

## Examining the Effects of Exercise on Frustration-Induced Anxiety-Like Behavior in Rats

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**ABSTRACT.** Frustration is an emotional event arising from decreases in expected reward following motivated behavior and is associated with stress and anxiety in humans, albeit rarely studied in rodents. Rodent studies have shown that anxiety-like behavior is a potential side effect of frustration, although the mechanisms and potential preventative actions for frustration are unknown. To study anxiety interventions in rodents, running wheels are used to consistently decrease anxiety-like behavior. However, wheel running has not been used to study its effects on frustration-induced anxious behavior. Thus, we modeled frustration in both control and running rats, and predicted that running would buffer anxiogenic effects of frustration. Long-Evans rats ( $N = 16$ ) were randomly assigned to either control or exercise conditions. All rats were trained on a progressive variable ratio (VR) lever pressing schedule up to VR20. After reaching criterion, rats went through a frustration trial, during which no reward was given. After both VR20 and frustration trials, corticosterone was measured from tail blood, and anxiety-like behavior was analyzed in an open field. Last, hippocampal tissue was analyzed for dendritic spine density. Control rats had increased anxiety-like behavior,  $t(7) = 4.84$ ,  $p = .002$ , and corticosterone levels,  $t(8) = 3.31$ ,  $p = .011$ , following induced-frustration. However, running rats showed no such increases,  $t(7) = -0.24$ ,  $p = .82$ , and had higher spine density throughout the hippocampus,  $t(4) = -8.21$ ,  $p = .001$ . The present findings suggest exercise as a preventative intervention against the maladaptive effects of frustration on physiology and anxious behavior.

**Keywords:** frustration, anxiety-like behavior, running, corticosterone, hippocampus

Anxiety disorders are the most prevalent mental illnesses among adults in the United States, with a lifetime prevalence rate upward of 33% in the general population (Kessler, Petukhova, Sampson, Zaslavsky, & Wittchen, 2012), and this number is unlikely to have changed over the past two decades (Bandelow & Michaelis, 2015). Additionally, anxiety disorders create a burden, with an annual cost between 50–100 billion dollars in the United States (Kessler & Greenberg, 2002; Shirneshan, 2013). This demonstrates a critical need to develop more effective and accessible treatment options.

### Anxiety-Like Behavior in Rodents

Rodent studies allow the ability to model anxiety disorders in an ethologically appropriate manner to discover their etiology and mechanisms for potential treatments (Lister, 1990). For example, the open field test, a common procedure used to measure general locomotor behavior, can be used to assay anxiety in rats (Prut & Belzung, 2003). Reduced exploration of the more threatening parts of the open field (e.g., the center regions) is a behavior that models novelty avoidance and caution, which are observed in anxiety disorders in humans (Frenkel et al., 2015). Although most

rodent studies have investigated baseline anxiety levels, it is important that studies also understand the environmental impact on developing *anxiety-like behavior* in rodents (reviewed in Schoenfeld & Cameron, 2015). Two different environmental experiences, *frustration* and *running*, exert opposite effects on anxious behavior in both humans and rodents (Anderson & Shivakumar, 2013; Cuenya, Fosachea, Mustaca, & Kamenetzky, 2012; Fulk et al., 2004; Keenan & Newton, 1984), so we sought to investigate the interplay of both on anxiety-like behavior in rats.

### Frustration as an Anxiogenic Tool

Frustration is the emotional sensation experienced when progress toward seemingly achievable goals is hindered by obstacles such that an individual perceives a lack of control (Meindl et al., 2018). Frustration is related to human anxiety in the workplace (Keenan & Newton, 1984) and school (Brotman, Kircanski, Stringaris, Pine, & Leibenluft, 2017; Wigfield & Meece, 1988). In rodents, frustration has been induced through the removal of expected reward in operant tasks such as lever pressing (Burokas, Gutiérrez-Cuesta, Martín-García, & Maldonado, 2012). Scull, Davies, and Amsel (1970) operationally defined this frustration effect originally as an increase in the intensity of response rate following a sudden period of nonreward. Although more rarely studied, there are more generalized emotional side effects to frustrative-nonreward in addition to those standard effects on lever pressing behavior. Behavioral analysis during frustration trials suggested that rats displayed consummatory behavior that resembles the state of anxiety in other tests (Cuenya et al., 2012). Specifically, Cuenya and associates (2012) demonstrated that social isolation produced both anxiety-like behavior in the elevated plus-maze—another common apparatus used to measure anxiety in rodents—and atypical consummatory behavior during a sucrose test (ambulatory behavior and rearing) theorized to resemble anxiety. In addition, anxiolytic medications reduced these anxiety-like consummatory behaviors during frustration trials (Flaherty, 1990; Mustaca, Bentosela, & Papini, 2000), suggesting that frustration elicited emotional side effects that resemble anxiety in rodents. However, no studies have directly investigated if frustration produces anxious behavior outside of the frustrating scenario, like the open field, nor if exercise prevents such anxiety-like behavior. Therefore, frustrative-nonreward is an understudied mechanism we seek

to utilize to measure potential effects on anxiety-like behavior of a more emotional kind.

### Exercise Effects on Anxiety and Stress Hormones

Conversely, aerobic exercise reduces anxiety in patients with anxiety disorders (Anderson & Shivakumar, 2013), and wheel running is considered a rodent model of aerobic exercise that routinely decreases anxiety-like behavior (Fulk et al., 2004; Schoenfeld et al., 2014). Wheel running, then, is commonly used with rodents to study effects of exercise on anxiety-like behavior and possible biological mechanisms that underlie its anxiolytic effects. Chronic wheel running buffered the release of *corticosterone*, the main stress hormone in rodents, which was increased by stressful experiences such as electric shock and physical restraint (Benaroya-Milshtein et al., 2004; Hare, Beierle, Toufexis, Hammack, & Falls, 2014), and further buffered the anxiogenic effects of stress (Lapmanee, Charoenphandhu, & Charoenphandhu, 2013). Despite these findings using physical stressors, little is known about the effects of wheel running to buffer more emotionally driven sources of anxiety-like behavior. Therefore, the primary purpose of the present study was to investigate the role of wheel running in rodents as a potential intervention on frustration-induced increases in anxiety-like behavior. In addition, corticosterone was measured to investigate physiological measures of stress following frustration in addition to behavioral measures of anxiety-like activity.

### Structural Change in the Hippocampus

The *hippocampus* is a brain area involved in the perception of stressful contexts and the production of anxious behavior (Adhikari, Topiwala, & Gordon, 2010) and is implicated as a key brain area for developing new interventions to treat anxiety disorders (Gorman, 2003). All three major subregions of the hippocampus (i.e., the dentate gyrus (DG) and areas CA3 and CA1) form the trisynaptic circuit and each have been functionally implicated in moderating anxious behavior (Jimenez et al., 2018; Kheirbek et al., 2013; Schumacher et al., 2018). Interestingly, these areas are all highly plastic and undergo many structural changes in response to environmental stimuli. One of these alterations—increases in dendritic spines—reflects neuron growth and is positively associated with stress recovery and resilience (Sousa, Lukoyanov, Madeira, Almeida, & Paula-Barbosa, 2000; Yang, Shirayama, Zhang, Ren, & Hashimoto, 2015). Chronic running

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(at least ten days) produced increases in dendritic spine density of all subregions of the hippocampus (Eadie, Redila, & Christie; 2005; Lin et al., 2012; Stranahan, Khalil, & Gould, 2007), suggesting that structural plasticity throughout the hippocampus is both sensitive to environmental manipulations and a mechanism for stress resilience, although these changes take time. Changes in dendritic spines within the hippocampus likely reflect key adaptations in the brain produced by exercise to prevent future anxiety-like behavior (Schoenfeld, Rada, Pieruzzini, Hsueh, & Gould, 2013). Therefore, we investigated dendritic structure as a potential mechanism involved in frustration-induced anxiety-like behavior.

Although anxiolytic medications reversed learning deficits following frustration (Morales, Torres, Megias, Candido, & Maldonado, 1992), and exercise prevented effects of physical stressors on anxiety-like behavior (Greenwood et al., 2013; Lapmanee, Charoenphandhu, Teerapornpuntakit, Krishnamra, & Charoenphandhu, 2017), it is unknown how an experience like exercise impacts the effects of a less physical form of stress (i.e., frustration) on anxiety-like behavior. Currently, there is a gap in knowledge of the emotional side effects and physiological mechanisms of frustration. Therefore, we utilized frustration to explore the effects of wheel running on anxiety-like behavior and the physiological and neuronal circuits that underlie these behavioral effects. We hypothesized that running rats would display less anxiety-like behavior in the open field compared to nonrunning control rats, and that this difference would be heightened following reward-based frustration. In addition, we predicted that running rats would have decreased corticosterone expression and increased spine density within hippocampal neurons compared to control rats that would provide information about possible mechanisms for exercise effects on frustration-induced anxious behavior.

## Method

### Participants

Eight-week-old male Long-Evans rats (Envigo) were used and randomly assigned to running and control conditions. Rats were given *ad libitum* access to food and water, then kept on a restricted diet (~16g chow/rat/day) schedule starting the week prior to operant training. All rats were group-housed (2–3 rats/cage) and maintained on a 12-hour light-dark cycle (lights on at 6 a.m.). All animal protocols conformed to the Institute of Laboratory Animal

Research and approved by Belmont University IACUC.

### Apparatuses

Rats were housed in two different environments, based on treatment group. Control rats ( $n = 8$ ) were housed in standard laboratory cages (25 cm x 45 cm), whereas running rats ( $n = 8$ ) were housed in an otherwise standard cage, albeit larger (40 cm x 50 cm), because it contained a large running wheel directly in the cage (Lafayette Instruments) and provided them free access to running all day. Although running cages were bigger, the nonwheel areas were similar in size (23 cm x 50 cm) to standard nonrunning cages.

For operant training, rats learned to lever press for 45 mg sucrose pellets (Bioserv) in Student Learning Chambers (Lafayette Instruments) equipped with two levers and lights to act as discriminative stimuli.

For anxiety-like behavior, rats were tested in an open field (1 m x 1 m). To measure corticosterone levels following anxiety testing, rats were briefly restrained (Harvard Apparatus) and tail blood serum was collected using microvette capillary tubes (KentScientific) and a centrifuge (Eppendorf). Serum was analyzed using a corticosterone ELISA kit (Enzo Life Sciences) and 1420 multilabel counter (PerkinElmer).

To analyze brain tissue, brains were cut on a sliding microtome (American Optical), reacted with a Golgi stain (FD Neurotechnologies), and analyzed using an Olympus BX50 brightfield microscope aided by an Infinity 3S-1 camera (Lumenera) and ImageJ software (NIH).

### Procedure

**Experimental design.** As depicted in Figure 1A, both control and running rats ( $n = 8$  each) were housed in their respective cage environments for two weeks before operant training began at 10 weeks old. Rats first went through magazine training and then performed progressively higher VR schedules until completing the VR20 schedule (see below). After the first VR20 trial, all rats were tested in the open field for anxiety-like behavior, and blood was analyzed from a subset of rats ( $n = 5$  from each group) for corticosterone levels. Next, all rats went through a frustration trial, immediately after which blood was collected again for corticosterone, and anxiety-like behavior was tested in the same open field with new context cues. At the end of testing, brains were extracted, and dendritic spines

were analyzed from a subset of rats ( $n = 3$ ).

**Operant learning and frustration.** Progressive ratio operant training was adapted from Rossi and Yin (2012). The same 45 mg sucrose pellets used for magazine training were given to rats in their home cage to develop motivation for reward. Rats were first trained on a fixed ratio of one (FR1), with each lever press yielding one pellet. Rats were then trained on an increasing VR schedule, receiving one pellet after an average of  $n$  lever presses. Starting at VR2, rats progressed through VR3, VR5, VR10, VR15, ending in VR20. Criterion of a successful trial was operationally defined as achieving 50 rewards within an hour. Three consecutive successful trials at a given VR schedule were required to move to the next level. Time to reach criterion (with a maximum of 60 minutes) was recorded each trial. For each VR schedule, time to reach criterion was averaged across all attempted trials (successful and unsuccessful) and used for data analysis. Twenty-four hours after the final VR20 trial, frustration was induced by placing rats back into the operant chamber for a duration of 30 minutes but with the lever deactivated from delivering reward. The number of lever presses every 5 minutes was recorded. All lever press and reward data were tabulated by automatic counters (Lafayette Instruments).

**Corticosterone measurements and anxiety-like behavior.** After the first VR20 trial, rats were tested for baseline exploratory behavior during a 10-minute interval in the open field. The open field had a smooth plastic floor finish with walls covered in laminated green construction paper and scented with lavender (LorAnn Oils) for context. Onto the floor of the open field, a 5 x 5 grid was created using colored tape to produce 25 equal squares (20 cm x 20 cm each) over which rats could freely explore. The total number of grid intersections crossed, center intersections crossed (operationally defined as crossings within the middle 3x3 grid of 9 squares), and total time in the center was collected by hand during the entire 10-minute window. Center crossings and time are inversely related with anxiety-like behavior, while total crossings reflect general locomotion (Prut & Belzung, 2003).

Directly following the frustration trial, rats were placed back into the open field to measure frustration-induced anxiety-like behavior. To prevent habituation effects, context was altered during the second open field test by covering the floor with purple fine grade sandpaper, decorating the wall with laminated black and white diagonal stripes, and rosemary scent (LorAnn Oils) was used.

For both trials, blood was collected from the tail vein 20 minutes after removal from the open field to assess anxiety-related corticosterone levels. To do so, rats were briefly restrained in a clear Plexiglas tube (Harvard Apparatus) and the tail vein near the end was nicked with a razor blade. Blood was collected into microvette capillary tubes, and after 1–2 hours, blood was centrifuged at 14,000 RPM, plasma was extracted, and samples were frozen until the assay was performed. For the corticosterone assay, procedures were followed directly from the ELISA kit manual.

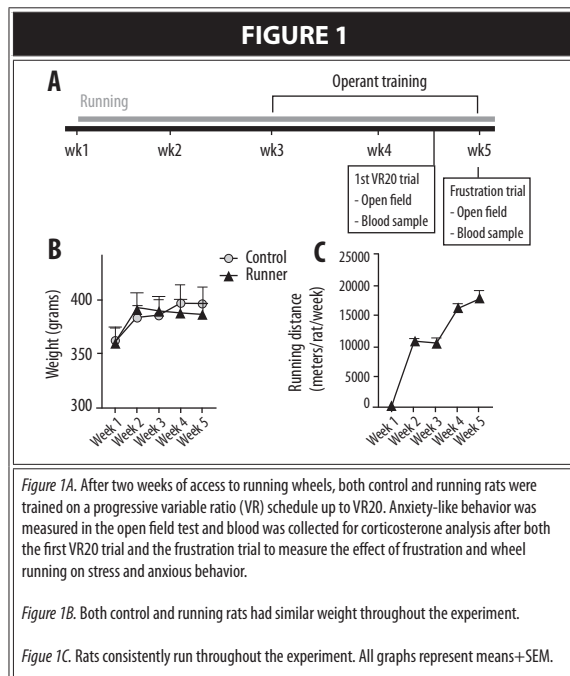
**Dendritic spine density in the DG, CA3, and CA1 of the hippocampus.** To measure how wheel running induces changes in dendritic complexity in the hippocampus, rats were rapidly decapitated and whole brains extracted and processed using Golgi impregnation to fully label neurons in the hippocampus. Briefly, brains were rinsed, cut into one-inch chunks, and incubated in Golgi-Cox solution (Rapid GolgiStain kit; FD Neurotechnologies) for 3 weeks in the dark. Chunks were transferred to RapidGolgi Stain solution for 48 hours, after which brains were lightly frozen with dry ice, and 100  $\mu$ m sections throughout the hippocampus were cut using a Microtome and mounted onto SuperFrost slides (ThermoFisher Scientific). Neurons were visualized by using a RapidGolgi Stain developing solution, graded ethanol, and cleared with xylene before being coverslipped with Permount.

All slides were coded before analysis and analyzed blind to treatment condition. Neurons that were fully impregnated (with full dendritic trees for granule neurons in DG and both apical and basal dendritic trees for pyramidal neurons in CA3 and CA1, without trees being clearly cut off due to sectioning or incomplete staining) and in isolation (without confound of overlapping neighboring neurons) were located using brightfield microscopy and analyzed for dendritic spine density (analyzed at 100x objective). Within each subregion of the hippocampus, five separate neurons with a pronounced nucleus and clearly defined dendrites were selected for analysis. One secondary or tertiary dendrite was isolated from each granule cell in the DG and apical dendrites of pyramidal neurons in CA3 and CA1 and captured with an Infinity 3S-1 monochrome camera (Lumenera). Photographed sections were then analyzed using ImageJ. For each dendritic branch, a 30  $\mu$ m section was isolated and manually counted for dendritic spines and used for density measurements. The average of all five neurons per subregion was calculated and used for

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statistical analysis.

### Statistical Analysis

For all analyses, running was a between-subjects variable; however, all other variables were repeated-measures variables and analyzed as such. To measure weight gain over five weeks of the experiment, a  $2 \times 5$  (Running  $\times$  Week) mixed-factorial Analysis of Variance (ANOVA) was conducted. To measure running distances over the four weeks of running, group cage distances were measured and analyzed on a per-rat basis, and then a one-way repeated-measures ANOVA was conducted. To measure the effect of running on lever press behavior throughout the six VR schedules learned, a  $2 \times 6$  (Running  $\times$  VR Schedule) mixed-factorial ANOVA was conducted. To measure the effect of running on extinction during the frustration trial, a  $2 \times 6$  (Running  $\times$  Time) mixed-factorial ANOVA was conducted to analyze lever pressing behavior at 5-minute intervals. To measure the effect of running and frustration on open field behavior and corticosterone release,  $2 \times 2$  (Running  $\times$  Frustration) mixed-factorial ANOVAs were conducted comparing post-VR20 and postfrustration trials. To measure the effect of running on dendritic spine density in the hippocampus, independent-samples  $t$  tests were conducted for each subregion separately. For all ANOVAs, Bonferroni pairwise comparisons were used to analyze main effects of repeated-measures variables, and effect sizes ( $\eta^2$ ) were determined for

all analyses. For all analyses, an alpha level of .05 was used to determine significant effects.

## Results

### Basic Characteristics of Control and Running Rats

To compare weight gain over the course of the experiment between control and running rats, a  $2 \times 5$  (Running  $\times$  Week) mixed-factorial ANOVA was performed on weight of all rats (Figure 1B). A main effect of week followed by Bonferroni pairwise comparisons showed that both control and running rats gained weight while on an *ad libitum* diet, but had no change in weight after Week 2, when the restricted diet began,  $F(4, 56) = 24.71$ ,  $p < .001$ ,  $\eta^2 = .64$ . There were no effects of running on weight overall or at any given week of the experiment: main effect running,  $F(1, 14) < .01$ ,  $p = .96$ ,  $\eta^2 < .01$ , interaction,  $F(4, 56) = 1.86$ ,  $p = .13$ ,  $\eta^2 = .12$ .

Because rats were group-housed, individual rodent running distances could not be calculated. However, to verify group activity in the running cages, distance was measured weekly in each running cage (Figure 1C). A one-way within-subjects ANOVA followed by Bonferroni pairwise comparisons showed that running distances increased from Weeks 1 and 2 to Weeks 3 and 4,  $F(3, 21) = 25.63$ ,  $p < .001$ ,  $\eta^2 = .79$ .

### Running Hastens Learning and Buffers Frustration-Induced Anxiety-Like Behavior

To determine if running impacts the progression of rats through increasing-VR ratios during operant training, the average time to reach criterion (across all attempted trials) among control and running rats were compared at each schedule of VR training (Figure 2A). A  $2 \times 6$  (Running  $\times$  VR Schedule) mixed-factorial ANOVA showed a main effect of running, with running rats reaching criterion faster than control rats,  $F(1, 14) = 4.85$ ,  $p = .045$ ,  $\eta^2 = .26$ . A main effect of VR schedule,  $F(5, 70) = 11.80$ ,  $p < .001$ ,  $\eta^2 = .46$ , followed by Bonferroni pairwise comparisons showed that all rats spent similar amounts of time reaching criteria for the first three VR schedule (all  $p > .1$ ). However, the last three VR schedule all took more time to reach criterion than VR5 (all  $p < .001$ ). There was no interaction effect of running on learning VR schedule ( $p > .1$ ).

To validate frustration during the last trial, lever press rate was measured during the 30-minute frustration trial in 5-minute intervals for all rats (Figure 2B). A  $2 \times 6$  (Running  $\times$  Time) mixed-factorial ANOVA showed a main effect of time,  $F(5, 70) = 12.90$ ,  $p < .001$ ,  $\eta^2 = .48$ , with Bonferroni

pairwise comparisons detailing that lever press rate was slower at the end of the frustration trial than the beginning for all rats ( $p = .003$ ). There was no main effect of running nor a Running  $\times$  Time interaction on lever press rate ( $p > .1$ ), suggesting that all rats extinguished similarly during the frustration trial.

To determine if frustrative-nonreward differentially affects anxiety-like behavior in running and control rats, time exploring the center of an open field test was compared between running and control rats after both the first VR20 and frustration trials (Figure 2C). A 2  $\times$  2 (Running  $\times$  Frustration) mixed-factorial ANOVA showed no main effects of either running or anxiety trial on exploration through the open field. However, a marginal interaction effect,  $F(1, 14) = 3.43$ ,  $p = .085$ ,  $\eta^2 = .20$ , followed by simple effects analyses showed that control rats had an increase in anxiety-like behavior from VR20 to frustration trial by exploring the center of the open field less,  $t(7) = 4.84$ ,  $p = .002$ , whereas running rats had no increase in anxiety-like behavior,  $t(7) = -0.24$ ,  $p = .82$ . This effect on exploration was not due to general locomotion because there were no main effects of running and anxiety trial, nor an interaction on total exploration through the open field, depicted by the total number of grid crossings during the test (all  $ps > .1$ , see Figure 2D).

### Running Decreases Frustration-Elicited Corticosterone Release and Increases Dendritic Spines Throughout the Hippocampus

To identify a possible biological mechanism for differences in anxiety-like behavior, blood was drawn from a subset of rats after both open field tests and examined for corticosterone levels (Figure 3A). A 2  $\times$  2 (Running  $\times$  Frustration) mixed-factorial ANOVA did not yield a main effect of frustration nor an interaction effect ( $p > .1$ ), but running rats had significantly less corticosterone overall than control rats,  $F(1, 8) = 7.29$ ,  $p = .027$ ,  $\eta^2 = .48$ . Simple effects analyses showed that this main effect was entirely driven by corticosterone levels after the frustration trial, when running rats had significantly less corticosterone than control rats,  $t(8) = 3.31$ ,  $p = .011$ , whereas running and control rats had similar corticosterone levels following VR20 trial,  $t(8) = 0.82$ ,  $p = .44$ .

Because the hippocampus provides negative feedback onto the hypothalamic pituitary adrenal (HPA) axis stress response (Herman & Cullinan, 1997), we measured dendritic spines throughout the hippocampus in the brains of a subset of both

running and control rats (Figure 3B). Independent-samples  $t$  tests were conducted and in all three regions of the hippocampus measured (DG, CA3, and CA1), running rats had increased spine density compared to control rats: DG,  $t(4) = -8.21$ ,  $p = .001$ ,  $\eta^2 = .94$ ; CA3,  $t(4) = -3.39$ ,  $p = .027$ ,  $\eta^2 = .74$ ; CA1,  $t(4) = -3.42$ ,  $p = .027$ ,  $\eta^2 = .75$ .

## Discussion

In the present study, we investigated the effects of exercise on frustration-induced anxiety-like

FIGURE 2

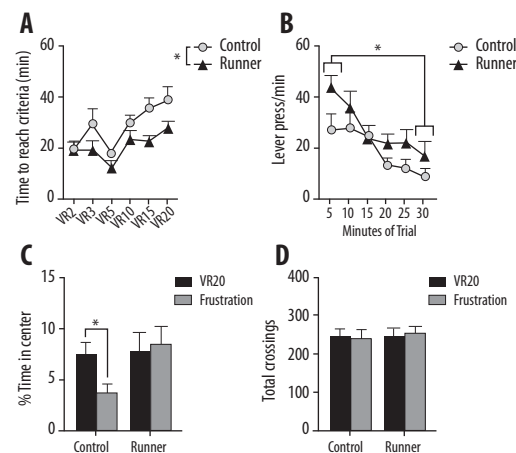


Figure 2A. Running rats progressed through variable ratio schedules more quickly, especially during later schedule with higher motivation.

Figure 2B. All rats, independent of exercise, extinguished lever pressing behavior during the frustration trial.

Figure 2C. Sedentary rats displayed more anxiety-like behavior by exploring the center of the open field less, however runners were buffered from this response.

Figure 2D. All rats explored the open field as a whole similarly.

\*  $p < .05$  compared to control or beginning of frustration trial. All graphs represent means  $\pm$  SEM.

FIGURE 3

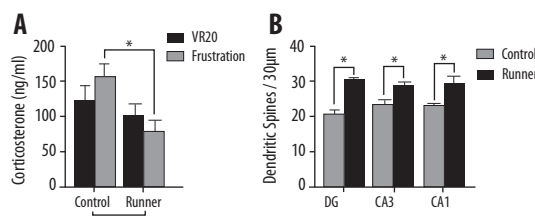


Figure 3A. Running rats had lower corticosterone release during open field exploration, especially following the frustration trial.

Figure 3B. Running increased dendritic spine density within the dentate gyrus (DG), CA3, and CA1 regions of the hippocampus.

\*  $p < .05$  compared to control. All graphs represent means  $\pm$  SEM.

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behavior in rats and potential mechanisms mediating these effects. All rats were trained to lever press at high rates for reward following a progressively increasing VR schedule.

Although runners performed moderately faster than control rats, all rats reached criterion for learning the VR20 schedule. To induce frustration, all rats were put into a nonrewarded trial for 30 minutes, during which all rats, regardless of experimental group, extinguished lever pressing behavior, suggesting that all rats experienced nonreward similarly. Importantly, a few days before the frustration trial, runner and control rats showed similar anxiety-like behavior in the open field test and corticosterone levels in blood serum following a rewarded operant trial. However, after the frustration trial, control rats displayed more anxious behavior and had increased blood corticosterone levels, compared to runners. In a subset of these rats, dendritic morphology was analyzed in the hippocampus, and runners were found to have widespread increases in dendritic spine density in each major subregion of the hippocampus, providing a possible biological mechanism for the exercise effects on stress and anxiety-like behavior. Together, these effects suggest that wheel running rats have a blunted stress response to frustration, which may act toward a prevention of anxiety-like behavior following frustrating events.

#### **Effects of Running on Operant and Anxiety-Like Behavior**

Wheel running in rodents is commonly utilized as a rodent model of human exercise. Similar to anxiolytic actions of physical exercise in human patients (Anderson & Shivakumar, 2013; Carek, Laibstain, & Carek, 2011; Salmon, 2001), wheel running decreased basal anxiety-like behavior in both unstressed and chronically stressed experimental rodents across many studies (Fulk et al., 2004; Lapmanee et al., 2013; Schoenfeld et al., 2014). In addition, running prevented increases in anxiety-like behavior following both physical and social stressors (Greenwood et al., 2013; Lapmanee et al., 2017; Patki et al., 2014), concluding that exercise can buffer the effects of environment stress. Our findings extend this literature by suggesting that wheel running prevented frustration-induced anxious behavior in rats. Frustration-induced emotional changes have been compared similarly to anxious behaviors (Gray, 1978), suggesting that similar mechanisms work to reduce emotional behaviors in running rats following stressful or frustrating events

One additional explanation is that exercised rats were less frustrated following removal of a reward because of enhanced motivated behavior, and therefore their emotional behavior was less affected. Running rats in our study demonstrated enhanced motivation because they were faster to reach criterion across different VR schedules, but also progressed from one VR level to the next more quickly than sedentary controls. Long-Evans rats given access to running wheels overate following a period of caloric restriction (Evans, Messina, Knight, Parsons, & Overton; 2005), which suggests that our running rats, on food restriction for operant training, may rebound by being more motivated to lever press for food when given the chance. Although the internal state of rats is impossible to determine, both sedentary and running rats behaved in the same manner during the frustration trial, which serves as an important manipulation check. Both rats lever pressed at a high rate at the beginning of the frustration trial and extinguished lever pressing behavior as the trial continued. Therefore, even if running rats were more motivated to lever press for reward, they were not hypermotivated to the point of ignoring the nonreward case. Assuming both running and sedentary rats notice the lack of reward, only running rats were prevented from this frustrating situation impacting their emotional behavior.

Interestingly, exercised rats were no less anxious than controls when tested in the open field test after the VR20 trial, despite having run for four weeks by that point. Other studies have shown that four weeks of running was sufficient to be anxiolytic in rodents (Binder, Droste, Ohl, & Reul, 2004; Salam et al., 2009), although we only showed differences due to exercise following the frustration trial. One difference in our study is that all rats were trained to lever press for reward in addition to just running or being sedentary. Although reported research is unclear whether instrumental reward learning produces changes in anxiety-like behavior in rodents, one well-regarded theory of the anxiolytic effects of exercise is that it is dependent on the rewarding nature of running in rodents (Brené et al., 2007). Many forms of exercise (forced and voluntary, wheel and treadmill) produced anxiolytic responses, activated reward circuitry in the brain, and produced conditioned place preference to running arenas, indicative of reward value (Greenwood et al., 2011; Herrera et al., 2016). Therefore, because of the rewarding nature of operant training, it is possible that

sedentary rats have less anxiety-like behavior than expected. Importantly, despite no difference in baseline anxiety-like behavior, sedentary rats displayed increased anxiety-like behavior following frustration, which was prevented by chronic exercise. Although we measured anxiety-like behavior in the open field test, this test measures avoidance behavior in only one domain, exploration of a novel arena. Exploration through the center of the field is accepted to reflect anxious behavior in the open field; however, some other factors are worth considering as potential confounds. First, increased exploration in the open field may not reflect anxiety but may just reflect increased activity levels because of wheel running behavior. Second, one potential caveat in repeated open field testing is the use of fine-grade sandpaper as a tactile component on the second test that may add a stressful component to that specific test compared to the first test with a smooth floor. To address this second factor, although home cage sandpaper flooring (instead of normal sawdust bedding) is slightly aversive to rodents (Tokunaga et al., 2007), sandpaper flooring is commonly used in behavioral tests to manipulate tactile textures without affecting behavior by sandpaper alone (Brydges & Hall, 2017). In addition, the smooth floor of the open field for the first test has a glossy finish that reflects light, so any anxiogenic qualities of sandpaper would be outweighed by increased reflection of aversive light in the first test. Importantly for both potential confounds, total exploration, defined by the number of grid crossings throughout the arena, did not change as a result of running or arena floor, suggesting that neither of these variables influenced general locomotion throughout the arena. The only exploration that was changed was into the more threatening parts of the field, the center, so we are confident that behavioral differences between running and control rats following frustration reflect anxiety-like behavior. In future studies, counterbalancing of open field arena configuration would be helpful to fully eliminate any contextual element of the second open field from potentially increasing anxiety-like behavior on its own. Last, other tests of anxiety-like behavior, the elevated plus-maze and light-dark box, utilize more salient threats, namely height and intense white light (Lezak, Missig, & Carlezon, 2017). Comparatively, it is possible that the open field is an anxiety test that is less sensitive to environmental stressors like frustration. In addition, other anxiety tests measure more defensive behaviors such as the

marble burying test and acoustic startle. Therefore, future studies should utilize various anxiety tests measuring both avoidance and defensive behaviors to capture the whole effects of frustration and exercise on anxiety-like behaviors in rats.

### **Impact of Stress Processing and the Hippocampus on Behavior**

Frustration induced an increase in corticosterone in sedentary rats, but not running rats, mirroring changes in anxiety-like behavior. Previous research showed that a frustration effect elicited activation of the HPA axis stress response through increased release of corticosterone (Goldman, Coover, & Levine, 1973; Romero, Levine, & Sapolsky, 1995). Although open field exploration released corticosterone on its own (Campbell, Morrison, Walker, & Merchant, 2004), prior stress further increased corticosterone, negatively correlating with exploratory activity (Marin, Cruz, & Planeta, 2007). This suggests that increased corticosterone released through frustration acts as a stressor with potential causative effects on anxiety-like behavior. Although the previous study (Marin et al., 2007) described a correlational relationship between glucocorticoid release and anxiety-like behavior, pharmacological activation of the HPA axis through injections of corticotropin-releasing hormone (CRH) is anxiogenic. Global injections of CRH decreased exploratory and anxiety-like behavior in the open field when it is novel and under bright light conditions (Koob & Thatcher-Britton, 1985; Kumar & Karanth, 1996; Valdez et al., 2002). In addition, through a host of studies using agonist and antagonist drugs (see review by Lalonde & Strazielle, 2017), it is a central tenet that activation of the HPA axis produces anxiety-like behavior in the open field.

Similar to our findings, previous research suggested that rodent exercise not only reduced stress-elicited anxiety-like behavior, but prevented corticosterone increases measured 30 minutes later (Benaroya-Milshtein et al., 2004). One potential mechanism for this corticosterone difference is that exercise quickened the reduction of corticosterone levels following activation of the HPA axis during stress (Hare et al., 2014). Following this, it is known that the hippocampus functions as a negative feedback loop onto the HPA axis, inhibiting HPA axis activity following its activation (Herman & Cullinan, 1997). Therefore, alterations in the hippocampus through long-term exercise provide one mechanism to affect responses to environmental stressors.

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To directly examine this, we measured dendritic spine density of granule and pyramidal neurons within the DG and regions CA3 and CA1 of the hippocampus as an indicator of hippocampal growth. Like previous studies, we found robust increases in dendritic spines within all subregions of the hippocampus (Eadie et al., 2005; Lin et al., 2012; Stranahan et al., 2007). Although increases in dendritic spines in the hippocampus were typically correlated with memory enhancements (Sorra & Harris, 2000), they should enhance other functions of the hippocampus, like negative feedback of the HPA axis as well. Indeed, an inverse relationship between dendritic spines in the hippocampus and stress-induced corticosterone is typically reported in the literature. Stress resulted in spine loss and elevated corticosterone (Magariños, McEwen, Flügge, & Fuchs, 1996), whereas enrichment increased spine density and decreased corticosterone response (Hutchinson et al., 2012). Therefore, induced growth of hippocampal dendritic spines through exercise may be sufficient to prevent negative effects of frustration by inhibiting HPA axis activation during frustrating situations.

### Limitations

Only a subset of rats was used to measure corticosterone response and dendritic spine density in running and control rats due to budgetary and time constraints, potentially limiting the power and reliability of these specific findings in relation to behavior. However, moderate running effect sizes for corticosterone data, notably a highly variable measure (Segar, Kasckow, Welge, & Herman, 2009), and robust effect sizes for hippocampal spine density in running rats, a reliable finding in the literature, suggest that these effects are strong, despite the limited sample size. The biggest limitation with these subsets, then, was the inability to run correlational analyses to determine if dendritic spine density was negatively correlated with corticosterone release and positively correlated with exploratory behavior in the open field within each experimental condition separately. However, group differences suggested this correlation to be a strong possibility and future experiments should investigate this in greater depth.

Additionally, it would be informative to analyze the correlation between individual rat wheel running distances and our dependent measures to determine if running is an all-or-none effect or graded, depending on the amount of exercise exerted. However, because rats were group housed,

it is impossible to quantitate actual individual rat running distances. Research suggested that the positive neurological effects of wheel running was prevented by social isolation housing (Stranahan, Khalil, & Gould, 2006), so group housing was purposefully chosen to maintain positive effects of wheel running. Although this makes it difficult to determine if all rats ran the same amount, qualitatively we observed all rats taking turns running, and even having multiple rats running at a time, so it is possible the wheel running distances actually underestimate the average individual distance for given rats. Future research may be able to utilize activity-tracking technology (Freund et al., 2013) to keep group housing of rats but track individual running distances to perform these sorts of analyses.

Similar to this, we were only able to test the relationships between running, corticosterone, hippocampus structure, and anxiety-like behavior following frustration. Although running rats were less anxious, had lower corticosterone in their blood, and increased dendritic spines throughout the hippocampus, this does not mean that changes in hippocampal structure and/or corticosterone release caused changes in anxiety-like behavior. Manipulating dendritic spines within the hippocampus without affecting other processing is currently unattainable in neuroscience methods. However, experiments can be performed that directly manipulate HPA axis function. To address this issue, adrenalectomized (ADX) rats given low-dose corticosterone replacement treatment in drinking water allows for baseline corticosterone levels to be present without stress-induced increases in corticosterone following activation of the HPA axis. Comparing ADX rats to sham controls would allow us to test whether increases in corticosterone are what causes the increase in anxiety-like behavior following a frustrating event. Although beyond the scope of the present study, future studies should look to investigate this.

Due to limitations in rodent colony room availability, we were only able to measure our effects in male rats, so we are unable to generalize our results to female rats. Wheel running reduced anxiety-like behavior and corticosterone release in female rats (Jones, Gupton, & Curtis, 2016; Robinson, Christ, Cahill, Aldrich, & Taylor-Yeremeeva, 2019). However, corticosterone responses in male and female rats differed following environmental manipulations (Kent et al., 2017). To our knowledge, no studies have been conducted on frustration-induced anxious behavior in female rats, so it would be

interesting to see if there are sex differences in anxiety-like responses to emotional experiences, given reliable sex differences in stress responses to emotional stressors in humans (Kirschbaum, Wüst, & Hellhammer, 1992).

Last, another potential limitation is the difficulty in dissociating anxiolytic effects of running from potential anxiolytic effects of instrumental learning using reward. Because both running and sedentary rats displayed similar anxiety-like behavior following VR20, it is possible that lever pressing for reward has similar anxiolytic properties as running, at least at baseline and when rats are sated. Although future experiments should specifically test whether the rewarding nature of operant conditioning produces anxiolytic responses, we are confident that our results showed that running does cause rats to be more resilient toward environmental stressors, allowing for greater exploration despite frustrating circumstances. The impacts of exercise on stress resilience are well-known (Kochi et al., 2017; Sciolino et al., 2015), and this resilience allows rats to remain active and adaptive to changing environments.

## Conclusion

This study utilized wheel running as a rodent model of exercise to investigate the effects of exercise in preventing anxiety-like behavior in rats following an emotionally stressful situation. We found that running caused a decrease in anxious behavior following frustration, coinciding with lower stress hormone release and increased dendritic spine density in the hippocampus. Overall, the results suggested that exercise buffers an anxiety-like response following a frustrating situation in rats and that this effect may be mediated by inhibition of stress hormones and dendritic spine changes within the hippocampus. These findings extend the literature on the anxiolytic effects of exercise and broaden the types of environmental experiences that reliably elicit anxious behavior in rodents. From an ethological viewpoint, rats demonstrating less anxious behavior in the open field following frustration may correspond to increased exploratory behavior in the wild despite previous exposure to unrewarding situations. For a sedentary rat, acting cautiously in a new environment after failing to find a reward is not adaptive nor conducive to proactive foraging behavior needed to survive in the wild, so exercise reflects adaptive behavior attributed to strong hippocampal functioning (Glasper, Schoenfeld, & Gould, 2012). These findings also implicate aerobic

activity as a potential stress buffer for frustrating and unrewarding experiences for people worldwide. Frustration has been linked with aggression, anxiety disorders, and clinical depression (Harrington, 2006; Hokanson, 1961), so these findings extend exercise as a potential therapeutic intervention to decrease effects of frustration.

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This study was supported by a Winter Undergraduate Research Grant provided by Psi Chi, the International Honor Society in Psychology, and internal research support from the College of Science and Mathematics at Belmont University.

Special thanks to *Psi Chi Journal* reviewers for their support.

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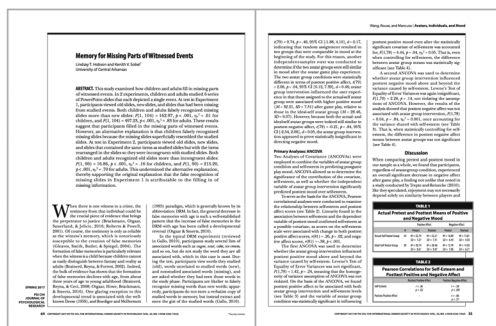
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