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Validation of a method to measure total spontaneous physical activity of sedentary and voluntary running mice

M. Silvennoinen[a,*], T. Rantalainen[b,c], H. Kainulainen[a]

[a] Neuromuscular Research Center, Department of Biology of Physical Activity, University of Jyväskylä, Finland
[b] Department of Health Sciences, University of Jyväskylä, Finland
[c] Centre for Physical Activity and Nutrition Research, School of Exercise and Nutrition Sciences, Deakin University, Melbourne, Australia

HIGHLIGHTS

- Novel method for measuring spontaneous activity of mice was developed.
- The system is valid for measuring activity of mice with or without a running wheel.
- Running wheels triple the total spontaneous activity of mice.
- Running wheels increase both the intensity and time of activity.

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ABSTRACT

Background: Running wheels are commonly used to stimulate physical activity of mice. To control the effects of physical activity on study results, it is important to measure the total activity (all movements) of both sedentary and running wheel stimulated mice.
New method: Because there was a lack of a validated system, we built a force-plate based system specifically for this purpose. The validity of the system and its variables (activity index, activity time and distance) were tested in calibration measurements and in situ by measuring the activity of eight mice both with and without running wheels. Four mice served as sedentary controls. Activity index adds changes in vertical reaction forces induced by moving mice. The system records simultaneously all the activity, thus the wheel running is not distinguished from other activity.
Results: There were very strong associations between measured activity variables and their true values ($R^2 = 1$, $p < 0.01$). The mean differences to true values were: activity index −9.7% (95% limits of agreement (LOA), −28.7 to 9.4%), activity time +0.9% (LOA, −1.3 to 3.0%) and distance +0.7% (LOA, −4.7 to 6.1%). The running wheels increased activity index 211 ± 40% (mean ± SE), activity time 39 ± 3% and activity intensity 94 ± 16%. Activity index ($R^2 = 0.982$, $p < 0.01$), activity time ($R^2 = 0.618$, $p < 0.01$) and intensity ($R^2 = 0.920$, $p < 0.01$) were positively associated with running distance.
Comparison with existing methods: To our knowledge, this is the first method properly validated for this purpose.
Conclusions: The system is valid for the quantitation of total physical activity of mice housed in cages with or without running wheels.

1. Introduction

Mice are commonly used as experimental animals in many types of scientific experiments. Physical activity is nowadays considered as an important background factor that may have a significant effect on study results and their interpretation (Martin et al., 2010). Mice are naturally active animals. However, in ordinary laboratory conditions they have only few stimuli for physical activity. Because mice like wheel running (Meijer and Robbers, 2014), running wheels are often used to stimulate physical activity of experimental

Abbreviations: LOA, limits of agreement; CV_{rms}, the average root-mean-square coefficient of variation.

* Corresponding author at: University of Jyväskylä, P.O. Box 35, 40014 Jyväskylä, Finland. Tel.: +358 40 733 8864; fax: +358 14 260 2071.
E-mail addresses: mika.silvennoinen@sport.jyu.fi, mmjsilvennoinen@gmail.com (M. Silvennoinen).

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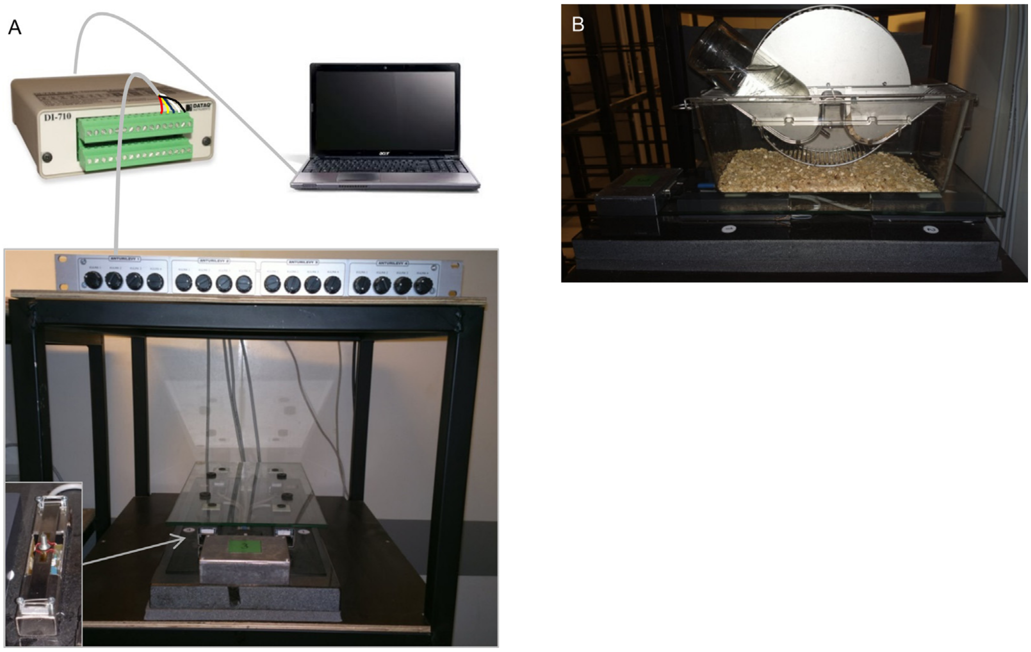

Fig. 1. (A) The main components of the activity measurement system: rack, cellular plastic sheet cushioning, granite base, strain gauge based sensors (enlarged picture in the lower left corner), sensor amplifier, glass plate with rubber ring adapters, controller unit, A/D converter and computer. (B) Side view of the plate with a cage.

mice. Depending on the strain, age and sex, mice run on average 2–10 km/day (Lightfoot et al., 2004) and up to 20.5 km/day when specifically bred for voluntary running (Eisenmann et al., 2009). There are also large inter-individual differences in running distances and the physiological responses to wheel running (Rinnankoski-Tuikka et al., 2012; Coletti et al., 2013; Ma et al., 2010). In typical voluntary running studies that include sedentary groups without running wheels e.g. (Silvennoinen et al., 2013), the running distances are presented as a measure of physical activity for running groups, but there are no comparable measures for physical activity of sedentary groups. Even if all the mice had running wheels, the running distances do not provide an accurate measure of total physical activity, because the wheel running is only one part of the daily activity and the measurement instrument (running wheel system) is reinforcing the measured behavior (de Visser et al., 2005). Thus, to be able to measure total physical activities, special activity measurement systems are needed. There is a variety of methods available to analyze physical activities and behavior, such as video tracking (Dielenberg et al., 2006; Pan et al., 1996; Rantalainen et al., 2011; Brodkin et al., 2014), infrared photo-beam systems (Teicher et al., 1996; Beninger et al., 1985), force-plate actometers (Biesiadecki et al., 1999; Chiesa et al., 2006; Fowler et al., 2001) and touch-pad transducers (Kao et al., 1995), but there is a lack of validated methods that are capable of measuring total physical activity (horizontal and vertical movements) from both cages with and without running wheels. Consequently, the aim of present study was to develop and validate such a system.

2. Materials and methods

2.1. Force-plate system

For the home cage activity analysis, a ground reaction force measurement system was developed in our laboratory. The plates were located on their own shelves (damping rubber sheets between the legs and ground) to avoid cross talk between the plates. To minimize the vibration from the surroundings, cellular plastic sheets (thickness15 mm) were placed between the shelf and the base of the force plate. Granite plate (thickness 35 mm, width 255 mm, length 580 mm, weight 14.3 kg) was used as a stabilizing base on top of which the four force sensors were attached in a rectangular formation (Fig. 1.). The core of the force sensor is the bridge formed by stainless steel sheet fixed from both of its ends. There are two strain gauges (1-LY41-6/700 (HBM, Darmstadt, Germany) attached on both the lower and upper surface of the sheet. The strain gauges are connected so that the classical Wheatstone bridge is formed. The output voltage from the sensor is directly related to the vertical force bending the strain gauges. The forces are mediated by a pin (diameter 4 mm) that is attached on the top of the steel bridge in the middle of two strain gauges. The pins of the four sensors form a rectangle (width 120 mm and length 280 mm) and a glass plate (thickness 5 mm, width 250 mm, length 450 mm) lies on top of them. Horizontal movement of the glass plate is prevented by rubber ring adapters that are attached underneath the glass plate. Similar rubber rings, on the other side of the glass, fix the cage in place on top of the glass. The force plates can measure ground reaction forces from all cage typesregardless of the equipment inside the cage. In the present study, the model of the cage was1284L Eurostandard Type II L (365 mm × 207 mm × 140 mm, Tecniplast, Italy). The output voltages from the sensors were preamplified (AD620, Analog Devices, Norwood, MA, USA) before data collection. The amplifications were adjusted to 0.077 kg/V in each sensor. After amplification, the signals pass through the controller unit that has the capability to zero all sensors. A 14 bit A/D converter (DI-710, DATAQ Instruments, Akron, Ohio, USA) was used for digitizing the data at a sampling rate of 80 Hz. The converter was operated and the data stored with WinDaq/Lite (DATAQ Instruments, Akron, Ohio, USA) data acquisition software. A measurement range of ±192.5 g was used, while the digitization precision was <0.02 g. The force data was turned into activity variables using Java-based analysis software that was programmed in house. The source code can be downloaded from following link: https://github.com/tjrantal/indeksi2011 and it is free to use.

2.2. Activity index

Activity index was originally developed by Biesiadecki et al. (1999) for using laboratory balance as an activity measurement