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Novel technology for modulating locomotor activity as an operant response in the mouse: implications for neuroscience studies involving “exercise” in rodents

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Abstract

We have developed a novel, low-cost device designed to monitor and modulate locomotor activity in murine subjects. This technology has immediate application to the study of effects of physical exercise on various neurobiological endpoints, and will also likely be useful in the study of psychomotor sensitization and drug addiction. Here we demonstrate the capacity of these devices to establish locomotor activity as an operant response reinforced by food pellet presentations, and show that schedules of reinforcement can reliably control this behavior. Importantly, these data show that varying degrees of increased locomotor activity (in other words, “exercise”) can be elicited and maintained in mice by manipulating the schedule of reinforcement. Our findings argue that the present technology might reduce the imposition of stress and motivational bias inherent in more traditional procedures for establishing exercise in laboratory rodents, while allowing for true random assignment to experimental groups. As interest in physical exercise as a modulating factor in numerous clinical conditions continues to grow, technologies like the one proposed here are likely to become critical in conducting future experiments along these lines.

Keywords

locomotor activity; operant behavior; positive reinforcement; schedule of reinforcement; exercise; mouse; running wheel; treadmill

Introduction

In recent years, preclinical research has increasingly focused on the effects of physical exercise on a range of neuroscientific endpoints, including sensitivity to drugs of abuse (Cosgrove et al., 2002; Larson and Carroll, 2005; Smith et al., 2008a,b; Kanarek et al., 2009;

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Zlebnik et al., 2010), depression (Bjørnebekk et al., 2006; Zheng et al., 2006; Ernst et al., 2006; Greenwood et al., 2007; Duman et al., 2008), expression of neurotrophic factors (Neeper et al., 1996; Bjørnebekk et al., 2005; Aberg et al., 2008), cognition and hippocampal plasticity in aging (Wolf et al., 2006; Nichol et al., 2007; Parachikova et al., 2008; Pietropaolo et al., 2008), and recovery after ischemia and stroke (Marin et al., 2003; Luo et al., 2007; Ploughman et al., 2007). Essentially all of these studies have used laboratory rodents, and engendered high levels of physical activity through the use of running wheels or treadmills. Both of these approaches have specific limitations.

In this regard, the use of freely-accessible running wheels has often been described as “voluntary exercise”, while automated running wheels or treadmills are typically referred to as “forced exercise”. Studies have documented important differences in outcomes elicited by “voluntary” versus “forced” exercise (Leasure and Jones M, 2008). Subjecting rodents to automated treadmill activity induces significant stress responses manifested as increased plasma corticosterone (Coleman et al., 1998), up-regulation of mitogen activated protein kinases in skeletal muscle (Nakamura et al., 2005), damage to intestinal musculature (Rosa et al., 2008) and increased susceptibility to influenza infection (Murphy et al., 2008). There are inherent motivational factors associated with “forced” exercise as well, such that mice placed in a wheel that is already rotating will operate a switch to stop it, although if the wheel is stopped by the experimenter, subjects will operate another switch to start it rotating again (Kavanau 1963, 1967). Thus, using “forced exercise” to establish physical activity introduces significant stress and motivational effects which may represent an unavoidable confound to the endpoint of interest – particularly in regards to drug abuse (Goeders, 2003; Koob, 2008; Sinha, 2008). Similarly, the use of freely-accessible running wheels often eliminates true random assignment to experimental groups, as inter-subject variability in wheel running activity is high. Thus, many studies employing this approach to establish physical exercise must resort to a median split, or simply drop animals failing to achieve some post-hoc minimum level of activity.

Somewhat related to this later point, it is important to note that the opportunity to engage in wheel running itself functions as a reinforcer, as rodents will engage in operant behaviors maintained by the temporary unlocking of a wheel (Kagan and Berkun, 1954; Collier and Hirsch, 1971; Collier et al., 1990; Iversen, 1993; Belke, 1997; Belke and Wagner, 2005), by the temporary operation of a motorized wheel (Kavanau 1963, 1967) or by access to an area containing a wheel (Collier et al., 1989; Sherwin, 1996; Sherwin and Nicol, 1996), which may confound the findings of studies combining this form of exercise with the opportunity to sample other reinforcers (e.g., drugs of abuse, food pellets, electrical brain stimulation). Thus, any differences observed between the reinforcing effects of a stimulus in animals with or without a wheel running history may potentially be unrelated to exercise-induced physiological changes and instead related to behavioral variables involving the choice between the motivational effects of one stimulus (wheel running) and another (a drug). Indeed, a common feature of so-called “enriched environments” is free access to a running wheel (Solinas et al., 2008), confounding any effects of exercise with those of environmental enrichment.

The methodological challenges presented by these two most common animal models of exercise, running wheels and treadmills, are disappointing as they limit the validity of experimental approaches to investigate the potentially important roles of physical exercise against a range of endpoints of interest. It seems clear that the development of an animal model of physical exercise which could avoid the imposition of stress and motivational bias inherent in the current techniques, and allow for true random assignment to experimental groups, would greatly benefit our ability to assess the effects of exercise on brain and behavior. Wheel-running activity has previously been demonstrated to come under operant

control when food presentation was contingent on this behavior (Skinner and Morse, 1958), and here we elaborate on that model to establish spontaneous locomotor activity within the home cage as an operant response in the mouse.

Methods

Animals

All studies were carried out in accordance with the Guide for Care and Use of Laboratory Animals as adopted and promulgated by the National Institutes of Health. Experimental protocols were approved by the Institutional Animal Care and Use Committee at the University of Arkansas for Medical Sciences. All experiments were conducted in adult male NIH Swiss mice housed in an Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) accredited animal facility. Mice were maintained on an inverted light : dark cycle (lights on at 1900 hrs, off at 0700 hrs) to facilitate conduct of behavioral studies during the most active phase of the subjects' circadian cycle.

Surgical methods

All subjects were surgically implanted with 1 cm diameter, 0.3 cm thick disc-shaped neodymium magnets (K&J Magnetics, Inc., Jamison, PA) for the duration of the study. The small magnets were sealed in Parafilm and gas-sterilized prior to implantation. Following appropriate anesthesia using ketamine (100 mg/kg, i.p.) and xylazine (10 mg/kg, i.p.), the abdominal area of each mouse was shaved and sanitized with iodine swabs. Mice were positioned on a clean Plexiglas surgical surface using silastic restraint cuffs around the limbs. A rostral-caudal cut approximately 1.0 cm in length was made approximately 1.5 cm off the midline using skin scissors. A small subcutaneous pocket was then created across the midline via blunt dissection of the underlying fascia with curved microforceps. The sterilized magnet was inserted into the subcutaneous pocket using non-magnetic titanium forceps, and the incision was closed using absorbable suture material. Surgeries were performed at least 7 days before initiation of experiments. Following surgery, mice were individually housed in Lab Products, Inc. Super Mouse 750™ Micro-Isolator™ cages (floor area: >483 sq cm, cage dimensions 32.7 × 19.0 × 14.3 cm) placed atop customized platforms within light- and sound-attenuating chambers (see below.)

Apparatus

We have developed novel experimental chambers to assess and control ambulatory behavior in murine subjects (Figure 1). Briefly, these chambers utilize an array of 16 Hall-effect switches (Digi-Key Corporation, Thief River Falls, MN) mounted to a platform which fits beneath each subject's cage. The Hall effect refers to the potential voltage difference across a thin sheet of conducting or semiconducting material through which an electric current is flowing; such current is momentarily created by a magnetic field applied perpendicular to the Hall element. The surgically implanted magnets described above thus allow subjects to activate the switches beneath their cages as they ambulate over them. Hall effect sensors are readily available from a variety of different manufacturers, and are widely used in various applications, such as fluid flow sensors, power sensors, and pressure sensors. Hall effect devices produce a very low signal level, thus many devices now sold as "Hall effect sensors" are in fact a device containing both the sensor described above and a high gain integrated circuit (IC) amplifier in a single package. Hall effect devices commonly used in motion sensing and motion limit switches can offer enhanced reliability in challenging environments. Since there are no moving parts within the sensor or magnet, life expectancy is improved compared to traditional electromechanical switches. Additionally, the sensor and magnet may be encapsulated in an appropriate protective material. When thus protected, Hall effect switches are essentially immune to dust, dirt, and liquids. These characteristics

make Hall effect devices better for position sensing than alternative means, particularly in an animal laboratory setting.

Switches are activated by a magnetic field of approximately 40 Gauss, outputting transistor-transistor logic (TTL) pulses to an interfaced computer running Med-PC v.4 software (Med-Associates, Inc., St. Albans, VT). The behavioral sciences have several major suppliers of laboratory equipment. Two of the premier companies in this regard are Med Associates, Inc. and Coulbourn Instruments. Both companies supply testing devices, software to run these devices, and a system to interface this equipment with a computer. Essentially, the interface converts digital signals from the computer to (TTL) pulses (which operate the peripheral behavioral equipment), and converts TTL pulses from the peripheral devices to digital signals (which are “understood” by the controlling computer.) The active operation of a TTL logic gate rapidly removes stored charge from the output stage transistors, making TTL a reasonably fast option for switching. A small amount of current must be drawn from a TTL input to ensure proper logic levels, and all standardized common TTL circuits operate with a 5 volt power supply. Thus, essentially any standard computer interface from either of the aforementioned companies could be trivially modified to comport with the proposed technology.

Each Hall-effect platform is enclosed within a light- and sound-attenuating cubicle (Med-Associates, Inc., St. Albans, VT) equipped with a 45 Watt bulb (Figure 1, A) connected to a digital timer in order to establish a 12 hr light : 12 hr dark photoperiod. An exhaust fan (Figure 1, D) is also present, and serves as a source of constant noise to partially mask extraneous laboratory sounds. Each cubicle is equipped with a house light (Figure 1, B), a ceramic-based piezoelectric Sonalert (Figure 1, C), a pellet feeder (Figure 1, E), a stainless steel spout to direct food pellets into the home cage (Figure 1, F), a red stimulus light (Figure 1, G) mounted proximal to the food spout, and a relay to provide an audible feedback click each time the mouse emits the appropriate ambulatory response (Figure 1, H). Since the neodymium magnets used require neither battery changes nor calibration, constant data collection is possible for as long as the surgical preparation can be maintained. In this regard, we have maintained magnets in mice for over seven months without any sign of infection or eruption through the skin. This was not a rigorous tolerability experiment, but rather was accomplished simply by shelving the first 6 mice used in these studies until the last group was finished with all experimental observations. That period of time was just over seven months.

Operant control of ambulatory activity

Two distinct behavioral procedures were used in separate groups of mice to establish home cage activity levels. After recovering from surgery for at least 7 days, mice were food-restricted to 85% of their pre-surgery free feeding weights, then randomly assigned to one of two groups. Non-contingent control mice were run in daily sessions where nutritionally complete, grain-based 20 mg food pellets (product number F0163, Bio-Serv, Frenchtown, NJ) were delivered according to a fixed-time 72 sec (FT72) schedule (described below). Operant mice were reinforced with food pellets for emitting ambulatory activity in the presence of discriminative light and tone stimuli under fixed ratio 30 (FR30) or FR100 schedules (described below). No other food was available at any time for the duration of these studies. Operant schedules were programmed in MedState Notation using Trans IV software (Med-Associates, Inc., St. Albans, VT). All sessions were conducted 7 days per week, and took place between approximately 0900 and 1500 hrs (during the subjective dark phase).

All subjects were initially trained under the FT72 program for 7 days in order to habituate them to the light and sound stimuli, as well as to the 20 mg food pellets delivered by the

feeder. After this habituation phase, there were no procedural changes for control mice in the FT72 group. In contrast, operant mice were initially reinforced on an FR1 schedule, and work requirements were gradually increased up to FR30 or FR100, commensurate with individual performance (i.e., obtaining at least 90% of all available reinforcing pellets.) Mice were weighed daily prior to experimental sessions, and were provided with supplemental chow (Laboratory Rodent Diet #5001, PMI Feeds, Inc., St. Louis, MO) at the end of the day in order to maintain 85% of their pre-surgery free feeding weights.

During the first hr of each daily session, all stimulus lights and tones were off, but completion of one ambulation (operationally defined as activation of one Hall-effect switch, then activation of a different switch) operated the relay to produce an audible feedback click. Ambulatory counts were thus quantified and collected in 5 min bins. One hour after session start, the house light and red stimulus light were illuminated. In the presence of these discriminative stimuli, every 30th (FR30) or 100th (FR100) ambulation was reinforced with delivery of one 20 mg grain-based dietary food pellet and operation of the Sonalert tone for 0.5 sec. A 120 sec limited hold was in effect for each reinforcer opportunity, such that if mice failed to complete the required number of ambulatory counts before the limited hold elapsed, that reinforcer opportunity was lost. A 60 sec timeout was imposed after each reinforcer delivery, during which time the red stimulus light was extinguished, and ambulatory behavior operated the feedback relay upon consecutive switch activations, but was not counted towards the next fixed-ratio. After the completion of 50 reinforcer opportunities, all stimulus lights were extinguished and ambulatory behavior operated the feedback relay, but was otherwise not reinforced, for 1 hr. This pattern repeated for three such cycles per day.

Data analysis

Raw data from three individual subjects are presented in Figure 2. In Figure 3, data are presented as individual mean $\pm$ SEM for groups where $n=6$. Statistical analyses were conducted using one-way ANOVA and post hoc pairwise multiple comparisons on significant effects and interactions were accomplished using Tukey's HSD. All statistical tests were executed using commercially available software, and significance was judged at $P<0.05$.

Results

All mice tolerated the implanted magnets well and recovered within 7 days. Stable motor activity ($\pm 20\%$ for 3 consecutive days) under the FT72 schedule developed quickly, within 3 to 5 sessions, but shaping mice to stability under the terminal FR30 and FR100 schedules required 9.67 ± 1.28 and 29.17 ± 2.17 sessions, respectively. Figure 2 presents single-session data from individual mice maintained under the three schedules of food pellet presentation used to engender ambulatory behavior. Under the FT72 schedule, ambulatory activity was emitted at low rates throughout the session (Figure 2, left panel). However, for mice maintained under the FR30 and FR100 schedules, ambulatory behavior was elevated during periods where food presentation was under operant control, and returned to low levels similar to those observed under the FT72 schedule when the schedules of food presentation were suspended (Figure 2, middle and right panels). These findings were consistent across all mice in each of the three groups. Figure 3 illustrates the schedule dependence of ambulatory activity. Rates of ambulatory behavior when food was available under the FT72 schedule did not significantly differ from rates observed when the FT72 schedule was suspended ($P>0.05$). In contrast, mice maintained under the FR30 ($q=8.156$, $P<0.05$) or FR100 ($q=19.455$, $P<0.05$) schedules exhibited significantly more ambulatory activity when this behavior was reinforced by food pellet presentation. Furthermore, mice maintained under the FR30 ($q=8.658$, $P<0.05$) and FR100 ($q=20.376$, $P<0.05$) schedules

exhibited significantly more ambulatory activity than FT72 mice during periods when these schedules were in effect. Importantly, mice maintained under the FR100 schedule exhibited significantly more ambulatory activity than those under the FR30 schedule ($q=12.429$, $P<0.05$), with an average rate of ambulatory behavior greater than 1 switch activation per second. For some subjects, ambulatory behavior was slightly elevated in the first unreinforced component in comparison to the other two, perhaps due to handling and repositioning of the cage just prior to session start. Nevertheless, in all subjects maintained under the FR30 or FR100 schedules, ambulatory activity during reinforced components occurred at a rate 10- to 30-fold greater than during unreinforced components.

Discussion

The studies described in this report replicate and extend previous work by Skinner and Morse (1958), demonstrate that spontaneous locomotor activity can function as an operant response, and that schedules of reinforcement can reliably control this behavior. Importantly, these data show that varying degrees of increased locomotor activity (in other words, “exercise”) can be elicited and maintained in mice by manipulating the schedule of reinforcement. All mice in these experiments earned an identical number of reinforcing pellets, equating dietary variables across groups, and perhaps reducing issues of behavioral contrast that may detract from the validity of running wheel studies. In other words, since all subjects in these studies had equal exposure to food pellets, it is unlikely that asymmetrical motivational effects would develop. It may also be important to note that all groups also had an equal opportunity to run (there was no consequence for increased ambulatory activity under the FT72, and contingencies were only in effect for approximately 3 hours per day.) Figure 3 shows that there were no significant differences in ambulatory activity (which was very low for all groups) between groups when contingencies were not in effect.

Because animals are tested in their home cages using this technology, long-term data collection can be performed without the confound of exposure to environmental novelty. Similarly, unlike “forced exercise” procedures involving treadmills or automated wheels, studies involving food-maintained behavior employing more traditional operant responses (lever presses, nose-pokes, etc.) are generally not considered to be stressful for animal subjects, although future studies using the present techniques to establish locomotor activity as an operant response should attempt to quantify stress hormones in experimental subjects to confirm this notion, as surgical intervention and food deprivation may induce unavoidable stress in the present model. Finally, we note that random assignment of mice to experimental groups resulted in orderly data, with statistically significant differences obtained among the reinforcement schedule manipulations here used. All of these findings would seem to argue that the present procedure might reduce the imposition of stress and motivational bias, while allowing for true random assignment to experimental groups, and may therefore provide a unique opportunity to assess the effects of exercise on brain and behavior free from some common experimental confounds inherent in the more common techniques.

In addition to the specific application of this technology toward the study of locomotor activity as an operant response, it should also be noted that these devices are very easily maintained. There are no moving parts to the Hall-effect platforms, and since rodent cages are simply placed atop them there is essentially no contact with bedding, feces, fluid from water bottles or urine, etc. Similarly, subcutaneously implanted neodymium magnets require neither calibration nor power, and can therefore provide measurable signals to the equipment for as long as the preparation can be maintained. We have not yet had reason to maintain subjects for much longer than seven months, but, by way of comparison, battery-powered telemetry probes sized for mice and capable of monitoring spontaneous locomotor activity (e.g., Data Sciences International PhysioTel models TA-F10, PA-C10, ETA-F10 and F20-

EET) have battery lives on the order of 1 to 6 months. Finally, this equipment is comparatively inexpensive: a single unit cost about \$50 to construct, and neodymium magnets of this size are widely available online for approximately \$0.20 each. Of course, employing the use of devices such as food pellet dispensers and stimulus lights, as well as interfacing the technology with Med-PC software to control experimental events, would involve a substantial investment. We were lucky to be able to salvage all of this associated equipment from a laboratory upgrade.

As with more traditional models of “exercise” and techniques for monitoring locomotor activity, this model possesses some limitations. For example, Figure 3 shows that differences in absolute locomotor activity were observed across animals – this is the source of the error bars around each point. We have previously described how this is also a limitation with “voluntary” wheel running, but it should be noted that this is not a concern when “forced” exercise procedures are employed. Nevertheless, the variability observed in the present studies was not particularly large, and did not preclude statistical comparisons between groups. Another potential drawback of the present technology is that the position of each subject is not constantly tracked. In other words, mice could be between sensors where the magnet is “out of range” to be detected. Larger magnets than those presently described could be used, but size and weight of implanted devices likely impacts normal behavior, and preliminary trials with bigger magnets sometimes resulted in simultaneous activation of adjacent switches, which was not easily dealt with by our software. Ultimately we opted to use the smaller magnets, both to minimize the invasiveness of the surgical procedure, and because we were able to reliably obtain consistent data. However, since the interface does occasionally lose track of subjects, it is not possible to definitively convert our ambulatory counts to “distance traveled,” which is perhaps the most common metric of locomotor activity. It is conceivable that mice could move significant distances between sensors, and if this were to occur, none of this activity would be measured by the present technology. The same could be said, however, for photobeam systems using a limited number of emitter and detector arrays. Since each individual sensor in our devices is a known distance from each other sensor, and is wired to the interface as a separate input, we could modify our programs to track movement from one specific sensor to another across the session, which would likely allow for the computation of a reasonably close approximation of total distance traveled.

This technology also has implications beyond the relatively narrow topic of physical exercise. Locomotor responses, particularly sensitization of locomotor responses, to various drugs of abuse have long been argued to be critically involved in their potential for addiction (Wise and Bozarth, 1987; Robinson and Berridge, 1993; Steketee and Kalivas, 2011). However, to our knowledge, it appears that almost none of these studies have been designed to include a *consequence* for the expression of drug-induced locomotor activity. In this regard, it is well known that behavioral contingencies can profoundly impact a wide range of drug effects, including effects on response rate (Dews, 1955), withdrawal signs (Siegel, 1988), discriminative stimulus properties (Ator and Griffiths, 1992), lethal effects (Dworkin et al, 1995), and even neurochemical and neuropharmacological measures (Hemby et al, 1997; Stefanski et al, 1999; Fantegrossi et al., 2004). Similarly, Schuster and colleagues (1966) described a situation in which tolerance rapidly developed to rate increasing effects of amphetamine only when increased rates resulted in missed reinforcer opportunities. In these studies, animals thus “resisted” drug effects that decreased reinforcement density. It would be interesting to explore analogous situations using the presently described technology. For example, behavioral contingencies could be arranged such that animals would receive reinforcing pellets every *X* seconds unless *Y* ambulations were to occur first. The impact of psychostimulants on the locomotor activity of subjects maintained under such a schedule might be very different than what is commonly observed in a “consequence-free”

locomotor activity apparatus, and may be more relevant to the human condition where expressing a drug effect often has drastic consequences.

In summary, we have developed a novel, low-cost device designed to monitor and modulate locomotor activity in murine subjects. This technology has immediate application to the study of effects of physical exercise on various neurobiological endpoints, and will also likely be useful in the study of psychomotor sensitization and drug addiction. We believe these devices offer unique opportunities to study the relationships between locomotor activity (an extremely common behavioral endpoint in neuroscience research) and its consequences, as well as the impact of pharmacological agents on these relationships. As interest in physical exercise as a modulating factor in numerous clinical conditions continues to grow, technologies like the one proposed here are likely to become critical in conducting future experiments along these lines.

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Highlights

- We have developed a novel, low-cost technology to monitor and modulate locomotor activity in murine subjects.
- These devices can be used to establish locomotor activity as an operant response reinforced by food pellet presentations.
- Using this technology, schedules of reinforcement can reliably modulate motor activity.
- These devices may be used to study various effects of physical exercise, psychomotor sensitization, and drug addiction.

Figure 1.

Photo of the equipment used to establish locomotor activity as an operant response in mice. A: chamber light to establish the photoperiod, B: house light, C: tone generator, D: exhaust fan, E: pellet dispenser, F: chute to direct pellets into the cage, G: stimulus light, H: audible feedback relay. (Note that since experiments were conducted during the subjective dark phase, the house light and stimulus light were only illuminated when the chamber light was off.) Further information is presented in the Apparatus section of the text.

Figure 2.

Representative data from mice performing ambulatory activity maintained by food pellet presentation under an FT72 schedule (left panel), FR30 schedule (middle panel), or FR100 schedule (right panel). Closed symbols represent 60 min periods where ambulatory behavior activated the feedback clicker, but had no other programmed consequences, while open symbols represent periods where food pellets were available under the schedules indicated. Numbers above each set of data points indicate overall response rates (in ambulations per second) for that session component. *Abscissae*: Session time (in minutes). *Ordinates*: Ambulatory behavior, collected in 5 minute bins.

Figure 3.

Overall ambulatory response rates (per second) observed during 60 min periods when ambulatory behavior activated the feedback clicker, but had no other programmed consequences (filled circles), and under the three schedules of food presentation (open circles). Asterisks indicate significant differences between rates observed in the presence and absence of behavioral contingencies within a given schedule, hash marks indicate significant differences from rates maintained under the FT72 schedule, and bullseyes indicate significant differences from rates maintained under the FR30 schedule. Symbols without error bars indicate that the variability is contained within the data point. *Abcissae*: Schedule of food presentation. *Ordinates*: Ambulatory response rate (per second).