Evaluating a novel rehabilitation paradigm designed to enhance motor recovery in a rat model of endothelin-1 induced ischemic injury

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Introduction

Stroke is the leading cause of permanent neurological disability. Its neurological impact produces devastating impairment in motor, sensory, and cognitive function. Therefore, there is a pressing need for the development of effective rehabilitation paradigms that promote maximal recovery of function during the early stages of the post-stroke period.

A variety of rehabilitation paradigms have been developed using multiple animal models to demonstrate the benefits of post-stroke physical therapies on motor function. However, these different rehabilitation paradigms often only provided the animal models with limited recovery, and exact mechanisms that underlie these recoveries are still unknown.

The objective of this experiment was to develop a new rehabilitation paradigm that utilizes short reaching and enriched environment physical therapy sessions to improve our understanding of the relationship between enriched environment activities and recovery in motor function. A combination of positive aspects of rehabilitation paradigms from previous studies was manipulated to generate this new and potentially superior rehabilitation routine for use in pre-clinical models of ischemic stroke.

Conclusion

A statistically significant difference was observed between rehabilitation and non-rehabilitation groups on the staircase reaching test at 5 weeks post stroke.

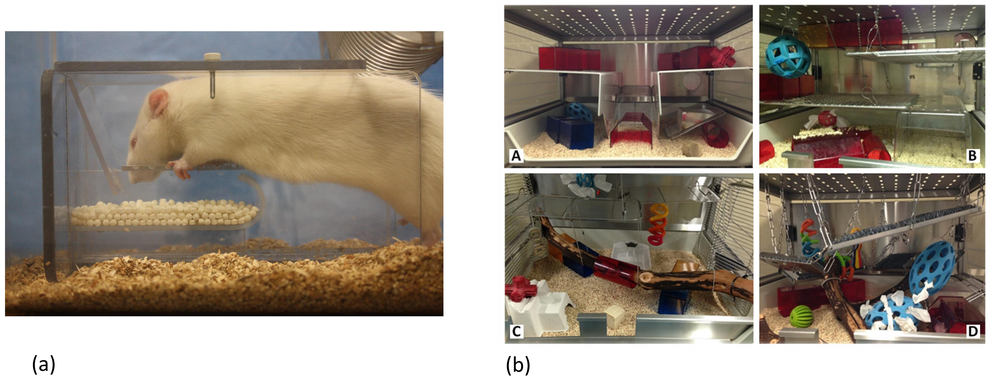
Although the differences observed on the beam test were not statistically significant, the rehabilitation group appeared to perform more successfully than the non-rehabilitation group. A replication of this experiment may be required in order to achieve statistical significance of this measure.

The measurement of infarct volumes showed that the non-rehabilitation group had larger stroke damage than the rehabilitation group. This could indicate that stroke damage is a confounding variable for interpreting the effects of rehabilitation. However, this data is only from the first 2 out of 12 animals per group and could be subject to change.

For these reasons, the results obtained in this study are encouraging, but do not fully demonstrate that this rehabilitation paradigm is effective.

Results

Rehabilitation paradigm



(a) (b)

Figure 1: The two parts to the newly developed rehabilitation paradigm. **(a)** reach training. **(b)** enriched environment cage configuration for (A) week one, (B) two, (C) three, and (D) four of the rehabilitation protocol.

Behavioural testing

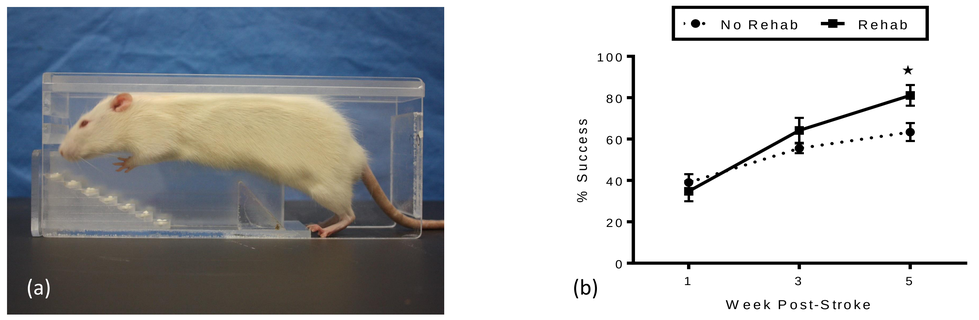


Figure 2: **(a)** staircase reaching test. **(b)** results show that rats in the rehabilitation group performed significantly better than the non-rehabilitation animals at 5 weeks post-stroke.

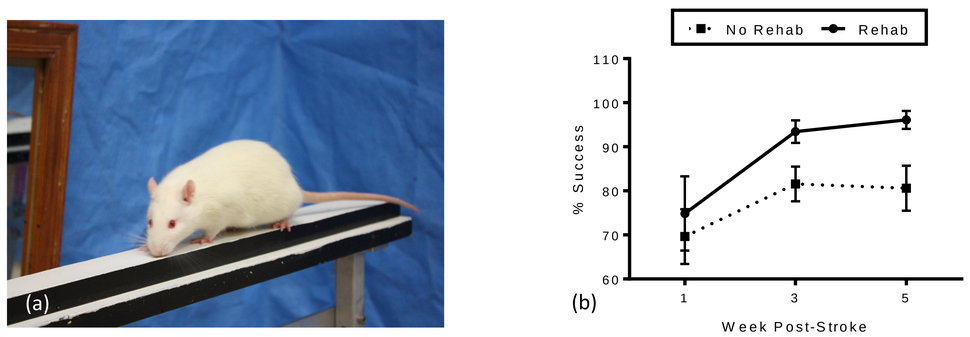


Figure 3: **(a)** beam-walking task. **(b)** although the rats in the rehabilitation group performed better than the non-rehabilitation animals at 5 weeks post-stroke, no significant differences were detected between groups for the hindlimb on the beam-walking task.

Histological examination

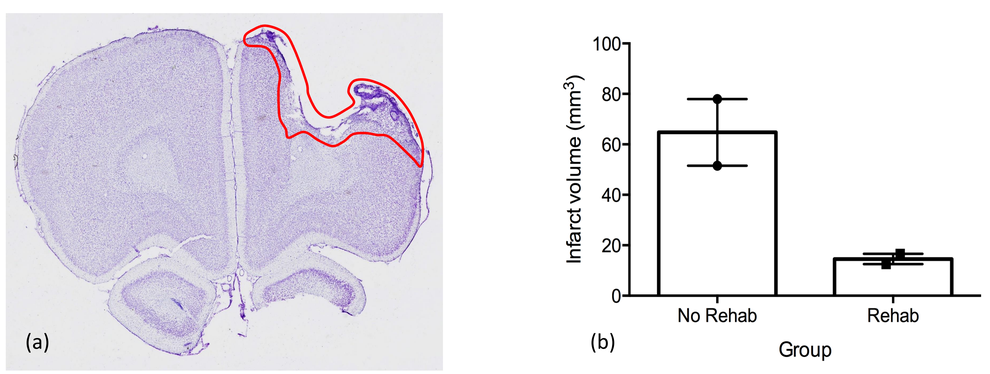


Figure 4: (a) Section of a post-stroke brain that has been histologically prepared with a cresyl violet stain. Stroke damage is outlined in red. **(b)** the non-rehabilitation group had larger stroke damage than the rehabilitation group.

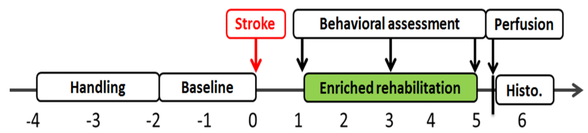
Methodology

Pre-stroke behavioural assessment:
24 rats were randomized into two groups: those that would receive rehabilitation, and those that would not receive rehabilitation. Pre-stroke behavioural assessment took place for two weeks, during which, all rats were trained for 14 days in the staircase test, and two days in the beam walking test.

Post-stroke rehabilitation schedule:
Following the endothelin-1 induced focal ischemia, the two experiment groups of rats were separated. The rehabilitation group was placed in enriched environment cages in groups of 6, for 4 hours, 5 days a week. The contents of the enriched environment cage were changed once a week to give the rats more variation in motor, cognitive, and social stimulation. After each enriched environment shift, the rats were exposed to 4, 15 minute sessions of reaching rehabilitation per day. This rehabilitation schedule lasted for 4 weeks post-stroke.

Post-stroke behavioural assessment:
After the 3rd and 5th week post-stroke, the same behaviour assessments as pre-stroke were conducted on both the rehabilitation, and non-rehabilitation groups.

Processing the brain tissue:
All rats were perfused, and the brain tissue was processed for the histological examination of infarct volumes of each stroke. The processing included freezing the brains with isopentane and dry ice, cutting the tissue into sections using a cryostat, and staining the tissue with cresyl violet.



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