



## Review

### Effects of Stroke on Motor Function in Laboratory Animals

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#### Introduction

Stroke is the fourth leading cause of death in the United States [1], and there are currently only two treatments that are approved by the Food and Drug Administration in emergency management-thrombectomy and tissue plasminogen activator [2]. However, these treatments are very difficult to administer because they have to be given within hours post stroke. These treatments have limited restorative effects which can lead to the development of motor function impairments [3]. Studies conducted in small and large animal stroke models, such as rodents and pigs, can be used to measure how stroke affects motor function [4,5]. Most preclinical stroke studies have been conducted using rodent models. While rodents are easy to test, they do not have similar brain size as humans, therefore making it more difficult to yield applicable results [4]. Testing motor function changes in large animal models, such as swine, may be advantageous because their brain more closely resembles the human brain. A pig's brain is gyrencephalic and resembles the human brain more in anatomy, growth and development than rodents, and thus may be a more translational model to study stroke [5]. A number of assessment modalities have been developed to measure changes in fine and gross motor function as well as gait after stroke. For example, the cylinder test, ledged tapered beam test, and the grid walking test have been utilized in rodent stroke models to assess forelimb, hindlimb, and gait function, respectively. In addition, quantitative gait analysis has been performed in swine after stroke to measure changes in spatiotemporal gait parameters. Although extensive research has made much progress in treating stroke, the two approved treatments for stroke do little to improve motor function. Therefore, therapies that restore motor function, such as multimodal rehabilitation therapy and Rota-rod training, are being tested in preclinical models [6,7]. Rehabilitation therapy has been the most effective so far post stroke due to its specific focus on improving

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motor function [8]. In this review, we will discuss the methods and modalities used to recognize changes in motor function in rodents, examine the methods and modalities used to recognize changes in motor function post stroke in swine, and look into potential treatments that can be used to aid motor function.

#### Rodent Motor Function Assessment

Different tests are used in animal stroke models to assess changes in limb function and gait. The ability to recognize changes in motor function in stroke animal models may help to advance current understanding of stroke induced motor function deficits in human stroke patients. These tests include the cylinder test, which measures forelimb function, the ledged tapered beam test, which measures hind limb function, and the grind walking test, which measures gait functionality [9,10].

Following a stroke that affects upper or lower extremity function, humans tend to develop a reliance on their less-affected limb [11]. Therefore, researchers fear that the learned non-use of the affected limb post stroke can impede potential recovery [12]. An example of this is shown through the results from the cylinder test. Roome, et al., found that when stroke-induced rats are placed in the cylinder, they rely more heavily on their unaffected forelimb paw for support, therefore resulting in fewer touches with the affected paw [13]. Similar results were observed with the ledged tapered beam test. In this test, animals must walk across an elevated beam that tapers at one end. Any type of misstep on the beam is viewed as deficits in hindlimb function [14]. Tahamtan M, et al., has showed that the number of missteps increases on the affected hindlimb post stroke and become more reliant on the unaffected hindlimb [15]. The grid walking test has also been utilized to determine if rodents develop a heavier reliance on their less affected limb after stroke. The grid walking test has been found to objectively demonstrate motor coordination deficits and rehabilitation effects after stroke [11]. The animal is placed on grid that is elevated with a small opening. An intact animal can do the test without any fault [14], however, animals post-stroke make a significant amount of missteps throughout the test [16]. Different tests and studies are being conducted to determine the correlations between forelimb, hindlimb, and gait assessment throughout rodent models [17]. Additional studies and trials are needed to be done in different animals to adequity assess and conclude a potential therapy treatment in humans, not just rodents.

#### Swine Motor Function

Although past stroke models have heavily relied on rodents, researchers are questioning how applicable a rodent stroke model is to a human stroke due to the differences anatomically and physiologically [18,19]. Therefore, stroke models are being tested in swine because they are more similar in gray to white matter composition, blood flow, gyral patterning, metabolism, and brain size in humans [20]. Through gait analysis and open field testing, researchers can determine the changes in motor functions post stroke in swine models. Gait analysis is different from the grid walking test, cylinder test, and other

common motor function assessments because it provides a more sensitive means to analyze changes in motor function [21].

For gait analysis, the pigs are trained to walk through a semi-circular track and are recorded with high speed cameras to determine changes in gait parameters. Gait analysis in a healthy pig demonstrates symmetry in hindlimb and forelimb swing and stance times, step length, step velocity, and maximum hoof height. A study conducted by Duberstein, et al., recorded gait post stroke in swine. His results exhibited lower maximum front hoof height on the affected stroke side, as well as shorter swing time and longer stance time on the affected hindlimb. This suggests that gait analysis is a highly sensitive detection method for changes in gait parameters in swine [22]. Webb, et al., further demonstrated this through his study that tested gait in untreated post stroke swine, and neural stem cell treated swine post stroke. After 28 days post stroke, the treated pigs exhibited a significant increase in temporal and spatial gait parameters in comparison to untreated pigs. In treated swine, there were improvements in velocity, cadence, and swing percent of cycle [21].

In open field testing, a pig is put in a fenced in area for a certain amount of time and observed [23]. Tracking software is used to analyze the movement of the pigs throughout the time spent in the open field area and measures changes in motor activity, such as distance travelled [22]. Pre-stroke pigs exhibited high mobility and thus travelled more distance compared to stroke pigs. Stroke pigs travelled significantly less distance the first week post stroke which indicates that mobility may have been impaired. However, after seven days post stroke, pigs treated with neural stem cells recovered while control pigs were still significantly impaired [21]. Only a few studies have been done analyzing changes in motor function post stroke in swine. Therefore, more studies need to be conducted to determine the changes in motor functions in swine after strokes.

## Stroke Treatment

A stroke can lead to life altering physical disabilities. Currently, both Food and Drug Administration approved treatments, thrombectomy and tissue plasminogen activator, do not have restorative effects which may lead to the development of motor function impairments [2]. Therefore, different rehabilitation therapies are being tested in effort to provide people with the best quality of life post stroke. Trials are being run in rodents using Multimodal rehabilitation and Rota-rod training to see how motor function improves [23-27]. Multimodal rehabilitation aims to improve long-term perception of recovery, as well as balance, gait, grip strength, and working memory post stroke [24]. In a study conducted by Wang, et al., multimodal rehabilitation therapy for rodents includes balance beam training, rotating stick training, and self-made roller training. The rats were trained to do three different things: Crawl on the balance beam to develop walking balance and coordination abilities, crawl on a stick to develop dynamic balance, rotate a hand crank to develop the grasping and rotating motor function [24]. The rats receiving multimodal rehabilitation improved their scores on the Bederson neurological function, balance beam, and screen test. Therefore illustrating that the multimodal rehabilitation has been a success in rodents thus far. Another study conducted by Yagura, et al., suggested that after multimodal rehabilitation program, motor function and activities in daily life of the subjects were improved. His study also found that the earlier the rehabilitation began post stroke, the better rehabilitative effects in the subjects [25].

A study was conducted by Ding, et al., to determine if complex motor training on Rota-rod can aid motor function improvement as compared to simple locomotors exercise on a treadmill. The Rota-rod performance test is a performance test based on a rotating rod with forced motor activity being applied [26]. The test evaluates balance, grip strength, and motor coordination of the rodents. Motor function was evaluated by a testing foot fault placing, parallel bar crossing, rope and ladder climbing before and at 14 or 28 days after training procedures in both ischemic and normal rodents. Compared with both treadmill exercised and non-trained animals, Rota-rod-trained animals with or without a stroke significantly improved motor performance of all tasks except for foot fault placing after 14 days of training, with normal rats having better performance [27]. A similar study found the same results after testing adult male rats post stroke with treadmill training, motor training on the Rota-rod, or both Rota-rod and treadmill training.

Through different assessments such as limb placement, Seo HG, et al., was able to conclude that Rota-rod training showed more improvement in motor function and coordination than treadmill training [28]. The implications of Rota-rod training in humans and also treadmill training has been found to have the possibility to help keep the remaining cortical tissue in the brain intact, therefore improving motor function [29].

## Conclusion

Though there are only two approved treatments for strokes in humans. However, both of these treatments are restricted by time constraints and do not have regenerative properties, leading to a lifetime of therapy that inhibits a normal life. To find a regenerative therapy that medicates these effects, strokes are being conducted in swine and rodent models to determine a potential treatment for humans. Changes in motor function are closely observed in rodents using the cylinder test, ledged tapered beam test, and grid walking test. These tests analyze forelimb and hindlimb changes, and illustrate how reliant rodents become on the unaffected side limbs of the body post stroke. Although these tests are useful, rodent's brains do not closely resemble human brains. A pig model is more indicative of future human success due to the similarities in brain matter between humans and swine. Therefore, it is of interest to analyze the effect of stroke on motor function and motor activity behaviors in swine by using gait analysis and open field testing, respectively. A limited number of studies have been conducted using swine, so additional studies are needed to determine the effects of stroke on motor function in swine. Because none of the current stroke treatments in emergency management account for motor function impairment, different therapies are being tested to see how it improves motor functions in rodents. These therapies include the multimodal rehabilitation therapy and Rota-rod therapy, which have promising results thus far. Additional research needs to be done in order to find a better treatment for stroke that encompasses all aspects of the healing process.

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