

## Brain Morsels: Packet 6



**EACH BRAIN MATTERS**  
THE CENTER FOR NEUROSCIENCES FOUNDATION

Exercise: Does the brain really care?

And, while we are on the subject of creativity...

Remember that there are 5 pillars of brain health: nutrition, exercise, sleep, social connections and intellectual challenge. In this Brain Morsels, we'll address exercise and why it matters to the brain.



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The simplest idea behind the usefulness of exercise to our brain health is that the brain has high oxygen (O<sub>2</sub>) and glucose requirements – some 20% of our O<sub>2</sub> requirement and 25% of our glucose requirement. Exercise increases our cardiovascular health and thus supports delivery to the brain of both O<sub>2</sub> and glucose, as well as removal of metabolic wastes and carbon dioxide. Hence the frequently heard recommendation that ensuring cardiac health will help to ensure brain health. Ho-hum. Does that make you want to exercise?

In recent years, however, research has begun to focus on exactly how exercise supports brain health, and it turns out to be an astonishing set of findings that show a whole array of ways that physical activity enhances brain health, not just that effect on the cardiovascular system.

We need to start by recognizing that much of the research addresses *exercise* – what we do voluntarily to improve our fitness, but exercise is actually a subset of the full range of physical activity in which we engage. As a species, physical activity has been central to our lives for nearly the entirety of our history. It is no surprise, then, that the very recent transformation of our once highly physically active lifestyle to one that is chiefly sedentary threatens our brains in many ways. Now many of us find ourselves needing to add exercise for the sake of getting physical activity into our lives.

But let's focus on what that activity does in the way of *enhancing* brain health, beginning with what we mean when we talk about brain health. That's a very broad concept, but in general, a healthy brain tends to be more emotionally stable (fewer large emotional swings and better emotional regulation), has a strong cognitive capacity, is resilient to stress, exhibits a high level of plasticity (i.e., the ability to adapt to changing situations), and supports the birth of new neurons in the hippocampus (a hugely important memory center), among other capabilities.

Here's a fun fact for you. You surely know people who just *love* to exercise, to be out and about moving and moving. Likely you also know people who are totally disinterested in exercise and think of going to the gym every day as the ultimate punishment. Which are

you? While there are many factors affecting this inclination in one direction or the other, it turns out that certain genes push us one way or the other. So, some of us are genetically programmed to like and to seek out exercise to a much greater extent than others are. The thing is: you may *not* use this as an excuse not to be physically active!!

Recent research is revealing an amazing interplay of multiple cellular and molecular signaling pathways in the periphery (outside the brain), in the brain itself, and in the interconnections among the gut, brain and microbes in the gut. Some of these pathways even end up modifying the way certain genes are read out, changing the regulation of the genes to make them more or less active! Neurons are affected as are the other major cells in the brain, the glial cells.

Below is a short list of what physical activity does for us. Central to these effects is the release of various factors from exercising muscle, especially BDNF, lactate, VEGF, and IGF (never mind the weird names). These are carried in the blood, can pass into the brain, and there affect various metabolic pathways in neurons and glial cells.

- BDNF is a protein that has important roles in the production of new neurons, in the survival of neurons, in the formation of new connections between neurons (synapses), in cognition, and in regulation of energy. While contracting muscles release BDNF, this factor is so important that it is also produced in the brain.
- Lactate is a byproduct of muscle activity that is essential for the health of brain blood vessels.
- VEGF is a factor that increases the formation of new blood vessels.
- IGF1 is a factor that activates BDNF. It increases the birth and survival of new neurons and also enhances brain plasticity.



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largely by increasing BDNF. Greater brain plasticity also usually translates into better ability to handle stress!

#### Effect on energy production in the brain.

Mitochondria generate energy in cells. Exercise can increase the production of new mitochondria in the neurons and glial cells. It also improves the elimination of damaged mitochondria, something that is harder to do as we age. These effects appear to depend on BDNF (reviewed in Di Liegro et al., 2019)<sup>1</sup>.

#### Increased brain plasticity.

Brain plasticity allows us to learn and adapt to changing internal and external environments. The process involves modifying the connections (synapses) between neurons, strengthening some, adding some, and eliminating others. Exercise increases brain plasticity

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<sup>1</sup> Di Liegro, Schiera, Proia, Di Liegro (2019) *Genes* doi:10.3390/genes10090720

### Increased birth of new neurons in the hippocampus.

It was once thought that all the neurons you were going to have in the brain were present by early childhood. That idea has been debunked, but we get to add new neurons only to the hippocampus, that important memory region in the temporal lobe. We do so throughout our lives although the rate of addition slows some as we age. As the new neurons become incorporated into the hippocampal network, we strengthen our memory-forming capacity. The increase in BDNF that exercise generates enhances the production of new neurons and also increases the size of the neuronal receiving branches – the dendrites, as well as the density of special synaptic structures along the branches (Ben-Zeev et al., 2022)<sup>2</sup>. More new neurons, more synapses, more cognitive and memory capacity.

### Improved health of blood vessels in the brain.

As we age, our blood vessels of course age, too. Certain signaling pathways become less effective with the result that the blood vessels of the brain become narrower, less responsive to situations that normally would increase blood flow to active parts of the brain, and often become inflamed. Exercise promotes the formation of new blood vessels and increases vessel health (Bliss et al., 2021)<sup>3</sup>, in part in response to the release of lactate and a molecule called VEGF from exercising muscles. Both of these changes enhance the health of brain neurons and glial cells, in turn supporting good cognition. A small note though: in this study, daily exercise was best (darn), especially if the form of exercise was varied each day.

The importance of good health in our brain blood vessels should be taken very seriously. The dementia burden around the world is most closely associated with low-level educational achievement, chronic renal disease, diabetes, hypertension, and physical inactivity. All of these are characterized by poor health of blood vessels. In the brain, that condition can impair brain function, eventually to the point of dementia (Bliss et al., 2021)<sup>4</sup>.

### Increased production of dopamine, opioids and endocannabinoids.

Voluntary physical activity is especially good at increasing dopamine concentration. Dopamine comes mostly from clusters of neurons in the brain stem. Those neurons send processes to the prefrontal cortex (executive function) as well as to several centers that are important in emotions. Dopamine helps to motivate us, to regulate emotions and to anticipate reward. It also increases BDNF (reviewed in Di Liegro et al., 2019)<sup>5</sup>.

Exercise also increases the concentration of natural opioids – think runner’s high.

### Reduced frequency and intensity of depression, decreased anxiety.

It is known that depression is associated with a decrease of new neurons in the hippocampus. You also now know that BDNF increases the birth of new neurons; the increase in BDNF helps to relieve depression.

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<sup>2</sup> Ben-Zeev, Shoenfeld, Hoffman (2022) *IMAJ* 24:533-538.

<sup>3</sup> Bliss, Wong, Howe, Mills (2021) *J Cerebral BI Flow Metab* 41:447-70.

<sup>4</sup> Ibid

<sup>5</sup> Di Liegro, Schiera, Proia, Di Liegro (2019) *Genes* doi:10.3390/genes10090720

Reduced neuroinflammation and activation of certain glial cells that play a role in neurodegenerative disorders of the brain.

Microglia are the primary immune cells of the CNS. In their resting state, they conduct surveillance of their territory of the brain matrix. When they are activated by some disruption of normal activity in their territory, they can enter one of two states: in one they promote inflammation, which we don't want in the brain; in the other they release anti-inflammatory factors. Exercise regulates microglial activation to increase release of anti-inflammatory factors (reviewed by Mee-inta et al., 2019)<sup>6</sup>.

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It is now becoming clear that **the type of exercise also matters** (Ben-Zeev et al., 2022)<sup>7</sup>. Aerobic (like sustained activities that increase your heart and breathing rate) and anaerobic (like high-intensity short-duration programs) exercises increase the expression of BDNF, lactate and VEGF. The muscles involved in resistance exercises (like lifting weights or using resistance bands) release signaling molecules like BDNF and IGF1 and breakdown products like lactate into the circulation. These cross the blood-brain barrier into the brain and affect the functions of neurons and glial cells in the active parts of the brain. Endurance exercises affect brain plasticity by increasing BDNF and the birth of new neurons in the hippocampus.



So, what do you do if you are not one of those who loves to exercise, who would rather never set foot in a gym? Well, find a physical activity you like to do and do it regularly or, better, identify a bunch of activities you like to do and pick something for each day so that you don't get terminally bored and gradually back off, ending up in front of a computer or in a recliner, and once more just sitting. One interesting result came about when the scientists thought about the boring-exercise problem. They tested BDNF levels after exercise like running (continued same activity) vs. exercise that requires more attention (Pickleball anyone? Or table tennis? Or video games requiring some motion?) or exercise that simply is more enjoyable (Bliss et al., 2021<sup>8</sup>.) The latter kind of exercise yielded greater BDNF levels.

The Department of Health and Human Services has issued **activity guidelines for older adults. They're very simple – do as much aerobic and muscle-strengthening activities as you can, based on individual health conditions.**

Finally, even if you have some mild cognitive impairment, you can gain with exercise. An analysis of 27 studies with total of 2077 subjects with mild cognitive impairment reported that physical

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<sup>6</sup> Mee-inta, Zhao, Kuo (2019) *Cells* doi: 10.3390/cells8070691.

<sup>7</sup> Ben-Zeev, Shoenfeld, Hoffman (2022) *IMAJ* 24:533-538.

<sup>8</sup> Bliss, Wong, Howe, Mills (2021) *J Cerebral BI Flow Metab* 41:447-70.

exercise improved overall cognitive function, executive function and certain kinds of memory (Biazus-Sehn et al., 2020)<sup>9</sup>.

**Final message about exercise: The brain really does care that you are physically active!!**

Here are some ideas for increasing your physical activity. According to <https://www.humangood.org/resources/senior-living-blog/low-impact-exercises-for-older-adults>, these activities are designed to:

- Put minimal strain on joints
- Pose a low fall risk
- Develop balance and coordination
- Stimulate appetite
- Promote better sleep
- Enhance immune response
- Improve mental health

**Water Aerobics** Especially good for avoiding stress on joints.

**Pilates, Yoga, & Tai Chi** For strength, enhanced flexibility and mindfulness

**Barre** Fosters mobility and strength without the pressure of performance

**Walking** Overall good exercise, especially if you can make it fairly brisk

**Swimming** Good for avoiding stress on joints, is also a cardio workout.

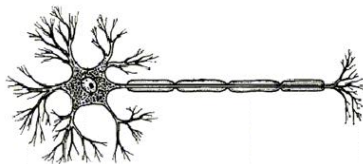
**Cycling** Spin or stationary bikes to build strength, mobility and stamina.

**Weight Training** Resistance exercising.

**Resistance Bands** Mobility and strength

### **What else benefits from all the effects of exercise? The creative process!**

A brain that is not receiving all the fine effects of exercise: better oxygen delivery, better glucose delivery, enhanced birth and survival of neurons - that list from a few pages back – will struggle to be creative. So, consider the possibility that you can be creative with exercise plans, too. One day this, another day that, or figuring out how to make exercise more enjoyable.



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<sup>9</sup> Biazus-Sehn, Schuch, Firth, Stigger (2020) *Arch Gerontol Geriatr* 89:104048.

## And while we're on the subject of creativity.....

Let's delve a little further, beyond the usefulness of exercise. Remember this one thing about creative ideas – it is hard to force them or call them up on demand. When you *try* to be creative, you are quickly reminded that your brain has a mind of its own. Fortunately, most humans possess the bare necessities for creativity: a repertoire of prior knowledge – personal and cultural, memories and impressions gathered over lifetimes, rich emotional lives and histories, language and metaphor, the ability to imagine a future, and perhaps most important here– the ability to see connections between things and to create meaning. Usually all it takes is providing the right mental and environmental conditions and the right physiological state (enhanced by exercise, of course!) for your very own unique brain to reward you with its creative genius.

Even with the right conditions though, you can't bludgeon your mind into giving up new ideas. It takes a gentler approach, and sometimes you must free up your brain by doing something seemingly unrelated. For example, instead of focusing on the thing you are trying to tackle, take a break. Daydream, doodle, dance, or create something unrelated – a new casserole, a garden bed, a quilt piece. Try it. You just might astonish yourself.

And what about the role of mistakes in creativity? Suppose you are sculpting creatures out of clay with your grandchild. What you intended to be horse turns out to look a whole lot more like an animal that is a cross between a kangaroo and a horse. Do you tell yourself you just don't have any skill at sculpting or do you look at it as a new species and name it, say, a kangahorse, and what the heck, make up a story about it with your grandchild.

Or you are drawing an elephant near a house, and you realize that this so-called elephant looks absolutely nothing like an elephant. Do you remind yourself that you can't draw and ball up the paper, or do you make the elephant into a fine bush near the house?



Mistakes certainly can highlight fundamental issues of inadequate knowledge or skill, and they can be the consequences of high stress or sleep deprivation or poor judgement, but often they can reveal an alternative path to solving a problem or creating something unexpected. They can be steppingstones to creativity, unleashing the brain centers responsible for motivation and perseverance and combining them with curiosity and a growth mindset that allows the brain to “play.”

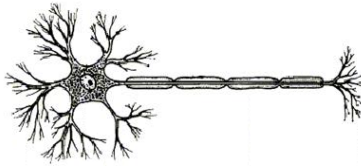
Flashes of creativity can be the result of downtime, when the brain is using the default mode network and is not actively engaged in or focused on specific tasks. When this network is active, the brain is less critical of itself, freeing it to make connections it might otherwise never make. Give yourself the time to abandon your lists and must-do's and all that logical and rational and



reasonable brain activity. Let your brain loose. Even your mistakes can be turned into something wonderful!

**Activity:** For discussion with friends: Do devices help or hinder creativity?

**Activity:** We've included in the puzzle section a coloring page with images of the brain. You *could* color each lobe of the brain so that the divisions in the cortex become obvious. Or, you could go crazy with color and make a truly wild and weird and gorgeous piece of art. You could even draw pictures of what each lobe does..... Try out your creative streak!



## Puzzles

### Puzzle 1

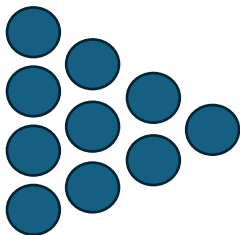
Here's a fun thing to do with others around a table. This game comes from *The Book of Think*, by Marilyn Burns, ISBN:0-316-11742-0. The words below seem to have little in common. Try to think of links among them. You can try to find links across the whole group, or across the column, or across the rows. Be creative. There are no right answers.

Pencil	Apple	Football
Flower	Lamp	Lemon
Basket	Stapler	Clay
Tree	Phone	Clock

### Puzzle 2

A 10-coins problem

Arrange 10 coins (all the same size) so that they make a triangle.



Now move just 3 coins to make the triangle point in the opposite direction.

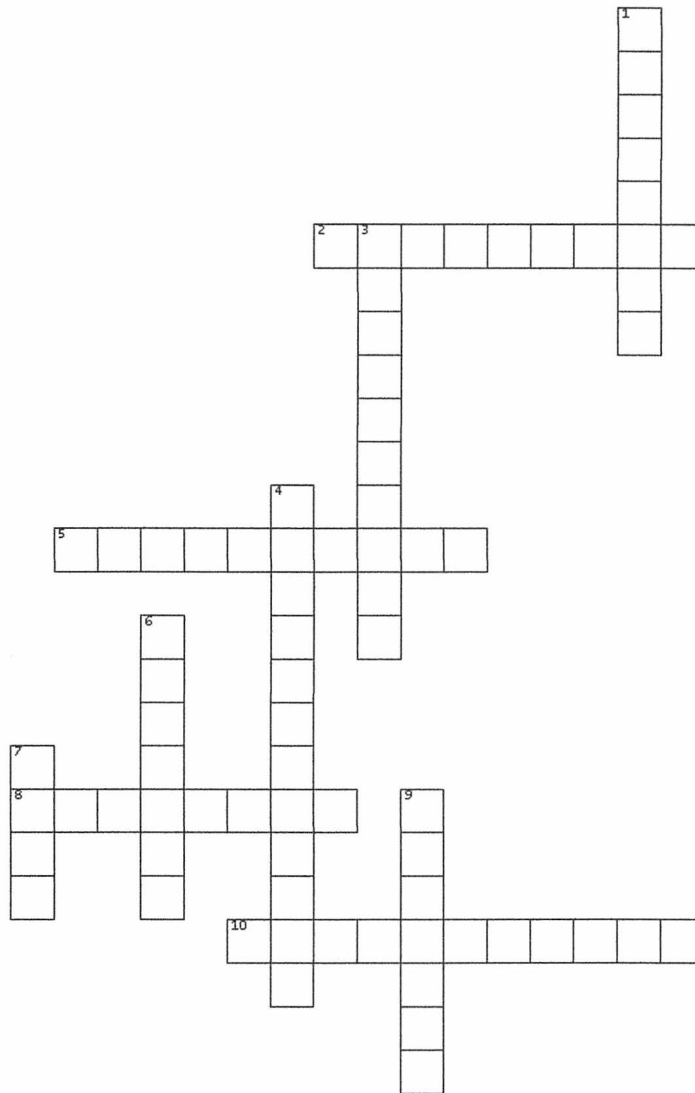
### Puzzle 3

A child's grandmother is only 5 years older than the child's mother. Please explain how this could be.

**Puzzle 4.**

This crossword puzzle includes words from Packet 6 that are related to how exercise affects the brain. Have fun!

## exercise and the brain



**ACROSS**

- 2. the primary immune cells of the central nervous system
- 5. brain's capacity to learn and adapt to changing internal and external environments
- 8. helps to motivate us, to regulate emotions, to anticipate reward, and to increase BDNF
- 10. part of the human brain in which new neurons are born in the adult

**DOWN**

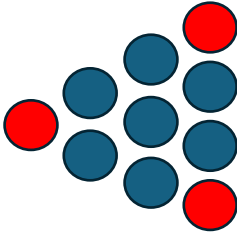
- 1. voluntary activities to improve fitness
- 3. one contributor to increased risk of dementia
- 4. cellular components that generate energy in cells
- 6. a byproduct of muscle activity that is essential for the health of brain blood vessels
- 7. a factor that promotes birth of new neurons
- 9. describes sustained activities that increase your heart and breathing rates



Answers on the following page

## Answers

### Puzzle 2



The red coins are the ones that must move.

### Puzzle 3

The child's other grandmother is the mother's mother.

### Puzzle 4

1. exercise
2. microglia
3. inactivity
4. mitochondria
5. plasticity
6. lactate
7. BDNF
8. dopamine
9. aerobic
10. hippocampus