How Individual Macronutrients Affect Cognition and Cognitive Health

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Three macronutrients comprise most of our food: carbohydrates, which provide energy; fats, which reserve that energy; and proteins, which provide structure. Changing the amount of each macronutrient consumed can impact one's health. Cognitive status — the ability to sustain mental processes within the brain — is one aspect of health that is affected by our diets through the gut-brain axis. This review aimed to analyze how different levels of consumption of each individual macronutrient influence cognitive ability. I searched PubMed for journal articles relevant to individual macronutrients and cognition and chose 39 articles whose abstracts directly addressed this relationship. Simple carbohydrates can be neuroinflammatory and, therefore, cause long-term damage to the brain and cognition, while complex carbohydrates may be beneficial. Similarly, saturated fatty acids are detrimental to cognitive function and can lead to neurodegenerative diseases, but unsaturated fatty acids are neuroprotective, beneficial, and necessary for body functions. Meanwhile, proteins are difficult to isolate and study and even harder to obtain consistent results.

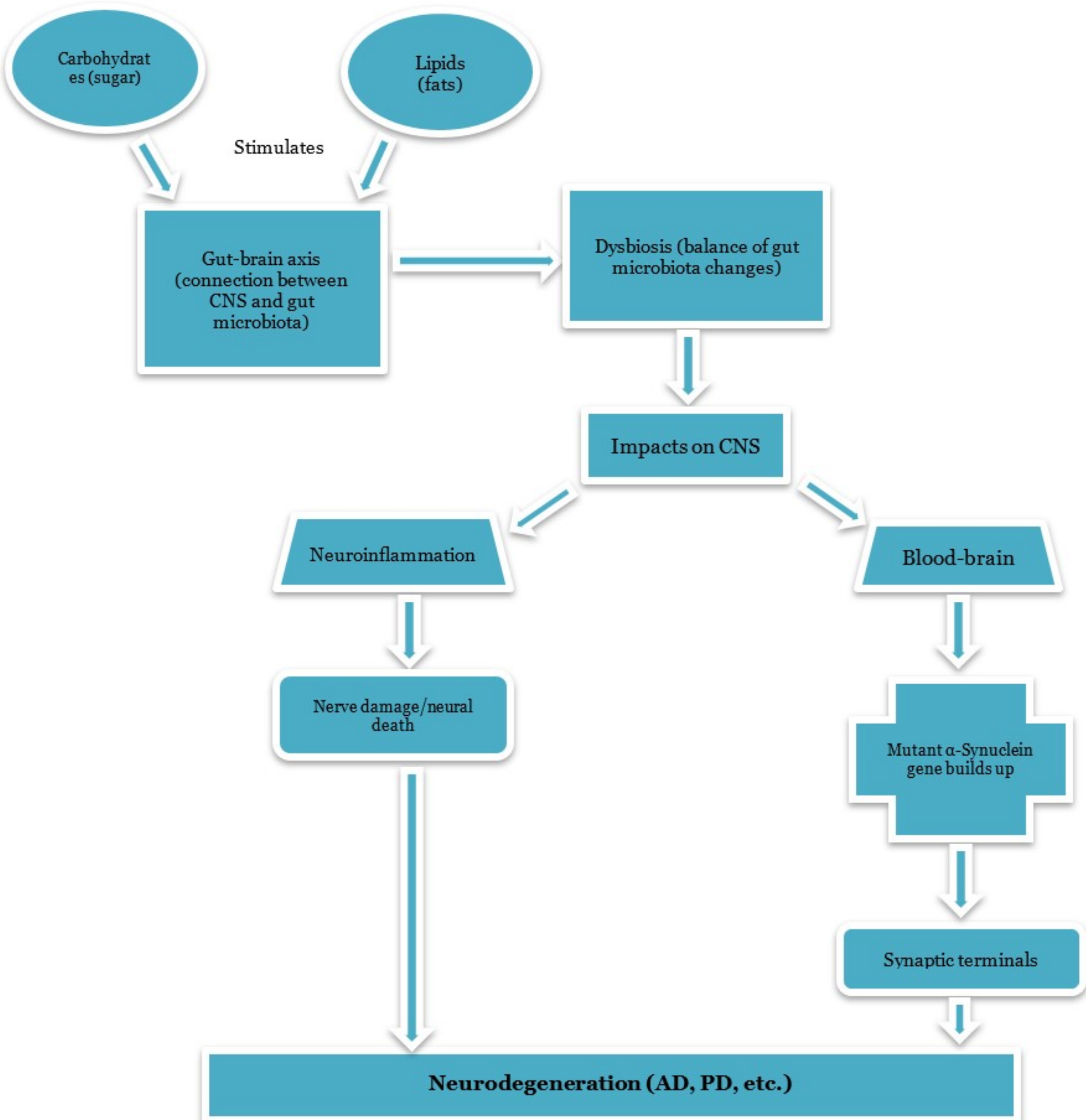
Keywords: macronutrients, carbohydrates, fats, protein, cognition, neurodegenerative, Western diet, Mediterranean diet

Introduction

Food is often called the fuel for the body and the brain. As such, foods with different nutrients result in varying levels of cognitive function. Macronutrients - carbohydrates, fats, and proteins - are the nutrients our bodies need in the highest quantities to function. Glucose is the body's primary energy source, especially during movement. Since carbohydrates are the simplest to convert to glucose, they are the body's main fuel, so the majority of calorie intake should come from them. Conversely, fats reserve energy, protect vital organs, and absorb necessary fat-soluble vitamins, such as A, D, E, and K[1]. Meanwhile, protein provides structure to tissue and contributes to the homeostasis of pH within the body[2]. The Food and Nutrition Board of the Institutes of Medicine recommends that, despite the unique needs of every individual based on a body weight formula, an acceptable range of daily caloric intake for each macronutrient is 45-65% carbohydrates, 10-35% protein, and 20-35% fats[3].

One common diet with high levels of refined carbohydrates and saturated fats is referred to as the Western diet, which emphasizes high-calorie, processed foods and the prevalence of fried and pre-packaged foods. This diet vastly differs from those recommended ranges, leading to higher rates of obesity, diabetes, cardiovascular diseases, and cancer, as well as a drop in immunity[4]. In turn, obesity is correlated with risks of mood and cognitive disorders. On the other hand, one diet known to be neuroprotective is called the Mediterranean diet, the traditional diet in the Mediterranean regions, which prevents inflammation of neural pathways due to its higher levels of omega-3 unsaturated fats and antioxidants. In contrast to the Western diet, it adheres closer to the recommended values, consisting of higher consumption of less processed, plant-based foods, lower consumption of red meats and processed meats, and heavy usage of olive oil as its primary source of fats[5]. Other examples of diets comply with or stray from the recommended ranges, but the Mediterranean and Western diets are the most prevalent examples in available literature of each, respectively.

Cognition refers to any mental processes that occur within the brain, such as thought, attention, language, learning, memory, and perception[6]. The central nervous system (CNS), including the brain and spinal cord, is connected to the stomach via the gut-brain axis, which uses neurotransmitters and neuromodulators for bidirectional interaction between the body's brain, gut, and gut microbiome[7]. This circuit responds to sugar and fats, seen in the signaling pathways that activate and function when the stimuli are past the taste buds. This results in a preference for foods with more of these macronutrients, independent of taste[8]. The balance of gut microbiota changes as one ages, affecting neurotransmitters and impacting the CNS, including regulation of inflammation and the blood-brain barrier[9]. As a result, this change in microbiota, known as dysbiosis, can lead to neuroinflammation — causing neural damage and eventually

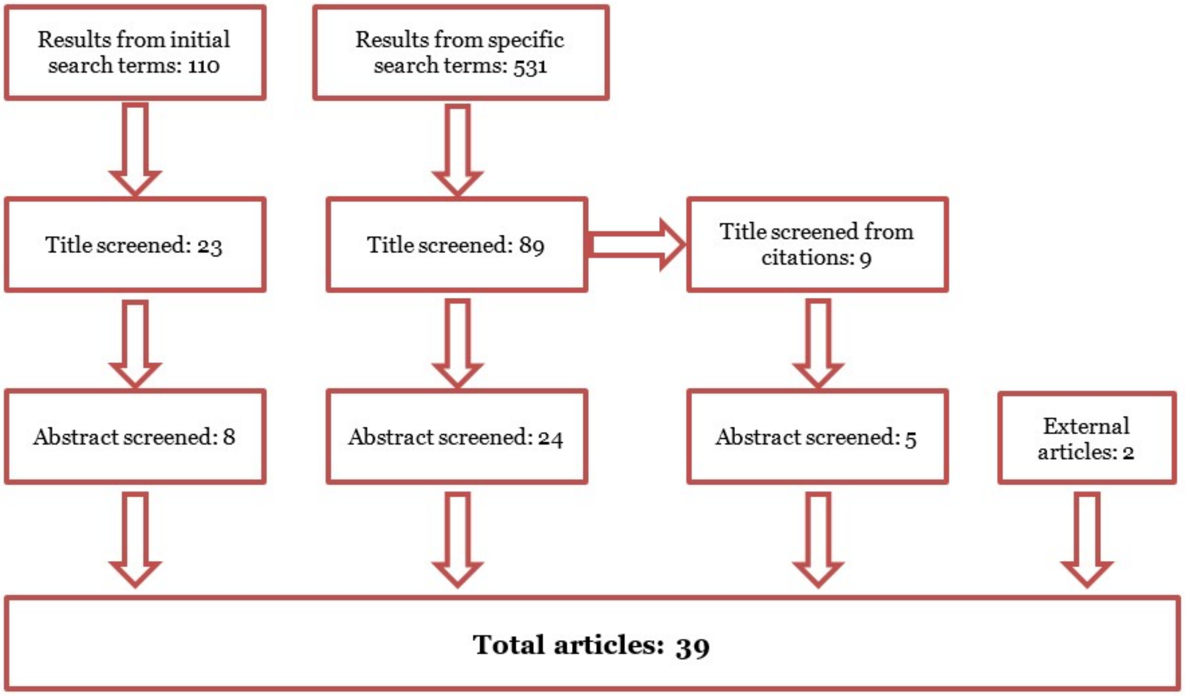


neural death characteristic of dementia or, more specifically, Alzheimer's Disease (AD)[7]. The dysbiosis' influence on the blood-brain barrier can also allow an accumulation of a mutated version of the α-Synuclein gene, resulting in the degradation of synaptic terminals like the one for dopamine. Interestingly, dopamine deficits are linked to another neurodegenerative disease — Parkinson's Disease[10].

Potential connections between individual macronutrient consumption and cognitive abilities were studied to further explore the connection between the stomach and cognition. To do so, I searched PubMed for keywords related to my question and hand-searched the results.

Methodology

One investigator searched PubMed exclusively for articles written in English and published through to July 2023 and hand-searched the results based on the abstracts. I started from background knowledge with the keywords "macronutrients," "cognition," and "gut-brain axis." I also searched for individ-



ual macronutrients, with my keywords narrowing to "carbohydrates," "fats," and "protein," while still including "cognition." I then specified classes of each macronutrient in my search terms, such as "simple carbohydrates," "complex carbohydrates," "saturated fatty acids," "trans fatty acids," and "unsaturated fatty acids." Inclusion criteria were results with the macronutrient name and some aspect of cognition in the title, as well as those that directly addressed the relationship in their abstracts. I also looked through the citations on those results. I then split the 39 final articles into categories based on the macronutrient.

Results and Discussion

The Effect of Carbohydrates on Cognition

One of the most frequent variables in experiments regarding diets and cognition is the macronutrient carbohydrates since they primarily provide the main energy source of the body and the brain. Carbohydrates can be further categorized into simple and complex carbohydrates. Simple carbohydrates are sugars absorbed more quickly than complex carbohydrates, defined as digestible polysaccharides made of a long chain of sugar molecules and found in untreated plant-based foods [11]. There are few decisive studies on the effects of complex carbohydrates on cognition. Even among those conducted, the results are not entirely distinct and rely upon previous nourishment. For example, consuming a breakfast of a grain cake improved cognitive function only in children nutritionally at-risk; in fact, they may have impaired cognitive scores among well-nourished children despite not significantly affecting blood sugar levels [12]. Also, diets rich in complex carbohydrates like fiber have been associated with positive brain aging, improving long- and short-term memory [13].

In contrast, the type of carbohydrates most commonly manipulated or measured to test cognition are simple carbohydrates, such as the monosaccharides glucose and fructose. The Western diet and lifestyle, which includes large amounts of these refined carbohydrates, have led to a rise in rates of type-2 diabetes. In turn, adults with type-2 diabetes have been seen to experience accelerated global cognitive decline in areas such as verbal fluency, working memory, and cognitive control over five-year periods. This cognitive decline is a marker for enhanced brain aging and dementia risk, making type-2 diabetes a disease recognized as a significant contributor to cognitive decline and dementia in older adults [14].

A study by Wolraich et al. in 1994 observed the behavior and cognitive function of 48 children, all aged ten years old or younger, while on diets high in refined sugars, using tests such as Paired Associate Learning — which measures memory and learning — and the Grooved Pegboard Test — which evaluates fine-motor speed and coordination. One of the sugars used in this experiment was sucrose, a disaccharide of simple carbohydrates. In most children aged six to ten, sucrose consumption did not significantly alter their cognitive function, except for during the Grooved Pegboard Test, in which they were significantly slower on the sucrose diet [15]. Conversely, when testing adults during a

1994 study, Benton et al. found that higher blood glucose values enhanced performance on the Rapid Information Processing Test and the Stroop Test thirty minutes after consumption. On the other hand, this rise in performance level was followed by a steep drop in the same tests in the longer term, seventy minutes after consumption, whereas results were much more consistent through time without a change in glucose levels[16].

Also, imbibing too much glucose can be detrimental to performance, as chronic consumption of refined carbohydrates has been linked to relative neurocognitive deficits, such as impacted memory, especially if the overexposure is in early life[17]. This danger of overconsumption is especially true in AD patient populations, where a higher-glycemic diet was positively correlated with the concentration of cerebral amyloid, a precursor to AD[18]. Additionally, foods high in refined sugars trigger the release of insulin. If this persists, it can lead to the development of insulin-resistant tissue, which is linked to the origination of inflammation. Therefore, the inflammatory nature of prolonged diets with higher levels of refined sugar can result in chronic neuroinflammation, which in turn causes damage to the brain tissue and increases the chances of age-related brain disorders or other cognitive deficits[19].

The Effect of Fats on Cognition

The body utilizes fats to absorb essential vitamins and nutrients, such as Vitamins A, D, E, and K, to protect vital organs and reserve energy[1]. The main types of dietary fatty acids (FAs) are unsaturated FAs (UFA), saturated FAs (SFA), and trans FAs (TFA). TFA and SFA have been shown to have much more detrimental effects on the body than UFA; for example, across 1254 randomized controlled trials and observational studies of adults, replacing SFA with polyunsaturated fats tended to the risk of stroke, diabetes, and coronary heart disease[20]. The fatty acid composition of the brain is directly related to dietary fatty acid intake, which means that neuroinflammation can spread on a pro-inflammatory diet heavy in SFA and TFA. At the same time, it can be relieved or reduced by anti-inflammatory diets rich with monounsaturated FAs and omega-3 polyunsaturated acids[21]. One review looking into the effect of dietary fats on type-2 diabetes found that although total fat intake had no link to the disease and its correlated cognitive deficits, the results were more varied based on the source of the fat. For example, even with the same kind of FA, those sourced from plants were associated with a lower risk of type-2 diabetes[22]. Similarly, the specific type of omega-3 fatty acid found in plant-based foods correlated slightly with improved cardiovascular health[23].

Long-term consumption of the Western diet, which is a diet high in fats, can impair memory and worsen attention and reaction times. This detriment is caused by decreasing synaptic plasticity in the hippocampus, which is responsible for short-term memory, and by damaging synaptic receptors[24]. However, the diet also includes high levels of refined sugars, and in at least one experiment, the subjects lived immensely inactive lifestyles; these factors have also been shown to affect cognitive performance, so the results are not necessarily definitive about fat consumption.

In one 2011 study conducted by Holloway et al., participants' caloric intakes were manipulated to be composed of over 75% fats. After only five days of this diet, when participants took a computerized Cognitive Drug Research assessment measuring attention, episodic and working memory, and self-reported mood, they demonstrated diminished attention and retrieval speed, as well as increased rates of depression[25,26]. One 2023 study conducted by Currenti et al. used questionnaires sent to Italian adults over the age of 50 to evaluate their consumption of different FA classes before measuring their cognitive function through the short portable mental status questionnaire (SPMSQ), which quantifies cognitive decline by the number of errors made; patients with three or more errors are considered cognitively impaired. Increased intake of some SFA often corresponded to cognitive impairment, along with higher concentrations of amyloid-beta build-up and chances of compromising the blood-brain barrier. Meanwhile, other SFAs, especially short-chain and medium-chain FAs, had inverse relationships with cognitive decline; short-chain FAs regulate the gut-brain axis by improving bacterial diversity in the gut, preventing some potentially harmful molecules from entering the bloodstream and bolstering cognitive performance and stress relief. However, these results were found within this narrow population, so results may be skewed or influenced by unrelated factors[27].

In Hanson et al.'s 2015 study, adults deemed to have "normal cognition" or no previous cognitive impairments were studied. Memory scores were lower for the group who consumed a high-fat meal comprised of 50% fat total — of which 25% was SFAs — when compared to those who had a meal within the recommended total fat range (25-30%). In contrast, the memory scores were higher after the high-fat meal in subjects with some form of cognitive impairment. These changes were linked to changes in glucose, insulin, and plasma levels, along with increased lipid triglyceride. Therefore, while high-fat diets may be helpful for the cognitive function of those with cognitive impairment, for those without it, a high-fat diet will be detrimental[28].

Conversely, a review of the possible benefits of omega-3 FAs, which are generally associated with reduced risk of AD or other cognitive impairments, found increased attention and processing speed for patients with cognitive impairment other than dementia. However, no effect was observed on memory, recall, or executive function in healthy populations or populations with AD[29]. One process crucial for physical and cognitive function is protein synthesis. Proteostasis is the regulation leading to a balance of protein folding and degradation and is thought to be affected by aging. A failure of this process results in misfolded proteins, contributing to the pathogenesis of neurodegenerative diseases, such as AD, Parkinson's disease, and Huntington's disease. The adenosine monophosphate-activated protein kinase (AMPK) signaling network is a core process connected to changes in proteostasis, and it includes dietary components as an activator[30]. Even with caloric deprivation, a high-fat/low-carbohydrate diet increased AMPK phosphorylation, impacting proteostasis and possibly reducing cognitive decline[31].

The Mediterranean diet emphasizes UFAs, especially extra-virgin olive oil. This oil contains 54%—82% monounsaturated FAs and has the potential to significantly reduce the risks or symptoms of neurodegenerative diseases like AD by stimulating these AMPK pathways. Consumption of olive oil decreases levels of the amyloid plaque that precedes AD. It does this by increasing protein processing and increasing autophagy to clear the plaque[32].

The Effect of Proteins on Cognition

Protein is made of amino acids necessary in the body for protein synthesis in skeletal muscle and other tissues and for producing certain substances needed for metabolism[33]. High protein intake is correlated with higher absorption of some micronutrients, such as vitamins D, B2, and B6[34]. However, due to difficulties in monitoring or manipulating protein content without changing other factors, results regarding the impact on cognition are varied. For example, according to a 1976 study by Pirie, protein's effects and nutritional values are difficult to measure due to variable portions of smaller components of foods, even in high-protein foods like meats[35]. Moreover, even in foods with the same protein content, effects may vary due to different macronutrient content, such as the concentration of various amino acids and FAs. Effects with meat may also vary based on the age or sex of the subject, resulting in weak evidence for conclusions in either direction[36]. Also, it was not possible to get a complete view of this macronutrient's effect on cognitive health because the adverse effects of chronic protein overconsumption would make it unsafe to increase protein in a diet disproportionately. Breaking down protein into usable glucose is strenuous, including releasing and detoxifying ammonia, urea, and NH4. This is a taxing process for the kidneys, liver, and intestines, especially in the absence of carbohydrate consumption, and as such, consuming more than 2g/kg-of-body-weight of protein can cause effects anywhere from intestinal discomfort to death[33].

In one study from Sakurai et al. in 2023, the effects of a protein-balanced diet were compared to that of a high-carbohydrate diet among an elderly Japanese population. The cohort with the protein-balanced diet displayed higher scores for both a Memory Performance Index and the more detailed Neurocognitive Index. However, the high-carbohydrate group also had significantly higher ages than the protein-balanced one[37]. A separate study conducted in 2010 by Vizuete et al. investigating subjects over 65 showed a negative correlation between meat intake and cognitive functioning. However, there was a positive association in subjects below the median age of 83[38]. Varying results can also be linked to different protein sources; among U.S. adults over 60 who are not institutionalized, cognitive function was positively associated with proteins from meats, eggs, and legumes but negatively associated with higher dairy-protein intake[39].

Conclusion

Simple carbohydrates have noticeable effects on cognition, although it is less so for children ten years old or younger than it is for adults. Conversely, for adults, an increase in glucose results in a spike in short-term performance before a drop in the more long-term one, both within two hours, contrasting with a more consistent result without changes in glucose. Because simple carbohydrates can be neuroinflammatory, prolonged consumption of them can lead to damage to brain tissue and increased chances of brain disorders, such as AD, and other cognitive deficits. Meanwhile, although understudied, complex carbohydrates may be positively linked with cognitive function and health.

High-fat diets, specifically those with high levels of SFA, negatively impact some cognitive functions, such as memory, attention, and reaction time. They can also be associated with the build-up of amyloid plaque, causing neurodegeneration and AD. Meanwhile, UFA can improve attention and processing speed in patients with cognitive impairment, as well as decrease the chances of neurodegenerative diseases. High-fat diets can also help keep bodily processes going to avert the loss of neurologic function, although this is not applicable in all populations. On the other hand, due to difficulties in isolating dietary protein to measure, results can vary or be unreliable. While more research needs to be done on complex carbohydrates and general fats and proteins, a diet low in carbohydrates, but focused on complex ones, and high in fats, especially UFAs, seems the most beneficial to cognitive function and preventing its loss.

Limitations and Future Study

In currently published works, there has been a lot of research into how different diets or macronutrients can impact cognitive decline among the elderly, especially in patient populations such as those developing dementia or other neurodegenerative diseases, with little to no work done without monitoring cognitive decline. Additionally, in existing literature, the primary macronutrient monitored or altered was carbohydrates, or more specifically, simple glucose, while works exploring the other two macronutrients have varying results due to complications in testing them individually. Proteins especially require more study due to the difficulties and dangers of isolation. Also, this review focused on individual macronutrients, but different combinations should also be researched in the future. For example, patterns other than the Western and Mediterranean diets, various antagonistic or synergistic reactions between different macronutrients, or the changes to nutritional value from different preparation methods and the impact on cognition from all of these should be explored further.

As we see rising rates of obesity and neurodevelopmental disorders in younger populations, analysis of how all the macronutrients affect cognitive function during development in a younger demographic with or without diagnoses of cognitive issues becomes increasingly relevant, despite continuing to be understudied. As a result, future studies should focus on these less-represented fields.

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