Examine®

Memory & Focus Supplement Guide

Table of Contents

Introduction

Having good days and bad days is a universal experience. Some mornings we feel sharp, attentive, and capable of completing any task quickly and effectively. Other days feel slow, foggy, and daily life activities can seem impossible. Why does this occur? Which factors most impact cognitive function?

For one, a sleepless night can turn a routine day at work into a slog. Tasks that previously seemed automatic and effortless now drain energy and result in frustration, loss of productivity, and poor mood.

Sleep deprivation and short-term focus issues can also be problems in the context of non-habitual brain processing, such as thinking through complex topics in a difficult class or job, or developing new ideas in creative ways. This type of brain activity relies on the prefrontal cortex region of the brain, which can be especially compromised by sleep deprivation.[1]

Aging is also associated with changes in cognitive ability and processing. “Brain fog” days can become more frequent. Short-term recall becomes more difficult: words sit on the tip of your tongue for a little longer, names are more elusive, and memories don’t seem to stick.

These challenges can also pose health issues because they make it more difficult to track prescription medication timings and refills. If you are taking one or more different prescription medications at various times throughout the day, memory and focus is vital.

Whether it’s from an invigorating workout, a wicked hangover, a good night’s sleep, or aging, cognitive function is subject to short and long-term modulation by genes, the immediate environment, and our actions. Understanding what makes a healthy brain focused is key to gaining proactive control over our cognitive abilities and staying sharp, attentive, and in tune with ourselves.

Defining cognitive function

Focus and memory are two aspects of “cognitive function,” a broad term used to describe a number of related concepts. Factors that affect cognitive function will change one or more of the following:

- Memory — Typically “explicit” memory, or the ability to consciously store and recall information like a name, song, or string of numbers.
- Attention or focus — The ability to direct concentration while ignoring other stimuli.
- Executive function — The ability to modulate behaviors and thoughts, and engage in planning, reasoning, and problem solving.
- Mood — The internal, subjective state of feeling that is generally categorized as “positive” or “negative.”

Optimizing memory and focus is a matter of maximizing positive and minimizing negative effectors of cognitive function.

What do our brains need for top-notch cognition?

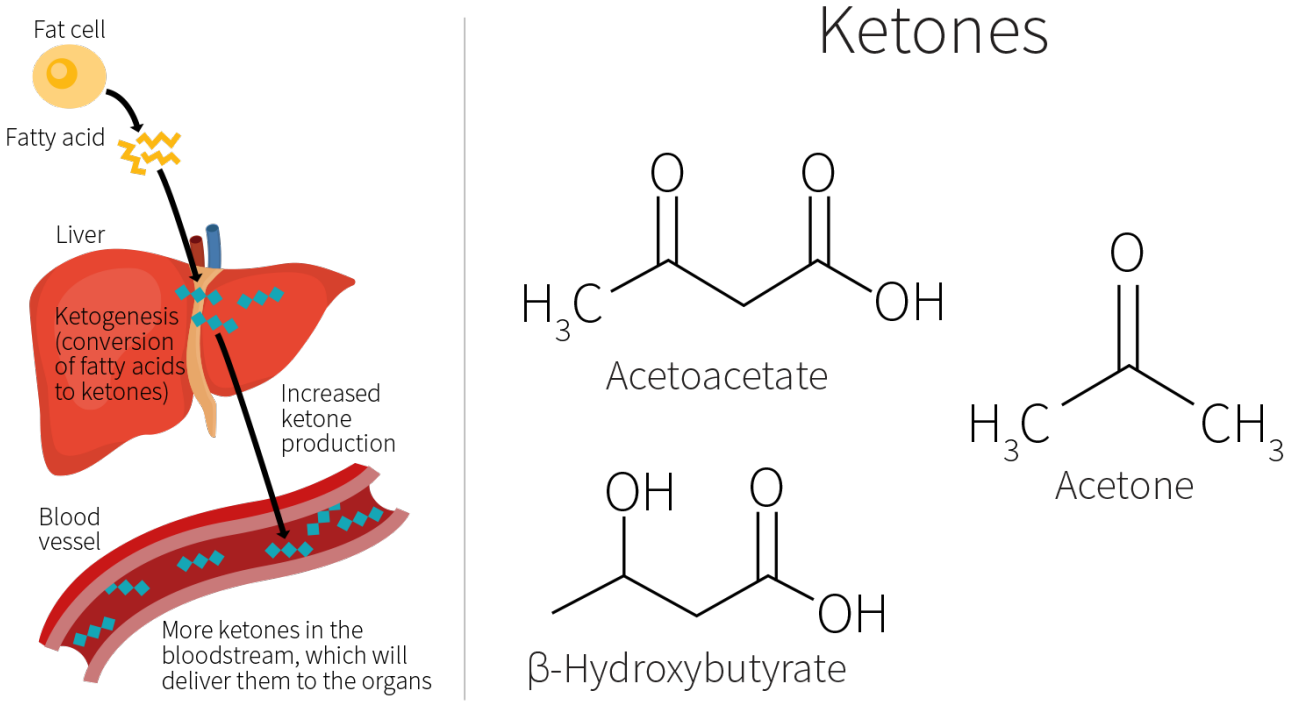
Adequate energy supply

First and foremost, our brains need fuel to keep the lights on. Glucose is the preferred energy substrate, which is taken into neurons in an insulin-independent manner. Glucose can be transported quickly even at very low concentrations, which ensures that the brain *always* gets glucose, if it's available. Once inside the cell, glucose undergoes ordinary glycolysis before it enters the Krebs cycle and the electron transport chain to produce ATP, the "universal energy currency."

The brain can also utilize ketone bodies and convert them to the same molecule generated by glycolysis. The liver produces ketone bodies from fatty acids during an extended fast or ketogenic diet. There is also some research that suggests ketones may provide a specific benefit for cognition.

But what happens when both glucose and ketones are scarce, such as on an extreme hypocaloric diet? Although the body has a number of ways to generate energy in a pinch, such as ramping up autophagy (which literally means, "self-eating"), hypocaloric diets that don't allow for sufficient glucose production or supply enough fats to make ketones can challenge cognitive function. Bodybuilders prepping for contests or athletes cutting weight are all-too familiar with the side-effects of aggressive calorie restriction; mood impairment and "brain fog" are common side effects.

Ketone production



Nutrients such as B vitamins, alpha-lipoic acid, magnesium, zinc, and manganese are required as substrates, cofactors, and enzyme components in a number of these metabolic reactions, so deficiencies can impair cognitive function by disrupting the production, uptake, or utilization of energy in neurons. Supplementing these nutrients can consequently support proper energy supply, especially for people who are deficient.

Adequate blood supply

The brain is a demanding organ, using about 15% of the blood moved by the heart with each beat. Proper blood flow in the brain is essential for the delivery of oxygen, glucose (sometimes ketones), and other macro and micronutrients, so supporting cardiovascular function is intimately tied to maintaining proper cognitive function.

Exercise increases blood flow in the brain acutely and in the long term because it results in heart[2] and

blood vessel adaptations.[3] Some nutrients, such as folic acid, potassium, and vitamin C, have been shown to reduce the risk of stroke, while smoking and alcohol consumption likely increase the risk. Anything that supports or impairs the health of blood vessels is likely to affect cerebral blood flow.

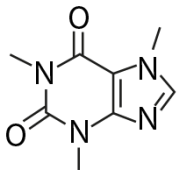
Proper neurotransmitter synthesis and activity

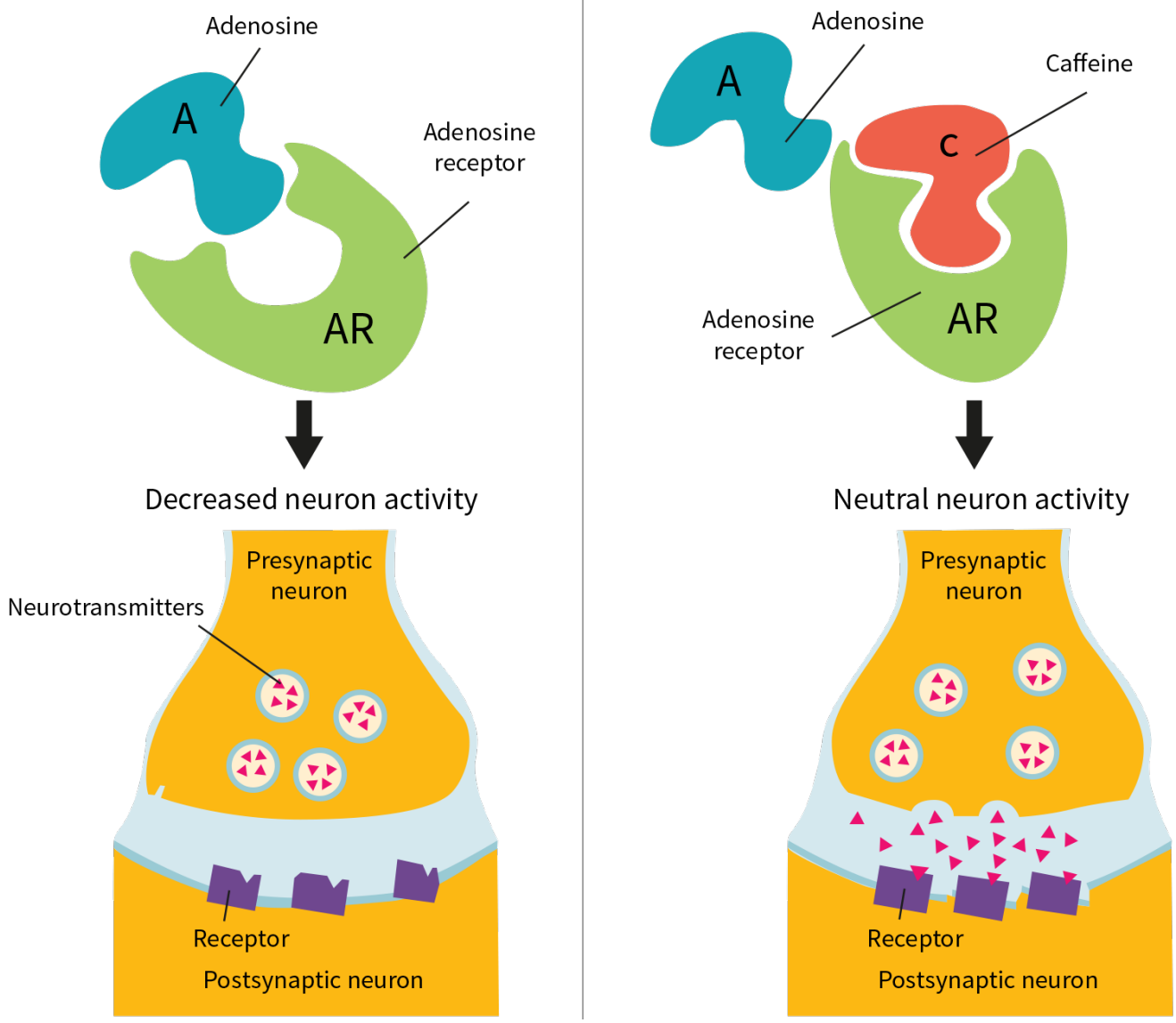
Neurons transmit information in two ways: electrically, in the form of action potentials within the cell, and chemically, in the form of neurotransmitters between cells. Neurotransmitters vary in their chemical structure and include classes of molecules like amino acids (e.g., GABA), amines (e.g., dopamine), gasses (e.g., nitric oxide), peptides (e.g., oxytocin), purines (e.g., ATP), and many others.

In many cases, neurotransmitters are synthesized from amino acids in reactions involving several B vitamins. Certain neurotransmitters require additional nutrients for their synthesis, such as vitamin C, zinc, and choline. Once these neurotransmitters are synthesized, they can be released into the synapse to bind to other neurons. Nutrients are likely to affect neurotransmitter binding, too. Studies have shown how two forms of vitamin B_6 can inhibit GABA binding to postsynaptic receptors[4] and that B_6 deficiency during gestation and lactation can change dopamine receptor number and strength in rats.[5]

Like in energy metabolism, adequate levels of amino acids and micronutrients are required for correct neurotransmitter synthesis, and deficiencies can result in health issues. Additionally, psychoactive drugs exert their effects by altering neurotransmitter release or by binding to receptors meant for other molecules. Caffeine, for example, acts in part by binding to the adenosine receptor, which prevents adenosine itself from binding. Adenosine is one of the molecules responsible for producing the feeling of fatigue, so when caffeine inhibits its binding to the adenosine receptor, we feel more alert.

The mechanism of caffeine





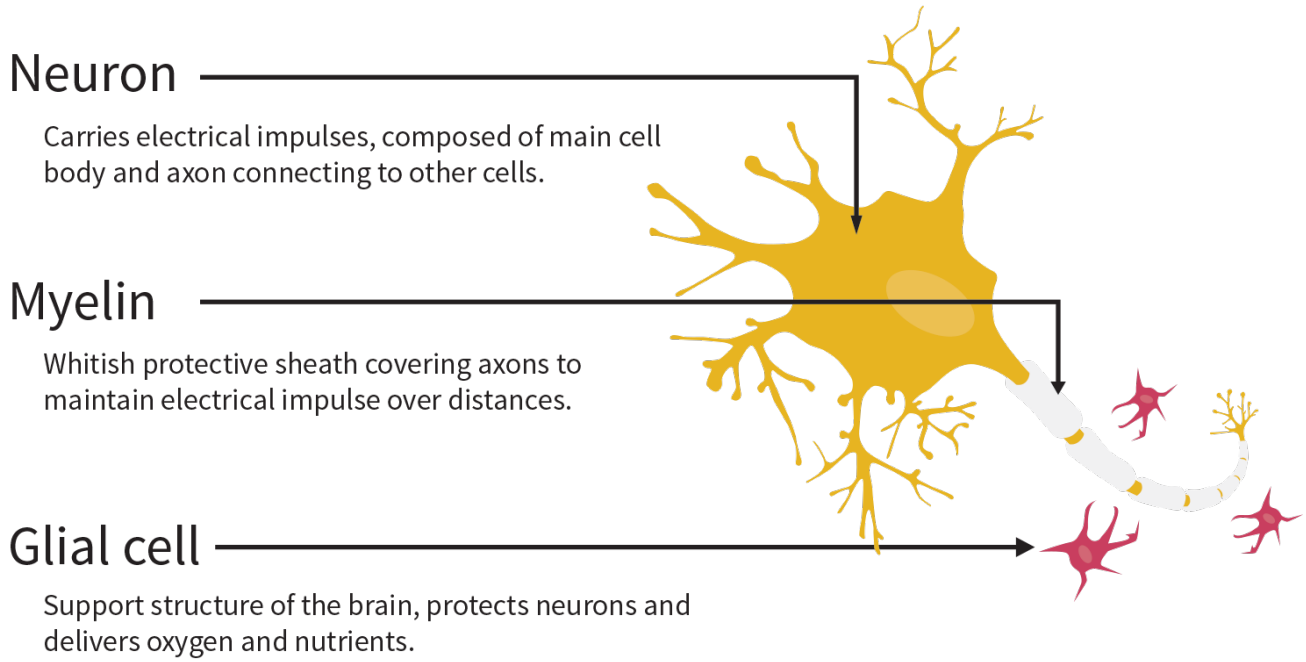
Proper nerve signaling and propagation

Information is also transmitted electrically in neurons in the form of an action potential, which is a change in positive or negative charge that moves from the body of the neuron down the axon. This is caused by the movement of ions across the cell membrane. The axon of the neuron, also called the nerve fiber, is insulated by myelin, a lipid-dense substance that also insulates the neuron, much like the plastic covering an electrical wire. Myelin is segmented along the axon, leaving small gaps called nodes of Ranvier, where the action potential can be strengthened by the additional movement of ions across the cell membrane.

When the myelin layer, or “sheath” of axons, is damaged or degraded, cognitive function can be compromised. Multiple sclerosis (MS) is an autoimmune disease in which the body attacks and degrades myelin. While it is well known that MS causes muscle weakness and loss of motor function, a lesser known symptom is impaired cognitive function and memory loss.[6] The importance of the myelin sheath for

cognitive function is further underscored by the role of myelin damage in Alzheimer's disease pathology.[7]

Brain cells and connections



Nutritional factors influence both action potential generation and myelin synthesis. Folic acid and vitamin B12 are required for maintaining existing myelin, and iron is needed by oligodendrocytes, the cells that produce myelin. Additionally, vitamin B1 (thiamine) is required to maintain the neuron's membrane potential, which is critical for the effective transmission of an action potential.

What can make cognitive function worse?

Hangovers

As fun as a big night out can be, you're likely to experience a number of cognitive impairments the following day, including a reduction in memory,[8] attention,[9] executive function,[10] and increased mental fatigue and anxiety.[11] These effects likely stem from the depletion of vitamins[12] and minerals[13], disruption of metabolic intermediates required for energy production,[14] and the toxicity of acetaldehyde, which is produced by the metabolism of alcohol.

Inflammation

Although the relationship between inflammation and cognition is still being actively explored, inflammation is likely to affect memory and mood, and there is also some evidence suggesting it can reduce attention and executive function.[15] These effects are most likely caused by reduced hippocampal neurogenesis[16] and reduced neurotransmitter synthesis and activity.[17]

When central nervous system (CNS) inflammation is present, microglia, the resident macrophages in the brain, are usually the culprit. When activated, microglia interact with neurons and can influence whether they survive or die. Although microglia play an important role in development by helping regulate the

formation of new synapses and pruning away those that aren't needed, pathological activation later in life can lead to excessive inflammation and, at least in animal models, impaired cognitive function.[18]

Sleep deprivation

Sleep deprivation results in reduced alertness and attention,[19] and worse mood.[20] Some aspects of executive function[21] are also affected. The mechanisms of this effect are complicated and not completely understood, although it's potentially caused by neuronal "tiredness," characterized by desensitized neuronal receptors and cellular machinery that ceases to function effectively [22]. Although the mechanism has yet to be discovered in detail, sleep disturbances may play a role in mild cognitive impairment and Alzheimer's disease, possibly due to increased microglial cell activation.[23]

Although sleep loss degrades several aspects of cognitive function, it seems to hit memory and focus particularly hard. Sleep is essential for memory consolidation,[24] the process through which recent learned experiences are solidified into long-term memory. If you've ever crammed all night for an exam and performed well on the test the next day, only to find that you couldn't really recall a lot of the information a week later, you have likely experienced the effect of sleep deprivation on memory consolidation.

Sleep deprivation also affects working memory, which is the ability to retain, process, and manipulate several pieces of information at once. Working memory comes into play during tasks like remembering and responding to new information gleaned during a conversation, or associating new concepts with previous ideas when learning something new.

Aging

One side effect of the increasing human lifespan is that aging results in greater susceptibility to cognitive decline and neurodegenerative disease. The good news is that some aspects of cognitive function can improve with age, up to a point. Crystalized intelligence, which refers to abilities and knowledge that accumulate over time, remains stable or even improves up to 60 or 70 years of age.[25] In contrast, fluid intelligence, which includes executive function, processing speed, and problem solving, has been estimated to peak in the third decade of life, before it slowly declines in old age.[25]

As the years go by, the risk of transitioning from expected cognitive changes associated with aging to cognitive impairment and neurodegenerative diseases, such as Alzheimer's disease or dementia, steadily increases.

Alzheimer's disease

Discovery

Although dementia is a condition that has been recognized for thousands of years, the underlying causes have only been identified and studied within the last century. In 1907, Aloysius Alzheimer published a paper in which he described the symptoms of a 51-year-old patient under his care:[26]

> *"Her memory is seriously impaired. If objects are shown to her, she names them correctly, but almost immediately afterwards she has forgotten everything. When reading a test, she skips from line to line*

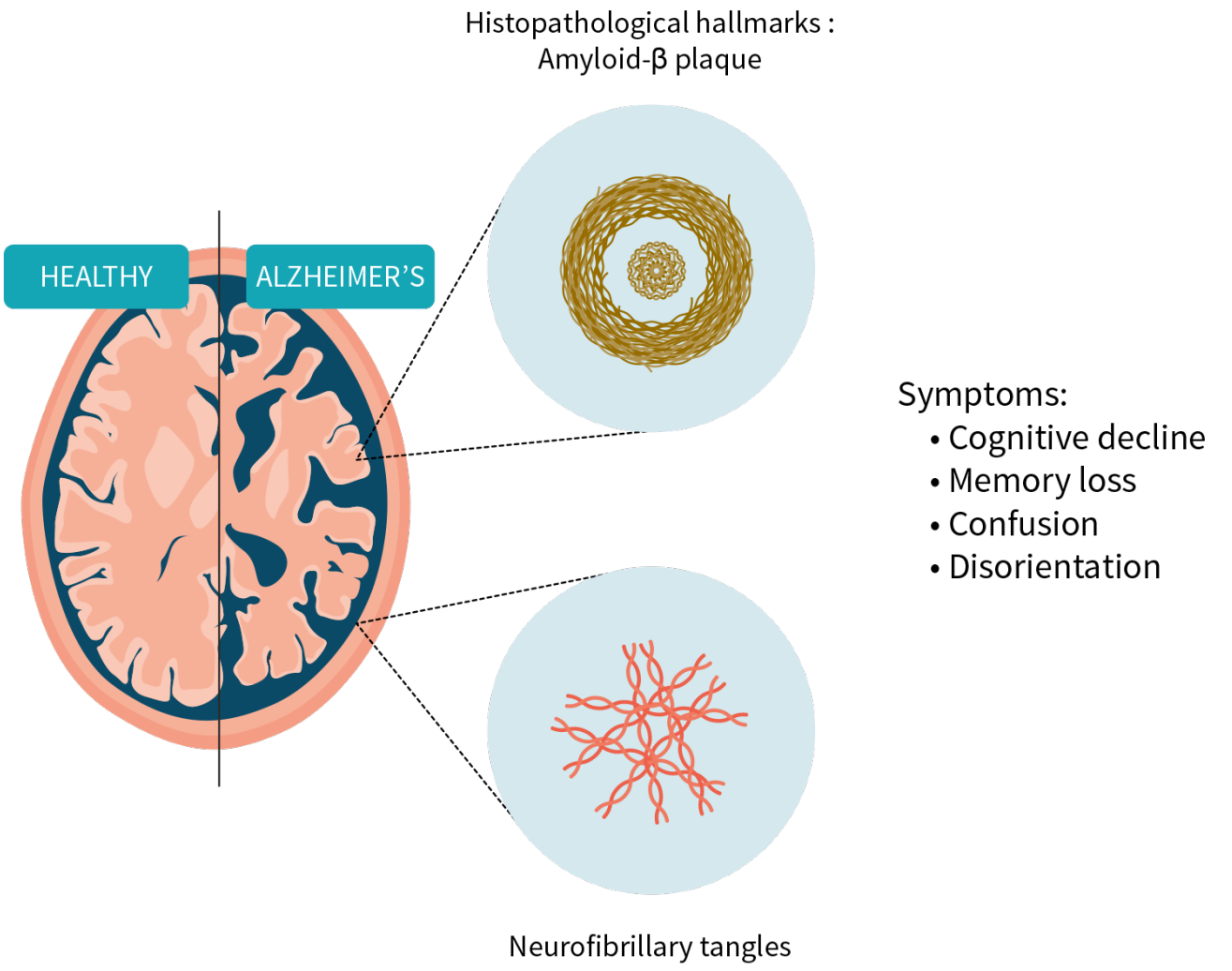
or reads by spelling the words individually, or by making them meaningless through her pronunciation. In writing she repeats separate syllables many times, omits others and quickly breaks down completely. In speaking, she uses gap-fills and a few paraphrased expressions ("milk-pourer" instead of cup); sometimes it is obvious she cannot go on. Plainly, she does not understand certain questions. She does not remember the use of some objects."

After the patient died, Alzheimer used a new histology technique to examine the patient's brain tissue under a microscope and observed the presence of amyloid plaques for the first time, a signature of the disease that was named after him.

Pathology

The pathology of Alzheimer's mirrors that of other neurodegenerative diseases such as Parkinson's disease, Huntington's disease, or amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease) in that all involve the misfolding of various proteins in the brain, leading to aggregation and amyloid plaque deposits. Whether the plaque deposits are a cause or an effect of brain dysfunction isn't completely understood. Nonetheless, progressive loss of neurons and synapses is the main driving force of cognitive decline.

Pathology of Alzheimer's disease



Risk factors

APOE is the gene responsible for encoding low density lipoprotein cholesterol carrier proteins. There are

several variants of APOE in the human population, with APOE ε3 being the most common. Having one or more copies of the APOE ε4 variant is a risk factor for late-onset Alzheimer's disease.

People who express one copy of the gene have a three-fold increased AD risk, while people who express two copies have an eight-fold increased risk.[27] While there are many ongoing experiments to test various theories as to how this risk factor can be mitigated, there aren't definitive answers as of this writing. The best strategy for people that express the APOE ε4 variant may be to make an extra effort to avoid developing co-risk factors, such as diabetes, a smoking habit, and high blood pressure.

Since APOE ε4 is also linked to poor outcomes after traumatic brain injury and even further increased risk for Alzheimer's, people that carry one or more copies of this high-risk allele should consider avoiding careers or activities that are associated with an increased risk of physical injury, such as full-contact sports, construction work, and horseback riding.

How can you reduce your risk of cognitive decline and dementia?

While we can't control the genes we've inherited from our parents, we can still do our best to mitigate risk for cognitive decline and dementia. The World Health Organization (WHO) has published material summarizing interventions that can reduce overall risk, detailed in the figure below.

WHO guidelines for reducing risk of cognitive decline and dementia

"STRONGLY" RECOMMENDED INTERVENTIONS

INTERVENTION	STRENGTH OF EVIDENCE
Adults with normal cognitive cognition should engage in physical activity to reduce the risk of cognitive decline	Moderate
A healthy, balanced diet that follows WHO guidelines is recommended for all adults	Low to High (depending on the dietary component, with fruits, veggies, and fish having the best evidence)
People who use tobacco should stop since it may reduce cognitive decline and dementia, but also greatly improves overall health	Low

"CONDITIONALLY" RECOMMENDED INTERVENTIONS

INTERVENTION	STRENGTH OF EVIDENCE
A Mediterranean-style diet may reduce the risk of cognitive decline in people with normal cognition or mild cognitive impairment	Moderate
Reducing high, harmful levels of drinking may reduce the risk of cognitive decline and dementia	Moderate (but observational)
People with overweight or obesity at mid-life may cognitively benefit from weight loss as they age	Low to moderate
Managing high cholesterol at mid-life can reduce the risk of cognitive decline and dementia later on	Low
Adults with mild cognitive impairment may be recommended to engage in physical activity to reduce the risk of cognitive decline	Low
Cognitive training in adults with normal cognition or mild cognitive impairment may reduce the risk of cognitive decline and dementia	Very low to low
Managing hypertension may reduce the risk of cognitive decline and dementia	Very low (for dementia outcomes, but WHO suggests management for other health benefits in many cases)
Managing diabetes may reduce the risk of cognitive decline and dementia	Very low (concerning cognitive outcomes, but WHO still thinks health benefits outweigh the harms in many cases)

Reference: World Health Organization. *Risk reduction of cognitive decline and dementia*. WHO Guidelines. 2011. ISBN:978-92-4-155054-3

The brain is a very active and sensitive organ. Many factors can boost or hinder its performance through a variety of mechanisms. It's also the most mysterious organ. In many respects, researchers are still limited in their ability to measure its activity, let alone create strong, reliable interventions to alter targeted aspects of cognition. As the secrets of the brain are revealed and new methods for studying the brain are discovered, researchers will gain a deeper understanding of the cellular and molecular controls that are key to a high-functioning brain.

This understanding will lead to better, more targeted interventions, some of which may be covered in future editions of the Supplement Guides. In the meantime, this guide covers a number of supplements with a proven track record for brain health.

However, we strongly recommend you don't stop at supplementation. As we've discussed, lifestyle and individual choices play a significant role in cognitive function. Before adding supplements to a routine, it's important to take care of the foundational aspects of a high-performing brain: minimize negative effectors and maximize the positive. That means getting enough sleep on a consistent basis, eating a healthy diet, and engaging in regular exercise.

Bill Willis, senior researcher
PhD in Biomedical Science

Nicholas Milazzo, researcher
MSc in Medical Science, MPH(c)

Combos

Core Combo

There is only one core supplement for Memory & Focus: the humble blueberry.

Each day, take one of the following forms and amounts of blueberries:

- Blueberry anthocyanins: 0.5–1 gram (500–1,000 mg)
- Blueberry powder: 12 grams
- Freeze-dried blueberries: 24 grams
- Fresh blueberries: 60–120 grams
- Pure blueberry juice: 500 mL (17 oz)

Blueberries can be swapped for other dark berries. If you choose to drink juice, make sure the juice is made of actual berries, not berry-flavored sugars!

> 💡 ***Tip:*** **Try one combo alone for a few weeks**
>
> Taking too many supplements at once may prevent you from determining which ones are truly working. Start with just one of the combos suggested here for a couple of weeks before you consider making any modification, such as adding another supplement, altering a supplements dosage, or incorporating the supplements from an additional combo.
>
> When adding another supplement to your regimen, be methodical. For example, you may wish to take all the supplements from two combos. Select the combo that you wish to try first and take this for a couple of weeks. Then, add one supplement from the second combo and wait another week to see how it affects you. Continue this process until you've added all the supplements you wish to.
>
> If a supplement appears in two combos you wish to combine, don't stack the doses; instead, combine the ranges. For instance, if the range is 2–4 mg in one combo and 3–6 mg in the other, your new range becomes 2–6 mg. Always start with the lower end of the range — especially in this case, since the reason why one of the ranges has a lower ceiling in one combo may be due to a synergy with another supplement in the same combo. Reading through the full supplement entry may help you decide which dose to aim for, but if you're not sure, lower is usually safer.

Specialized Combos

For people who want to improve their long-term memory formation

Take the core blueberries, as described above. Take *Bacopa monnieri* (150 mg of bacosides) with food. In addition, select one of the three following options:

- Take 500–2,000 mg of CDP-choline per day.
- Three times per day, take 400 mg of alpha-GPC (1,200 mg/day total) with or without 250–500 mg of UMP (750–1,500 mg/day total).
- Three times per day, take 400 mg of alpha-GPC (1,200 mg/day total) with or without 25–50 mg of TAU (75–150 mg/day total).

For people who want to improve their attention span

Take the core blueberries, as described above. Take 200 mg of both caffeine and theanine (400 mg total) about 30 minutes before you need increased focus and attention.

If you're not used to caffeine, start with 50 mg of caffeine and 100 mg of theanine. Conversely, veteran coffee drinkers may need more than 200 mg of caffeine to experience its cognitive benefits, in which case the accompanying dose of theanine should be 300 mg. Even higher doses of theanine may not be dangerous, but there is no evidence suggesting higher doses have a greater beneficial effect.

Caffeine should be cycled based on its stimulatory effects. If it is no longer providing noticeable benefits, stop supplementation for 2–4 weeks to reset tolerance.

If you drink tea (*Camelia sinensis*) several times a day, you may not need to supplement theanine. Similarly, caffeine can be consumed in pill form, but also through coffee, tea, energy drinks, and other beverages. You could try replacing 200 mg of caffeine with either 50–75 mg of guarana (assuming a 9% caffeine content) or 1 gram of yerba mate leaf powder (about 17.5 mg of caffeine), but neither option is recommended, and both should be avoided if you take amphetamines (e.g., Adderall).

Other options

People who don't frequently eat meat can add creatine (3–5 grams taken with food) to any combo. Additionally, take 100–160 milligrams per day of soy isoflavones with or without food.

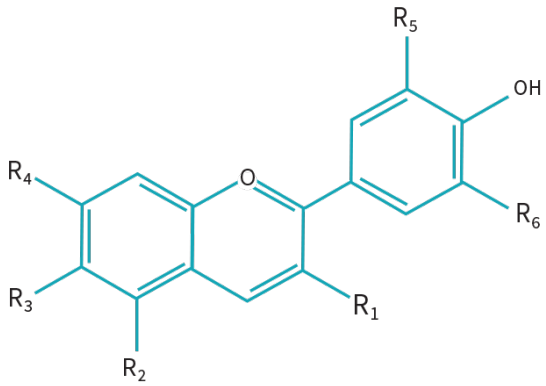
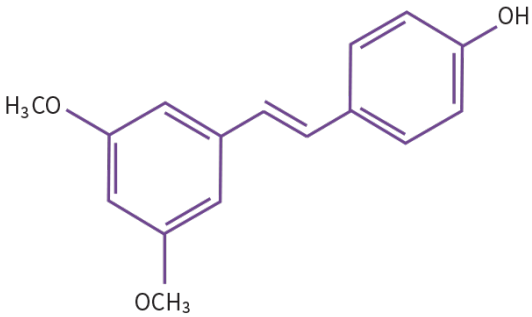
Primary Supplements

Blueberry

What makes *blueberries* a core supplement

The anthocyanins and pterostilbene in blueberries can help protect the brain and reduce cognitive decline.[28] Episodic memory and executive function are most likely to benefit — the former especially in adults with mild cognitive impairment (MCI). Working memory might benefit too, but the evidence is mixed.

Differences between anthocyanins and pterostilbene

Anthocyanins	Pterostilbene
	
Pigments that often give a red, purple, or blue color to the plants that have them	A derivative of resveratrol, the antioxidant found in red wine
Some have antioxidant or anti-inflammatory properties	May possess antioxidant and anticancer properties
More than 635 anthocyanins have been identified	Can help reduce blood glucose and improve insulin sensitivity

Anthocyanins are also the probable reason why blueberries can increase the activity of *nerve growth factor* (NGF), a neurotransmitter protein that allows neurons to communicate with each other. NGF helps neurons grow, branch toward each other, and thus communicate better. In seniors, a diet high in blueberries can improve cognitive ability in as little as six weeks.[29][30][31][32][33]

On average, 100 grams of fresh blueberries contains 200 mg of anthocyanins[34] and 4 mcg (0.004 mg, or 4,000 ng) of pterostilbene,[35][36][37] but actual contents depend on variety, soil, season, weather, farming method, shipping time, storage conditions, and storage duration.

Nanograms (ng) of pterostilbene per gram (g) of blueberry (dry mass)

STUDY	SAMPLES	CULTIVARS	RANGE	AVERAGE
2011	6	1	—	11

STUDY	SAMPLES	CULTIVARS	RANGE	AVERAGE
2005	17	9	12–274	54
2004	3	2	9.9–52	26

References: Rodríguez-Bonilla et al. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2011.[35] ● Rimando and Barney. *Acta Hortic*. 2005. DOI:10.17660/ActaHortic.2005.680.20 ● Rimando et al. *J Agric Food Chem*. 2004. DOI:10.1021/jf040095e

Blueberries are not known to interact negatively with any supplements or pharmaceuticals. However, anthocyanins and pterostilbene are both mildly hypoglycemic, so it is theoretically possible (though not probable) for the blueberry doses listed below to cause low blood sugar (i.e., hypoglycemia) when taken with other supplements or pharmaceuticals that can lower blood sugar, such as most diabetes medicines.

How to take *blueberries*

Studies support the following protocols:

- Blueberry anthocyanins: 0.5–1 g/day
- Blueberry powder: 12 g/day
- Freeze-dried blueberries: 24 g/day
- Fresh blueberries: 60–120 g/day
- Pure blueberry juice: 500 mL/day (17 oz/day). Cheaper "blueberry juices" made with artificial flavoring and added sugar more than with actual blueberries will have little to no anthocyanins. Be sure to check the ingredients label.

💡 ***Tip:*** **Why don't you recommend brands or specific products?**

For two reasons:

- We don't test physical products. What our researchers do — all day, every day — is analyze peer-reviewed studies on supplements and nutrition.
- We go to great lengths to protect our integrity. As you've probably noticed, we don't sell supplements, or even show ads from supplement companies, even though either option would generate a lot more money than our Supplement Guides ever will — and for a lot less work, too.

If we recommended any brands or specific products, our integrity would be called into question, so … we can't do it. That being said, in the interest of keeping you safe, we drew a short list of steps you should take if a product has caught your interest.

Secondary Supplements

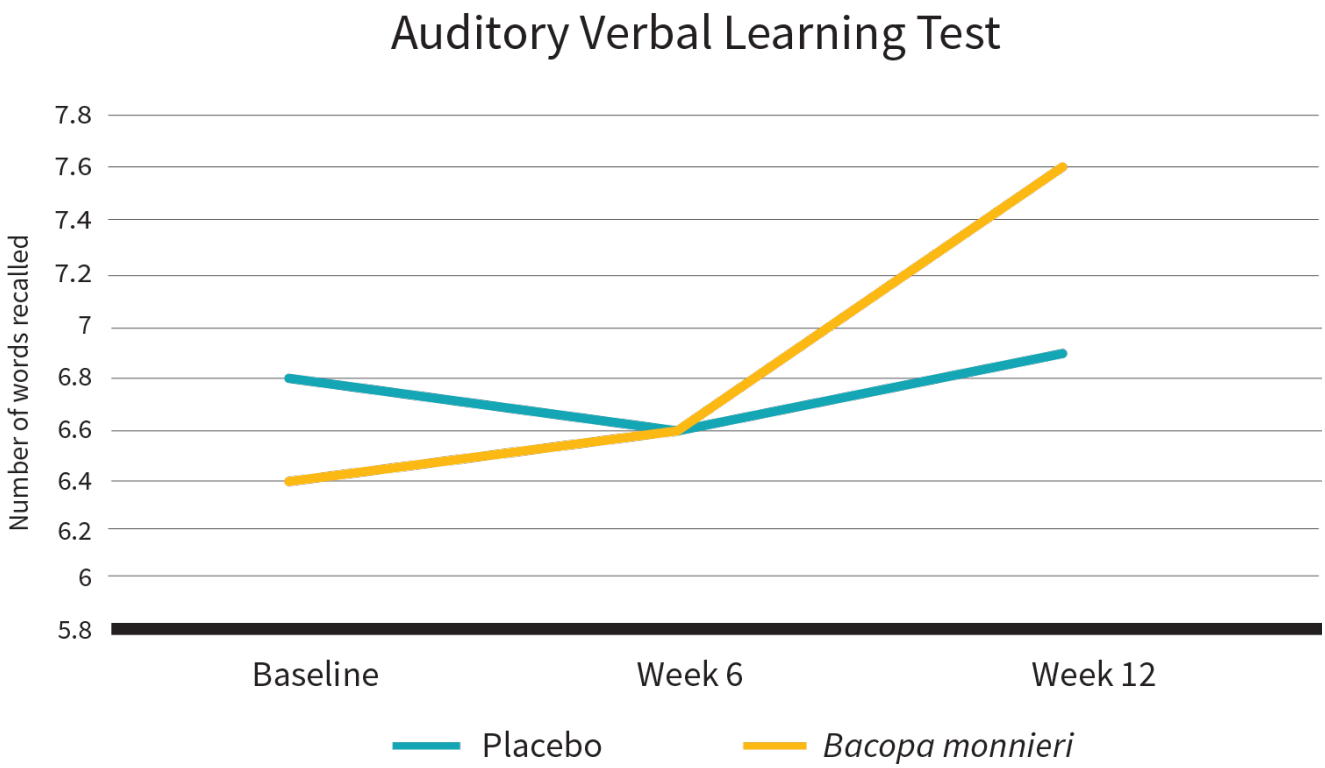
Bacopa monnieri

What makes *Bacopa monnieri* a primary option

Bacopa monnieri is a swamp plant used in traditional Indian medicine to improve memory and cognition. While most effective for elderly people, it can provide benefits for all age groups, but only after one month of supplementation.

Bacopa monnieri's memory-enhancing effects

Extended supplementation with *Bacopa monnieri* may be able to enhance memory recall. During an Auditory Verbal Learning Test (AVLT), the group taking Bacopa monnieri was able to recall more words read off to them from a list of 15 words.



Reference: Calabrese et al. *J Altern Complement Med.* 2008.[38]

Bacopa monnieri reliably improves working memory (to use a computer metaphor, your RAM, so to speak, which determines how much information you can keep at the forefront of your mind). Further research is needed to determine if it can affect verbal fluency, word processing, and attention span.

Bacopa monnieri is not a core supplement because more research is needed to ascertain that it does not interact negatively with pharmaceuticals.

How to take *Bacopa monnieri*

Take a dose once a day with food. Take 150 mg of bacosides, the active compound in *Bacopa monnieri*, so about 300 mg of an extract with a 55% bacoside content.

To supplement the leaf powder, assuming a 10–20% bacoside content, take 750–1,500 mg. Further research is needed to determine the efficacy and safety of higher doses.

Caffeine with Theanine

What makes *caffeine with theanine* a primary option

Theanine is an amino acid with relaxing, but not sedating, properties. It neither interacts with sedative neurotransmitters nor causes feelings of fatigue. It can reduce the overexcitability often caused by caffeine without impairing caffeine's stimulatory effect. In fact, the improvements in concentration (focus and attention span) induced by caffeine and theanine respectively have been shown to be synergistic.

Caffeine is not innocuous. Regular consumption leads to tolerance and often to dependence and withdrawal. You can experience caffeine *dependence* when you become *tolerant* to some of its effects. When tolerance occurs, and you stop consuming caffeine, you can experience symptoms of withdrawal, such as fatigue, irritability, headaches, and — ironically — sleeplessness.

Caffeine also interacts dangerously with several pharmaceuticals, notably tizanidine and a type of antidepressant called *monoamine oxidase inhibitors* (MAOIs). It can also interfere with glucose metabolism, raise blood pressure, raise heart rate, and increase urination (though the effect is usually mild), but those four effects fade away as your tolerance to caffeine develops.

Caffeine can also decrease blood lithium levels. Suddenly eliminating all caffeine from your diet may cause your lithium levels to rise. If you are on lithium medication, keep your day-to-day caffeine intake roughly the same.[39] If you wish to stop taking caffeine, talk with your physician about slowly weaning yourself from it.

You might already be consuming more caffeine than you think. When you calculate your daily intake, consider all your beverages, foods, and supplements (pre-workouts and energy boosters, particularly). Bear in mind that caffeine can be "hidden" in a product — for instance, if you read "guarana seeds" on a label, remember that those are richer in caffeine than coffee seeds.

Caffeine upper limit (400 mg) in number of drinks

References: McCusker et al. *J Anal Toxicol*. 2006.[40] ● Desbrow et al. *Nutr Health*. 2019.[41] ● Ludwig et al. *Food Funct*. 2014.[42] ● Fox et al. *J Agric Food Chem*. 2013.[43] ● McCusker et al. *J Anal Toxicol*. 2003.[44] ● Angeloni et al. *Food Res Int*. 2019.[45]

How to take *caffeine with theanine*

Take 200 mg of both caffeine and theanine (400 mg total) some 30 minutes before you need increased focus and attention. The effects of caffeine and theanine are typically most potent in the first 2 hours after ingestion.

People not used to caffeine should start with 50 mg of caffeine and 100 mg of theanine. Conversely,

veteran coffee drinkers may need more than 200 mg of caffeine to experience its cognitive benefits, in which case the accompanying dose of theanine becomes 300 mg (even higher doses of theanine may not be dangerous, but neither have they shown greater benefits).

Supplementing caffeine on an empty stomach can increase the rate of absorption, but it can also cause stomach upset.

Caffeine should be cycled based on its stimulatory effects. Should it no longer provide noticeable benefits, stop supplementation for 2 to 4 weeks to reset tolerance.

Monitor your overall caffeine intake to ensure you're not consuming unsafe levels.

- For *healthy adults*, caffeine intakes up to 400 mg/day don't raise any general health concerns.[46][47][48] While you *can* consume more, 400 mg is how much caffeine most healthy people can regularly consume in a day without suffering lasting harm.
- If you are *pregnant or breastfeeding*, the scientific evidence differs on what constitutes a safe upper intake: either 200 or 300 mg of caffeine per day.[46][48][49][50][51] The clinical evidence being scarce, it is advisable to keep consumption on the lower side of these recommendations.
- If you have *cardiovascular health concerns*, the long-term implications of regular caffeine intake are less clear — low to moderate intakes could be safe, but consult your physician first.[49][52]

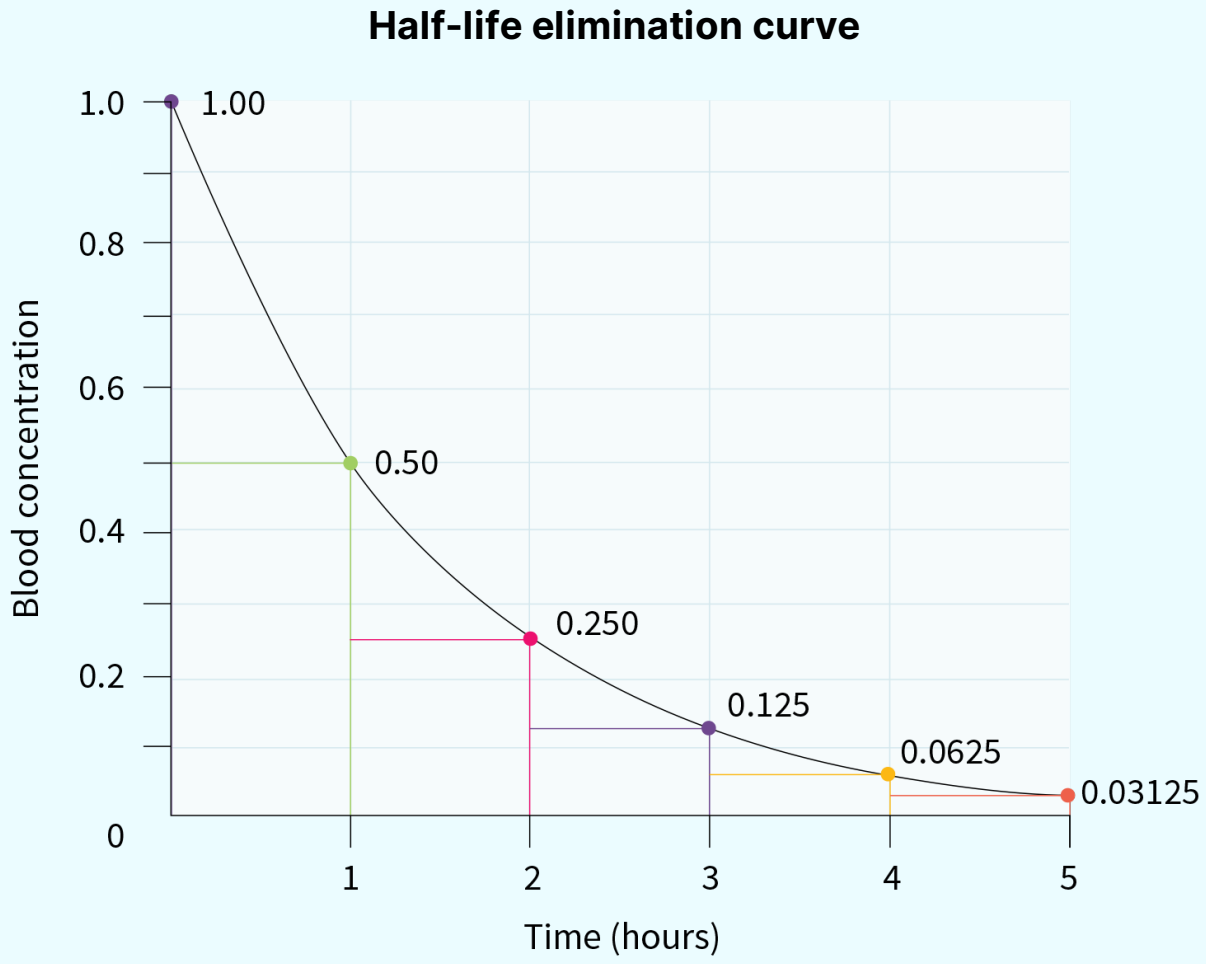
Caffeine can disrupt sleep when consumed in the evening, or even in the afternoon; even if it does not prevent you from falling asleep, caffeine will impair the *quality* of your sleep.

In healthy adults, the average half-life of caffeine falls between 5 and 6 hours, but this number can vary greatly between individuals, from 1.5 to 9.5 hours, because of genetics and other factors — heavy smoking can double the rate of caffeine metabolism, pregnancy can halve it,[53] etc.[54]

🔍 ***Digging Deeper:*** **What is half-life?**

In its simplest definition, half-life is the time it takes for a compound to reach half of its initial concentration in the blood. For example, say you consume one cup of coffee that contains 200 milligrams of caffeine. In 5–6 hours, the caffeine concentration in your blood should drop to 100 milligrams, on average.

Below is an example of a half-life elimination curve. For the hypothetical compound being measured, it has a half-life elimination rate of 1 hour. This means that for every hour that goes by its concentration in the bloodstream is reduced by 50%.



Adapted from: Hallare et al. *StatPearls*. 2020.[55]

Promising Supplements

Atypical Caffeine Sources (Guarana, Yerba Mate)

What makes *atypical caffeine sources* a secondary option

Both guarana (*Paullinia cupana*) and yerba mate (*Ilex paraguariensis*) contain caffeine but also unknown bioactive compounds, so avoid those herbs if you take amphetamines (e.g., Adderall).

Preliminary evidence suggests that both herbs have cognitive benefits beyond those conferred by their sole caffeine content, but further research is needed to confirm this effect.

How to take *atypical caffeine sources*

Different batches can contain different amounts of caffeine and other bioactive compounds, so always start with very low doses.

Some 30 minutes before you need increased focus and attention, take 200 mg of theanine with either 50–75 mg of *guarana* (assuming a 9% caffeine content) or 1 g of *yerba mate* leaf powder (about 17.5 mg of caffeine).

Both herbs may be supplemented as teas, but this makes accurate dosing difficult. Too high of a dose can lead to excessive stimulation and cardiac complications, such as an irregular heartbeat (i.e., an arrhythmia).

Cholinergics

What makes *cholinergics* a secondary option

A supplement is said to be cholinergic when it increases the brain's levels of acetylcholine, a major neurotransmitter associated with memory and attention span. Cholinergics may improve cognitive function in people experiencing cognitive decline, and very preliminary evidence indicates they might benefit people with dementia.[56]

CDP-choline (citicoline) and alpha GPC can provide the brain with the choline it needs to produce more acetylcholine (choline bitartrate is much cheaper, but little of it seems to reach the brain). CDP-choline is also a source of uridine, which itself may improve cognition. In addition, CDP-choline might improve vision in people suffering from glaucoma, a disease state which can cause damage to an eye's optic nerve.

Some temporary side effects, such as nausea and heartburn, have been documented in people taking CDP-choline. The interactions between CDP-choline and other supplements and pharmaceuticals are not well known.

The cholinergic Huperzine-A can inhibit acetylcholinesterase, an enzyme that breaks down the neurotransmitter acetylcholine; as a result, the brain's levels of acetylcholine increase. Its half-life exceeds 24 hours (i.e., after 24 hours, more than half of the dose you took will still be in your system), so it accumulates in the body when taken daily, which is problematic since long-term studies are scarce.

There is a possibility that, over time, the body could adapt by producing more acetylcholinesterase, which would lead to reduced acetylcholine levels and a withdrawal period after huperzine-A supplementation has ceased. While the doses used in the studies (0.2–0.99 mg) were deemed safe in the short term, long-term supplementation cannot be recommended.

How to take *cholinergics*

To supplement with *CDP-choline* for cognitive improvements, take 500–2,000 mg/day.

To supplement with *CDP-choline* against glaucoma, take 1,600 mg/day.[57]

In a single study study, 400 mg of *alpha-GPC* taken thrice a day improved the symptoms of people with mild to moderate Alzheimer's. However, if you suffer, or suspect you suffer from, Alzheimer's, consult a medical professional before taking any supplement. Pairing alpha-GPC with uridine might provide synergistic benefits.

Creatine

What makes *creatine* a secondary option

Supplementing with creatine monohydrate increases the body's creatine stores, which are located primarily in the skeletal muscles. Your cells use creatine to regenerate *adenosine triphosphate* (ATP), life's energy currency, before they turn to burning glucose.

Creatine is a particularly important source of fuel for neurons. A genetic developmental disorder called *creatine transporter defect* (CTD) can cause a creatine deficiency and result in severe cognitive impairment. CTD can be treated with creatine supplementation.

More research is needed to determine whether creatine supplementation can benefit cognition in people who are not deficient. While most people produce enough creatine naturally to prevent cognitive complications, vegans, vegetarians, and seniors might benefit from supplementation more than omnivores. Creatine levels are more likely to be suboptimal in these populations.

Decades of research have demonstrated that creatine is generally well tolerated. The only recorded adverse effects are nausea, diarrhea, and stomach cramps in people taking more than 10 grams at once, and even at such high doses, these effects are rare.[58] Still, should you find yourself particularly sensitive to creatine's digestive side-effects, split your daily dose, take it with some food, and drink more fluids. You could also try *micronized* creatine monohydrate, which dissolves more easily in liquids.

Creatine can cause water retention, which may notably increase body weight. This effect is largely harmless and is reversed when creatine supplementation is stopped. Theoretically, this water retention could harm people whose kidney disorder is being treated with diuretics,[59] which causes water loss.[58] This possible harm is based on known mechanisms rather than human trial data.

Blood levels of creatin*ine* (a byproduct of energy production) are used as an indicator of kidney function, but elevated levels caused by supplemental creatine are not a sign that your kidneys underperform.[60][61] The current evidence does *not* support the persistent notion that creatine supplementation causes kidney damage. In both long- and short-term studies, daily doses up to 10 grams were found *not* to impair kidney function in people with healthy kidneys.[58][62][63][64][65][66][67][68] Daily doses above 10 grams were also found *not* to impair kidney function in people with healthy kidneys, but there are fewer long-term trials on such high doses.[58]

Creatine's ability to raise creatinine levels may, however, mask underlying issues. Consider having your creatinine levels tested (blood and urine tests are available) before you start taking creatine, so as to both get a baseline measurement and check up on your kidney function. If you are already taking creatine yet plan to have your creatinine tested, cease supplementation 3 weeks prior to testing so as to prevent a false positive.

Out of caution, people taking medicines that increase the risk of harm or damage to the kidneys (i.e., nephrotoxic drugs) should skip creatine supplementation.

How to take *creatine*

Take 3–5 grams of *creatine monohydrate* with food (other forms of creatine may be more *expensive*, but studies have not found them to be more *effective*). People with more muscle mass may benefit from as much as 10 g/day, but this claim is not fully supported by the evidence. To supplement with 10 g/day, take 5 grams twice a day.

Loading creatine means taking a high dose for a few days (e.g., 25 g/day for 5 days) before moving down to a smaller maintenance dose, which can be taken indefinitely. This is not necessary for effective supplementation, however; benefits may be felt sooner through loading, but they normalize after a few weeks.

If you wish to load creatine, take 20–25 g/day for 7 days (you may help prevent intestinal discomfort by splitting your daily intake into smaller doses, taking them with some food, and drinking more fluids). Take 5 g/day thereafter.

Some people are creatine nonresponders: the creatine they ingest largely fails to reach their muscles.[69][70] Note that even if supplemental creatine fails to enter your muscles it can still benefit you in other ways, such as by improving your body's methylation status (methylation being a way for your cells to help manage gene expression).

Alternate forms of creatine, such as creatine ethyl-ester, have been marketed to nonresponders, but they lack scientific support. Currently, the best way to lessen creatine nonresponse is to take 5 grams twice a day, each time with protein and carbs, preferably close to a time of muscle contraction (i.e., before or after your workout).

If you are *not* a creatine nonresponder, you need not worry about supplementation timing, though you should remember that taking your dose with food lowers the risk of an upset stomach.

Creatine can be added to any liquid, but it must be drunk within the day, because creatine in liquids degrades into creatinine over time (the higher the temperature and the lower the pH, the faster the degradation). If you add creatine to a hot liquid, increase your dose a little to compensate for potential degradation.

Soy Isoflavones

What makes *soy isoflavones* a secondary option

Isoflavones are bioactive compounds found predominantly in soy products.[71] They are considered phytoestrogens because they are natural, plant-derived (hence the Greek root "phyto-") molecules that exhibit estrogen-like action in the human body. It is important to note that their estrogenic activity is comparably low and whether they increase or decrease estrogen signaling depends on many environmental factors.[72]

However, isoflavones' estrogenic activity may be important for enhancing cognition, since estrogen receptors are found in pretty high quantities in two important brain areas: the hippocampus[73], which plays a major role in memory formation, and the prefrontal cortex[74], which is where a lot of higher reasoning capacity takes place. The theory that isoflavones can improve cognitive function has been bolstered in mouse models, where isoflavones have been shown to improve aging- and drug-related memory problems in otherwise healthy mice.[75]

A systematic review and meta-analysis published in early 2020 evaluated 16 *randomized controlled trials* (RCTs) of 1,386 participants which assessed the effect of soy isoflavones on cognitive function.[76] Postmenopausal females made up 90% of all participants, while males (8%) and premenopausal females (2%) made up the rest (mean age of 60 years).

Intake of soy isoflavones was associated with a very small improvement in overall cognition and memory. The effect on memory tended to be more potent in studies with a duration of less than six months, dosage of more than 100 milligrams per day, and in younger participants (<60 years of age).

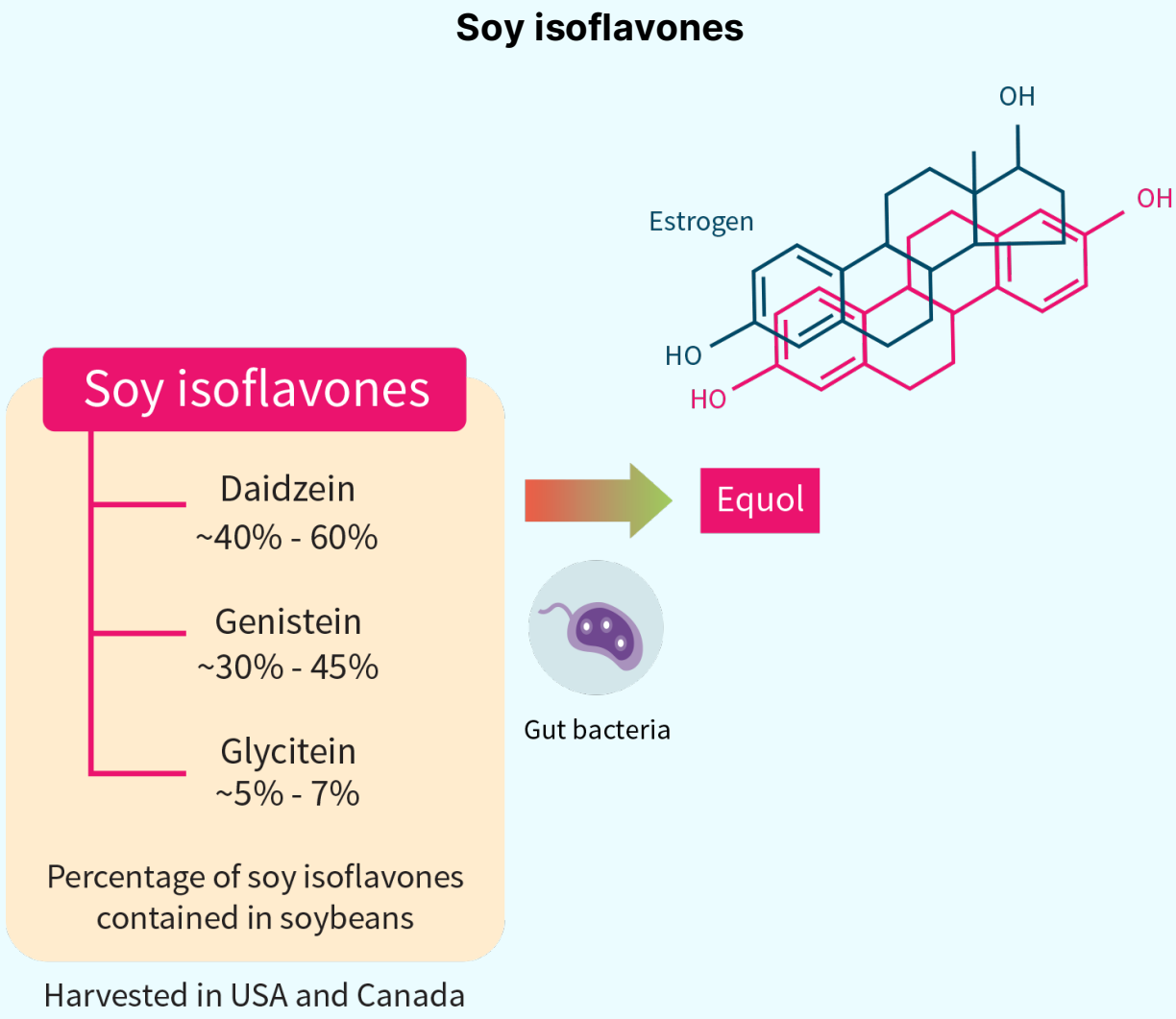
This study also suggests a dose-response relationship for the minimal improvement in cognition and memory from soy isoflavone intake, but these effects may also plateau after extended use. This implies that a high dose (more than 100 milligrams per day) of soy isoflavones could initially enhance cognition, but continued intake may not result in consistent benefits. Moreover, younger people appear to benefit more, suggesting that the potential of soy isoflavones to reduce the risk of cognitive decline in the elderly (>60 years of age) may be slim.

It should be noted that nearly half of the studies in the meta-analysis were rated as "low quality" by the researchers. Several studies reported incomplete outcome data and were not clear on blinding practices, randomization, and allocation concealment. Moreover, the mild benefits reported mainly apply to postmenopausal women, as they comprised 90% of all participants. So, these findings may not directly apply to people outside of this population.

Across all studies, no severe adverse effects or safety concerns were reported.

🔍 ***Digging Deeper:*** **Types of isoflavones in soy**

There are several kinds of isoflavones, but the main ones contained in soybeans are genistein, daidzein, and glycitein, respectively.[77] As you can see below, genistein and daidzein make up most of the isoflavones in soy in roughly equal amounts, and glycitein levels are low in comparison.[78] Daidzein is metabolized by specific gut bacteria to produce equol, the metabolite with greater binding affinity for the beta estrogen receptor.



References: Nakamura et al. *J AOAC Int.* 2000.[78]

How to take *soy isoflavones*

Take 100–160 milligrams per day of *soy isoflavones* with or without food.

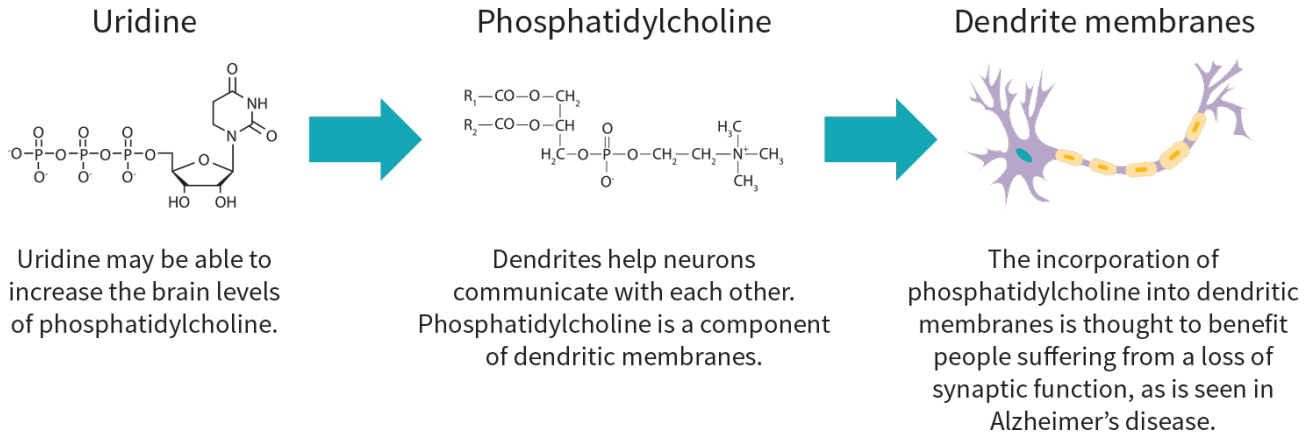
Foods like soybeans, soy nuts, natto, tempeh, and soy protein (water washed, not alcohol washed) tend to be higher in isoflavones, but isoflavone content can range widely depending on the source.[79] Isoflavone content also varies depending on the country of cultivation. For example, the isoflavone content of 100 grams of soybeans from Taiwan is about half that of soybeans from the U.S. For these reasons, if you wish to ensure a sufficient dose, a supplement is preferable.

Uridine

What makes *uridine* a secondary option

Uridine is required to create neuronal membranes; it can also increase the rate of neuronal growth and turnover. There is little uridine in food. While the body can synthesize enough to satisfy its basic needs, preliminary evidence suggests that supplementation can benefit cognition.

How uridine could benefit cognition: mechanistic chart



Uridine has only been shown to be safe in the short term; more research is needed before long-term supplementation can be recommended. On the bright side, the benefits to cognition appear to be lasting (if new neurons are formed thanks to additional uridine, they do not just die off when supplementation is discontinued).

Uridine is thought to be synergistic with blueberry and *Bacopa monnieri*, though more research is needed to confirm this, too.

How to take *uridine*

Uridine is usually supplemented through uridine monophosphate (*UMP*), which is ⅔ uridine. The standard dosage for uridine is 250–500 mg twice a day (i.e., 500–1,000 mg/day), which translates as 375–750 mg of UMP twice a day (i.e., 750–1,500 mg/day).

Other options include triacetyluridine (TAU) and CDP-choline. Following oral supplementation, both appear to be effective in reaching the human brain.

If *TAU* is indeed seven times more bioavailable than an equimolar amount of uridine, as one study noted, then much lower doses could be used: 35–70 mg twice a day (i.e., 70–140 mg/day). Research on this compound is still scarce, however, which makes it hard to recommend.

As for CDP-choline, it is a source both of cytidine, which the body converts into uridine, and of choline, which the brain converts into acetylcholine. To supplement CDP-choline for its pro-uridine content, high doses are required: 500–1,000 mg twice a day (i.e., 1–2 g/day).

Further research is needed to determine if taking uridine with food is more effective than taking it on an empty stomach.

Unproven Supplements

Coleus Forskohlii with Artichoke Extract

What makes *Coleus forskohlii with artichoke* extract an unproven supplement

Long-term potentiation (LTP) refers to a persistent strengthening of synapses. *Chemically induced long-term potentiation* (CILTeP) refers to the initiation of LTP through the use of compounds that increase cell levels of cyclic adenosine monophosphate (cAMP). Elevated cAMP levels in brain cells are associated with improved cognition, memory formation, and muscle contractions.

The standard CILTeP combo associates forskolin (the bioactive constituent in *Coleus forskohlii*), to increase cAMP production, with luteolin (the bioactive constituent in artichoke extract), to inhibit cAMP deactivation. However, there is no evidence to suggest that this combination works. Forskolin and luteolin are flavonoids, which tend to be poorly absorbed. Most probably, neither compound reaches the brain to exert its desired effect.

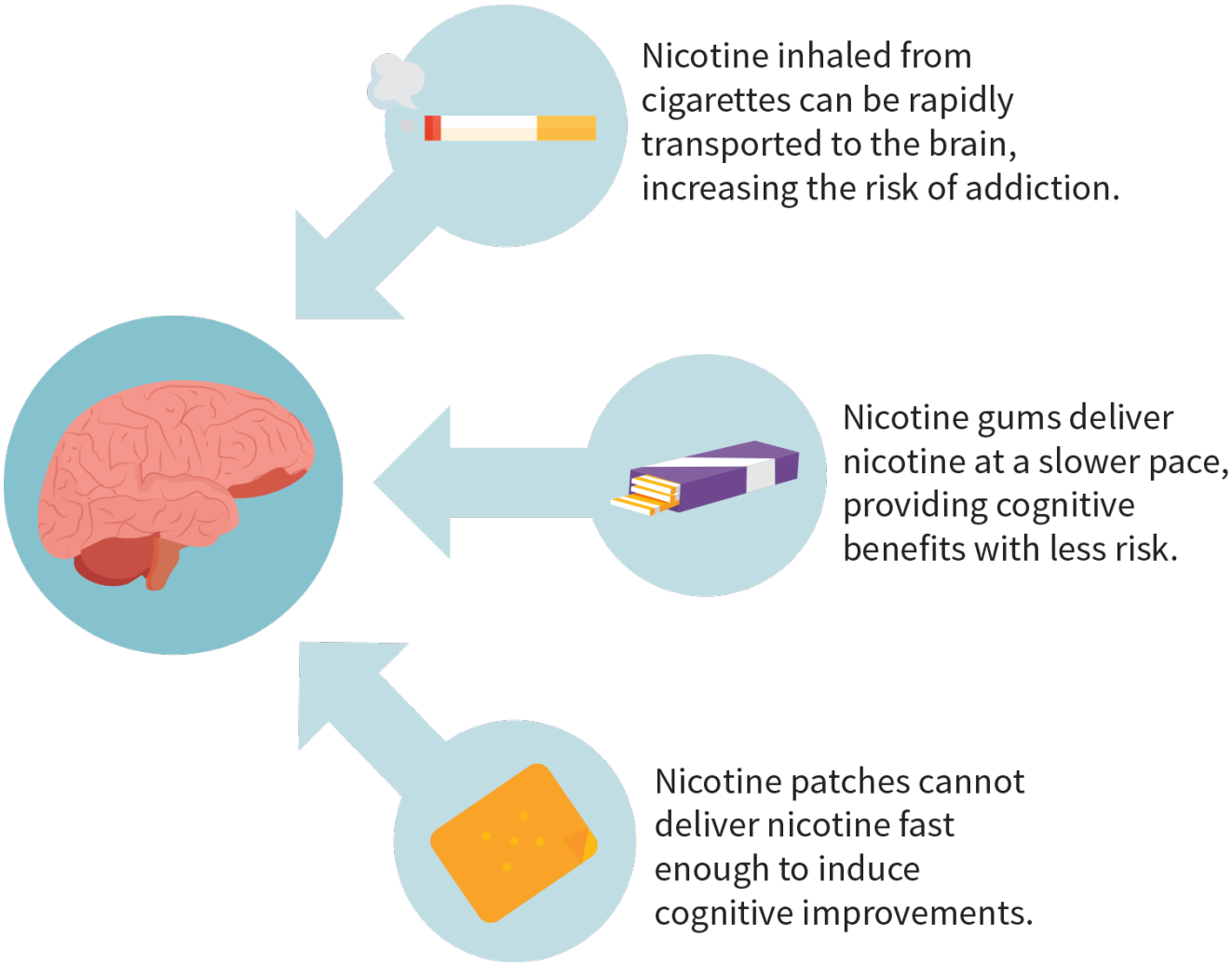
Though forskolin and luteolin work in isolated brain cells, real-world supplementation does not increase cAMP levels. This "CILTeP combo" does not belong in any combo designed to improve memory and focus.

Nicotine

What makes *nicotine* an unproven supplement

Nicotine's addictive properties vary depending on the dose taken and the speed at which it enters the bloodstream. When inhaled, nicotine reaches the blood quickly, which makes this delivery method especially addictive. At the other end of the spectrum, patches are the least addictive delivery method, but they act too slowly to provide an acute stimulatory effect.

A model showing the benefits of nicotine on mental function



When it comes to speed of delivery, nicotine gum holds the middle ground. Chewing nicotine gum while working on a mentally demanding task (2 mg of nicotine at a time, no more than 10 mg in one day) has theoretical advantages. Making this a daily habit, however, would allow tolerance to develop, and only ceasing supplementation entirely (for a couple of weeks) would allow sensitivity to return. Increasing the dose instead would, sooner or later, lead to nicotine withdrawal. Even the minimum dose, taken regularly, is potentially addictive, and thus potentially harmful.

Of course, tobacco is still the most noxious source of nicotine, and not just because it contains some seventy carcinogens.[80] As noted above, when inhaled, nicotine reaches the blood quickly, which makes it especially addictive. In addition, several other compounds in tobacco, such as *monoamine oxidase inhibitors* (MAOIs), amplify the addictive effects of nicotine. Finally, the acquired need to suck on something contributes to the addictive properties of cigarettes, cigars, and smoking pipes (and thumbs, for little children).

Inadvisable Supplements

Of the supplements we have reviewed, none currently fit the above description.

FAQ

Q. What about the supplements not covered in this guide?

Our guides are regularly updated, often with new supplements. We prioritize assessing (and reassessing) the most popular of them and those most likely to work. However, if there is a specific supplement you'd like to see covered in a future update, please let us know by filling out this survey.

Q. Can I add a supplement not covered in this guide to my combo?

Supplement with your current combo for a few weeks before attempting any change. Talk to your physician and research each potential addition. Check for known negative interactions with other supplements and pharmaceuticals in your current combo, but also for synergies. If two supplements are synergistic or additive in their effects, you might want to use lower doses of each.

Q. Can I modify the recommended doses?

If a supplement has a recommended dose range, stay within that range. If a supplement has a precise recommended dose, stay within 10% of that dose. Taking more than recommended could be counterproductive or even dangerous. Taking less could render the supplement ineffective, yet starting with half the regular dose could be prudent — especially if you know you tend to react strongly to supplements or pharmaceuticals.

Q. At what time should I take my supplements?

The answer is provided in the "How to take" section of a supplement entry whenever the evidence permits. Too often, however, the evidence is either mixed or absent. Starting with half the regular dose can help minimize the harm a supplement may cause when taken during the day (e.g., fatigue) or in the evening (e.g., insomnia).

Q. Should I take my supplements with or without food?

The answer is provided in the "How to take" section of a supplement entry whenever the evidence permits. Too often, however, the evidence is either mixed or absent. Besides, a supplement's digestion, absorption, and metabolism can be affected differently by different foods. Fat-soluble vitamins (A, D, E, K), for instance, are better absorbed with a small meal containing fat than with a large meal containing little to no fat.

Q. What are DRI, RDA, AI, and UL?

The Dietary Reference Intakes (DRIs) is a system of nutrition recommendations designed by the Institute of Medicine (a US institution now known as the Health and Medicine Division). RDA, AI, and UL are part of this system.

- Contrary to what the name suggests, a *Recommended Dietary Allowance* (RDA) doesn't represent an *ideal* amount; it represents the *minimum* you need in order to avoid deficiency-related health issues. More precisely, it represents an amount just large enough to meet the minimum requirements of 97.5% of healthy males and females over all ages — which implies that the RDA is too low for 2.5% of healthy people.
- The *Adequate Intake* (AI) is like the RDA, except that the number is more uncertain.
- The *Tolerable Upper Intake Level* (UL) is the maximum safe amount. More precisely, it is the maximum daily amount deemed to be safe for 97.5% of healthy males and females over all ages — which implies that the UL is too high for 2.5% of healthy people.

As a general rule, a healthy diet should include at least the RDA of each nutrient — but less than this nutrient's UL. This rule has many exceptions, though. For instance, people who sweat more need more salt (i.e., sodium), whereas people who take metformin (a diabetes medicine) need more vitamin B12.

Moreover, the DRIs are based on the median weight of adults and children in the United States. Everything else being equal (notably age, sex, and percentage of body fat), you likely need a lesser amount of nutrients if you weigh less, and vice versa if you weigh more. The numbers, however, are not proportional — if only because the brains of two people of very different weights have very similar needs. So you can't just double your RDIs for each nutrient if you weigh twice as much as the median adult of your age and sex (even if we overlook that people weighing the same can differ in many respects, notably body fat).

Q. What's the difference between anthocyanins and anthocyanidins?

Anthocyanins contain anthocyanidins. To be more precise, an anthocyanidin is simply an anthocyanin without its sugar molecule(s).

Q. Can I replace blueberries with other anthocyanin-rich foods?

Most studies are on blueberries, and the total amount of anthocyanins does not tell the whole story, because different *types* of anthocyanins can be found in different amounts in different berries. Studies on cognition have reported benefits from blue-purple anthocyanins, notably cyanidin and delphinidin, whereas red anthocyanins, such as pelargonidin, lack the same scientific backing.

So dark berries (blueberries, blackberries, elderberries …) might be interchangeable for the purpose of enhancing cognition, whereas red berries (strawberries, raspberries …), although also rich in anthocyanins, are likely not suitable alternatives.

Blue-purple anthocyanins can be found in foods other than dark berries, such as purple cauliflower, purple

potatoes, and purple rice, but keep in mind that some blue-purple plants derive their color from betalains, not anthocyanins — for instance, beetroot.

Phytochemical profiles of select berries
(mg per 100 grams of edible portion)

FRUIT	TOTAL ANTHOCYANIDINS*	TOTAL FLAVAN-3-OLS**	TOTAL FLAVONOLS***
Chokeberry, raw	437.22	—	8.90
Bilberry	430.91	4.13	—
Black raspberry	324.02	—	—
Currant, black, raw	272.44	1.17	12.69
Blueberry	163.52	51.71	9.72
Blackberry	90.46	42.50	2.49
Red raspberry, raw	38.68	6.63	1.32
Strawberry	33.63	4.51	1.60
Cranberry, dried, sweetened	0.72	—	6.91
Cranberry juice cocktail	0.46	0.19	1.79
Cranberry sauce, canned, sweetened	0.14	—	5.11
Cranberry juice, unsweetened	—	0.92	20.82
Mulberry, raw	—	—	2.47

* Total anthocyanidins (cyanidin, delphinidin, peonidin, petunidin)

** Total flavan-3-ols ((−)-epicatechin, (−)-epicatechin-3-gallate, (−)-epigallocatechin, (−)-epigallocatechin-3-gallate, (+)-catechin, (+)-gallocatechin)

*** Total flavonols (kaempferol, myricetin, quercetin)

Adapted from Basu et al. *Nutr Rev.* 2010.[81]

Q. Are organic blueberries better?

In terms of anthocyanin content, not really: anthocyanin levels appear to be almost identical (within 5%) in organic and non-organic blueberries cultivated in the same area.[34] On the other hand, there appear to be large differences depending on the soil. For example, even within the United States, the anthocyanin content can range from 144 to 823 mg per 100 grams of blueberries, depending on the region where the bushes are grown.[34]

Q. Can fish oil improve memory and focus?

Preliminary evidence suggests that fish oil may benefit cognition, but more research is needed before supplementation can be recommended for this specific purpose. Including more fatty fish in your diet may nevertheless be a good, healthy idea. Cod, salmon, and sardines are the best fish to eat, since they have high levels of omega-3 fatty acids but low levels of mercury. If you cannot change your diet and want to supplement fish oil, you can take a 1-g capsule daily.

Q. Why are there no racetams in this Supplement Guide?

While racetams (e.g., piracetam, aniracetam, oxiracetam) are thought to improve cognition, they are not recommended in this guide because they are pharmaceuticals and because human evidence is lacking. Further research is needed on their long-term safety and efficacy.

Q. I've heard that I should "load" creatine. What does that mean?

Loading creatine means taking a high daily dose for a few days before moving down to a smaller maintenance dose, which can be taken indefinitely. This is not necessary for effective supplementation, however; benefits may be felt sooner through loading, but they normalize after a few weeks.

If you wish to load creatine, take 20–25 g/day for 7 days (splitting your daily intake into smaller doses, taking them with some food, and drinking more fluids may help prevent intestinal discomfort). Take 5 g/day thereafter.

Q. Creatine doesn't seem to work for me. What should I do?

Some people are creatine nonresponders: the creatine they ingest largely fails to reach their muscles. Alternate forms of creatine, such as creatine ethyl-ester, have been marketed to nonresponders, but they lack scientific support. Currently, the best way to lessen creatine nonresponse is to take 5 grams twice a day, each time with protein and carbs, preferably close to a time of muscle contraction (i.e., before or after your workout).

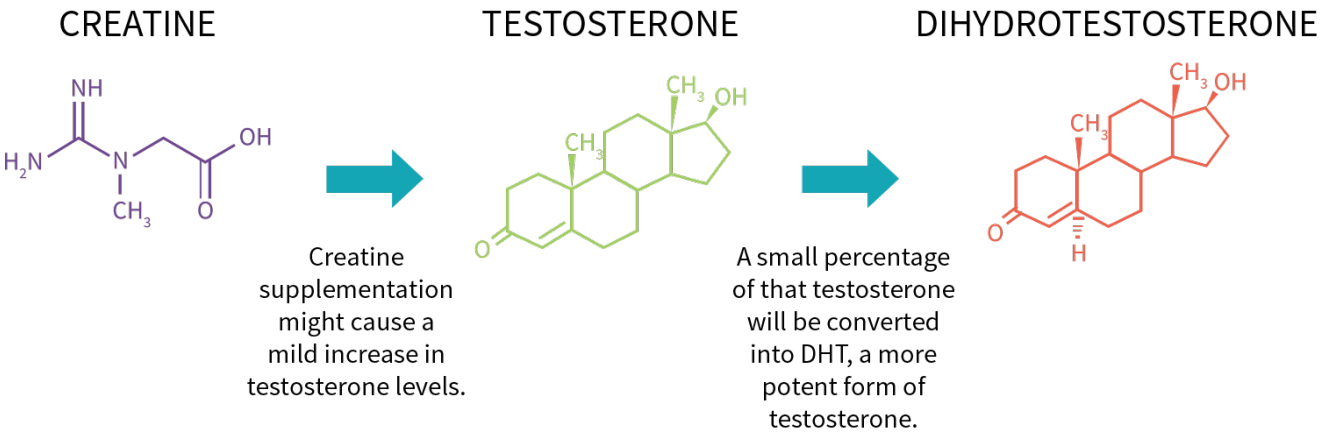
Note that even if supplemental creatine fails to enter your muscles it can still benefit you in other ways, such as by improving your body's methylation status (methylation being a way for your cells to help manage gene expression).

Q. Will creatine cause hair loss?

The idea that creatine *might* increase hair loss stems from a single randomized controlled trial (RCT) whose participants (20 healthy, young, male rugby players) saw a small but statistically significant increase in *dihydrotestosterone* (DHT) after supplementing with creatine for 21 days.[82] When DHT, a potent metabolite of testosterone, binds to DHT receptors on the hair follicles of the scalp, those follicles may shrink and stop producing hair.[83][84]

To date, this RCT is the only one to have tested creatine's effects on DHT. However, a number of RCTs have examined creatine's effects on testosterone. Out of 12 additional RCTs, two saw a significant increase in testosterone,[85][86] but 10 saw no effect.[82][87][88][89][90][91][92][93][94][95] Of those 12 RCTs, five also tested creatine's effects on free testosterone, the form that gets converted into DHT, and all saw no significant increases.[87][88][90][92][94]

A proposed mechanism behind creatine's effect on testosterone



Creatine *could* nonsignificantly increase free testosterone yet significantly increase DHT (i.e., a small increase in free testosterone, which can convert into DHT, could lead to a much greater increase in total DHT). So while it's *technically* possible that creatine might have some effect on hair loss, current evidence and mechanistic data indicate it's quite unlikely.

There is a preregistered 6-month RCT in the works to more directly answer the question of creatine's effect on hair growth. When these results are available, we will update this FAQ.

Q. Isn't soy protein *bad* for males?

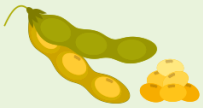
Phytoestrogens are plant compounds structurally similar to estradiol, the main estrogen in males and premenopausal females. Because soy contains isoflavones, a type of phytoestrogen, concern has been raised about soy affecting male health.

To this day, two case reports have documented adverse effects (gynecomastia, hypogonadism, reduced libido, and erectile dysfunction) from an estimated 360 mg of soy isoflavones per day for 6–12 months. However, a meta-analysis of 15 *randomized controlled trials* (RCTs, a much higher level of evidence than case reports) found that males' levels of total and free testosterone were not notably affected by either 60–240 mg of isoflavones or 10–70 grams of soy protein per day.

Accordingly, a couple of scoops of soy protein powder are unlikely to have estrogenic effects in males. If you'd like to take more, however, look for a soy protein concentrate or isolate produced through the alcohol-wash method, which dramatically lowers the isoflavone content.[96]

Keep in mind that the isoflavone content of different soy products can vary depending on several factors, such as the variety of soybeans used, differences in growing and storage conditions, and differential food processing techniques employed.[97] You can see how it varies below.

Isoflavone content of common soy foods

Food category	Food	Milligrams of isoflavones per 100 g of food		
		Average	Minimum	Maximum
 Traditional unfermented soy foods	Edamame	18	14	19
	Soybeans (boiled)	65	23	128
	Soybeans (raw)	155	10	440
	Soybean sprouts	34	0	107
	Soy milk (unsweetened)	11	1	31
	Soy nuts	148	2	202
	Tofu	30	3	142
 Traditional fermented soy foods	Miso	41	3	100
	Miso soup	1.5	1.5	1.5
	Miso soup mix (powder)	70	54	126
	Natto	82	46	124
	Soy sauce	1	0	3
	Tempeh	61	7	179
 Second-generation soy foods	Soy-based veggie “meats”	9	0	23
	Soy cheeses	26	3	59
	Soy yogurt	33	10	70
 Soy flours and protein powders	Soy flour (defatted)	151	74	324
	Soy flour (full-fat)	165	130	260
	Soy infant formula (powder)	28	21	31
	Soy protein concentrate (alcohol wash)	12	2	32
	Soy protein concentrate (water wash)	95	61	167
	Soy protein isolate	91	46	200

Reference: USDA FoodData Central Databases. Accessed Jan 18, 2019.

Q. Is a keto diet or supplemental ketones useful for treating cognitive decline?

For cognitive decline, one pressing issue is that the brain can fail to obtain enough energy to function properly, be it from vascular problems or insulin resistance.[98][99][100] A keto diet is believed to provide a neuroprotective benefit by reducing oxidative stress and increasing mitochondrial respiration.[101]

A keto diet is also believed to provide benefit by reducing the oxidation of glucose and leading to calorie restriction,[101] neither of which would necessarily be present with the use of exogenous ketone supplements. The few studies available on patients with Alzheimer's disease suggest that a ketogenic diet may hold value but ultimately needs to overcome a brain energy deficit.[102] By this logic, exogenous ketones could be beneficial by allowing for both glucose and ketones as fuel sources for the brain.

Research investigating the role of exogenous ketones in neurodegenerative diseases and cognitive decline is lacking. What studies are available test cognitive function in healthy adults after a bout of endurance exercise. These studies suggest that supplementing with exogenous ketones either benefits cognitive function when combined with carbohydrates, as compared with carbohydrates alone,[103] or provide no benefit when taken alone, as compared with a noncaloric placebo.[104]

Q. What are the stages of Alzheimer's disease?

There's no universal, single assessment used to determine the stages of Alzheimer's disease. However, one scale developed in the early 1980s is commonly used. It is called the Global Deterioration Scale (GDS)[105] and has seven stages:

1. No impairment.
2. Very mild impairment: forgetfulness without impacting daily living, and no clear objective signs of clinical decline.
3. Mild decline: Objective evidence of memory problems appear, but only with a comprehensive clinical evaluation.
4. Moderate decline: In this stage, complex tasks start becoming more difficult, and withdrawing from difficult tasks is a common behavior.
5. Moderately severe decline: This stage is considered early dementia, and some assistance is often required for daily living at this stage. Some major facts about the person's life can no longer be recalled. People in this stage can still perform some basic functions of daily living, but can have trouble with many others, especially those that involve cognitive processing or choice.
6. Severe decline: This is considered middle dementia. At this point, the person cannot effectively remember recent events, and memory of past events is spotty, at best. Significant assistance is needed to live daily life at this point.
7. Very severe decline: This is considered late dementia: the ability to speak is mostly or completely gone, and motor skills are severely degraded.

Diagnostic guidelines for Alzheimer's disease from the National Institute on Aging (NIA) break it down into three categories:[106]

1. Preclinical: the disease is progressing at a physiological level, but no symptoms can be observed.
2. Mild cognitive impairment (MCI): episodic memory loss occurs, but daily life is not strongly impacted.
3. Dementia: In this stage, daily function is impacted.

References

1. Alhola P, Polo-Kantola P Sleep deprivation: Impact on cognitive performance. *Neuropsychiatr Dis Treat*. (2007)
2. Dae Yun Seo, Hyo-Bum Kwak, Amy Hyein Kim, Se Hwan Park, Jun Won Heo, Hyoung Kyu Kim, Jeong Rim Ko, Sam Jun Lee, Hyun Seok Bang, Jun Woo Sim, Min Kim, Jin Han Cardiac adaptation to exercise training in health and disease. *Pflugers Arch*. (2020 Feb)
3. Daniel J Green, Maria T E Hopman, Jaume Padilla, M Harold Laughlin, Dick H J Thijssen Vascular Adaptation to Exercise in Humans: Role of Hemodynamic Stimuli. *Physiol Rev*. (2017 Apr)
4. M Ebadi, B Klangkalya, J D Deupree Inhibition of GABA binding by pyridoxal and pyridoxal phosphate. *Int J Biochem*. (1980)
5. T R Guilarte, H N Wagner Jr, J J Frost Effects of perinatal vitamin B6 deficiency on dopaminergic neurochemistry. *J Neurochem*. (1987 Feb)
6. Kristen Rahn, Barbara Slusher, Adam Kaplin Cognitive impairment in multiple sclerosis: a forgotten disability remembered. *Cerebrum*. (2012 Nov)
7. Ewa Papuć, Konrad Rejdak The role of myelin damage in Alzheimer's disease pathology. *Arch Med Sci*. (2018 Aug 28)
8. Adele McKinney, Kieran Coyle Next day effects of a normal night's drinking on memory and psychomotor performance. *Alcohol Alcohol*. (Nov-Dec 2004)
9. Lydia E Devenney, Kieran B Coyle, Joris C Verster Memory and attention during an alcohol hangover. *Hum Psychopharmacol*. (2019 Jul)
10. Craig Gunn, Graeme Fairchild, Joris C Verster, Sally Adams The Effects of Alcohol Hangover on Executive Functions. *J Clin Med*. (2020 Apr 17)
11. Sarah Benson, Elizabeth Ayre, Harriet Garrisson, Mark A Wetherell, Joris C Verster, Andrew Scholey Alcohol Hangover and Multitasking: Effects on Mood, Cognitive Performance, Stress Reactivity, and Perceived Effort. *J Clin Med*. (2020 Apr 17)
12. Charles S Lieber Relationships between nutrition, alcohol use, and liver disease. *Alcohol Res Health*. (2003)
13. G Kaysen, R H Noth The effects of alcohol on blood pressure and electrolytes. *Med Clin North Am*. (1984 Jan)
14. Penning R, van Nuland M, Fliervoet LA, Olivier B, Verster JC The pathology of alcohol hangover. *Curr Drug Abuse Rev*. (2010 Jun)
15. Jessica Bollen, Leanne Trick, David Llewellyn, Chris Dickens The effects of acute inflammation on cognitive functioning and emotional processing in humans: A systematic review of experimental studies. *J Psychosom Res*. (2017 Mar)
16. Rachel A Kohman, Justin S Rhodes Neurogenesis, inflammation and behavior. *Brain Behav Immun*. (2013 Jan)
17. Alvin Lim, Katarina Krajina, Anna L Marsland Peripheral inflammation and cognitive aging. *Mod Trends Pharmacopsychiatry*. (2013)
18. Elise C Cope, Elizabeth A LaMarca, Patrick K Monari, Lyra B Olson, Susana Martinez, Anna D Zych, Nicole J Katchur, Elizabeth Gould Microglia Play an Active Role in Obesity-Associated Cognitive Decline. *J Neurosci*. (2018 Oct 10)
19. Gregory Belenky, Nancy J Wesensten, David R Thorne, Maria L Thomas, Helen C Sing, Daniel P Redmond, Michael B Russo, Thomas J Balkin Patterns of performance degradation and restoration during sleep restriction and subsequent recovery: a sleep dose-response study. *J Sleep Res*. (2003 Mar)
20. Gabriel Natan Pires, Andreia Gomes Bezerra, Sergio Tufik, Monica Levy Andersen Effects of acute sleep deprivation on state anxiety levels: a systematic review and meta-analysis. *Sleep Med*. (2016 Aug)
21. Ning Ma, David F Dinges, Mathias Basner, Hengyi Rao How acute total sleep loss affects the attending brain: a meta-analysis of neuroimaging studies. *Sleep*. (2015 Feb 1)
22. Yuval Nir, Thomas Andrillon, Amit Marmelshtein, Nanthia Suthana, Chiara Cirelli, Giulio Tononi, Itzhak Fried Selective neuronal lapses precede human cognitive lapses following sleep deprivation. *Nat Med*. (2017 Dec)
23. Victoria M Pak, S-Hakki Onen, Donald L Bliwise, Nancy G Kutner, Katherine L Russell, Fannie Onen Sleep Disturbances in MCI and AD: Neuroinflammation as a Possible Mediating Pathway. *Front Aging Neurosci*. (2020 May 8)
24. Robert Stickgold Sleep-dependent memory consolidation. *Nature*. (2005 Oct 27)
25. Timothy Salthouse Consequences of age-related cognitive declines. *Annu Rev Psychol*. (2012)
26. Mark W Bondi, Emily C Edmonds, David P Salmon Alzheimer's Disease: Past, Present, and Future. *J Int Neuropsychol Soc*. (2017 Oct)
27. Katzman R. et al. The epidemiology of dementia and Alzheimer disease. *Alzheimer disease*. (1994)
28. Hein S, Whyte AR, Wood E, Rodriguez-Mateos A, Williams CM Systematic Review of the Effects of Blueberry on Cognitive Performance as We Age. *J Gerontol A Biol Sci Med Sci*. (2019 Jun 18)
29. Krikorian R, Shidler MD, Nash TA, Kalt W, Vinqvist-Tymchuk MR, Shukitt-Hale B, Joseph JA Blueberry supplementation improves memory in older adults. *J Agric Food Chem*. (2010 Apr 14)
30. Boespflug EL, Eliassen JC, Dudley JA, Shidler MD, Kalt W, Summer SS, Stein AL, Stover AN, Krikorian R Enhanced neural

activation with blueberry supplementation in mild cognitive impairment. *Nutr Neurosci*. (2018 May)

31. Miller MG, Hamilton DA, Joseph JA, Shukitt-Hale B Dietary blueberry improves cognition among older adults in a randomized, double-blind, placebo-controlled trial. *Eur J Nutr*. (2018 Apr)
32. Whyte AR, Cheng N, Fromentin E, Williams CM A Randomized, Double-Blinded, Placebo-Controlled Study to Compare the Safety and Efficacy of Low Dose Enhanced Wild Blueberry Powder and Wild Blueberry Extract (ThinkBlue™) in Maintenance of Episodic and Working Memory in Older Adults. *Nutrients*. (2018 May 23)
33. Bowtell JL, Aboo-Bakkar Z, Conway ME, Adlam AR, Fulford J Enhanced task-related brain activation and resting perfusion in healthy older adults after chronic blueberry supplementation. *Appl Physiol Nutr Metab*. (2017 Jul)
34. Stevenson D, Scalzo J Anthocyanin composition and content of blueberries from around the world. *J Berry Res*. (2012 Sep)
35. Rodríguez-Bonilla P, López-Nicolás JM, Méndez-Cazorla L, García-Carmona F Development of a reversed phase high performance liquid chromatography method based on the use of cyclodextrins as mobile phase additives to determine pterostilbene in blueberries. *J Chromatogr B Analyt Technol Biomed Life Sci*. (2011 May 1)
36. Rimando AM, Kalt W, Magee JB, Dewey J, Ballington JR Resveratrol, pterostilbene, and piceatannol in vaccinium berries. *J Agric Food Chem*. (2004 Jul 28)
37. Rimando A, Barney D Resveratrol and naturally occurring analogues in _vaccinium_ species. *Acta Hortic*. (2005)
38. Calabrese C, Gregory WL, Leo M, Kraemer D, Bone K, Oken B Effects of a standardized Bacopa monnieri extract on cognitive performance, anxiety, and depression in the elderly: a randomized, double-blind, placebo-controlled trial. *J Altern Complement Med*. (2008 Jul)
39. Mester R, Toren P, Mizrachi I, Wolmer L, Karni N, Weizman A Caffeine withdrawal increases lithium blood levels. *Biol Psychiatry*. (1995 Mar 1)
40. McCusker RR, Goldberger BA, Cone EJ Caffeine content of energy drinks, carbonated sodas, and other beverages. *J Anal Toxicol*. (2006 Mar)
41. Desbrow B, Hall S, Irwin C Caffeine content of Nespresso® pod coffee. *Nutr Health*. (2019 Mar)
42. Ludwig IA, Mena P, Calani L, Cid C, Del Rio D, Lean ME, Crozier A Variations in caffeine and chlorogenic acid contents of coffees: what are we drinking?. *Food Funct*. (2014 Aug)
43. Fox GP, Wu A, Yiran L, Force L Variation in caffeine concentration in single coffee beans. *J Agric Food Chem*. (2013 Nov 13)
44. McCusker RR, Goldberger BA, Cone EJ Caffeine content of specialty coffees. *J Anal Toxicol*. (2003 Oct)
45. Angeloni G, Guerrini L, Masella P, Bellumori M, Daluiso S, Parenti A, Innocenti M What kind of coffee do you drink? An investigation on effects of eight different extraction methods. *Food Res Int*. (2019 Feb)
46. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) Safety of caffeine. *EFSA Journal*. (2015 MAY)
47. Food and Nutrition Board Caffeine in Food and Dietary Supplements: Examining Safety: Workshop Summary.. *The National Academies Press*. (2014 APR)
48. Nawrot P, Jordan S, Eastwood J, Rotstein J, Hugenholtz A, Feeley M Effects of caffeine on human health. *Food Addit Contam*. (2003 Jan)
49. Wikoff D, Welsh BT, Henderson R, Brorby GP, Britt J, Myers E, Goldberger J, Lieberman HR, O'Brien C, Peck J, Tenenbein M, Weaver C, Harvey S, Urban J, Doepker C Systematic review of the potential adverse effects of caffeine consumption in healthy adults, pregnant women, adolescents, and children. *Food Chem Toxicol*. (2017 Nov)
50. Giannelli M, Doyle P, Roman E, Pelerin M, Hermon C The effect of caffeine consumption and nausea on the risk of miscarriage. *Paediatr Perinat Epidemiol*. (2003 Oct)
51. Morgan S, Koren G, Bozzo P Is caffeine consumption safe during pregnancy?. *Can Fam Physician*. (2013 Apr)
52. Voskoboinik A, Kalman JM, Kistler PM Caffeine and Arrhythmias: Time to Grind the Data. *JACC Clin Electrophysiol*. (2018 Apr)
53. Knutti R, Rothweiler H, Schlatter C The effect of pregnancy on the pharmacokinetics of caffeine. *Arch Toxicol Suppl*. (1982)
54. Committee on Military Nutrition Research, Food and Nutrition Board Caffeine for the Sustainment of Mental Task Performance: Formulations for Military Operations.
55. Jericho Hallare, Valerie Gerriets Half Life.
56. De Jesus Moreno Moreno M Cognitive improvement in mild to moderate Alzheimer's dementia after treatment with the acetylcholine precursor choline alfoscerate: a multicenter, double-blind, randomized, placebo-controlled trial. *Clin Ther*. (2003 Jan)
57. Parisi V, Coppola G, Centofanti M, Oddone F, Angrisani AM, Ziccardi L, Ricci B, Quaranta L, Manni G Evidence of the neuroprotective role of citicoline in glaucoma patients. *Prog Brain Res*. (2008)
58. Kreider RB, Kalman DS, Antonio J, Ziegenfuss TN, Wildman R, Collins R, Candow DG, Kleiner SM, Almada AL, Lopez HL International Society of Sports Nutrition position stand: safety and efficacy of creatine supplementation in exercise, sport, and medicine. *J Int Soc Sports Nutr*. (2017 Jun 13)
59. Diuretics.
60. Williamson L, New D How the use of creatine supplements can elevate serum creatinine in the absence of underlying kidney pathology. *BMJ Case Rep*. (2014 Sep 19)

61. McCall W, Persky AM Pharmacokinetics of creatine. *Subcell Biochem*. (2007)
62. Poortmans JR, Francaux M Adverse effects of creatine supplementation: fact or fiction?. *Sports Med*. (2000 Sep)
63. Farquhar WB, Zambraski EJ Effects of creatine use on the athlete's kidney. *Curr Sports Med Rep*. (2002 Apr)
64. Pline KA, Smith CL The effect of creatine intake on renal function. *Ann Pharmacother*. (2005 Jun)
65. Francaux M, Poortmans JR Side effects of creatine supplementation in athletes. *Int J Sports Physiol Perform*. (2006 Dec)
66. Persky AM, Rawson ES Safety of creatine supplementation. *Subcell Biochem*. (2007)
67. Kim HJ, Kim CK, Carpentier A, Poortmans JR Studies on the safety of creatine supplementation. *Amino Acids*. (2011 May)
68. Gualano B, Roschel H, Lancha AH Jr, Brightbill CE, Rawson ES In sickness and in health: the widespread application of creatine supplementation. *Amino Acids*. (2012 Aug)
69. Syrotuik DG, Bell GJ Acute creatine monohydrate supplementation: a descriptive physiological profile of responders vs. nonresponders. *J Strength Cond Res*. (2004 Aug)
70. Hadjicharalambous M, Kilduff LP, Pitsiladis YP Brain serotonin and dopamine modulators, perceptual responses and endurance performance during exercise in the heat following creatine supplementation. *J Int Soc Sports Nutr*. (2008 Sep 30)
71. Zaheer K, Humayoun Akhtar M An updated review of dietary isoflavones: Nutrition, processing, bioavailability and impacts on human health. *Crit Rev Food Sci Nutr*. (2017 Apr 13)
72. Oseni T, Patel R, Pyle J, Jordan VC Selective estrogen receptor modulators and phytoestrogens. *Planta Med*. (2008 Oct)
73. Shanmugan S, Epperson CN Estrogen and the prefrontal cortex: towards a new understanding of estrogen's effects on executive functions in the menopause transition. *Hum Brain Mapp*. (2014 Mar)
74. Maki PM, Dennerstein L, Clark M, Guthrie J, LaMontagne P, Fornelli D, Little D, Henderson VW, Resnick SM Perimenopausal use of hormone therapy is associated with enhanced memory and hippocampal function later in life. *Brain Res*. (2011 Mar 16)
75. Bansal N, Parle M Soybean supplementation helps reverse age- and scopolamine-induced memory deficits in mice. *J Med Food*. (2010 Dec)
76. Chendi Cui, Rahel L Birru, Beth E Snitz, Masafumi Ihara, Chikage Kakuta, Brian J Lopresti, Howard J Aizenstein, Oscar L Lopez, Chester A Mathis, Yoshihiro Miyamoto, Lewis H Kuller, Akira Sekikawa Effects of Soy Isoflavones on Cognitive Function: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Nutr Rev*. (2020 Feb 1)
77. Křížová L, Dadáková K, Kašparovská J, Kašparovský T Isoflavones. *Molecules*. (2019 Mar 19)
78. Nakamura Y, Tsuji S, Tonogai Y Determination of the levels of isoflavonoids in soybeans and soy-derived foods and estimation of isoflavonoids in the Japanese daily intake. *J AOAC Int*. (2000 May-Jun)
79. Rizzo G, Baroni L Soy, Soy Foods and Their Role in Vegetarian Diets. *Nutrients*. (2018 Jan 5)
80. Samir S Khariwala, Dorothy Hatsukami, Stephen S Hecht Tobacco carcinogen metabolites and DNA adducts as biomarkers in head and neck cancer: potential screening tools and prognostic indicators. *Head Neck*. (2012 Mar)
81. Basu A, Rhone M, Lyons TJ Berries: emerging impact on cardiovascular health. *Nutr Rev*. (2010 Mar)
82. van der Merwe J, Brooks NE, Myburgh KH Three weeks of creatine monohydrate supplementation affects dihydrotestosterone to testosterone ratio in college-aged rugby players. *Clin J Sport Med*. (2009 Sep)
83. Hamada K, Randall VA Inhibitory autocrine factors produced by the mesenchyme-derived hair follicle dermal papilla may be a key to male pattern baldness. *Br J Dermatol*. (2006 Apr)
84. Trüeb RM Molecular mechanisms of androgenetic alopecia. *Exp Gerontol*. (2002 Aug-Sep)
85. Vatani DS, Faraji J, Soori R, Mogharnasi M The effects of creatine supplementation on performance and hormonal response in amateur swimmers. *SCI SPORT*. (2011 NOV)
86. Arazi H, Rahmaninia F, Hosseini K, Asadi A Effects of short term creatine supplementation and resistance exercises on resting hormonal and cardiovascular responses. *SCI SPORT*. (2015 APR)
87. Cook CJ, Crewther BT, Kilduff LP, Drawer S, Gaviglio CM Skill execution and sleep deprivation: effects of acute caffeine or creatine supplementation - a randomized placebo-controlled trial. *J Int Soc Sports Nutr*. (2011 Feb 16)
88. Cooke MB, Brabham B, Buford TW, Shelmadine BD, McPheeters M, Hudson GM, Stathis C, Greenwood M, Kreider R, Willoughby DS Creatine supplementation post-exercise does not enhance training-induced adaptations in middle to older aged males. *Eur J Appl Physiol*. (2014 Jun)
89. Crowe MJ, O'Connor DM, Lukins JE The effects of beta-hydroxy-beta-methylbutyrate (HMB) and HMB/creatine supplementation on indices of health in highly trained athletes. *Int J Sport Nutr Exerc Metab*. (2003 Jun)
90. Hoffman J, Ratamess N, Kang J, Mangine G, Faigenbaum A, Stout J Effect of creatine and beta-alanine supplementation on performance and endocrine responses in strength/power athletes. *Int J Sport Nutr Exerc Metab*. (2006 Aug)
91. Eijnde BO, Hespel P Short-term creatine supplementation does not alter the hormonal response to resistance training. *Med Sci Sports Exerc*. (2001 Mar)
92. Volek JS, Ratamess NA, Rubin MR, Gómez AL, French DN, McGuigan MM, Scheett TP, Sharman MJ, Häkkinen K, Kraemer WJ The effects of creatine supplementation on muscular performance and body composition responses to short-term resistance training overreaching. *Eur J Appl Physiol*. (2004 May)

93. Faraji H, Arazi H, Vatani D, Hakimi M The effects of creatine supplementation on sprint running performance and selected hormonal responses. *S AFR J RES SPORT PH*. (2010)

94. Rahimi R, Faraji H, Vatani DS, Qaderi M Creatine supplementation alters the body's hormonal response to exercise. *Kinesiology*. (2010 JAN)

95. Volek JS, Boetes M, Bush JA, Putukian M, Sebastianelli WJ, Jraemer WJ Response of Testosterone and Cortisol Concentrations to High-Intensity Resistance Exercise Following Creatine Supplementation. *J STRENGTH COND RES*. (1997)

96. Anderson RL, Wolf WJ Compositional changes in trypsin inhibitors, phytic acid, saponins and isoflavones related to soybean processing. *J Nutr*. (1995 Mar)

97. Erdman JW Jr, Badger TM, Lampe JW, Setchell KD, Messina M Not all soy products are created equal: caution needed in interpretation of research results. *J Nutr*. (2004 May)

98. Philip B Gorelick, Scott E Counts, David Nyenhuis Vascular cognitive impairment and dementia. *Biochim Biophys Acta*. (2016 May)

99. Martin Dichgans, Didier Leys Vascular Cognitive Impairment. *Circ Res*. (2017 Feb 3)

100. Christian Benedict, Claudia A Grillo Insulin Resistance as a Therapeutic Target in the Treatment of Alzheimer's Disease: A State-of-the-Art Review. *Front Neurosci*. (2018 Apr 10)

101. Dariusz Włodarek Role of Ketogenic Diets in Neurodegenerative Diseases (Alzheimer's Disease and Parkinson's Disease). *Nutrients*. (2019 Jan 15)

102. Cunnane SC, Courchesne-Loyer A, Vandenberghe C, St-Pierre V, Fortier M, Hennebelle M, Croteau E, Bocti C, Fulop T, Castellano CA Can Ketones Help Rescue Brain Fuel Supply in Later Life? Implications for Cognitive Health during Aging and the Treatment of Alzheimer's Disease. *Front Mol Neurosci*. (2016 Jul 8)

103. Mark Evans, Brendan Egan Intermittent Running and Cognitive Performance after Ketone Ester Ingestion. *Med Sci Sports Exerc*. (2018 Nov)

104. Hunter S Waldman, Steven A Basham, Ffi G Price, JohnEric W Smith, Harish Chander, Adam C Knight, Ben M Krings, Matthew J McAllister Exogenous ketone salts do not improve cognitive responses after a high-intensity exercise protocol in healthy college-aged males. *Appl Physiol Nutr Metab*. (2018 Jul)

105. Reisberg B, Ferris SH, de Leon MJ, Crook T The Global Deterioration Scale for assessment of primary degenerative dementia. *Am J Psychiatry*. (1982 Sep)

106. Jack CR Jr, Albert MS, Knopman DS, McKhann GM, Sperling RA, Carrillo MC, Thies B, Phelps CH Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. (2011 May)