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Research report

Procedural learning as a measure of functional impairment in a mouse model of ischemic stroke

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HIGHLIGHTS

- In this study, we examined functional deficits in a murine stroke model (MCAO).
- MCAO caused significant impairments in the rotarod and amphetamine tests.
- In an operant task, MCAO affected the way mice learned a motor sequence.
- This finding is congruent with cognitive impairments experienced by stroke victims.

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ABSTRACT

Basal ganglia stroke is often associated with functional deficits in patients, including difficulties to learn and execute new motor skills (procedural learning). To measure procedural learning in a murine model of stroke (30 min right MCAO), we submitted C57Bl/6J mice to various sensorimotor tests, then to an operant procedure (Serial Order Learning) specifically assessing the ability to learn a simple motor sequence. Results showed that MCAO affected the performance in some of the sensorimotor tests (accelerated rotating rod and amphetamine rotation test) and the way animals learned a motor sequence. The later finding seems to be caused by difficulties regarding the chunking of operant actions into a coherent motor sequence; the appeal for food rewards and ability to press levers appeared unaffected by MCAO. We conclude that assessment of motor learning in rodent models of stroke might improve the translational value of such models.

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1. Introduction

Ischemic strokes represent a major healthcare concern in industrialized and developing countries [1,2]. The sudden obstruction of a major brain vessel causes a state of prolonged ischemia, which in turn leads to the infarction of brain tissues, and ultimately to severe and chronic disabilities. Various animal models of stroke (most of them relying on rodents) have been elaborated to unfold the pathophysiology of cerebral ischemia [3–5]. A better understanding of ischemia carried the hope of developing novel "neuroprotective" drugs that could alleviate brain injuries when administered shortly after stroke. Unfortunately, although numerous compounds showed to be effective in reducing histological damages in rodent models, they failed to demonstrate any efficacy in clinical trials [6]. This particular issue in stroke research has been referred to as a "translational roadblock" [7].

There are many possible ways to improve preclinical stroke research, which could contribute to overcome this roadblock (for example, expanded international collaboration [8], implementation of Good Laboratory Practice [9] or more rigorous study design [10]). Noticeably, experts recommend that stroke studies should include diverse and valid markers of stroke outcome (biological as well as behavioural) [11,12]. Indeed, since significant functional improvements in patients should be the endpoint of any intervention, a reduction in histological damages is not a sufficient condition to substantiate the potential therapeutic value of a new treatment. Consequently, behavioural testing is a necessary step in experimental studies using rodents. There have already been multiple efforts to develop neurobehavioral test batteries relevant to stroke

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models. Ideally, such a battery should include tests that (1) identify long-term functional alterations, (2) be sensitive to the effects of a treatment, (3) be easily reproducible, and (4) match the symptomatology reported in human stroke victims.

Sensory and motor impairments are some of the most debilitating consequences of ischemic stroke. Therefore, functional assessment in stroke models has been primarily focused on sensory and motor abilities, using standardized tests that are easily replicable. Open-field, beam-walking, accelerated rotating rod, staircase test, skill-reaching task or wire-hanging test have all become household names in neurobehavioural research. Nonetheless, up to now there is no general agreement on which tests are the most appropriate to use in stroke models [13]. Indeed, the literature reports inconsistencies in their capacity to screen for long-lasting markers of functional impairment. Thus, in order to isolate the tasks that will provide the most accurate and relevant measures of functional impairment it remains necessary to carry on characterization of the post-stroke sensory and motor status in the different animal models.

Besides sensory and motor impairments, cognitive deficits are largely prevalent in stroke victims and rarely recover over time [14,15]. Noticeably, difficulties regarding procedural learning have been consistently identified among stroke victims [16–19], but rarely addressed in rodent stroke studies. Procedural memory is regarded by cognitive psychologists as a type of implicit, non-declarative memory, which is used to acquire, store and execute highly automatized behaviours (*i.e.*, habits and skills) [20]. Examples of procedural-dependant activities include driving a car, biking or typing on a keyboard. The acquisition of any type of procedural knowledge requires organising motor units into a coherent sequence. As procedural learning takes place, the motor sequence becomes automatic: actions or sequences of actions are triggered by external cues (without explicit recall), with the need for little cognitive resources.

In humans, puzzles and problem-solving tasks that are greatly dependent on the organisation and ordering of motor actions proved to be especially sensitive to the effect of basal ganglia (BG) stroke. In the Serial Reaction Time Task (a test designed to evaluate the ability to learn a simple visuo-motor sequence), the presence of a BG infarct negatively affected the procedural performance [17]. In the Towers of Hanoi test (a puzzle commonly used in clinical settings to assess planning and execution of motor sequences), patients who had suffered from a left BG stroke needed more moves to solve the problem, while patients with right BG infarct failed to improve their performance over repeated trials. Congruently, weaker performances in the Porteus maze (another neuropsychology test reflecting procedural abilities) have been reported in patients with either left or right BG infarct, when compared to matched controls [16]. Many other examples of procedural impairments related BG stroke can be found in the literature [21–25], and further investigation suggested they might result from an inability to chunk motor units in a coherent motor sequence [26,27].

Investigation of procedural deficits as markers of stroke damages is especially relevant to the middle cerebral artery occlusion (MCAO) model. Indeed, the middle cerebral artery supplies blood to a territory that is roughly equivalent to the BG. Therefore, procedural impairments appear as relevant indicators of functional MCAO-related damages. Several animal studies employing MCAO already pointed out behavioural anomalies that may be related to poor procedural abilities. Bingham et al. found that an unilateral MCAO-induced cortical infarct caused a weaker performance in rats during non-spatial Morris water maze (MWM) training, while spatial cognition was relatively preserved. They suggested this finding is explained by deteriorated sensorimotor and procedural abilities, rather than memory impairments [28]. Cain and Boon showed that bilateral MCAO affected MWM performance in both spatial and non-spatial trials [29]. Other authors reported an alteration of the search strategy to find the hidden platform following MCAO in rats that might be as well related to procedural impairments [30]. MCAO in mice also deteriorated performance in non-spatial MWM trials, suggesting the presence of procedural impairments in murine models too [31]. Finally, the learning curve in different sensorimotor tests (beam-walking, parallel bar crossing, rope and ladder climbing) is also impacted by MCAO, a result that can be interpreted as deficient motor learning [32]. Despite these evidences, procedural learning has never been specifically appraised in rodent stroke models, in a way that it could not be confounded with pre-existing motor impairments.

The first purpose of the present work was to investigate the capacity of a sample of sensory and motor tests to detect stroke-related deficits, in order to further clarify what is affected and what is preserved after MCAO in mice and which tests can be used as long-term measurements. We focused on accelerated rotating rod (rotarod), corner test, and open-field locomotion; all of these tests do not require extended training, and have already been applied to rodent stroke models, but still lead to inconclusive results. In addition, we introduce the amphetamine-induced rotation test, which has been often been used in Parkinson's disease research to highlight unilateral motor impairments due to striatal impairments [33], but has only been seldom employed in preclinical stroke research, and never with murine models.

We also decided to determine whether procedural learning would be a pertinent indicator of cognitive impairment in the MCAO model. Several studies already demonstrated the suitability of operant conditioning for behavioural assessment in rodent models of either focal or global ischemia [34–40]. Hence, we used a specific operant procedure to study procedural abilities following MCAO surgery. The Serial Order Learning (SOL) task is a practicable rodent operant schedule, in which animals have to learn and perform an ordered motor sequence (namely a left lever-press immediately followed by a right lever-press) [41,42]. The SOL task appears to be a relevant task to investigate motor (procedural) learning in a rodent stroke model known to elicit substantial subcortical infarction (*i.e.*, the BG, including caudoputamen and pallidum).

In addition to various sensory and motor performances, we hypothesize that experimental cerebral ischemia might disrupt the learning of a motor sequence in an operant procedure, providing another valid measure of functional impairment. We subjected C57Bl/6J mice to right MCAO (30 min) that later were submitted to different sensory and motor tasks (accelerated rotarod, corner test, open-field and amphetamine-induced rotation) and, finally, to an operant SOL procedure appraising the integrity motor learning processes. Along 12 daily SOL sessions, we monitored several behavioural parameters to provide a precise description of potential deficits in the learning of a simple motor sequence. Our aim was to show that with stroke rodent models (as it is with other brain pathologies), simple automatized operant tasks could help to pinpoint relatively long-lasting and valid cognitive impairments.

2. Material and methods

2.1. Animals

All experimental treatments and animal maintenance were reviewed by the Animal Care and Experimentation Committee of the Université de Liège. The Animal Care and Experimentation Committee gave its approval according to the Belgian implementation of the animal welfare guidelines laid down by the European Community (EEC Council Directive N°86/609 of the 24 November 1986; Directive for the Protection of Vertebrate Animals used for Exper-

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