Conditional Modulation of Sensitization of the Stimulant Effects of Cocaine by Wheel Running

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ABSTRACT

Conditional Modulation of Sensitization of the Stimulant Effects of Cocaine by Wheel Running

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Repeated exposure to stimulant drugs such as cocaine makes animals more sensitive to their stimulant effects—a phenomenon that is known as 'behavioural sensitization'. However, the magnitude of behavioural sensitization is not fixed but can vary according to life experiences and their interaction with biological factors. This thesis explores whether and how wheel running influences sensitization of the stimulant effects of cocaine as measured after repeated exposure to cocaine or to stress in the rat. Wheel running was chosen because of its natural variability among individuals and because it has been shown to act, at least in part, on the same neuronal substrate as drugs and stress. Three studies were conducted. In the first study we showed that engaging in high levels of wheel running activity protects against cocaine-induced behavioral sensitization. To demonstrate the generalizability of these findings, in the second study, using stress exposure instead of stimulant drugs to induce a sensitized behavioral response, we found that running also protects against stress-induced behavioral sensitization to cocaine and more so in animals that run the most. Finally, in the third study, we showed that engaging in high levels of wheel-running activity, after the fact, once a sensitized behavioral response to cocaine has already been established reverses this typically enduring phenomenon. The findings reported here reveal, for the first time, the regulatory effects wheel running can have on behavioral sensitization and highlight the importance of taking into account individual differences in running when

studying the effects of this behavior. What is more, our behavioral model suggests running-mediated neuroplasticity within the neural circuitry involved in behavioral sensitization and may prove useful in studying the role of gene-environment interactions in experience-dependent neuroplastic changes.

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CONTRIBUTION OF AUTHORS

Chapter 1:

I designed and performed the research, analyzed the data, prepared the figures, and wrote the manuscript.

D. Siontas and J. Mendoza performed the research and contributed to the preliminary analysis and discussion of the results.

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A. Arvanitogiannis guided and designed the research and provided comments on the manuscript.

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Annexe 1

General Introduction

The brain is anything but static; in fact, in response to an ever-changing environment the brain undergoes diverse structural and functional changes throughout the life span. To try to understand the manner in which experience-dependent neuroplastic changes take place researchers have focused on animal models involving well-characterized behaviors and brain circuits. A case in point being behavioral sensitization to stimulant drugs and the associated plastic changes within the mesocorticolimbic dopamine system (Nestler, 2008; Pascoli, Turiault, & Lüscher, 2011; Robinson & Kolb, 2004). This model denotes the heightened locomotor response to a psychostimulant challenge of animals that have been previously treated with the drug (Post & Rose, 1976), and persists long after the cessation of drug treatment (Henry & White, 1995; Post, Weiss, & Pert, 1988; Robinson & Becker, 1986). Like stimulant drug intake, stressful life events also alter the mesocorticolimbic dopamine system. As such, animals that have never been exposed to stimulant drugs, but that are exposed to a stressor exhibit a heightened behavioral response to the first drug exposure (Antelman, Eichler, Black, & Kocan, 1980; Herman, Stinus, & Le Moal, 1984; Kalivas & Stewart, 1991; Robinson & Becker, 1986). Examining the process of behavioral sensitization and the diverse factors that can modulate it has and continues to improve our understanding of the mechanisms regulating experience-dependent neuroplastic changes.

Wheel-running behavior, an animal model of exercise, also produces similar functional changes within the mesocorticolimbic dopamine system (C. Chen et al., 2016; Greenwood et al., 2011; Herrera et al., 2016; Meeusen, Smolders, Sarre, & De Meirleir, 1997; Werme et al., 2002). What is more, as with drug-taking behavior, animals voluntarily engage in wheel-running behavior (Meijer & Robbers, 2014; Sherwin, 1998), spend more time in a context that has been previously paired with wheel running (Basso

& Morrell, 2015; Belke & Wagner, 2005; Greenwood et al., 2011; Herrera et al., 2016) and press on a lever to get access to a running wheel (Belke & Wagner, 2005; Iversen, 1993). Like most behaviors, there exists individual differences in running behavior; that is, some animals voluntarily run more than others (Ekkekakis & Hall, 2005; Ferreira et al., 2006; Tarr, Kellaway, Gibson, & Russell, 2004). Interestingly, differences in running performance have been shown to promote distinct changes in striatal function (Aguiar et al., 2010; Park et al., 2016; Waters et al., 2008; Wilson & Marsden, 1995) and to modulate the behavioral response to the first stimulant exposure (Ferreira et al., 2006; Larson & Carroll, 2005).

Given that running produces similar changes within the mesocorticolimbic dopamine system as exposure to drugs or stress, the goal of the present thesis was to determine whether wheel-running activity can synergistically influence cocaine- and stress-induced behavioral sensitization to cocaine. Because individual differences in running behavior are known to produce distinct changes in striatal dopamine function, I also wanted to determine whether any effect of wheel running on behavioral sensitization to cocaine would vary according to an animal's natural tendency to wheel run.

Psychostimulant-induced sensitization

Exposure to stimulant drugs, such as amphetamine or cocaine, produces changes in behavior that are thought to reflect distinct drug-induced changes in the brain. A key pathway in the study of stimulant-induced plasticity is the mesocorticolimbic dopamine system, which involves ventral tegmental area dopamine neurons that project to the nucleus accumbens and prefrontal cortex (Kalivas & Stewart, 1991; Lüscher & Malenka,

2011; Thomas, Kalivas, & Shaham, 2008; Vezina, 2004). Within this pathway, an acute injection of a stimulant drug, by targeting the dopamine reuptake system, results in a temporary dose-dependent increase in extracellular dopamine concentrations and in locomotor activation (Kalivas & Duffy, 1990; 1993; Kalivas, Duffy, DuMars, & Skinner, 1988).

In contrast to acute stimulant exposure, repeated exposure produces far greater, long-lasting, neurobehavioral changes (Kalivas & Stewart, 1991; Nestler, Kelz, & Chen, 1999; Robinson & Kolb, 2004; Thomas et al., 2008; Vezina, 2004; Vezina & Leyton, 2009). For instance, animals that have been previously treated with stimulant drugs, as opposed to drug-naïve animals, exhibit heightened extracellular dopamine concentrations in the nucleus accumbens in response to a drug-challenge injection (Kalivas & Duffy, 1990; 1993; Singer et al., 2009). In addition to increased neuronal sensitivity, repeated psychostimulant exposure is thought to reorganize synaptic connectivity within the mesocorticolimbic system, as animals treated with amphetamine and cocaine have been shown to exhibit persistent changes in cellular structure. Specifically, neurons in the nucleus accumbens and prefrontal cortex of drug-treated animals, compared to saline-treated animals, display longer dendrites and more dendritic spines (Robinson, Gorny, Mitton, & Kolb, 2001; Robinson & Kolb, 1997). A molecular mechanism that has been linked to various forms of experience-dependent neuroplastic changes (Perrotti, Hadeishi, & Ulery, 2004; Pitchers et al., 2013; Wallace et al., 2008; Werme et al., 2002) and that is thought to underlie some of the functional changes observed within the mesocorticolimbic system following repeated stimulant exposure is the transcription factor DeltaFosB (Kelz, Chen, Carlezon, & Whisler, 1999; Nestler, 2008; Perrotti et al., 2008). In stimulant-treated rats this molecule has been

shown to accumulate in the prefrontal cortex and in nucleus accumbens medium spiny dynorphin-containing neurons (Hiroi et al., 1997; Moratalla, Elibol, Vallejo, & Graybiel, 1996; Perrotti et al., 2008). Blocking DeltaFosB transcriptional activity in the nucleus accumbens has been shown to impede the morphological changes generally observed in this brain region following repeated exposure to stimulant drugs (Maze et al., 2010; Robison & Nestler, 2011; Russo et al., 2010). These stimulant-mediated chemical, morphological, molecular and functional changes are detectable long after the discontinuation of the drug treatment and are thought to underlie the concomitant sensitization in the behavioral effects of psychostimulant drugs (Colby, Whisler, Steffen, Nestler, & Self, 2003; Heidbreder, Thompson, & Shippenberg, 1996; Kalivas & Duffy, 1993; Kelz et al., 1999; Lorrain, Arnold, & Vezina, 2000; Maze et al., 2010; Nestler, 2008; Perrotti et al., 2008; Robinson et al., 2001; Robinson & Kolb, 1997, 1999; 2004; Self, 2004; Vezina & Leyton, 2009; Vezina, Lorrain, Arnold, Austin, & Suto, 2002; Zapata, Chefer, Ator, & Shippenberg, 2003).

Amongst the behavioral changes that result from repeated psychostimulant exposure is a heightened locomotor response to a drug challenge injection. This phenomenon, known as behavioral sensitization, denotes the significantly higher drug-induced behavioral activation of animals that have been previously treated with drugs as opposed to those that have not (Post & Rose, 1976). Like drug-mediated changes in the brain, behavioral sensitization can last long after cessation of drug intake (Henry & White, 1995; Post et al., 1988; Robinson & Becker, 1986). At the core of the sensitized behavioral response is an increase in nucleus accumbens extracellular dopamine levels (Kalivas & Duffy, 1990; 1993), as amphetamine-treated animals that do not express behavioral sensitization to the drug challenge injection fail to exhibit this heightened

dopaminergic response (Scholl, Feng, Watt, Renner, & Forster, 2009). Similarly, increases in dendritic spine density within the core subregion of the nucleus accumbens have only been observed in animals that exhibit robust behavioral sensitization (Li, Acerbo, & Robinson, 2004). Though the specific role of such morphological changes in the sensitizing process has recently been debated (Singer et al., 2009). Research in the molecular neurobiology of sensitization has provided evidence consistent with the notion that drug-mediated accumulation of the transcription factor DeltaFosB in the nucleus accumbens is a key process underlying the sensitized behavioral response to drugs (Kelz & Nestler, 2000; Nestler, 2008; Nestler, Barrot, & Self, 2001). Compared to controls, transgenic mice in which DeltaFosB overexpression can be specifically induced in nucleus accumbens medium spiny dynorphin-containing neurons show a sensitized locomotor response to the first cocaine injection (Kelz et al., 1999).

As with most behaviors there are individual differences in the behavioral effects of psychostimulant drugs. Interestingly, variability in the locomotor response to the first psychostimulant injection has been shown to predict the magnitude of the sensitized behavioral response (Bardo, Neisewander, & Kelly, 2013; Yamamoto et al., 2013). That is, animals that exhibit the lowest locomotor activation in response to the first cocaine injection subsequently exhibit greater behavioral sensitization to the drug challenge injection (Nelson, Larson, & Zahniser, 2009; Sabeti, Gerhardt, & Zahniser, 2003). Differences in mesocorticolimbic dopamine function, such as the number of striatal dopamine transporters, are thought to underlie the distinct patterns of behavioral sensitization observed in the high- versus low-cocaine responders (Nelson et al., 2009; Sabeti et al., 2003; Yamamoto et al., 2013).

Stress-induced sensitization to psychostimulant drugs

Stressor exposure, like stimulant drug intake, produces long-lasting molecular (Nestler, 2008; 2015), morphological (Brown, Henning, & Wellman, 2005; Christoffel et al., 2011; Cook & Wellman, 2004; Robinson & Kolb, 2004) and neurochemical (Kalivas & Duffy, 1989; Kalivas & Stewart, 1991; Sorg & Kalivas, 1991; 1993) changes within the mesocorticolimbic dopamine system. Specifically, in contrast to non-stressed animals, rats that are exposed to a stressor exhibit DeltaFosB accumulation in the nucleus accumbens and frontal cortex (Perrotti et al., 2004), show more dendritic branching and dendritic spines in accumbal neurons (Roitman, Na, Anderson, & Jones, 2002) and show heightened levels of extracellular dopamine concentrations in the nucleus accumbens (Abercrombie, Keefe, DiFrischia, & Zigmond, 1989; Kalivas & Duffy, 1995; Sorg & Kalivas, 1991) and medial prefrontal cortex (Abercrombie et al., 1989; C. Chen et al., 2016).

These stress-mediated plastic changes are thought to modify the way in which the dopamine system subsequently reacts to psychostimulant drugs. For instance, various research groups have found that exposure to a stressor, such as footshock, food restriction or physical restraint, exacerbates stimulant-induced changes in neuronal structure (Esparza et al., 2012) as well as extracellular dopamine levels in the nucleus accumbens (Garcia-Keller et al., 2013; Rougepont, Marinelli, LeMoal, Simon, & Piazza, 1995; Sorg, 1992; Sorg & Kalivas, 1991; Sorg & Steketee, 1992). The stress-mediated changes, in particular, within the mesolimbic dopamine system, are accompanied by an enhancement in the behavioral response to psychostimulant drugs. That is, in contrast to their non-stressed controls, animals that are exposed to a stressor will show a sensitized behavioral response to the first psychostimulant exposure (Antelman et al., 1980; Garcia-Keller et al., 2013; Herman et al., 1984; Nikulina, Covington, Ganschow, Hammer, &

Miczek, 2004; Roitman et al., 2002; Rougepont et al., 1995; Sorg & Kalivas, 1991; Sorg & Steketee, 1992; Yap & Miczek, 2008).

As with drug taking behaviors, there are individual differences in response to stressor exposure. Interestingly, these differences have been shown to predict the extent of the behavioral response to stimulant drugs. A model that has been widely used to examine the impact individual differences in response to a stressor can have on stimulant-induced behavioral actions involves an animal's initial ambulatory response to a novel environment. Exposure of animals to this form of mild stressor distinguishes between high and low novelty responders. The former, as opposed to the latter, show a heightened behavioral response to the first stimulant injection (Hooks, Colvin, Juncos, & Justice, 1992; Hooks, Jones, Smith, Neill, & Justice, 1991b; Piazza, Deminière, Le Moal, & Simon, 1989). Following repeated exposure to stimulant drugs these animals also show greater behavioral sensitization in response to a drug challenge injection (Dietz, Tapocik, Gaval-Cruz, & Kabbaj, 2005; Hooks, Jones, Neill, & Justice, 1992; Hooks, Jones, Smith, Neill, & Justice, 1991a). Studies examining the mechanisms underlying the high- and low-novelty responders' distinct response to drugs have revealed presynaptic and postsynaptic differences within the mesocorticolimbic dopamine system of these two phenotypes (Bardo et al., 2013; Dietz et al., 2005; Hooks, Colvin, et al., 1992; Hooks et al., 1991b).

Exercise-induced sensitization of the mesocorticolimbic dopamine system

As with psychostimulant intake and stressor exposure, engaging in running behavior has been shown to promote similar molecular, structural and chemical changes within the mesocorticolimbic dopamine system (Chaouloff, 1989; C. Chen et al., 2016; Greenwood et al., 2011; Herrera et al., 2016; Meeusen & De Meirleir, 1995; Meeusen,

Piacentini, & De Meirleir, 2001; Toy et al., 2014; Werme et al., 2002). For instance, long-term running has been found to produce an accumulation of the transcription factor DeltaFosB primarily in accumbal dynorphin-containing neurons (Greenwood et al., 2011; Herrera et al., 2016; Werme et al., 2002), as well as to increase dendritic spine density and the number of synapses in the striatum, as indicated by heightened postsynaptic density protein 95 and synaptophysin levels (Toy et al., 2014). Running has also been shown to increase the activity of dopamine neurons in the ventral tegmental area, as measured by tyrosine hydroxylase ribonucleic acid (Greenwood et al., 2011; Herrera et al., 2016), and to heighten the concentrations of dopamine and its metabolites in the striatum (Hattori, Naoi, & Nishino, 1994; Meeusen et al., 1997; Sabol, Richards, & Freed, 1990) and medial prefrontal cortex (C. Chen et al., 2016).

Importantly, running is not an all-or-none behavior; some animals spontaneously run more than others (Ekkekakis & Hall, 2005; A. Ferreira et al., 2006; Tarr et al., 2004). Though the mechanisms underlying individual differences in running behavior are not fully understood, studies using selectively bred animals have shown that running performance is tightly linked to nucleus accumbens dopaminergic function (Knab, Bowen, Hamilton, Gulledge, & Lightfoot, 2009; Rhodes, Gammie, & Garland, 2005; Roberts et al., 2013; 2012). Using bitransgenic mice, researchers have demonstrated that inducing DeltaFosB overexpression in striatal dynorphin- or enkephalin-containing neurons can, respectively, increase or decrease running performance (Werme et al., 2002). In addition to the differences in striatal function that are thought to underlie the motivation to run, actually running, and the individual differences in performing this behavior, produces distinct alterations in striatal plasticity and function (Aguiar et al., 2010; Freed & Yamamoto, 1985; Hattori et al., 1994; Rhodes et al., 2005; Wilson & Marsden, 1995). Accordingly, the speed at which an animal runs has been positively

linked to striatal dopamine release (Freed & Yamamoto, 1985) and turnover (Hattori et al., 1994). Voluntarily engaging in more running behavior has also been shown to enhance extracellular dopamine levels in the accumbens following a running session (Wilson & Marsden, 1995). By promoting specific neurochemical changes in the striatum, variability in running performance may thus lead to distinct stimulant-induced behavioral activation. Studies have indeed shown that the locomotor response to the first stimulant injection varies as a function of running performance (Ferreira et al., 2006; Larson & Carroll, 2005). Little is known, however, about the impact individual differences in wheel-running activity can have on stimulant-induced behavioral sensitization.

The present thesis

Here we examine if wheel-running activity, which has been shown to alter the mesocorticolimbic dopamine system in a similar manner as stimulant drugs and stressors, can exacerbate behavioral sensitization to cocaine. Because the running-mediated changes within the mesocorticolimbic dopamine system can vary as a function of running performance, we also examine individual differences in this behavior and its impact on behavioral sensitization. In the first chapter we assess the effects of individual differences in wheel-running activity on cocaine-induced behavioral sensitization. To determine the generalizability of our findings and to better understand the mechanisms underlying the effects of running on behavioral sensitization to cocaine, in the second chapter we examine the effects of wheel-running activity on stress-induced behavioral sensitization to cocaine. Lastly, in the third chapter, we examine whether an established sensitized behavioral response to cocaine can be modulated after the fact by giving animals access to a running wheel, and whether the results vary according to an animal's natural tendency to wheel run.

Collectively, the findings presented here reveal that individual differences in wheel-running activity can regulate drug- and stress-induced behavioral sensitization to cocaine. These behavioral findings provide indirect support for running-mediated metaplastic changes within the mesocorticolimbic dopamine system and highlight the significance of gene-environment interactions in experience-dependent neuroplasticity.

Chapter 1

High levels of wheel running protect against behavioral sensitization to cocaine

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Repeated exposure to stimulant drugs such as cocaine produces enhancement of their locomotor stimulating effects (Post & Rose, 1976). This phenomenon, termed behavioral sensitization, has been studied extensively because it provides a model system for studying the neuronal adaptations that mediate drug-induced changes in behavior. Recent studies have solidified the view that behavioral sensitization results from long-term plastic changes within the neural circuitry activated pharmacologically by drugs, and specifically the mesocorticolimbic dopamine system and its targets in striatum and medial prefrontal cortex (Nestler, 2008; Pascoli et al., 2011; Robinson & Kolb, 2004). Nonetheless, the effects of drugs on behavior cannot be accounted for within purely a pharmacological perspective. Past research has pointed to many individual variables, including gender (M. Hu & Becker, 2003) and response to novelty (Piazza et al., 1989), and experiential variables, including time of day (Arvanitogiannis, Sullivan, & Amir, 2000), perinatal insults (Aguilar-Valles, Flores, & Luheshi, 2010) and conditioning (Yetnikoff & Arvanitogiannis, 2005), that can modulate the behavioral and neural changes that are seen following repeated exposure to stimulant drugs. The goal of the present study was to examine whether chronic physical activity in the form of chronic wheel running would influence behavioral sensitization to cocaine.

Previous research has drawn some interesting parallels between wheel running and drugs. There is evidence that rats lever-press for access to running wheels (Belke & Wagner, 2005) and show conditioned place preferences to environments paired with wheel running (Belke & Wagner, 2005; Greenwood et al., 2011; Lett, Grant, Byrne, & Koh, 2000) just as they do for drugs (Tzschentke, 1998; Wise, 2002). Moreover, long-term experience with both wheel running and drugs produces similar molecular changes in the brain (Greenwood et al., 2011; Nestler, 2008; Werme et al., 2002). Such observations suggest that an interaction might occur between wheel running and drugs. In fact,

wheel running has been found to suppress responding for cocaine on a progressive ratio schedule of reinforcement, and more so in animals that ran the most (Smith, Schmidt, Iordanou, & Mustroph, 2008).

Indeed, there are substantial individual differences in wheel running; some animals run innately more than others. Such differences have been shown to affect several behavioral (Burghardt, Pasumarthi, Wilson, & Fadel, 2006; Ferreira et al., 2006; García-Capdevila, Portell-Cortés, Torras-Garcia, Coll-Andreu, & Costa-Miserachs, 2009), physiological, and neurochemical measures (Waters et al., 2008). Running tempo is tightly linked to dopamine turnover in the striatum (Freed & Yamamoto, 1985; Hattori et al., 1994) and dopamine function is altered in mice bred selectively for high wheel running (Rhodes et al., 2005). Interestingly, locomotor activity in response to an acute amphetamine injection has been shown to vary as a function of phenotypic differences in wheel running (Ferreira et al., 2006). These findings suggest that individual differences in wheel running may play an important role in the interaction between wheel running and the sensitizing behavioral effects of repeated psychostimulant exposure. Inasmuch as the duration of the wheel-running regime determines the total amount of wheel running, duration could also play a role in this interaction.

In the research reported here, we examined whether chronic wheel running could modulate behavioral sensitization to cocaine. We also evaluated whether the effects of wheel running on behavioral sensitization were contingent on individual differences in wheel running and/or the duration of the wheel-running regime.

Seventy-two male Wistar rats (200–250 g) were divided into two cohorts that were housed for 5 and 10 weeks, respectively, in individual cages equipped with running wheels (Nalgene, Rochester, New York). The number of wheel revolutions in each cage was monitored continuously with ClockLab software. Lighting was

maintained on a 12-hr light/12-hr dark cycle (lights on at 8:00 a.m.) and food and water were available ad libitum.[1] Subjects from each cohort were assigned to three groups of 12 animals: low-runner (LWR), high-runner (HWR), and non-runner (NWR). Animals in the first two groups had access to running wheels that were free to revolve. A median split on the average daily wheel running scores prior to behavioral testing (determined regardless of the duration of the wheel running regime) formed the LWR and HWR groups. For the third group of animals (Group NWR), the running wheels were locked, thus preventing running.

Once the 5- or 10-week wheel running regimes were completed, the experiment examining behavioral sensitization began. Locomotor activity was assessed for 30 min at a time in activity chambers[2] fitted with two photocells located along the longitudinal axis of each chamber. One count of locomotor activity was defined as a consecutive interruption of each photocell. On Day 1, all subjects were habituated to the activity chambers. On each of the next 5 days, half of the animals in each group were tested with cocaine (10 mg/kg of cocaine hydrochloride dissolved in 0.9% saline and injected intraperitoneally; Medisca, Quebec, Canada) and the other half with saline.[3] Two weeks later, a final test for sensitization was made when saline and cocaine pre-exposed groups were all tested with a challenge dose of cocaine (5 mg/kg), so selected as to prevent drug-induced stereotypy. Sensitization was measured by the difference between cocaine and saline pre-exposed groups on this last test.

Figure 1 shows the mean locomotor activity counts recorded during the test for sensitization. A 2 (regime duration: 5 weeks or 10 weeks) □ 3 (group: LWR, HWR, or

[1] All experimental procedures took place at the beginning of the light phase.
[2] These were wooden boxes (43.2 × 22.2 × 30.5 cm) with Plexiglass front panels and wire-mesh floors.
[3] Following each of these sessions animals were taken back to their respective home cages.

NWR) × 2 (treatment: cocaine or saline) analysis of variance (ANOVA) revealed a main effect of treatment, $F(1,60) = 38.69$, $p < .001$. This effect was modulated by a two-way interaction between group and treatment, $F(2,60) = 4.85$, $p = .011$. The three-way interaction was not significant and neither was any other interaction or main effect of regime duration. Planned comparisons for the 5-week condition demonstrated a significant effect for treatment in Groups NWR, $t(10) = 3.67$, $p = .004$, $d = 2.12$, and LWR, $t(10) = 2.88$, $p = .016$, $d = 1.66$, indicating behavioral sensitization to cocaine. Similar findings were found for the Groups NWR, $t(10) = 4.50$, $p = .001$, $d = 2.60$, and LWR, $t(10) = 3.77$, $p = .004$, $d = 2.18$, following 10-weeks of wheel running. Crucially, however, planned comparisons demonstrated that in Group HWR the difference in activity levels between cocaine- and saline-treated animals was not significant following either 5 weeks, $t(10) = 1.30$, $p = .224$, $d = .75$, or 10 weeks of wheel running, $t(10) = .21$, $p = .835$, $d = .12$, suggesting that wheel running prevented behavioral sensitization to cocaine in this group.

On the whole, these findings demonstrate that experience with wheel running protects against behavioral sensitization to cocaine but only in animals with a natural tendency to run the most. This outcome occurred regardless of the duration of the wheel running regime: following either 5 or 10 weeks of wheel running, LWRs sensitized to cocaine, whereas HWRs did not. Collapsing the data over the duration of the wheel running regime highlights the effects that the level of wheel running had on cocaine sensitization (see Figure 2). Because after 10 weeks of wheel running the cumulative wheel running of Group HWR ($M = 195.8$ km, $SD = 57.5$) was 2-fold greater than that of Group LWR ($M = 95.4$ km, $SD = 37.4$), had the duration—and hence the overall amount of wheel running—been of importance in the observed pattern of results, we would

have expected LWRs to be as protected against behavioral sensitization after 10 weeks of wheel running as HWRs were after 5 weeks. This was not seen, and it is therefore reasonable to suppose that differences in the neural mechanisms that underlie sensitized responding may be responsible for the contrasting pattern of results in the LWR and HWR groups. Such differences may precede or follow a period of chronic wheel running, which in itself produces long-lasting neuronal adaptations in the same neural substrate as drugs (Greenwood et al., 2011; Nestler, 2008; Werme et al., 2002). What is clear is that future research aimed at uncovering the neurobiological basis of the interaction between wheel running and the enduring effects of drugs should consider the distinction between HWRs and LWRs.

It is well known that individual differences can moderate the behavioral effects of drugs. For example, previous research has demonstrated that individual differences in the response to novelty and in the initial responsiveness to stimulant drugs are important predictors of the potential for behavioral sensitization (Piazza et al., 1989; Sabeti et al., 2003). This raises the question of whether individual differences in wheel running could be secondary to individual differences in the response to novelty or to the first injection of cocaine. The answer is no, as illustrated in Figure 3, which shows that the three groups in the present study did not differ either with respect to the locomotor response to novelty as measured on Day 1 during the test for habituation or with regard to the locomotor response to the first cocaine exposure. Similarly, saline-treated rats that received their first injection of cocaine during the test for sensitization showed similar levels of locomotor activity among groups (see Figure 1). Notably, these results rule out the possibility that the failure to detect differences between saline- and cocaine-treated animals during the test for sensitization in Group HWR is merely a consequence of initial cocaine hypersensitivity in HWRs.

Finally, we must acknowledge that the results of the present study are incompatible with those of recent studies showing that chronic exposure both to wheel running (Greenwood et al., 2011; Werme et al., 2002) and to drugs (Nestler, 2008) induces DeltaFosB in the nucleus accumbens and linking directly overexpression of DeltaFosB in this region to increases in drug sensitization (Kelz et al., 1999). Although we did not examine DeltaFosB expression, there is no a priori reason to doubt that DeltaFosB was expressed in the animals of the present study, especially those exposed to both wheel running and cocaine together. If so, the idea that DeltaFosB is causally linked to sensitization is not easily reconcilable with our finding that high levels of wheel running actually protect against sensitization to the locomotor stimulating effects of cocaine. The dissociation between HWRs and LWRs in terms of behavioral sensitization may prove useful for future studies on its molecular basis.

Figure 1. Mean ± SEM locomotor activity counts expressed by the NWR, LWR and HWR groups on the test for sensitization. Black bars and gray bars represent the cocaine- and saline-treated animals, respectively. * $p < .05$.

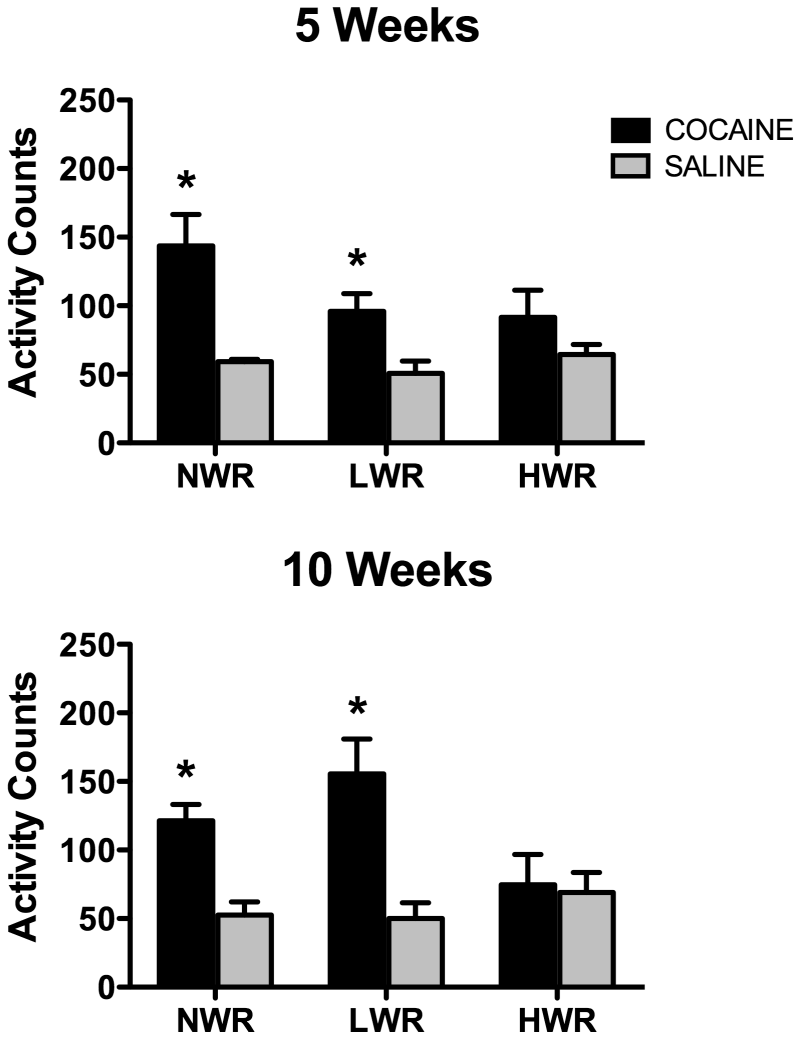

5 Weeks
Activity Counts
250
200
150
100
50
0
COCAINE
SALINE
*
*
NWR
LWR
HWR
10 Weeks
Activity Counts
250
200
150
100
50
0
*
*
NWR
LWR
HWR

Figure 2. Mean ± SEM locomotor activity counts expressed by the NWR, LWR and HWR groups on the test for sensitization after collapsing the data over the duration of the wheel running regime. Black bars and gray bars represent the cocaine- and saline-treated animals, respectively. * $p < .05$.

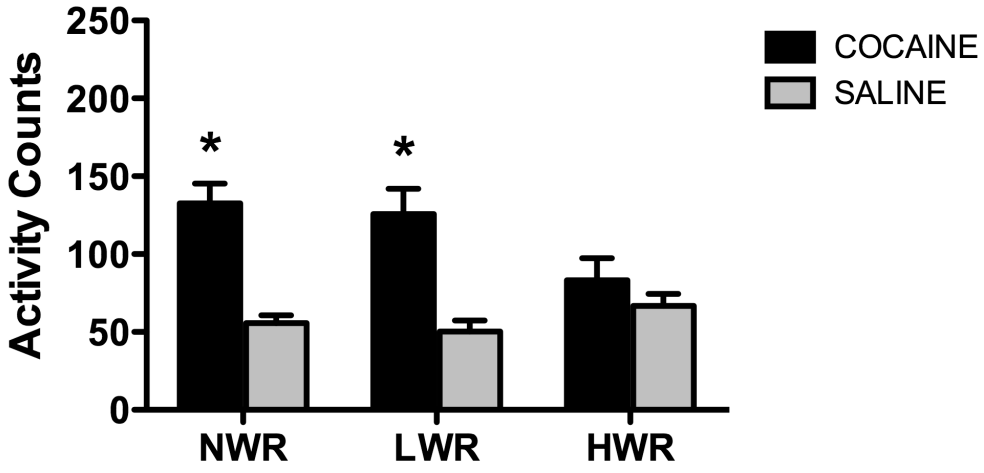
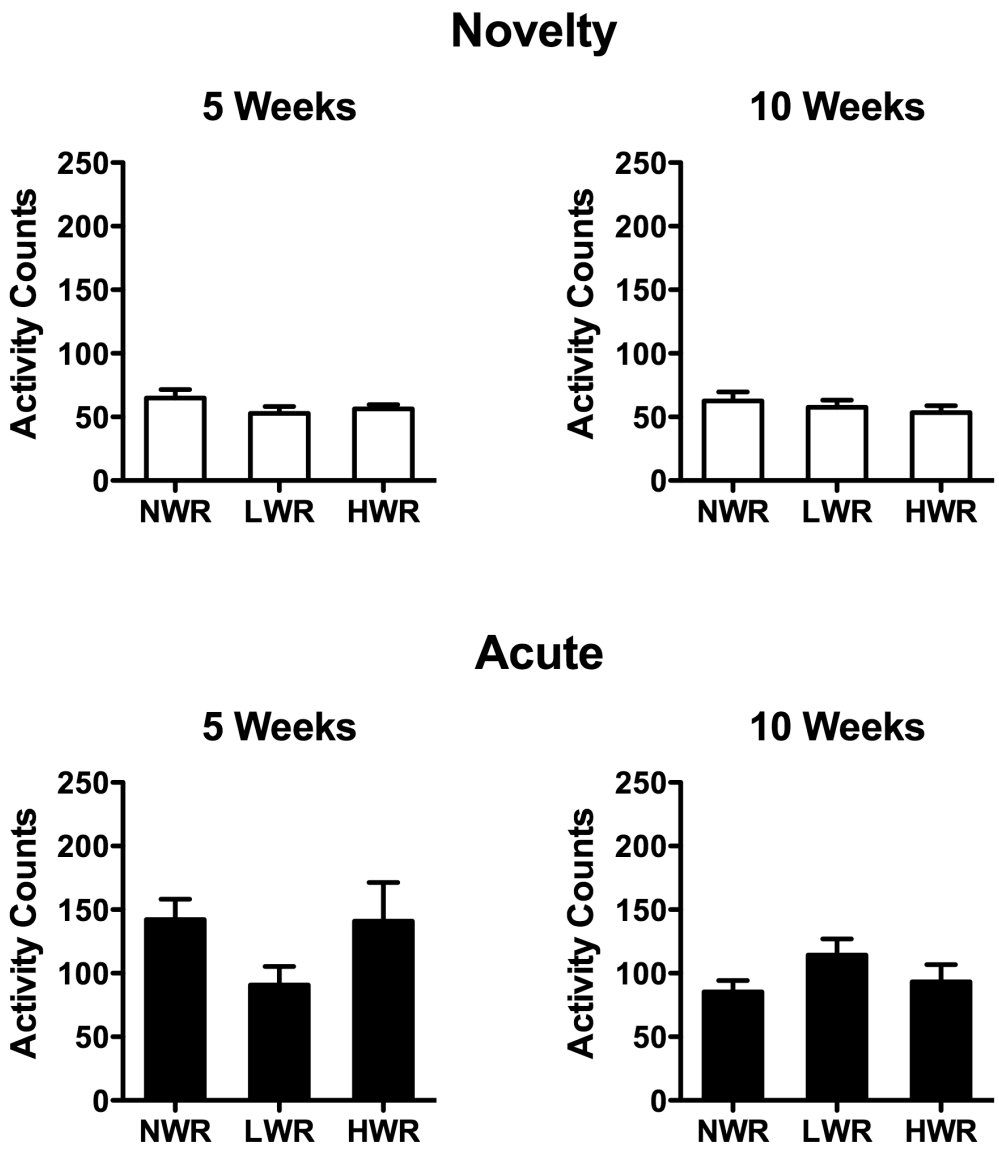

250
200
150
100
50
0
Activity Counts
*
*
NWR
LWR
HWR
COCAINE
SALINE

Figure 3. Mean ± SEM locomotor activity counts expressed by the NWR, LWR and HWR cocaine-treated animals in response to novelty (top) and to the first injection of cocaine (bottom) following 5 or 10 weeks of wheel running.


Novelty
5 Weeks
10 Weeks
Activity Counts
250
200
150
100
50
0
NWR
LWR
HWR
Acute
5 Weeks
10 Weeks
Activity Counts
250
200
150
100
50
0
NWR
LWR
HWR

Chapter 2

Wheel running can protect against stress-induced behavioral sensitization to cocaine

Laura Renteria Diaz, Jessica K Argento, Maxence Bernier, and Andreas Arvanitogiannis*

Despite their different nature and physiological actions, stimulant drugs and stressors share a common denominator: They both increase the synaptic concentration of dopamine in the mesolimbic system and this effect becomes sensitized following their repeated exposure (Kalivas & Duffy, 1989; 1990; Kalivas & Stewart, 1991; Pacchioni, Gioino, Assis, & Cancela, 2002; Sorg, 1992; Sorg & Kalivas, 1991). In addition to the sensitization of dopaminergic responsiveness, repeated exposure to stimulant drugs or stress has been associated with the enhancement of the long lasting behavioral response to a drug challenge injection (Antelman et al., 1980; Herman et al., 1984; Kalivas & Stewart, 1991; Robinson, Angus, & Becker, 1985; Robinson & Becker, 1986). Because this phenomenon, known as behavioral sensitization, may be accompanied by enduring increases in the incentive value of drugs (Robinson & Berridge, 2008; Vezina, 2004), the cellular and molecular mechanisms that underlie it have been the focus of considerable study. Cellular-level studies of synaptic changes that increase excitability of dopamine neurons and molecular-level studies that delineate lasting neuronal adaptations in striatal terminal regions of dopamine neurons have revealed overlapping mechanisms underlying drug- and stress-induced behavioral sensitization (Esparza et al., 2012; Garcia-Keller et al., 2013; Nestler, 2008; Niehaus, Murali, & Kauer, 2010; Perrotti et al., 2004; Saal, Dong, Bonci, & Malenka, 2003).

A notable feature of behavioral sensitization that makes it an excellent model system to study experience dependent plasticity is that sensitized responding can be powerfully regulated by experiential factors (Robinson, Browman, Crombag, & Badiani, 1998; Vezina & Leyton, 2009). Most relevant to the present study, we have shown that, in rats, chronic wheel running can prevent cocaine-induced sensitization to the locomotor activating effects of cocaine (Renteria Diaz, Siontas, Mendoza, & Arvanitogiannis, 2013). Similar results have since been reported in mice (Geuzaine &

Tirelli, 2014; Lespine & Tirelli, 2015). It has yet to be shown, however, whether the protective effects of running extend to behavioral sensitization resulting from repeated exposure to stress.

Demonstrating generalizability would be an important first step toward gaining mechanistic insights into the link between exercise and behavioral sensitization. Accordingly, in the present study we investigated whether a 10-week-long period of wheel running can prevent footshock stress-induced sensitization to the locomotor activating effects of cocaine. As stress-induced behavioral sensitization is contingent on heightened plasma corticosterone levels (Deroche et al., 1995; 1992; Marinelli & Piazza, 2002; Prasad, Ulibarri, & Sorg, 1998; Rougepont et al., 1995), and running has been found to affect this stress hormone (Stranahan, Lee, & Mattson, 2008), we also assessed the impact running has on basal corticosterone levels and on footshock-mediated corticosterone release.

Ninety-six male Wistar rats (200-250 g), purchased from Charles River Farms (St. Constant, QC, Canada), were singly housed in plastic cages (50 × 26.8 × 36.4 cm) equipped with a running wheel (34.5 cm in diameter, Nalgene, Richester, NY). For half the subjects (WR, wheel running group), wheel running was recorded by ClockLab software (Actimetrics, Wilmette, IL, USA) detecting microswitch closures; for the other half (NWR, no wheel running group), wheel running was not possible because the running wheels were blocked with a metal rod. Lighting was maintained on a 12-hr light/dark cycle (lights on at 8:00 am). Food and water were available ad lib. All experimental procedures took place at the beginning of the light phase. This study was approved by the Concordia University Animal Research Ethics Committee.

After a 10-week period of housing in the running wheel-equipped cages, we divided the WR and NWR groups into subgroups according to treatment: half the

animals in each of the WR and NWR groups were randomly assigned to receive footshock (FS condition) and the other half no-footshock (NFS condition). Animals in the FS condition were placed in grid-floor shock boxes (40.6 × 15.9 × 21.3 cm) wired to a shock source and solid-state grid scrambler (Med Associates Inc., Burlington, VT, USA) and were given 30 intermittent and inescapable electric footshocks at an intensity of 0.5 mA within a 10-min session, each day for five days. The distribution of the inter-shock intervals was such that the arrival times of the shocks were random and approximated a Poisson process, subject to the constraints that the minimum interval was 1 s and the total number of shocks in the session was 30. Animals in the NFS condition were also placed in the shock boxes but did not receive footshocks. At the end of each footshock phase animals were taken back to their respective home cages.

During the footshock phase plasma corticosterone levels were measured in a subset of 24 animals representing all four subgroups. On the first and last days of the footshock phase, immediately before and after the 10-min sessions, blood was collected from the animals tail vein, centrifuged at 10000 rpm for 5 min, and the extracted plasma was stored at -80 °C. Corticosterone levels were measured using a commercially available Enzyme Linked ImmunoSorbent Assay (Assay Designs, Ann Arbor, MI, USA). It is important to note that the procedure used to collect plasma corticosterone, namely tail bleeding, is a stressor (e.g., (Houshyar, Manalo, & Dallman, 2004)). These animals were therefore excluded from the remainder of the study.

Two weeks after the last footshock session, we injected the remaining 72 animals with cocaine (5 or 10 mg/kg ip; Medisca, St-Laurent, QC, Canada) or saline. Forward locomotion in response to the challenge injection was measured for 40 min in activity boxes (43.2 □ 22.2 □ 30.5 cm) equipped with two evenly spaced photocell beams that cut

across the width of the box. An activity count was defined as a consecutive interruption of each photocell beam. Stress-induced behavioral sensitization to cocaine was reached when stressed animals showed a statistically significant increase in locomotor activation in response to a cocaine challenge, compared to their non-stressed controls.

Figure 1 shows the mean locomotor activity counts in response to an injection of saline (**S**) or cocaine, 5 (**C5**) or 10 (**C10**) mg/kg, in stressed and non-stressed animals from the NWR and WR groups. As can be seen, the rats with no wheel-running access showed stress-induced behavioral sensitization in response to both doses of the cocaine challenge. In contrast, stress-exposed animals with access to a running wheel did not show behavioral sensitization to either dose of the drug challenge. In fact, in this group the stressed and non-stressed running animals showed similar locomotor activation in response to cocaine, irrespective of the drug dose. Using a 3 (challenge injection: S, C5 or C10) □ 2 (treatment: FS or NFS) between-subjects analysis of variance separately for each group (NWR and WR), we found a statistically significant main effect of Challenge injection, $F(2,30) = 54.37$, $p < .001$, and Treatment, $F(1,30) = 9.34$, $p = .005$, for the NWR group, but only a statistically significant main effect of Challenge injection, $F(2,30) = 22.51$, $p < .001$, for the WR group. We further examined differences between the stressed animals and their non-stressed counterparts within the WR and NWR groups using planned independent-samples *t* tests. Differences were considered statistically significant when $p < .05$. The 95% confidence intervals for the means were reported and effect sizes were estimated using *Hedges g**. Stressed rats with no access to a running wheel did not behaviorally differ from their non-stressed controls in response to a saline injection, $t(10)=0.71$, $p= .495$, *95% CI* [-14.30, 27.63], *Hedges g**=0.38, but did show a statistically significant increase in locomotor activity following 5 and 10 mg/kg of

cocaine (**C5**: $t(10)=2.41$, $p=.037$, *95% CI* [1.71, 42.96], *Hedges g**=1.29; **C10**: $t(10)=2.29$, $p=.045$, *95% CI* [1.56, 111.78], *Hedges g**=1.22), thereby exhibiting stress-induced behavioral sensitization to cocaine. Supporting these conclusions is the three-fold difference in the magnitude of the effect size in the saline- versus cocaine-challenged rats. By contrast, stressed and non-stressed running animals showed similar activity levels in response to the saline and cocaine challenge (**S**: $t(10)=0.92$, $p=.379$, *95% CI* [-7.10, 17.10], *Hedges g**=0.49; **C5**: $t(10)=0.50$, $p=.626$, *95% CI* [-24.03, 38.03], *Hedges g**=0.27; **C10**: $t(10)=1.16$, $p=.274$, *95% CI* [-31.80, 100.47], *Hedges g**=0.62), clearly indicating that behavioral sensitization to the drug did not occur in this group. The measures of effect size were similar whether animals were challenged with saline or cocaine thereby further attesting to the fact that stress-induced behavioral sensitization to cocaine was prevented in animals with access to a running wheel.

Previously, we demonstrated that the protective effects of running on cocaine-induced behavioral sensitization are only applicable for those animals that run the most (Renteria Diaz et al., 2013). In the present study, because of the restricted sample size used in each condition, we examined the association between magnitude of wheel running and the behavioral response to the cocaine challenge using separate Pearson *r* tests for stressed and non-stressed animals. Magnitude of wheel running was defined as the average daily distance covered by each rat during the 10-week running period. Because the extent of the behavioral response to cocaine is tightly linked to the dose of the drug this variable was determined by standardizing the activity counts (convert into *z*-scores) of rats injected with 5 or 10 mg/kg of cocaine, and combining them. The results shown in Figure 2 reveal that there was a statistically significant inverse correlation between magnitude of wheel running and behavioral response to the cocaine challenge ($r=-.80$, $p=.002$) for animals in the FS condition, but not for animals in the NFS condition

(r=-.31, p=.322). As an added control, we then examined the correlation coefficient between magnitude of wheel running and the standardized locomotor response to the saline challenge injection. There was no statistically significant correlation between magnitude of wheel running and saline-induced locomotor activation for animals in FS (r=-.03, p=.951) or NFS (r=-.33, p=.528) conditions (see Figure 2). Thus, a significant inverse correlation between magnitude of wheel running and behavioral response to the challenge injection was only found in stress-exposed rats challenged with cocaine.

So why didn't the stress-exposed animals with running access show behavioral sensitization to cocaine? Given that we have previously shown that running can protect against cocaine-induced behavioral sensitization, perhaps running protects against stress-induced behavioral sensitization via neurobiological substrates common to both stimulant drugs and stress. Alternatively, given the well-documented role of corticosterone in stress-induced behavioral sensitization (Deroche et al., 1995; 1992; Marinelli & Piazza, 2002; Prasad et al., 1998; Rougepont et al., 1995), and the fact that exercise has been shown to modulate this stress hormone (Campbell, Rakhshani, Fediuc, Bruni, & Riddell, 2009; Campeau et al., 2010; Droste, Chandramohan, Hill, Linthorst, & Reul, 2007; Fediuc, Campbell, & Riddell, 2006), the protection against stress-induced behavioral sensitization observed in running animals may stem from running-mediated alterations in the corticosterone response to stress. As can be seen in Figure 3, we found that wheel running did not blunt basal corticosterone concentrations nor footshock-mediated corticosterone secretion; thereby challenging the assumption that the buffering effects of wheel running on stress-induced behavioral sensitization could be due to changes in plasma corticosterone levels. Using a three-way analyses of variance, with one within-subjects factor (time: day 1 or day 5) and two between-subjects factors (group: WR or NWR; treatment: FS and NFS), we first analyzed the basal levels of

corticosterone. We found that only the main effect of Time was significant, $F(1,20)=6.95$, $p=.016$. That is, basal levels of corticosterone were higher on day 1 than on day 5. No statistically significant differences emerged in regards to Treatment, Group, nor any of the interactions. We then analyzed the stress-induced corticosterone response, computed by subtracting the amount of corticosterone present in plasma before a footshock session from the amount present following a footshock session. Using a two-way analyses of variance, with one within-subjects factor (time: day 1 or day 5) and one between-subjects factor (group: WR or NWR) we found a significant main effect of Time, $F(1,10) = 15.54$, $p = .003$, but no significant main effect of Group, nor Group × Time interaction. As illustrated in Figure 3 the corticosterone response to footshock stress did not differ as a function of wheel-running access and similarly decreased from day 1 to day 5 in both groups.

In the present study, we found that chronic wheel running buffered sensitization to cocaine caused by repeated exposure to footshock stress. This result was further supported by a correlation between average daily wheel running and sensitized responding to cocaine; the more an animal ran each day, the less it responded to a cocaine challenge following repeated exposure to footshock stress. These findings are consistent with our previous report that wheel running protects against the behavioral sensitizing effects of repeated cocaine exposure, but only in animals with a natural tendency to engage in high levels of running (Renteria Diaz et al., 2013).

Had the results from the present study been incongruent with our previous findings the modulation of sensitization by wheel running could not have involved the neurobiological substrates common to both stimulant drugs and stress. This was not the case. Instead, taken together the two studies suggest that the link between wheel

running and behavioral sensitization may involve actions on the shared neuronal and molecular substrates responsible for stimulant-and stress-induced behavioral sensitization. For example, recent research has identified ΔFosB as one of the key elements that underlie both drug- and stress-induced sensitization (Nestler, 2008; Perrotti et al., 2004). It would be interesting to examine whether the effects of wheel running on behavioral sensitization involve the modulation of ΔFosB expression and how this might be achieved given that wheel running causes rather similar effects on ΔFosB as found for stimulant drugs and stress (Greenwood et al., 2011; Herrera et al., 2016; Werme et al., 2002).

Despite the fact that running can block both cocaine- and stress-induced behavioral sensitization there still remains the possibility that running affects these phenomena via distinct mechanisms. A case in point being the stress hormone corticosterone, because of its critical role in stress-induced behavioral sensitization, but not cocaine-induced sensitization (Marinelli & Piazza, 2002; Prasad, Sorg, Ulibarri, & Kalivas, 1995; Prasad, Ulibarri, Kalivas, & Sorg, 1996; Prasad et al., 1998), and the fact that running has been shown to regulate it (Stranahan et al., 2008). In the present study we assessed this possibility and found that chronic wheel running had no effect on either basal corticosterone concentrations or on corticosterone reactivity in response to footshock stress. Other studies have also shown that although chronic wheel running may attenuate the corticosterone response to mild stressors, such as exposure to a novel environmental context, it fails to do so in the case of more intense stressors, including footshock and restraint stress (Campbell et al., 2009; Campeau et al., 2010; Droste et al., 2007; Fediuc et al., 2006). Though it is unlikely that running blocked stress-induced behavioral sensitization by dampening the corticosterone response to footshock stress, it

could be that running altered specific corticosterone binding sites, namely glucocorticoid receptors located on midbrain dopamine neurons, which are believed to be involved in stress-induced sensitization of the mesolimbic dopamine system (Barrot et al., 2000; Daftary, Panksepp, Dong, & Saal, 2009; de Jong & de Kloet, 2004; Deroche et al., 1995; Hensleigh & Pritchard, 2013; Marinelli & Piazza, 2002; Saal et al., 2003).

Although our results do not ascertain that wheel running affects cocaine- and stress-induced behavioral sensitization via a common substrate, they do raise the intriguing possibility that chronic wheel running interferes with the long-term processes responsible for sensitization. Future studies will be required to determine the mechanisms for this regulation.

Figure 1. Mean ± SEM locomotor activity counts expressed by the NWR and WR groups in response to a challenge injection of saline (S) or cocaine (C5 or C10). Filled and open symbols represent the footshock and no-footshock conditions, respectively. * $p < .05$ different from no-footshock control.

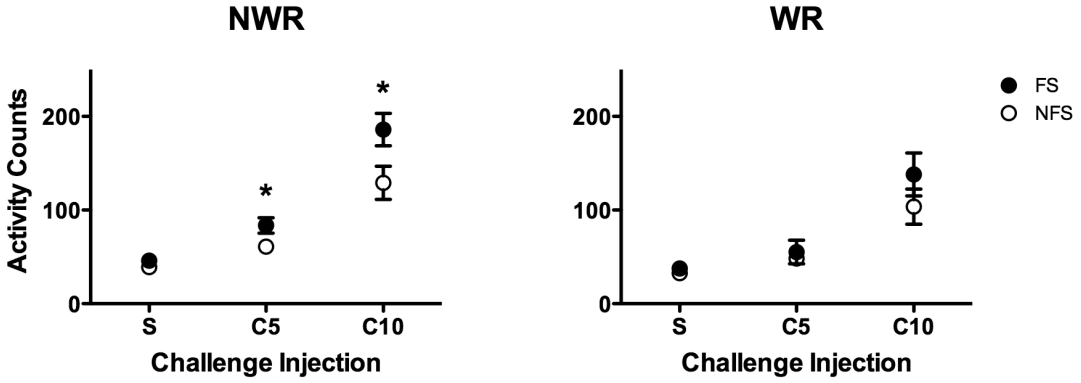

NWR
WR
Activity Counts
200
100
0
S
C5
C10
Challenge Injection
*
*
FS
NFS

Figure 2. Scatter plots depicting the correlation between average daily wheel running distance and standardized scores of locomotor activity counts in response to cocaine or saline. Filled and open symbols represent the footshock and no-footshock conditions, respectively. A statistically significant correlation between average daily wheel running and locomotor activation was only found in footshock-stress exposed animals given a challenge injection of cocaine.

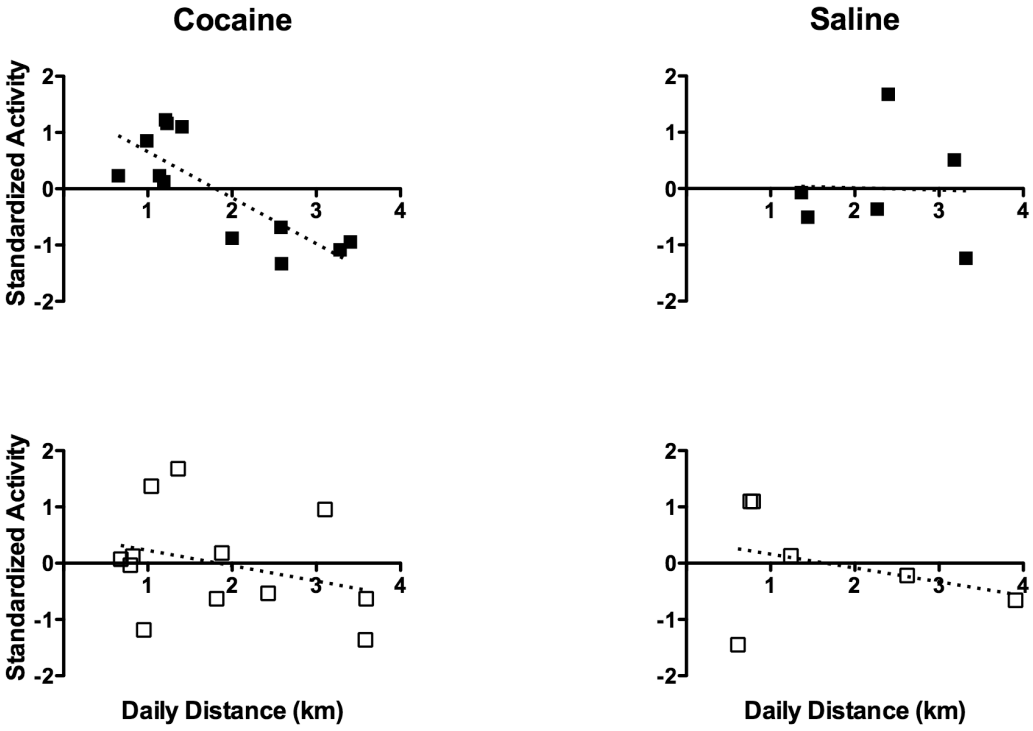
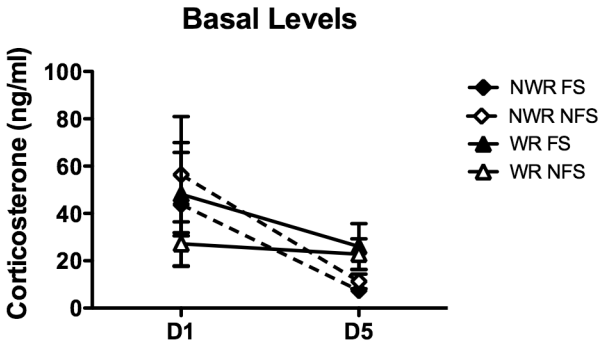
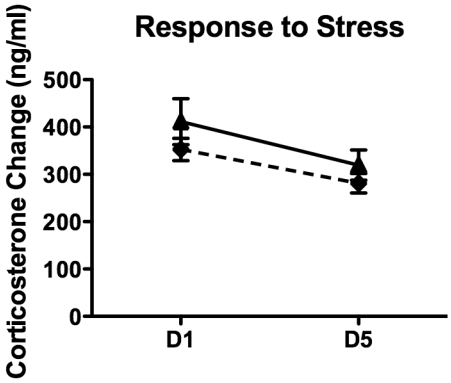

Cocaine
Saline
Standardized Activity
Standardized Activity
Daily Distance (km)
Daily Distance (km)
2
1
0
-1
-2
1
2
3
4

Figure 3. Mean ± SEM basal corticosterone levels (top) and stress-induced changes in corticosterone (bottom) of NWR and WR groups on the first and last day of the stress phase. Filled and open symbols represent the footshock and no-footshock conditions, respectively. No statistically significant differences in basal or stress-induced corticosterone levels were found between the different treatment groups.


Basal Levels
Corticosterone (ng/ml)
100
80
60
40
20
0
D1
D5
NWR FS
NWR NFS
WR FS
WR NFS


Response to Stress
Corticosterone Change (ng/ml)
500
400
300
200
100
0
D1
D5

Chapter 3

Reversal of behavioral sensitization to cocaine in animals with a natural tendency to run

Laura Renteria Diaz, Lalou Tisseyre, Daniel C Palacios, and Andreas Arvanitogiannis*

Repeated exposure to psychostimulant drugs produces long-term changes in the brain and behavior. Animals previously treated with cocaine, for example, exhibit an enhanced behavioral response to a subsequent drug-challenge injection (Post & Rose, 1976). This phenomenon referred to as behavioral sensitization is the hallmark of specific neuroplastic changes in the mesocorticolimbic dopamine system - a pathway involving neurons whose cell bodies reside in the ventral tegmental area and which send their projections to the nucleus accumbens and prefrontal cortex (Nestler, 2008; Pascoli et al., 2011; Robinson & Kolb, 2004). Though sensitization to drugs results from repeated drug exposure, various non-pharmacological agents (Anagnostaras & Robinson, 1996; Arvanitogiannis et al., 2000; Badiani, Anagnostaras, & Robinson, 1995; Badiani, Camp, & Robinson, 1997; Crombag & Robinson, 2004; Robinson et al., 1998; Vezina & Leyton, 2009; Yetnikoff & Arvanitogiannis, 2005) have been found to impact this process.

Voluntary wheel-running activity, an animal model of exercise, which is known to be both rewarding and reinforcing (Belke & Wagner, 2005; Iversen, 1993; Lett et al., 2000), and to modulate the same brain regions as stimulant drugs (Greenwood et al., 2011; Herrera et al., 2016; Meeusen et al., 1997; Werme et al., 2002), has been shown to protect against cocaine- (Geuzaine & Tirelli, 2014; Lespine & Tirelli, 2015; Renteria Diaz et al., 2013) and stress-induced behavioral sensitization (Renteria Diaz, Argento, Bernier, & Arvanitogiannis, Manuscript in preparation). Importantly, we have demonstrated that the protective effects of running depend on an animal's natural propensity to run. Only rats that voluntarily engage in high levels of wheel-running activity are protected against cocaine-induced behavioral sensitization (Renteria Diaz et al., 2013).

To date, the effects of running on behavioral sensitization have only been studied when wheel-running access is given prior to drug exposure. It remains unknown,

however, whether engaging in wheel-running activity *after* repeated drug treatment – that is, after a sensitized behavioral response has already been established – induces similar protective actions. Accordingly, in the present study we examined if wheel running can be used therapeutically to reverse behavioral sensitization to cocaine and whether the outcome differed as a function of running performance.

Seventy-two adult male Wistar rats (200-250g) from the Charles River breeding farms (St-Constant) were used in this study. All subjects had access to standard rat chow and water ad libitum throughout the course of the experiment, and were housed in a 12-h light/12-h dark cycle (lights on at 08:00 a.m.). Experiments took place at the beginning of the light phase. Experimental procedures were approved by the Animal Care Committee of Concordia University, and followed the guidelines of the Canadian Council on Animal Care.

Upon arrival, rats were individually housed in clear plexiglass shoebox cages (43.2 × 20.3 × 21.6 cm) with woodchip lining the floor. Five days later all animals, but one, who unexpectedly died, were transported from their home cages to locomotor activity chambers (43.2 × 22.2 × 30.5 cm) equipped with two infrared photocells evenly spaced along the longitudinal axis of the chamber. One count of locomotor activity was defined as a consecutive interruption of each photocell. On the first day, each animal's basal behavioral response to this novel environment was measured for 30 min. Rats were then transported back to their home cages. The following day, animals were initially placed in the locomotor chambers for 30 minutes in order for them to habituate to the environment. Half the animals were then treated with cocaine (10 mg/kg of cocaine hydrochloride dissolved in 0.9% saline and injected intraperitoneally; Medisca, Quebec, Canada) and the other half with saline (1.0 ml/kg), and left in the locomotor

activity chambers for an additional 30 minutes during which time locomotor activity was recorded. Rats were subsequently returned to their shoebox cages until the next day. Following five consecutive days of treatment rats were left undisturbed in their home cages until the first-test session, one week later.

At the beginning of the first-test session, subjects were placed in the locomotor activity chambers for 30 minutes of habituation. All of the rats were then injected with 5 mg/kg of cocaine, and placed back into the locomotor chambers for an additional 30 minutes during which time locomotor activity was recorded. Following this first-test session animals were individually housed in new plastic cages (50 × 26.8 × 36.4 cm) equipped with a running wheel (34.5 cm in diameter, Nalgene, Richester, NY). Here 48 rats (24 saline- and 24 cocaine-treated), which would later be categorized into the low-wheel running (LWR) or high-wheel running (HWR) groups, had unrestricted access to running wheels, while 23 rats (11 saline- and 12 cocaine-treated) did not, the no-wheel running (NWR) group, because their wheels were locked with a metal rod. Activity data of animals with access to a running wheel were transmitted from the wheels to the computer via a magnetic microswitch, and recorded continuously with ClockLab software. Five-weeks later animals were taken back to the locomotor activity chambers for the second-cocaine challenge where they received the exact same challenge injection as during the first-test session. At this point running animals were categorized as low or high runners by calculating the cutoffs delimiting the bottom and top 30^{th} percentiles of the average daily wheel running scores amongst the saline- and cocaine-treated rats separately. Behavioral sensitization to cocaine was reached during a test session when drug-treated animals, compared to their saline-treated controls, showed a statistically significant increase in locomotor activation in response to the cocaine challenge. Three cocaine-treated animals, one from each group (NWR, LWR and HWR), were excluded

from any statistical analyses, as they did not show an increase in locomotor activation on the first- nor second-test sessions.

Figure 1 illustrates the locomotor activity of cocaine- and saline-treated animals in response to the first- and second-drug challenge separately for each group. As can be seen, on the first-test session, all groups exhibited behavioral sensitization to cocaine. Five-weeks later, on the second-test session, the LWR and NWR groups still expressed behavioral sensitization to cocaine, but remarkably the HWR group did not. Using separate 2 □ 2 mixed-factor analyses of variance for each group, with Test Session (**T1**: first-test session; **T2**: second-test session) as the within-subject factor and Treatment (cocaine and saline) as the between-subjects factor, we found a significant main effect of Treatment for the NWRs, $F(1, 20) = 14.64$, $p = .001$, and LWRs, $F(1, 12) = 11.46$, $p = .005$. No other statistically significant results were found for these two groups. In contrast, a mixed-factor analysis of variance revealed a statistically significant main effect of Treatment, $F(1, 12) = 4.82$, $p = .049$, as well as a Test Session □ Treatment interaction, $F(1, 12) = 5.19$, $p = .042$, in the HWR group. We further examined differences between the cocaine- and saline-treated animals within each group using planned independent-samples *t* tests. Differences were considered statistically significant when $p < .05$. The 95% confidence intervals for the means were reported and effect sizes were estimated using *Hedges g**. Behavioral sensitization to cocaine was exhibited on both test-sessions by the NWR (**T1**: $t(20) = 3.75$, $p = .001$, *95% CI* [22.41, 78.50], *Hedges g**=1.54; **T2**: $t(20) = 2.59$, $p = .018$, *95% CI* [6.84, 63.52], *Hedges g**=1.06) and LWR (**T1**: $t(12) = 2.99$, $p = .011$, *95% CI* [16.83, 107.17], *Hedges g**=1.50; **T2**: $t(12) = 2.56$, $p = .025$, *95% CI* [7.06, 88.08], *Hedges g**=1.28) groups. Though the HWR group exhibited behavioral sensitization in response to the first-cocaine challenge, $t(12) = 2.93$, $p = .013$, *95% CI* [13.53, 92.19], *Hedges*

g^*=1.47, they did not in response to the second drug challenge injection, $t(12) = 0.48$, $p = .641$, *95% CI* [-26.94,42.08], *Hedges* g^*=0.24. That is, the initial sensitized behavioral response to cocaine of the HWR group was reversed following wheel-running availability. The six-fold difference in the magnitude of the effect size between T1 and T2 further supports this conclusion.

Given that the measure of behavioral sensitization is highly dependent on the association between the saline- and cocaine-treated animals, we wanted to assess whether animals in distinct treatment conditions were properly matched in regards to wheel-running activity and body weight. As can be seen in Figure 2, similar patterns of running behavior were observed in cocaine- and saline-treated animals from both running groups. Irrespective of treatment condition, the LWR group exhibited a slight increase in running activity at the beginning of the running regime, while the HWR group exhibited a steady increase in running behavior throughout. Using separate mixed-factor analyses of variance for the LWR and HWR groups, with Day (days 1 to 35) as the within-subject factor and Treatment (cocaine and saline) as the between-subjects factor, we found a statistically significant main effect of Day, $F(34, 408) = 8.66$, $p < .001$, and Day □ Treatment interaction, $F(34, 408) = 1.67$, $p = .012$, for the LWR group, and a statistically significant main effect of Day, $F(34, 408) = 15.40$, $p < .001$, for the HWR group. There was, however, no significant main effect of Treatment for either LWR or HWR groups. With regard to body weight, in all groups, running or not, rats gained weight from the first- to the second-test session, irrespective of treatment condition (Figure 3). Separate 2 □ 2 mixed-factor analyses of variance with Test Session (**T1**: first-test session; **T2**: second-test session) as the within-subject factor and Treatment (cocaine and saline) as the between-subjects factor, revealed a statistically significant main effect

of Test Session for all groups (NWR: $F(1, 20) = 570.63$, $p < .001$; LWR: $F(1, 12) = 494.78$, $p < .001$; HWR: $F(1, 12) = 201.44$, $p < .001$), but no statistically significant main effect of Treatment or Test Session × Treatment interaction.

Because an animal's locomotor response to a novel environment (Piazza et al., 1989) or to the first cocaine injection (Sabeti et al., 2003) can be used to predict the propensity for behavioral sensitization to stimulant drugs, we next examined the behavioral response to novelty and to the treatment phase separately for each group. As can be seen in Figure 4, all rats showed similar baseline locomotor activation in response to novelty, irrespective of their subsequent treatment conditions. Not surprisingly, once the treatment phase began locomotor differences between the cocaine- and saline-treated animals started to emerge in all groups. Separate 6 × 2 mixed-factor analysis of variance with Session (baseline: B; treatment days: D1, D2, D3, D4, D5) as the within-subject factor and Treatment (cocaine and saline) as the between-subjects factor revealed a statistically significant main effect of Treatment (NWR: $F(1, 20) = 91.07$, $p < .001$; LWR: $F(1, 12) = 14.57$, $p = .002$; HWR: $F(1, 12) = 45.96$, $p < .001$) and Session × Treatment interaction (NWR: $F(2.94, 58.81) = 10.13$, $p < .001$; LWR: $F(2.45, 29.39) = 12.70$, $p < .001$; HWR: $F(2.69, 32.31) = 6.47$, $p = .002$) for all groups. A statistically significant main effect of Session, $F(2.45, 29.39) = 6.34$, $p = .003$, was also found for the LWR group. Mauchly's test indicated that the assumption of sphericity had been violated in all three analyses (NWR: $X^2(14) = 43.11$; LWR: $X^2(14) = 46.74$; HWR: $X^2(14) = 41.75$; $p < .001$), the degrees of freedom were therefore corrected using Greenhouse-Geisser estimates of sphericity (NWR: $\varepsilon = .59$; LWR: $\varepsilon = .49$; HWR: $\varepsilon = .54$). Significant Session × Treatment interactions were further analyzed separately for each group using independent-sample *t*-tests with Bonferroni adjusted alpha levels of .008 to take into account the problem of multiple

unplanned comparisons (.05/6). For all groups, we found that rats' locomotor response to a novel environment did not differ as a function of future treatment condition (NWR: $t(20) = 0.28$, $p = .782$; LWR: $t(12) = -1.37$, $p = .197$; HWR: $t(12) = 0.45$, $p = .66$). In response to the first treatment injection the NWR, $t(20) = 5.07$, $p < .001$, and HWR, $t(12) = 3.14$, $p = .008$, cocaine-treated animals exhibited statistically significant enhanced locomotor activation compared to their saline controls, while the LWR did not, $t(12) = 1.97$, $p = .073$. Similar results were found in response to the second treatment injection (NWR: $t(20) = 5.61$, $p < .001$; HWR: $t(12) = 3.92$, $p = .002$; LWR: $t(12) = 2.39$, $p = .034$). It was only in response to the third treatment injection that the cocaine-treated rats from all groups showed a statistically significant increase in locomotor activation compared to their saline-treated controls (NWR: $t(20) = 5.68$, $p < .001$; HWR: $t(12) = 3.88$, $p = .002$; LWR: $t(12) = 3.71$, $p = .003$). Similar results were found on the fourth (NWR: $t(20) = 6.86$, $p < .001$; HWR: $t(12) = 4.30$, $p = .001$; LWR: $t(12) = 3.91$, $p = .002$) and last day (NWR: $t(20) = 6.70$, $p < .001$; HWR: $t(12) = 8.23$, $p < .001$; LWR: $t(12) = 4.99$, $p < .001$) of the treatment phase (see Figure 4). Despite distinct locomotor activation during the treatment phase, the magnitude of the sensitized response during the first-test session was similar across groups as emphasized by the measures of effect size.

To determine whether running performance, above and beyond the other variables, could be used to predict the behavioral response to the second-cocaine challenge, we next conducted a hierarchical multiple regression. We used two models to predict the cocaine-treated running rats' behavioral response to cocaine on the second-test session (T2). In the first model we considered the following predictors: locomotor response to novelty (B), locomotor response to the first day of drug treatment (D1), locomotor response on the first-test session (T1) and body weight on the day of the second-test session (W T2). In the second model we added running performance

(Running) as a predictor. All cocaine-treated running animals, as opposed to the top and bottom 30th percentiles of runners, were used in this statistical analysis, as various predictor variables were included in the models. Both Model 1 (B, D1, T1, W T2), $F(4, 17) = 4.64$, $p = .01$, and Model 2 (B, D1, T1, W T2, Running), $F(5, 16) = 5.77$, $p = .003$, contributed significantly to the regression model. The first Model accounted for 52% of the variation in T2, while introducing the Running variable explained an additional 12% of the variation in T2 and this change in R^2 was statistically significant, $F(1, 16) = 5.44$, $p = .033$. What is more, though in the first model D1 was the only statistically significant predictor of T2, $t(17) = 2.23$, $p = .039$, in the second model, in which the variable Running was added, D1 no longer made a statistically significant contribution to the prediction of T2, $t(16) = 2.10$, $p = .052$. Interestingly, at this point only the variable Running made a statistically significant contribution in predicting T2, $t(16) = -2.33$, $p = .033$ (see Table 1). Clearly, the contribution of running performance in predicting the locomotor response to the second-cocaine challenge is greater than the contribution made by the other predictors.

The results from the present study reveal that chronic wheel running can be used to reverse an already established behavioral sensitized response to cocaine. What is more, as in our previous study prolonged access to a running wheel lead to distinct outcomes depending on a rat's wheel-running behavior. That is, whereas the LWR group still expressed a sensitized behavioral response to cocaine after running, the HWR group did not. The present findings also confirm that the protection against behavioral sensitization observed in HWRs follows, rather than precedes, the actual running behavior, as the HWR group did exhibit behavioral sensitization to cocaine prior to running, but failed to do so after. This finding further confirms that the effect of

wheel running on behavioral sensitization to cocaine is tightly linked to individual differences in running performance.

In a previous study we argued that the impact an animal's propensity to wheel run has on the magnitude of behavioral sensitization is not simply a derivative of previously studied individual differences (e.g. locomotor response to novelty or to the first cocaine injection (Piazza et al., 1989; Sabeti et al., 2003)). Our present findings further support this hypothesis. Indeed, all groups showed behavioral sensitization in response to the first-cocaine challenge (Figure 1) despite the fact that the magnitude of the locomotor response to the first-treatment injection varied across groups (Figure 4). Furthermore, we found that individual differences in running performance, not in ambulatory response to novelty or to the first-cocaine injection, could predict an animal's behavioral response to the second-drug challenge. These findings support the uniqueness of our model and highlight the importance of considering individual differences in running when studying the therapeutic effects of this behavior.

Though various research groups have previously found that non-pharmacological agents can be used to protect against behavioral sensitization to stimulant drugs, the present study is one of the few in which a non-pharmacological agent is used *after* a sensitized behavioral response has already been established (Anagnostaras & Robinson, 1996; Solinas, Chauvet, Thiriet, Rawas, & Jaber, 2008). Similar to our findings, Solinas et al. (2008) demonstrated that subjecting sensitized animals to an enriched environment reverses behavioral sensitization to cocaine. Interestingly, animals housed in enriched environments show reduced levels of DeltaFosB in the striatum following repeated cocaine exposure (Solinas, Thiriet, Rawas, Lardeux, & Jaber, 2009), a transcription factor induced by various drugs of abuse (Perrotti et al., 2008) and believed to be involved in the sensitization process (Nestler,

2008). Because environmental enrichment typically includes access to a running wheel, perhaps the therapeutic effects of wheel running observed in the present study reflect a running-mediated reduction of striatal DeltaFosB levels in animals treated with cocaine. This possibility does not seem likely, however, in light of the individual differences observed in the present study. That is, if wheel running like environmental enrichment blunts cocaine-induced DeltaFosB levels in the striatum, and that this transcription factor is indeed involved in behavioral sensitization, then both the LWR and HWR groups should have failed to exhibit behavioral sensitization to cocaine on the second-test session. Yet, this was not the case.

So what are the mechanisms regulating the reversal of behavioral sensitization in animals that engage in high levels of wheel-running activity? As behavioral sensitization results from drug-mediated long-lasting neuroplastic changes within the mesocorticolimbic system, reversing this process in HWRs must involve reversing these drug-mediated plastic changes. Recent studies using optogenetic manipulations have found that reversing cocaine-induced synaptic potentiation, a process known as depotentiation, in the nucleus accumbens reverses behavioral sensitization to cocaine (Pascoli et al., 2011). Regulation of accumbal synaptic plasticity is thought to involve activation of the extracellular signal-regulated kinase (ERK) cascade via D1 dopamine receptor and NMDA glutamate receptor combined stimulation (Girault, Valjent, Caboche, & Hervé, 2007; Pascoli et al., 2011). Various drugs of abuse have been shown to activate this pathway in the nucleus accumbens and blocking it has been shown to block behavioral sensitization to stimulant drugs (S. Kim, Shin, Yoon, & Kim, 2011; Valjent, Corvol, Trzaskos, Girault, & Hervé, 2006; Valjent et al., 2005). Interestingly, high-intensity running has been shown to reduce ERK phosphorylation in the striatum (Aguiar et al., 2010). It is therefore reasonable to suggest that in the present study

engaging in high levels of wheel-running activity lead to a reduction in striatal ERK phosphorylation thereby resulting in synaptic depotentiation and ultimately in the reversal of behavioral sensitization. Future studies are needed to examine this intriguing possibility.

Figure 1. Mean ± SEM locomotor activity counts expressed by the NWR, LWR and HWR groups in response to the first- (T1) and second-test (T2) for sensitization. Black and gray symbols represent the cocaine- and saline-treated animals, respectively. * $p < .05$ different from saline-treated control.

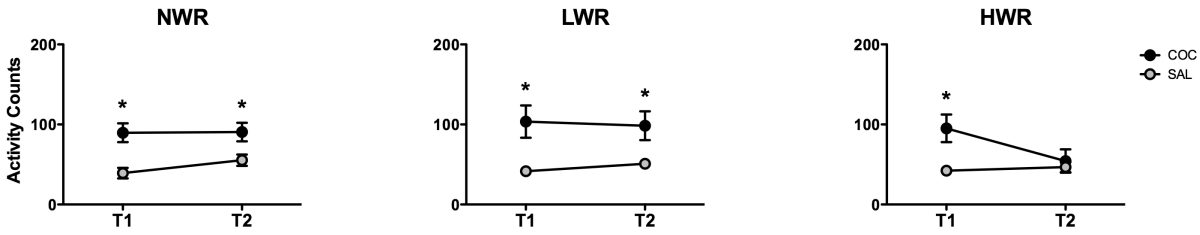

NWR
LWR
HWR
Activity Counts
200
100
0
T1
T2
*
COC
SAL

Figure 2. Average daily wheel-running activity of LWR (cocaine: $n = 7$; saline: $n = 7$) and HWR (cocaine: $n = 7$; saline: $n = 7$) groups during the 5-week running regime. Black and gray symbols represent the cocaine- and saline-treated animals.

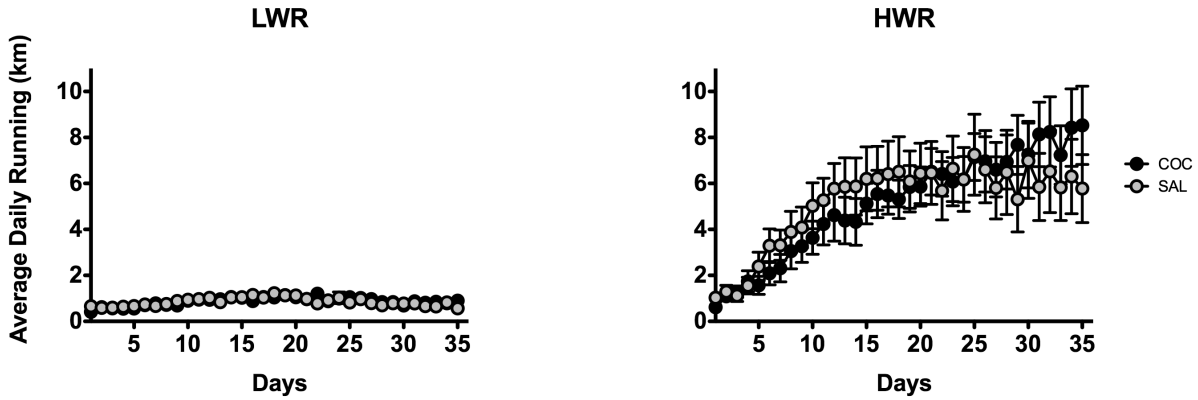

LWR
HWR
Average Daily Running (km)
Days
Days
COC
SAL

Figure 3. Mean ± SEM weights (g) of the NWR, LWR and HWR groups on the first- (T1) and second-test (T2) for sensitization. Black bars and gray bars represent the cocaine- and saline-treated animals, respectively. * Statistically significant increase in body weight from T1 to T2 at $p < .05$.

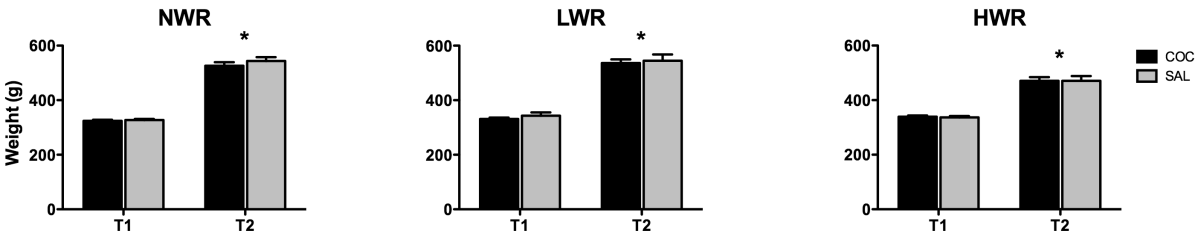

NWR
LWR
HWR
Weight (g)
600
400
200
0
T1
T2
*
COC
SAL

Figure 4. Mean ± SEM locomotor activity counts expressed by the NWR, LWR and HWR groups during the treatment phase. Black and gray symbols represent the cocaine- and saline-treated animals, respectively. * $p < .008$ different from saline control.

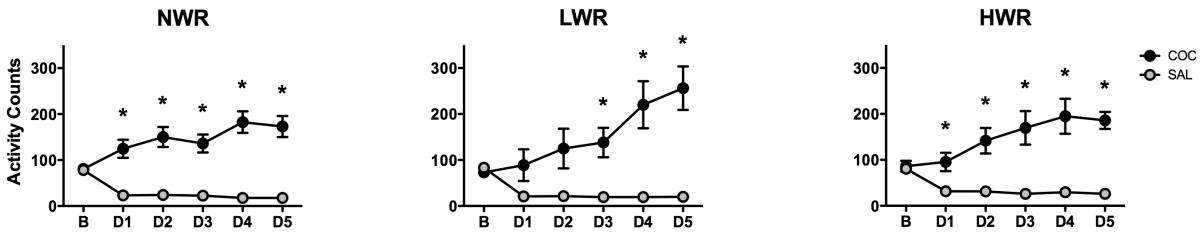

NWR
LWR
HWR
Activity Counts
300
200
100
0
B
D1
D2
D3
D4
D5
COC
SAL

Table 1

Summary of Hierarchical Multiple Regression Analysis for Variables predicting Activity on T2

		b	*SE b*	*β*
Model 1				
	Constant	-148.06	109.80	
	B	-0.10	0.36	-.05
	D1	0.29	0.13	.41*
	T1	0.25	0.16	.30
	W T2	0.37	0.19	.36
Model 2				
	Constant	50.00	129.52	
	B	0.05	0.33	.03
	D1	0.24	0.12	.35
	T1	0.22	0.14	.26
	W T2	0.02	0.23	.02
	Running	-0.01	0.004	-.52*

Note. $R^2 = .52$ for Model 1; $\Delta R^2 = .12$ for Model 2. * $p < .05$.

General Discussion

We had a very straightforward hypothesis that derived from very straightforward considerations. On the basis of neurochemical, morphological, and molecular evidence, we hypothesized that running, by inducing similar changes within the mesocorticolimbic dopamine system as stimulant drugs and stress, would exacerbate the behavioral response to a cocaine-challenge injection. Clearly, this was not the case. Instead, the experiments presented here reveal, for the first time, that wheel running can protect against cocaine- and stress-induced behavioral sensitization, as well as reverse an already established sensitized behavioral response. Importantly, the protective actions of wheel-running activity on behavioral sensitization to cocaine were found to be contingent on an animal's running performance.

Our findings highlighting the protective effects of wheel running on cocaine-induced behavioral sensitization have since been demonstrated in mice (Geuzaine & Tirelli, 2014), and have been shown to persist long after wheel-running cessation (Lespine & Tirelli, 2015). In as much as behavioral sensitization has been associated to drug-seeking and -taking behaviors (Hooks, Duffy, Striplin, & Kalivas, 1994; Lorrain et al., 2000; Steketee & Kalivas, 2011; Vezina & Leyton, 2009), our results are in agreement with previous studies reporting that chronic running, applied concomitantly or non-concomitantly with access to drugs, can attenuate the rewarding (H. I. Chen et al., 2008; Fontes-Ribeiro, Marques, Pereira, Silva, & Macedo, 2011; Mustroph, Stobaugh, Miller, DeYoung, & Rhodes, 2011) and reinforcing actions of stimulant drugs (Cosgrove, Hunter, & Carroll, 2002; Lynch, Piehl, Acosta, Peterson, & Hemby, 2010; Ogbonmwan, Schroeder, Holmes, & Weinshenker, 2015; Smith, Schmidt, et al., 2008; Smith & Pitts, 2011; Smith, Walker, Cole, & Lang, 2011; Thanos et al., 2012; Zlebnik, Anker, Gliddon, & Carroll, 2010). It is important to note, however, that contrasting findings have been

reported. For instance, some research groups have shown the rewarding/reinforcing actions of cocaine to persist (Geuzaine & Tirelli, 2014) or even increase (Mustroph et al., 2011; Smith, Gergans, Iordanou, & Lyle, 2008; Thanos et al., 2012) as a result of wheel running.

Perhaps pertinent to the discrepancies found in the literature, here we demonstrate that individual differences in running performance regulate behavioral sensitization to cocaine. Specifically, only animals that voluntarily engage in high levels of wheel-running activity were found to be protected against cocaine-induced behavioral sensitization (Renteria Diaz et al., 2013). In line with our findings, Smith, Schmidt, and colleagues (2008) reported a negative correlation between voluntary running output and willingness to work for cocaine, as measured by a progressive ratio of drug reinforcement. Though in a subsequent study, this same research group failed to find a significant correlation between wheel-running activity and acquisition of cocaine self-administration (Smith & Pitts, 2011), the contrasting results could reflect the different phases of the self-administration paradigm or the fact that in the second study food restriction was used to facilitate the drug-acquisition phase. This procedure could have obscured the results of the correlational analysis as, in addition to enhancing drug self-administration, food restriction alters energy balance which has been shown to modulate wheel-running activity (Novak, Burghardt, & Levine, 2012). The animal model of behavioral sensitization, which does not comprise this potentially confounding variable, can thus be used to best understand how individual differences in running behavior modulate psychostimulant-induced neurobehavioral changes.

Individual differences in running behavior are thought to arise from (Knab et al., 2009; Rhodes et al., 2005; Roberts et al., 2013; 2012; Waters et al., 2008; Zhu, Ottenheimer, & DiLeone, 2016) as well as induce (Aguiar et al., 2010; Park et al., 2016; Waters et al.,

2008; Wilson & Marsden, 1995) various changes in striatal dopamine function. Consequently, to best characterize the mechanisms underlying the effects of individual differences in running on behavioral sensitization, in the third chapter, we examined whether the HWRs' protection against behavioral sensitization preceded or followed wheel-running availability. The fact that the HWRs exhibited a sensitized behavioral response before running, but failed to do so after, suggests that the basal striatal state of the HWRs cannot, solely, account for their protection against behavioral sensitization. Instead, the actual running behavior, by producing specific plastic changes within the brain, seems to be at the core of this protection.

So what feature of the HWRs' running behavior protects them against the process of sensitization? Needless to say, we categorized rats as HWRs because they voluntarily ran longer daily distances than LWRs. In the first chapter, however, we clearly show that the distance ran by the HWR group could not, alone, account for the protective effects of running as allowing the LWR group to run for a longer period of time, thereby simulating the distance covered by the HWR group in half the time, did not block behavioral sensitization to cocaine in this group. The protective effects of engaging in high levels of wheel-running activity must therefore be tightly linked to the speed and/or intensity at which the behavior is performed.

To try to understand the mechanisms underlying the association between running and behavioral sensitization to cocaine, we next focus our attention on the sensitization process, which includes two stages: initiation and expression. The initiation refers to the initial drug-induced neurobehavioral changes that animals exhibit during the drug-treatment phase. The expression reflects the long-lasting consequences of these initial drug-induced changes as it can be observed in response to a drug-challenge injection weeks to months after cessation of the drug treatment (Pierce & Kalivas, 1997;

Steketee & Kalivas, 2011). Ample evidence has linked each stage to partially distinct brain regions and neuroadaptations (Cador, Bjijou, & Stinus, 1995; J.-C. Chen, Chen, & Chiang, 2009; Cornish & Kalivas, 2001; Kalivas & Weber, 1988; Pierce & Kalivas, 1997; Steketee & Kalivas, 2011; Vanderschuren & Kalivas, 2000; Vezina, 2004; Vezina & Stewart, 1990).

With regard to our findings, in the first chapter we showed that engaging in high levels of wheel-running activity blocked the expression of behavioral sensitization to cocaine, as high-running animals that had been previously treated with cocaine did not differ from the saline-treated controls in their behavioral response to the cocaine challenge injection. These results, do not however, exclude the possibility that wheel running had previously prevented the initiation of the sensitized response. In fact, since publishing our study it has been reported that, in mice, 10 weeks of wheel running blunts the development (Geuzaine & Tirelli, 2014) as well as the long-term expression (Lespine & Tirelli, 2015) of behavioral sensitization to cocaine. To clarify this issue, we present here unpublished data from the first chapter (see Annex 1). This figure depicts each group's behavioral activation in response to the five-treatment days. As can be seen, the drug regimen used in this study produced similar results in all groups, irrespective of wheel-running access. This suggests that, at least in rats, it is the expression of behavioral sensitization that is regulated by running.

So how does wheel running modulate the expression of behavioral sensitization to cocaine? Theoretically the simplest explanation underlying this phase of behavioral sensitization is an increase in stimulant-induced dopamine concentrations in the nucleus accumbens of drug-treated rats (Heidbreder et al., 1996; Kalivas & Duffy, 1990). Animals repeatedly treated with amphetamine but that fail to exhibit heightened extracellular dopamine levels in the nucleus accumbens do not express behavioral sensitization in

response to a drug challenge (Scholl et al., 2009). What is more, as with the expression of behavioral sensitization the accumbal dopaminergic response to a stimulant challenge increases the longer the drug-withdrawal period (Heidbreder et al., 1996). As such, when an environmental or genetic factor protects animals against the expression of behavioral sensitization it is only natural to suspect an attenuation of stimulant-induced dopaminergic release in the accumbens. Well, as stated in the general introduction, when animals are exposed to treadmill running they exhibit an increase, rather than a decrease, in extracellular dopamine levels in the striatum (Meeusen et al., 2001; 1997), and more so in animals that run the most (Wilson & Marsden, 1995) or the fastest (Freed & Yamamoto, 1985; Hattori et al., 1994). No changes in accumbal dopamine transporter protein levels (H. I. Chen et al., 2008) have been found to accompany this running-mediated hyperdopaminergic state, and rats selectively bred for high-aerobic capacity show similar dopamine transporter mRNA levels than their low-aerobic capacity counterparts after 11 weeks of running (Park et al., 2016). Interestingly, though like stimulant drugs chronic running increases extracellular dopamine levels in the striatum, running has been shown to blunt the striatal dopaminergic response to the first stimulant injection (H. I. Chen et al., 2008; Marques et al., 2008). Whether such an effect persists following repeated drug administration is unknown. Nevertheless, in the present thesis a running-mediated generalized reduction in the dopaminergic response to the cocaine challenge injection is unlikely given that not all running animals were found to be protected against behavioral sensitization to cocaine.

Also accompanying the expression of behavioral sensitization are diverse postsynaptic changes. Of particular interest is the heightened responsiveness of D1 dopamine receptors located on accumbal medium spiny neurons (Creed, Pascoli, & Luscher, 2015; Henry & White, 1991; X.-T. Hu et al., 2002; Pascoli et al., 2011;

Vanderschuren & Kalivas, 2000). Not so much because they are believed to be directly linked to the regulation of behavioral sensitization, as psychostimulant-treated animals do not exhibit a sensitized behavioral response to a systemic (Vanderschuren, Schoffelmeer, Mulder, & De Vries, 1999) or intra-accumbens D1 dopamine agonist injection (Pierce & Kalivas, 1995), but rather because of their impact on other receptors located on accumbal medium spiny neurons (Creed et al., 2015; Vanderschuren & Kalivas, 2000). Though chronic running has not been found to alter the mRNA or protein expression of D1 dopamine receptors in the nucleus accumbens (H. I. Chen et al., 2008; Clark et al., 2014; Greenwood et al., 2011; Obici et al., 2015) and no difference in accumbal D1 dopamine receptor mRNA expression has been found between rats selectively bred for high- and low-aerobic capacity after 11 weeks running (Park et al., 2016), changes in the responsiveness of these receptors as a function of running performance have yet to be examined. A potential manner in which running may modulate D1 dopamine receptor signalling is by altering the function of A1 adenosine receptors (Clark et al., 2014), which are co-localized on accumbal medium spiny neurons expressing D1 dopamine receptors (Ferré et al., 1994). Adenosine receptors have been shown to regulate dopamine signalling (Ferré, 1997; Ferré et al., 1994) and microinjections of adenosine receptor agonists directly into the nucleus accumbens core have been found to attenuate the expression of behavioral sensitization to cocaine (Hobson, Merritt, & Bachtell, 2012). Nevertheless, findings reported by Clark and colleagues (2014) suggest that running, like stress, may actually reduce the efficacy of adenosine-mediated dopamine signaling inhibition in accumbal medium spiny neurons, thereby rendering these neurons more easily excitable.

Given the key role of the nucleus accumbens in the expression of behavioral sensitization to stimulant drugs it is important to note that other than dopaminergic

projections from the ventral tegmental area, the nucleus accumbens receives glutamatergic projections from diverse brain regions including the prefrontal cortex (Pascoli et al., 2011; Pierce & Wolf, 2013; Steketee & Kalivas, 2011). The regulation of glutamatergic input by nucleus accumbens medium spiny neurons primarily involves AMPA glutamate receptors, whose function has been tightly linked to D1 dopamine receptor activation (Hobson et al., 2013; Wolf, 2010). These glutamatergic receptors have been shown to play a key role in the expression of behavioral sensitization that results from repeated cocaine (Boudreau & Wolf, 2005; Churchill, Swanson, Urbina, & Kalivas, 1999; Creed et al., 2015; Pierce, Bell, Duffy, & Kalivas, 1996; Terrier, Lüscher, & Pascoli, 2016) or stress exposure (Esparza et al., 2012; Garcia-Keller et al., 2013).

AMPA glutamate receptors are the major regulators of fast excitatory neurotransmission in the mammalian brain and are believed to be a crucial component underlying diverse forms of experience-dependent neuroplastic changes including sensitization. For example, only rats that exhibit behavioral sensitization to cocaine show significantly greater levels of the AMPA-type glutamate receptor subunit, GluR1, in the nucleus accumbens after three-weeks, but not 24 hours, of drug withdrawal (Churchill et al., 1999). A similar increase in accumbal GluR1 expression is observed in stress-exposed rats given an injection of cocaine three-weeks later (Esparza et al., 2012). What is more, AMPA microinjections directly into the nucleus accumbens core enhances locomotor activation only in rats that had previously undergone cocaine sensitization (Pierce et al., 1996) or that had been exposed to restraint stress (Garcia-Keller et al., 2013). Finally, microinjecting the AMPA receptor antagonist, CNQX, directly into the accumbens core has been found to block the expression of cocaine- (Pierce et al., 1996) and stress-induced behavioral sensitization (Esparza et al., 2012; Garcia-Keller et al., 2013).

What is more, AMPA glutamate receptor trafficking in the nucleus accumbens also parallels the expression of behavioral sensitization. For instance, only rats that express behavioral sensitization to cocaine show greater surface expression of the AMPA-type glutamate receptor subunits, GluR1 and GluR2/3, in the nucleus accumbens after a three-week, but not a one-day, drug-free period (Boudreau & Wolf, 2005). Similarly, only rats that have been repeatedly exposed to stress show an increase in the surface expression of GluR1 in nucleus accumbens neurons in response to an injection of cocaine three-weeks later (Esparza et al., 2012). This cocaine- and stress-mediated redistribution of AMPA glutamate receptors to the neuronal surface is thought to potentiate synaptic transmission in the accumbens, and to be a key component underlying the expression of behavioral sensitization. There have, however, been conflicting reports to this effect (Bachtell & Self, 2008; Brebner et al., 2005; Ferrario et al., 2010).

Recently, through the use of optogenetics, a causal link has been revealed between cocaine-induced synaptic potentiation of cortico-striatal signaling and sensitization, as restoring cortico-accumbens signaling to a pre-cocaine basal state was found to reverse behavioral sensitization to cocaine. Specifically, the authors showed that optogenetic depotentiation of cortex to accumbens signaling 45 minutes before the cocaine-challenge injection completely reversed the sensitized behavioral response of mice previously treated with cocaine (Pascoli et al., 2011). Regulation of accumbal synaptic plasticity is thought to involve the activation of diverse molecular signals, one of which is the extracellular signal-regulated kinase (ERK). Various drugs of abuse activate the ERK pathway in accumbal medium spiny neurons via the combined stimulation of D1 dopamine and NMDA glutamate receptors (Girault et al., 2007; Pascoli et al., 2011; Valjent et al., 2005). Interestingly, ERK phosphorylation can

modulate AMPA glutamate receptor trafficking (Derkach, Oh, Guire, & Soderling, 2007; Song et al., 2013). In sensitized rats both ERK phosphorylation and AMPA glutamate receptor surface expression in the nucleus accumbens increase during a two-week drug-free period and normalize 24 hours after a challenge injection of cocaine (Boudreau, Reimers, Milovanovic, & Wolf, 2007). Pharmacologically inhibiting ERK phosphorylation directly in the nucleus accumbens has been found to block the expression of behavioral sensitization to stimulant drugs (S. Kim et al., 2011).

The findings pertaining to the reversal of behavioral sensitization by cortico-accumbens synaptic depotentiation begs the question of whether engaging in high levels of wheel-running activity produces the same behavioral outcome by naturally reversing cocaine-induced strengthening of cortex to accumbens synaptic neurotransmission? Well, though long-term moderate treadmill running has been shown to increase total GluR1 protein levels in the dorsal striatum (Real, Ferreira, Hernandes, Britto, & Pires, 2010), high-intensity treadmill running for 28 days has not been found to alter total protein expression of GluR1 within the dorsolateral striatum and has actually been found to increase the phosphorylation of GluR2 at serine 880 (VanLeeuwen et al., 2010) which is known to lead to rapid AMPA glutamate receptor internalization and hence to decreased synaptic strength (Jiang, Suppiramaniam, & Wooten, 2006). What is more, mice exposed to a high-intensity running regime for nine weeks show decreased striatal phosphorylation of ERK (Aguiar et al., 2010), a molecular signal involved in AMPA glutamate receptor membrane insertion (Derkach et al., 2007; Song et al., 2013). Engaging in high levels of voluntary wheel-running activity may thus protect against behavioral sensitization by counteracting cocaine-driven ERK phosphorylation, which would affect AMPA glutamate receptor trafficking, ultimately stabilizing cortex to

accumbens synaptic neurotransmission. Future studies will need to examine this possibility.

Another molecular signal that has been widely linked to stimulant-mediated neuroplastic changes is the transcription factor DeltaFosB (Colby et al., 2003; Kelz et al., 1999; McClung, Ulery, Perrotti, & Zachariou, 2004; Nestler et al., 2001; Perrotti et al., 2008; Robison & Nestler, 2011). Various drugs of abuse increase the expression of this transcription factor within the nucleus accumbens (Perrotti et al., 2008), and accumulation of DeltaFosB within accumbal medium spiny dynorphin-containing neurons expressing D1 dopamine receptors has been shown to induce behavioral sensitization to cocaine (Kelz et al., 1999). Various non-pharmacological agents such as stress, sucrose and sex have also been shown to induce DeltaFosB in the nucleus accumbens and to cross-sensitize with stimulant drugs (Gosnell, 2005; Herman et al., 1984; McClung et al., 2004; Perrotti et al., 2004; Pitchers et al., 2010; 2013; Wallace et al., 2008). Similarly, wheel running produces an accumulation of DeltaFosB in dynorphin-containing neurons in the nucleus accumbens (Greenwood et al., 2011; Herrera et al., 2016; Obici et al., 2015; Werme et al., 2002) and running performance is enhanced when DeltaFosB is overexpressed in these striatal neurons (Werme et al., 2002). Accordingly, animals that voluntarily run the most, by overexpressing DeltaFosB levels in striatal dynorphin-containing neurons, would be expected to exhibit enhanced behavioral activation in response to a drug challenge injection. The findings presented here challenge this assumption as behavioral sensitization to cocaine was prevented and reversed only in these animals. It is important to note, however, that though both running and stimulant drugs induce DeltaFosB in the nucleus accumbens, their combined effects on this transcription factor are unknown and may actually be diametrically opposed to their separate effects. Relevant to this issue, one study has

found that environmental enrichment, which includes wheel-running access, induces DeltaFosB expression in the accumbens of drug-naïve mice, but produces the opposite in animals that have been repeatedly treated with cocaine (Solinas et al., 2009). Whether running regulates DeltaFosB expression in a similar manner as enrichment remains to be seen. But if so, how could it account for our findings regarding the impact running performance has on behavioral sensitization. Future studies are needed to characterise the role, if any, of DeltaFosB in the suppression of behavioral sensitization by high wheel-running performance.

Conclusion

In recent years there has been much interest regarding the various neuroplastic effects of exercise and the resulting behavioral changes. Little consideration has, however, been given to the impact individual differences in exercise performance can have on the brain and behavior. In the present thesis, using an animal model of human exercise, we revealed, for the first time, that engaging in high levels of wheel-running activity can protect against and reverse the expression of behavioral sensitization to cocaine. This observed dissociation in terms of behavioral sensitization between high- and low-wheel runners may be used in future studies to identify the neuroplastic changes that regulate this long-lasting phenomenon. What is more, the behavioral expression of metaplasticity reported in the present thesis can serve, at a more general level, to best characterize how the brain processes experiential change.

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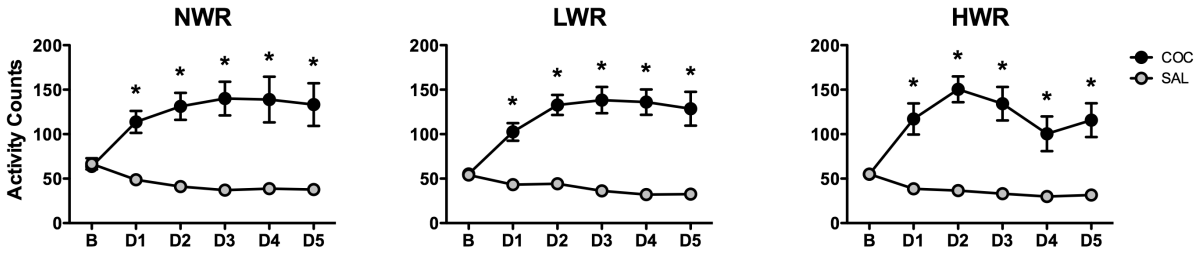
Annexe 1

Figure 1. Mean ± SEM locomotor activity counts expressed by the NWR, LWR and HWR groups during the treatment phase, unpublished data from Chapter 1. Black and gray symbols represent the cocaine- and saline-treated animals, respectively. * $p < .008$ different from saline control.


NWR
LWR
HWR
Activity Counts
200
150
100
50
0
B
D1
D2
D3
D4
D5
COC
SAL