REVIEW

Voluntary exercise and depression-like behavior in rodents: are we running in the right direction?

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Abstract

Acute or chronic exposure to stress can increase the risk to develop major depressive disorder, a severe, recurrent and common psychiatric condition. Depression places an enormous social and financial burden on modern society. Although many depressed patients are treated with antidepressants, their efficacy is only modest, underscoring the necessity to develop clinically effective pharmaceutical or behavioral treatments. Exercise training produces beneficial effects on stress-related mental disorders, indicative of clinical potential. The pro-resilient and antidepressant effects of exercise training have been documented for several decades. Nonetheless, the underlying molecular mechanisms and the brain circuitries involved remain poorly understood. Preclinical investigations using voluntary wheel running, a frequently used rodent model that mimics aspects of human exercise training, have started to shed light on the molecular adaptations, signaling pathways and brain nuclei underlying the beneficial effects of exercise training on stress-related behavior. In this review, I highlight several neurotransmitter systems that are putative mediators of the beneficial effects of exercise training on mental health, and review recent rodent studies that utilized voluntary wheel running to promote our understanding of exercise training-induced central adaptations. Advancements in our mechanistic understanding of how exercise training induces beneficial neuronal adaptations will provide a framework for the development of new strategies to treat stress-associated mental illnesses.

Key Words

- ▶ voluntary wheel running
- ▶ physical activity
- ▶ stress resilience
- ▶ depression
- ▶ forced swim test

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Introduction

Depression is a common neuropsychiatric disorder with enormous social and financial burden on modern society (Greenberg *et al.* 2003, Kessler *et al.* 2005, 2007). Depression is diagnosed based on a cluster of highly variable symptoms (see *Diagnostic and Statistical Manual of Mental Disorders, 5th edition*; DSM-VTR), which in addition to a depressed or irritable mood can include cognitive, emotional, homeostatic and psychomotor symptoms (Association 2013). To date, no single

abnormality has proven robust or consistent enough to either diagnose depression in humans or validate an animal model, nor have highly penetrant genetic causes of depression have been identified (Krishnan & Nestler 2008, Nestler & Hyman 2010). Nonetheless, it is accepted that stress and emotional loss are strong risk factors to develop depression. Remarkably, not all humans develop posttraumatic stress disorder or depression in the face of acute or chronic adversity (Charney 2004, Yehuda 2004,

Kessler *et al.* 2005). Such resilience, or the ability to successfully cope with adversity, is associated with the development of adequate molecular, behavioral and psychological adaptations to stress (Hoge *et al.* 2007, Krishnan & Nestler 2008, Feder *et al.* 2009, Russo *et al.* 2012). Recently, preclinical studies have substantially advanced our understanding of molecular adaptations in the brain underlying susceptibility and resilience to stress, and this insight offers a crucial dimension for the development of novel therapeutic treatments that prevent and treat stress-related disorders (de Kloet *et al.* 2005, Yehuda *et al.* 2006, Joels *et al.* 2007, Krishnan *et al.* 2007, McEwen 2007, Krishnan & Nestler 2008, Pittenger & Duman 2008, Russo *et al.* 2012).

In 1969, Morgan demonstrated that physically unfit patients were more depressed than their fit counterparts (Morgan 1969). Since this initial observation almost 50 years ago, many studies have investigated the interaction between exercise training and mental health. Collectively, these studies indicate that exercise training is associated with beneficial effects on mental well-being (Stephens 1988, North *et al.* 1990, Sothmann *et al.* 1996, Steptoe & Butler 1996, Steptoe *et al.* 1996, 1997, Fox 1999, Dimeo *et al.* 2001, Lawlor & Hopker 2001, Salmon 2001, Dishman *et al.* 2006, Lai *et al.* 2006, Greenwood & Fleshner 2008, Stranahan *et al.* 2008, Fuss & Gass 2010, Perraton *et al.* 2010, Carek *et al.* 2011, Krogh *et al.* 2011, Blumenthal *et al.* 2012, Asmundson *et al.* 2013, Josefsson *et al.* 2014, Rowe *et al.* 2014). Nonetheless, the molecular mechanisms and the brain circuitries underlying the beneficial effects of exercise remain poorly understood. Although the development of non-invasive imaging techniques to study human brain structure and function has seen significant progress in the recent years, ethical and practical difficulties of examining the living human brain still put important limitations on our understanding of the physiology and molecular biology of the human brain. Therefore, exercise paradigms are used in rodents to model human exercise training, and such preclinical studies have substantially advanced our understanding of central molecular adaptations that potentially underlie the health benefits of exercise training in humans (Dishman *et al.* 2006, Patterson & Levin 2008, Stranahan *et al.* 2008, Garland *et al.* 2011, Novak *et al.* 2012, Voss *et al.* 2013, Rowe *et al.* 2014). Behavioral paradigms that are frequently used to model human exercise training in rodents include, but are not limited to, forced treadmill running, forced wheel running and voluntary wheel running (VWR). This review will focus on the latter, as popularity of this behavioral paradigm is rapidly increasing, and as discussed below,

this behavioral paradigm appears suited to gain insight in the exercise training-induced central adaptations. In this review, I highlight several neurotransmitter systems that have been identified in preclinical studies as putative mediators of the beneficial effects of VWR on stress resilience, and I review recent rodent studies that utilized VWR to promote our understanding of exercise training-induced central adaptations.

Self-reinforcing aspects of VWR

Several lines of evidence indicate that rodents perceive VWR as rewarding. Rodents will run voluntarily on running wheels, and several biological factors, including genotype, gender, reproductive hormone levels, housing conditions and age of the experimental model influence running behavior (Valentinuzzi *et al.* 1997, Lightfoot *et al.* 2004, Stranahan *et al.* 2008). Rodents will develop a conditioned place preference for an environment associated with the after-effects of wheel running (Lett *et al.* 2000, Belke & Wagner 2005, Greenwood *et al.* 2011, Trost & Hauber 2014). Rodents will also work vigorously during an operant response to gain access to a running wheel (Premack 1962, Iversen 1993, Belke 1997). On a molecular level, VWR induces adaptations along the ventral tegmental area (VTA) – nucleus accumbens (NAc) axis (Werme *et al.* 2002, Greenwood *et al.* 2011, Obici *et al.* 2015), two key nuclei of the reward-related brain circuitry, in rodents. Lastly, mice in the wild run voluntarily on running wheels, suggesting that VWR is a natural behavior and not just restricted to laboratory animals (Meijer & Robbers 2014). Collectively, these findings indicate that VWR is rewarding for rodents. To identify biological factors that contribute to the reinforcing nature of VWR, genomic, genetic and pharmacological approaches have started to shed light on the biology of exercise physiology (Rhodes *et al.* 2003, Troxell *et al.* 2003, Dubreucq *et al.* 2013, Fernandes *et al.* 2015, Obici *et al.* 2015, Ruegsegger & Booth 2017, Ruegsegger *et al.* 2017). Recently, technological advances, including optogenetic and chemogenetic manipulation of specific brain circuits or neuron populations, have also been used to investigate neuronal contributions to aspects of exercise reinforcement (Hsu *et al.* 2014, Zhu *et al.* 2016, Foldi *et al.* 2017). These approaches will promote greater insight into the biology of VWR and enhance the utility of this animal model for the etiological examination of stress resilience conferred by exercise training. Although VWR clearly is self-reinforcing behavior in rodents, the exact nature of VWR remains unclear, and this behavior shows analogies with stereotypic and addictive behavior (Richter *et al.* 2014).

VWR is a physiological stressor

VWR is frequently used in preclinical studies with the incentive that this behavioral intervention has a rewarding and voluntary nature, as discussed earlier, compared to the involuntary and stressful nature of forced wheel running or treadmill running. It should, however, be noted that VWR is clearly associated with the activation of sympathetic nervous system, resulting in epinephrine production, as well as activation of the hypothalamic–pituitary–adrenal (HPA) axis, resulting in glucocorticoid production and HPA axis feedback (Reul & Droste 2005, Stranahan *et al.* 2008, Reul *et al.* 2015). Thus, as VWR is a threat to homeostasis, it should be considered a physiological stressor, albeit a voluntary and controllable stressor with a distinct temporal profile. This observation underlies the ‘cross-stressor adaptation’ hypothesis, which suggests that a stressor of sufficient intensity and/or duration (e.g. VWR) will induce adaptations along the stress response systems, and these adaptations become apparent under other similarly taxing states (Sothmann *et al.* 1996, Stranahan *et al.* 2008). However, despite several similarities, long-term VWR and chronic stress result in distinct adaptations along the HPA axis (Bhatnagar & Dallman 1998, Droste *et al.* 2007). For example, long-term VWR and chronic stress training are associated with opposite effects on neurogenesis in the hippocampus (van Praag *et al.* 1999a,b, McEwen 2001, van Praag 2008). As discussed below, a possible explanation for these differential observations is differential activation of reward-related brain circuitry, and the subsequent induction of adaptations herein, during long-term VWR compared to chronic stress.

The temporal aspects of VWR on stress hormone biology and stress-related behavior are striking. Plasma corticosterone levels in wheel-running male Sprague-Dawley rats are elevated during the first 21 days of VWR, before returning to normal during the fourth week (Fediuc *et al.* 2006). Similarly, daily wheel-running distances in rodents generally increase during the initial 14–21 days, before plateauing around a stable level and then slowly declining again over time (Fediuc *et al.* 2006, Droste *et al.* 2007, Obici *et al.* 2015). The effects of VWR on caloric intake are also temporary. For example, male Wistar or Sprague-Dawley rats initially show hypophagia compared to sedentary controls, which generally fades away during the second or third week (Droste *et al.* 2007, Obici *et al.* 2015). In contrast, mice generally demonstrate hyperphagia (Girard & Garland 2002, Droste *et al.* 2003), potentially resulting from their smaller body size and higher metabolic

demands. Both rats and mice demonstrate temporal and dynamic activation of the neuroendocrine stress axis and stress-related brain circuitry, although species differences have been observed frequently (Stranahan *et al.* 2008, Reul *et al.* 2015). For example, 4-week wheel-running mice had reduced corticotrophin-releasing hormone (CRH) mRNA expression in the paraventricular nucleus of the hypothalamus compared to sedentary controls, suggestive of an attenuated stress response, whereas this was not observed in rats running the same duration of running (Droste *et al.* 2003, 2007). One potential explanation for this species difference is the observation that rats and mice differ substantially in their initial and subsequent behavioral responses to running wheels. For example, male C57BL/6J and BALBc/J mice run vigorously on their first days of running wheel access (~4–5 km), whereas male Wistar or Sprague-Dawley rats usually run approximately one kilometer, or even less, during their first several days of access (Droste *et al.* 2007, Richter *et al.* 2014, Obici *et al.* 2015, Mul *et al.* 2016). Unquestionably, many factors influence VWR behavior, including gender, age, metabolic condition and sensitivity to stress or reward (Valentinuzzi *et al.* 1997, Lightfoot *et al.* 2004, Stranahan *et al.* 2008, Novak *et al.* 2012, Richter *et al.* 2014, Obici *et al.* 2015).

Basal plasma corticosterone levels as well as corticosterone release in response to an acute stressor appear positively correlated with voluntary running distances (Stranahan *et al.* 2008). In line with these observations, rats with a loss-of-function mutation in the melanocortin 4 receptor, which have an attenuated HPA sensitivity (Ryan *et al.* 2014), demonstrated lower daily running distances, persistent decreases in caloric intake and dysregulation of the brain reward-related circuitry compared to wild-type controls during VWR (Obici *et al.* 2015). However, it has yet to be determined if these effects are related to metabolic efficiency or central adaptations associated with motivation to run or stress sensitivity. In summary, the temporal aspects of behaviors modulated by (long-term) VWR suggest that dynamic, distinct and even partially overlapping adaptations are recruited in stress-related and reward-related brain circuitry. In humans, a similar complex picture has emerged. Many combinations of psychological and physiological stress are present, depending on the intensity and duration of an exercise regimen, which probably accounts for the wide variety of human glucocorticoid responses to exercise (Tharp 1975, Sothmann *et al.* 1996). In this light, how does the daily running distance of a mouse (i.e. ~5–10 km/night) compare to, for example, a twice-weekly morning run of several kilometers? Given the variety and temporal nature

of individual responses to physical activity in humans, as well in different rodent species, it is currently difficult to compare the suitability of mouse or rat VWR models and their translational value based on the available literature.

Rodent models of depression and their validity

As listed in the DSM-VTR, depression is diagnosed based on a variety of highly variable symptoms (Association 2013). To provide more definitive evidence on the presence of a depressive-like state in an animal model, it has been suggested that a combination of emotional (anhedonia), homeostatic (body weight, sleep, appetite) or psychomotor symptoms (locomotor activity, immobility- and anxiety-like behavior) or direct assessment of the reward circuitry of the brain should be measured (Nestler & Hyman 2010, Mul *et al.* 2016). There is a general need for valid animal models to study the pathophysiology of depression and identify potential therapeutic interventions. In turn, animal models can help identify potential therapeutic interventions and provide mechanistic insight underlying the beneficial effects of such therapeutic interventions.

Unfortunately, the development of animal models of depression with construct, face and predictive validity remains a major challenge (for excellent review on this topic see (Nestler & Hyman 2010). As a result, current animal models have substantial limitations ranging from weak validation to poor predictive power of drug efficacy in human disease (Markou *et al.* 2009, Nestler & Hyman 2010, Belzung & Lemoine 2011). *Construct* (or etiologic) validity refers to disease relevance of the methods by which a model is constructed. In other words, a model with construct validity would ideally recreate the etiologic processes in an animal model that cause disease in humans, thus replicating neural and behavioral features of the illness (Chadman *et al.* 2009, Nestler & Hyman 2010). *Face* validity refers to the recapitulation of important anatomical, biochemical, neuropathological or behavioral features of human disease (Chadman *et al.* 2009, Nestler & Hyman 2010). Because of the absence of known neurobiological abnormalities in humans, behavioral features reminiscent of human disorder are commonly required to achieve face validity. *Predictive* (or pharmacological) validity refers to a response of animal models to treatments that predicts the effects of those treatments in humans (Chadman *et al.* 2009, Nestler & Hyman 2010). Unfortunately, adherence to these validities is far too often not addressed in depression-related rodent studies, and should be discussed to put the results in a bigger perspective.

To date, several etiologically valid models utilizing chronic stress are commonly used in rodents to induce maladaptive adaptations in the reward- and stress-related circuitry, often resulting in a depressive-like state. Chronic social defeat stress (CSDS) is a common paradigm that involves subjecting rodents to bouts of physical and social subordination, as well as stressful sensory housing and induces long-term physiological and behavioral depression-like phenotypes, including social avoidance, anhedonia and homeostatic and anxiety-like symptoms (Kudryavtseva *et al.* 1991, Koolhaas *et al.* 1997, Rygula *et al.* 2005, Krishnan *et al.* 2007, Mul *et al.* 2016). CSDS is sometimes used to investigate the molecular processes underlying 'resilience', as some rodents fail to develop physiological and behavioral depression-like phenotypes (Krishnan *et al.* 2007). A limitation of the social defeat paradigm is that it relies on intermale confrontation. However, a recent study reported that vicarious social defeat can induce depression-related outcomes in female mice (Iñiguez *et al.* 2017). CSDS stress exhibits features of construct, face and predictive validity (Nestler & Hyman 2010). Because several behavioral maladaptations following CSDS are sensitive to chronic, but not acute, antidepressant treatment, this paradigm is suitable to study the aspects of depression and posttraumatic stress disorder (Berton *et al.* 2006, Rygula *et al.* 2006).

Chronic unpredictable stress (CUS), which usually involves a series of daily unpredictable physical stressors (e.g. physical restraint, cage tilt, cold temperature, social stress, foot shock, no bedding) for weeks, also induces long-term physiological and behavioral depression-like phenotypes, including anhedonia, and homeostatic and anxiety-like symptoms (Willner *et al.* 1992, Willner 2005). CUS exhibits features of construct, face and predictive validity (Nestler & Hyman 2010). The stressors during CUS are usually milder compared to intense social defeat stress, but of longer duration, so researchers should decide which model is a more appropriate tool to investigate the neurobiology of behavior of interest.

Early-life stress, which includes maternal separation or limited bedding and nesting, induces life-long behavioral and neuroendocrine abnormalities in rodents (Meaney 2001, Krugers *et al.* 2017, Walker *et al.* 2017). This animal model exhibits features of construct, face and predictive validity.

Rodents are social animals. Therefore, chronic social isolation can induce maladaptive adaptations in the brain (e.g. Δ FosB downregulation in reward-related circuitry), resulting in a variety of aberrant behavior, including anxiety-like behavior and anhedonia (Wallace *et al.* 2009,

Vialou *et al.* 2010). This animal model exhibits features of construct, face and predictive validity (Wallace *et al.* 2009).

To date, several reports have utilized the 5-day repeated forced swim stress (5d-RFSS) paradigm with the intention to induce a depression-like state in rodents (Stone & Lin 2011, Sun *et al.* 2011, Serchov *et al.* 2015). During this test, animals are forced to swim for a brief time on several successive days, and behavior during forced swim stress is analyzed. Notably, 5d-RFSS induced increased immobility during successive forced swim stress in young, adult male C57BL/6J and BALB/cJ mice, but failed to induce emotional (anhedonia), homeostatic (body weight, food intake) or psychomotor (locomotor and anxiety-like behavior during an open-field test) symptoms (Mul *et al.* 2016). A recent commentary by Delcourte and colleagues suggested this result was obtained because the mice were forced to swim during the inactive light phase (Delcourte *et al.* 2017). The authors then went on to show immobility behavior from forced swim tests (i.e. coping behavior) of mice that were forced to swim during the night phase (Delcourte *et al.* 2017). Unfortunately, no other parameters of depression-like behavior were reported in this commentary (Delcourte *et al.* 2017). As discussed below, increased immobility during forced swim tests should be interpreted as coping behavior, and without the additional presence of emotional, homeostatic or psychomotor symptoms, should not be accepted as *bona fide* evidence of a depression-like state. As such, the 5d-RFSS paradigm exhibits features of predictive validity (Stone & Lin 2011, Sun *et al.* 2011, Serchov *et al.* 2015, Mul *et al.* 2016, Delcourte *et al.* 2017), but at least in young male C57BL/6J and BALB/cJ mice, appears to lack construct or face validity (Mul *et al.* 2016).

Repeated restraint stress induces stress-related behavioral abnormalities in rodents, including anhedonia and anxiety-like behavior (Seo *et al.* 2016) and exhibits features of construct, face and predictive validity.

Finally, animal models involving genetic (e.g. animal models with mutations) or pharmacological (e.g. continuous administration of corticosterone) modulation of the HPA axis are also utilized and can induce anhedonia and modify stress-related behavior in rodents (Muller & Holsboer 2006, Nicolas *et al.* 2015). However, abnormalities in the HPA axis are highly variable in human depression, which means that researchers using HPA axis abnormalities to argue for construct or face validity should explicitly defend these choices and ideally rely on additional validators (Nestler & Hyman 2010).

Current assessment of depression-like behavior in rodents

The symptoms of depression that can be objectively measured in rodents are limited to emotional (anhedonia), homeostatic (sleep, appetite, body weight) and psychomotor (locomotor activity and anxiety-like behavior) symptoms (Nestler & Hyman 2010). Nonetheless, several treatment-based screens (i.e. forced swim test (FST), tail-suspension test (TST) and learned helplessness test (LHT)) are commonly used to report on depression-like behavior in rodents, often without any additional measurements of emotional, homeostatic or psychomotor symptoms. In the FST and TST, animals are forced to swim or suspended from their tail, respectively, and behavioral aspects, such as mobility, are quantified as the animal deals with the acute inescapable stressor. In the LHT, animals are exposed to inescapable stress, usually footshock stress, which eventually results in behavioral despair. Of all these treatment-based screens, the FST is by far the most popular, due to the ease to perform the test in a high-throughput manner and interlaboratory reliability. Unfortunately, behavioral observations in the FST are often incorrectly interpreted as *bona fide* depressive-like behavior. This is surprising and unfortunate, as plethora of behavioral and mechanistic studies have demonstrated that increased immobile behavior during the FST is coping behavior and does not provide any conclusive evidence on depression-like behavior (Hawkins *et al.* 1978, Molendijk & de Kloet 2015, de Kloet & Molendijk 2016). To clarify, the FST has *predictive* validity (i.e. it can be used to screen for compounds with antidepressant potential), but lacks *construct* (i.e. patients usually do not become depressed from repetitively being forced to swim) or *face* (i.e. increased immobility in a swimming pool is not a known human depressive phenotype) validity (Nestler & Hyman 2010). The traditional 2-day FST entails an initial swim session, and a second session (retest) 24 h later to test the acquired immobility (Porsolt *et al.* 1977b, 1978a,b). In between the sessions, substances can be administered to test their effect on escape-related behavior. Because some antidepressants were shown to reduce immobility in the retest (Porsolt *et al.* 1977b), the 2-day FST can be used as a screening procedure to test antidepressant *potential* of substances or treatments (Slattery & Cryan 2012). An open-field test should always be used to control for general changes in activity, as changes could generate false-positive or false-negative results in the FST. In mice, a 1-day FST is commonly used (Porsolt *et al.* 1977a, 1978b). One-day FSTs are also used in rats. The above-mentioned

critical notions about the *face* and *construct* validity of the FST can also be applied to the TST.

To examine the beneficial effects of VWR on stress-related behavior, rodents can be exposed to acute stress, followed by subsequent assessment of stress hormone dynamics and stress-related behavior. Common examples of acute stress are a single bout of social defeat (Lancel *et al.* 2003) or a single session of restraint stress (Fediuc *et al.* 2006).

Effects of VWR in chronic stress-induced models of depression

Chronic social defeat stress (CSDS)

In male C57BL/6 mice, electrophysiological analyses of striatal neurons revealed that 24 h of VWR immediately following 3 days of social defeat could rescue stress-induced changes in sensitivity of GABA synapses to cannabinoid receptor activation (Rossi *et al.* 2008). In this same mouse strain, 2-h access to a running wheel immediately after each defeat session during 10 days of CSDS potentially ameliorated stress-related effects on social behavior, although the study seems to suffer from being underpowered (Otsuka *et al.* 2015). We have observed in male C57BL/6J mice that 21 days of VWR, prior to 10 days of CSDS, prevented the onset of anhedonia and social avoidance (Mul, personal communication). Furthermore, these effects were dependent on functional accumulation of the long-lasting transcription regulator Δ FosB in the nucleus accumbens (Mul, personal communication), suggesting that VWR induction of Δ FosB in the nucleus accumbens is a key mechanistic adaptation underlying pro-resilient action of VWR in mice (see also *nucleus accumbens* section). In a mild social conflict model, male wheel-running and sedentary C57BL/6N mice showed equal increases in stress responses to the 15-min social conflict (Lancel *et al.* 2003). However, VWR for 28 days increased plasma corticosterone levels, but not adrenocorticotrophic hormone levels and revealed opposite changes in non-rapid eye-movement sleep in response to the social conflict compared to sedentary controls (Lancel *et al.* 2003). These findings suggest that adaptations in the HPA axis of wheel-running mice positively affects sleep quality and has protective effects.

Chronic unpredictable stress (CUS)

In C57BL/6J mice that underwent CUS for 42 days, concurrent VWR delayed but not prevented the induction

of anhedonia compared to sedentary mice (Solberg *et al.* 1999). In the same study, VWR decreased immobility scores during a 1-day FST, independent of CUS application (Solberg *et al.* 1999). Another study with male C57BL/6 mice demonstrated that a 6-week CUS paradigm induced a depression-like state, as indicated by anhedonia in the sucrose preference test and decreases in body weight, while VWR for 2 h every day during a 6-week CUS paradigm prevented this (Huang *et al.* 2017). VWR also prevented and blunted increases in immobility scores in the FST and TST, respectively, compared to sedentary stressed animals (Huang *et al.* 2017). Notably, just VWR for 2 h did not alter behavior in the sucrose preference test, FST or TST compared to unstressed controls (Huang *et al.* 2017).

In male Sprague-Dawley rats, VWR for 3 weeks prior to the start of CUS and during 4 subsequent weeks of CUS did not prevent the onset of anhedonia compared to unstressed wheel-running controls (Grippe *et al.* 2003). However, CUS negatively affected running behavior and no sedentary controls were included in this study (Grippe *et al.* 2003), so it cannot be assessed if VWR was protective compared to sedentary conditions. Zheng and colleagues also used male Sprague-Dawley rats and allowed the rats to run during 1 acclimatization week, 4 CUS weeks and 2 recovery weeks (Zheng *et al.* 2006). This study revealed protective effects of VWR against CUS-induced anhedonia and blunted body weight gain (Zheng *et al.* 2006).

Early-life stress

Early-life stress has long-lasting consequences for later cognition and hippocampal plasticity, including changes in adult hippocampal neurogenesis (Korosi *et al.* 2012). Notably, in group-housed female C57BL/6J mice that had been exposed to early-life stress, VWR for 42 days at 8 months of age failed to induce hippocampal proliferation compared to age-matched control animals that had not been exposed to early-life stress (Abbink *et al.* 2017). These observations suggest that long-lasting adaptations are induced by early-life stress, which prevent the beneficial effects of VWR on hippocampal flexibility many months after the occurrence of early-life stress.

Social isolation

Eight weeks of social isolation promotes susceptibility to social defeat stress in young-adult C57BL/6J mice (Vialou *et al.* 2010). Similarly, 10–12 weeks of social isolation induces anxiety-like behavior and anhedonia in Sprague-Dawley rats (Wallace *et al.* 2009). Remarkably, prior

social isolation as well as additional stressors during the experiment (i.e. handling and injection) can modulate the effects of VWR on neurogenesis in the hippocampus of male Sprague-Dawley rats (Stranahan *et al.* 2006). For example, male Sprague-Dawley rats that were individually housed for 1 week before the onset of VWR demonstrated increased neurogenesis in the hippocampus after 48, but not 24, days of VWR (Stranahan *et al.* 2006). Changes in circadian corticosterone dynamics are a likely explanatory mechanism for these molecular observations (Stranahan *et al.* 2006, 2008). These findings indicate that housing conditions prior to the onset of VWR, an experimental variable often not mentioned in published experimental designs, as well as additional stressors during an experiment (i.e. handling and injection) can have profound and differential effects on subsequent molecular and behavioral responses to VWR.

Repeated forced swim stress

5d-RFSS induces coping behavior (i.e. increased immobility during forced swim tests) in wild-type male C57BL/6J and BALB/cJ mice without the induction of emotional, homeostatic or psychomotor symptoms (Mul *et al.* 2016). Whether 5d-RFSS can induce emotional, homeostatic or psychomotor symptoms in aged rodents or genetic lines with increased stress susceptibility, or when it is applied during the dark phase, remains debated (Serchov *et al.* 2015, Mul *et al.* 2016, Delcourte *et al.* 2017). In line with the predictive validity of 5d-RFSS (Stone & Lin 2011, Sun *et al.* 2011, Serchov *et al.* 2015), 5d-RFSS induced coping behavior and VWR for 28 days after 5d-RFSS normalized immobility scores during a final swim test toward non-stressed controls (Mul *et al.* 2016). Similarly, male Wistar rats that were exposed to daily swim stress for 10 days developed coping behavior (i.e. increased immobility), and 21 days of subsequent VWR ameliorated this behavior (Eldomiaty *et al.* 2017).

Effects of VWR in treatment-based screens

Forced swim test (FST) and tail-suspension test (TST)

Several studies have reported that VWR, following various durations, can alter subsequent behavior in treatment-based screens like the FST, TST and LHT. For example, in male C57BL/6J mice or Swiss mice, 14–21 days of VWR decreases immobility scores in a 1-day FST and TST compared to sedentary controls (Duman *et al.* 2008,

Cunha *et al.* 2013, Yau *et al.* 2014). Notably, the magnitude of these effects was similar to the antidepressant amitriptyline (Duman *et al.* 2008). VWR, presumably for 28 days, decreased immobility scores in a 1-day FST in wild-type mice, but VWR was ineffective in mice with heterozygous loss of the VGF nerve growth factor ($Vgf^{+/-}$) (Hunsberger *et al.* 2007).

In rats, VWR is also associated with decreased immobility scores. In Sprague-Dawley rats, VWR for 21 days lowered immobility scores during the second day of a 2-day FST at the onset of darkness (Chen *et al.* 2016). In Flinders Sensitive Line and Flinders Resistant Line rats, the former being a genetic animal model of depression and the latter a control line, VWR for 30 days decreased and increased, respectively, immobility behavior in a 1-day FST compared to their respective sedentary controls (Bjornebekk *et al.* 2005). In an additional study with Flinders Sensitive Line rats, 28 days of VWR also decreased immobility behavior (Bjornebekk *et al.* 2010). These observations suggest that altered genetic makeup of Flinders Sensitive Line and Flinders Resistant Line rats seems to have opposite effects on their coping behavior in response to acute swim stress. In a rat model of fetal alcohol spectrum disorder, VWR for 12 days ameliorated behavioral abnormalities in a 1-day FST, but this effect was specific for males (Brocardo *et al.* 2012).

The effects of VWR on FST behaviors are unfortunately not always consistent. For example, several studies with C57BL/6J mice failed to observe differences in immobility scores between wheel-running and sedentary mice during a 1-day FST (Fuss *et al.* 2010, Nishijima *et al.* 2013b). Similarly, VWR for 21 days in several cohorts of male C57BL/6J cohort did also not modulate immobility scores compared to sedentary controls days during a light-phase 1-day FST (Mul, personal communication). Lastly, in male Wistar rats, VWR for 21 days did not affect behavior in a 1-day FST compared to sedentary controls (Eldomiaty *et al.* 2017). These inconsistent observations might be explained by methodological differences, such as time of day when test is performed, sound isolation of the room, acclimatization to test room and behavior scoring methods (automated vs manual). It is therefore important to report such experimental factors in detail during publication.

Learned helplessness test (LHT)

In the LHT, behavioral depression or learned helplessness is induced by exposure to stressful events (e.g. foot shock) over which the organism has no control (Greenwood &

Fleshner 2008). In male C57BL6/J mice, 21 days of VWR decreases failure and latency scores in an LHT compared to sedentary controls (Duman *et al.* 2008). Female Sprague-Dawley rats that had access to running wheels for 9–12 weeks demonstrated shorter latency to escape foot shock, and this was associated with altered norepinephrine and serotonin dynamics in several brain regions (Dishman *et al.* 1997). In male Sprague-Dawley rats, VWR for 6 weeks reduced the effects of uncontrollable stress on shuttle box escape and freezing behavior (Greenwood *et al.* 2003). This study also identified adaptations in the serotonergic brain circuitry as a likely mediator of these effects (Greenwood *et al.* 2003). The protective effects of VWR on shuttle box escape behavior and molecular adaptations in the serotonergic brain circuitry appear to be sensitive to the duration of prior VWR, as these effects were observed after 6, but not 3, weeks of VWR in adult male Fischer F344 rats (Greenwood *et al.* 2005). One study reported that VWR for 3 weeks in C57BL6/J mice did not affect LH behavior compared to sedentary controls (Fuss *et al.* 2010).

Effects of VWR on anhedonia

Anhedonia is defined as the inability to experience pleasure from an activity usually found enjoyable. In rodents, stress-induced anhedonia is commonly assessed by analyzing sucrose preference or sexual behavior, which are examples of consummatory and motivational anhedonia, respectively. Yau and colleagues reported that VWR for 14 days increased preference for a 2% sucrose solution (i.e. prohedonia) in wild-type mice suggested to have a C57BL6/J background, an observation that was likely potentiated by an unusually low (~75%) baseline sucrose preference (Yau *et al.* 2014, Mul *et al.* 2016). In addition, given the caloric value of the sugar solution, it is difficult to determine if VWR truly altered emotionality of the mice or the increased consumption of the sugar solution reflects changes in caloric demands. In several cohorts of wild-type male C57BL/6J, which demonstrated a basal preference of around 90% that is typical for C57BL/6J mice (Pothion *et al.* 2004, Mul *et al.* 2016), VWR for 21 days did not modulate preferences for a 1% sucrose solution compared to sedentary control days during a 3-day sucrose preference test (Mul, personal communication). Therefore, it might be possible that the effects of VWR on sucrose preference are only visible during low baseline preferences. In addition, palatable solutions without caloric content could potentially shed light on the effects of VWR on anhedonia.

Responses to acute stress following VWR

Restraint stress

VWR for 4 weeks induced adaptations along the HPA axis in male C57BL6/N mice and increased plasma corticosterone levels in response to 30-min restraint stress (Droste *et al.* 2006). In male Sprague-Dawley rats, conflicting results have been observed. VWR for 35 days, plus 7 days of VWR following recovery from carotid artery surgery, blunted plasma adrenocorticotrophic hormone (ACTH) excursions, but did not affect plasma corticosterone excursions, following a 20-min restraint stress (Fediuc *et al.* 2006). In contrast, 30-min restraint stress induced similar increases in plasma corticosterone and ACTH levels in 42-day trained and sedentary rats (Campeau *et al.* 2010). Because the running duration is similar in both rat studies, stress associated with the surgical procedure or with the collection of blood (relatively stress-free via carotid cannula vs tail vein puncture) could be potential methodological explanations for the differential results.

Novelty stress

VWR for 4 weeks induced adaptations along the HPA axis in male C57BL6/N mice and blunted plasma corticosterone levels in response to 30-min exposure to a clean novel environment, independent of the presence of a clean running wheel in that novel environment (Droste *et al.* 2006). A study in 28-day trained male Sprague-Dawley rats showed less exploratory behavior, and more lying on the cage floor, in response to 30-min exposure to a clean environment (Droste *et al.* 2007). Also in male Sprague-Dawley rats, 42 days of VWR blunted corticosterone and ACTH responses to a clean novel environment or 85dB noise (Campeau *et al.* 2010). These observations indicate that VWR modulates behavioral response to mild novelty stress.

Anxiety-like behavior

Several studies have investigated the effects of VWR on anxiety-like behavior. Binder and colleagues found that 28 days of VWR in male C57BL6/N mice resulted in decreased anxiety-related behavior and 'impulsiveness', as measured in the open-field test, the modified hole board test, the elevated plus maze and the dark-light box (Binder *et al.* 2004). Similarly, 21 days of VWR in male C57BL6/J mice decreased anxiety-related behavior in the open-field test and elevated plus maze, although timing

of the experiments during or after wheel access seemed to influence mouse behavior (Duman *et al.* 2008). In male Sprague-Dawley rats, VWR for 28 or 56 days generally showed decreased activity in the elevated plus maze and open-field test, in support of 'defensive behavior' or decreased impulsiveness (Burghardt *et al.* 2004).

In contrast, one report demonstrated that 21–28 days of VWR in male C57BL/6J mice produced increased anxiety-related behavior, as measured in the open-field test, the elevated O-maze and the dark-light box (Fuss *et al.* 2010). The inconclusive effects of VWR on anxiety-like behavior likely result from methodological differences. As such, it is important to report when exactly the behaviors were assessed during the day.

Brain circuitry, molecular adaptations and neurotransmitters mediating beneficial effects of VWR

Hippocampus

The hippocampus is as a major site where changes occur that are induced by exercise and is a key brain region involved in learning and memory. Within the hippocampus, the neurotransmitter brain-derived neurotrophic factor (BDNF) is a key mediator of the beneficial effects of VWR on learning, memory and stress-related behavior (Cotman & Berchtold 2002, Duman & Monteggia 2006, Duzel *et al.* 2016, Cooper *et al.* 2017). In male C57BL/6J mice, VWR for 27 days increased BDNF protein levels in whole hippocampus samples (Fuss *et al.* 2010) and hippocampal BDNF protein levels remained elevated for 14 days following cessation of VWR (Berchtold *et al.* 2010). In the same mouse strain, VWR increases *Bdnf* mRNA in the dentate gyrus and CA1 of the hippocampus, the latter being observed after 21 days, but not 7 days, of running (Duman *et al.* 2008). The same group went on to show that VWR for 7 days increased *Bdnf* and *Vgf* mRNA, and BDNF and VGF protein levels, in the hippocampus of male C57BL/6J mice (Hunsberger *et al.* 2007). VGF is a secreted neuropeptide involved in energy balance and synaptic plasticity (Hahm *et al.* 1999, Alder *et al.* 2003), making it a likely candidate for some of the effects of VWR on energy homeostasis and stress sensitivity.

VWR-mediated increases in hippocampal BDNF and subsequent neuronal adaptations seem to play a role during behavioral responding to an acute stressor, as decreased immobility during an FST following 21 days of VWR was not observed in mice heterozygous for a deletion of *Bdnf* (Duman *et al.* 2008). Furthermore, intraperitoneal

administration of the specific MAPK kinase inhibitor PD184161 during a 2-day FST abolished the effects of VWR on immobility behavior during the retest, whereas it had no effect in sedentary controls (Duman *et al.* 2008). Finally, VWR for 28 days had no effect on FST behavior in *Vgf*^{fl/-} mice (Hunsberger *et al.* 2007). However, it is possible that this behavior reflects a developmental issue, as *Vgf*^{fl/-} mice demonstrated baseline changes in FST behavior as well as normal VWR induction of hippocampal VGF protein (Hunsberger *et al.* 2007).

In male C57BL/6J mice, VWR for 14 days increased BDNF protein in the dentate gyrus, but not in the whole hippocampus, and this effect was independent of whole-body loss of adiponectin (Yau *et al.* 2014). Adiponectin is an adipocyte-secreted protein with profound beneficial effects on glucose and energy homeostasis (Kubota *et al.* 2007), as well as protective effects in the brain (Arnoldussen *et al.* 2014). Because adiponectin can mimic many of the metabolic effects of exercise, Yau and colleagues investigated the role of adiponectin during VWR and demonstrated that adiponectin is an important mediator of the effects of VWR on hippocampal neurogenesis and in treatment-based screens (Yau *et al.* 2014). Furthermore, conditional adiponectin-knockout mice had decreased hippocampal insulin-like growth factor-1 (IGF-1), a growth factor upregulated in the hippocampus by chronic antidepressant treatment (Khawaja *et al.* 2004) and compromised activation of hippocampal AMPK following 14 days of VWR (Yau *et al.* 2014). Another study observed normal hippocampal neurogenesis in adiponectin-knockout mice during environmental enrichment (Nicolas *et al.* 2015). IGF-1 is further implicated in the beneficial effects of VWR on stress-related behavior, as subcutaneous anti-IGF-1 antibody administration using a mini-pump during 28 days of VWR prevented the effects of VWR on immobility scores in a 1-day FST in male C57BL/6J mice (Duman *et al.* 2009). Fuss and colleagues observed that 27 days of VWR in C57BL/6J mice was associated with decreased cell death and increased cell differentiation, but not cell proliferation, in the subgranular zone of the dentate gyrus (Fuss *et al.* 2010). Furthermore, 14 days of VWR in C57BL/6J mice was associated with clear increases in newborn cells, cell differentiation and proliferation in the dentate gyrus, and these effects were abolished in adiponectin knockout mice (Yau *et al.* 2014). VEGF also plays a likely role, as peripheral blockade of VEGF abolished VWR-induced hippocampal neurogenesis in group-housed male C57BL/6J mice (Fabel *et al.* 2003).

Similar observations have been observed in wheel-running rats. In male Sprague-Dawley rats, already 2

nights of VWR are sufficient to increase *Bdnf* mRNA in the hippocampus and neocortex compared to untrained rats (Neeper *et al.* 1995, 1996). Moreover, VWR induction of hippocampal BDNF protein levels continued to rise with VWR duration, measured up to 90 days of VWR (Berchtold *et al.* 2005). Interestingly, intermittent access to running wheels induced hippocampal BDNF protein to similar level as continuous access (Berchtold *et al.* 2005). An elegant recent study demonstrated that moderate intermittent amounts of VWR, which might more closely relate to human exercise paradigms, are superior to continuous daily VWR at promoting hippocampal neurogenesis during 30-day access to running wheels (Nguemeni *et al.* 2017). In Wistar rats, 4-week VWR, prior to 4 weeks of restraint stress, increased mobile behavior during an FST compared to sedentary controls, and these effects were associated with increased hippocampal BDNF protein levels (Lapmanee *et al.* 2017).

In Flinders Resistant Line rats, but not Flinders Sensitive Line rats, VWR increased *Bdnf* mRNA and cell proliferation in the dentate gyrus, but not in other regions of the hippocampus or neocortex (Bjornebekk *et al.* 2005). Consistently, both research teams observed a positive correlation between daily running distances and *Bdnf* mRNA in the dentate gyrus (Neeper *et al.* 1995, Bjornebekk *et al.* 2005, 2008). Furthermore, increased immobility during a 1-day FST and increased BrdU-immunoreactive cells in the dentate gyrus following 30–35 days of VWR was positively associated with hippocampal neuropeptide Y (*NPY*) and *NPY-Y1* receptor mRNA in Flinders Sensitive Line rats, (Bjornebekk *et al.* 2006, 2010). *NPY* is a neuropeptide involved in energy homeostasis as well as stress-related behavior (Bosker *et al.* 2011, Morton *et al.* 2014). Stress-related behavioral differences between Flinders Sensitive Line and Flinders Resistant Line rats might partially be explained by a single-nucleotide polymorphism in the *NPY* promoter, resulting in altered *NPY* function in the hippocampus (Melas *et al.* 2013).

Locus coeruleus

The brainstem nucleus locus coeruleus is major source of norepinephrine and is involved in stress responses, motivation and learning and memory. In Sprague-Dawley rats, VWR for 21 days increased prepro-galanin mRNA in the locus coeruleus (Sciolino *et al.* 2012, 2015). Although sedentary and trained rats displayed similar behavior in the elevated plus maze, shock probe defensive burying and defensive withdrawal tests, VWR did have a

protective effect when pharmacological or physical stress was induced (Sciolino *et al.* 2012, 2015).

Prefrontal cortex

Twenty-one days of VWR or chronic intracerebroventricular administration of galanin attenuated stress-evoked dopamine flux in the medial prefrontal cortex (PFC) and prevented stress-evoked loss of dendritic density in this region following stress (Sciolino *et al.* 2015). However, intracerebroventricular administration of a galanin receptor antagonist failed to prevent the effects of VWR on stress-evoked dopamine flux, suggesting that these VWR-mediated adaptations are likely galanin independent (Sciolino *et al.* 2015).

Dorsal raphe nucleus

Hyperactivity of serotonin neurons in the dorsal raphe nucleus are implicated in mediating learned helplessness behaviors (for excellent review see (Greenwood & Fleshner 2011). VWR prevents learned helplessness (Dishman *et al.* 1997, Greenwood *et al.* 2003, 2005, Duman *et al.* 2008), and attenuated activity of serotonergic neurons in the dorsal raphe nucleus during VWR might be a likely underlying mechanism (Greenwood & Fleshner 2011).

Nucleus accumbens

Long-term VWR promotes accumulation of the transcription regulator Δ FosB in the nucleus accumbens, an important brain reward-associated area (Werme *et al.* 2002, Greenwood *et al.* 2011, Obici *et al.* 2015). VWR also induces Δ FosB in the hippocampus, most notably the dentate gyrus (Nishijima *et al.* 2013a). Δ FosB, a particularly stable Fos family member, heterodimerizes with Jun family proteins to form activator protein-1 (AP-1) transcription factor complexes and regulates the transcription of hundreds of genes (Hope *et al.* 1994, McClung & Nestler 2003). Many preclinical studies support the notion that Δ FosB in the nucleus accumbens is strongly implicated in neuronal adaptations to repetitive exposure to drugs of abuse, natural rewards and stress (Robison & Nestler 2011, Russo & Nestler 2013, Nestler 2015). Using murine models of 21-day VWR prior to 10-day CSDS, we have observed that VWR promotes resilience to CSDS-induced anhedonia and social isolation in male C57BL/6J mice and that viral-mediated functional loss of Δ FosB in the nucleus accumbens during VWR negated these protective effects (Mul, personal communication). This suggests that

VWR induction of nucleus accumbens Δ FosB plays a key role in some of the beneficial effects of VWR on stress susceptibility in mice. On a circuitry level, a hippocampus – amygdala – nucleus accumbens pathway mediates some of the mnemonic aspects of stress-induced behavioral impairments (Ramirez *et al.* 2015), confirming the gateway position of neurons in the nucleus accumbens, a key output nucleus of the brain reward circuitry, to translate input from other stress-related brain nuclei into behavior. Involvement of the infralimbic cortex cannot be excluded in these effects, as ventromedial PFC outputs to downstream limbic targets, including the nucleus accumbens, modulates stress resilience during enriched environmental housing conditions, which included running wheels (Lehmann & Herkenham 2011).

Although VWR-mediated upregulation of BDNF and VGF in the hippocampus are clearly associated with beneficial effects on stress-related behaviors (Duman & Monteggia 2006, Hunsberger *et al.* 2007, Cooper *et al.* 2017), upregulation of these proteins in the nucleus accumbens appears to be associated with negative behavioral outcomes (Eisch *et al.* 2003, Berton *et al.* 2006, Krishnan *et al.* 2007, Wook Koo *et al.* 2016, Jiang *et al.* 2017). To the best of my knowledge, NAc BDNF protein levels following VWR have not been adequately assessed to date. First, Marais and colleagues reported that 6-week VWR increased NAc BDNF protein levels in rats compared to sedentary controls, although it has to be noted that all experimental animals had been subjected to maternal separation (Marais *et al.* 2009). As noted earlier, increased striatal BDNF activity is associated with stress-susceptible phenotypes, and the occurrence of early-life stress before the onset of VWR makes it difficult to draw firm conclusions from this study. Second, studies investigating NAc *Bdnf* mRNA remain inconclusive, as striatal *Bdnf* mRNA levels were not changed after 7-day VWR (Neepor *et al.* 1996), either too low to be analyzed (Van Hooymissen *et al.* 2003) or not compared to sedentary controls (Roberts *et al.* 2012). In the latter study, rats selected for high or low VWR activity did not show differences in NAc *Bdnf* mRNA following 6 days of VWR and 1 day rest (Roberts *et al.* 2012). Finally, VWR for 21 days increased *Bdnf* mRNA in the ventral tegmental area/substantia nigra areas, an area with abundant *Bdnf* expression, although it has to be noted that these rats were subjected to a daily saline injection paradigm and a subsequent stress effect cannot be excluded (Van Hooymissen *et al.* 2003). In summary, more work is required to determine the role of BDNF dynamics in the ventral tegmental area – nucleus accumbens axis on stress-related behavior in response to VWR.

Exercise myokines

Recent studies have identified several myokines (i.e. muscle-derived signaling molecules) that appear to be released during exercise and induce beneficial effects in the brain. Agudelo and colleagues demonstrated, using sedentary genetic mouse models, that muscle peroxisome proliferator-activated receptor gamma coactivator 1-alpha 1 (PGC-1 α) can modulate kynurenine metabolism, thereby mediating resilience to stress-induced depression (Agudelo *et al.* 2014). Although molecular evidence for upregulation of muscle kynurenine-related enzymes and plasma kynurenic acid was presented following 56 days of VWR (and with selection of high runners), direct evidence in mice that kynurenine metabolism is underlying the beneficial effects of VWR on stress resilience was not provided (Agudelo *et al.* 2014). In humans, exercise training clearly affects muscle kynurenine metabolism (Agudelo *et al.* 2014, Schlittler *et al.* 2016). However, extreme endurance cycling (150-km road cycling time trial), but not eccentric exercise (100 drop jumps), increased plasma kynurenic acid and lowered plasma quinolinic acid-to-kynurenic acid ratio levels (Schlittler *et al.* 2016), suggesting that only high-intensity long-duration physical activity might acutely modulate plasma kynurenic metabolism. Similarly, 12-week training periods, at three different levels of intensity (mild, moderate, vigorous), were not associated with long-lasting changes in plasma kynurenine or kynurenic acid levels (Millischer *et al.* 2017). Finally, plasma kynurenic acid was increased after marathon running, but not after a short treadmill exercise test (Lewis *et al.* 2010). Although a direct role for kynurenic acid metabolism during exercise remains to be demonstrated in humans, increased plasma quinolinic acid-to-kynurenic acid ratio levels have been associated with depressive behavior (Muller & Schwarz 2007).

Another PGC-1 α -driven myokine is irisin, the secreted form of the muscle protein fibronectin type III domain-containing protein 5 (Bostrom *et al.* 2012). In C57BL/6 mice, VWR for 30 days increased PGC-1 α -dependent *Fndc5* and *Bdnf* mRNA expression specifically in the hippocampus (Wrann *et al.* 2013). The physiological role of irisin in exercise biology has been debated (Jedrychowski *et al.* 2015).

In C57BL/6 mice, VWR for 30 days increased cathepsin B plasma levels, suggesting it might be an exercise myokine, and increased hippocampal Cathepsin b mRNA expression (Moon *et al.* 2016). In this study, VWR had no effect on behavior in the sucrose consumption test, FST or open-field test in wild-type mice. However, the effects of

VWR on memory and hippocampal neurogenesis appear to be dependent on Cathepsin B, as Cathepsin B-knockout mice failed to demonstrate these effects (Moon *et al.* 2016). Finally, changes in plasma Cathepsin B levels were increased in humans and rhesus monkeys following treadmill training and associated with improved cognitive skills in humans (Moon *et al.* 2016).

Conclusions and perspectives

The usage of VWR to model adaptations in humans during exercise training has generated substantial insight into molecular adaptations and brain circuitry involved in the beneficial effects of exercise on several aspects of behavior, including energy homeostasis, cognition and memory and stress susceptibility (Fig. 1). The recent introduction of innovative transgenic, pharmacogenetic and optogenetic techniques allows unprecedented analysis of the complexity of exercise biology at the molecular, cellular and neuronal circuit levels, which will lead to a new understanding of the beneficial adaptations underlying exercise training. An additional important challenge that remains is the ability to predict individual responses to different intensities of training, as exercise tailored to different stress sensitivity of individuals will promote compliance and success of therapeutic exercise programs. Newly discovered exercise myokines hold strong potential for therapeutic use, but need to be based on realistic expectations. For example, increases in plasma kynurenic acid were observed after a 150-km road cycling time trial, but not after 100 drop jumps, indicating that kynurenic acid metabolism might not be affected by 5-km slow-pace run. Even more, comparison of exercise

intensity and duration between rodents and humans, and even between mice and rats, remains a challenge.

CSDS, a widely used etiologically valid animal model of depression, is based on intermale dominance and only applied to males. As such, the insight generated by this model is always in the context of a male background. Fortunately, a recent report now also suggests that CSDS can be applied to induce depression-like behavior in female rodents (Iñiguez *et al.* 2017). Furthermore, early-life stress seems to affect males but not female rodents, suggesting susceptibility or resilience in either sex (Oomen *et al.* 2009). Given the sex-dependent vulnerability to stress-related disorders, in a perfect world, an equal distribution in sexes should be investigated in preclinical models.

Animal models of aerobic exercise are used frequently; yet, animal models of anaerobic exercise are rare. For example, anaerobic resistance training or treadmill training in adult male Sprague-Dawley rats for 42–56 days revealed no effect of adult hippocampal neurogenesis, whereas VWR clearly did (Nokia *et al.* 2016). However, in women, both aerobic (running) and anaerobic (weight lifting) exercise for 56 days improved depression-related measures (Doyne *et al.* 1987). Given the popularity of anaerobic exercise, especially in younger generations, studies using valid animal models of anaerobic exercise will be a valuable addition to the field of exercise biology.

Several imaging techniques are now being utilized to visualize exercise training-induced in brain circuitry. For example, using MRI, it was demonstrated that $\text{VO}_{2\text{max}}$ fitness or frequent walking is associated with greater hippocampal volume in humans (Erickson *et al.* 2009, 2010). Similarly, MRI demonstrated that 35-day VWR was associated with greater hippocampal volume in Flinders Sensitive Line rats (Sierakowiak *et al.* 2014). In mice, brain blood oxygen level-dependent (BOLD) MRI was used to examine functional changes in the brain induced by CUS or VWR, and several brain regions were identified as differentially activated (Huang *et al.* 2017). In human volunteers, resting state functional connectivity is different between young-adult endurance athletes and healthy controls and included enhanced connectivity between the frontoparietal network and frontal cortex (Raichlen *et al.* 2016). Another study conducted the Montreal Imaging Stress Task in lowly trained and highly trained young men, with or without aerobic exercise prior to the test and found no clear differences between training state, although acute exercise increased activity in the hippocampus and decreased activity in the prefrontal cortex (Zschucke *et al.* 2015). Many studies assess molecular adaptations after a

Figure 1

Summary of molecular and behavioral adaptations associated with altered stress-related behavior following VWR. 5d-RFSS, 5-day repeated forced-swim stress; FST, forced-swim test; LHT, learned helplessness test; HPA, hypothalamic-pituitary-adrenal.

given duration of VWR. However, several aspects of VWR, such as its effects on corticosterone dynamics or caloric intake, are temporal (Fediuc *et al.* 2006, Obici *et al.* 2015). Similarly, (behavioral) adaptations often only become visible after a minimal duration of VWR (Greenwood *et al.* 2005, Stranahan *et al.* 2006). Non-invasive *in vivo* imaging studies that visualize the temporal dynamics of the underlying central molecular adaptations are valuable (translational) tools that can improve our understanding how exercise duration and intensity affect individual responding to exercise. In summary, combining state-of-the-art imaging techniques with classic molecular and genetic approaches will aid in the characterization of exercise training-induced adaptations in neurons of the stress- and reward-related brain circuitries. This insight may identify new targets for the development of much-needed effective therapeutic treatments for stress-related disorders, including depression.

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