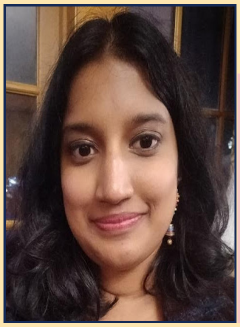
Origins of Exercise-Induced Neurogenesis



My name is Sanjana Venkataraman and I am a Senior majoring in Psychology. Apart from my work with Brain Matters, I enjoy photography and have been a part of the Flashpoint Photography Club. I also enjoy travel and singing. I have worked as a research assistant at the Rhodes Lab since I was a Freshman and enjoy doing research in Behavioural Neuroscience. My research experience and interest in playing an active role in the communication of Neuroscience motivated me to write for Brain Matters.

There are numerous widely accepted short-term and longitudinal benefits of exercise. Established health benefits include the prevention of several diseases and illnesses, lowering the risk of cardiovascular disease, diabetes, and certain kinds of cancers (Clague and Bernstein, 2012; Chapman et al., 2013). Exercise also positively impacts mental health by reducing likelihoods of developing depression and anxiety, and generally improving overall quality of life. These positive effects of exercise make it a rich, constructive area of study in the fields of psychology and neuroscience (Mandolesi et. al., 2018).

Moreover, physical exercise has been known to positively impact the process of acquiring knowledge, or cognition in humans as well as rodents. There is evidence to support the idea that voluntary exercise has aided in combating some biological symptoms of diseases associated with the degeneration of the brain and nervous system (Adlard, et al., 2005; Voss et al., 2013). Apart from studies that show improved cognitive ability in older adults, exercise has also shown to improve cognitive health across the lifespan (Voss et al., 2011). This has been further established by examining different regions of the brain and their relationship with physical activity.

A diverse variety of research has examined the changes in brain regions associated with exercise, with the most outstanding being those that take place in the region widely known to be responsible for learning and memory, the hippocampus. Studies in humans have consistently corroborated this, with randomized clinical trials demonstrating increased volume and blood flow to the hippocampus (Chaddock–Heyman et al., 2016; Erickson et al., 2009).

Across all brain regions that have been studied, the hippocampus is considered to be the most robust in its association with exercise. Hippocampal activity has also been correlated with the speed of running (Li et al., 2012; Chen et al., 2011). Neuronal indicators of hippocampal activity when mice voluntarily run on wheels have also raised the question of whether the activity generated by exercise is chiefly responsible for the observed survival of new cells in the dentate gyrus, a sub region of the hippocampus (Clark et al., 2010, 2011), adding another dimension to the improved cognitive effects of exercise.

Given the abundance of research on exercise induced neurogenesis and its effects on improved cognitive behaviour and function, it is important to scrutinize the crucial connection between the hippocampus and physical activity, so that we better understand the origins of the brain and behaviour related benefits of exercise. By doing so with recent and well established lines of research that have pervaded the neuroscientific community, upcoming research can be contextualized appropriately and appreciated for its relevance to our own daily lives.

Neurogenesis is the growth of new neurons in the brain and has been studied substantively over the last two decades. Rodent models have consistently supported the relationship between exercise and neurogenesis, suggesting that exercise increases the total number of neurons in the hippocampus by two to six-fold (Mustroph et al., 2012.; Rhodes et al., 2003).

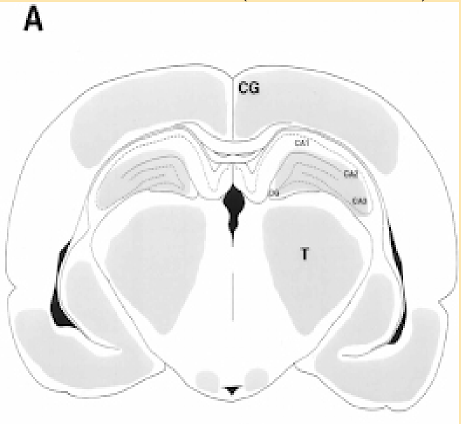
There are two primary hypotheses that address the origins of hippocampal neurogenesis. The first one is the muscle hypothesis that postulates signals associated with this neurobiological change originates from contracting muscles that are actively engaged during exercise (Wrann et. al. 2013). The second leading hypothesis, which will be the focus of this review, suggests that the signals are generated from within the brain itself. This hypothesis holds that interactions within the central nervous system rather than the peripheral are associated with increased hippocampal plasticity, neurogenesis, and improved cognitive performance.

Running results in the immediate activation of the brain that lasts for the duration of the exercise. This can be seen through the lenses of theta oscillations and gamma oscillations as well as immediate early gene (IEG) induction. Immediate early genes are genes that are activated briefly in response to external stimuli thus becoming markers of neuronal activity. Theta oscillations are neural oscillations that occur in the brain and are best viewed through an electroencephalogram (EEG).

Theta waves have been rigorously studied in relation to the hippocampus. Hippocampal theta activity is observed during several different tasks, an important one being motor activity. Theta activations have been related to several different functions like memory, motor behavior, and attention. Studies have demonstrated the positive correlation between voluntary movements and theta oscillation in the hippocampal formation or HPC (the hippocampus and related structures of the dentate gyrus and subiculum). In a running wheel experiment, the speed of running initiation was directly related to the onset frequency of HPC theta oscillations (Bland and Oddie, 2001, Vanderwolf, 1969).

Correlations between speed and hippocampal theta have been reported in several different studies. Li et al. (2012) reported that theta frequency is correlated with speed during the preparatory and initiation phases of wheel running while theta rhythms of middle frequency (6.5-9.5 Hz) are correlated with speed consistently throughout an entire wheel running episode. Hippocampal gamma waves mirror this speed-dependent effect. Gamma waves are a neural oscillatory pattern implicated in working memory and attention. Disruptions in gamma rhythm are commonly seen in disorders such as epilepsy and Alzheimer's disease which further validate its significance and its role in exercise and hippocampal activity. Mice running on linear and Y-shaped paths showed speed modulated increases in gamma frequencies. Interestingly, theta-gamma coupling – the process whereby low frequency that oscillations modulate high frequency gamma oscillations – was also observed to increase with speed (Chen et al., 2011; Ahmed and Mehta, 2012).

Moreover, research into IEGs corroborates the phenomenon of activation in the brain following an acute bout of exercise. IEG-positive cells in the dentate gyrus and other regions of the hippocampus are significantly positively correlated with average running speed over an acute 90-minute period prior to euthanasia (Rhodes et al., 2003). A study using the IEG c-fos (an indicator for neuronal activity) demonstrated that rodents running on treadmills at higher speeds showed greater c-fos expression or neuronal activity in sub-regions of the hippocampus, specifically the dentate gyrus and CA1 and CA3 areas (Lee et al., 2003).



Schematic coronal view of a rodent brain section outlining the hippocampus, and within it, the dentate gyrus, CA1 and CA3 regions. Adapted from "Reovirus Infection and Tissue Injury in the Mouse Central Nervous System Are Associated with Apoptosis by Oberhaus," S. M. et al., 1997, Journal of Virology, 71(3), 2100–2106

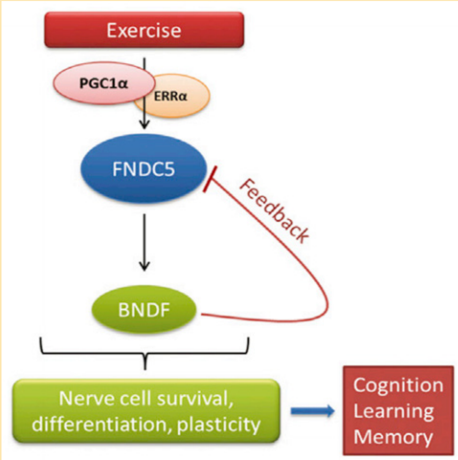
Wheel running is a commonly used model of exercise and has been implemented extensively in the study of exercise-induced neurogenesis. Early studies established that voluntary running in mice given access to wheels was enough to increase neurogenesis. Mice injected with BrdU, an analog for thymidine that incorporates itself into the cellular DNA and acts as a marker for neurogenesis, demonstrated twice as many surviving proliferating cells after being given access to a wheel for an extended period of time (Mustroph et al., 2012; van Praag et al., 1999).

In a study by Clark et al. (2010), we see an even clearer direct connection between IEG expression and neurogenesis in wheel running mice. The study examined the induction of the c-fos and neurogenesis in terms of cell proliferation and survival of new neurons in the dentate gyrus. Results indicated that cell survival at the 25-day mark after the last BrdU injection appeared to double in wheel running mice. Exercise-induced c-fos expression also appeared to elevate and attenuate in accordance with cell survival, corresponding with peak levels of neurogenesis in the initial days of running. It is worth noting that elevations in exercise-induced c-fos expression and cell survival coincided with one another, adding another dimension to neuronal activity and

The abundance of evidence in support of the central hypothesis makes it hard to dispute the role of endogenous brain activity in hippocampal neurogenesis.

Recent research has investigated a new perspective on exercise - brain interactions, focusing on the idea that factors released from the muscles in the peripheral nervous system themselves travel across the blood brain barrier, and form the basis for hippocampal neurogenesis. Among the initial molecules studied were insulin-like growth factor (IGF) and vascular endothelial growth factor (VEGF) (Rendeiro and Rhodes, 2018).

The recently studied FNDC5, is a protein that has its expression regulated by PGC-1α, another protein released from contracting skeletal muscles. A study demonstrated that FNDC5, when delivered through peripheral injections, results in increased levels of the cleaved product of FNDC5, a protein called irisin (Wrann et al., 2013). Several other studies have corroborated the role of irisin/FNDC5 in the muscle hypothesis, some in conjunction with the neurotrophic factor brain derived neurotrophic factor (BDNF) (Delezie and Handschin, 2018; Lourenco et al., 2018).



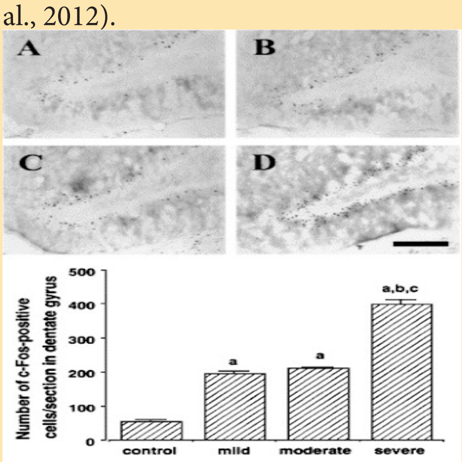
Graphic illustrating the effect of exercise on the relationship between BDNF, FNDC5 and PGC-1α, and their collective influence on neurogenesis and learning. Adapted from "Exercise Induces Hippocampal BDNF through a PGC-1α/FNDC5 Pathway," Wrann, C. D. et al., 2013, Cell Metabolism, 18(5), 649–659

BDNF, a member of the neurotrophin family, is among the most robustly researched factors that are associated with exercise induced hippocampal neurogenesis. BDNF has been demonstrated to peak in its expression a few weeks after birth, during the change from embryonic phase to adult phase in neurogenesis in mice. It is also shown to increase through gene expression in the hippocampus from treadmill and aerobic exercise (Liu and Nusslock, 2018). In wheel running mice, levels of BDNF mRNA within the dentate gyrus of the hippocampus increased within a few days of exercise itself (Neeper et al, 1995).

Further, hippocampal plasticity is also seen as an outcome of the administration of AICAR. AICAR can be defined as an agonist of the enzyme AMP-activated protein kinase, (AMPK) which works by restoring cellular energy levels, i.e. ATP, when they are low by transporting glucose-oxidizing fatty acids in response to muscle contractions such as those that occur during exercise (Schimmack et al., 2006). In a study by Guerrieri and van Praag (2015), mice were administered with AICAR while remaining sedentary or tasked to run with a vehicle (control substance) injection for varying periods of time. Mice in the group that were administered with AICAR and that were made to run for 14 days showed significant increases in AMPK levels compared to the control group. Furthermore, both 7 and 14-day running groups showed a higher number of BrdU positive cells compared to controls, indicating neurogenesis (Guerrieri and van Praag, 2015).

AMPK is also implicated in research aiming to establish the role of the myokine Cathepsin B (CTSB) in exercise - brain interactions. In a simulation of exercise conditions, AICAR was administered in vitro to muscle cells. CTSB protein levels in the cultured cells increased significantly at 6 hour and 12 hour time points when treated with AICAR as compared to controls. The same study also reported elevated levels of CTSB plasma levels due to running as well as elevated CTSB expression in the hippocampus (Moon et al., 2016). The extent to which several of these factors, when isolated or operating in combination with one another can solely be considered responsible for the benefits of running and exercise is very much in dispute. More research in this area is needed for a cause-and-effect relationship to be formed between circulating myokines and effects of exercise (Rendeiro and Rhodes, 2018).

Having now established the consistency with which we see neurogenesis due to wheel running and myokines, as well as concomitant with hippocampal activity, it is important to revisit one of the driving forces behind this area of study. Neurogenesis has several important implications for behaviours demonstrating learning and memory and cognitive performance in general. Tasks like Novel Environment Exploration and the Morris water maze form an important part of the repertoire of measures that aim to assess learning and memory in rodents. Mice with running wheels had twice the number of new neurons compared to sedentary mice and hence displayed a two-fold increase in the number of Zif268+ (protein product of an IEG) cells following tasks like Novel environment exploration and the Morris Water Maze, both of which are tests to gauge spatial learning and memory. This suggests that the neurons generated by running are recruited in hippocampus-engaging tasks and behaviours. Therefore, wheel running-induced neurogenesis can potentially play a functional role in behaviours that engage the hippocampus (Clark et al., 2012).



i) Representative images of IEG cfos indicating neuronal activity in the dentate gyrus during control, mild, moderate and severe treadmill exercise. A = control group; B = mild-exercise group; C = moderate exercise group; D = severe-exercise groupGreater number of black dots indicate more cfos+ cells in the dentate gyrus of the hippocampus. ii) c-Fos positive cells in each group. Adapted from "Dependence of rat hippocampal c-Fos expression on intensity and duration of exercise." by Lee, T.H., et. al, 2003, Life sciences, 72(12), 1421–1436.

These findings with improved measurable behaviour are also supported by studies exploring the subject from a muscle-brain axis perspective. Wild type mice treated with AICAR demonstrate improved spatial memory (Kobilo et al., 2011). The study by Moon et al. (2016) found that CTSB knockout mice that were made to run did not display improvements in spatial memory as gauged by the Morris Water Maze task.

Recent advances in molecular biology, such as optogenetics (the use of light to manipulate cellular activity through micro-LED implants) and cellular tracing techniques, have enabled us to identify and localize cells within the hippocampus that play significant roles in memory. Furthermore, cells responsible for particular brain functions like those relating to memory, can be manipulated to recapitulate an experience as if it were happening in real time (Liu et. al., 2014). Artificial recapitulation of complex experiences like exercise would allow us to assess the role of brain activity in neurogenesis.

Moreover, attempts are being made to isolate the main physiological constituents of exercise. The novel e-stim model attempted to evaluate the extent to which electric stimulation of hindlimb muscles in mice while they are anaesthetized or do not have their hippocampus activated, is sufficient to increase hippocampal neurogenesis. Interestingly, there was a greater proportion of BrdU positive cells in the dentate gyrus of the e-stim mice compared to a control group that was given a sham treatment, but the cells were identified as astrocytes, cells that support and nourish neurons (Gardner et al., 2020). This brings us closer to delineating the causal mechanisms that are at play and other processes like astrogliogenesis (formation of new astrocytes) that may occur as a result of exercise.

The growing body of research on the relationship between exercise like hippocampal activation as well as skeletal muscle contraction, and improved cognitive behaviour is vital for therapeutic interventions for neurodegenerative diseases like Alzheimer's disease and their symptomatology. Localizing the specific effects of muscle contractions, myokines and hippocampal activation are key to giving our understanding of exercise-brain interactions more depth and progressing towards clinical interventions in human research.

References

Adlard, P. A., Perreau, V. M., Pop, V., & Cotman, C. W. (2005). Voluntary exercise decreases amyloid load in a transgenic model of Alzheimer's disease. The Journal of neuroscience : the official journal of the Society for Neuroscience, 25(17), 4217–4221. https://doi.org/10.1523/JNEUROSCI.0496-05.2005

Ahmed, O. J., & Mehta, M. R. (2012). Running speed alters the frequency of hippocampal gamma oscillations. The Journal of neuroscience : the official journal of the Society for Neuroscience, 32(21), 7373–7383. https://doi.org/10.1523/JNEUROSCI.5110-11.2012

Bland, B. H., & Oddie, S. D. (2001). Theta band oscillation and synchrony in the hippocampal formation and associated structures: The case for its role in sensorimotor integration. Behavioural Brain Research. https://doi.org/10.1016/S0166-4328(01)00358-8

Chaddock-Heyman L, Erickson KI, Chappell MA, Johnson CL, Kienzler C, Knecht A, Drollette ES, Raine LB, Scudder MR, Kao SC, Hillman CH, Kramer AF (2016) Aerobic fitness is associated with greater hippocampal cerebral blood flow in children. Developmental Cognitive Neuroscience 20:52-58. https://doi.org/10.1016/j.dcn.2016.07.001

Chen, Z., Resnik, E., McFarland, J. M., Sakmann, B., & Mehta, M. R. (2011). Speed controls the amplitude and timing of the hippocampal gamma rhythm. PloS one, 6(6), e21408. https://doi.org/10.1371/journal.pone.0021408

Clague, J., & Bernstein, L. (2012). Physical activity and cancer. Current oncology reports, 14(6), 550–558. https://doi.org/10.1007/s11912-012-0265-5

Clark, P. J., Bhattacharya, T. K., Miller, D. S., & Rhodes, J. S. (2011). Induction of c-Fos, Zif268, and Arc from acute bouts of voluntary wheel running in new and pre-existing adult mouse hippocampal granule neurons. Neuroscience, 184, 16–27. https://doi.org/10.1016/j.neuroscience.2011.03.072

Clark, P. J., Kohman, R. A., Miller, D. S., Bhattacharya, T. K., Haferkamp, E. H., & Rhodes, J. S. (2010). Adult hippocampal neurogenesis and c-Fos induction during escalation of voluntary wheel running in C57BL/6J mice. Behavioural brain research, 213(2), 246–252. https://doi.org/10.1016/j.bbr.2010.05.007

Clark, P. J., Bhattacharya, T. K., Miller, D. S., Kohman, R. A., DeYoung, E. K., & Rhodes, J. S. (2012). New neurons generated from running are broadly recruited into neuronal activation associated with three different hippocampus-involved tasks. Hippocampus, 22(9), 1860–1867. https://doi.org/10.1002/hipo.22020

Delezie, J., & Handschin, C. (2018). Endocrine crosstalk between Skeletal muscle and the brain. Frontiers in Neurology, 9(AUG). https://doi.org/10.3389/fneur.2018.00698

Erickson, K. I., Prakash, R. S., Voss, M. W., Chaddock, L., Hu, L., Morris, K. S., White, S. M., Wójcicki, T. R., McAuley, E., & Kramer, A. F. (2009). Aerobic fitness is associated with hippocampal volume in elderly humans. Hippocampus, 19(10), 1030–1039. https://doi.org/10.1002/hipo.20547

Gardner, J. C., Dvoretskiy, S. V., Yang, Y., Venkataraman, S., Lange, D. A., Li, S., Boppart, A. L., Kim, N., Rendeiro, C., Boppart, M. D., & Rhodes, J. S. (2020). Electrically stimulated hind limb muscle contractions increase adult hippocampal astrogliogenesis but not neurogenesis or behavioral performance in male C57BL/6J mice. Scientific reports, 10(1), 19319. https://doi.org/10.1038/s41598-020-76356-z

Guerrieri, D., & van Praag, H. (2015). Exercise-mimetic AICAR transiently benefits brain function. Oncotarget, 6(21), 18293–18313. https://doi.org/10.18632/oncotarget.4715

Kobilo, T., Guerrieri, D., Zhang, Y., Collica, S. C., Becker, K. G., & van Praag, H. (2014). AMPK agonist AICAR improves cognition and motor coordination in young and aged mice. Learning & memory (Cold Spring Harbor, N.Y.), 21(2), 119–126. https://doi.org/10.1101/lm.033332.113

Lee, T. H., Jang, M. H., Shin, M. C., Lim, B. V., Kim, Y. P., Kim, H., Choi, H. H., Lee, K. S., Kim, E. H., & Kim, C. J. (2003). Dependence of rat hippocampal c-Fos expression on intensity and duration of exercise. Life sciences, 72(12), 1421–1436. https://doi.org/10.1016/s0024-3205(02)02406-2

Liu, X., Ramirez, S., & Tonegawa, S. (2013). Inception of a false memory by optogenetic manipulation of a hippocampal memory engram. Philosophical transactions of the Royal Society of London. Series B, Biological sciences, 369(1633), 20130142. https://doi.org/10.1098/rstb.2013.0142

Liu, P. Z., & Nusslock, R. (2018). Exercise and hippocampal neurogenesis: a dogma re-examined and lessons learned. Neural regeneration research, 13(8), 1354–1355. https://doi.org/10.4103/1673-5374.235225

Lourenco, M. V., Guerra, L. A., Wilcock, D. M., Kincheski, G. C., Alves-Leon, S., Zhang, H., … Beckman, D. (2018). Exercise-linked FNDC5/irisin rescues synaptic plasticity and memory defects in Alzheimer's models. Nature Medicine, 25(1), 165–175. https://doi.org/10.1038/s41591-018-0275-4

Mustroph, M. L., Chen, S., Desai, S. C., Cay, E. B., DeYoung, E. K., & Rhodes, J. S. (2012). Aerobic exercise is the critical variable in an enriched environment that increases hippocampal neurogenesis and water maze learning in male C57BL/6J mice. Neuroscience, 219, 62–71. https://doi.org/10.1016/j.neuroscience.2012.06.007

Moon, H. Y., Becke, A., Berron, D., Becker, B., Sah, N., Benoni, G., Janke, E., Lubejko, S. T., Greig, N. H., Mattison, J. A., Duzel, E., & van Praag, H. (2016). Running-Induced Systemic Cathepsin B Secretion Is Associated with Memory Function. Cell metabolism, 24(2), 332–340. https://doi.org/10.1016/j.cmet.2016.05.025

Neeper, S. A., Gómez-Pinilla, F., Choi, J., & Cotman, C. W. (1996). Physical activity increases mRNA for brain-derived neurotrophic factor and nerve growth factor in rat brain. Brain research, 726(1-2), 49–56. https://doi.org/10.1016/0006-8993(96)00273-9

Oberhaus, S. M., Smith, R. L., Clayton, G. H., Dermody, T. S., & Tyler, K. L. (1997). Reovirus infection and tissue injury in the mouse central nervous system are associated with apoptosis. Journal of virology, 71(3), 2100–2106. https://doi.org/10.1128/JVI.71.3.2100-2106.1997

Rendeiro, C., & Rhodes, J. S. (2018). A new perspective of the hippocampus in the origin of exercise-brain interactions. Brain structure & function, 223(6), 2527–2545. https://doi.org/10.1007/s00429-018-1665-6

Rhodes, J. S., Garland, T., Jr, & Gammie, S. C. (2003). Patterns of brain activity associated with variation in voluntary wheel-running behavior. Behavioral neuroscience, 117(6), 1243–1256. https://doi.org/10.1037/0735-7044.117.6.1243

Schimmack, G., DeFronzo, R.A., Musi, N. (2006) AMP-activated protein kinase: role in metabolism and therapeutic implications. Diabetes, Obesity and Metabolism, 8(6), 591-602. https://doi.org/10.1111/j.1463-1326.2005.00561.x

Vanderwolf CH (1969) Hippocampal electrical activity and voluntary movement in the rat. Electroencephalogr Clin Neurophysiol 26(4):407–418. https://doi.org/10.1016/0013-4694(69)90092-3

Van Praag, H., Shubert, T., Zhao, C., & Gage, F. H. (2005). Exercise enhances learning and hippocampal neurogenesis in aged mice. The Journal of neuroscience : the official journal of the Society for Neuroscience, 25(38), 8680–8685. https://doi.org/10.1523/JNEUROSCI.1731-05.2005

Voss, M. W., Nagamatsu, L. S., Liu-Ambrose, T., & Kramer, A. F. (2011). Exercise, brain, and cognition across the life span. Journal of applied physiology (Bethesda, Md. : 1985), 111(5), 1505–1513. https://doi.org/10.1152/japplphysiol.00210.2011

Voss, M. W., Vivar, C., Kramer, A. F., & van Praag, H. (2013). Bridging animal and human models of exercise-induced brain plasticity. Trends in cognitive sciences, 17(10), 525–544. https://doi.org/10.1016/j.tics.2013.08.001

Wrann, C. D., White, J. P., Salogiannnis, J., Laznik-Bogoslavski, D., Wu, J., Ma, D., Spiegelman, B. M. (2013). Exercise induces hippocampal BDNF through a PGC-1α/FNDC5 pathway. Cell Metabolism, 18(5), 649–659. https://doi.org/10.1016/j.cmet.2013.09.008