Chapter 2
Considerations for Small Animal Physical Rehabilitation

Sarah M. Greising, Alec M. Basten, Albino G. Schifino, and Jarrod A. Call

Abstract Translational and preclinical investigations of regenerative rehabilitation approaches are dependent on an ability to appropriately design and implement physical rehabilitation intervention able to facilitate physiologically beneficial adaptations. To continue to drive success and translation in the field of regenerative rehabilitation a comprehensive understanding of rehabilitation approaches in rodents is necessary. The goal of this chapter is to provide an overview on commonly used physical rehabilitation techniques in mice and rats, with specific emphasis on ideal physiologic overload and tissue-specific targets.

Keywords Physical therapy · Running · Electrical stimulation · Methodology · Task-specific rehabilitation

2.1 Introduction

Regenerative rehabilitation can affect all tissues and organ systems of the body. As noted in Chap. 1, it is operationally defined by the field as a therapy that "*integrates regenerative technologies with rehabilitation clinical practices to restitute function and quality of life in patients with disabilities due to otherwise irreparable tissues or organs damaged by disease or trauma*" (Perez-Terzic and Childers 2014). The ideal physical rehabilitation approach for a given investigation depends on the objective of the strategy. To begin, a fundamental understanding of targeted effects (Thompson 2002) for whole-body function, tissue morphology or size, or functional capacity is necessary to address the question at hand. Targeting whole-body function would include physical rehabilitation modalities aimed at improving aerobic capacity (i.e.,

---

S. M. Greising (✉) · A. M. Basten
School of Kinesiology, University of Minnesota, Minneapolis, MN, USA
e-mail: grei0064@umn.edu

A. G. Schifino · J. A. Call
Regenerative Bioscience Center, University of Georgia, Athens, GA, USA

Department of Kinesiology, University of Georgia, Athens, GA, USA

S. M. Greising, J. A. Call (eds.), *Regenerative Rehabilitation*, Physiology in Health and Disease, https://doi.org/10.1007/978-3-030-95884-8_2

VO_{2max}), endurance (e.g., time maintaining a consistent speed), and/or anaerobic capacity (e.g., O_2 deficit). While improving functional capacity is more related to skeletal muscle endurance, power, strength, and motor performance, for example. The goal of this chapter is to provide a broad overview of commonly used physical rehabilitation modalities in rodents. We provide considerations for their use, physiologic targets, and general pros and cons to consider in methodological design; spanning methodology for conscious and unconscious rodents. Indeed, many of these approaches are addressed in subsequent chapters of this work.

2.2 Rehabilitation in Rodents

Rodents, both mice and rats, are a common research animal model with many benefits for their use (e.g., lifespan, abundant genetic resources, physiology) (Bryda 2013). The homogeneous nature of rodents allows for easy randomization into experimental groups. Additionally, significant experimental control over diet, genetics, environment, and training protocols is a primary advantage of using rodents. All of which supports research designs that are highly sensitive and reproducible within a lab or across many labs. In studies utilizing various physical rehabilitation approaches rodents provide an attractive model system for reproducible training paradigms. These rehabilitation paradigms being evaluated in rodents have the potential for scale-up to large animals, as well as translation into the clinical population to further support evidence-based rehabilitation for injured patients.

2.3 What Is the Ideal Rehabilitation Method?

In both rodent models and the clinical population, the objective of rehabilitation, or physical therapy, is to act upon the systems of the body to facilitate physiologically beneficial adaptations. Adaptations can be targeted to a specific physiologic system or to the whole body. It is imperative for investigators to weigh the pros and cons of each rehabilitation approach to best fit with their research question. For example, if the goal of rehabilitation is to improve endurance performance and aerobic capacity as in disrupted metabolic signaling cases, then treadmill or wheel running may be the ideal rehabilitation. Alternatively, if the goal of rehabilitation is to improve strength, as in the case of sarcopenia (i.e., the age-related loss of muscle size and function), then resistance mimicking activities or neuromuscular electrical stimulation may be more appropriate. We will overview commonly used rehabilitation modalities and their benefits and limitations for consideration in this chapter, with the foundation that the ideal rehabilitation method is the one that physiologically addresses the research question posed.

2.4 Common Rehabilitation Methods Implemented in Rodents

Physical rehabilitation in rodents will be discussed in two categories, those modalities conducted while the rodent is conscious and those conducted when the rodent is unconscious.

2.4.1 Conscious Methods

Short- and long-term interventions commonly utilize conscious rodents. Various methodologies range from rodents conducting tasks in a fully voluntary manner, to tasks requiring external motivation. Methodologies such as treadmill running and voluntary wheel running represent widespread approaches to impart whole-body or tissue-specific (i.e., bone and skeletal muscle) adaptations to rodents.

2.4.1.1 Treadmill Running

A common physical rehabilitation methodology that has direct clinical translation is treadmill walking and running. During a typical rehabilitation session, rodents will be placed on a motorized belt and the investigator will have precise control of belt speed and grade (e.g., uphill/downhill). Similar to human treadmill exercise, the session will provide a stimulus to the cardiovascular (Feng et al. 2019; Lund et al. 2015; Kemi et al. 2002; Wisloff et al. 2002), respiratory, and musculoskeletal systems (Kemi et al. 2002; Davies et al. 1981). There are two primary utilization of treadmill running often observed in the literature: acute endurance tests and chronic aerobic training. Acute endurance test protocols are one-time sessions in which treadmill belt speed, and/or grade, are progressively increased until rodents, despite external motivation provided from the investigator, can no longer participate/sustain treadmill running. At the time of exhaustion, the duration and total distance covered are recorded, often in conjunction with a measure of blood lactate taken from venous tail blood as an indirect assessment of anaerobic metabolism/fatigue (Ferreira et al. 2007). Acute endurance tests are sensitive to detecting the adaptations to aerobic exercise training and detraining, and thus serve as a measure of the efficacy of exercise training and/or exercise mimetic programs (Seldeen et al. 2018, 2019).

Treadmill aerobic training protocols vary in intensity, duration, frequency, and progression (Poole et al. 2020). For example, there are protocols available for high-intensity interval training (Seldeen et al. 2018, 2019; Picoli et al. 2018) as well as moderate intensity (Wang et al. 2017; Navarro et al. 2004; Boveris and Navarro 2008) and ramped intensities (Poole et al. 2020). Regardless, treadmill aerobic training has considerable utility and widespread efficacy as a model for inducing beneficial adaptations across pathologies and injuries (Lund et al. 2015; Wisloff et al. 2002; Goh et al. 2019; Davies et al. 1981).

A primary benefit of treadmill rehabilitation is that the investigator can control the rehabilitation dose by modulating the frequency, duration, and intensity of the sessions. For example, if the goal is to achieve one kilometer of distance per day, that can be precisely administered. This approach can also be helpful when working with rodent models that do not demonstrate consistent voluntary running behavior if provided a running wheel (e.g., rats) (Rodnick et al. 1989). However, the "involuntary" nature of this approach is also a limitation to consider, as rodents are neither free to modulate their time engaging with the treadmill, nor are they able to self-select a running speed. Some studies also utilize shock grids, stiff bristle brushes, and puffs of air to motivate rodents to accomplish a standardized distance or to maintain a certain speed for a given amount of time. These motivation tactics to ensure training compliance may induce stress responses (Svensson et al. 2016) that should be considered as a factor in study design. Indeed, researchers have demonstrated that 100% training compliance can be accomplished without motivational assistance; however, considerable time must be spent familiarizing rodents with the desired task (>10 sessions) (Arnold and Salvatore 2014). When utilizing the treadmill as a rehabilitation tool, it might be necessary to briefly acclimate rodents in 2–3 short sessions prior to initiating treadmill training. Furthermore, identifying "good runners" and then allocating these specific rodents into the experimental groups can aid in reducing the influence of intraspecies variability in exercise compliance/capacity.

2.4.1.2 Voluntary Wheel Running

Voluntary wheel running involves placing a wheel in the cage of a singly housed rodent and recording the number of revolutions completed per day. Similar to treadmill running, voluntary wheel running is a whole-body activity that provides a stimulus to the cardiovascular (Allen et al. 2001; Judge et al. 2005), respiratory, and musculoskeletal systems (Ikeda et al. 2006; Boveris and Navarro 2008; Gurley et al. 2016). Rodents are nocturnal animals, and the majority of the total running distance will occur during the vivarium lights-off phase. Initially designed as a purely aerobic training paradigm, voluntary wheels can be modified to add a load or resistance training component (Ishihara et al. 1998). Resistance or load components, i.e., high-resistance wheel running, can be modulated by adhering weights to the circumference of the wheel (White et al. 2016; Soffe et al. 2016), fastening a manual tensioning device (Call et al. 2010; Konhilas et al. 2005), or through servo-motor generated resistance brakes (Fig. 2.1a–c) (Ishihara et al. 1998; Mobley et al. 2018). Both low- and high-resistance wheel running paradigms induce beneficial adaptations across several diseases and injuries (White et al. 2016; Call et al. 2010; Brooks et al. 2018).

A primary benefit of wheel running is that the rodent can self-select running speed and engagement with the running wheel (in contrast to treadmill running), creating a

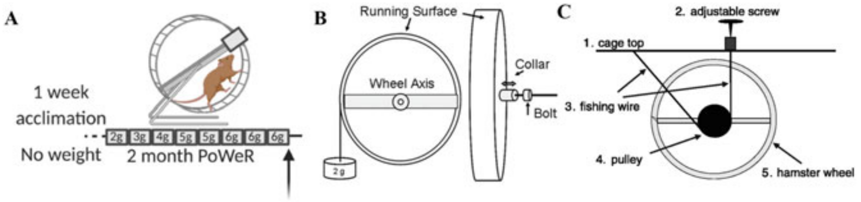

Fig. 2.1 Examples of unweighted and weighted (resistance) voluntary wheels. (**a**) A schematic showing a series of masses that are adhered to the circumference of the wheel to add resistance (Murach et al. 2020). (**b**) A schematic showing a threaded cuff on the wheel axle that is turned to add resistance (Call et al. 2010). (**c**) A schematic of a pulley system that is used to add resistance to a wheel (Konhilas et al. 2005). Schematics are reprinted with permission from John Wiley & Sons

less stressful rehabilitation environment. Twenty-four-hour access to the running wheel means that the rodent can assume its natural pattern aligning to circadian rhythms, while the training volume (i.e., distance covered) is often much greater than that which can be reasonably accomplished with treadmill running (e.g., 10 km/day) (Lightfoot et al. 2004; Lerman et al. 2002). Although, it is important to note beneficial adaptations are possible with as little as 1.5 km/day (Warren et al. 2007; Landisch et al. 2008; Goh and Ladiges 2013). The time demand on the investigator is also much less compared to the treadmill as the rehabilitation sessions happen spontaneously and independent of investigator input. Some limitations of voluntary wheel running include study design and investigator tolerance for the potential of considerable between- and within-animal running distance variability. In contrast to treadmill running where a set distance can be prescribed each day, it is common for there to be 1–2 km/day differences among rodents and sometimes for the same rodents across days of the week (Manzanares et al. 2018). In fact, taking advantage of the between-animal distance variability by the selective breeding of high-distance voluntary wheel running mice has demonstrated several unique characteristics across organ systems compared to normal distance runners (Swallow et al. 2005; Garland et al. 2002; Rhodes et al. 2005; Lightfoot et al. 2004).

2.4.1.3 Whole-Body Vibration

Vibration therapy is an emerging therapeutic modality that requires a mechanical device to augment oscillatory movement (accelerations). Vibration therapy can be applied locally to specific regions with handheld devices, mimicking massage therapy. More often, vibration therapy is administered at the whole-body level via a standing platform (Fig. 2.2). Whole-body vibration therapy requires a cyclic mechanical device (actuator or motor) that can be adjusted to specific magnitudes (g) and frequencies (Hz), which is applied through the standing platform or surface (Novotny et al. 2013). Vibration therapy is administered passively to rodents independently housed and fully conscious inside compartments atop the vibrating platform (Novotny et al. 2013). Vibration supplied through a platform provides

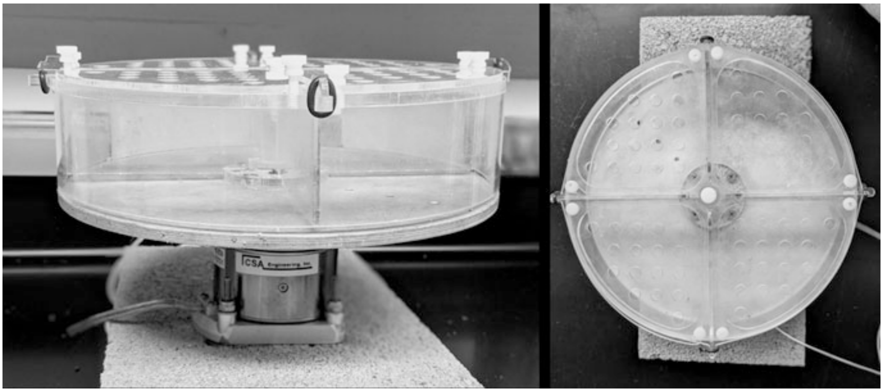

Fig. 2.2 Example of a custom-built small-animal vibration plate (Novotny et al. 2013). A concrete base is used to anchor a linear actuator. A Plexiglas cage for mice is centered on an aluminum platform and has a low ceiling height (6.3 cm) to limit rearing and jumping by the mice during the rehabilitation sessions. This custom-built vibration plate has four compartments to deliver rehabilitation to four mice simultaneously

mechanical stimuli to semi-rigid body structures and can elicit low levels of muscle activation, and metabolic stimulation (Park and Martin 1993; McKeehen et al. 2013; Ren et al. 2020). The biological response of skeletal muscles, muscle spindles, and nerve-endings to vibration stimulus is characterized as the “tonic vibration reflex” (Park and Martin 1993; Bongiovanni and Hagbarth 1990; Zaidell et al. 2013). This passive reflex is proposed to be the result of minor alterations to muscle length under tension, activating muscle stretch-receptors, known as muscle spindles, and coordinating the proprioceptive response of the musculoskeletal system (Burke et al. 1976; Weill et al. 1976). When administered as a chronic therapy, vibration has been shown to improve bone integrity, wound healing (Xie et al. 2006; Vanleene and Shefelbine 2013; Chung et al. 2014; Rubin et al. 2001), skeletal muscle function (McKeehen et al. 2013; Xie et al. 2008; Novotny et al. 2014), and even mimics exercise in rodent models of disease and disuse (McGee-Lawrence et al. 2017; Novotny et al. 2014; Ren et al. 2020).

Vibration therapy serves as a passive modality that can induce muscle activation and increase physical activity independent of voluntary participation or central governing processes. Vibration therapy is a time-effective (<60 min/session), specified mechanotherapy that can be administered free of anesthetics to fully conscious, ambulatory rodents. Vibration therapy can be precisely modulated in frequency, magnitude, and duration, which aids in further understanding vibration stimulus parameters that are crucial for favorable adaptation. Notably, vibration therapy can be both beneficial and destructive, as vibration administered beyond what is considered “low magnitude” (<1.0 g) can instigate muscle injury and impair circulation/vasculature (e.g., Raynaud’s phenomenon) (Murfee et al. 2005; Necking et al. 1996). The risk of overexposure to vibration is well-documented, and thus any utilization of vibration for rehabilitation purposes should be aware of overexposure risk and consider utilizing an external accelerometer to provide live feedback of vibrational accelerations. Commercially available vibration platforms for human use lack the precision to administer vibration therapy suitable for rodents and other small animals. Therefore, custom-designed systems developed by research teams are required to consistently and reliably administer whole-body vibration therapy in rodents (Novotny et al. 2013). Vibration therapy can cause mild stress and exacerbate aggressive behavior; thus, animals should receive therapy either individually or simultaneously in separated compartments. Vibration therapy serves as a clinically relevant rehabilitation approach, with minimal risk, and clear evidence for application across various tissues, diseases, and species of small animals (Xie et al. 2006; Weinheimer-Haus et al. 2014; McGee-Lawrence et al. 2017; Xie et al. 2008).

2.4.1.4 Alternative Resistance Training Approaches

Rehabilitation modalities that target skeletal muscle size and strength absent from cardiovascular and respiratory stimuli (such as that from treadmill and voluntary wheel running) are at times needed to better model a clinical setting or because the research design is not powered to deal with variance from other organ system adaptations. Several resistance training approaches have been validated with the specific intent to overload the skeletal muscle system and produce muscle fiber hypertrophy (i.e., increase in cross-sectional area) and greater muscle force/strength. A weighted vertical ladder climbing technique (Fig. 2.3a) uses a cylinder or plank with horizontal wooden ladder pegs and a top platform with a food reward to encourage rodents to climb (Hellyer et al. 2012). Upon acclimation, weight (e.g., 80% of body mass) can be attached to the tail. Cage tops have also been modified to lift a weight in order for rodents to reach their food supply, effectively creating a squat rack (Fig. 2.3b) (Cui et al. 2020; Barauna et al. 2005; Tamaki et al. 1992). There is also a weight-pulling system where rodents pull weighted carts down a narrow corridor (Fig. 2.3c) (Zhu et al. 2021). Flywheel pulley systems have also been created to allow for resistance training in muscle atrophy study designs (e.g., hindlimb suspension) (Fluckey et al. 2002; Dupont-Versteegden et al. 2006). Across the preceding techniques, investigators should adhere to the training principle of progressive overload (i.e., adjusting the weight-load overtime to maximize muscle overload) to optimize muscle size and strength adaptations in healthy and diseased mice (Leite et al. 2013; Souza et al. 2014; Duncan et al. 1998).

A primary benefit of these alternative resistance training modalities is their ability to specifically target the neuromusculoskeletal system for adaptation. Modalities such as the squat rack (Fig. 2.1b) have the benefit of being a self-selected rehabilitation in which sessions can occur spontaneously without extensive investigator input (similar to voluntary wheel running). When the distance the weight is being moved vertically (squat rack and vertical ladder) or horizontally (weighted carts) is known, along with the timing/velocity of the movement, then both work and power can be calculated serving as complementary outcomes to clinical settings. Similar to treadmill running, a potential consideration for vertical ladder and weighted-cart

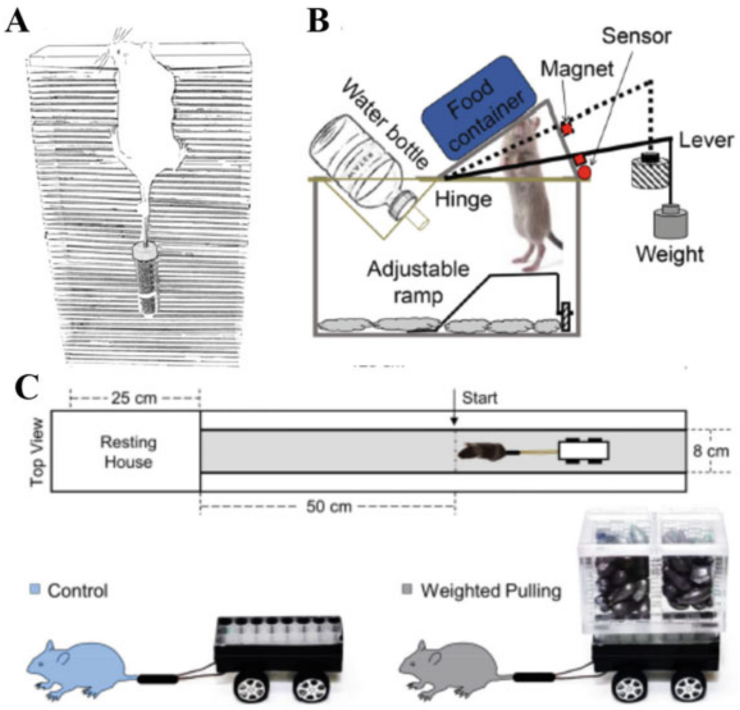

Fig. 2.3 Examples of resistance training methods. (**a**) A drawing depicting an animal climbing a vertical ladder with a weighted conical tube attached to its tail (Hellyer et al. 2012). (**b**) A cartoon depicting a mouse performing a squat-like movement in order to access food against the load of a weighted lever (Cui et al. 2020). (**c**) A schematic depicting the length of a narrow track for a weight-pulling exercise. Cartoons depict animals with unweighted and weighted carts attached to their tails (Zhu et al. 2021). Drawings, cartoons, and schematics are reprinted with permission from MDPI and LWW publishers (references noted).

pulling is animal stress, especially if significant encouragement is needed for animals to complete the task (i.e., strong bristled brushes, electrical shocks). These two techniques also require active participation by the investigator.

2.4.1.5 Swimming

The use of swimming to promote whole-body cardiovascular and oxidative improvements is common in rodents (Kaplan et al. 1994; Dawson and Horvath 1970; Wang et al. 2020; Strickland and Smith 2016), especially in rats. Rats will naturally swim without further intervention, allowing for a physical rehabilitation modality that is self-motivating but lower impact than wheel running. Although less common, mice have also been used in swimming intervention (Spaulding and Selsby 2018; Hsu et al. 2021). More akin to treadmill exercise bouts, swimming bouts are prescribed to a single whole-body activity and can mimic an aerobic intervention. In contrast to wheel running that consists of multiple small sessions over a period of time, swimming does not have a stop-and-go aspect. This allows the investigator precise control of the rehabilitation dose, which can be progressively overloaded over a multi-week intervention. Additionally, akin to the progressive overload rehabilitation described above, an external load can be added to the body or tail of the rodents during their swimming bouts (Hsu et al. 2021). In rodent models of neuromuscular trauma, swimming is beneficial when an injury to limbs is present that could preclude treadmill running, and there is no potential additional injury to the rodent's feet (Seo et al. 2014). Swimming interventions can be utilized after incomplete spinal cord injury and have shown improvements in motor recovery (Loy and Bareyre 2019).

Necessary considerations for utilizing swimming protocols are water temperature, and prompt drying (and possibly warming) of the rodent following the swimming bout to maintain body temperature. Often swimming interventions can be accomplished in a laboratory with less sophisticated and costly equipment than other intervention types described here. Dedicated investigator observation during all swimming bouts is necessary, requiring active participation during all interventions. Investigators must monitor rodents for noncontinuous swimming behaviors such as diving, floating, or bobbing throughout the rehabilitation bout. Prior work has suggested implementing varying levels of swimming overload in rodents spanning low to high intensity based on time (20 min, 60 min, >90 min per bout, respectively) (Seo et al. 2014; Wang et al. 2020). As a non-weight bearing activity, swimming is not imparting stress on the skeletal system and thus bone overload is not expected, with the exception of the load produced from muscle contractions. Indeed, no impacts on bone mineral density have been indicated in rodent models of swimming (Portier et al. 2020). Swimming may induce stressful stimuli to some rodents (Kaplan et al. 1994), that can confound potential results (Strickland and Smith 2016). Swimming interventions also introduce the risk of drowning, which may be increased in highly diseased rodent models. Finally, for nontreatment groups, investigators should consider placing rodents in shallow water to control for the impact of water exposure on experimental outcomes.

2.4.1.6 Task-Specific Rehabilitation

Increasingly, physical rehabilitation is becoming highly specialized more akin to occupational therapy in the clinical setting. In rodent models of stroke, traumatic brain injury, and spinal cord injury, these specialized rehabilitation tasks are designed primarily to target and strengthen neural pathways, improving motor recovery (Fenrich et al. 2021). Notably, in some models, these tasks can be utilized as overuse designs for musculoskeletal models (Xin et al. 2017; Barbe et al. 2021). In both cases, the use of task-based rehabilitation often requires rodent motivation much like the resistance-style rehabilitation approaches noted in previous sections. The tasks the rodents are trained to complete can be vast but commonly they revolve around the forelimb to include grasping to retrieve food/treats (Okabe et al. 2017; Dutcher et al. 2021; Joa et al. 2017) or lever pulling (Xin et al. 2017; Barbe et al. 2021). In some instances of neurovascular injuries, the research design may be most appropriate for the initial task training to occur to induction of injury, representing a "re-learning" of the tasks as rehabilitation occurs (DeBoer et al. 2021), more akin to occupational therapy in the clinic.

During familiarization and training for tasks, ongoing modification to the ability to obtain the reward may be necessary, starting from no threshold to a further reach that requires a greater force of activation. While the investigators have an initial involvement in the familiarization as the tasks are learned, the rehabilitation can become more rodent-driven as time progresses. Targeted tasks, such as grasping, represent a more appropriate rehabilitation modality than wheel running, for example, which stresses larger muscle groups responsible primarily for weight-bearing and whole-body physiology. In part, this represents a limitation of wheel running, as it imparts limited neurologic stimulus. Conversely, forelimb rehabilitation is more appropriate to target small muscle groups, responsible for fine motor skills.

2.4.2 Unconscious Methods

Methodologies for physical rehabilitation can also be undertaken in unconscious, or anesthetized, rodents. In many instances, the ability to motivate rodents is limited or not possible and other modalities are necessary to impart physiologic changes. Collectively, there is a major limitation to the use and repeated use of anesthetics, due to the various effects that dose and type of anesthetic have on neuromuscular function (Ingalls et al. 1996). With this, a major investigator consideration is consistency in dose and type of anesthetic across studies and experimental groups. Additionally, limitations with repeated anesthesia are known and provide various stressors to the rodents (Hohlbaum et al. 2017, 2018; Peng et al. 2021).

2.4.2.1 Repeated In Vivo Electrical Stimulation

In vivo functional assessment of skeletal muscle (e.g., isometric, isokinetic, fatigability) is often used to evaluate torque (Corona et al. 2021; Lovering et al. 2011; Mintz et al. 2016; Call et al. 2011, 2013; Ingalls et al. 2004; Warren et al. 1999). The methodology also has the utility to conduct repeated rehabilitation sessions in rodents in a minimally invasive manner to stimulate muscle hypertrophy, muscle-specific metabolism, and neuromuscular function. In vivo muscle stimulation using needle electrodes (Greising et al. 2018), implantable nerve cuffs (Walters et al. 1991; Warren et al. 1998), and fully implantable wireless stimulating electrodes (Deshmukh et al. 2020; Koo et al. 2018) all provide options to directly and precisely stimulate terminal nerves innervating of skeletal muscles across the body. For this, investigators use an external stimulator to precisely control the frequency of the nerve stimulation and thus the action potential and magnitude of force generation in a species-dependent manner. Specifically for 50% and 100% activation of peak isometric force in healthy skeletal muscle in the mouse stimulation at 30 Hz and 125 Hz are required, while the rat would need 50 Hz and 150 Hz, respectively. The ability for the investigator to also ensure maximal activation of all motor units is possible by stimulating at high frequencies (e.g., >200 Hz). Investigators also have the ability to control strictly all aspects of the rehabilitation bout, such as contraction number, rest periods, and muscle activation.

The primary advantage to in vivo electrical stimulation as a repeated rehabilitation is the independence of rodent motivation which is in direct contrast to training protocols that stimulate resistance style training and require motivation (Sect. 2.4.1.4) in some form in conscious models as noted in previous sections. Additionally, electrical stimulation is capable of specifically reproducing effects of resistance training overload unilaterally allowing for an intra-animal control (Lowe and Alway 2002). For electrical stimulation via percutaneous electrodes, needle electrodes are inserted through the skin to directly stimulate a nerve. One benefit to the use of needle electrodes is that it does not require invasive surgical implantation of a device. Needle electrodes are also limited to superficial nerves, such as the peroneal nerve, which branches off the sciatic to innervate the tibialis anterior muscle. Additionally, stimulation of muscle groups or units could be possible with stimulation of the sciatic nerve superiorly. Repeated insertions of needle electrodes can result in scar tissue formation and accumulation, and the exact electrode placement between sessions may vary slightly compared to an electrode that is surgically implanted. A nerve cuff is a surgically implanted electrode cuff that surrounds a nerve of interest. While nerve cuffs have been utilized on superficial nerves, surgical implantation does allow for targeting nerves that may not be accessible to needle electrodes, for example, the tibial nerve or the phrenic nerve (Fenik et al. 2001). Electrodes are often housed externally on the back of the neck and the nerve cuff method for electrical stimulation permits chronic and direct stimulation of a nerve for months (Warren et al. 1998). However, this method may be more invasive than using percutaneous needle electrodes that do not require surgery for implantation. Additionally, time between implantation and rehabilitation initiation is needed. Recently, newer methods for wireless implantation of electrodes have been developed. These methods are similar to the implantable nerve cuff except that the electrodes are controlled by radio waves and powered by batteries using wireless power transmission technology to eliminate the need for external wires (Deshmukh et al. 2020). An important consideration for translating any electrode implantation into a human population is that a secondary surgery is necessary for the removal of the device (Ju et al. 2020). However, developing technologies such as bioresorbable wireless electrodes may become more available, eliminating the need for a secondary surgery for removal (Koo et al. 2018).

2.4.2.2 Range of Motion

Continuous passive range of motion uses passive joint movement to mitigate muscle, tendon, and joint stiffness. This type of physical rehabilitation is common in knee pathologies clinically (D'Amore et al. 2021). Although less common than other rehabilitation methods in rodents, the use of passive range of motion in rehabilitation is known to improve joint range of motion following eccentric and rotator cuff injuries (Chang et al. 2015; Matsuo et al. 2015). Using various techniques, most of which involve computer-controlled servomotors, investigators control the angle and duration of movement at specific joints. An advantage of using passive range of motion is that it is non-weight bearing in nature and does not require muscle fiber innervation to be effective (Greising et al. 2018). Notably, in rat models of spinal cord injury, range of motion exercise has been conducted while the rat is conscious (Keller et al. 2017), with investigators manually performing all the exercises; for this, timing in each position was accomplished using a standard metronome. However, investigator-controlled range of motion exercise could induce more variability than the servomotor-controlled rehabilitations. It is also important to note that timing (i.e., start of rehabilitation post-injury, duration, frequency) and range of motion parameters will play a role in the effectiveness and physiological response. For example, earlier implementation of passive range of motion caused a higher rate of recurrent tendon tears in rotator cuff injury (Chang et al. 2015), suggesting a delayed start of range of motion rehabilitation should be considered. Additionally, fast repetitive stretching was more effective in suppressing muscle fibrosis in rats with denervated sciatic nerve than slower stretching (Tanaka et al. 2017). Passive range of motion could also be performed in conjunction with other modes of rehabilitation, such as intermittent in vivo electrical stimulation, which represents a rehabilitation regimen that is readily translatable to the clinic, even while patients are non-weight bearing (Greising et al. 2018).

2.5 Importance of Functional Outcomes and Future Considerations

To fully leverage preclinical animal studies in building a foundation to develop evidence-based rehabilitation practices for humans, there needs to be a focus on functional outcomes and clinically relevant techniques. Functional outcomes will vary depending on the organ system of interest. For example, function outcomes for skeletal muscle are typically measurements of muscle force and/or torque (Call and Lowe 2016), whereas functional outcomes for tendons may include in vivo passive stiffness about a joint or assessing ex vivo stiffness properties of isolated tendons (Wang et al. 2006). Some organ systems require indirect functional outcome measurements such as the central and peripheral nervous systems where outcomes such as grasping task successes vs. failures, novel object recognition tasks, and/or maze orientation are valuable (Noble et al. 2019; Zemmar et al. 2015; Wolf et al. 2016). A functional outcome is perhaps the strongest way to advance the efficacy of any rehabilitation approach.

Many of the approaches emphasized in this chapter can serve a dual role as both rehabilitative approaches and endpoint measurements of adaptation (i.e., functional outcomes). For example, a treadmill can be used to administer weekly rehabilitation of a set distance (e.g., 1 km/day), and an acute treadmill fatigue test can be an important endpoint outcome to evaluate the extent to which rehabilitation resulted in whole-body adaptations (i.e., greater treadmill running endurance compared to a control) (Dougherty et al. 2016). Similarly, a stimulating electrical nerve cuff can be used to precisely activate a particular muscle group and provide repeated rehabilitation. The nerve cuff approach can be combined with a torque transducer to measure muscle strength prior to and at the conclusion of the rehabilitation window to determine beneficial remodeling of the targeted muscle group (Call et al. 2011).

The relationship between the preclinical and clinical rehabilitation environments is dynamic and ever-evolving. Sometimes techniques evolve or manifest first in the clinical or commercial rehabilitation environments prior to preclinical testing. For example, whole-body cryotherapy, in which the body is treated with extremely cold air in hopes of lessening muscle soreness, is a commercial practice with little to no evidence-based proof of effectiveness (Costello et al. 2015). For their part, preclinical researchers should consider the scalability and clinical relevance of their rehabilitative approach. Several techniques highlighted in this chapter both scale up well and are clinically feasible. For example, treadmill exercise is effective in the mouse, pig, and humans across different disease conditions (Hyzewicz et al. 2015; McDermott 2018; Robles and Heaps 2015). Vibration, discussed as an option for mice in this chapter, has served as a rehabilitation approach in both equines (Halsberghe 2017) and humans (Ritzmann et al. 2018). The future of developing and validating rehabilitative techniques can be strengthened by partnerships between the researcher and clinician to best deliver a bench to clinic model.

Funding

This work was supported by funding from the Department of Defense, Clinical & Rehabilitative Medicine Research Program: W81XWH-18-1-0710 and W81XWH-20-1-0885 (SMG and JAC) Opinions, interpretations, conclusions, and recommendations are those of the authors and are not necessarily endorsed by the Department of Defense.

Declaration of Interests The authors declare that they have no potential or actual conflict of interest.

References

Allen DL, Harrison BC, Maass A, Bell ML, Byrnes WC, Leinwand LA (2001) Cardiac and skeletal muscle adaptations to voluntary wheel running in the mouse. J Appl Physiol (1985) 90(5): 1900–1908. https://doi.org/10.1152/jappl.2001.90.5.1900

Arnold JC, Salvatore MF (2014) Getting to compliance in forced exercise in rodents: a critical standard to evaluate exercise impact in aging-related disorders and disease. J Vis Exp 90. https://doi.org/10.3791/51827

Barauna VG, Batista ML Jr, Costa Rosa LF, Casarini DE, Krieger JE, Oliveira EM (2005) Cardiovascular adaptations in rats submitted to a resistance-training model. Clin Exp Pharmacol Physiol 32(4):249–254. https://doi.org/10.1111/j.1440-1681.2005.04180.x

Barbe MF, Harris MY, Cruz GE, Amin M, Billett NM, Dorotan JT, Day EP, Kim SY, Bove GM (2021) Key indicators of repetitive overuse-induced neuromuscular inflammation and fibrosis are prevented by manual therapy in a rat model. BMC Musculoskelet Disord 22(1):417. https://doi.org/10.1186/s12891-021-04270-0

Bongiovanni LG, Hagbarth KE (1990) Tonic vibration reflexes elicited during fatigue from maximal voluntary contractions in man. J Physiol 423:1–14. https://doi.org/10.1113/jphysiol.1990.sp018007

Boveris A, Navarro A (2008) Systemic and mitochondrial adaptive responses to moderate exercise in rodents. Free Radic Biol Med 44(2):224–229. https://doi.org/10.1016/j.freeradbiomed.2007.08.015

Brooks MJ, Hajira A, Mohamed JS, Alway SE (2018) Voluntary wheel running increases satellite cell abundance and improves recovery from disuse in gastrocnemius muscles from mice. J Appl Physiol (1985) 124(6):1616–1628. https://doi.org/10.1152/japplphysiol.00451.2017

Bryda EC (2013) The Mighty Mouse: the impact of rodents on advances in biomedical research. Mo Med 110(3):207–211

Burke D, Hagbarth KE, Lofstedt L, Wallin BG (1976) The responses of human muscle spindle endings to vibration of non-contracting muscles. J Physiol 261(3):673–693. https://doi.org/10.1113/jphysiol.1976.sp011580

Call JA, Lowe DA (2016) Eccentric contraction-induced muscle injury: reproducible, quantitative, physiological models to impair skeletal muscle's capacity to generate force. Methods Mol Biol 1460:3–18. https://doi.org/10.1007/978-1-4939-3810-0_1

Call JA, McKeehen JN, Novotny SA, Lowe DA (2010) Progressive resistance voluntary wheel running in the mdx mouse. Muscle Nerve 42(6):871–880

Call JA, Eckhoff MD, Baltgalvis KA, Warren GL, Lowe DA (2011) Adaptive strength gains in dystrophic muscle exposed to repeated bouts of eccentric contraction. J Appl Physiol (1985) 111(6):1768–1777. https://doi.org/10.1152/japplphysiol.00942.2011

Call JA, Warren GL, Verma M, Lowe DA (2013) Acute failure of action potential conduction in mdx muscle reveals new mechanism of contraction-induced force loss. J Physiol 591(Pt 15): 3765–3776. https://doi.org/10.1113/jphysiol.2013.254656

Chang KV, Hung CY, Han DS, Chen WS, Wang TG, Chien KL (2015) Early versus delayed passive range of motion exercise for arthroscopic rotator cuff repair: a meta-analysis of randomized controlled trials. Am J Sports Med 43(5):1265–1273. https://doi.org/10.1177/0363546514544698

Chung SL, Leung KS, Cheung WH (2014) Low-magnitude high-frequency vibration enhances gene expression related to callus formation, mineralization and remodeling during osteoporotic fracture healing in rats. J Orthop Res 32(12):1572–1579. https://doi.org/10.1002/jor.22715

Corona BT, Call JA, Borkowski M, Greising SM (2021) In vivo measurement of hindlimb dorsiflexor isometric torque from pig. J Vis Exp. https://doi.org/10.3791/62905

Costello JT, Baker PR, Minett GM, Bieuzen F, Stewart IB, Bleakley C (2015) Whole-body cryotherapy (extreme cold air exposure) for preventing and treating muscle soreness after exercise in adults. Cochrane Database Syst Rev (9):CD010789. https://doi.org/10.1002/14651858.CD010789.pub2

Cui D, Drake JC, Wilson RJ, Shute RJ, Lewellen B, Zhang M, Zhao H, Sabik OL, Onengut S, Berr SS, Rich SS, Farber CR, Yan Z (2020) A novel voluntary weightlifting model in mice promotes muscle adaptation and insulin sensitivity with simultaneous enhancement of autophagy and mTOR pathway. FASEB J 34(6):7330–7344. https://doi.org/10.1096/fj.201903055R

D'Amore T, Rao S, Corvi J, Jack RA 2nd, Tjoumakaris FP, Ciccotti MG, Freedman KB (2021) The utility of continuous passive motion after anterior cruciate ligament reconstruction: a systematic review of comparative studies. Orthop J Sports Med 9(6):23259671211013841. https://doi.org/10.1177/23259671211013841

Davies KJ, Packer L, Brooks GA (1981) Biochemical adaptation of mitochondria, muscle, and whole-animal respiration to endurance training. Arch Biochem Biophys 209(2):539–554. https://doi.org/10.1016/0003-9861(81)90312-x

Dawson CA, Horvath SM (1970) Swimming in small laboratory animals. Med Sci Sports 2(2): 51–78

DeBoer SR, Hubbard R, Mersha M, Pinilla Monsalve G, Winter S, Zeiler SR (2021) Enhanced spontaneous motor recovery after stroke in mice treated with cerebrolysin. Neurorehabil Neural Repair 35(6):525–533. https://doi.org/10.1177/15459683211000734

Deshmukh A, Brown L, Barbe MF, Braverman AS, Tiwari E, Hobson L, Shunmugam S, Armitage O, Hewage E, Ruggieri MR Sr, Morizio J (2020) Fully implantable neural recording and stimulation interfaces: peripheral nerve interface applications. J Neurosci Methods 333: 108562. https://doi.org/10.1016/j.jneumeth.2019.108562

Dougherty JP, Springer DA, Gershengorn MC (2016) The treadmill fatigue test: a simple, high-throughput assay of fatigue-like behavior for the mouse. J Vis Exp (111). https://doi.org/10.3791/54052

Duncan ND, Williams DA, Lynch GS (1998) Adaptations in rat skeletal muscle following long-term resistance exercise training. Eur J Appl Physiol Occup Physiol 77(4):372–378. https://doi.org/10.1007/s004210050347

Dupont-Versteegden EE, Fluckey JD, Knox M, Gaddy D, Peterson CA (2006) Effect of flywheel-based resistance exercise on processes contributing to muscle atrophy during unloading in adult rats. J Appl Physiol (1985) 101(1):202–212. https://doi.org/10.1152/japplphysiol.01540.2005

Dutcher AM, Truong KV, Miller DD, Allred RP, Nudi E, Jones TA (2021) Training in a cooperative bimanual skilled reaching task, the popcorn retrieval task, improves unimanual function after motor cortical infarcts in rats. Behav Brain Res 396:112900. https://doi.org/10.1016/j.bbr.2020.112900

Feng R, Wang L, Li Z, Yang R, Liang Y, Sun Y, Yu Q, Ghartey-Kwansah G, Sun Y, Wu Y, Zhang W, Zhou X, Xu M, Bryant J, Yan G, Isaacs W, Ma J, Xu X (2019) A systematic comparison of exercise training protocols on animal models of cardiovascular capacity. Life Sci 217:128–140. https://doi.org/10.1016/j.lfs.2018.12.001

Fenik V, Fenik P, Kubin L (2001) A simple cuff electrode for nerve recording and stimulation in acute experiments on small animals. J Neurosci Methods 106(2):147–151. https://doi.org/10.1016/s0165-0270(01)00340-5

Fenrich KK, Hallworth BW, Vavrek R, Raposo PJF, Misiaszek JE, Bennett DJ, Fouad K, Torres-Espin A (2021) Self-directed rehabilitation training intensity thresholds for efficient recovery of skilled forelimb function in rats with cervical spinal cord injury. Exp Neurol 339:113543. https://doi.org/10.1016/j.expneurol.2020.113543

Ferreira JC, Rolim NP, Bartholomeu JB, Gobatto CA, Kokubun E, Brum PC (2007) Maximal lactate steady state in running mice: effect of exercise training. Clin Exp Pharmacol Physiol 34(8):760–765. https://doi.org/10.1111/j.1440-1681.2007.04635.x

Fluckey JD, Dupont-Versteegden EE, Montague DC, Knox M, Tesch P, Peterson CA, Gaddy-Kurten D (2002) A rat resistance exercise regimen attenuates losses of musculoskeletal mass during hindlimb suspension. Acta Physiol Scand 176(4):293–300. https://doi.org/10.1046/j.1365-201X.2002.01040.x

Garland T Jr, Morgan MT, Swallow JG, Rhodes JS, Girard I, Belter JG, Carter PA (2002) Evolution of a small-muscle polymorphism in lines of house mice selected for high activity levels. Evolution 56(6):1267–1275. https://doi.org/10.1111/j.0014-3820.2002.tb01437.x

Goh J, Ladiges WC (2013) A novel long term short interval physical activity regime improves body composition in mice. BMC Res Notes 6:66. https://doi.org/10.1186/1756-0500-6-66

Goh Q, Song T, Petrany MJ, Cramer AA, Sun C, Sadayappan S, Lee SJ, Millay DP (2019) Myonuclear accretion is a determinant of exercise-induced remodeling in skeletal muscle. Elife 8. https://doi.org/10.7554/eLife.44876

Greising SM, Warren GL, Southern WM, Nichenko AS, Qualls AE, Corona BT, Call JA (2018) Early rehabilitation for volumetric muscle loss injury augments endogenous regenerative aspects of muscle strength and oxidative capacity. BMC Musculoskelet Disord 19(1):173. https://doi.org/10.1186/s12891-018-2095-6

Gurley JM, Griesel BA, Olson AL (2016) Increased skeletal muscle GLUT4 expression in obese mice after voluntary wheel running exercise is posttranscriptional. Diabetes 65(10):2911–2919. https://doi.org/10.2337/db16-0305

Halsberghe BT (2017) Long-term and immediate effects of whole body vibration on chronic lameness in the horse: a pilot study. J Equine Vet Sci 48:121–128.e122. https://doi.org/10.1016/j.jevs.2015.12.007

Hellyer NJ, Nokleby JJ, Thicke BM, Zhan WZ, Sieck GC, Mantilla CB (2012) Reduced ribosomal protein s6 phosphorylation after progressive resistance exercise in growing adolescent rats. J Strength Cond Res 26(6):1657–1666. https://doi.org/10.1519/JSC.0b013e318231abc9

Hohlbaum K, Bert B, Dietze S, Palme R, Fink H, Thone-Reineke C (2017) Severity classification of repeated isoflurane anesthesia in C57BL/6JRj mice-assessing the degree of distress. PLoS One 12(6):e0179588. https://doi.org/10.1371/journal.pone.0179588

Hohlbaum K, Bert B, Dietze S, Palme R, Fink H, Thone-Reineke C (2018) Impact of repeated anesthesia with ketamine and xylazine on the well-being of C57BL/6JRj mice. PLoS One 13(9): e0203559. https://doi.org/10.1371/journal.pone.0203559

Hsu YJ, Lee MC, Huang CC, Ho CS (2021) The effects of different types of aquatic exercise training interventions on a high-fructose diet-fed mice. Int J Med Sci 18(3):695–705. https://doi.org/10.7150/ijms.52347

Hyzewicz J, Ruegg UT, Takeda S (2015) Comparison of experimental protocols of physical exercise for mdx mice and duchenne muscular dystrophy patients. J Neuromuscul Dis 2(4): 325–342. https://doi.org/10.3233/JND-150106

Ikeda S, Kawamoto H, Kasaoka K, Hitomi Y, Kizaki T, Sankai Y, Ohno H, Haga S, Takemasa T (2006) Muscle type-specific response of PGC-1 alpha and oxidative enzymes during voluntary wheel running in mouse skeletal muscle. Acta Physiol (Oxf) 188(3–4):217–223. https://doi.org/10.1111/j.1748-1716.2006.01623.x

Ingalls CP, Warren GL, Lowe DA, Boorstein DB, Armstrong RB (1996) Differential effects of anesthetics on in vivo skeletal muscle contractile function in the mouse. J Appl Physiol 80(1): 332–340

Ingalls CP, Wenke JC, Nofal T, Armstrong RB (2004) Adaptation to lengthening contraction-induced injury in mouse muscle. J Appl Physiol (1985) 97(3):1067–1076. https://doi.org/10.1152/japplphysiol.01058.2003

Ishihara A, Roy RR, Ohira Y, Ibata Y, Edgerton VR (1998) Hypertrophy of rat plantaris muscle fibers after voluntary running with increasing loads. J Appl Physiol (1985) 84(6):2183–2189. https://doi.org/10.1152/jappl.1998.84.6.2183

Joa KL, Moon S, Kim JH, Shin DW, Lee KH, Jung S, Kim MO, Kim CH, Jung HY, Kang JH (2017) Effects of task-specific rehabilitation training on tau modification in rat with photothrombotic cortical ischemic damage. Neurochem Int 108:309–317. https://doi.org/10.1016/j.neuint.2017.05.004

Ju C, Park E, Kim T, Kim T, Kang M, Lee KS, Park SM (2020) Effectiveness of electrical stimulation on nerve regeneration after crush injury: comparison between invasive and non-invasive stimulation. PLoS One 15(5):e0233531. https://doi.org/10.1371/journal.pone.0233531

Judge S, Jang YM, Smith A, Selman C, Phillips T, Speakman JR, Hagen T, Leeuwenburgh C (2005) Exercise by lifelong voluntary wheel running reduces subsarcolemmal and interfibrillar mitochondrial hydrogen peroxide production in the heart. Am J Physiol Regul Integr Comp Physiol 289(6):R1564–R1572. https://doi.org/10.1152/ajpregu.00396.2005

Kaplan ML, Cheslow Y, Vikstrom K, Malhotra A, Geenen DL, Nakouzi A, Leinwand LA, Buttrick PM (1994) Cardiac adaptations to chronic exercise in mice. Am J Physiol 267(3 Pt 2):H1167–H1173. https://doi.org/10.1152/ajpheart.1994.267.3.H1167

Keller A, Rees K, Prince D, Morehouse J, Shum-Siu A, Magnuson D (2017) Dynamic “range of motion” hindlimb stretching disrupts locomotor function in rats with moderate subacute spinal cord injuries. J Neurotrauma 34(12):2086–2091. https://doi.org/10.1089/neu.2016.4951

Kemi OJ, Loennechen JP, Wisloff U, Ellingsen O (2002) Intensity-controlled treadmill running in mice: cardiac and skeletal muscle hypertrophy. J Appl Physiol (1985) 93(4):1301–1309. https://doi.org/10.1152/japplphysiol.00231.2002

Konhilas JP, Widegren U, Allen DL, Paul AC, Cleary A, Leinwand LA (2005) Loaded wheel running and muscle adaptation in the mouse. Am J Physiol Heart Circ Physiol 289(1):H455–H465. https://doi.org/10.1152/ajpheart.00085.2005

Koo J, MacEwan MR, Kang SK, Won SM, Stephen M, Gamble P, Xie Z, Yan Y, Chen YY, Shin J, Birenbaum N, Chung S, Kim SB, Khalifeh J, Harburg DV, Bean K, Paskett M, Kim J, Zohny ZS, Lee SM, Zhang R, Luo K, Ji B, Banks A, Lee HM, Huang Y, Ray WZ, Rogers JA (2018) Wireless bioresorbable electronic system enables sustained nonpharmacological neuroregenerative therapy. Nat Med 24(12):1830–1836. https://doi.org/10.1038/s41591-018-0196-2

Landisch RM, Kosir AM, Nelson SA, Baltgalvis KA, Lowe DA (2008) Adaptive and nonadaptive responses to voluntary wheel running by mdx mice. Muscle Nerve 38(4):1290–1303

Leite RD, Durigan Rde C, de Souza Lino AD, de Souza Campos MV, Souza M, Selistre-de-Araujo HS, Bouskela E, Kraemer-Aguiar LG (2013) Resistance training may concomitantly benefit body composition, blood pressure and muscle MMP-2 activity on the left ventricle of high-fat fed diet rats. Metabolism 62(10):1477–1484. https://doi.org/10.1016/j.metabol.2013.05.009

Lerman I, Harrison BC, Freeman K, Hewett TE, Allen DL, Robbins J, Leinwand LA (2002) Genetic variability in forced and voluntary endurance exercise performance in seven inbred mouse strains. J Appl Physiol (1985) 92(6):2245–2255. https://doi.org/10.1152/japplphysiol.01045.2001

Lightfoot JT, Turner MJ, Daves M, Vordermark A, Kleeberger SR (2004) Genetic influence on daily wheel running activity level. Physiol Genomics 19(3):270–276. https://doi.org/10.1152/physiolgenomics.00125.2004

Lovering RM, Roche JA, Goodall MH, Clark BB, McMillan A (2011) An in vivo rodent model of contraction-induced injury and non-invasive monitoring of recovery. J Vis Exp (51). https://doi.org/10.3791/2782

Lowe DA, Alway SE (2002) Animal models for inducing muscle hypertrophy: are they relevant for clinical applications in humans? J Orthop Sports Phys Ther 32(2):36–43. https://doi.org/10.2519/jospt.2002.32.2.36

Loy K, Bareyre FM (2019) Rehabilitation following spinal cord injury: how animal models can help our understanding of exercise-induced neuroplasticity. Neural Regen Res 14(3):405–412. https://doi.org/10.4103/1673-5374.245951

Lund J, Hafstad AD, Boardman NT, Rossvoll L, Rolim NP, Ahmed MS, Florholmen G, Attramadal H, Wisloff U, Larsen TS, Aasum E (2015) Exercise training promotes cardioprotection through oxygen-sparing action in high fat-fed mice. Am J Physiol Heart Circ Physiol 308(8):H823–H829. https://doi.org/10.1152/ajpheart.00734.2014

Manzanares G, Brito-da-Silva G, Gandra PG (2018) Voluntary wheel running: patterns and physiological effects in mice. Braz J Med Biol Res 52(1):e7830. https://doi.org/10.1590/1414-431X20187830

Matsuo S, Suzuki S, Iwata M, Hatano G, Nosaka K (2015) Changes in force and stiffness after static stretching of eccentrically-damaged hamstrings. Eur J Appl Physiol 115(5):981–991. https://doi.org/10.1007/s00421-014-3079-3

McDermott MM (2018) Exercise rehabilitation for peripheral artery disease: a review. J Cardiopulm Rehabil Prev 38(2):63–69. https://doi.org/10.1097/HCR.0000000000000343

McGee-Lawrence ME, Wenger KH, Misra S, Davis CL, Pollock NK, Elsalanty M, Ding K, Isales CM, Hamrick MW, Wosiski-Kuhn M, Arounleut P, Mattson MP, Cutler RG, Yu JC, Stranahan AM (2017) Whole-body vibration mimics the metabolic effects of exercise in male leptin receptor-deficient mice. Endocrinology 158(5):1160–1171. https://doi.org/10.1210/en.2016-1250

McKeehen JN, Novotny SA, Baltgalvis KA, Call JA, Nuckley DJ, Lowe DA (2013) Adaptations of mouse skeletal muscle to low-intensity vibration training. Med Sci Sports Exerc 45(6): 1051–1059. https://doi.org/10.1249/MSS.0b013e3182811947

Mintz EL, Passipieri JA, Lovell DY, Christ GJ (2016) Applications of in vivo functional testing of the rat tibialis anterior for evaluating tissue engineered skeletal muscle repair. J Vis Exp (116). https://doi.org/10.3791/54487

Mobley CB, Holland AM, Kephart WC, Mumford PW, Lowery RP, Kavazis AN, Wilson JM, Roberts MD (2018) Progressive resistance-loaded voluntary wheel running increases hypertrophy and differentially affects muscle protein synthesis, ribosome biogenesis, and proteolytic markers in rat muscle. J Anim Physiol Anim Nutr (Berl) 102(1):317–329. https://doi.org/10.1111/jpn.12691

Murach KA, McCarthy JJ, Peterson CA, Dungan CM (2020) Making mice mighty: recent advances in translational models of load-induced muscle hypertrophy. J Appl Physiol 129(3):516–521. https://doi.org/10.1152/japplphysiol.00319.2020

Murfee WL, Hammett LA, Evans C, Xie L, Squire M, Rubin C, Judex S, Skalak TC (2005) High-frequency, low-magnitude vibrations suppress the number of blood vessels per muscle fiber in mouse soleus muscle. J Appl Physiol (1985) 98(6):2376–2380. https://doi.org/10.1152/japplphysiol.01135.2004

Navarro A, Gomez C, Lopez-Cepero JM, Boveris A (2004) Beneficial effects of moderate exercise on mice aging: survival, behavior, oxidative stress, and mitochondrial electron transfer. Am J Physiol Regul Integr Comp Physiol 286(3):R505–R511. https://doi.org/10.1152/ajpregu.00208.2003

Necking LE, Lundstrom R, Lundborg G, Thornell LE, Friden J (1996) Skeletal muscle changes after short term vibration. Scand J Plast Reconstr Surg Hand Surg 30(2):99–103. https://doi.org/10.3109/02844319609056390

Noble EE, Hsu TM, Liang J, Kanoski SE (2019) Early-life sugar consumption has long-term negative effects on memory function in male rats. Nutr Neurosci 22(4):273–283. https://doi.org/10.1080/1028415X.2017.1378851

Novotny SA, Mehta H, Lowe DA, Nuckley DJ (2013) Vibration platform for mice to deliver precise, low intensity mechanical signals to the musculoskeleton. J Musculoskelet Neuronal Interact 13(4):412–417

Novotny SA, Mader TL, Greising AG, Lin AS, Guldberg RE, Warren GL, Lowe DA (2014) Low intensity, high frequency vibration training to improve musculoskeletal function in a mouse model of Duchenne muscular dystrophy. PLoS One 9(8):e104339. https://doi.org/10.1371/journal.pone.0104339

Okabe N, Himi N, Maruyama-Nakamura E, Hayashi N, Narita K, Miyamoto O (2017) Rehabilitative skilled forelimb training enhances axonal remodeling in the corticospinal pathway but not the brainstem-spinal pathways after photothrombotic stroke in the primary motor cortex. PLoS One 12(11):e0187413. https://doi.org/10.1371/journal.pone.0187413

Park HS, Martin BJ (1993) Contribution of the tonic vibration reflex to muscle stress and muscle fatigue. Scand J Work Environ Health 19(1):35–42. https://doi.org/10.5271/sjweh.1506

Peng L, Zhu M, Yang Y, Lu F, Liu X, Guo Q, Zhong T (2021) Repeated neonatal isoflurane exposure is associated with higher susceptibility to chronic variable stress-induced behavioural and neuro-inflammatory alterations. Neuroscience 465:166–176. https://doi.org/10.1016/j.neuroscience.2021.04.024

Perez-Terzic C, Childers MK (2014) Regenerative rehabilitation: a new future? Am J Phys Med Rehabil 93(11 Suppl 3):S73–S78. https://doi.org/10.1097/PHM.0000000000000211

Picoli CC, Romero P, Gilio GR, Guariglia DA, Tofolo LP, de Moraes SMF, Machado FA, Peres SB (2018) Peak velocity as an alternative method for training prescription in mice. Front Physiol 9: 42. https://doi.org/10.3389/fphys.2018.00042

Poole DC, Copp SW, Colburn TD, Craig JC, Allen DL, Sturek M, O'Leary DS, Zucker IH, Musch TI (2020) Guidelines for animal exercise and training protocols for cardiovascular studies. Am J Physiol Heart Circ Physiol 318(5):H1100–H1138. https://doi.org/10.1152/ajpheart.00697.2019

Portier H, Benaitreau D, Pallu S (2020) Does physical exercise always improve bone quality in rats? Life (Basel) 10(10). https://doi.org/10.3390/life10100217

Ren Z, Lan Q, Chen Y, Chan YWJ, Mahady GB, Lee SM (2020) Low-magnitude high-frequency vibration decreases body weight gain and increases muscle strength by enhancing the p38 and AMPK pathways in db/db mice. Diabetes Metab Syndr Obes 13:979–989. https://doi.org/10.2147/DMSO.S228674

Rhodes JS, Gammie SC, Garland T Jr (2005) Neurobiology of mice selected for high voluntary wheel-running activity. Integr Comp Biol 45(3):438–455. https://doi.org/10.1093/icb/45.3.438

Ritzmann R, Stark C, Krause A (2018) Vibration therapy in patients with cerebral palsy: a systematic review. Neuropsychiatr Dis Treat 14:1607–1625. https://doi.org/10.2147/NDT.S152543

Robles JC, Heaps CL (2015) Adaptations of the endothelin system after exercise training in a porcine model of ischemic heart disease. Microcirculation 22(1):68–78. https://doi.org/10.1111/micc.12174

Rodnick KJ, Reaven GM, Haskell WL, Sims CR, Mondon CE (1989) Variations in running activity and enzymatic adaptations in voluntary running rats. J Appl Physiol (1985) 66(3):1250–1257. https://doi.org/10.1152/jappl.1989.66.3.1250

Rubin C, Turner AS, Bain S, Mallinckrodt C, McLeod K (2001) Anabolism. Low mechanical signals strengthen long bones. Nature 412(6847):603–604. https://doi.org/10.1038/35088122

Seldeen KL, Lasky G, Leiker MM, Pang M, Personius KE, Troen BR (2018) High intensity interval training improves physical performance and frailty in aged mice. J Gerontol A Biol Sci Med Sci 73(4):429–437. https://doi.org/10.1093/gerona/glx120

Seldeen KL, Redae YZ, Thiyagarajan R, Berman RN, Leiker MM, Troen BR (2019) Short session high intensity interval training and treadmill assessment in aged mice. J Vis Exp (144). https://doi.org/10.3791/59138

Seo DY, Lee SR, Kim N, Ko KS, Rhee BD, Han J (2014) Humanized animal exercise model for clinical implication. Pflugers Arch 466(9):1673–1687. https://doi.org/10.1007/s00424-014-1496-0

Soffe Z, Radley-Crabb HG, McMahon C, Grounds MD, Shavlakadze T (2016) Effects of loaded voluntary wheel exercise on performance and muscle hypertrophy in young and old male C57Bl/6J mice. Scand J Med Sci Sports 26(2):172–188. https://doi.org/10.1111/sms.12416

Souza MV, Leite RD, Souza Lino AD, Marqueti Rde C, Bernardes CF, Araujo HS, Bouskela E, Shiguemoto GE, Andrade Perez SE, Kraemer-Aguiar LG (2014) Resistance training improves body composition and increases matrix metalloproteinase 2 activity in biceps and gastrocnemius muscles of diet-induced obese rats. Clinics (Sao Paulo) 69(4):265–270. https://doi.org/10.6061/clinics/2014(04)08

Spaulding HR, Selsby JT (2018) Is exercise the right medicine for dystrophic muscle? Med Sci Sports Exerc 50(9):1723–1732. https://doi.org/10.1249/MSS.0000000000001639

Strickland JC, Smith MA (2016) Animal models of resistance exercise and their application to neuroscience research. J Neurosci Methods 273:191–200. https://doi.org/10.1016/j.jneumeth.2016.08.003

Svensson M, Rosvall P, Boza-Serrano A, Andersson E, Lexell J, Deierborg T (2016) Forced treadmill exercise can induce stress and increase neuronal damage in a mouse model of global cerebral ischemia. Neurobiol Stress 5:8–18. https://doi.org/10.1016/j.ynstr.2016.09.002

Swallow JG, Rhodes JS, Garland T Jr (2005) Phenotypic and evolutionary plasticity of organ masses in response to voluntary exercise in house mice. Integr Comp Biol 45(3):426–437. https://doi.org/10.1093/icb/45.3.426

Tamaki T, Uchiyama S, Nakano S (1992) A weight-lifting exercise model for inducing hypertrophy in the hindlimb muscles of rats. Med Sci Sports Exerc 24(8):881–886

Tanaka A, Yoshimura Y, Aoki K, Okamoto M, Kito M, Suzuki S, Takazawa A, Ishida T, Kato H (2017) Prediction of muscle strength and postoperative function after knee flexor muscle resection for soft tissue sarcoma of the lower limbs. Orthop Traumatol Surg Res 103(7): 1081–1085. https://doi.org/10.1016/j.otsr.2017.07.005

Thompson LV (2002) Skeletal muscle adaptations with age, inactivity, and therapeutic exercise. J Orthop Sports Phys Ther 32(2):44–57. https://doi.org/10.2519/jospt.2002.32.2.44

Vanleene M, Shefelbine SJ (2013) Therapeutic impact of low amplitude high frequency whole body vibrations on the osteogenesis imperfecta mouse bone. Bone 53(2):507–514. https://doi.org/10.1016/j.bone.2013.01.023

Walters TJ, Sweeney HL, Farrar RP (1991) Influence of electrical stimulation on a fast-twitch muscle in aging rats. J Appl Physiol (1985) 71(5):1921–1928. https://doi.org/10.1152/jappl.1991.71.5.1921

Wang VM, Banack TM, Tsai CW, Flatow EL, Jepsen KJ (2006) Variability in tendon and knee joint biomechanics among inbred mouse strains. J Orthop Res 24(6):1200–1207. https://doi.org/10.1002/jor.20167

Wang N, Liu Y, Ma Y, Wen D (2017) High-intensity interval versus moderate-intensity continuous training: superior metabolic benefits in diet-induced obesity mice. Life Sci 191:122–131. https://doi.org/10.1016/j.lfs.2017.08.023

Wang R, Tian H, Guo D, Tian Q, Yao T, Kong X (2020) Impacts of exercise intervention on various diseases in rats. J Sport Health Sci 9(3):211–227. https://doi.org/10.1016/j.jshs.2019.09.008

Warren GL, Ingalls CP, Armstrong RB (1998) A stimulating nerve cuff for chronic in vivo measurements of torque produced about the ankle in the mouse. J Appl Physiol 84(6): 2171–2176

Warren GL, Lowe DA, Armstrong RB (1999) Measurement tools used in the study of eccentric contraction-induced injury. Sports Med 27(1):43–59. https://doi.org/10.2165/00007256-199927010-00004

Warren GL, Moran AL, Hogan HA, Lin AS, Guldberg RE, Lowe DA (2007) Voluntary run training but not estradiol deficiency alters the tibial bone-soleus muscle functional relationship in mice. Am J Physiol Regul Integr Comp Physiol 293(5):R2015–R2026

Weill F, Bourgoin A, Eisenscher A, Aucant D, Tuetey JB, Duval JM (1976) [Ultrasonic aspect of abdominal fluid collections. Ascites, abscess, hematoma]. J Radiol Electrol Med Nucl 57 (8–9): 618

Weinheimer-Haus EM, Judex S, Ennis WJ, Koh TJ (2014) Low-intensity vibration improves angiogenesis and wound healing in diabetic mice. PLoS One 9(3):e91355. https://doi.org/10.1371/journal.pone.0091355

White Z, Terrill J, White RB, McMahon C, Sheard P, Grounds MD, Shavlakadze T (2016) Voluntary resistance wheel exercise from mid-life prevents sarcopenia and increases markers of mitochondrial function and autophagy in muscles of old male and female C57BL/6J mice. Skelet Muscle 6(1):45. https://doi.org/10.1186/s13395-016-0117-3

Wisloff U, Loennechen JP, Currie S, Smith GL, Ellingsen O (2002) Aerobic exercise reduces cardiomyocyte hypertrophy and increases contractility, Ca2+ sensitivity and SERCA-2 in rat after myocardial infarction. Cardiovasc Res 54(1):162–174. https://doi.org/10.1016/s0008-6363(01)00565-x

Wolf A, Bauer B, Abner EL, Ashkenazy-Frolinger T, Hartz AM (2016) A comprehensive behavioral test battery to assess learning and memory in 129S6/Tg2576 mice. PLoS One 11(1): e0147733. https://doi.org/10.1371/journal.pone.0147733

Xie L, Jacobson JM, Choi ES, Busa B, Donahue LR, Miller LM, Rubin CT, Judex S (2006) Low-level mechanical vibrations can influence bone resorption and bone formation in the growing skeleton. Bone 39(5):1059–1066. https://doi.org/10.1016/j.bone.2006.05.012

Xie L, Rubin C, Judex S (2008) Enhancement of the adolescent murine musculoskeletal system using low-level mechanical vibrations. J Appl Physiol (1985) 104(4):1056–1062. https://doi.org/10.1152/japplphysiol.00764.2007

Xin DL, Hadrevi J, Elliott ME, Amin M, Harris MY, Barr-Gillespie AE, Barbe MF (2017) Effectiveness of conservative interventions for sickness and pain behaviors induced by a high repetition high force upper extremity task. BMC Neurosci 18(1):36. https://doi.org/10.1186/s12868-017-0354-3

Zaidell LN, Mileva KN, Sumners DP, Bowtell JL (2013) Experimental evidence of the tonic vibration reflex during whole-body vibration of the loaded and unloaded leg. PLoS One 8(12):e85247. https://doi.org/10.1371/journal.pone.0085247

Zemmar A, Kast B, Lussi K, Luft AR, Schwab ME (2015) Acquisition of a high-precision skilled forelimb reaching task in rats. J Vis Exp (100):e53010. https://doi.org/10.3791/53010

Zhu WG, Hibbert JE, Lin KH, Steinert ND, Lemens JL, Jorgenson KW, Newman SM, Lamming DW, Hornberger TA (2021) Weight pulling: a novel mouse model of human progressive resistance exercise. Cells 10(9). https://doi.org/10.3390/cells10092459