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Use of the parallel beam task for skilled walking in a rat model of cerebral ischemia: A qualitative approach

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ABSTRACT

The parallel beam task (PBT), in which animals walk across two elevated parallel beams, is commonly used to assess motor deficits in laboratory rodents. Performance of the PBT challenges postural balance, inter-limb coordination and skilled walking abilities, and is typically assessed by quantitative measures such as number of foot slips and/or successful traversals. We proposed that including qualitative movement analysis of skilled walking would increase resolution and sensitivity of PBT assessments in rats with cortical ischemic lesion. Pre-trained rats with a unilateral devascularization of the primary motor cortex and controls were recorded from lateral and ventral views as they traversed a PBT made of two parallel metal beams. The new qualitative skilled walking scoring system analyzed four elements of posture, limb placement, and targeting (limb rotation and position, number of placing attempts and foot slips) based on frame-by-frame video analysis. The analysis revealed that motor cortex lesions produced significant deficits in contralateral limb rotation and limb placement in both fore- and hind limbs, compared to ipsilateral limbs and control animals. Fore- and hind limbs showed different patterns in limb placement impairments. The results indicate that forelimb foot slips are a more sensitive measure of lesion-induced deficits than hind limb foot slips. Thus, the PTB is an effective task for the assessment of skilled walking and motor learning strategies especially when combined with qualitative movement analysis in rodent models of stroke.

1. Introduction

Damage to the nervous system causes varying degrees of motor impairments. Animal models of neurodegenerative diseases, as well as stroke and spinal cord injury require the use of detailed and sensitive tasks of skilled and non-skilled motor function in order to unambiguously identify motor loss and potential functional recovery. Many behavioural assays are available to measure motor function in rodents. The inclusion of qualitative scoring techniques along with quantitative assessments is essential to for comprehensive identification of motor recovery and compensation (Jones & Roberts, 1968; Hamm, Pike, O'Dell, Lyeth, & Jenkins, 1994; Carter, Morton, & Dunnett, 2001; Metz & Whishaw, 2002; Luong, Carlisle, Southwell, & Patterson, 2011). Lesion animals may learn to perform a task using compensatory actions and mask true

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deficits (Metz, Antonow-Schlorke, & Witte, 2005; Moon, Alaverdashvili, Cross, & Whishaw, 2009; Kirkland, Smith, & Metz, 2012; Wallace, Winter, & Metz, 2012; Girard, Murray, Rothwell, Metz, & Allan, 2014). In the absence of a qualitative measure, remaining subtle deficits and aspects of compensation versus genuine recovery may go unnoticed. Therefore, both quantitative and qualitative analyses are required for the unambiguous assessment of motor impairments.

Detailed analysis of motor function can give an indication of potential clinical outcomes when identifying potential pharmaceutical or behavioural therapies in animal models of nervous system damage (Rivlin & Tator, 1977). Analysis of locomotion allows identification of posture, coordination and limb placement of all four limbs simultaneously (Metz & Whishaw, 2002; Whishaw, Li, Whishaw, Gorny, & Metz, 2003). Additionally, most skilled walking tasks require little or no training, making them time- and cost-effective. Common locomotor tasks include the accelerated rotarod (Jones & Roberts 1968; Whishaw et al., 2003), the ladder rung walking task (Metz & Whishaw, 2002), the balance beam (Wallace, Krauter, & Campbell, 1980), and the ledged tapered beam task (Schallert, Woodlee, & Fleming, 2002; Zhao, Puurunen, Schallert, Sivenius, & Jolkkonen, 2005). In the accelerated rotarod, an animal is placed on a spinning rod and the time it is able to maintain balance before falling off is measured (Carter et al., 2001; Buitrago, Schulz, Dichgans, & Luft, 2004). It can be difficult to analyze all four limbs simultaneously on the accelerated rotarod because the animal's body wraps around the spinning drum (Whishaw et al., 2003, 2008). By contrast, the ladder rung walking task is a series of metal rungs arranged at regular or irregular distances and enclosed by Plexiglas walls. This apparatus leaves all four limbs visible when videorecorded from a ventral view in order to score limb placement on the rungs while an animal is traversing (Metz & Whishaw, 2009). In the balance beam animals traverse a single dowel, while the width and shape of the dowel can vary to determine movement difficulty.

Movements in skilled motor tasks challenge posture and limb coordination as opposed to normal overground locomotion, such as open field or footprint analysis (Merrett, Kirkland, & Metz, 2010; Klapdor, Dulfer, Hammann, & Van der Staay, 1997; Schaar, Brenneman, & Savitz, 2010). The challenging surface of these walking tasks along with the opportunity for descriptive movement analysis renders them particularly sensitive to subtle motor deficits induced by stress (Metz, Schwab, & Welzl, 2001), motor cortex and subcortical lesions (Metz & Whishaw, 2002).

The present study uses a parallel beam task (PBT) to re-examine the potential in using it for descriptive, qualitative movement analysis of motor status in rats. The PBT requires accurate inter-limb coordination and balance while left and right limbs are maneuvered along two distant parallel beams. While performance in the PBT traditionally is assessed by quantitative measures, such as foot slips and percent of successful traversals, the aim of this study was to introduce a new qualitative skilled walking scoring system for the analysis of performance in the PBT. The findings show that the new qualitative assessment, which includes evaluation of balance and coordination, enhances sensitivity for inter-group comparisons after motor system lesions.

2. Material and methods

2.1. Animals

Twenty-three male Long-Evans rats, 3-month old and weighing 260–330 g, were used. Twelve rats received motor cortex devascularization lesions and eleven served as non-lesion control rats. Animals were housed in pairs in traditional Macrolon shoebox cages with a 12:12 light-dark cycle, with lights on at 7:30 AM Room temperature was maintained at $22 \pm 1°$ C. Animals had access to food and water ad libitum. All procedures were approved by the Animal Care Committee of the University of Lethbridge in accordance with the guidelines of the Canadian Council of Animal Care.

2.2. Motor cortex lesion

Animals were anesthetized using 4% isoflurane and placed on a stereotaxic frame. Isoflurane was then reduced to 2% for maintenance with an oxygen flow rate of 2.0 L/min. All animals received 0.05 mg/kg of Buprenorphine (Reckitt Benckiser Health Care, UK) prior to surgery. The skin above the skull was incised to expose the skull. Unilateral lesions were induced on either left ($N = 6$) or right ($N = 6$) hemispheres. Using a fine dental drill, rectangular craniotomies were made at 1–4.5 mm mediolateral to the midline and −1.0 to 4 mm anterior-posterior to bregma (Zucchi et al., 2010). In this area, vascular tissue was carefully removed with microscissors and sterile saline-soaked cotton swabs, ensuring that the brain was not punctured or compressed. Bleeding was controlled using sterile cotton swabs dipped in saline solution. The scalp was sutured after surgery and the animals were placed in transport cages on heating pads until fully awake before being returned to their home cages. Animals received 1 mg/kg Metacam (Boehringe Ingelheim, Canada) following surgery. Animals were observed for one week following surgery for signs of pain and treated with additional doses of Metacam if necessary.

2.3. Parallel beam task (PBT)

2.3.1. Apparatus

The PBT consisted of two horizontal, parallel flat metal beams, each 100 cm long and 1 cm wide, spaced at 3.5 cm apart. The PTB was framed by Plexiglas side walls 9 cm apart, 19 cm in height, along the length of the parallel beams. The beam was elevated 30 cm above the ground. One end of the beam was connected to a neutral start platform, with a refuge (the

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