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Richard J. Stevenson , Heather Francis
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CHAPTER 1

Introduction

1.1 Introduction

The aim of this book is to provide a comprehensive account of the acute and chronic impacts of human diet on the brain and mind. Importantly, this is distinct from the much larger literature studying how the brain and mind affect food intake. It is distinct because in this book, the presumed causal arrow generally points from food → to brain and mind. A further aspect of this book is its emphasis on humans. This is both pragmatic (e.g., for health and policy implications) and reflects our interests in understanding the effects of diet on the human brain and mind. While there is a primary human focus, we have by necessity drawn on the animal literature. Unlike human studies, animal research can get nearly 100% compliance with experimental dietary regimens, and it is possible to undertake studies that are difficult to do with people, especially those concerning mechanism. Inclusion of animal data is also based on the premise that humans and animals share much common biology. In Sir Austin Bradford Hill's consideration of how to establish causality (Hill, 1965), scientific plausibility (i.e., is there a mechanism?) and coherence with known facts were two key criteria. Animal data is very important as they are particularly useful for understanding mechanism (i.e., scientific plausibility), and for experimental demonstrations of dietary effects on brain and mind (i.e., coherence).

As the title implies, the book investigates the impacts of diet on brain *and* mind. It seems important to study both, although the relative emphasis shifts between chapters dependent on what is known and the topic. It is essential to study effects on mind (operationalised as behaviour and cognition) because this level of explanation has great practical utility. If breakfast makes children concentrate better, intermittent hunger makes people immoral, and fruit and vegetables make people happy, it is important to know this *irrespective* of how diet causes these effects in the brain. Notwithstanding, it is also important to determine how diet does these

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things to the brain. This establishes mechanism, with its implications for the biological plausibility of any observed effect on mind. It can also provide information for human betterment, via say developing nutraceuticals, drugs or other forms of treatment that target the neural mechanism. That aside, the pursuit of knowledge for its own sake is a worthy goal, and it was in this spirit that our book was conceived and written.

There have been many excellent and pioneering books on diet, brain and mind, all of which have appeared as edited volumes (e.g., Lieberman, Kanarek, Nehlig, Dye, Watson). However, these can sometimes lack a consistent approach between chapters, with, for example, greater or lesser emphasis on animal data, epidemiology over experimental work, or whatever. Coverage of the field is also sometimes limited to particular parts, reflecting the interests and expertise of those authors and editors. To date, nobody has tried to pull all of the different strands that make up the field of diet, brain and mind into one volume. Nor has there been a consistent focus on humans, with an interest in both brain and mind. As we have discovered, the field is much larger than we originally thought, it is also very diverse and its parts are often disconnected – but it is endlessly fascinating. The field also faces some significant methodological challenges, both in accurately measuring and manipulating human diet and in measuring brain and behaviour. However, scientists are an ingenious bunch and they have risen to the challenge.

The book proper starts with Chapter 2 on pregnancy, breastfeeding and infancy, followed in Chapter 3 by the acute effects of food intake, looking both at specific meals (e.g., breakfast) and specific nutrients (e.g., particular amino acids). Chapter 4 examines the chronic effects of food intake, with special emphasis on the major dietary pattern found in developed, and now developing, countries: a Western-style diet, rich in saturated fat, salt and added sugar. Chapter 5 explores the acute and chronic effects of dietary neurotoxins, coming both from foods and their contaminants (e.g., fungi, pesticides). Diet can also have an important protective effect on brain and mind, and indeed this is increasingly being recognised as a potential intervention for psychiatric, neurological and neurodegenerative conditions. This is all examined in Chapter 6. In addition, both Chapters 4 and 6 include emerging data on how diet affects the microbial ecology of our large intestine, as these organisms may have an important role in how diet impacts brain and mind. The food and drink we consume are the major routes for ingesting two of the world's most popular drugs, alcohol and caffeine. It has also been suggested that certain foods – ultra-processed items that bear little resemblance to the ingredients from which they are

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made – may exert drug-like effects (e.g., dependence, craving) in consumers. Drugs and food form the basis for Chapter 7. Chapter 8 examines the science of starvation, both its acute and chronic effects in and outside of the laboratory, and the use of energy-restrictive diets for life extension. Chapter 9 looks at the impact on brain and mind of specific nutrient deficiencies (i.e., vitamins, minerals and certain essential macronutrients). Finally, Chapter 10 provides a reflection on this content, its implications and where the field might (and perhaps should) be heading.

The remainder of this first chapter has two aims. The first is to provide a brief overview of the core knowledge and methods that underpin research into diet, brain and mind, and their limitations. We have included this because readers coming afresh to this area may have experience in one domain (e.g., nutrition) but not another (e.g., psychology, brain science), or indeed no experience at all. The second concerns our focus. We have already identified that the emphasis is on humans, and brain and mind, but there is another aspect to our approach that is best discussed with some understanding of the strengths and weakness of the available methods, as they relate to measuring diet. Hence, we have left a discussion of this topic until the end of the chapter, assuming that those unfamiliar with the nutrition literature will first read the following relevant parts first.

1.2 Basic Nutritional Concepts

The main purpose of eating is to satisfy the body's energy needs (Woods & Seeley, 2000). In addition, eating provides the materials for growth and/or maintenance of all bodily systems. In humans, eating and drinking are also a major source of pleasure – if not an art as gastronomy – and a major vehicle for intoxication (e.g., alcohol, caffeine). These more uniquely human aspects of ingestion are of great social and scientific interest. This is because they contribute in no small part to: (1) overeating and obesity; (2) drug abuse, with alcohol being one of the most frequently misused; and (3) to the abuse of other substances which hijack multiple aspects of the brain's appetite/reward systems that support feeding.

Humans obtain energy from four main constituents of what they eat and drink – carbohydrates, proteins, fats and alcohol (Eschleman, 1996). Setting aside alcohol, the three main energy-yielding constituents of food are termed macronutrients. The amount of energy in a food or a drink is measured either in the SI unit the joule (and typically in kilojoules (kJ)) – which is used in this book – or alternatively, and mainly in the United States, by the calorie (and again typically as the kilocalorie (kcal); to

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convert, 1 kcal = 4.18 kJ, and 1 kJ = 0.24 kcal). The formal definition of the calorie is a lot easier to grasp than the formal definitions of the joule. The calorie is defined as the energy required to heat a gram of water by one degree centigrade. The joule is easier to define informally as the energy required to lift a large tomato one metre into the air (or if you prefer more formally – the amount of work done when a force of one Newton is used to move an object one metre in the direction of the applied force (i.e., 1 N·m)).

The energy needs of an individual vary markedly, dependent on age, body composition (muscle vs fat), body weight, pregnancy, lactation, health, activity and climate (Eschleman, 1996). A person's basic energy requirement is the amount of food in kJ they need to eat to maintain their basal metabolic rate. Basal metabolic rate reflects the essential operations of the body necessary to maintain life at rest (i.e., cellular metabolism and maintenance). A man requires around 4.2 kJ per kilogram per hour to maintain basal metabolic rate and a woman around 3.8 kJ. Thus an average US man has a daily energy requirement just to meet basal metabolic rate of around 8,000 kJ and a woman needs around 7,000 kJ. Basal metabolic rates vary markedly over the lifespan, and hence so do energy needs. An infant requires 9.3 kJ per kg per hour, while an elderly woman needs 3.4 kJ per kg per hour. Illness can dramatically increase basal metabolic rate. A change in body temperature from 37 to 41 degrees centigrade due to a fever requires an approximately 60% increase in basal metabolic rate. This is one reason why infection has more lethal effects among starving people.

The other important component in determining energy needs is to establish that spent on moving around and doing things. As activity levels are generally quite low in the developed world, multiplying the adult basal metabolic rate requirement by 1.3 gives a rough guide to typical ideal adult energy intakes (i.e., 10,400 kJ for a man and 9,100 kJ for a woman). For a highly active adult (e.g., a lumberjack), doubling the basal metabolic rate requirement is necessary to satisfy total energy needs.

All of the three macronutrients (and alcohol) can be metabolised to provide energy for the body, and surplus energy from all three sources (and alcohol) can be stored as fat (Eschleman, 1996). Carbohydrates and proteins yield around 17 kJ per gram, while fats provide 38 kJ per gram. Under normal circumstances, carbohydrates provide the main energy source for humans. In our ancestral environment, complex carbohydrates were the principal energy source in the form of starch (e.g., tubers (potatoes, cassava), grass seeds (wheat, rice)), with indigestible complex

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carbohydrates providing fibre (cellulose, inulin). Starch is composed of multiple glucoses units connected by covalent bonds. This is broken down in the digestive system into glucose. Glucose is a monosaccharide, and is used by the body as an energy source. It is present in blood at around 1,400 mg per litre in a healthy adult, and is stored in small amounts in various bodily depots as glycogen. Glycogen is a polysaccharide, with chains of glucose attached to a glycogenin protein core. Depots of glycogen are found in muscles (about 500 g in total) and the liver (about 100 g). Maintaining adequate supplies of glucose is essential because it is the primary energy source for the brain, where the *only* alternative fuel is ketone bodies (essentially an emergency fuel when all potential sources of glucose are exhausted). Nerve cells are unable to store glucose as glycogen.

In contrast to ancestral diets, a significant source of carbohydrates in modern diets comes from one particular disaccharide – sucrose or sugar. Disaccharides are composed of two monosaccharide units. Glucose is a monosaccharide, and there are two other important monosaccharides. Fructose, which is particularly sweet, and galactose, which is not that sweet – with both of these found in small quantities in certain fruits. The most important dietary sugar is the disaccharide sucrose, which is made of one glucose unit and one fructose unit. In the United States, each person consumes an average of 20 teaspoons (80 g) of sucrose per day (Drewnowski & Rehm, 2014). Other important dietary disaccharides are lactose ('milk' sugar), found in mammalian milk (composed of a glucose and a galactose unit), and maltose, found in beer (composed of two glucose units). Neither lactose nor maltose are particularly sweet.

As noted earlier, glucose is the principal fuel for the brain as well as being a major bodily fuel (Sembulingam & Sembulingam, 2016). In the presence of oxygen (i.e., aerobically) it is converted into pyruvate-liberating energy, and further energy can be released by the conversion of pyruvate into acetyl coenzyme A. All of this takes place in the cytosol (i.e., in the main portion of the cell). Acetyl coenzyme A is then fed into the Krebs cycle, which takes place inside mitochondria (a cellular organelle), liberating yet more energy (see Figure 1.1). Under conditions of high exertion, when the body cannot supply sufficient oxygen to muscle tissues for aerobic respiration (i.e., energy generation), both glucose and pyruvate can be metabolised without oxygen (i.e., anaerobically) in the cytosol, providing a brief burst of energy, but leading to a rapid build-up of lactic acid, which inhibits further anaerobic respiration.

In the absence of adequate supplies of carbohydrate, protein can serve as a good fuel substitute, as approximately half of the protein available in diet

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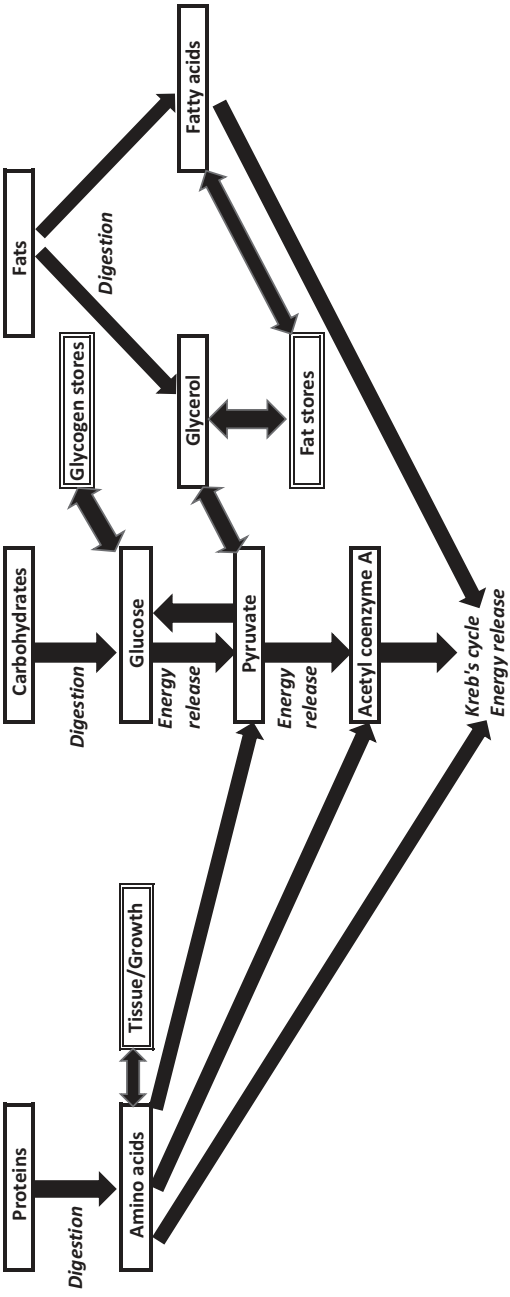

Figure 1.1 Basics of energy metabolism

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can be metabolised to pyruvate, which can then be converted back to glucose (Sembulingam & Sembulingam, 2016). The remaining half can be fed directly into the Krebs cycle, the major energy-generation pathway for the body (see Figure 1.1). In the main, dietary protein, which is built from multiple, different amino acids, is essential for tissue maintenance and growth (i.e., creation of new proteins (e.g., enzymes) and biomolecules – like neurotransmitters), and for fluid balance. Humans require 20 different amino acids, some of which have to come from dietary sources as they cannot be synthesised by the body. Meat provides all of the required amino acids. A solely plant-based diet can as well, but care is needed to avoid insufficiency.

While fats are a good source of energy (see Figure 1.1), they are a poor source of glucose and are not used as a fuel by the brain. Fats are composed of a glycerol molecule, which can be converted to glucose, with three fatty acid tails attached, which cannot be converted (Sembulingam & Sembulingam, 2016). The type of fatty acid attached to the glycerol molecule dictates the type of fat – saturated, monounsaturated, polyunsaturated and trans-saturated. Type is based upon the presence/absence and location of carbon double bonds, and subtype by the length of the fatty acid chain. Different types of fats tend to be found in different types of food. Saturated fats, which are solid at room temperature, are generally from animals (e.g., meat, dairy), with the exception of palm and coconut oil. All of these are associated with an unhealthy blood lipid profile and have been linked to coronary arteriosclerosis and heart disease, although this is no longer a universal conclusion (Chowdhury et al., 2014). Monounsaturated fats have plant-based sources (e.g., olive oil, canola oil), and are linked to a beneficial blood lipid profile. With polyunsaturated fats, which are liquid at room temperature (as with monounsaturated fats), one common type is found in nuts and seafood (omega 3) and another in plants (omega 6). Both are linked to beneficial blood lipid profiles. Trans-saturated fats are factory-made from plant-based unsaturated sources. They have very useful properties in that they do not readily oxidise (i.e., go rancid) giving foods made from them a long shelf life. Unfortunately, they seem to have a worse effect on blood lipid profile than saturated fats and they have been banned in several countries. While fats are a major source of energy, they have many other important functions. They form key parts of cell membranes, and nerve fibre myelin sheaths, and they are needed for hormone synthesis, the digestion of certain vitamins, thermal insulation (subcutaneous fat), energy storage and organ padding.

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In addition to the macronutrients, the body needs a range of micronutrients, all of which are provided in a typical omnivorous diet (Eschleman, 1996). Micronutrients are divided into vitamins and minerals. Vitamins are a heterogenous collection of organic compounds that the body cannot synthesise, which are necessary for normal function, and so have to come from food. Vitamins are usually grouped into those that are fat-soluble (A, D, E and K) and those that are water soluble (B, C). Dietary insufficiency in particular vitamins is linked to specific deficiency diseases, many of which have a long and tragic history (e.g., beriberi, scurvy, pellagra). In the past, these diseases were not recognised as resulting from a dietary cause (e.g., scurvy was thought to be a manifestation of syphilis). Identifying the cause required use of a scientific method. This was applied to scurvy by English naval physician James Lind in 1797. It revealed scurvy's dietary basis and probably represents the first ever clinical trial (Carpenter, 2003).

Mineral elements (beyond carbon, hydrogen, nitrogen and oxygen) are the other necessary dietary components. These are classified as either macrominerals (requirements greater than 100 mg per day) – calcium, phosphorous, sodium, sulphur, chlorine, potassium and magnesium – or microminerals (<100 mg per day) – iron, iodine, fluorine, selenium, zinc and several others. Deficiencies in these microminerals can produce severe disease (e.g., iodine deficiency, goitre and cretinism) and in some instances either too much or too little can be harmful (e.g., sodium/chlorine (salt); selenium).

1.3 Basics of Digestion and Regulation

The preparation for digestion starts before eating, as a variety of processes are triggered by the thought, sight or smell of food (think Ivan Pavlov, bells, and salivating dogs – the cephalic phase response). Food in the mouth is mechanically broken up by the action of chewing. It is mixed with saliva and formed into a bolus for swallowing (Longenbaker, 2017). Saliva contains the enzyme alpha amylase, which acts rapidly to break down starch into sugars. Whether this is to aid digestion or to promote consumption by making a starchy food taste somewhat sweet is not known.

The swallowed bolus passes down the oesophagus into the upper part of the stomach where it is ground into even small particles by this organ's muscular action. This ground food is then moved into the body of the stomach where it is mixed with acid and enzymes, forming a semi-liquid

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called chyme which collects in the lower part of the stomach. The chyme is then expelled via the pyloric sphincter into the small intestine, which is the main organ for the absorption and digestion of nutrients in the human body.

The small intestine is a muscular tube 2–3 cm in diameter and 6–7 m in length (but probably less, as these measurements are based on cadavers with 'relaxed' muscles; Longenbaker, 2017). The small intestine has waves of muscular action (peristalsis) so as to move its contents progressively along its length. Because the wall of the small intestine is heavily invaginated and covered with a myriad small projections of tissue (microvilli), it has a large surface area, around 60 m^2 in an adult (a quarter of a tennis court). This assists effective nutrient absorption. The arrival of food into the small intestine triggers the release of cholecystokinin (CCK). This hormone stimulates the production of bile to break down fat, and the release of pancreatic juices to break down protein and carbohydrates. CCK also acts to slow the release of chyme from the stomach. Amino acids, glucose, fatty acids, vitamins and minerals then pass (some actively (i.e., energy driven transporters) and some passively) through the endothelial lining of the gut into cells. In these cells fatty acids are packaged into chylomicrons, which, together with other nutrients, are released into the hepatic portal vein for transport to the liver and other bodily tissues.

The remaining unabsorbed material passes into the large intestine, which is 1–2 m in length, and called 'large' due to its 6–7 cm diameter (Longenbaker, 2017). While digestively of lesser importance than the small intestine, it nonetheless has several functions. The large intestine is home to a vast number of microorganisms, which feed on the undigested produce coming from the small intestine. This microbial ecosystem is increasingly being recognised for its impact on health, as the type of organisms present influences the production of ketones, which serve as both an energy source, but also act to preserve the integrity of the endothelial (i.e., gut–body) barrier (Berding et al., 2021). Leakage of material from the gut, other than nutrients, may initiate a number of disease processes, possibly including dementia, as amyloid beta is produced in abundance by certain types of bacteria, but not by others. Many other factors also influence the integrity of the gut–body barrier, in particular the type of bacteria present. Diet can result in fairly rapid changes in this microbial ecosystem, for the better (plant-based foods) or worse (processed foods). Fermentation by gut microbes is also important in the production of certain B vitamins, and for vitamin K, and these alongside water and ketones are absorbed by this part of the digestive tract. Compactification

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occurs, followed by temporary storage in the rectum, before defecation ends the digestive process.

The digestive system and the brain are connected in several ways. The brain's sensory systems 'see', 'smell', 'taste' and 'feel' food as it is eaten, providing information to prepare the organism for feeding and to terminate a feeding bout. The vagus nerve links the brain and gut, carrying sensory information (e.g., nutrient sensing, gut fullness) from gut to brain (most traffic) and some signals from brain to gut. Hormonal signals released by digestion, the digestive system and fat stores all impact brain function and regulation (Lowell, 2019). These include grehlin released by the stomach when empty, CCK when the stomach is filling or full, and leptin from fat, indicating the extent of bodily fat stores. All of these hormones affect appetite and exert influences well beyond this domain (e.g., grehlin promotes learning – a good idea if one is to remember a food source). The brain also monitors a range of physiological parameters which provide information about the nutritional status of the body, such as signals of muscle usage and blood glucose, for example. This information feeds into a number of brain areas that are known to be involved in the regulation of appetite (Logue, 2015). The most well-known component is the hypothalamus, particularly the lateral and ventromedial parts, which are early processors of sensory, gut, hormonal and metabolic signals and set up a general brain state either favourable or not for eating. The striatum, frontal cortex, orbitofrontal cortex, insula and hippocampus interact to regulate eating based on both hypothalamic outputs and in many cases via the same sensory, gut, hormonal and metabolic signals as well. These latter structures are the probable basis for the conscious aspects of eating, underpinning sensation, pleasure, feelings of fullness and hunger, thoughts about food, and broader conceptual considerations such as dieting, morality of meat eating or gourmet dining, for example.

While the brain is a major controller of food intake, certain regulatory aspects of digestive/ingestive processes are more peripheral. Glucose and fat are two important examples, reflecting the operation of short-term and long-term energy management systems, respectively. Increases in glucose, typically after eating, are kept in check by the release of insulin from beta cells in the pancreas, which sequesters excess glucose into muscle or liver cells as glycogen. In contrast, falling blood glucose leads to the secretion of glucagon by alpha cells in the pancreas, which liberates glucose from glycogen. For fat stores, which are the body's energy reserve against starvation, fat cells continuously release a hormonal signal leptin, which reflects bodily fat content. As leptin levels fall, indicating a reduction in

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