UNDERGRADUATE RESEARCH IN NATURAL AND CLINICAL SCIENCE AND TECHNOLOGY (URNCST) JOURNAL
Read more URNCST Journal articles and submit your own today at: https://www.urncst.com

RESEARCH PROTOCOL OPEN ACCESS

Protocol for Exploring the Role of Irisin in the Enhancement of Spatial Learning Mediated by Aerobic Physical Exercise in Adult Mice

Brahmleen Kaur, BSc [1]

[1] Department of Biology & Psychology, University of Toronto Mississauga, Mississauga, Ontario, Canada L5L 1C6

*Corresponding Authors: brahmleen.kaur@mail.utoronto.ca

Abstract

Introduction: Age-related cognitive decline decreases with aerobic physical exercise in many animal models and humans. Irisin, a myokine and its' precursor FNDC5, has increased hippocampal development to improve learning and memory. This study aims to determine the association between irisin, physical activity and enhancement of spatial learning in adult mice.

Methods: Three experimental studies will be conducted to explore the role of FNDC5/irisin in spatial learning. Study 1 will test the spatial learning ability in C57BL/6 mice using Morris Water Maze (MWM) task in WT, FNDC5+/- and FNDC5-/- mice strains. Study 2 will test the changes in the MWM task due to exogenous administration of FNDC5/irisin in the hippocampus, specifically in the dentate gyrus region. Study 3 aims to test the effect of aerobic physical activity on irisin levels in the dentate gyrus region and the changes in the MWM task.

Anticipated Results: Study 1 results are expected to show that WT mice perform better compared to the FNDC5+/- and FNDC5-/- in completing the MWM task. Study 2 is anticipated to show that hippocampal administration of FNDC5/irisin can rescue the spatial learning phenotype. Study 3 is expected to show that PE improves spatial learning in all mice strains by regulating FNDC5/irisin levels.

Discussion: FNDC5/irisin play a role in enhancing neurogenesis and synaptic plasticity by regulating downstream signalling pathways that are involved in cognitive functions. Aerobic PE enhances this mechanism, resulting in improved spatial learning.

Conclusion: Aerobic PE is expected to significantly regulates hippocampal FNDC5/irisin, which is associated with enhancing spatial learning and cognitive functions.

Keywords: FNDC5; irisin; spatial learning; physical exercise; C57BL/6 mice

Introduction

As age increases, the progressive decline of cognitive functions persists. This decline in cognition varies among functions such as attention, spatial learning and language acquisition [1]. Salthouse, A. (2019) discusses the trends found in normal cognitive aging, where it was discovered that aspects of cognition such as spatial memory, learning and latency declined steadily approximately after age 60 in humans [1]. Furthermore, Yamamoto, N., & Degirolamo, G. J. (2012) describe the adverse effects of normal aging on spatial learning by studying cognitively healthy human adults aged 18-60 [2]. The task required the participants to view four distinct environments on a computer screen from different perspectives and then recall 10 landmarks [2]. Results indicated that senior subjects showed less accuracy when asked to locate landmarks than young participants [2]. This deterioration is variable among a population; however, the declining trend remains a factor across species. Cognitive decline in mice is primarily studied in aging research through the elevated path tests and Morris Water Maze (MWM) test [3]. The MWM test involves learning and remembering spatial information, allowing researchers to measure learning quantitatively [3]. Similarly, the elevated path test examines spatial navigation by having mice navigate to the nearest platform from the center of the bridge or fall off the bridge [3]. The effects of these tests are examined in the hippocampus, a brain region essential to learning, memory and neurogenesis [4]. In one study, mice aged 5-23 months were obtained and tested using the elevated path test and MWM test at ages 6-24 months [3]. The results of the elevated path test showed the latency of mice falling from each bridge, with young mice falling later than older mice, thus portraying that age affects spatial navigation function [3]. In the MWM, the speed to find the quadrant containing the platform in the maze was significantly greater in young mice, indicating an associated decline in spatial ability with age [3]. Taken together, as age progresses, deterioration of general and acute cognitive function such as spatial learning is evident across humans and non-human animals.

Physical activity has been shown to reduce the impact of age-related cognitive decline. Physical exercise (PE) is a subtype of physical activity that is planned, repeated, and structured to improve physical fitness [5]. In more detail, aerobic PE (APE) is a subcategory focusing on cardiovascular conditioning rather than strength training [5]. APE has been studied for its effect on brain plasticity, cognition, and neuroprotection [5]. In mouse models, APE is studied using running wheels to analyze its impact on cognition (via spatial tasks), executive function and the effect of locomotor activity on cognitive decline [6]. In a study by van Praag et al., 3-month-old mice were randomly assigned to runner and control conditions and were trained on the MWM test [7]. The runner group ran approximately 4.8 km/day on a running wheel located in the cage [7]. Both conditions received an injection of bromodeoxyuridine (BrdU), a marker used to label dividing cells and monitor cell proliferation [7]. The study's results demonstrate that mice in the runner group found the platform more quickly, took a shorter path and spent more time in the platform quadrant than the control group [7]. The study demonstrates that running improves spatial navigation and MWM test performance [7]. Furthermore, van Praag et al. suggest that running may improve learning based on the evidence of increased neurogenesis in the runner group with a higher cell count of BrdU labelled cells in the hippocampus [7]. Similarly, Kronenberg et al. found similar results with mice that voluntarily ran on a running wheel in their cage [8]. In this study, the mice assigned to the physical activity (PA) condition were injected with BrdU and provided access to a running wheel in their cages [8]. The results show hippocampal neurogenesis prominently observed in PA condition mice [8]. Additionally, runner condition mice showed an increased number of cells after exercise compared to their controls at six months, one year and two years [8]. These results suggest that although age-related cognitive decline persists, the deterioration can be delayed with PE. Taken together, PE is shown to associate with better spatial task performance, indicating an underlying mechanism that increases neurogenesis in the hippocampus.

Many mechanisms of the association between PE and cognition have come to light. Many researchers have suggested the role of metabolic processes in maintaining and improving cognition. In a 2012 study by Bostrom et al., myokine irisin was discovered as an essential hormone that regulates glucose homeostasis and metabolic processes [9]. This peptide with 112 amino acid residues is derived from the precursor protein, Fibronectin type III domain-containing protein 5 (*Fndc5)*, expressed by the FNDC5 gene and cleaved at the C-terminal [4,9]. Bostrom et al. show that increased circulating irisin levels transform white adipose tissue to brown, indicating improved glucose homeostasis in mice [9]. More specifically, irisin is associated with increased mitochondrial gene expression, improved glucose tolerance and decreased fasting insulin levels [9]. The role of irisin in PE was observed in a human study with 11 inactive participants aged 15 who performed APE and resistance exercise (RE) [4]. The APE consisted of exercising for 45 minutes with a 60% heart rate reserve [4]. RE consisted of participants performing eight muscle training exercises, including chest presses and arm and leg curls [4]. LeBlanc et al. conclude that irisin levels increased significantly after APE, not RE, indicating a positive association between APE and irisin [10]. In addition to its role in PE, irisin is involved in delaying or suppressing neurodegeneration in the brain [11]. In mouse hippocampal lines, a proliferation assay was conducted to test cell proliferation as a direct result of irisin [11]. Results show that 50-100 nM of irisin increased cell proliferation by 80% compared to the control treatment line [11]. The researchers also tested the role of irisin in the Signal Transducer and Activator of Transcription 3 (STAT3)/Adenosine Monophosphate-activated Protein Kinase (AMPK)/Extracellular Signal-regulated Kinase (ERK) pathway, which maintains hippocampal development [11]. Irisin only increased cell proliferation in the STAT3 by activating this signalling pathway [11].

Based on previous studies, PE is associated with improved spatial learning and memory, although the neurological mechanism underlying enhanced learning remains unknown. Irisin has been demonstrated to be involved in hippocampal development, where learning and memory processes are centralized. Thus, irisin could play a role in the neurological process by which PE enhances spatial learning and memory. Therefore, this protocol aims to determine the association between irisin, PE, spatial learning, and memory enhancement in adult mice.

Methods

Learning and memory tests will be conducted using adult C57BL/6 (P40) mice. A total of 3 mice strains will be used in these studies; wildtype (WT; FNDC5+/+), partial knockout (FNDC5+/-) and complete knockout (FNDC5-/-). Each study will use 8 mice from each strain. Mice will be housed in 22℃ cages in groups of 4 with a standard diet and water for meals.

Statistical Analysis

Data will be analyzed using Analysis of Variance (ANOVA) with statistical significance set to $p < 0.05$. Data analysis will include comparing latencies in the following tests: MWM during the retention and reversal phases for studies 1, 2 and 3.

Study 1: Morris Water Maze Learning in All Mice Strains

This study will test spatial learning phenotype in all three mice strains and compare their cognitive abilities at the baseline level [3].

Pretraining: The apparatus for MWM will be covered with opaque black cloth to prevent the presentation of spatial cues [3]. At the beginning of each trial, mice will be placed in quadrant 1 (start location) and allowed to explore the

maze for the platform. The latency to find and climb onto the platform will be recorded. Each trial will be 90 seconds long or will end when the mouse found the platform. Each session will consist of 7 trials, with 5-minute resting intervals between each trial. This phase will consist of 2 sessions per day, for 2 days, with a 2.5-hour break between sessions.

Training: Following the last day of pretraining, 2 sessions of the training phase will be conducted, following the session design from the pretraining phase [3]. The opaque, black cloth will be removed from the apparatus to allow the presentation of standardized spatial cues. In each trial, mice will be placed in quadrant 1 and will be allowed to reach the platform in the target quadrant. The latency of locating and climbing onto the platform was recorded. After the last trial in session 2, a probe trial will be conducted, in which the platform will be removed, and mice will be tested to determine if they remembered the platform location. The time spent in the target quadrant will be recorded.

Reversal: This phase will comprise 4 sessions [3]. For 2 sessions, the platform will be in the upper right quadrant (location A), and the remaining 2 will be in the lower left quadrant (location B). The sessions will run following the procedure from study 1. The starting location and spatial cues will remain the same as in the previous phases. Reversal testing will take place 24 hours after the last training phase.

Study 2: Overexpression of FNDC5 to Test for Sufficiency

This study will examine the effect of artificially administering FNDC5 into mice and test their spatial learning ability using the MWM task [4]. A recombinant adenovirus will be constructed, expressing FNDC5. A new set of WT, FNDC5-/- and FNDC5+/- strains will be divided into experimental and control groups. The adenovirus will be inserted into the experimental group's dentate gyrus (DG).

Surgery: Both mice groups will be anesthetized [4]. Needles will be inserted into target regions of the DG, and FNDC5 (experimental) or scramble sequence (control) will be injected. For recovery, the mice will be placed in their cages for 6 days before micro-injections.

MWM Test: The MWM test will be conducted, repeating the methodology from Study 1 [4].

Study 3: Exploring Effects of PE on Spatial Learning

This study will examine the role of PE-induced FDNC5/irisin regulation with spatial learning [7]. A new mice strain set will be trained to conduct APE using a treadmill paradigm. The mice in each strain will be divided into PE vs. no PE conditions, with those in the PE group undergoing the treadmill paradigm and the no PE group remaining in the home cage.

Treadmill Study Design: Mice will be trained during the dark portion of the light-dark cycle. They will be habituated to the treadmill in familiarization sessions lasting 15 minutes.

Habituation: First, mice will be placed on the stationary treadmill to habituate to the setup for 10 minutes/day for 5 days. Next, the mice will be placed on the operating treadmill starting with the lowest speed at 5 m/minute for 10 minutes/day for 5 days. The speed will be increased in 5m/minute increments until it reaches 45 m/minute.

Experimental Paradigm: The PE condition mice will perform an exercise bout for 30 minutes daily for 7 days before half the mice will be euthanized, have their brains extracted, and will have DG irisin levels measured using an Enzyme-linked Immunoassay (ELISA) assay. The remaining mice will be placed in the MWM test, identical to study 1.

Anticipated Results

Study 1: Reversal Learning

Analysis of the training phase of the MWM is expected to reveal that WT mice would have the shortest latency compared to the FNDC5+/- and FNDC5-/- mice. Additionally, FNDC5+/- would have a shorter latency than FNDC5-/-. The reversal phase of the MWM test is expected to reveal that FNDC5-/- mice may struggle to find the locations compared to the control group. It is anticipated that FNDC5-/- may not find the new location in the given time (90 seconds) to find the platform in the training and reversal phases [4]. FNDC5+/- mice are anticipated to find the platform, taking longer than WT mice in the training and reversal phases of the MWM test.

Study 2: FNDC5 overexpression in spatial learning

Administration of FNDC5 in the DG region of FNDC5-/- mice is anticipated to rescue the spatial learning phenotype. In other words, after administration of the precursor protein, the FNDC5-/- and FNDC5+/- mice are expected to improve their performance in finding the platform in the training and the reversal phases of the MWM test compared to their baseline controls. WT mice are expected to significantly improve their performance on the MWM task from their baseline controls in study 1.

Study 3: Aerobic PE May Enhance FNDC5/Irisin Expression Through Spatial Learning

WT mice in the PE condition are expected to show shorter latency in the MWM condition compared to their controls in the no PE condition, which are not significantly different from the study 1 baseline results for this group. FNDC5+/- and FNDC5-/- mice in PE conditions are expected to show decreased latency in the MWM test compared to the no PE group. This result is similar to the study by Islam et al. (2021), which has demonstrated that FNDC5-/- mice show little to no improvement in spatial learning after voluntary running,

which is when mice can freely access and run on a running wheel placed in their cages, in the MWM reversal phase [12]. In contrast, these WT mice, who were also voluntarily running, showed shorter latency in the reversal phase, similar to the WT mice in this study undergoing the strict exercise regime.

For the ELISA assay and protein study, WT and FNDC5+/- mice may show increased FNDC5/irisin levels in the DG region compared to their counterparts in the no PE condition. FNDC5-/- mice are expected to show little to no increase in FNDC5/irisin levels either in the PE or no PE groups.

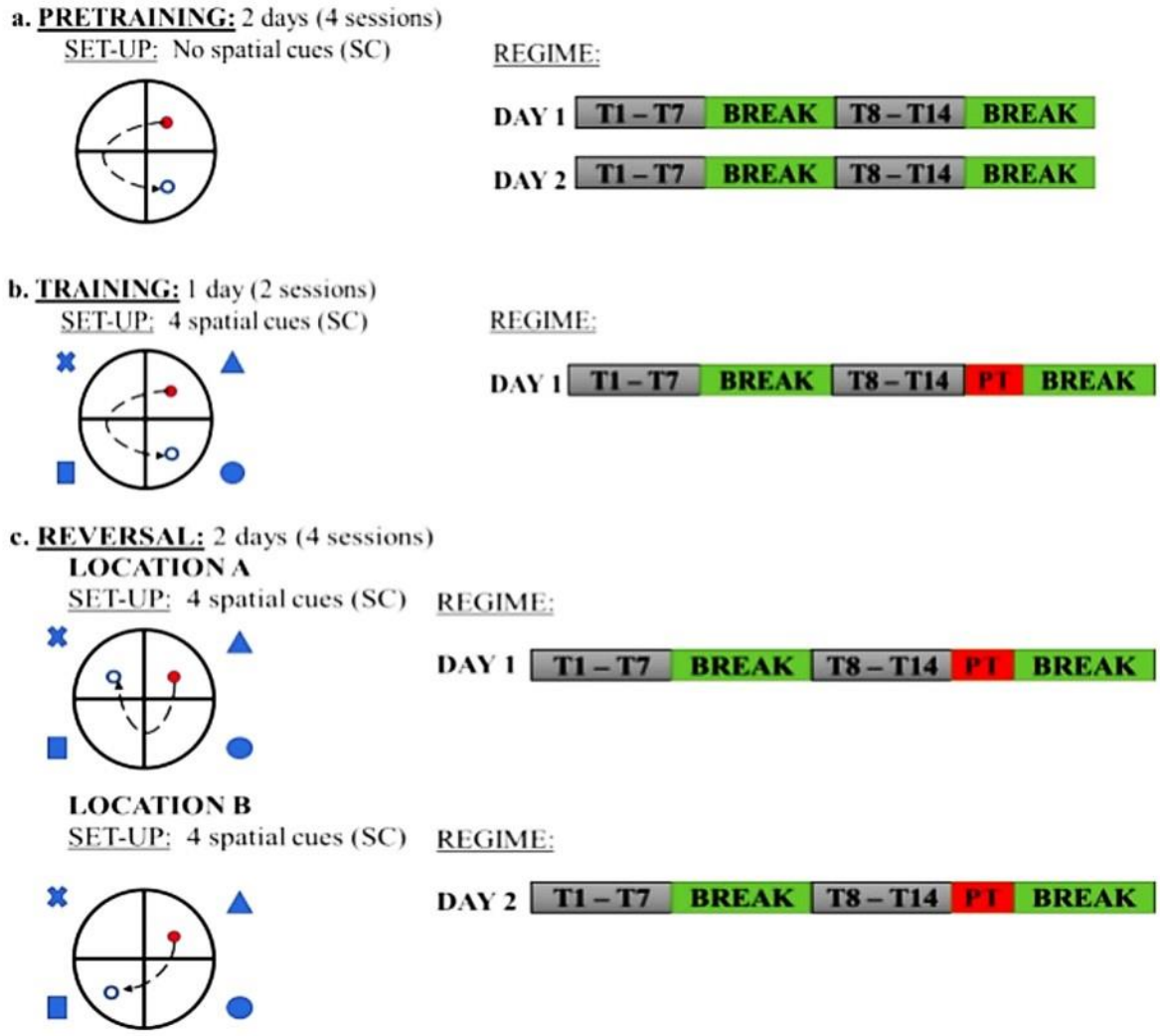

Figure 1. Experimental Protocol for Study 1 - Morris Water Maze (MWM) Test. The large black circle with a horizontal and a vertical line represents the MWM chamber. The small red circle is the starting location. The small blue circle is the platform. T represents 1 trial. Breaks are 2.5 hours long. 1a) Pretraining phase. There are no spatial cues (blue cross, square, triangle and circle) present in this phase. Mice are placed at the red dot and recorded until they find the platform (blue circle). This phase lasts for 2 days. 1b) Training phase. There are 4 spatial cues in this phase, each represented by a blue triangle, square, circle and cross symbols. The cues are placed around the apparatus, identical to the diagram. This phase consists of PT, which represents a Probe Trial. 1c) Reversal phase. The set-up is identical to figure 1b, except for the platform's location. The platform location is changed for locations A and B. This phase consists of PT for each location. This figure was created using Powerpoint™.

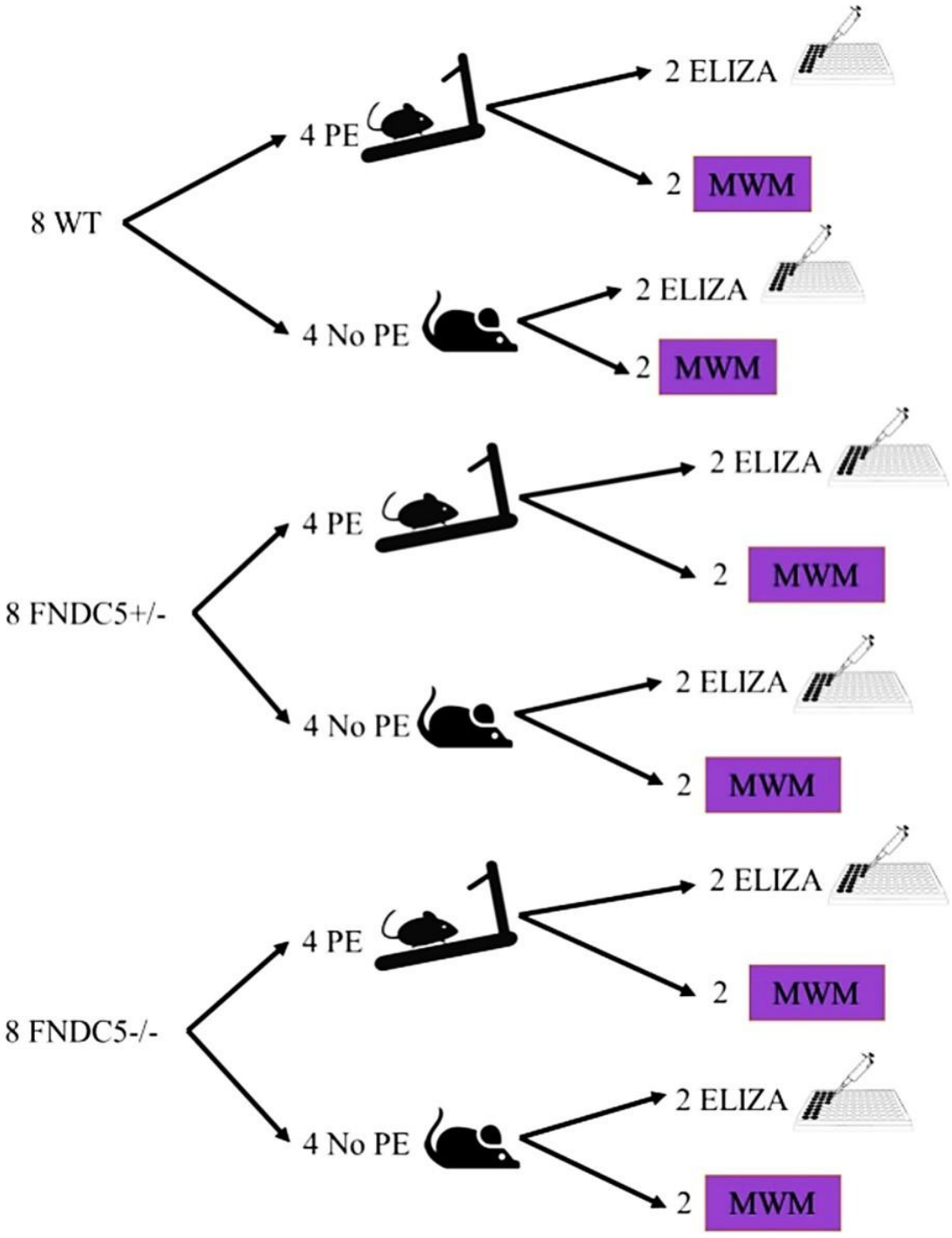

Figure 2. Experimental Protocol for Study 3 - PE, Irisin and Spatial Learning. WT, FNDC5+/- and FNDC5+/+ are divided into PE versus No PE conditions. PE condition trains mice to run on the treadmill, while the No PE condition does not. From both conditions, mice were divided to either complete the MWM test or euthanized in preparation for the ELISA assay to measure irisin levels in the dentate gyrus. The MWM test is identical to the procedure described in Figure 1. This figure was created using Powerpoint™.

Discussion

The reversal phase of the MWM test measured spatial learning in C57BL/6 mice and is expected to show shorter latency in WT and FNDC5+/- mouse strains compared to the FNDC5-/- strain. This result can be interpreted as an association between FNDC5 and spatial learning. Irisin, the end product of FNDC5, may play a role as a regulator of downstream signalling processes in spatial learning, which helps mice navigate through the MWM protocol using spatial cues. Evidence suggests FNDC5/irisin acts within the Peroxisome proliferator gamma coactivator 1-alpha (PGC-1α)/FNDC5 pathway, a process activated by exercise, which affects cognitive function that plays a role in spatial learning [13]. Wrann et al. (2013) have demonstrated that FNDC5/irisin increases with exercise [13]. In addition, the study shows the effects of forced expression of FNDC5 and altering Brain-derived neurotrophic factor (BDNF) expression in the hippocampus. The PGC-1α pathway regulates BDNF, a neurotrophic factor that plays a role in neurogenesis and brain development associated with enhanced spatial learning [13]. The increase in hippocampal BDNF levels is associated with synaptic plasticity, enhanced cognition, and spatial learning.

Since WT mice are expected to have the shortest latency compared to the other strains, the ability of spatial learning may depend on the amount of FNDC5 present in the brain to produce significant levels of irisin. FNDC5+/- are expected to spend longer finding the platform than WT. Furthermore, FNDC5-/- mice are anticipated to struggle to find the platform. Many mice may be unable to do so in 90 seconds, indicating an impairment associated with the lack of FNDC5 in the spatial learning process. The impairment can result from the inactive PGC-1α pathway with decreased expression of FNDC5/irisin, and thereby decreased expression of hippocampal BDNF levels, leading to worse performance in the MWM spatial learning task [13]. However, other associating factors, such as short trial duration or confounding variables affected by the absence of FNDC5 irrelevant to cognition, may have limited the observations.

Administration of FNDC5 in the DG area is expected to improve latency in FNDC5+/- significantly- and FNDC5-/- mice strains, except for the WT strain, where latency remained the same. This observation shows that exogenous FNDC5 is sufficient to rescue the spatial learning phenotype, thus playing a critical role in spatial learning by regulating cell proliferation, maturation and differentiation [4]. These results have also been demonstrated in rats, where FNDC5 knockout Wistar rats treated with irisin injections in the DG region showed shorter latency in the MWM test [14]. These observations suggest that the targeted administration of FNDC5/irisin can rescue spatial learning phenotype by improving hippocampal function. Moreover, the administration of artificial FNDC5/irisin has been associated with increased BDNF levels in the hippocampus [13]. This association would suggest that artificially triggering the activation of the PGC-1α pathway through FNDC5/irisin injections increases hippocampal BDNF expression, leading to improved spatial learning.

The exercise regime in Study 3 is expected to show significant improvement in latency for the MWM test and higher irisin levels in the ELISA assay for WT and FNDC5+/- strains. This observation indicates that PE and FNDC5 are positively correlated variables that play a role in improving spatial learning. This improvement can be the product of BDNF increasing in the presence of FNDC5/irisin [13,14]. Wrann et al. tested direct and peripheral administration of FNDC5/irisin in mice and observed increased hippocampal BDNF [14]. Furthermore, increased circulating FNDC5/irisin has been demonstrated in studies in which mice complete an aerobic PE regime [13]. Together, evidence from these studies indicates that circulating FNDC5/irisin due to aerobic PE is associated with increased hippocampal BDNF. Therefore, increased BDNF and FNDC5/irisin levels after PE improved cognitive functions via neurogenesis and increased synaptic plasticity in the hippocampus.

Altogether, the three studies are anticipated to demonstrate a connection between PE, FNDC5/irisin and spatial learning. It is suggested that FNDC5/irisin is regulated by the PGC-1α pathway, a process regulated by PE [13]. Wrann et al. (2013) show that BDNF levels in the hippocampus correlate positively with FNDC5/irisin levels in circulation [13]. Since PE is expected to increase circulating FNDC5/irisin levels, it can be predicted that FNDC5/irisin uses the PGC-1α pathway, activated through PE, to increase BDNF levels in the hippocampus, therefore enhancing spatial learning. Although this is a proposed molecular pathway, it can potentially indicate an association of PE with increased FNDC5/irisin and improved spatial learning. Further research requires to understand better the underlying neurological mechanism involving FNDC5/irisin, PGC-1α, and BDNF in spatial learning. Such studies may also lead to further exploration of therapeutic applications using FNDC5 treatment for cognitive impairments or neurodegenerative diseases, such as Alzheimer's Disease and Parkinson's Disease. Additionally, further studies are required to confirm the sufficiency of FNDC5 administration to rescue spatial learning.

Conclusions

Overall, the results support the hypothesis that FNDC5/irisin plays a critical role in the neurological mechanism by which PE enhances cognitive processes such as spatial learning and memory. The MWM test shows significant improvement in the spatial learning ability of C57BL/6 mice strains once introduced to the aerobic PE condition. Study 1 results expect that WT mice strain to do well in the spatial learning task, the MWM test, compared

to the FNDC5+/- and FNDC5-/- strains. Anticipated results of Study 2 indicate that administration of FNDC5/irisin to the hippocampus can restore spatial learning phenotype in FNDC5/irisin knockout mice strains. Study 3 results are expected to show that aerobic PE can improve spatial learning by regulating the production of FNDC5/irisin. Taken together, it can be further suggested that the molecular mechanism of BDNF-induced synaptic plasticity by which FNDC5/irisin regulates cognitive improvement is associated with PE. These results can be implicated in future studies exploring potential treatments for cognitive impairments using aerobic training and administration of irisin.

List of Abbreviations Used
MWM: morris water maze
PE: physical exercise
APE: aerobic physical exercise
BrdU: bromodeoxyuridine
PA: physical activity
FNDC5: fibronectin type III domain-containing protein 5
WT: wildtype
RE: resistance exercise
STAT3: signal transducer and activator of transcription 3
AMPK: adenosine monophosphate-activated protein kinase
ERK: extracellular signal-regulated kinase
ANOVA: analysis of variance
DG: dentate gyrus
ELISA: enzyme-linked Immunoassay
SC: spatial cues
PT: probe trial
T: trial
PGC-1α: peroxisome proliferator gamma coactivator 1-alpha
BDNF: brain-derived neurotrophic factor

Conflicts of Interest
The author, Brahmleen Kaur, declares they have no conflict of interest.

Ethics Approval and/or Participant Consent
This study did not require ethics approval as the proposed studies have not been conducted.

Authors' Contributions
BK: made contributions to the conception of study designs, drafted the manuscript, conducted in-depth research of data interpretation, and gave final approval of the version to be published.

Acknowledgements
The author would like to acknowledge Bi-ru Amy Yeung for their contribution in writing, assistance and general mentorship in supervising the completion of this manuscript.

Funding
This study was not funded.

References
[1] Salthouse TA. Trajectories of normal cognitive aging. Psychol Aging. 2019 Feb;34(1):17–24. https://doi.org/10.1037/pag0000288
[2] Yamamoto N, DeGirolamo G. Differential effects of aging on spatial learning through exploratory navigation and map reading. Front Aging Neurosci. 2012;4. https://doi.org/10.3389/fnagi.2012.00014
[3] de Fiebre NC, Sumien N, Forster MJ, de Fiebre CM. Spatial learning and psychomotor performance of C57BL/6 mice: age sensitivity and reliability of individual differences. AGE. 2006 Sep 1;28(3):235–53. https://doi.org/10.1007/s11357-006-9027-3
[4] Mohammadi S, Oryan S, Komaki A, Eidi A, Zarei M. Effects of Hippocampal Microinjection of irisin, an exercise-induced myokine, on spatial and passive avoidance learning and memory in male rats. Int J Pept Res Ther. 2020 Mar 1;26(1):357–67. https://doi.org/10.1007/s10989-019-09842-2
[5] Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: Definitions and distinctions for health-related research. Public Health Rep. 1985;100(2):126–31.
[6] Mandolesi L, Polverino A, Montuori S, Foti F, Ferraioli G, Sorrentino P, et al. Effects of physical exercise on cognitive functioning and wellbeing: Biological and psychological benefits. Front Psychol. 2018;9. https://doi.org/10.3389/fpsyg.2018.00509
[7] van Praag H, Christie BR, Sejnowski TJ, Gage FH. Running enhances neurogenesis, learning, and long-term potentiation in mice. Proc Natl Acad Sci. 1999 Nov 9;96(23):13427–31. https://doi.org/10.1073/pnas.96.23.13427
[8] Kronenberg G, Bick-Sander A, Bunk E, Wolf C, Ehninger D, Kempermann G. Physical exercise prevents age-related decline in precursor cell activity in the mouse dentate gyrus. Neurobiol Aging. 2006 Oct 1;27(10):1505–13. https://doi.org/10.1016/j.neurobiolaging.2005.09.016
[9] Boström P, Wu J, Jedrychowski MP, Korde A, Ye L, Lo JC, et al. A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. Nature. 2012 Jan;481(7382):463–8. https://doi.org/10.1038/nature10777
[10] Blizzard LeBlanc DR, Rioux BV, Pelech C, Moffatt TL, Kimber DE, Duhamel TA, et al. Exercise-induced irisin release as a determinant of the metabolic response to exercise training in obese youth: the EXIT trial. Physiol Rep. 2017;5(23):e13539. https://doi.org/10.14814/phy2.13539
[11] Lee B, Shin M, Park Y, Won SY, Cho KS. Physical exercise-induced myokines in neurodegenerative diseases. Int J Mol Sci. 2021 Jan;22(11):5795. https://doi.org/10.3390/ijms22115795

[12] Islam MR, Valaris S, Young MF, Haley EB, Luo R, Bond SF, et al. Exercise hormone irisin is a critical regulator of cognitive function. Nat Metab. 2021 Aug;3(8):1058–70. https://doi.org/10.1038/s42255-021-00438-z

[13] Wrann CD, White JP, Salogiannnis J, Laznik-Bogoslavski D, Wu J, Ma D, et al. Exercise induces hippocampal BDNF through a PGC-1α/FNDC5 pathway. Cell Metab. 2013 Nov 5;18(5):649–59. https://doi.org/10.1016/j.cmet.2013.09.008

[14] Wrann CD. FNDC5/Irisin – Their role in the nervous system and as a mediator for beneficial effects of exercise on the brain. Brain Plast. 2015 Jan 1;1(1):55–61. https://doi.org/10.3233/BPL-150019

Article Information
Managing Editor: Jeremy Y. Ng
Peer Reviewers: Bi-ru Amy Yeung, Tara Kuhn
Article Dates: Received Sep 06 22; Accepted Dec 15 22; Published Jan 12 23

Citation
Please cite this article as follows:
Kaur B. Protocol for exploring the role of irisin in the enhancement of spatial learning mediated by aerobic physical exercise in adult mice. URNCST Journal. 2023 Jan 12: 7(1). https://urncst.com/index.php/urncst/article/view/436
DOI Link: https://doi.org/10.26685/urncst.436