HHS Public Access

Author manuscript

Neurosci Biobehav Rev. Author manuscript; available in PMC 2015 June 04.

Published in final edited form as:

Neurosci Biobehav Rev. 2012 March ; 36(3): 1001–1014. doi:10.1016/j.neubiorev.2011.12.012.

The use of a running wheel to measure activity in rodents: Relationship to energy balance, general activity, and reward

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Abstract

Running wheels are commonly employed to measure rodent physical activity in a variety of contexts, including studies of energy balance and obesity. There is no consensus on the nature of wheel-running activity or its underlying causes, however. Here, we will begin by systematically reviewing how running wheel availability affects physical activity and other aspects of energy balance in laboratory rodents. While wheel running and physical activity in the absence of a wheel commonly correlate in a general sense, in many specific aspects the two do not correspond. In fact, the presence of running wheels alters several aspects of energy balance, including body weight and composition, food intake, and energy expenditure of activity. We contend that wheel-running activity should be considered a behavior in and of itself, reflecting several underlying behavioral processes in addition to a rodent's general, spontaneous activity. These behavioral processes include defensive behavior, predatory aggression, and depression- and anxiety-like behaviors. As it relates to energy balance, wheel running engages several brain systems—including those related to the stress response, mood, and reward, and those responsive to growth factors—that influence energy balance indirectly. We contend that wheel-running behavior represents factors in addition to rodents' tendency to be physically active, engaging additional neural and physiological mechanisms which can then independently alter energy balance and behavior. Given the impact of wheel-running behavior on numerous overlapping systems that influence behavior and physiology, this review outlines the need for careful design and interpretation of studies that utilize running wheels as a means for exercise or as a measurement of general physical activity.

Keywords

Running wheel; Wheel-running activity; Energy balance; Reward; Brain

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1. Introduction

Measurement of physical activity in laboratory rodents has enabled the widespread use of the running wheel. Most rodents readily run in wheels, and it has become an uncomplicated, easily quantifiable measure of physical activity (Sherwin, 1998). The running wheel is commonly used in studies of obesity and energy balance as a surrogate for general activity —that is, the tendency of a rodent to be more or less active. The interest in this area has increased along with evidence that non-exercise activity and the associated energy expenditure (non-exercise activity thermogenesis, or NEAT) is associated with resistance to obesity (Church et al., 2007; Hamilton et al., 2007; Levine et al., 1999, 2005; van Baak et al., 2003; Weinsier et al., 1998). Perhaps even more compelling are suggestions that low physical activity (i.e., sitting) is in itself a risk factor for cardiovascular and metabolic disease (Chomistek et al., 2011; Danaei et al., 2009; Hamilton et al., 2007; Sisson et al., 2009; Stamatakis et al., 2011; Stephens et al., 2011). In humans and in animals, the tendency to be more or less active is shaped by both genetic and environmental factors (Bassett et al., 2004; Joosen et al., 2005; Kaprio et al., 1981; Lanningham-Foster et al., 2003; Novak and Levine, 2007). In order to tease apart the neural, endocrine, and physiological mechanisms underlying individual differences in physical activity, experimental models are employed and physical activity is assessed. The running wheel is often used to assess levels of general physical activity, and other times to model the effects of exercise (Haskell-Luevano et al., 2009; Patterson and Levin, 2008). The purpose of this review is to systematically examine how running wheels complicate the investigation of energy balance and behavior in rodents. Previous reviews have described a range of behavioral effects that a running wheel had on animals and pondered what wheel running might represent in a rodent (Sherwin, 1998); the neurobiology underlying physical activity and wheel running (Garland et al., 2011); and translational studies on the use of the running wheel to model the effects of exercise on health, the brain, and behavior (Haskell-Luevano et al., 2009; Patterson and Levin, 2008). Here, we hypothesize that wheel-running behavior is not solely reflective of the tendency to be physically active, but is a complex and dynamic behavior that interacts with genetics and the environment. We will describe how the running wheel alters rodent behavior and several components of energy balance, delineate how and why this may occur, consider the implications to study design and interpretation, and finally give recommendations regarding the use of running wheels to examine rodent behavior.

2. Access to a running wheel amplifies activity and alters elements of energy balance

Exercise has several well-known benefits to health and fitness (Haskell-Luevano et al., 2009; Patterson and Levin, 2008), as well as neural and cognitive effects (Cotman and Engesser-Cesar, 2002), in humans and laboratory animals; these are outside of the scope of this review. In this section, we will focus on how a running wheel can have unintended consequences on rodent energy balance. Here, we define *energy balance* as the biological homeostatis of energy in an organism, encompassing energy intake, storage, efficiency, and internal and external work produced. Table 1 outlines studies documenting the effects of wheel-running activity on these different aspects of energy balance. Commonly, when a

running wheel is introduced, activity levels are intensified. The amount of wheel running shown by rodents exhibits extreme variability both between and within species, however (Friedman et al., 1992). Though it is rarely noted in publications, it is not unusual to have a small but conspicuous fraction of rodents fail to engage in any significant wheel running, particularly when dealing with mice, which show large strain-related differences in wheel running (de Visser et al., 2006; Lerman et al., 2002). Other rodents are more consistent. For example, Syrian hamsters show very large amounts of wheel running, and the resultant increase in energy expenditure may drive the increased food intake in hamsters (Coutinho et al., 2006b). Body fat mass also decreases in hamsters with wheel running, demonstrating that, even with the increased food intake, negative energy balance is achieved. Similarly, when rats are given free access to a running wheel, they will show high levels of wheel-running activity and increase their food intake compared to rats without wheels (Dixon et al., 2003). Lastly, mice show increased food intake when given access to a wheel (Swallow et al., 2001).

The alterations in food intake and energy balance that occur after wheel access serve to underscore the fact that access to running wheels amplifies activity in most rodents (see Table 1 for examples), thereby increasing the need for calories. Even though some studies consider them interchangeable, measuring wheel-running activity is not the same as measuring general cage activity. On the contrary, running wheels have been conclusively demonstrated to alter home cage activity in both mice and rats (de Visser et al., 2005; Hoffmann et al., 1987). In mice with access to wheels, less time is spent in their shelter and ambulating about their home cage compared to mice that were not provided a wheel; the temporal pattern of activity was also altered in mice with access to wheels (de Visser et al., 2005). Recently, it has become more common to investigate physical activity using both wheels as well as general cage activity in succession (Pistilli et al., 2011); this allows for direct comparison between the two methods. Several investigators have identified correlations between wheel running and spontaneous or home-cage physical activity, either according to group or, less commonly, within individual animals (Coyle et al., 2008; Malisch et al., 2008; Morgan and Pfaff, 2001, 2002; Pistilli et al., 2011; Richter et al., 2008; Schmidt et al., 2008; Simoncic et al., 2008). While the two types of activity are usually correlated in a general sense, wheel running intensifies activity, increases variability between individuals, and can amplify group differences in activity. Though variation is seen between species and individuals in the magnitude of the effect, running wheels have a general tendency to increase activity and activity energy expenditure in rodents (Table 1). This then has downstream effects on other aspects of energy balance. When investigating physical activity as a component of energy balance, it is prudent to use a method other than, or in addition to, the running wheel.

Running wheels have the potential to influence several components of energy balance apart from the effects of wheel running on energy expenditure. In female rats over their estrous cycle, “scalloping” of wheel running is often observed, with an advance in the onset of running and increases in wheel-running activity occurring on the morning of estrus (Dixon et al., 2003). This also coincides with decreased energy intake. This effect is subject to species differences which may be linked to high circulating concentrations of estradiol (Cushing and Cawthorn, 1996; Cushing et al., 1995). The influence of the estrous cycle on

activity is much more salient when observing wheel running compared to home cage activity. When female rats are placed on a restricted feeding schedule, they develop activity-based anorexia: activity will increase sharply but food intake will not increase to compensate, and weight loss results (Dixon et al., 2003). This in turn disrupts estrous cyclicity. Similarly, an altered response to wheel-induced disruption of energy balance is also seen in rats lacking CCK-A receptors (OLETF rats). These rats are normally obese, diabetic, and hyperphagic. The introduction of wheels at 8 weeks of age normalized food intake, body weight, and circulating leptin and glucose (Bi et al., 2005). The negative energy balance seen in OLETF rats with running wheels was much more pronounced than that seen in their control counterparts: the OLETF rats ate less when presented with a running wheel, whereas the control rats ate more. These studies highlight how the effect of a running wheel on specific aspects of energy balance varies depending on the species, sex, genetic background, and environment. As detailed below, wheel running corresponds more with exercise than general non-exercise activity, at least in how it affects metabolism.

In general, when a rodent is presented with a running wheel, activity will increase sharply, then continue to increase before plateauing, with a concomitant increase in food intake that is presumed to meet the increased energy demands (Cabeza de Vaca et al., 2007; Engel et al., 2009; Hickey et al., 2008; Murray et al., 2010; Pham et al., 2005; Richter et al., 2008) (see Table 1 for examples). This highlights the difference between activity in a running wheel compared to general cage activity. Often, a wheel is introduced to assess the effects of exercise rather to assess physical activity levels (Coutinho et al., 2006a,b; Moraska and Fleshner, 2001; Wood, 2002). Indeed, the physiological results of wheel-running activity in rodents closely parallel the results of exercise in humans, including increased muscle insulin sensitivity, increased skeletal muscle citrate synthase, and decreased visceral fat relative to times when the rats cannot run in wheels (Booth et al., 2008; Davidson et al., 2006; Henriksen and Halseth, 1995). Though voluntary wheel running appears to be a fitting model of physiological effects of aerobic exercise (Booth et al., 2008; Cotman and Engesser-Cesar, 2002; Meeusen, 2005), this does not imply that it is an equally fitting model for the motivation to exercise. What about the processes underlying the motivation of the rodent to voluntarily run in the wheel? Is it analogous to the motivation to exercise in humans? Are the mechanistic processes and motivations that predispose a rodent to run in their wheel for extended distances and time periods the same processes and motivations that result in a more active rodent in the absence of a wheel? In general, evidence does not support this assertion; several factors are known to differentially alter physical activity versus wheel running, which will be discussed in the following sections.

3. Running wheels can alter daily activity patterns

Activity wheels are customarily used to measure circadian activity rhythms in all suborders of rodents. The introduction of an activity wheel can also alter the temporal pattern of activity (see Table 1). The murid rodent *Arvicanthis niloticus* shows diurnal activity in the field (Blanchong et al., 1999); a study using timed trapping devices showed that *A. niloticus* were found outside of their burrow almost exclusively during the daytime hours (Blanchong et al., 1999), leading to the conclusion that they are strictly diurnal. This parallels their general cage activity in the absence of a wheel (Blanchong et al., 1999). In the laboratory

setting, however, access to a running wheel induces a very distinct pattern of activity. A subset of the animals will "switch" to a pattern of activity that appears to be nocturnal; removal of the wheel returns the animal to its previous diurnal pattern of activity (Blanchong et al., 1999; Katona and Smale, 1997). The change in activity pattern is abrupt, indicating that a circadian phase shift is unlikely to underlie this phenomenon. Blanchong et al. (1999) also found that the propensity to switch activity patterns in the presence of a wheel is inherited (Blanchong et al., 1999). The effect of a wheel on activity in *A. niloticus* is likely to be due to masking, or the direct influence of environmental lighting conditions on activity rather than underlying circadian processes. When lights are turned on intermittently throughout the light phase of the cycle (subjective day) the animals will run on their wheels primarily during the dark periods. Without wheels, however, the animals will be active preferentially when lights are on (Redlin and Mrosovsky, 2004). In this diurnal species, access to a running wheel profoundly alters the daily pattern of activity, and it is likely that brain regions activated by arousal and reward mediate this "switch" (Castillo-Ruiz et al., 2010). A similar wheel-induced alteration in the temporal pattern of activity can be seen in another rodent, *Octodon degus*. A subset of degus invert their phase preference from diurnal to nocturnal when housed with a running wheel. The activity pattern immediately switches back to diurnal upon removal of the wheel (Kas and Edgar, 1999). The running wheel has the ability to dramatically alter the temporal pattern of activity in these rodent species. In one case, this phenomenon is subject to individual differences which appear to be heritable, potentially through single-gene inheritance of an autosomal dominant gene with incomplete penetrance, sex-linked inheritance, or epigenetic mechanisms (Blanchong et al., 1999). These findings support the assertion that wheel-running activity is distinctly different from general activity. Moreover, it is likely that the neural systems underlying these different types of activity overlap, but not completely. This theme is reinforced when one examines how caloric restriction differentially modulates wheel-running versus general physical activity.

4. Food availability affects wheel running and spontaneous physical activity differently

Alterations in food availability affect physical activity, both with and without the running wheel. In general, acute starvation increases general physical activity over the short term in several species, presumably as a foraging response (Lynn et al., 2003; Novak et al., 2005; Williams et al., 2002). In contrast, long-term starvation decreases levels of physical activity (Novak et al., 2005; Severinsen and Munch, 1999), apparently to conserve energy. The complete absence of food (starvation/food restriction) has different effects than caloric restriction, wherein rodents are fed a reduced number of calories each day, most commonly 60–70% of pre-restriction levels. Caloric restriction suppresses physical activity levels in rats (Severinsen and Munch, 1999). This is generally interpreted as an effort to conserve energy in the face of decreased food availability. In mice, on the other hand, caloric restriction decreases dark-phase physical activity but increases light-phase activity, resulting in no net change in daily physical activity (Overton and Williams, 2004; Williams et al., 2002).

How does complete or partial caloric restriction affect activity in a wheel in rodents? As described above, in female rats, starvation and caloric restriction both increase wheel running to the detriment of the animal's health (Hebebrand et al., 2003; Morse et al., 1995; Pirke et al., 1993; Russell et al., 1987). [Activity-based anorexia or starvation-induced hyperactivity (Hebebrand et al., 2003) is not evident in mice (Rikke et al., 2003).] This paradoxical effect has been attributed to a response to peripheral energy balance signals such as leptin (Exner et al., 2000), an attempt to thermoregulate in response to change in ambient temperature (Gutierrez et al., 2002; Williams et al., 2002), or as a representation of foraging. Indeed, the running wheel has been used as a model of foraging whereby rodents must work (i.e., run) for food (Day and Bartness, 2001). Circadian influences should also be taken into account: caloric restriction usually entails giving the rodents food at a specific time each day. Because of a food-entrainable oscillator, the rodent will anticipate the time of food availability and increase their activity in the time period before the food arrives (Stephan, 2002).

Thus, several factors interact to determine how food availability alters general, spontaneous activity in rodents, including species, strain or genetic background, sex, phase of the estrous cycle, ambient temperature, the type and magnitude of food restriction, time of day, and of course the presence of a running wheel. Though innate general cage activity levels appear to be roughly correlated with wheel-running activity levels (Coyle et al., 2008; Waters et al., 2008), it is clear that the two are not equivalent. It is also apparent that wheel-running activity does not accurately represent general physical activity in rodents during caloric restriction, and that the presence of the wheel has profound effects on energy balance, especially in rats. In addition to the general tendency to be physically active, what other factors account for wheel-running activity in rodents? To answer this question, we will examine behavioral aspects of wheel running which, at first glance, may appear to be unrelated to the regulation of energy balance. Though the capacity for voluntary wheel running to influence stress and/or behavior has been reviewed several times (Dishman, 1997; Greenwood and Fleshner, 2008; Sothmann et al., 1996; Stranahan et al., 2008), here, we will focus on behaviors which have underlying neurochemical systems in common with energy balance regulation.

5. Behavioral aspects of wheel running: wheel running affects motivation and reward systems

Increased attention is being paid to the importance of brain reward system activation in energy balance regulation, especially as it relates to appetite (Fulton, 2010; Zheng et al., 2009). These same brain reward systems play a role in wheel-running behavior; examples are given in Table 2. In fact, the act of wheel running itself can become a self-perpetuating behavior that has the capacity to reach obsessive levels. Wheel-running behavior in rodents follows a fairly consistent pattern, increasing for several weeks until the total distance covered in a given period of time plateaus. Total running duration then decreases over time or with ageing. Beyond this general pattern of wheel-running behavior, it is important to recognize that a fair amount of individual variability occurs. This variance is likely due to the capacity of the animal to engage in wheel-running behavior coupled with the amount of

reward the animal experiences from wheel running, as well as other environmental factors (Table 2). Taken together, these factors will influence an animal's propensity and motivation to engage in wheel running.

5.1. Voluntary wheel running is rewarding and interacts with other reinforcers

Table 2 gives examples of evidence supporting the assertion that the running wheel is rewarding to rodents. Rats will lever-press for access to running wheels (Belke, 1997; Collier and Hirsch, 1971; Iversen, 1993; Kagan and Berkun, 1954), indicating that, similar to drug self-administration paradigms, wheel running is rewarding and rats will work for the opportunity to run. The rewarding aspect of voluntary wheel running suggests that neural pathways regulating reward to substances of abuse may also be activated by wheel running. This is supported by the finding that rats who exhibit the highest levels of lever-pressing also exhibit the highest levels of wheel running (Iversen, 1993), suggesting that those individuals that receive the most reward from wheel running are willing to work the hardest for it. In addition to rats' motivation to work for access to running wheels, it is apparent that unrestricted wheel running can reach levels that could be considered compulsive and extreme (Lattanzio and Eikelboom, 2003). Due to the reinforcing effect of wheel running, the running wheel is becoming a more frequently used tool to investigate the rewarding properties of drugs of abuse. For example, rats that are considered “addiction prone”—they are more likely to self-administer addictive drugs than rats from other strains—also exhibit excessive levels of voluntary wheel running (Werme et al., 1999); examples are cited in Table 2. Female rats given access to running wheels in combination with food restriction will further escalate their running behavior and will forego the opportunity to eat, ultimately leading to their death (Routtenberg and Kuznesof, 1967; Spigelman et al., 1991). This behavioral pattern suggests that animals are willing to engage in wheel-running behavior in a way that parallels humans' willingness to engage in drug use despite dangerous or dire consequences (Robinson, 2004). Another parallel is the heightened activity seen with decreased caloric intake in human anorexics, resulting in profound negative energy balance (Hebebrand et al., 2003; Scheurink et al., 2010). Interestingly, anorexic patients also show alterations in the processing of rewarding stimuli (Jappe et al., 2011).

Similar to other reinforcers, the running wheel can be used in hedonic substitution as an alternate reinforcer (see examples in Table 2). For example, wheel running increases when mice are denied access to ethanol (Ozburn et al., 2008). It has been suggested that the running wheel can serve as an alternative source of motivation, replacing drugs of abuse such as cocaine (Smith et al., 2008) because voluntary wheel running can substantially decrease intravenous self-administration of cocaine in rodents (Cosgrove et al., 2002; Smith et al., 2008). Wheel running also decreases oral consumption of amphetamine in rats (Kanarek et al., 1995). More relevant to energy balance, studies demonstrate that wheel running also decreases motivation for natural reinforcers such as food (Iversen, 1993) and a sucrose solution (Satvat and Eikelboom, 2006). Conversely, food deprivation increases lever pressing for both cocaine and access to running wheels (Carroll, 1984; Finger, 1951; Pierce et al., 1986). Therefore, in addition to directly impacting metabolism through exercise and its downstream impact on energy expenditure and appetite, wheel running may also alter energy balance via indirect means: modulating appetite by affecting the rewarding and

reinforcing aspects of food. This hypothesized indirect alteration of energy balance by wheel running differs from the effect of general physical activity on energy balance, and is another source of individual variability in wheel running. Perhaps most importantly, these data support the idea that neural mechanisms controlling appetite and reward overlap, and that these brain systems are activated by wheel running.

5.2. Wheel running involves brain reward systems activated by drugs of abuse

The impact of the running wheel on reward and other reinforcing stimuli is reflected in alterations in brain reward mechanisms. Individual differences in wheel-running activity in rats mirrored differences in response to amphetamine, and exhibited a “cross-sensitization” between wheel running and amphetamine (Ferreira et al., 2006). This implies similar underlying mechanisms mediating wheel-running activity and addiction or reward (Ferreira et al., 2006). The mesolimbic and mesocortical dopamine systems have long been known to play a role in substance abuse (Feltenstein and See, 2008; Self, 1998), and the same dopaminergic systems are influenced by voluntary exercise (Meeusen and De Meirleir, 1995). Thirty minutes of voluntary wheel running increases dopamine metabolism in the striatum of mice (Bliss and Ailion, 1971). Eight weeks of wheel running resulted in elevated catecholamine concentrations (dopamine and norepinephrine) in the brain that were correlated with weight loss and hyperphagia induced by wheel running (de Castro and Hill, 1988).

In addition to the dopaminergic system, wheel running is known to influence endogenous opioids. Endogenous opioid systems are integrally related to mesolimbic and mesocortical dopaminergic function and regulate the response of these dopaminergic systems to drugs of abuse. Exposure to running wheels for 2 h a day over eight days promotes tolerance to morphine as measured by conditioned place preference (Lett et al., 2002), and wheel running itself induces conditioned place preference which is reversible by administration of the opioid receptor antagonist naloxone (Lett et al., 2001). Chronic wheel running decreases the analgesic properties of morphine (D'Anci et al., 2000; Kanarek et al., 1998; Mathes and Kanarek, 2001) with pain regulatory regions of the brain implicated in this response (Mathes and Kanarek, 2006). Further, dynorphin mRNA is increased in the medial caudate putamen following wheel running and cocaine administration (Werme et al., 2000). Recently, alterations in both dopamine and opioid systems in the basal fore-brain (Bjornebekk et al., 2008; Greenwood et al., 2011), as well as increased tyrosine hydroxylase mRNA levels in the ventral tegmental area, were reported following 6 weeks of voluntary wheel running (Greenwood et al., 2011). Levels of ΔFosB protein, known to be involved in drug reward (Hope et al., 1994; Nestler et al., 2001) and food reward (Teegarden et al., 2008), as well as c-Fos, were both increased following voluntary wheel running (Greenwood et al., 2011; Vargas-Perez et al., 2003). The authors also reported conditioned place preference in rats following six weeks, but not two weeks, of voluntary wheel running (Greenwood et al., 2011), linking the changes in neurochemistry to a behavioral endpoint. Lastly, reward system activation by wheel running depends on genetic background (Bjornebekk et al., 2006), thus the distinct neurocircuitry activation in different lines and strains of rodents may contribute to differential behavioral and neurochemical responses to voluntary running.

6. Behavioral aspects of wheel running: stress and anxiety-like/depression-like behavior

As summarized in Table 3, a number of studies have reported alterations in behavior following access to running wheels in both rats and mice. Often, these changes are attributed to exercise, and many of these effects depend on the duration of exposure to the running wheel. Eight weeks, but not 4 weeks, of voluntary wheel running increased measures of defensive behavior and risk assessment in rats (Burghardt et al., 2004). Lines of mice selected for high levels of voluntary wheel running also showed heightened levels of predatory aggression (Gammie et al., 2003). Extended access to running wheels appears to reduce learned helplessness: six weeks, but not 3 weeks, of running wheel access resulted in decreased escape latency in the shuttle-box test (Greenwood et al., 2005, 2003). Consistent with these results, changes in activation patterns in the amygdala, a limbic region involved in fear and anxiety, are found between sedentary and wheel-running groups following contextual fear conditioning. In this case, eight weeks of wheel running altered c-Fos levels in the amygdala following contextual fear conditioning (Burghardt et al., 2006b).

Access to a running wheel also alters depression-like behavior or coping strategies in rodents (Table 3). These behaviors are commonly assessed using a number of different tests including the forced swim test; in this test, immobility, or “floating,” is considered a measure of depression-like behavior (Cryan et al., 2005). Generally, decreases in immobility in the forced swim test have been reported following wheel running (Bjornebekk et al., 2005; Solberg et al., 1999). Further, wheel running produced a larger reduction in immobility compared to the antidepressant escitalopram in the forced swim test, and the effects of antidepressant compounds on immobility in the forced swim test are augmented by wheel running (Bjornebekk et al., 2008). In contrast, a recent study has reported increased immobility in the forced swim test following voluntary wheel running, which the authors attributed to increases in `passive coping' following extended wheel running (Collins et al., 2009). Wheel running in mice has been shown to decrease measures of anxiety-like behavior (Binder et al., 2004; Duman et al., 2008) and had an anti-depression-like effect (Duman et al., 2008).

The relationship between stress and weight gain has been recognized for some time, and the vilification of hormones in the stress axis (e.g., cortisol) tends to be fodder for a number of late-night infomercial remedies for obesity. The ability of stress-axis hormones (e.g., corticosterone, cortisol) to influence body weight and energy mobilization has been recognized for several decades. Further, there is evidence that wheel running can affect several levels of the HPA-axis in rats and mice (de Rijke et al., 2005; Droste et al., 2007, 2003). There also appears to be a reciprocal relationship between stress and wheel running as social isolation stress prior to wheel access inhibits hippocampal neurogenesis (Stranahan et al., 2006). Wheel running protects against decreases in hippocampal brain-derived neurotrophic factor (BDNF) mRNA expression following a single session of restraint stress (Adlard and Cotman, 2004). Wheel running also protects against reductions in growth factor mRNA levels in the hippocampus, reduced spatial learning, and consumption of sucrose solution following four weeks of chronic unpredictable stress (Zheng et al., 2006). In

addition, stress-induced reductions in BDNF levels do not appear to be directly related to circulating corticosterone (Adlard and Cotman, 2004; Zheng et al., 2006). Interestingly, the ability of wheel running to prevent decreases in hippocampal BDNF mRNA following stress may not be functionally relevant for the beneficial effects of wheel running to block learned helplessness behavior (Greenwood et al., 2007). These factors can be affected by low-intensity running as well, perhaps to an even greater degree than with high-intensity exercise, at least in juvenile rats (Lou et al., 2008). This opens up the possibility that non-exercise activity could affect neurogenesis and related factors in the brain, but possibly in a different manner than does high-intensity activity or wheel running.

Thus, the effects of wheel running on rodent behavior do not fit easily into one unified behavioral profile–increased predatory aggression and defensive behaviors, but decreased depression- and anxiety-like behaviors (Table 3). The lack of consensus may be due to several factors. First, there may be a tendency to anthropomorphize rodent behavior (Holmes, 2003), ultimately resulting in the development of misleading hypotheses. Second, the `control' group to which voluntary running is compared may influence the interpretation of results (Dubreucq et al., 2011) as would the time of day when the behavioral testing occurs (Hopkins and Bucci, 2010). Third, food restriction prior to behavioral testing can substantially influence behavior (Heiderstadt et al., 2000; Inoue et al., 2004; Jahng et al., 2007; McDermott and Kelly, 2008), although the magnitude and direction of this effect may very well depend on the metabolic profile of the animal. Fourth, the use of different species, strains of rats or mice, or selective breeding for various traits, can produce markedly different behavioral responses to a given behavioral test like the elevated plus maze, forced swim test, locomotor response to novelty, or wheel-running behavior (Berton et al., 1997; Dichter et al., 1996; Kabbaj et al., 2000; Overstreet and Rezvani, 1996; Tejani-Butt et al., 2003). With these caveats in mind, the interpretation of behavioral and metabolic effects of exercise must be clearly defined within the context of the experimental design as it is likely that these factors interact. When using wheel running to assess rodent energy balance, it is important to recognize that wheel-running behavior may both cause and/or be affected by changes in metabolic function. The use of the running wheel provides an exciting opportunity to address hypotheses relating to the relationship between mood and metabolism, particularly when considering the neurovegetative symptoms associated with several forms of depression, and given the comorbidity of affective/mood disorders with metabolic dysfunction (Lawrence and Kopelman, 2004; Sullivan et al., 1993) and emerging data indicating overlap in the brain systems that shape mood and energy balance (Lutter et al., 2008a,b; Novak et al., 2006; Teske et al., 2006; Zheng et al., 2009).

7. Behavioral aspects of wheel running: wheel running influences energy balance and behavior by changing the physical structure of the brain

Changes in brain structure are associated with changes in brain function and behavior, including behaviors that alter energy balance. Growth factors play a number of essential roles in brain function by influencing neuroplasticity, vascularization, and neurogenesis, ultimately leading to restructuring and rewiring of the brain. One of the most studied regions of the brain exhibiting plasticity is the hippocampus, an area rich in growth factors that plays

an integral role in memory and emotion. The hippocampus provides a robust example of the convergence of genetics and environment in altering plasticity of neural circuitry, and is one of the main regions where neurogenesis can be observed in the adult. Although most commonly associated with learning, memory, and emotion, there is evidence that the hippocampus is also involved in the regulation of energy balance (Davidson et al., 2007). Strikingly, the hippocampus contains both insulin and leptin receptors (Lathe, 2001), indicating this structure may be a direct target for peripheral peptides that signal energy status. In line with this, rats and humans with damage to the hippocampal formation show decreased inhibitory control of food intake (Hebben et al., 1985; Rozin and Dow, 1998) and increased appetitive behavior (Clifton et al., 1998; Schmelzeis and Mittleman, 1996), respectively. Therefore changes in hippocampal structure may have implications for a variety of behaviors including those related to energy management (Table 4 contains examples of wheel-running induced brain alterations).

A variety of environmental conditions and behaviors, including wheel running, have the ability to influence plasticity and neurogenesis through their actions on growth factor systems; examples are given in Table 4. The BDNF and fibroblast growth factor (FGF) families function in hippocampal plasticity; both BDNF and FGF are responsive to voluntary wheel running. Wheel running increases growth factor expression (Berchtold et al., 2005; Cotman and Berchtold, 2002; Hunsberger et al., 2007; Russo-Neustadt et al., 1999) and neurogenesis (van Praag et al., 1999) in the rodent hippocampus. It is noteworthy that interventions that alter growth factor expression, including antidepressant administration (Berton and Nestler, 2006; Mallei et al., 2002) and environmental enrichment (Ickes et al., 2000; Turner and Lewis, 2003), also bring about concurrent improvements in behavior. Moreover, wheel-running activity, but not other types of activity, significantly improved the ability of rats to learn a classical conditioning task (Green et al., 2011). It is clear, therefore, that wheel running produces differences in hippocampal growth factor expression that relate to behavioral endpoints.

Alterations in growth factor expression may be required for behavioral changes in response to exercise and antidepressants (Adachi et al., 2008; Russo-Neustadt et al., 1999). Interestingly, transient changes in several growth factor families occur after only a couple days of exercise. While growth factor alterations and behavior appear not to have a direct relationship (Bjornebekk et al., 2008; Greenwood et al., 2007), the relatively acute effect of wheel running on growth factor expression (Gomez-Pinilla et al., 1997) could potentially be a necessary precursor to functional and structural alterations in the brain that take several weeks to produce behavioral adaptations (Adlard et al., 2004; Burghardt et al., 2004, 2006b; Greenwood et al., 2005; Van Hoomissen et al., 2004). It should also be noted that there is a distinct time course for changes in mRNA levels compared to protein levels for BDNF following exercise (Adlard et al., 2004). Further emphasizing the importance of timing, a recent report has shown that the processes of vascularization and neurogenesis begin relatively quickly (within 10 days) after the introduction of running wheels (Van der Borght et al., 2009). Intriguingly, these changes are very labile and the increases in vascularization and neurogenesis found in the hippocampus after several days of wheel running returned to baseline levels 24 h after the cessation of wheel running (Van der Borght et al., 2009).

Therefore, the temporal effects of wheel running on neuroplasticity systems and behavior must be taken into account when animals are given access to running wheels.

Wheel running alters the neurochemical systems involved in plasticity and neurogenesis in the hippocampus (Bjornebekk et al., 2005; Hoffmann et al., 1990; Koehl et al., 2008; Pereira et al., 2007; Persson et al., 2004), as listed in Table 4, but how do these actions translate to changes in energy balance? Many of the growth factors and neuropeptide systems altered by running wheels impact the brain's control of energy balance. Specific examples are emerging that suggest wheel-running-induced changes in the hippocampus could impinge on hypothalamic circuitry controlling metabolism and behavior, including a potential role of BDNF (Adachi et al., 2008). First, BDNF and its receptor, trkB, impact food intake and energy expenditure through their actions in the hypothalamus (Wang et al., 2007a,b,c), and have recently been implicated as downstream regulators of melanocortin-system control of food intake (Bariohay et al., 2009). Second, the FGF family appears to be involved in regulating feeding (Oomura et al., 1992) as levels of FGF increase in cerebral spinal fluid postprandially or following a glucose infusion. Beyond changes in growth factor families, receptors for neuropeptides and hormones involved in energy management (e.g., leptin and insulin) are expressed in the hippocampus. This provides an opportunity for energy-management signals from the periphery to directly influence the function of the hippocampus, suggesting a role for the hippocampus in regulating food intake (Davidson et al., 2007). Indeed, leptin influences behavior via hippocampal circuitry (Liu et al., 2010; Lu et al., 2006) and has been shown to be neuroprotective (Tang, 2008). Further, improvements in hippocampal-dependent learning and memory, as well as in insulin receptor signaling and glucose oxidation in the hippocampus, are seen after voluntary wheel running in mice (Muller et al., 2011). Additionally, increases in NPY and NPY-1 receptor mRNA, a neuropeptide family long known to play a role in feeding, have been reported in the hippocampus following wheel running (Bjornebekk et al., 2010).

The overlap of processes underlying energy balance, wheel running, and neurogenesis is further illustrated by the report that the endogenous endocannabinoid system (eCB) is involved in hippocampal neurogenesis in response to wheel running (Hill et al., 2010); the eCBsystem is also known to modulate feeding and stress response (Fride, 2005). Additionally, eCB regulation of exercise may be related to metabolic status as the motivation for wheel running, and the wheel-running behavior itself, is differentially responsive to cannabinoid ligands in lean compared to obese Zucker rats (Smith and Rasmussen, 2010). Taken together, the apparent role for the hippocampus in energy management, coupled with the robust effect of exercise on hippocampal structure and function, indicate that the influence of wheel running on the hippocampus should not be discounted in studies of food intake and energy expenditure. It is well known that wheel running results in alterations in neuropeptide levels in brain areas more commonly associated with energy management (e.g., hypothalamus) (Bi et al., 2005; de Rijke et al., 2005; Lewis et al., 1993). It is becoming more apparent that wheel running has the potential to impact energy balance indirectly through alterations in brain regions such as the hippocampus and, as described above, brain reward systems.

8. Models for wheel running: mice and rats selectively bred for wheel running

Because of the varied effects of running wheels on physiology and behavior of rodents, and the variability of responses between different species and individual animals within species, a cohesive picture of rodent wheel running is lacking (Sherwin, 1998). One method that may clarify the underlying mechanisms behind these phenomena is selective breeding for high and low levels of wheel running. Such breeding programs have been undertaken for rats and mice. The results of these studies will be described in turn, as well as physical activity and wheel-running activity in rats selectively bred for other traits.

Mice have been selectively bred for high levels of wheel running for over 35 generations that display levels of wheel running 170% greater than control lines (Rezende et al., 2006; Swallow et al., 1998). Four replicate selected and control lines were created, and several variables have been measured in these mice compared to control-line counterparts. Selection for high wheel-running activity yields mice with lower body weight and fat content (Swallow et al., 1999, 2001). But does high wheel-running activity predetermine high activity in general? Using short (3 min) tests of open field activity (Bronikowski et al., 2001), or behavioral observation (Koteja et al., 1999), no differences were detected between high-wheel-running and control lines of mice (Bronikowski et al., 2001). Open-field activity is mostly used as a measure of stress, anxiety, or locomotor response to novelty rather than overall spontaneous activity levels (Stead et al., 2006). Indeed, when daily activity was measured, robust differences in cage activity were found between selected and control lines of mice (Malisch et al., 2008, 2009). It was suggested that wheel running motivation may be the key factor differentiating the running and non-running strains, and that this is not necessarily linked to performance capacity (Rezende et al., 2005). Mice selected for high levels of wheel running also display behaviors such as increased exploration and risk-taking, in addition to increased anxiety (Jonas et al., 2010). Together, these studies highlight the importance of standardized daily measures of physical activity, and illustrate the likelihood of overlap between the biological and behavioral systems governing daily physical activity and wheel running in rodents. Dopaminergic brain reward pathways are also heightened in mice bred for high wheel-running activity (Mathes et al., 2010), again supporting the hypothesis that wheel running is associated with changes in brain reward system activation, differentiating the neural systems underlying wheel running versus general physical activity.

Lines of rats showing high levels of voluntary wheel-running activity have also been established (Morishima-Yamato et al., 2005), with male Spontaneously-Running-Tokushima-Shikoku (SPORTS) rats running roughly six times longer than controls. Male SPORTS rats had lower body weight, circulating insulin, and visceral fat than controls, as well as increased skeletal muscle oxidative capacity (Morishima-Yamato et al., 2005). Here again, the authors concluded that the selected rats have a heightened “running motivation.” General activity in the absence of a wheel was not examined, so we do not know whether or not running motivation correlates with spontaneous daily activity in these rats.

Examining wheel running and spontaneous physical activity in other selectively bred rodents also gives insight into the behavioral and physiological traits underlying wheel-running and

spontaneous activity. Rats bred for high intrinsic aerobic capacity (HCRs) have high levels of both activity on running wheels (Burghardt et al., 2006a; Vaanholt et al., 2008; Waters et al., 2008) and general locomotor activity (Novak et al., 2010, 2009). Within each selected line, the level of variability between rats' general locomotor activity is surprisingly low (Novak et al., 2010, 2009), whereas there is a large amount of variance between the amount of activity on a wheel between rats, especially HCRs (Burghardt et al., 2006a; Waters et al., 2008). Interestingly, locomotor response to novelty does not differ between HCR and LCR rats (Burghardt et al., 2011). This hints that intrinsic aerobic capacity and physical activity may share underlying causes, and that some of these mechanisms—but not all—overlap with wheel-running activity.

Comparisons of different selected lines may also help us to understand the effects of diet on spontaneous activity. When rats or mice are fed a high-fat diet, physical activity typically declines (Bjursell et al., 2008; Novak et al., 2006) [though see (Simoncic et al., 2008)]. We have also recently found that both HCR and LCR rats share a similar decrease in physical activity after high-fat feeding (Novak et al., 2010). This effect is relatively consistent across most rodents studied, with the exception of rats bred specifically for resistance to weight gain on a high-fat diet (Novak et al., 2006). Moreover, there is an acute decrease in physical activity levels in mice, seen as soon as three days after giving the high-fat Western diet (Bjursell et al., 2008), making it less likely to be secondary to increases in body weight; a high-fat diet does not appear to affect wheel running in the same way (Vaanholt et al., 2008). In mice selected for high levels of wheel running, a high-fat diet increases spontaneous daily activity, and this effect was specific to female mice (Vaanholt et al., 2008). This further underlines how perturbations of energy balance differentially affect activity on versus off of a wheel, and how selected lines of rats and mice can be utilized to determine how these properties overlap.

9. Conclusions

An animal's locomotion about its environment is critical to its survival on many levels. More recently, the association of high intrinsic physical activity levels with a lean phenotype has been a topic of interest due to the ever-increasing prevalence of obesity and the need to find useful, effective obesity treatments. While it is not uncommon to see a positive association between high general physical activity levels and high wheel-running activity, it is unlikely that wheel running accurately represents inherent tendencies to be generally physically active in rodents. On the contrary, access to a running wheel affects several aspects of normal energy balance, most notably through the amplification of activity and energy expenditure, though other routes cannot be discounted. The myriad factors that differentially affect general cage activity and wheel-running activity are outlined in Fig. 1. Though many more recent investigations of physical activity utilize measures of general activity in the absence of or in addition to wheel-running activity (Pistilli et al., 2011), it is still not uncommon to refer to these two methods interchangeably. To more accurately and precisely characterize general physical activity in laboratory studies, the following guidelines are suggested:

(1) Be aware that a running wheel amplifies activity, and can also amplify differences in activity between groups of rodents (Burghardt et al., 2006a; Novak et al., 2010, 2009; Pistilli et al., 2011). Wheel running should be specified as such, and not referred to as physical activity or "spontaneous" activity.

(2) Just as rodents are given time to acclimate to their environment before their general cage activity is measured, acclimation time is also needed for a rodent to show stable wheel-running activity (Cabeza de Vaca et al., 2007; Engel et al., 2009; Hickey et al., 2008; Murray et al., 2010; Pham et al., 2005; Richter et al., 2008).

(3) For both general cage activity and wheel-running activity, at least 24-h measurements are needed for accurate assessment. Much longer measurements are often used for studies measuring wheel running. Short measurement periods (e.g., several hours) are not sufficient to detect group differences that are clearly and robustly shown when whole-day activity levels are assessed (Levin, 1991; Novak et al., 2010, 2006).

(4) Similarly, short-term activity measurements in a cage or an open field are not reflective of general cage activity (Burghardt et al., 2011; Novak et al., 2010, 2009). There may be some parallels, though, that are secondary to rodent "personality": energetically costly behaviors, differential activity in the open field, maximal metabolic rate, and general cage activity are correlated and may share some overlapping central mechanisms, but can be dissociated (Della Maggiore and Ralph, 2000; Engel et al., 2009; Jonas et al., 2010; Koteja et al., 1999; Lantova et al., 2011; Morgan and Pfaff, 2001, 2002; Ogawa et al., 2003; Zombeck et al., 2011).

(5) Be aware of how wheel access alters metabolism and behavior, and how this is expressed differently according to several factors including sex, age, strain, species, and diet (see Fig. 1).

Apparent contradictions and confusion can be avoided by following these guidelines when designing studies and considering the literature. Time and effort can be saved if investigators are aware of how running wheels will affect rodents in their studies.

Acknowledgements

We appreciate the assistance of Antonio Nunez, Lydia Heemstra, Peter Bodary, Maria Waselus, and Kate Dykhuis for comments on the manuscript during preparation.

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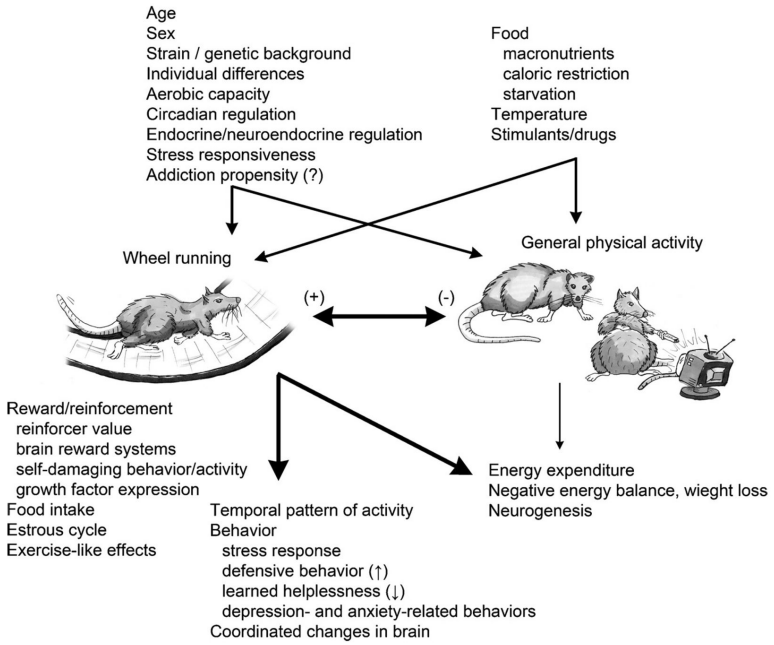

Fig. 1.

Several factors affect the amount of wheel running a rodent will display. These same traits and factors will also influence general physical activity, but often not in the same manner or to the same extent. Whereas levels of general physical activity positively correlate with wheel-running activity, the presence of a wheel will increase overall physical activity while decreasing non-wheel home-cage activity. Lastly, wheel running alters an array of behavioral and physiological variables in ways that general home-cage activity does not, and wheel-running activity has more profound effects on several aspects of metabolism than does general physical activity.

Table 1

Summary of alterations in energy balance caused by wheel running in rodents.

Species	Sex	Compartment of energy balance altered	Effect	Reference
Rat	Female	Amount of activity; food intake	Increased amount of activity; on a restricted diet, induced activity-based anorexia	Dixon et al. (2003)
OLETF rat	Male	Activity; food intake	Increased amount of activity; decreased food intake	Bi et al. (2005)
Mouse	Female and male	Food intake	Increased food intake, specific to mice bred for low body fat	Simoncic et al. (2008), Swallow et al. (2001)
Syrian hamster	Female and male	Amount of activity	Increased amount of activity; increased food intake; weight loss; loss of body fat	Coutinho et al. (2006a,b)
A. nitloticus	Female and male	Activity pattern, amount	Increased amount of activity; altered diurnal pattern of activity in subset of animals due to masking	Blanchong et al. (1999), Katona and Smale (1997), Redlin and Mrosovsky (2004)
Octodon degus	Female and male	Activity pattern, amount	Increased amount of activity; altered diurnal pattern of activity in subset of animals	Kas and Edgar (1999)

Table 2

Summary of reward-related behaviors altered by wheel running in rodents.

Species	Sex	Duration of access to wheel	Effect on behavior	Reference
Rat (Wistar)	Female and male	22 weeks unrestricted access	Food restriction increased wheel running, while increased access to food decreased wheel running	Finger (1951)
Rat (Sprague–Dawley)	Male	10 min per day	Rats lever-pressed for access to running wheels	Kagan and Berkun (1954)
Rat (albino from Holtzman Research)	Male	Up to 14 days, unrestricted access	Food was ignored upon presentation of wheel, resulting in self-starvation	Routtenberg and Kuznesof (1967)
Rat (Sprague–Dawley)	Male	Varied	Rats lever-pressed for access to running wheels	Collier and Hirsch (1971)
Rat (Long Evans)	Male	2 h per day, 5 days/week for 8 weeks	Increased brain catecholamine levels related to running, weight loss, and hyperphagia	de Castro and Duncan (1985)
Rat (Sprague–Dawley)	Female and male	Varied	Food deprivation increased lever pressing for access to a running wheel; acute wheel exposure during food deprivation decreased responding for food reward	Pierce et al. (1986)
Rat (Sprague–Dawley)	Male	Up to 70% of starting body-weight, or 20 days unrestricted access	Activity-induced anorexia (and death) was reduced by propylene glycol but not ethanol	Spigelman et al. (1991)
Rat (Long–Evans)	Female	Varied	Rats lever-pressed for access to running wheels	Iversen (1993)
Rat (Sprague–Dawley)	Male	Alternating access	Wheel access decreased oral amphetamine intake	Kanarek et al. (1995)
Rat (Wistar)	Male	Varied	Rats lever-pressed for access to running wheels; running behavior was dependent on duration of opportunity to run	Belke (1997)
Rat (Lewis and Fischer)		30 days, unrestricted Access	Addiction-prone rats exhibited higher levels of running compared to non-addiction-prone rats	Werme et al. (1999)
Rat (Sprague–Dawley)	Male	2-h controlled access on alternating days, over ~2 weeks	Wheel running induced conditioned place preference, which was reversible by the opioid antagonist naloxone	Lett et al. (2001)
Rat (Sprague–Dawley)	Male	2-h controlled access on alternating days, over ~2 weeks	Wheel running blocked the ability of morphine to produce conditioned place preference	Lett et al. (2002)
Rat (Long Evans)	Female	8 weeks unrestricted access	Wheel running decreased breakpoint on a progressive ratio schedule for cocaine self-administration	Cosgrove et al. (2002)
Rat (Sprague–Dawley)	Male	24 days, 2-h per day or unrestricted access	Escalated running with unrestricted access	Lattanzio and Eikelboom (2003)
Rat (Wistar)	Male	Varied	Rats developed conditioned place preference to context associated with wheel	Belke and Wagner (2005)
Rat (Sprague–Dawley)	Male	25 days	Wheel access suppressed sucrose and food intake	Satvat and Eikelboom (2006)
Rat (Long Evans)	Female	8 weeks unrestricted access	Wheel running increased conditioned place preference to cocaine	Smith et al. (2008)
Rat (Fischer 344)	Male	2 and 6 weeks	Increased conditioned place preference after 6 weeks of wheel running	Greenwood et al. (2011)
Mice (BALB-c)	Male	90 min	Wheel running induced c-Fos in nucleus accumbens (core)	Vargas-Perez et al. (2003)

Species	Sex	Duration of access to wheel	Effect on behavior	Reference
Mice (C57BL/6J)	Female	Varied	Wheel running increased in the absence of ethanol	Ozburn et al. (2008)
Mice (BALB-c-type and D2L receptor-deficient)	Male	30 min/day for 20 days	Wheel running engages dopamine and opioid reward systems; motivational state affects ability of wheel to engage these systems	Vargas-Perez et al. (2004), Vargas-Perez et al. (2008)
Syrian hamster	Male	Up to 35 days	Amount of wheel running was positively correlated with self-administration of testosterone, which has reinforcing properties	Wood (2002)

Table 3

Summary of behaviors altered by wheel running in rodents.

Species	Sex	Duration of access to wheel	Effect on behavior	Reference
Rat (JCR:LA-cp)	Male	Intermittent	Induced conditioned taste aversion; not secondary to novelty	Heth et al. (2001)
Rat (Long–Evans)	Male	22 days	Increased conditioned freezing	Van Hoomissen et al. (2004)
Rat (Sprague–Dawley)	Male	8 weeks (effect not seen at 4 weeks)	Increased defensive behavior; Increased risk assessment	Burghardt et al. (2004)
Rat (Flinders Sensitive/ Resistant Lines)	Male	30 days	Decreased immobility in FSL rats; showed a trend toward increased immobility in FRL rats	Bjornebekk et al. (2005)
Rat (Sprague–Dawley (2003) and Fischer F344 (2005)	Male	6 weeks (effect not seen at 3 weeks)	Reduced learned helplessness	Greenwood et al. (2005), Greenwood et al. (2003)
Rat (Sprague–Dawley)	Male	8 weeks	Increased contextual conditioned freezing	Burghardt et al. (2006a,b)
Rat (Sprague–Dawley)	Male	5–8 weeks unrestricted access	Protective against chronic unpredictable stress: reduced stress effect on spatial learning and consumption of sucrose solution	Zheng et al. (2006)
Rat (Flinders Sensitive Line)	Female	30 days	Decreased depression-like behavior	Bjornebekk et al. (2008)
Rat (Sprague–Dawley)	Male	4 weeks unrestricted access	Increased immobility in the forced swim test	Collins et al. (2009)
Mouse (C57BL/6J)	Not reported	9 weeks unrestricted access	Decreased immobility in forced swim test; delayed decreases in sucrose intake following chronic stress	Solberg et al. (1999)
Mouse	Female and male	N/A (artificially selected for high wheel running)	Increased predatory and maternal aggression	Gammie et al. (2003)
Mouse (C57BL/6J)	Male	4 weeks unrestricted	Increased anxiety-like behavior in open field, decreased anxiety-like behavior in elevated plus maze	Binder et al. (2004)
Mouse (C57BL/6J)	Male	3–4 weeks	Decreased depression-like behavior	Duman et al. (2008)
Mouse (CF1)	Not reported	4 weeks	Increased hippocampal-dependent learning	Muller et al. (2011)

Table 4

Summary of neuroanatomical changes secondary to wheel running in rodents.

Species	Sex	Duration of access to wheel	Effect on brain	Reference
Rats (spontaneously hypertensive)	Males	5–6 weeks	Wheel running increased CSF beta-endorphin	Hoffmann et al. (1990)
Rat (Sprague–Dawley)	Male	2–7 nights of running	Increased FGF2 mRNA and IR in hippocampus following 2 and 4 nights of running	Gomez-Pinilla et al. (1997)
Rat (Sprague–Dawley)	Not reported	20 days	Increased BDNF mRNA in hippocampus	Russo-Neustadt et al. (1999)
Rat (Sprague–Dawley)	Male	1–28 days unrestricted	Increased BDNF protein and mRNA (4 weeks of running was required)	Adlard et al. (2004)
Rat (Sprague–Dawley)	Male	2–90 days (continuous or alternating days)	Increased hippocampal BDNF with alternating and continuous running	Berchtold et al. (2005)
Rat (Sprague–Dawley)	Male	3–48 days	Neurogenesis in socially isolated rats (chronic wheel running was required)	Stranahan et al. (2006)
Mouse (C57BL/6J)	Male	7 days	Increased VGF mRNA and protein	Hunsberger et al. (2007)
Mouse (C57BL/6)	Male	3 weeks unrestricted	Protected against stress-induced decreases in hippocampal BDNF	Adlard and Cotman (2004)
Mouse (C57BL/6)	Not reported	2 weeks	Increased hippocampal neurogenesis which correlated with regional cerebral blood flow as measured by fMRI	Pereira et al. (2007)
Mouse (C57BL/6)	Female	12 days	Increased neurogenesis and neuronal survival in the hippocampus	van Praag et al. (1999)
Mouse (C57BL/6, beta-endorphin deficient)	Male	10 days or 39 days	Beta-endorphin was necessary for wheel-induced hippocampal cell proliferation	Koehl et al. (2008)
Mouse (C57BL/6)	Male	1, 3, or 10 days	Increased vascularization and neurogenesis in hippocampus	Van der Borght et al. (2009)
Mouse (CF1)	Not reported	4 weeks	Improved insulin receptor signaling and glucose oxidation in hippocampu	Muller et al. (2011)