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The bradykinesia assessment task: An automated method to measure forelimb speed in rodents

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HIGHLIGHTS

- The bradykinesia assessment task is an automated method to measure forelimb speed in rats.
- This novel task can quantify several parameters of forelimb function.
- Multiple aspects of the task can be adjusted to modify difficulty.
- Ischemic motor cortex and hemorrhagic striatal lesions both decrease all measures of performance.
- The isometric pull task is useful in assessing forelimb function in multiple models of brain damage.

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ABSTRACT

Bradykinesia in upper extremities is associated with a wide variety of motor disorders; however, there are few tasks that assay forelimb movement speed in rodent models. This study describes the bradykinesia assessment task, a novel method to quantitatively measure forelimb speed in rats. Rats were trained to reach out through a narrow slot in the cage and rapidly press a lever twice within a predefined time window to receive a food reward. The task provides measurement of multiple parameters of forelimb function, including inter-press interval, number of presses per trial, and success rate. The bradykinesia assessment task represents a significant advancement in evaluating bradykinesia in rat models because it directly measures forelimb speed. The task is fully automated, so a single experimenter can test multiple animals simultaneously with typically in excess of 300 trials each per day, resulting in high statistical power. Several parameters of the task can be modified to adjust difficulty, which permits application to a broad spectrum of motor dysfunction models. Here we show that two distinct models of brain damage, ischemic lesions of primary motor cortex and hemorrhagic lesions of the dorsolateral striatum, cause impairment in all facets of performance measured by the task. The bradykinesia assessment task provides insight into bradykinesia and motor dysfunction in multiple disease models and may be useful in assessing therapies that aim to improve forelimb function following brain damage.

1. Introduction

Rodent models have been extensively used to study motor learning as well as dysfunction after various types of brain damage. A diverse set of behavioral tasks is employed to measure various parameters of forelimb function. Several different pellet retrieval tasks provide insight into reach accuracy (Montoya et al., 1991; Whishaw et al., 1991; Buitrago et al., 2004; O'Bryant et al., 2007; Kleim et al., 1998) and range of motion (Ballermann et al., 2001; Metz et al., 2001), while pasta handling tasks are used to examine paw dexterity (Allred et al., 2008; Tennant et al., 2010). In addition, forelimb strength can be estimated (Remple et al., 2001; Ballermann et al., 2001) or quantified (Dunnett et al., 1998; Smith et al., 1995) using other methods. Data from these tasks have yielded important information describing forelimb function; however, additional parameters, such as speed of forelimb motion, are not automatically quantified by any existing tasks.

Bradykinesia is a common consequence associated with many motor diseases. Along with resting tremor, postural instability, and rigidity, bradykinesia is one of the hallmark features of Parkinson's disease (Nutt and Wooten, 2005; Teulings and Stelmach, 1991). Slowed movements are also prevalent in patients of stroke (Thielman et al., 2004; Cirstea and Levin, 2000), Huntington's disease (Quinn et al., 1997), and traumatic brain injury (Kuhtz-Buschbeck et al., 2003). Despite the need for a measure of bradykinesia in rodents, there are few existing methods to

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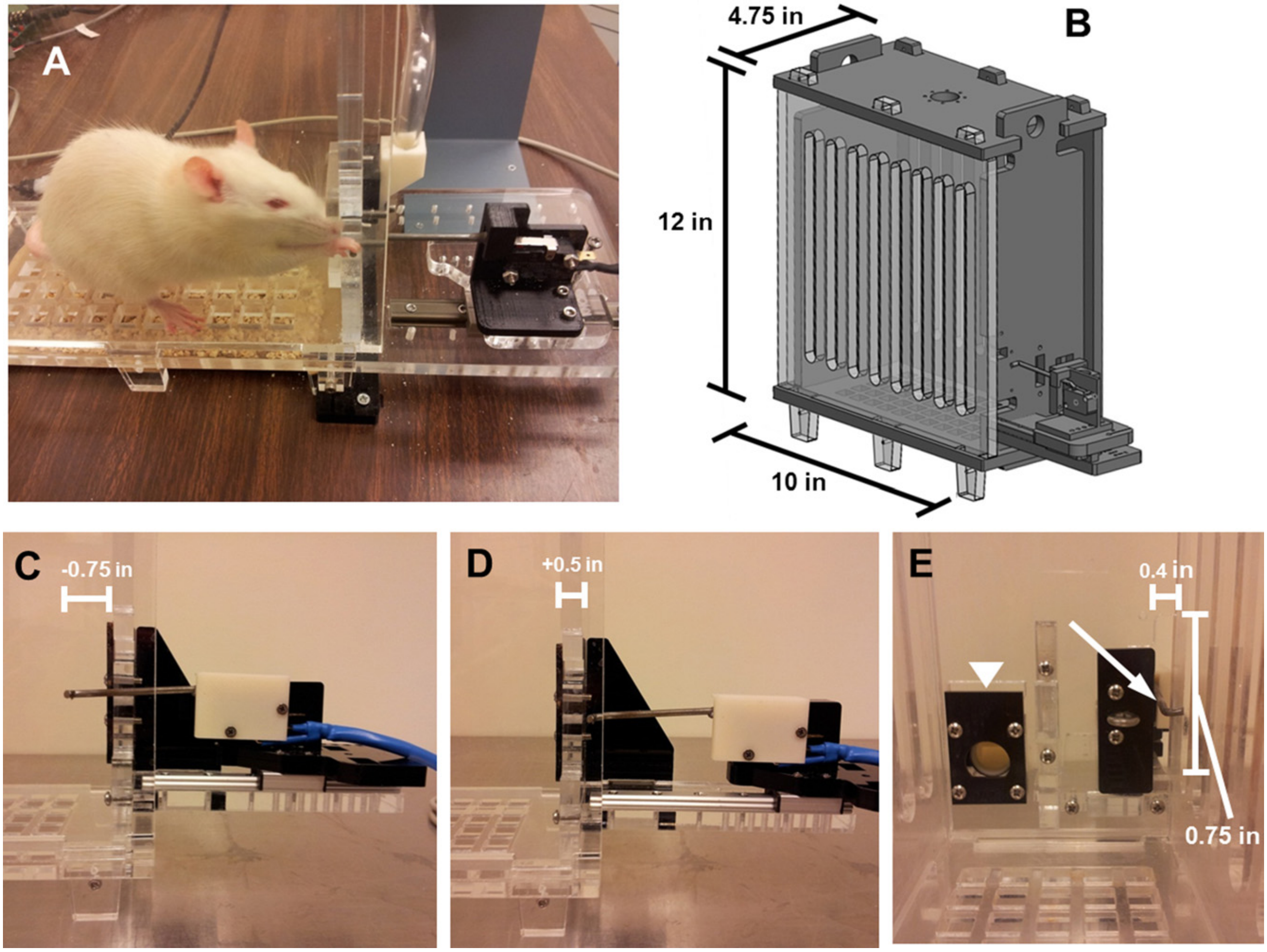

Fig. 1. Behavioral apparatus. (A) View of a rat performing the task. (B) Schematic drawing of the behavioral cage. Measurements are indicated in inches. The outermost cage wall is transparent for clarity. (C) Close up of the lever shown inside the cage. The marker depicts a −0.75 in. distance from the inside wall to the lever. (D) Lever retracted outside the cage. The marker depicts the +0.5 in. distance from the inside wall to the lever. (E) Inside view of the cage. The pellet receptacle is located on the left and marked by the arrowhead. The slot is on the right and outlined by markers, and the lever is marked by the arrow.

explicitly quantify forelimb speed. Bradykinesia is often measured as locomotion in an open field or platform (Fernagut et al., 2002; Guyot et al., 1997) or latency to fall off of a rotarod (Fernagut et al., 2002; Chuck et al., 2006; Hnasko et al., 2006). In other cases, movement speed is measured as the time needed for a rodent to turn and face downwards and descend a pole (Fernagut et al., 2002; Matsuura et al., 1997; Ohno et al., 1994; Ogata et al., 2003); however, all of these tasks are heavily reliant on hindlimb function as well as forelimb function. Video tracking can be used to estimate forelimb speed, but analysis is labor intensive and it is rarely used in rodents for quantitative measurements (Whishaw, 1996; Whishaw and Kolb, 1988). Other variations of operant lever tasks have been used to evaluate forelimb speed by measuring the speed to press a lever (Carelli et al., 1997) or to release a depressed lever in response to a tone (Spirduso et al., 1985). These methods are successful in providing quantitative measures of forelimb speed, but rely on response to a sensory cue and cannot dissociate forelimb speed from reaction time. Because of the prevalence of bradykinesia in motor disorders, it would be useful to have an automated assay to efficiently and accurately quantify forelimb movement speed in rodent models.

Here we describe the bradykinesia assessment task, a novel method to assess forelimb function in rats. Rats were trained to reach outside of a cage and press a lever twice in rapid succession. If the second press occurred within a predefined time window after the first press, a food reward was delivered. This task is fully automated, allowing multiple animals to be tested simultaneously while ensuring the unbiased and accurate measurements. The major advantage of the bradykinesia assessment task is that it can be used to automatically quantify a number of different parameters of forelimb function, including inter-press interval, number of presses per trial, and success rate. Rats initiate the trials and typically perform more trials than other forelimb tasks, thereby increasing the statistical power of this method. Three independent features of the task, distance to reach the lever, number of presses, and maximum inter-press interval, can be adjusted to alter difficulty. This flexibility allows the task to be tailored to a range of models. The apparatus restricts use to one forelimb, preventing compensation with the spared limb in models of unilateral impairment.

We show that two mechanistically distinct models of brain damage impair performance on all parameters measured by the bradykinesia assessment task. Ischemic lesions of primary motor cortex and hemorrhagic lesions of the striatum both cause a reduction in forelimb speed, capacity for forelimb use, and success rate on this task. These results demonstrate that the bradykinesia assessment task can be used to quantify several parameters of forelimb speed in multiple models of motor dysfunction.