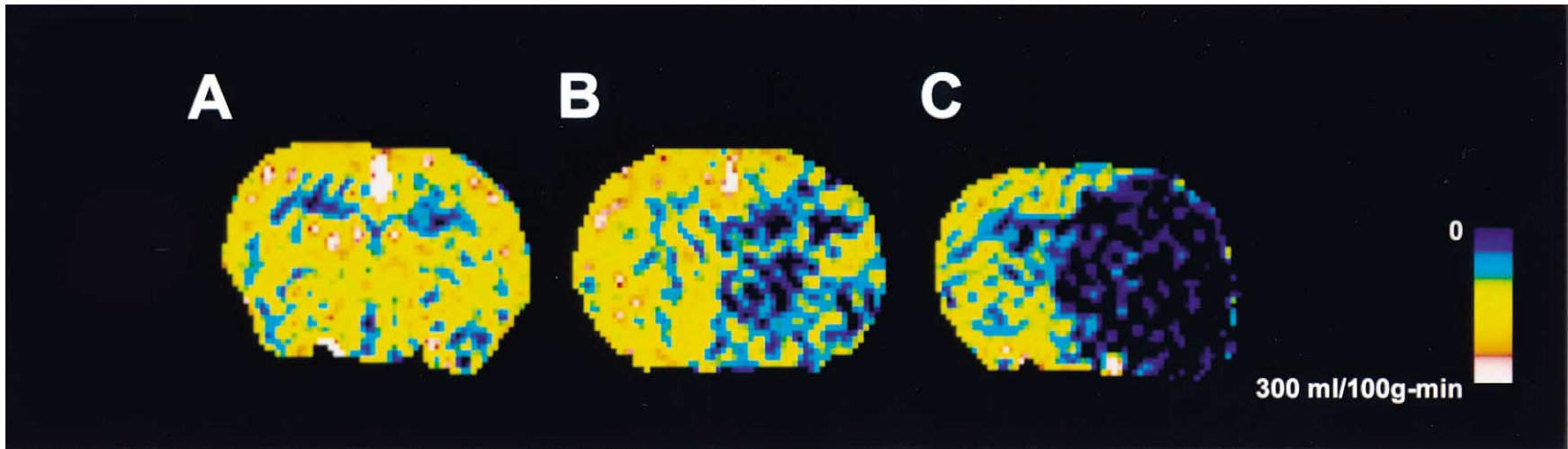


Fig. 1. Coronal images of perfusion weighted MRI. Reduction of CBF was not present in a sham operated mouse (A). However, occlusion of the MCA with a long (B) or short (C) embolus resulted in reduction of CBF in the cortical and subcortical areas (B) or primarily in the subcortical area (C).

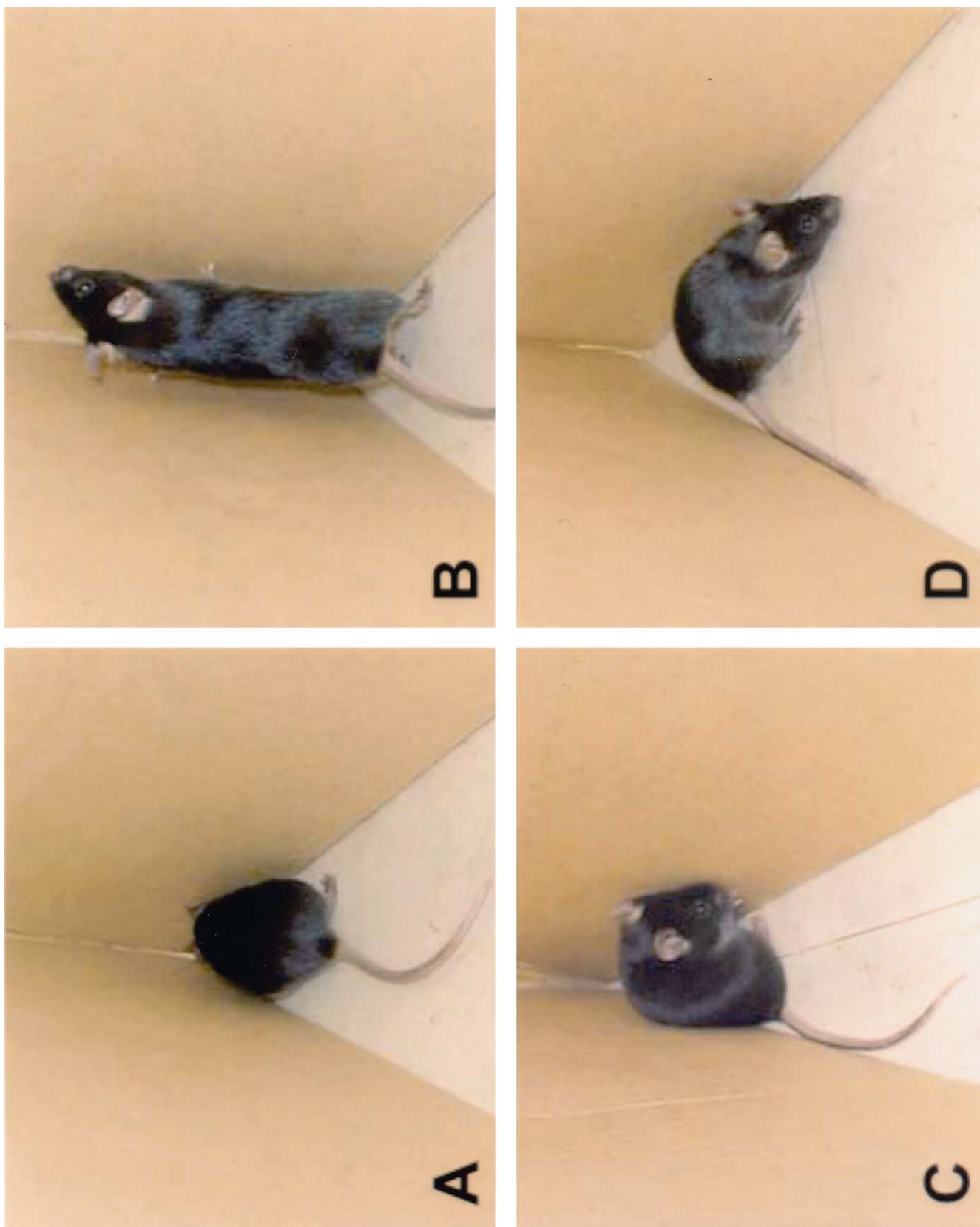


Fig. 2.

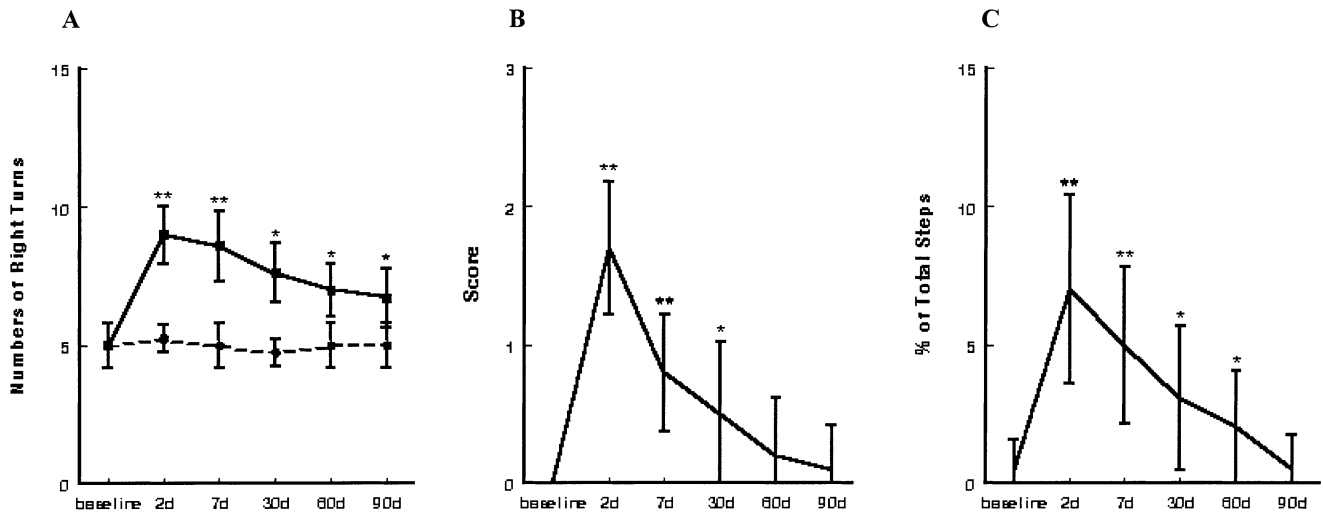


Fig. 3. Behavioral functional tests (mean ± S.D.) after ischemia. (A) Corner test: M sham, O ischemic; (B) Neurological score; (C) Foot-fault test. \*\**P* < 0.01, \**P* < 0.05. ... data from sham mice, — data from ischemic mice. Sham mice show no neurological deficits or foot faults over the 90 day testing period. Therefore, their data are not included in the respective figures.

Table 1  
Individual predictive ability (*R*<sup>2</sup>)

	Individual predictive ability			
Post ischemic days	2 days	7 days	30 days	60 days
Corner test	0.93 <sup>a</sup>	0.84 <sup>a</sup>	0.84 <sup>a</sup>	0.73 <sup>a</sup>
Neurological score	0.05	0.05	0.49	0.07
Foot-fault test	0.16	0.31	0.12	0.05

### 3.5. Foot-fault test

Animals subjected to ischemia showed a significant (*P* < 0.05) increase in the percentage of left forelimb foot faults compared with values from pre-ischemia and sham operated animals 2–60 but not at 90 days after MCA occlusion (Fig. 3C).

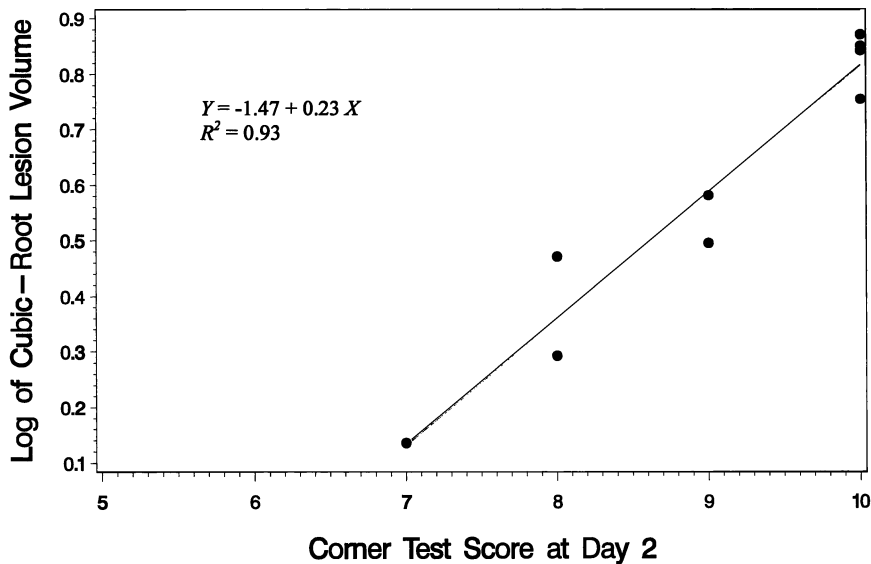


Fig. 2. The front view of the corner test from a representative mouse 90 days after MCA occlusion. The mouse walked forward until it reached the corner (A). The mouse then reared forward and upward, then turned back along the right side wall to face the open end (B–D).

### 3.6. Prediction and correlation

Table 1 shows the prediction values ( $R^2$ ) for 90 day infarct volume from individual tests at each time point. The corner test was most predictive of infarct volume, with the 2 day test achieving an  $R^2$  of 0.93 (Fig. 4) compared with 0.05 and 0.16 for the neurological score and foot-fault tests, respectively. The superior predictive ability of the corner test was maintained until 60 days. After multivariable analysis, only the corner test remained in the final multivariable model, indicating that the corner test independently predicts 3 month infarct volume. The correlation coefficients between behavior test score and infarct volume at 3 months are 0.31 ( $P = 0.38$ ) for foot-fault test, 0.50 ( $P = 0.14$ ) for neurological score and 0.92 ( $P = 0.0002$ ) for the corner test score.

## 4. Discussion

The goal in this study was to develop a test that is sufficiently sensitive to discriminate neurological functional deficits in mice during stroke recovery. To this end, we developed the corner test, which is very easy to carry out. The results show that the corner test can detect impairments of sensorimotor function even 90 days after mild focal cerebral ischemia. We also assessed neurological deficits in the same mice using the four point neurological score which is a commonly used test to measure neurological deficits in mice after ischemia (Choudhri et al., 1998; Huang et al., 1994), and the foot-fault test which is a sensitive indicator for detecting forelimb sensorimotor function deficits after ischemic insults in rats (Stroemer et al., 1995, 1998). The neurological score and the foot-fault test can detect sensorimotor deficits only up to 30 and 60 days, respectively, after ischemia. The observation of spontaneous functional recovery is consistent with previous studies on experimental stroke (Okada et al., 1995; Johansson and Grabowski, 1994; Witte et al., 2000). The assessment of long term functional recovery is important for evaluating therapies aimed at enhancing brain tissue plasticity after stroke (Schallert et al., 2000; Cuello, 1997). The corner test may take advantage of multiple partial sensory and motor asymmetries associated with cortical or striatal dysfunction, including vibrissae sensory, postural and limb use biases documented in rat models (Barth et al., 1990; Tillerson et al., 2001).

Assessment of functional deficits under different treatment strategies requires a clear understanding of the relationship between histopathological damage and functional consequences (Pineiro et al., 2000). The correlation between ischemic lesion volume and functional impairment has been investigated after MCA

occlusion in the rat (Rogers et al., 1997), and a significant correlation between infarct volume and functional impairment after ischemia was detected (Grabowski et al., 1993; Zhang et al., 2000; Zausinger et al., 2000). However, a high correlation between long-term (e.g. 90 days) functional impairment and infarct volume after MCA occlusion in the mouse has not been described for a single test. Our results show, for the first time, that there is a strong correlation between the infarct volume and the sensorimotor impairments measured by the corner test 90 days after MCA occlusion. In contrast, the infarct volume was poorly correlated with functional deficits measured by neurological score or foot-fault test. The location of the ischemic lesion is critical in determining functional outcome after focal cerebral ischemia (Bederson et al., 1986; Persson et al., 1989). In the present study, the ischemic lesion was primarily localized to the striatum in mice that survived for 90 days after ischemia, suggesting that the ischemic lesion in the striatum makes a primary contribution to the sensorimotor functional impairments detected by the corner test. A lack of correlation between the infarct volume and functional deficits measured by foot-fault test or the neurological score further demonstrates that these two tests are not suitable to assess long term neurological deficits and that there is little relationship between the degree of striatal lesion and these functional deficits.

Clinical studies have shown that an early neurological functional deficit is a major predictor of stroke outcome (Adams et al., 1999; Jongbloed, 1986). However, because of the lack of sensitive functional measurements on experimental stroke, the reduction of ischemic lesion volume is employed as the primary outcome measurement in testing therapeutic interventions (Park et al., 1988; Mohamed et al., 1985). Our study shows that the functional deficits measured by the corner test at early time points after ischemia predict the infarct volume measured 3 months after MCA occlusion and a worse asymmetry score on the corner test predicts a larger ischemic lesion volume. Neither the foot-fault test or the neurological score predicts the ischemic lesion at 3 months of ischemia.

In summary, the corner test is an easily performed and a sensitive and objective test, which can be applied to evaluate the long term functional deficits and to predict striatal infarct volumes in the mouse after stroke.

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