

RESEARCH ARTICLE OPEN ACCESS

Gene Expression After Exercise Is Disrupted by Early-Life Stress

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Correspondence: Taylor S. Campbell (tcamp@udel.edu)**Funding:** This research was funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), Grant 1R01HD087509-01 awarded to T.L.R., and the University of Delaware Doctoral Fellowship for Excellence awarded to T.S.C.**Keywords:** Bdnf | early-life adversity | epigenetics | exercise | Fndc5 | irisin | prefrontal cortex

ABSTRACT

Exercise can be leveraged as an important tool to improve neural and psychological health, either on its own or to bolster the efficacy of evidence-based treatment modalities. Research in both humans and animal models shows that positive experiences, such as exercise, promote neuroprotection while, in contrast, aversive experiences, particularly those in early development, are often neurologically and psychologically disruptive. In the current study, we employed a preclinical model to investigate the therapeutic benefits of exercise on gene expression in the brains of adult rats. Long Evans rats were exposed to maltreatment stress or nurturing care during infancy, with some rats later given voluntary running wheels as an aerobic exercise intervention from Postnatal Days 70 to 90. Our results showed that irisin gene expression, which promotes neuroprotection, was differentially affected by exercise and early exposure to stress. We add to a rapidly growing area of research on the neuroprotective benefits of exercise and shed light on important molecular mechanisms that may affect the efficacy of exercise in different individuals.

1 | Introduction

Since the 1990s exercise has been studied as a tool to improve neural and psychological health. Though there is still some debate on what exercise regimen is best for maintaining a healthy brain (Gregory, Gill, and Petrella 2013), a consensus remains that exercise is a useful treatment tool for preventing and treating neuropsychiatric and neurodegenerative diseases (De La Rosa et al. 2020; Swenson et al. 2020; van Praag 2009). However, while exercise seems to protect against these negative states, other experiences are known to exacerbate these risks. Experiencing adversity during early life leads to a higher rate of neuropsychiatric disorders and neurodegeneration later in life (Hoeijmakers et al. 2018; Perroud et al. 2013; Sideli et al. 2012), significantly affecting an individual's quality of life and longevity. Research on exercise interventions in children exposed to early-life stress is an area ripe for discovery. Our study here

aims to provide insight on the efficacy of exercise interventions in bolstering adaptive molecular activity in rodents exposed to early-life stress.

Developmental stress alters the activity of genes involved in neuroprotection in brain regions important for memory, cognition, and impulse control. One target is the *Brain-derived neurotrophic factor (Bdnf)* gene, which encodes for the brain-derived neurotrophic factor protein. This neurotrophin is heavily involved in brain development and function, and its expression is often decreased by stress (Roth et al. 2009; E. J. Huang and Reichardt 2001). In contrast to stress, aerobic exercise increases *Bdnf* expression (Hopkins, Nitecki, and Bucci 2011; Håkansson et al. 2016), though the mechanisms behind this relationship are still being elucidated. The relationship between *Bdnf* expression and environmental influences is particularly important when considering *Bdnf*'s role in psychological disorders. *Bdnf* gene

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expression is decreased in brains of individuals diagnosed with schizophrenia, depression, or bipolar disorder (Ray, Shannon Weickert, and Webster 2014), which helps explain the relationship between developmental stress and neurorisk later in life.

In 2012, a hormone, called irisin, was found to be secreted from skeletal muscle tissue into the bloodstream after exercise (Boström et al. 2012). Today, we know that irisin, coded by *Fndc5*, is partially responsible for many of the positive effects of exercise, including both physiological and neural benefits (Boström et al. 2012; Korta, Pocheć, and Mazur-Biały 2019; Lima-Filho et al. 2023). As such, scientists have begun focusing on exercise-induced *Fndc5* expression as a neural mechanism facilitating an upregulation of *Bdnf* expression following exercise (Chen, Wang, and Wang 2022; Bellettini-Santos et al. 2023).

FNDC5, or fibronectin type III domain-containing protein 5, is a precursor protein that, when cleaved, gives rise to irisin. Together, BDNF and FNDC5 make up two critical elements facilitating the relationship between exercise and brain health. With exercise, irisin crosses the blood brain barrier and stimulates BDNF production in the brain via several signaling cascades, including AMP-activated protein kinase activation, cyclic-AMP, and protein kinase A pathway activation (Rabiee et al. 2020). BDNF in turn works in the brain to enhance cognition and memory and protect the brain from disease (Lu, Nagappan, and Lu 2014).

Recently, our lab has investigated the ability of voluntary exercise to upregulate *Bdnf* gene expression in animals exposed to stress or nurturing care during infancy. In Campbell, Donoghue, and Roth (2024), we reported that exercise increases *Bdnf* gene expression in the adult rodent prefrontal cortex (PFC). We further targeted changes in *Bdnf* DNA methylation as a potential mechanism allowing for this gene-behavior interaction. While we noted significant changes in methylation caused by exercise (reported briefly in Table 2), there was some nuance in the data. We detected a main effect of exercise at *Bdnf* exon IX (total *Bdnf*) such that subjects who exercised had significantly lower methylation than sedentary subjects. However, this main effect was driven by a significant interaction in that subjects previously exposed to stress during early development showed significantly lower methylation compared to their sedentary counterparts. Given that exercise seemed to be more effective at reducing gene methylation in this group, one may have expected this to lead to a greater increase in *Bdnf* gene expression in the maltreatment group. Since this is not what our data showed, we hypothesized an additional mechanism might be irisin. Given the recent experiments showing that exercise upregulates irisin, and that irisin in turn upregulates *Bdnf*, using the same tissue collected for our previous study we sought to determine if irisin was upregulated and if irisin and *Bdnf* gene expression were associated.

In the current study, we took initial steps toward elucidating a mechanism wherein developmental stress impacts the brain's response to a behavioral treatment. Our study indicates that irisin upregulation in adult brain tissue after exercise is negatively impacted in rodents that experienced mild stress in the context of caregiving during infancy. Here we focused on the PFC for two main reasons. First, we know the developing PFC can be highly vulnerable to the effects of stress during infancy (Milbocker et al.

2021); however, the ability of exercise to modulate any negative effects has not been elucidated. Specifically, stress during early life can decrease *Bdnf* gene expression in the PFC and disrupt proper early circuitry development and refinement (Milbocker et al. 2021; Roth et al. 2009). Second, we sought to add to a recently growing body of evidence that exercise affects the PFC. It is widely accepted in the exercise neuroscience field that exercise positively impacts the hippocampus. However, recent experiments indicate that exercise increases PFC activation (Fujihara, Megumi, and Yasumura 2021) and synaptic protein expression (Sadri et al. 2024) and improves performance on executive functioning tasks (Park 2022).

We also show that irisin and *Bdnf* expression are not related in sedentary rats but are positively associated after exercise. This finding supports recent experiments revealing that irisin is at least partially responsible for inducing *Bdnf* expression after exercise (Chen, Wang, and Wang 2022; Bellettini-Santos et al. 2023). However, this association is not present in rats who experience stress during infancy, suggesting that stress during development may impact the brain's response to neuroprotective behaviors later in life. This study focuses on elucidating one of the maladaptive effects of adversity during early life; however, we recognize stress during development can also result in adaptive outcomes. We discuss the known vulnerability and resiliency outcomes of early-life stress in depth in Collins et al. (2023).

2 | Methods

2.1 | Subjects

Data were collected from 48 males and 48 female Long Evans rats obtained from in-house breeding (breeder males and dams procured via Charles River) as described previously (Campbell, Donoghue, and Roth 2024). All behavioral observations occurred during the light cycle. All animals were housed in standard polypropylene cages with wood shavings, and all procedures were approved by the University of Delaware Animal Care and Use Committee.

Our caregiving manipulations followed a validated model, termed the scarcity-adversity model (e.g., Roth et al. 2009; Doherty et al. 2017; Doherty et al. 2019). Rat pups from each experimental litter were randomly assigned to one of three postnatal caregiving conditions—maltreatment, normal maternal care, or cross-foster care—and experienced the assigned condition for 30 min daily from Postnatal Days (PNs) 1–7 (Figure 1). Pups were weighed on PNs 1–7 and PN 21 for health monitoring. During weigh-ins, pups were marked with a sharpie with an ID number and on PNs 1, 3, 7, and 21, photos were also taken of pup back patterns to be used as subject identifiers. Experimental litters were derived from the normal maternal care dam, and pups assigned to the normal care condition remained in the home cage with their biological dam for behavioral recording in the colony room. Pups from the same litter assigned to the maltreatment condition were moved to a novel environment and placed with a different lactating dam that was not given time to habituate or nesting material for behavioral manipulations. Pups from the same litter assigned to the cross-foster condition were placed into a novel environment with a different lactating dam that was given ample

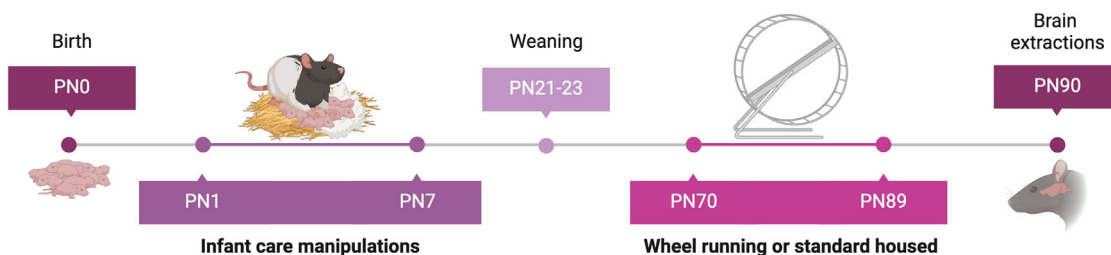


FIGURE 1 | Experimental timeline. On Postnatal Day (PN) 1, 24 h after birth, Long Evans rat pups were randomly assigned to normal maternal care, cross-foster care, or maltreatment infant conditions. Pups were weaned between PNs 21 and 23 and pair-housed under standard conditions. On PN 70, some pairs were randomly assigned to running wheel–equipped cages and remained under these conditions until brain extractions on PN 90. Figure made with Biorender.com.

TABLE 1 | Taqman probes.

<i>Fndc5</i>	Rn01519161_m1
<i>Bdnf</i> IX	Rn02531967_s1
<i>Tubb2</i>	Rn01435337_g1

time to habituate and sufficient nesting material. Immediately following each behavior recording session, the cross-foster and maltreatment pups were returned to their biological dam (normal care dam) in the home cage. The normal maternal care condition served as the nurturing care control group. The cross-foster condition served as an additional nurturing care control group but also controlled for any handling effects induced by the experimenter moving pups daily to the novel environment and exposure to another dam. All dams were matched in diet and postpartum age. Behavioral recordings were sectioned into 5-min time bins for time sample scoring. Occurrences of nurturing and aversive behaviors exhibited by the dams were hand-scored by two independent observers and interrater reliability reached at least 80% agreement for all videos. Maternal behavior results from these subjects are reported in Campbell, Donoghue, and Roth (2024).

Between PNs 21–23, pups were weaned and pair-housed with a same-sex, nonlittermate of the same infant condition. On PN 70, some rat pairs were randomly assigned to wheel-running (WR) exposure where they were given voluntary access to a running wheel until brain extractions on PN 90, as previously described (Campbell, Donoghue, and Roth 2024).

2.2 | Biochemistry

Immediately following extraction, brains were flash frozen using dry ice and 2-methylbutane and stored at -80°C . DNA and RNA were extracted from the PFC (Qiagen Allprep DNA/RNA Mini Kit), and extracted RNA was reverse transcribed (Qiagen QuantiTect Reverse Transcription Kit) to produce complementary DNA (cDNA) as previously described (Campbell, Donoghue, and Roth 2024). The cDNA was analyzed by real-time PCR, performed using Taqman probes (Fisher Life Technologies; Table 1) designed to amplify *Fndc5* mRNA and *Tubulin* mRNA (reference gene).

2.3 | Statistical Analysis

Relative *Fndc5* gene expression between maltreatment, normal maternal care, and cross-foster care was assessed by the comparative Ct method (Schmittgen and Livak 2008). Differences in gene expression (exercise and maternal care) were analyzed by a series of multiway ANOVAs and simple linear regression analyses. Statistical significance threshold was set to $p < 0.05$, as is standard in the field. Outliers were identified and removed using the ROUT method ($Q = 1\%$) prior to each analysis. All statistical analyses were conducted using GraphPad Prism (GraphPad Software Inc, version 10.1.2).

3 | Results

3.1 | Maternal Behavior, WR, and *Bdnf* Regulation

Full results regarding our maternal behavior manipulation, WR behavior, and *Bdnf* methylation and expression are reported in Campbell, Donoghue, and Roth (2024). Results are briefly summarized herein Table 2.

3.2 | *Fndc5* Gene Expression

ANOVAs analyzing the effects of infant condition, adult condition, and sex were conducted for *Fndc5* gene expression. A three-way ANOVA revealed a significant infant by adult condition interaction ($F(2, 84) = 6.82, p = 0.001$). We followed up with a two-way ANOVA with data collapsed across sex, revealing a significant interaction ($F(2, 89) = 5.36, p = 0.006$), in which post hoc testing indicated that WR exposed rats showed significantly higher *Fndc5* expression within the normal maternal care group only ($p = 0.01$; Figure 2).

3.3 | *Fndc5*–*Bdnf* Regression

Separate simple linear regression (SLR) analyses were utilized to determine if *Fndc5* expression predicted *Bdnf* expression (Figure 3). The *Bdnf* probe used here targeted exon IX of the *Bdnf* gene, which is the coding region of the gene and indicates *Bdnf* total gene expression. Data were collapsed across sex but separated by infant and adult condition based on the following: (1) results from the *Fndc5* expression analysis and (2) previous *Bdnf*

TABLE 2 | Behavior and *Bdnf* data analysis.

Maternal Behavior			
	<i>F</i>	Sidak's corrected <i>p</i> value	Finding
Maltreatment vs. CFC and NMC (main effect of infant condition)	52.73	$p < 0.0001^{***}$	Maltreatment ↑ aversive behaviors Maltreatment ↓ nurturing behaviors
Nurturing vs. aversive behaviors (interactions within conditions)	71.64	$p < 0.001^{**}$	CFC: ↑ nurturing behaviors NMC: ↑ nurturing behaviors MAL: ↓ nurturing behaviors
Accumulated wheel rotations			
Infant condition	1.56	0.226	—
Sex	72.81	$< 0.001^{**}$	Females ↑
<i>Bdnf</i> exon-specific methylation			
<i>Bdnf</i> exon IX	5.437	0.021*	WR ↓
<i>Bdnf</i> exon IV (female WR vs. female SH)	8.97	0.013*	WR ↓
<i>Bdnf</i> exon IV (sex x WR)	8.97	0.032*	Female WR ↓
<i>Bdnf</i> exon I	1.87	0.173	—
<i>Bdnf</i> gene expression			
<i>Bdnf</i> exon IX	5.96	0.016*	WR ↑

Abbreviations: CFC, cross-foster care; MAL, maltreatment; NMC, normal maternal care; SH, standard-housed; WR, wheel-running exposed. * $p < 0.05$, ** $p < 0.001$, *** $p < 0.0001$.

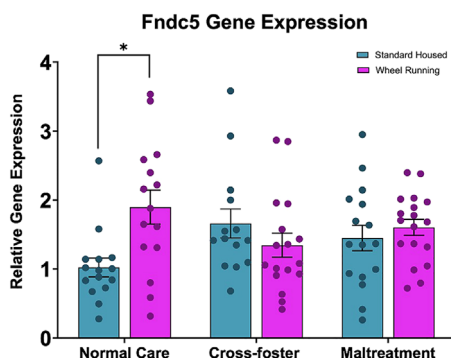


FIGURE 2 | *Fndc5* (irisin) gene expression in the whole PFC. * $p < 0.05$, error bars = SEM. $n = 7-9$ males and $7-10$ females per group.

IX methylation results (Campbell, Donoghue, and Roth 2024). We found that *Fndc5* expression predicted *Bdnf* expression in the WR subjects who were exposed to nurturing care during infancy (cross-foster WR: $R^2 = 0.52$, $F(1, 15) = 16.25$, $p < 0.01$; normal care WR: $R^2 = 0.27$, $F(1, 13) = 4.82$, $p = 0.04$) but not maltreatment care (maltreatment WR: $R^2 < 0.01$, $F(1, 16) = 0.09$, $p = 0.76$). *Fndc5* did not predict *Bdnf* expression in the standard-housed subjects, supporting the notion that exercise-induced *Fndc5* expression facilitates *Bdnf* (maltreatment SH: $R^2 = 0.19$, $F(1, 14) = 3.37$, $p = 0.09$; cross-foster SH: $R^2 = 0.06$, $F(1, 10) = 0.69$, $p = 0.42$; normal care SH: $R^2 < 0.001$, $F(1, 12) = 0.01$, $p = 0.91$).

4 | Discussion

4.1 | Summary

We found, for the first time, that exercise upregulates *Fndc5* expression in the PFC in subjects that experienced our normal care condition. *Fndc5* expression was not upregulated in subjects exposed to either cross-foster care or maltreatment during infancy. *Fndc5* expression positively predicted *Bdnf* gene expression in the PFC of rats exposed to nurturing care (both normal and cross-foster care conditions) during infancy and exercise in adulthood. *Fndc5* and *Bdnf* expression were not related in maltreated subjects or any of the standard housed groups. In summary, *Fndc5* activity is influenced by both exercise and early-life experiences, and future studies should investigate how this relationship may relate to disparities in treatment outcomes in exercise intervention experiments.

4.2 | Exercise and Neuroprotection

Over the past 20 years, the field of exercise neuroscience has gained a lot of traction, and we now know exercising benefits more than just the body. Exercising can elevate mood (Lane and Lovejoy 2001) and enhance memory and cognition (for review, see Voss et al. 2019), as well as decrease symptoms of anxiety and depression (Khanzada, Soomro, and Khan 2015). Several studies have revealed that these changes are related to structural and activation changes in the brain within and between regions important for cognition and emotion processing, such as the hippocampus (Erickson et al. 2011), cerebellum (T. Y. Huang et al.

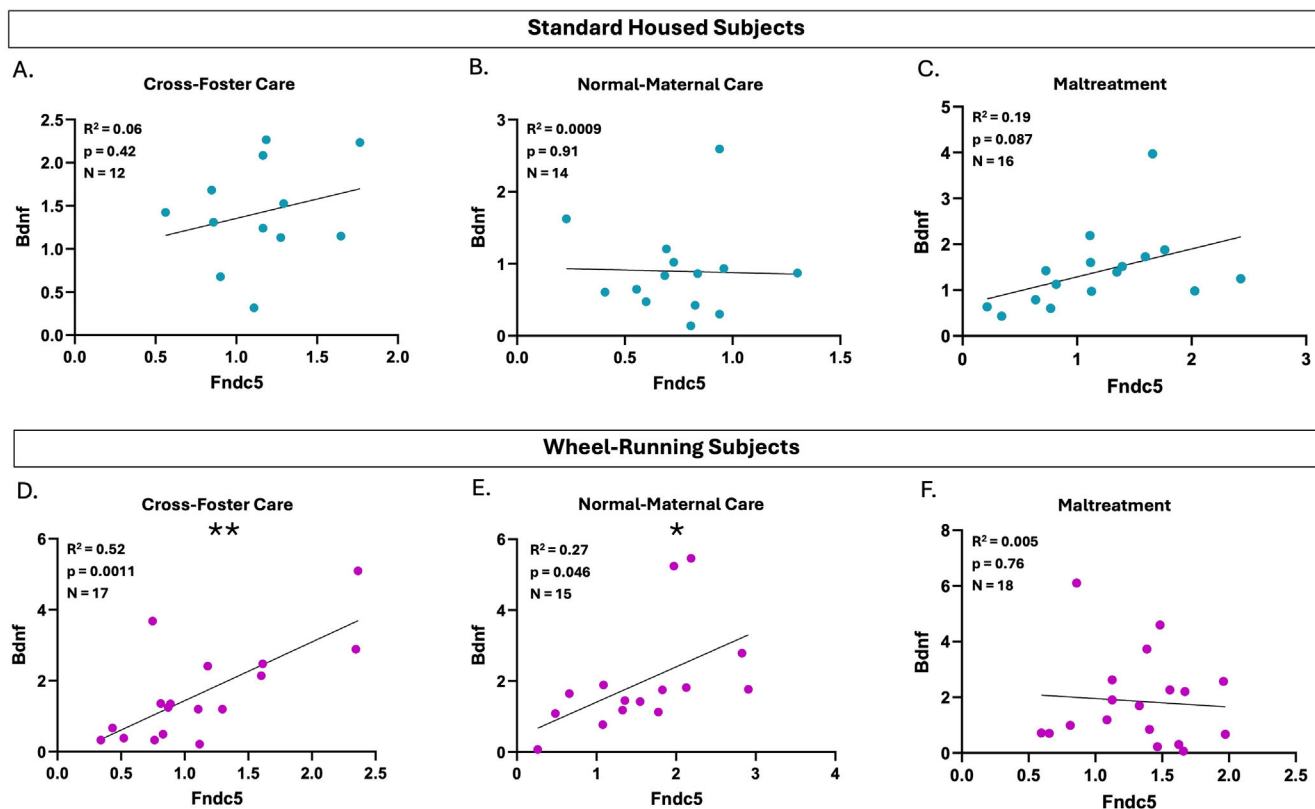


FIGURE 3 | *Fndc5* and *Bdnf* gene expression simple linear regression in the whole PFC in standard-housed (A–C) and exercise-exposed (D–F) subjects. *Fndc5* and *Bdnf* expressions were not related in standard-housed subjects regardless of infant condition (A–C). *Fndc5* expression positively predicted *Bdnf* expression in cross-foster care (D) and normal maternal care (E) subjects exposed to wheel running; however, there was no relationship between *Fndc5* and *Bdnf* in maltreated wheel-running subjects (F). * $p < 0.05$, ** $p < 0.01$, $N = 12$ –18 per group.

2012), striatum (Sacheli et al. 2019), and PFC (Erickson, Leckie, and Weinstein 2014; Moore et al. 2022).

The purpose of this study was to better understand some of the biological mechanisms that allow exercise to have adaptive effects in the brain. Previously our lab has targeted epigenetic regulation of *Bdnf* as a potential regulator of exercise-induced changes in the brain (for review, see Campbell et al. 2022). While there is a consensus that exercise generally upregulates *Bdnf* in the brain, the exact mechanisms that facilitate this are still being explored today. We expanded on this work by investigating a correlative relationship between exercise-induced *Bdnf* and irisin gene expression, as irisin has recently been postulated to upregulate *Bdnf* after exercise in both animal models and human studies. We chose to target the PFC since it is known to be affected by early-life stress, but few studies have investigated the effects of exercise in this region.

4.3 | Irisin and BDNF: Mental Health and Neurological Disease

Irisin is upregulated via exercise; however, it is also found at basal levels throughout the brain, where it is thought to play a neuroprotective role. Irisin expression is reduced in postmortem brains of humans with major depressive disorder (MDD) and in rodent models of depression (Lima-Filho et al. 2023). Experimental upregulation of irisin improves neurological symptoms

and reduces cell death after ischemic stroke (Jin et al. 2019) and reduces amyloid beta secretion in Alzheimer's models (Noda et al. 2018). A recent study by Jodeiri Farshbaf et al. (2020) showed that irisin injection into the hippocampus prevented stress-induced memory impairment and partially prevented anxietylike behaviors in male mice and significantly decreased stress-induced weight loss in both male and female mice. Another study by Islam et al. (2021) revealed that irisin knockout impaired cognitive function in exercised and Alzheimer's diseased mice independently. Taken together, these studies point to irisin as a critical mediator of neural health and resiliency.

The significance of this idea is underscored by the knowledge that early-life stress is a known risk factor for MDD and Alzheimer's Disease (Collins et al. 2022) and that stress alone can decrease BDNF expression (Duman, Deyama, and Fogaça 2021). Furthermore, individuals with depression often show a decrease in BDNF expression that increases with effective drug treatment (Ray, Shannon Weickert, and Webster 2014; Rana et al. 2021; Duman, Deyama, and Fogaça 2021). Several research studies reveal that exercising can improve neural outcomes after stroke (Saunders, Greig, and Mead 2014), improve cognitive function in Alzheimer's disease (Zhou et al. 2022), and lessen depression (Wegner et al. 2020; Zhao et al. 2020) and anxiety symptoms (Lin and Gao 2023). Exercise-induced increases in BDNF have been a major focal point when investigating the mechanisms behind the neuroprotective effects of exercise (Murawska-Ciałowicz et al. 2021; Ke et al. 2011; Piepmeier and Etnier 2015; Ribeiro et al.

2021). However, given that irisin promotes neuroprotection via activating several signaling cascades, it stands to reason that irisin may be an underlying mechanism involved in the BDNF–exercise relationship.

4.4 | Irisin, Early-Life Adversity, and Obesity

Stress is deleterious for the developing brain, in part by dysregulating *Bdnf* activity (Campbell et al. 2022; Campbell, Donoghue, and Roth 2024; Collins et al., 2021). Reductions in BDNF activity can leave the brain more vulnerable to additional insults by lowering natural neuroprotection. This is the first study, to our knowledge, investigating the relationship between early-life adversity and irisin gene expression in the brain. Importantly, we showed that the early-life caregiving environment negatively impacts exercise-induced irisin expression in the brain. This could alter the efficacy of exercise as a treatment intervention tool, though further research is required to fully explain how these factors are related.

The long-term impacts of developmental stress can extend beyond psychological and neurological health. Exposure to adversity during early development can disrupt hormone regulation, leading to dysregulation of metabolic health and feeding behaviors, which ultimately increases the risk for obesity (Colleluori et al. 2022). It is possible that changes in irisin regulation may help explain this outcome. In a 2014 study, Joung et al. (2014) were the first to show that serum levels of irisin are elevated in human adults exposed to early-life adversity independent of BMI or exercise. To our knowledge, this was the first, and remains the only, study to empirically analyze the relationship between early-life adversity and irisin in the central nervous system. Other studies have identified a positive association between peripheral irisin and obesity/BMI. Currently, this is thought to be indicative of a compensatory mechanism as irisin is known to facilitate adipose tissue browning (Huh et al. 2012; Shoukry et al. 2016). Converting white adipose tissue to brown is adaptive, as brown fat tissue burns calories via thermogenesis and regulates blood glucose (Huh et al. 2012). This is a new research area and further investigation is needed to solidify our understanding of the intersection of stress, irisin, and obesity risk.

5 | Conclusion and Future Directions

Previous research indicates that the positive effects of aerobic exercise extend well beyond just physical health (Abbink et al. 2017; van Praag et al. 2005; Voss et al. 2013). Exercising improves mental health and bolsters the brain against neurodegeneration, in part by upregulating BDNF. Understanding the relationship between stressful experiences, exercise, irisin, and BDNF will provide crucial insight into neural mechanisms underlying the brain's response to exercise. This study underscores the importance of uncovering the ways in which our genes and environments interact as the results of these interactions can impact the efficacy of treatment interventions. However, this study is not without limitations. Further research in this arena is needed to concretely elucidate the relationship between the early environment and neuroprotection later in life. Here, we have discovered a correlative association between *Bdnf* and irisin in the

brain following exercise. Future studies should experimentally investigate this relationship by utilizing irisin knockout models or short hairpin RNA interference to determine if preventing irisin expression following exercise prevents *Bdnf* upregulation. Importantly, this is just one study investigating the effects of one specific exercise intervention at one time point in rats exposed to mild caregiver stress during infancy. Additional studies should determine if the results reported here are generalizable across different experimental parameters, such as maternal separation stress, adolescent exercise, and a longer exercise exposure.

Improving physical education in schools and forming exercise community programs have been a popular topic over the past several years. Much of this idea stems from recent research indicating that exercise is a successful tool for staving off dementia in older adults (Law et al. 2020; De La Rosa et al. 2020) and improving symptoms in individuals with depression (Wegner et al. 2020; Zhao et al. 2020) and anxiety disorders (Lin and Gao 2023). However, studies such as this one may indicate that exercising does not affect all individuals equally. A better understanding of how exercising interacts with earlier life experiences may help inform potential exercise intervention strategies in human populations.

Author Contributions

Taylor S. Campbell: Conceptualization and literature review. **Taylor S. Campbell and Katelyn Donoghue:** Data collection. **Taylor S. Campbell:** Writing—original draft. **Taylor S. Campbell and Tania L. Roth:** Writing—review and editing. **Taylor S. Campbell:** Figure design. **Taylor S. Campbell and Tania L. Roth:** Supervision. **Tania L. Roth:** Funding acquisition. All authors have read and agreed to the published version of the manuscript.

Acknowledgments

For assistance with experiments, we thank Samantha Fern, Christina Nelson, Urmi Ghosh, Jessica Smith, and Aimee Skweres. We also thank the OLAM staff at the University of Delaware.

Ethics Statement

The authors have nothing to report.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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