Hippocampal Architecture and Neuroplasticity: Anatomical Foundations of Memory Circuits and Their Susceptibility to Dietary Modulators

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Abstract

Background: The hippocampal formation is a highly specialized medial temporal lobe structure that supports episodic memory, spatial navigation, and context-dependent learning through a tightly organized laminar architecture and stereotyped intrinsic circuitry. Its neuroanatomy is defined by distinct subfields—dentate gyrus, cornu ammonis (CA1–CA4), and the subicular complex—each characterized by unique cytoarchitecture, microcircuit motifs, and long-range connections that collectively enable encoding, pattern separation, pattern completion, and memory consolidation. Beyond gross morphology, hippocampal function depends on the alignment between cellular layers, afferent–efferent pathways (including entorhinal–hippocampal projections and fornical outputs), and a microvascular supply that must sustain high metabolic demand in selectively vulnerable neuronal populations, particularly within CA fields. Neuroplasticity in the hippocampus spans synaptic remodeling, activity-dependent gene expression, and regionally specialized network dynamics, with the dentate gyrus occupying a central position in input gating and adaptive circuit refinement. Increasing attention has focused on how dietary factors can modulate this anatomical–functional system, not only through systemic metabolic signaling but also through local effects on oxidative balance, vascular integrity, and cellular stress responses that may bias plasticity toward adaptation or injury. In this review, we integrate foundational hippocampal anatomy with key principles of neuroplasticity and connectivity, then frame the hippocampus as a metabolically sensitive structure whose circuits may be reshaped by dietary modulators, including sugar patterns and low-calorie sweeteners, as suggested by experimental models. This anatomical viewpoint provides a coherent scaffold for interpreting how nutritional exposures may influence hippocampal structure, resilience, and memory-related performance.

Keywords: *Hippocampal formation; Dentate gyrus; Cornu ammonis (CA1–CA4); Subiculum; Entorhinal cortex; Perforant path; Fornix; Limbic circuitry; Cytoarchitecture; Neuroplasticity; Pattern separation; Memory consolidation; Vascular supply; Metabolic vulnerability; Dietary modulators; Artificial sweeteners; Oxidative stress; Activity-dependent gene expression.*

Introduction

The limbic system represents a complex network of interconnected cortical and subcortical structures that plays a central role in emotional processing, memory formation, motivation, and behavioral regulation. Anatomically, it integrates structures distributed along the medial aspects of the cerebral hemispheres with deeper nuclei of the forebrain and diencephalon, forming a functional interface between cognitive and autonomic systems. These regions communicate through extensive fiber pathways that allow integration of sensory input, emotional responses, and higher cortical processing. The limbic network therefore acts as a critical mediator between primitive survival mechanisms and advanced cognitive functions such as learning, decision-making, and memory consolidation [1,2].

Historically, the concept of the limbic system evolved from early neuroanatomical observations describing a ring-like arrangement of cortical structures surrounding the brainstem and diencephalon. Subsequent models expanded this concept by including interconnected nuclei and pathways that participate in emotional and mnemonic processing. One of the most influential frameworks was the Papez circuit, which describes a neural pathway connecting the hippocampus, mammillary bodies, anterior thalamic nuclei, and cingulate cortex. This circuit highlighted the functional importance of reciprocal connectivity within the limbic system and established the hippocampus as a central hub linking memory processing with emotional expression [3,4].

Among the structures of the limbic system, the hippocampus occupies a particularly prominent position due to its essential contribution to memory encoding, spatial navigation, and contextual learning. Situated in the medial temporal lobe, the hippocampus forms part of a broader hippocampal formation that includes the dentate gyrus and subicular complex. These components are arranged in a characteristic curved configuration and interconnected through precisely organized neural circuits. Such anatomical specialization allows the hippocampus to transform incoming sensory information into durable memory representations while simultaneously interacting with cortical and subcortical networks involved in behavior and emotional regulation [5,6].

In addition to its structural organization, the hippocampus demonstrates remarkable capacity for neuroplasticity. Synaptic remodeling, activity-dependent gene expression, and continuous integration of neuronal inputs contribute to the adaptive remodeling of hippocampal circuits throughout life. This plastic nature enables the hippocampus to respond dynamically to environmental stimuli, learning experiences, and physiological changes. However, the same features that support plasticity also render hippocampal neurons vulnerable to metabolic disturbances, oxidative stress, and alterations in systemic homeostasis [7].

Recent research has therefore emphasized the influence of metabolic and dietary factors on hippocampal structure and function. Experimental and epidemiological evidence suggests that dietary patterns—including excessive sugar intake and the increasing consumption of artificial sweeteners—may affect hippocampal circuitry through mechanisms involving oxidative stress, neurotransmitter imbalance, and altered neuronal signaling. Because hippocampal neurons require high energy supply and exhibit selective vulnerability to metabolic insults, dietary modulators may influence memory performance and neuroplastic processes within this region [8–10].

Understanding the anatomical organization of the hippocampus is therefore essential for interpreting how such environmental influences interact with neural circuits responsible for cognition and behavior. This review aims to provide an integrated anatomical perspective of the hippocampal formation, highlighting its structural organization, connectivity, vascular supply, and neuroplastic characteristics. By linking these anatomical foundations with emerging evidence regarding dietary modulation of neural function, the review seeks to clarify how metabolic factors may influence hippocampal integrity and the neural mechanisms underlying memory and learning.

Organization of the Limbic System

The limbic system represents a complex anatomical and functional network of cortical and subcortical structures that collectively regulate emotional behavior, memory formation, motivation, and autonomic

responses. Rather than functioning as a single anatomical entity, the limbic system consists of several interconnected regions distributed across the medial surfaces of the cerebral hemispheres and deeper forebrain structures. These components communicate through extensive neural pathways that enable the integration of sensory information with emotional and cognitive processes [11,12].

Anatomically, the limbic system can be broadly divided into cortical and subcortical components. The cortical division, often referred to as the limbic lobe or rhinencephalon, includes structures such as the cingulate gyrus, parahippocampal gyrus, subcallosal region, and portions of the orbitofrontal cortex. These cortical areas form a ring-like arrangement surrounding the corpus callosum and diencephalon, providing a structural framework that links higher-order cognitive processing within the cerebral cortex to emotional and visceral responses mediated by deeper brain regions [11,12]. The cingulate cortex, in particular, plays an important role in emotional regulation, attention, and behavioral control through its extensive connections with the hippocampus, prefrontal cortex, and thalamic nuclei.

The subcortical portion of the limbic system includes several key nuclei such as the hippocampus, amygdala, septal nuclei, and nucleus accumbens, along with important hypothalamic structures including the mammillary bodies and preoptic regions. These nuclei participate in the regulation of emotional responses, reward processing, motivation, and neuroendocrine integration. The amygdala, for instance, acts as a central hub for emotional processing, particularly in the detection of fear-related stimuli and the modulation of behavioral responses to environmental challenges. Through its extensive connections with both cortical and subcortical structures, the amygdala integrates sensory information with emotional memory and autonomic output [13,14].

Within the limbic network, the hippocampus occupies a pivotal position due to its role in learning and memory consolidation. It communicates extensively with the entorhinal cortex, which serves as the principal gateway through which cortical information enters and exits the hippocampal formation. The entorhinal cortex receives inputs from multiple sensory association areas and transmits them to the hippocampus through the perforant pathway, thereby allowing the hippocampus to integrate multimodal sensory information into coherent memory representations [15]. This anatomical arrangement highlights the hippocampus as a central interface between cortical information processing and limbic emotional circuits.

One of the classical anatomical frameworks describing limbic connectivity is the Papez circuit. This circuit begins with projections from the hippocampus that travel through the fornix to the mammillary bodies of the hypothalamus. From there, signals are transmitted to the anterior thalamic nuclei via the mammillothalamic tract, followed by projections to the cingulate gyrus. The cingulate cortex then communicates with the parahippocampal region and entorhinal cortex, ultimately completing the circuit by returning information to the hippocampus. This loop provides an anatomical basis for the integration of emotional experience with memory processing [13].

White matter tracts play an essential role in maintaining communication among limbic structures. The fornix represents the primary efferent pathway of the hippocampus and connects it with septal nuclei, hypothalamic structures, and other components of the limbic system. Another major pathway, the cingulum bundle, links the cingulate cortex with the parahippocampal gyrus and entorhinal cortex, thereby facilitating interactions between cortical and hippocampal memory circuits. In addition, the uncinate fasciculus connects the anterior temporal lobe—including the amygdala—with the orbitofrontal cortex, supporting integration between emotional processing and decision-making networks [14].

Neurotransmitter systems further modulate limbic activity and influence emotional and cognitive behavior. Cholinergic projections originating from the basal forebrain enhance hippocampal plasticity and memory encoding, whereas serotonergic and noradrenergic pathways regulate mood, arousal, and stress responses. Dopaminergic inputs from the ventral tegmental area also interact with limbic circuits, particularly the nucleus accumbens, contributing to reward-related learning and motivational behaviors [16].

Overall, the limbic system functions as an integrated neural network that coordinates emotional

responses, memory formation, and behavioral adaptation. Its distributed architecture allows different components to contribute specialized functions while maintaining dynamic communication through interconnected pathways. Within this network, the hippocampus acts as a critical structural and functional hub, linking sensory experiences with emotional context and enabling the formation of long-term memories. Understanding the organization of the limbic system therefore provides essential anatomical context for interpreting the structural and functional roles of the hippocampus within broader neural circuits.

Gross Anatomy of the Human Hippocampus

Following the broader organization of the limbic system, the hippocampus emerges as one of its most structurally and functionally significant components. Located deep within the medial temporal lobe, the hippocampus forms an elongated structure that extends along the floor of the inferior horn of the lateral ventricle. In coronal sections it appears as a curved elevation projecting into the ventricular cavity, whereas in three-dimensional orientation it exhibits a characteristic C-shaped configuration that follows the curvature of the temporal lobe. This distinctive morphology reflects its developmental origin from the archicortex and its relationship with the choroidal fissure during brain development [17,18].

The hippocampus constitutes the central component of a broader anatomical entity known as the **hippocampal formation**, which includes three principal elements: the hippocampus proper (cornu ammonis), the dentate gyrus, and the subiculum. Together, these components form a continuous anatomical and functional unit responsible for processing memory-related information and coordinating spatial navigation mechanisms. Each subdivision demonstrates distinctive morphological characteristics and connectivity patterns that collectively support the complex integrative functions of the hippocampal network [18,19].

The hippocampus proper, often referred to as **Ammon's horn**, is subdivided into four regions designated CA1, CA2, CA3, and CA4. These regions differ in neuronal density, cellular morphology, and synaptic organization. The CA1 region forms the most lateral component and is particularly important for memory consolidation and retrieval. CA2 is a relatively narrow intermediate zone characterized by unique molecular features and specialized synaptic connections. CA3, located closer to the dentate gyrus, contains larger pyramidal neurons and plays a significant role in recurrent network activity that contributes to pattern completion during memory recall. The CA4 region, often referred to as the hilus, lies within the concavity of the dentate gyrus and participates in the integration of signals entering the hippocampal circuitry [19,20].

Adjacent to the hippocampus proper lies the **dentate gyrus**, a narrow, serrated band of cortex that forms the medial border of the hippocampal formation. The dentate gyrus displays a distinctive folded structure composed primarily of densely packed granule cells. These neurons receive afferent projections from the entorhinal cortex through the perforant pathway and represent the primary gateway through which cortical information enters the hippocampal circuitry. This anatomical arrangement allows the dentate gyrus to perform essential functions related to pattern separation and the encoding of new episodic memories [21].

The **subiculum** forms the transitional region between the hippocampus proper and the entorhinal cortex. It serves as the principal output region of the hippocampal formation, transmitting processed information to numerous cortical and subcortical structures including the thalamus, hypothalamus, and association cortices. Anatomically, the subiculum lies between the CA1 region and the parahippocampal cortex, forming an important relay station that channels hippocampal signals into broader neural networks responsible for cognitive integration and behavioral regulation [22].

From a macroscopic perspective, the hippocampus is typically divided into three segments: the **head, body, and tail**. The hippocampal head is located anteriorly within the temporal lobe and is characterized by several digitations that protrude into the temporal horn of the lateral ventricle. The body extends posteriorly along the ventricular floor, maintaining a relatively consistent thickness and curvature. The tail gradually tapers as it approaches the splenium of the corpus callosum and eventually continues into the crus of the fornix. This segmentation is clinically relevant because different hippocampal regions

may demonstrate varying vulnerability to pathological processes such as ischemia, neurodegeneration, or traumatic injury [17,18].

Several white matter structures are closely associated with the hippocampus and contribute to its connectivity within the limbic system. The **alveus** consists of a thin layer of myelinated fibers that cover the ventricular surface of the hippocampus. These fibers converge medially to form the **fimbria**, which continues posteriorly as the **fornix**, the major efferent pathway of the hippocampal formation. Through the fornix, hippocampal outputs reach the mammillary bodies, septal nuclei, and other limbic structures, thereby linking hippocampal processing with emotional and autonomic regulation [23].

The spatial orientation and connectivity of the hippocampus highlight its role as a central integrative hub within the limbic network. By receiving multimodal sensory input through the entorhinal cortex and distributing processed information through the fornical system, the hippocampus bridges cortical association areas with subcortical emotional circuits. This anatomical organization provides the structural basis for its critical involvement in episodic memory formation, spatial navigation, and the contextual modulation of behavior [24].

Comparative Anatomy of the Hippocampus in Humans and Rodents

Although the hippocampus is highly conserved across mammalian species, notable anatomical and organizational differences exist between humans and commonly studied experimental animals such as rodents. Comparative analysis of hippocampal structure has been particularly important in neuroscience research because many experimental investigations exploring memory mechanisms, neuroplasticity, and dietary influences on brain function are conducted using rodent models. Understanding similarities and distinctions between the human and rodent hippocampus therefore provides an essential framework for interpreting experimental findings and translating them into human neurobiology [25].

In both humans and rodents, the hippocampus belongs to the archicortex and displays a characteristic curved configuration within the medial temporal region. Despite species-specific differences in brain size and orientation, the basic structural components remain highly conserved. The hippocampal formation in both species includes the dentate gyrus, the cornu ammonis fields (CA1–CA4), and the subicular complex. These elements are arranged in a similar laminar pattern and connected through well-defined intrinsic pathways that form the fundamental circuitry responsible for memory encoding and spatial processing [26].

In rodents, the hippocampus exhibits a pronounced longitudinal axis that extends from the septal region rostrally toward the temporal region caudally. The structure often appears elongated and banana-shaped, reflecting its extended orientation along the dorsal–ventral axis of the brain. The outer surface of the hippocampus is covered by a thin layer of white matter known as the **alveus**, which contains myelinated axons originating from pyramidal neurons within the hippocampal formation. These fibers converge medially to form the **fimbria**, which subsequently continues as the **fornix**, the principal efferent pathway linking the hippocampus with other limbic structures [25].

The fornical system is particularly prominent in rodents and serves as a critical conduit for hippocampal outputs. The two crura of the fornix converge to form the body of the fornix, which lies superior to the thalamus and beneath the corpus callosum. Anteriorly, the fornix divides into columns that descend toward the hypothalamus. Some fibers pass posterior to the anterior commissure and terminate in structures such as the mammillary bodies and anterior thalamic nuclei, forming part of the classical Papez circuit. Other fibers travel anterior to the anterior commissure to reach the septal nuclei, ventral striatum, and prefrontal cortical areas. These projections illustrate the extensive influence of hippocampal signaling on emotional regulation, motivation, and cognitive processing [27].

A major functional interface between the hippocampus and the neocortex in both humans and rodents is the **entorhinal cortex**. This region serves as the primary gateway for cortical inputs to the hippocampus. Neurons from the entorhinal cortex project to the dentate gyrus and hippocampal pyramidal cells through the perforant pathway, delivering highly processed sensory information from multiple association areas of the cerebral cortex. In return, hippocampal outputs are transmitted back to the entorhinal cortex and subsequently distributed to widespread cortical regions. This bidirectional

communication supports the integration of new information with previously stored memories [28].

Despite these fundamental similarities, certain differences in hippocampal organization are observed between species. In rodents, the dorsal hippocampus is primarily associated with spatial learning and navigation, whereas the ventral portion contributes more strongly to emotional and motivational processing. In humans, however, these functional gradients are less sharply defined, reflecting the greater complexity and integration of hippocampal networks with higher-order cortical areas involved in cognition and behavior [29].

Experimental studies using rodent models have been instrumental in identifying specialized neuronal populations within the hippocampus, including **place cells**, which become active when an animal occupies a specific spatial location. These neurons provide an internal representation of the surrounding environment and contribute to spatial memory and navigation. Similar functional properties have been identified in primate and human hippocampal neurons, suggesting that spatial coding mechanisms are evolutionarily conserved across species [24].

The structural conservation of hippocampal circuitry between humans and rodents underlies the widespread use of rodent models in studies investigating neuroplasticity, neurodegeneration, and metabolic influences on brain function. At the same time, careful consideration of species-specific differences remains necessary when extrapolating experimental results to human neurobiology. Comparative neuroanatomy therefore continues to provide valuable insight into the organization of hippocampal networks and their role in cognitive and behavioral regulation.

Histological Organization and Cytoarchitecture of the Hippocampus

Beyond its gross anatomical structure, the hippocampus demonstrates a highly specialized microscopic organization that reflects its classification as an **allocortical structure**. Unlike the six-layered neocortex, the hippocampus contains fewer cellular layers arranged in a distinct laminar pattern that supports efficient synaptic transmission and neural plasticity. This cytoarchitectural organization allows precise integration of incoming signals, transformation of information within intrinsic circuits, and transmission of processed outputs to other limbic and cortical regions [30].

The hippocampal formation is composed of three principal histological components: the **dentate gyrus**, the **cornu ammonis (CA) fields**, and the **subicular complex**. Each of these subdivisions exhibits characteristic cellular architecture and specific functional roles in hippocampal circuitry. Differences in neuron morphology, cell density, and receptor expression distinguish these regions and contribute to their specialized contributions to memory processing and spatial cognition [31].

Dentate Gyrus

The dentate gyrus represents the primary input gateway to the hippocampal formation. Histologically, it consists of three main layers arranged from superficial to deep: the **molecular layer**, **granular cell layer**, and **polymorphic layer** (also known as the hilus). The molecular layer contains dendritic arborizations of granule cells and receives afferent projections from the entorhinal cortex through the perforant pathway. The granular layer is densely populated with small excitatory granule neurons whose axons project toward the CA3 region as **mossy fibers**, forming an essential link within the hippocampal trisynaptic circuit. Beneath this lies the polymorphic layer, which contains interneurons and mossy cells that participate in modulating excitatory activity within the hippocampal network [32].

The dentate gyrus plays a fundamental role in **pattern separation**, a process that enables the brain to distinguish between similar experiences or spatial environments. Its tightly packed granule cells and specialized synaptic organization allow incoming sensory information to be transformed into distinct neural representations before transmission to downstream hippocampal circuits [33].

Cornu Ammonis (CA Fields)

The cornu ammonis constitutes the central portion of the hippocampus proper and is divided into four regions: **CA1, CA2, CA3, and CA4**. These regions are distinguished primarily by variations in pyramidal neuron size, density, and synaptic organization. The pyramidal neurons represent the principal excitatory cells of the hippocampus and are arranged in a narrow cellular band known as the **stratum pyramidale** [31].

Surrounding this pyramidal layer are several additional laminae that reflect the orientation of neuronal processes and incoming fibers. The **stratum oriens**, located beneath the pyramidal cell layer, contains basal dendrites of pyramidal neurons as well as inhibitory interneurons. Above the pyramidal layer lies the **stratum radiatum**, which contains apical dendrites receiving synaptic inputs from other hippocampal regions. The outermost layer, the **stratum lacunosum-moleculare**, contains fibers originating primarily from the entorhinal cortex and plays an important role in integrating cortical inputs with intrinsic hippocampal circuitry [34].

Among the CA regions, **CA3** is notable for its extensive recurrent collateral connections, which allow pyramidal neurons to form an intrinsic excitatory network capable of amplifying and sustaining neural activity. These connections contribute to pattern completion during memory retrieval. In contrast, **CA1** receives projections from CA3 through the Schaffer collateral pathway and serves as a major output region for hippocampal information processing. Due to its high metabolic demand and receptor density, CA1 neurons are particularly vulnerable to ischemic injury and metabolic disturbances [30].

Subicular Complex

The **subiculum** forms the transitional zone between the hippocampus proper and the entorhinal cortex. Histologically, it contains pyramidal neurons arranged in a relatively broader layer compared with the CA regions. Beneath the pyramidal band lies a polymorphic zone containing interneurons and glial cells. The subiculum functions as the principal output pathway of the hippocampal formation, transmitting processed signals to numerous cortical and subcortical targets including the thalamus, hypothalamus, and prefrontal cortex [35].

Recent advances in neuroanatomical mapping techniques have revealed additional complexity within the hippocampal formation. Modern cytoarchitectonic and receptor-based studies have identified transitional regions such as the **prosubiculum**, **presubiculum**, and **parasubiculum**, which display distinct neuronal populations and connectivity patterns. These structures provide additional pathways linking hippocampal processing with parahippocampal and neocortical areas, thereby expanding the functional network through which memory and spatial information are integrated [36].

Functional Significance of Hippocampal Cytoarchitecture

The laminar organization of the hippocampus supports a highly ordered flow of information through the classical **trisynaptic circuit**. In this circuit, afferent projections from the entorhinal cortex reach the dentate gyrus via the perforant pathway. Granule cells of the dentate gyrus then transmit signals to CA3 pyramidal neurons through mossy fibers. Finally, CA3 neurons project to CA1 neurons through Schaffer collateral connections, allowing further processing before outputs are transmitted through the subiculum to cortical and subcortical targets. This sequential arrangement of synaptic connections ensures efficient processing of memory-related information and facilitates the dynamic plasticity required for learning and adaptation [33].

Overall, the histological organization of the hippocampus reflects a finely tuned architecture designed to support complex cognitive functions. The distinct layering patterns, specialized neuronal populations, and precisely arranged synaptic pathways collectively enable the hippocampus to transform sensory input into stable memory representations. At the same time, this highly organized structure also contributes to the selective vulnerability of hippocampal neurons to metabolic stress, ischemia, and neurodegenerative processes.

Vascular Supply and Venous Drainage of the Hippocampus

Following the description of hippocampal cytoarchitecture, understanding its vascular organization is essential because the metabolic demands of hippocampal neurons are among the highest within the brain. The hippocampus relies on a delicate network of small-caliber arteries and veins that ensure continuous perfusion of its highly active neuronal circuits. This vascular architecture is particularly important because hippocampal neurons—especially pyramidal cells in the CA1 region—are extremely sensitive to ischemia and metabolic disturbances. Consequently, even minor alterations in blood supply may lead to selective neuronal vulnerability and functional impairment [37].

Arterial Supply

The arterial supply of the hippocampus is derived primarily from branches of the **posterior cerebral artery (PCA)** and the **anterior choroidal artery (AChA)**. These vessels originate respectively from the vertebrobasilar and internal carotid arterial systems, providing a dual vascular contribution to the medial temporal lobe structures. The PCA generally supplies the majority of the hippocampal body and tail through several temporal branches, including the anterior and middle inferior temporal arteries as well as the splenial branches. In contrast, the anterior choroidal artery predominantly irrigates the anterior portion of the hippocampus, particularly the hippocampal head and uncus [17,37].

Detailed anatomical studies have demonstrated significant variability in the distribution of these arteries. In many individuals, the hippocampus receives a **combined vascular supply from both the PCA and the AChA**, forming an overlapping perfusion territory that helps maintain stable blood flow. This dual supply pattern has been observed in more than half of examined hemispheres, while other patterns include predominant supply by PCA branches or, less commonly, exclusive supply from the anterior choroidal artery. Such anatomical variations have important clinical implications because they may influence susceptibility to ischemic injury during vascular compromise or neurosurgical procedures [38].

Within the hippocampus itself, specialized branches known as **hippocampal arteries** penetrate the hippocampal sulcus and distribute blood to the internal layers of the hippocampal formation. These vessels further divide into smaller arterioles supplying distinct regions such as the dentate gyrus, CA fields, and subiculum. Some studies describe two principal arterial groups—referred to as **upper and lower hippocampal arteries**—that supply different portions of the cornu ammonis. The CA1 region, located at the border between these vascular territories, represents a watershed area that is particularly susceptible to ischemic injury [39].

Microsurgical investigations have also identified entry points through which these arteries reach the hippocampal tissue, including the **fimbriodentate sulcus** and the **hippocampal sulcus**. After penetrating the hippocampal surface, the vessels branch extensively within the molecular, pyramidal, and granular layers, providing metabolic support to neuronal and glial elements. Because these arteries are relatively small and fragile, they are prone to occlusion or thrombosis, which may lead to focal hippocampal damage and subsequent cognitive deficits [40].

Venous Drainage

The venous drainage of the hippocampus mirrors the complexity of its arterial supply. Several small venous channels collect blood from the hippocampal layers and converge into larger veins that ultimately drain into the deep venous system of the brain. Two principal types of intrahippocampal veins have been described: **sulcal intrahippocampal veins** and **subependymal intrahippocampal veins**.

The sulcal veins originate primarily from the CA1 and CA2 regions and course toward the superficial hippocampal sulcus, where they receive tributaries from the molecular layers of the hippocampus. In contrast, the subependymal veins run along the ventricular surface of the hippocampus and collect blood from deeper hippocampal structures including the CA2 region and the subiculum [41].

Superficially, these venous channels contribute to two longitudinal venous arcades that run along the **fimbriodentate sulcus** and the **superficial hippocampal sulcus**. These arcades converge anteriorly and posteriorly, forming connections with larger venous structures such as the **inferior ventricular vein** and the **medial atrial vein**. Ultimately, these vessels drain into the **basal vein**, which forms part of the deep cerebral venous system responsible for draining the medial temporal and diencephalic regions [41].

Functional and Clinical Implications

The unique vascular organization of the hippocampus contributes to its well-known susceptibility to metabolic and ischemic injury. The narrow caliber of hippocampal vessels and the presence of watershed zones, particularly within the CA1 region, predispose hippocampal neurons to hypoxic damage during systemic circulatory disturbances. Selective neuronal loss within these regions has been documented in several pathological conditions including transient global amnesia, vascular cognitive impairment, and neurodegenerative disorders such as Alzheimer's disease [42].

Furthermore, the delicate vascular network surrounding the hippocampus has important implications for

neurosurgical procedures involving the medial temporal lobe. Surgical interventions such as epilepsy surgery or aneurysm clipping near the ambient cistern require careful preservation of hippocampal vessels to prevent postoperative memory deficits. Advances in neuroimaging and microsurgical techniques have therefore focused on detailed mapping of hippocampal vasculature to minimize potential complications [40].

In summary, the hippocampus receives its blood supply from a complex and variable arterial network primarily derived from the posterior cerebral and anterior choroidal arteries. The corresponding venous drainage system ensures efficient removal of metabolic byproducts through connections with the deep cerebral venous circulation. This vascular arrangement supports the high metabolic activity required for hippocampal function but simultaneously contributes to the selective vulnerability of hippocampal neurons under pathological conditions.

Functional Organization of the Hippocampus and Mechanisms of Neuroplasticity

Building upon the structural and vascular organization of the hippocampus, its functional role within the brain is primarily related to memory processing, spatial navigation, and the integration of contextual information with emotional and behavioral responses. The hippocampus serves as a central node within the limbic network, receiving highly processed sensory inputs from cortical association areas and transforming them into stable memory representations. This integrative function relies on the coordinated activity of distinct hippocampal subregions and their connections with cortical and subcortical structures [43].

One of the most fundamental functions of the hippocampus is the consolidation of short-term memories into long-term storage. Incoming sensory information from multiple cortical areas converges in the entorhinal cortex before entering the hippocampus through the perforant pathway. Within the hippocampal circuitry, this information undergoes sequential processing through the dentate gyrus, CA3, and CA1 regions before being transmitted back to cortical areas through the subiculum. This organized information flow forms the basis of the **trisynaptic circuit**, a pathway that plays a key role in learning and memory formation [44].

Within this circuit, the dentate gyrus is responsible for **pattern separation**, allowing similar experiences to be encoded as distinct memory traces. This process reduces interference between overlapping inputs and enhances the brain's ability to distinguish between similar spatial or contextual environments. In contrast, the CA3 region is characterized by extensive recurrent excitatory connections that enable **pattern completion**, a mechanism that allows partial cues to trigger retrieval of entire stored memory representations. These complementary processes provide the neural basis for accurate encoding and retrieval of episodic memories [45].

The CA1 region serves as a critical output stage of hippocampal processing and integrates signals received from CA3 with direct inputs from the entorhinal cortex. Through this integration, CA1 neurons contribute to the temporal organization of memory and facilitate the transfer of processed information to the neocortex. Because of its strategic position within hippocampal circuitry and its high density of glutamatergic receptors, the CA1 region is particularly sensitive to metabolic stress and ischemic injury, further highlighting the importance of vascular and metabolic factors in hippocampal function [46].

Another essential aspect of hippocampal function involves its role in **spatial cognition**. Specialized neurons known as **place cells** become active when an individual occupies a specific location within an environment, forming an internal spatial map that guides navigation. These neurons were initially identified in rodent studies and have since been demonstrated in primates and humans. Through interactions with other spatially responsive cells in the entorhinal cortex, hippocampal circuits generate dynamic representations of spatial environments that are crucial for orientation and memory-guided behavior [47].

Beyond memory and spatial processing, the hippocampus also interacts with prefrontal and limbic structures to regulate emotional responses and decision-making. Reciprocal connections with the ventromedial prefrontal cortex allow hippocampal memory representations to influence behavioral choices, particularly in situations requiring evaluation of past experiences. Similarly, connections with

the amygdala enable emotional context to shape memory formation, strengthening memories associated with emotionally significant events [48].

A defining characteristic of hippocampal circuitry is its remarkable capacity for **neuroplasticity**. Synaptic plasticity mechanisms such as **long-term potentiation (LTP)** and **long-term depression (LTD)** modify the strength of synaptic connections in response to neural activity. These processes depend on glutamatergic neurotransmission and calcium-dependent signaling pathways, which regulate gene expression and structural remodeling within neurons. Activity-dependent molecular signaling ultimately leads to changes in dendritic spine density, synaptic efficacy, and network connectivity that support learning and memory [44].

The hippocampus is also one of the few regions of the adult mammalian brain capable of **ongoing neurogenesis**. New neurons are continuously generated within the subgranular zone of the dentate gyrus and integrate into existing neural circuits. These newly formed neurons contribute to cognitive flexibility, memory formation, and adaptation to environmental stimuli. Factors such as physical exercise, environmental enrichment, and metabolic state have been shown to influence the rate of hippocampal neurogenesis and synaptic plasticity [49].

Importantly, hippocampal plasticity is strongly influenced by metabolic and environmental conditions. Because hippocampal neurons have high energy requirements and dense synaptic connectivity, they are particularly sensitive to oxidative stress, inflammatory mediators, and metabolic disturbances. Experimental studies have suggested that dietary factors, including excessive sugar consumption and exposure to certain artificial sweeteners, may alter hippocampal neuronal activity and plasticity through mechanisms involving oxidative stress and neurotransmitter imbalance. These findings highlight the potential for nutritional factors to influence hippocampal function and cognitive performance [50].

In summary, the hippocampus represents a highly dynamic neural structure that integrates memory processing, spatial representation, and emotional regulation through complex synaptic networks. Its capacity for neuroplasticity enables adaptive responses to environmental stimuli and learning experiences, but also renders it vulnerable to metabolic and physiological disturbances. Understanding the functional organization of hippocampal circuits therefore provides an essential framework for exploring how dietary factors and metabolic influences may affect hippocampal structure and cognitive function.

Dietary Modulators and Metabolic Influences on Hippocampal Structure

Following the discussion of hippocampal neuroplasticity and functional circuitry, increasing attention has been directed toward the influence of metabolic and dietary factors on hippocampal structure and function. The hippocampus is highly metabolically active and depends on a stable supply of energy substrates to sustain synaptic transmission, neuronal signaling, and plasticity mechanisms. Consequently, alterations in metabolic balance—whether due to excessive caloric intake, obesity, or dietary modifications—can significantly influence hippocampal integrity and cognitive performance [51].

Obesity has emerged as a major global health concern and is strongly associated with metabolic disorders such as type 2 diabetes mellitus, cardiovascular disease, and nonalcoholic fatty liver disease. Beyond these systemic complications, growing evidence suggests that obesity can also affect brain structure and function. Epidemiological studies have reported associations between increased body mass index and structural changes in brain regions involved in memory and cognitive control, particularly within the hippocampus. These alterations are thought to arise from chronic metabolic stress, inflammation, and vascular dysfunction that may compromise neuronal health and synaptic plasticity [52].

Dietary sugar consumption represents another important factor influencing metabolic homeostasis and brain function. High intake of simple sugars, particularly in the form of sugar-sweetened beverages and processed foods, increases overall caloric density and contributes to weight gain and metabolic imbalance. Experimental studies have demonstrated that excessive sucrose consumption can impair hippocampal-dependent memory tasks in animal models. Such impairments are believed to result from

altered neuronal signaling, increased oxidative stress, and disruptions in neurotransmitter systems involved in learning and memory [53].

In response to concerns regarding excessive sugar consumption and obesity, artificial sweeteners have been widely introduced as alternatives to caloric sugars. These substances are designed to provide sweetness without significant caloric intake and are therefore frequently used in weight-management strategies. Several artificial sweeteners—including saccharin, sucralose, aspartame, acesulfame potassium, neotame, and advantame—have been approved as food additives by regulatory agencies such as the United States Food and Drug Administration. In addition, certain naturally derived non-nutritive sweeteners, including steviol glycosides extracted from *Stevia rebaudiana*, have been recognized as safe for human consumption in many countries [54,55].

The increasing use of artificial sweeteners in food and beverages has been accompanied by ongoing scientific debate regarding their long-term health effects. While some studies suggest that replacing sugar with low-calorie sweeteners may contribute to reduced energy intake and improved weight management, other research has reported potential associations between artificial sweetener consumption and metabolic disturbances. Observational studies and meta-analyses have described possible links between artificial sweetener intake and increased risk of metabolic disorders, hypertension, and cardiovascular disease, although causality remains uncertain and may be influenced by confounding lifestyle factors [56,57].

Beyond systemic metabolic effects, artificial sweeteners may also influence neural function through several biological mechanisms. Experimental research in animal models has demonstrated that certain artificial sweeteners, particularly aspartame, can induce oxidative stress and alter neurotransmitter balance within the brain. These biochemical changes may affect hippocampal neurons, potentially leading to modifications in synaptic plasticity and cognitive performance. Some studies have reported histological alterations in hippocampal tissue following chronic exposure to artificial sweeteners, suggesting that these compounds may influence neuronal morphology and activity within hippocampal circuits [50,58].

Conversely, naturally derived sweeteners such as stevia have attracted interest due to their potential antioxidant and neuroprotective properties. Extracts derived from *Stevia rebaudiana* contain polyphenolic compounds that may help mitigate oxidative stress and reduce cellular damage in neural tissues. Experimental studies in animal models have suggested that stevia-derived compounds may exert protective effects against metabolic and oxidative insults affecting brain structures, including the hippocampus [59].

These observations highlight the complexity of interactions between diet, metabolism, and neural function. Because the hippocampus is deeply involved in memory formation and cognitive processing, alterations in its cellular environment may have significant implications for learning, behavior, and neurological health. Dietary components—including both caloric sugars and artificial sweeteners—may therefore influence hippocampal structure and function through mechanisms involving oxidative stress, inflammation, neurotransmitter modulation, and metabolic signaling pathways.

In summary, dietary patterns and metabolic status represent important environmental factors capable of influencing hippocampal integrity and neuroplasticity. The growing prevalence of obesity and the widespread consumption of artificial sweeteners underscore the need to understand how these dietary factors may affect hippocampal circuits and cognitive function. Investigating these interactions is essential for clarifying the potential neurobiological consequences of dietary choices and for identifying mechanisms through which metabolic factors may contribute to hippocampal vulnerability.

Conclusion

The hippocampus represents one of the most structurally specialized and functionally dynamic regions of the brain. As a core component of the limbic system, it integrates multimodal sensory information and plays a central role in memory consolidation, spatial navigation, and the contextual regulation of behavior. Its unique anatomical organization—including the dentate gyrus, cornu ammonis subfields, and subicular complex—forms a highly organized network of neuronal circuits that enables precise

processing and storage of cognitive information. The laminar cytoarchitecture and tightly regulated synaptic pathways within this structure provide the foundation for complex processes such as pattern separation, pattern completion, and episodic memory formation.

In addition to its structural complexity, the hippocampus demonstrates remarkable neuroplasticity. Mechanisms such as long-term potentiation, synaptic remodeling, and adult neurogenesis allow hippocampal circuits to adapt dynamically to environmental stimuli and learning experiences. These adaptive capabilities are essential for maintaining cognitive flexibility and efficient memory processing throughout life. However, the same features that support hippocampal plasticity also render it particularly vulnerable to metabolic disturbances, oxidative stress, and vascular compromise.

Recent research has increasingly highlighted the influence of metabolic and dietary factors on hippocampal integrity. Conditions associated with altered energy balance, including obesity and excessive dietary sugar intake, may affect hippocampal neuronal activity and structural stability. Similarly, the growing use of artificial sweeteners as substitutes for caloric sugars has raised important questions regarding their potential effects on neural function. Experimental evidence suggests that certain sweeteners may influence hippocampal circuits through mechanisms involving oxidative stress, neurotransmitter imbalance, and altered neuronal signaling, although findings remain complex and sometimes contradictory.

Understanding the anatomical and physiological characteristics of the hippocampus is therefore essential for interpreting how environmental and dietary factors interact with neural circuits responsible for learning and memory. By integrating insights from neuroanatomy, histology, and functional neuroscience, the present review highlights the structural foundations that support hippocampal neuroplasticity while also emphasizing the susceptibility of this region to metabolic influences. Continued investigation of these relationships will contribute to a deeper understanding of how dietary exposures may affect hippocampal structure, neuronal activity, and cognitive performance.

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