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# The Hippocampus
## Plasticity and Functions

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# Meet the editor

Prof. RNDr. Ales Stuchlik, PhD, DSc (*1974), works as a head of the Department of Neurophysiology of Memory at the Institute of Physiology of the Czech Academy of Sciences, Prague, Czech Republic. He conducted his PhD thesis under the supervision of Dr. Jan Bures, DSc (1926–2012). In 2007, he was awarded the 40th Anniversary European Brain and Behavior Society Award for outstanding achievements during his early scientific career. His scientific interests involve basic and oriented research of spatial learning and memory, neuropharmacology, and animal models of neuropsychiatric disorders. He contributed to Czech translation of a book From Neuron to Brain. He has been involved in supervising multiple students ranging from high school and college to graduate students.

# Contents

# Preface

Normal brain functions in relation to behavior are precisely regulated within neuronal circuits by dynamics of neuronal ensembles, ensuring proper control of sensory gating, motor output, motivation and cognitive functions, including learning, memory and executive functions. Even most subtle alterations of this control can underlie pathophysiological processes leading to neuropsychiatric disorders. The hippocampus is an archicortical brain region strongly involved in multiple behavioral functions in both health and disease, including spatial and episodic learning and memory, cognitive coordination, behavioral inhibition, generation of behavioral strategies, coding of moving goals, recognition of places and others. Functions of neuronal populations in the hippocampus are regulated at all levels from gene expression and neuronal differentiation to firing of ensembles, neural oscillations and observable behavior. Importantly, neurons in the dentate gyrus of the hippocampus are born throughout the life, forming synaptic connections and incorporating into existing hippocampal networks. Additionally, the hippocampus is a site where many processes of synaptic plasticity, such as long-term potentiation, occur. Finally, cells with spatially tuned firing (place cells) were discovered in 1973 in this part of the brain. These cells can be neural substrates of cognitive maps, providing spatial and perhaps other memory functions of the hippocampus. Dysfunctions of the hippocampus are hallmarks of several devastating neurological and psychiatric disorders.

This book aims at collecting evidence of the immensely complex processes in the hippocampus in relation to computational functions of healthy and disordered brain. It discusses some of the most crucial topics related to the hippocampal function and its role in behavior. The book is divided into two sections: the first one discusses plasticity functions in the hippocampus in relation to external environment and electrophysiological phenomenon of long-term potentiation. The second section aims at physiological and pathophysiological aspects of the hippocampus functions. The first chapter by Zarif et al. discusses how external environment shapes hippocampal plasticity processes, which has profound consequences on the functions of this region. It focuses on enriched environment conditions and discusses their effect upon growth factors, neurotransmitters, hormones and other molecules. It even emphasizes the important role of immune cells within the brain. The review chapter by Zhang and Zhang provides insight into the factors regulating adult neurogenesis in the subgranular zone of the dentate gyrus. It stresses the important regulatory roles of various principal neurotransmitter systems and modulation by hormonal substances, including ghrelin, thyroid hormone and sex hormones. It also discusses the roles of trophic factors, signaling pathways, and physiological and pathological factors such as exercise, enriched environment, aging, stress and various insults. The review by Lisachev and Shtark shows changes

in gene expression induced by long-term potentiation with an emphasis on involvement of tumor protein p53 and its target genes, especially S100B.

The next chapter by Harland et al. from the group of Jean-Marc Fellous discusses the roles of longitudinal axis of the hippocampus in the multiscale representations of the complex and large environments and shows how genetic, neurochemical, and function gradients along this axis can contribute to mnemonic hierarchies in the spatial mapping and declarative memory system. The review by Grech et al. discusses two basic classes of behavioral strategies in the hippocampus-dependent spatial memory, i.e., allocentric and egocentric strategies, based on dissociable frames of reference. It stresses the importance of dissociating these search strategies in spatial tasks and also provides a view on neurobiological and clinical differences between these spatial reference frames**.** The final chapter by Barr et al. deals with the role of the ventral hippocampus as a crucial link for negative affect and vulnerability to relapse to psychostimulant drugs, such as cocaine, methamphetamine, amphetamine, etc. This work opens ways for identifying novel options of therapy that could alleviate negative affect and vulnerability to relapse in drug addiction.

In this book, we attempted to provide up-to-date evidence on various aspects of hippocampal function related to genes, neurons, circuits, and behaviors in health and disease. We hope this book will be useful for readers interested in the hippocampal formation and a wide plethora of its roles. I would like to express thanks to Tereza Nekovarova, Hana Brozka, Zdena Kristofikova, Stepan Kubik, Tomas Petrasek, Jan Svoboda, David Levcik, and other colleagues for their valuable help with reviewing the chapters and to all my colleagues for their great support. The works on this book were supported mainly by GACR grant 17-04047S and AZV grant 17-30833A. Additional support came from H2020 INFRADEV-01-2017 project ID-EPTRI (European Paediatric Translational Research Infrastructure). Institutional support was provided by RVO: 67985823.

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Section 1

# Plasticity of The Hippocampus Functions

Chapter 1

# How Does an Enriched Environment Impact Hippocampus Brain Plasticity?

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Additional information is available at the end of the chapter

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**Abstract**

Brain plasticity is profoundly impacted by one's living environment. The hippocampus, involved in learning and memory, is highly susceptible to plasticity. Raising rodents in an "enriched environment" (EE) increases learning and memorization aptitudes and decreases the anxiety of the animals. EE consists of a combination of running wheels for voluntary physical exercise, complex inanimate toys, nests, mazes, etc. all of which favor sensory stimulations and social enrichment. EE housing concomitantly increases proliferation and survival of neurons and glia in the dentate gyrus of the hippocampus, induces changes in neuronal morphology, modifies synaptic plasticity, and favors angiogenesis. The mechanisms underlying the effects of EE on plasticity, which have recently been investigated are reviewed here, including the role of glia, the involvement of molecular factors including neurotransmitters (glutamate), neurotrophic factors (BDNF), adipokines (leptin and adiponectin), chemokines, cytokines, and hormones (corticosteroid and thyroid hormones), and at a higher level, the various systems involved (neural networks and hormonal systems). We emphasize recent findings that demonstrate the major role of the immune system in modulating EE-induced changes to hippocampal plasticity. This process involves a variety of immune cells (including macrophages, microglia, natural killer, B-cells, and T-cells), although the mechanisms are yet to be fully elucidated.

**Keywords:** hippocampus plasticity, enriched environment, neurogenesis, synaptogenesis, synaptic plasticity, neurotrophic factors, cytokines, chemokines, hormones

## 1. Introduction

One's living environment has a profound impact on both health and brain plasticity. Indeed, an increasing number of studies show that exposure to prolonged stress can increase the risk

of not only cardiovascular diseases and cancers but also neuropsychiatric and neurodegenerative diseases [1]. In contrast, a stimulating environment can contribute to improve health and behavioral performances by optimizing brain plasticity. Neuroplasticity, also known as brain plasticity or neural plasticity, induces lasting change to the brain throughout an individual's life course. Neuroplasticity can be observed at multiple scales, from microscopic changes in individual neurons to larger scale changes, such as cortical remapping in response to injury. Although neuroplasticity is more efficient during development and in youth, it persists in adulthood [2]. Neuroplastic change through activity-dependent plasticity has significant implications for healthy development, behavior, learning, memory, and recovery from brain damage and can be elicited by thoughts, emotions, and environmental stimuli.

The hippocampus is involved in emotion and mood regulation, as well as learning and memory. This cerebral structure is very susceptible to plasticity. Hippocampal plasticity is a general term that describes many different phenomena at different levels. For instance, at the macroscopic level, a decrease in hippocampal volume has been observed in depressed patients [3]. Conversely, a stimulating environment, such as high-level spatial orientation training, leads to an increase in hippocampal volume [4]. At the cellular level, the number of new neurons that appears in the dentate gyrus of the hippocampus and their survival is linked to their insertion in the local hippocampal network. This response can also vary depending on the experience and enrichment of the living environment. Similarly, synaptic connections can be remodeled by experience, which can be measured both at the functional level (neurotransmitter release and electrophysiological recordings of spontaneous activity) and at the morphological level (number and shape of contacts between neurons). Finally, these changes can be accompanied by variations in the shape, number, and function of the other cells that surround the neurons, including glia, endothelial cells, and resident immune cells such as microglia and perivascular circulating macrophages.

Chronic stress and related pathologies, such as depression, induce "deleterious" effects on hippocampus plasticity and have been widely documented. However, the "positive" effects on brain plasticity, in response to an enriched and stimulating environment, have only been investigated more recently. An enriched environment (EE) can be modeled in rodents by housing mice in larger cages equipped with toys and nesting material to promote sensory stimulation and running wheels to promote voluntary physical activity. In addition, mice can be housed in large groups (10–12) to favor social interactions and the establishment of a hierarchy [5]. Depending on the studies, characteristics of EE housing can vary [6]. These variations include different strains, genotypes, or ages of mice and rats. The duration of EE, the type of enrichment objects, and the frequency of object changes also differ from one study to the other. Finally, standard "nonenriched" conditions (standard environment, SE which is used as control in comparison on the EE) vary, as some studies use isolated mice while others house up to five mice in a cage. A more standardized EE protocol would improve consistency between studies, and yet, in most cases, EE is shown to induce large benefits, including prevention or reduced incidence of a large number of diseases in both nonpathological and pathological conditions; depending on the duration, exposure to an EE can improve performance in a variety of hippocampus-dependent behaviors in rodent models, even in adulthood [7]. Enrichment has been shown to enhance memory function in various learning tasks [8]. Compared to mice housed in standard conditions, EE-housed animals perform better in

learning and memorization tests, such as the Morris Water Maze and the Barnes Maze which involve both working [9] and spatial memory [10, 11]. EE reduces the cognitive decline associated with aging [5] and decreases anxiety in mice [12]. EE also has remarkable beneficial effects on the behavior of animals with neurological disorders, as demonstrated in several models of neurodegenerative diseases or different types of brain lesions [13]. The aim of the present chapter is to review the increasing volume of data that report EE-induced changes in plasticity and to describe the proposed mechanisms of action underlying these changes.

## 2. Effect of EE on hippocampal plasticity

At the neuroanatomical level, EE increases the hippocampus volume [14]. This can be explained by an increase in the density of dendritic arborization [15, 16], the length and the volume of myelinated fibers [17], and the number of dendritic spines in hippocampus [18].

At the cellular level, EE has been shown to increase neurogenesis in the hippocampus dentate gyrus (DG) as measured by injections of BrdU, which labels dividing cells and can be detected using immunocytochemistry techniques days or weeks later to measure proliferation and survival [7, 19]. The extent of this increase in neurogenesis is dependent on the age of the mouse and the duration of EE housing. Indeed, the effects of EE are more pronounced for housing durations of 4–6 weeks, compared to 8 weeks, as well as in younger animals [20].

Synaptogenesis has also been shown to increase in response to EE housing [21, 22]. The establishment of new synapses can be evaluated from a morphological point of view (for instance by labeling the post-synaptic neurons and counting the spines using confocal microscopy) or from a functional point of view (using electrophysiology). It is now well established that functional activity–dependent changes parallel structural modifications [23–25], although a distinction between anatomical and functional synaptic structure has been observed [26, 27]. In the hippocampus, the majority of synapses that connect pyramidal neurons are located on dendritic spines, and synapse size is related to synapse strength [28–31]. Indeed, mice raised in EE present changes in synapse density, button morphology [32, 33], and hippocampal neuronal activity compared to mice raised in a SE; however, these changes can vary depending on the time spent in the housing environment and the age of the mouse (juvenile versus adult) [20]. Four weeks in EE increased the number of excitatory inputs received by pyramidal neurons in CA1 as measured by whole-cell patch clamp in acute hippocampus slices, in accordance with the observed increase in spinogenesis. However, for longer EE housing periods (6–8 weeks), despite maintenance of the increased number of spines, the number of excitatory inputs received by pyramidal neurons in CA1 returns to a lower level suggesting that synapses become silent by a homeostatic process of synaptic scaling [34]. Alternatively, the development of inhibitory synapses subsequent to habituation and the reduced attraction of the animals to their environment cannot be ruled out [35]. Overall, this suggests a distinction between anatomical spines and functional synaptic structures. Extra-spines could be maintained following enrichment periods even when they do not establish functional synapses. These silent structures could constitute a pool of synapses ready to be activated upon stimulation and might play a major role in learning, allowing EE mice to learn faster than their matched controls raised in standard conditions [36, 37].

EE also induces changes in long-term potentiation (LTP) as observed in field potentials recorded in the CA1 region after high-frequency stimulation of the Shaffer collaterals *in vitro* in acute hippocampal slices. However, these changes are complex and again depend on the protocol used. For example, EE has been shown to enhance [38–40], impair, or even have no effect on LTP at the CA3–CA1 synapse [41–44]. Because LTP induction and expression is age dependent [43, 45, 46], EE might have different consequences on plasticity of these synapses depending on the duration of enrichment and the postnatal developmental stage of the mice. This was demonstrated in an accurate kinetic analysis, where increases in LTP were found in adult mice after 4 weeks in EE, but decreases in LTP were observed after 4 weeks EE in juvenile mice, likely because CA3-CA1 excitatory synapses were already potentiated in these conditions, which induced a ceiling effect [20].

In accordance with EE regulation of morphology and function of excitatory synapses, EE can also regulate glutamatergic AMPA [47] and NMDA receptor subunit expression [48]. Similarly, in glutamatergic neurons, the expression of synaptic proteins such as PSD95, a post-synaptic scaffold protein, is also increased by EE housing [49, 50].

Immunomodulatory factors have recently been shown to play a key role in EE hippocampal plasticity effects [51–53]. Among them, two important players are CD200, which is a membrane glycoprotein expressed by various cell types (including B cells, a subset of T cells, thymocytes, endothelial cells, and neurons) and CX3CL1, also known as fractalkine, a chemokine which plays an important role in the neuronal control of microglia recruitment and activation [54, 55]. CX3CL1 was recently found to impact synaptic development and integrity. Indeed, CX3CR1 deficiency increases hippocampal plasticity and spatial memory, blunting the potentiating effect of EE [56] and thus showing that CX3CL1/CX3CR1 signaling is necessary for EE-dependent hippocampal plasticity processes.

In pathological conditions such as influenza infection, neuroinflammation alters hippocampal plasticity [57, 58]. This central inflammation is characterized by an increase in the hippocampal expression of proinflammatory cytokines (including IL-1$\beta$, IL-6, and TNF-$\alpha$) and a decrease in the expression of neurotrophic (BDNF and NGF) and neuromodulatory factors. EE attenuates hippocampal neuroinflammation and therefore prevents the plasticity alteration [59–61].

Finally, EE also stimulates gliogenesis [62] and favors angiogenesis [63–65], consequently improving nutrient availability for neurons and the elimination of toxic waste from brain.

## 3. Cellular and molecular mechanisms

### 3.1. Neurotrophic factors

At the molecular level, EE increases the expression of neurotrophic factors in the hippocampus. These factors include BDNF [66], IGF-1 [67], and NGF [68] and may affect hippocampal neurogenesis and synaptic plasticity [69].

It is not yet clear which cells produce these factors. They could be produced by neurons following increased neuronal activity upon stimulation, by glial or by endothelial cells.

However, the neurotrophic factors that are increased by EE conditions can act in various cell types, including neurons (promoting both neurogenesis in the DG and synaptogenesis), astrocytes (regulating metabolism, recycling and elimination of metabolites), microglia (regulating synaptic pruning), oligodendrocytes (promoting myelination), and endothelial cells (promoting angiogenesis). Mice raised in EE thus benefit from this virtuous circle; increased neuronal activity will increase neurotrophic factor release, which in turn will increase neurogenesis and synaptogenesis, thus promoting more neuronal activity.

### 3.2. Adipokines

EE also induces changes in levels of adipokines, cytokines that are produced by the white adipose tissue [70]. Examples include adiponectin (the concentration of which is increased by EE) either in plasma or CSF and leptin (decreased in EE), likely due to a decrease in fat mass in EE mice as a consequence of exercise [71, 72]. The variations in blood adipokines have consequences in the brain, including the hippocampus, as receptors of both adipokines are expressed within the central nervous system. For instance, it has been observed that in EE, microglia and perivascular circulating macrophages adopt an M2 anti-inflammatory profile *via* an adiponectin-dependent mechanism [73], likely contributing to the antidepressant effects of EE in a murine model of depression.

### 3.3. Hormones

Several hormonal systems are also regulated in EE. Indeed, EE has been shown to regulate levels of corticosterone and noradrenaline [71]. Muscular exercise could also increase the release in the blood of endogenous molecules such as endocannabinoids, BDNF, which may be released in response to cortisol [74] and beta-endorphins, which are released by muscle-afferent nerve endings upon exercise [75].

### 3.4. Immune system

The immune system is primarily involved in the surveillance of body tissues and in providing protection from infectious agents and various forms of injury. The idea that the immune system could be involved in normal neurobehavioral processes was suggested more than a decade ago, although initially, it did not receive much attention. Subsequent findings by Drs. M. Schwartz, J. Kipnis, and their colleagues showed that circulating T cells play a general supportive role in brain functioning, including cognitive abilities and hippocampus neurogenesis [76–81]. Additional work has shown that EE-induced neurogenesis is depressed in immunodeficient (SCID) mice, suggesting a putative role of T cells in EE-related effects on hippocampus plasticity [82]. The mechanisms by which T cells can influence hippocampal plasticity are still unknown. T cells do not enter the brain parenchyma in nonpathological conditions, but a small number of T cells are present in the brain blood vessels, in the choroid plexus, and in the meninges. T cells are thought to act at distance by releasing factors such as cytokines or chemokines in the blood or CSF or by interacting directly with endothelial or epithelial cells of the choroid plexus. Alternatively, T cells could act from the periphery by modulating the hormonal systems that regulate brain plasticity.

These innovative studies paved the way for future investigations of other immune cells, including but not limited to natural killer cells [83], B cells [84], macrophages [73] and monocytes [85], and their putative roles in modulating the effects of EE on hippocampal plasticity.

## 4. Conclusion

The effects of EE on the hippocampus are numerous and complex (**Figure 1**). They simultaneously involve multiple cell types and their interactions, both locally at the level of the

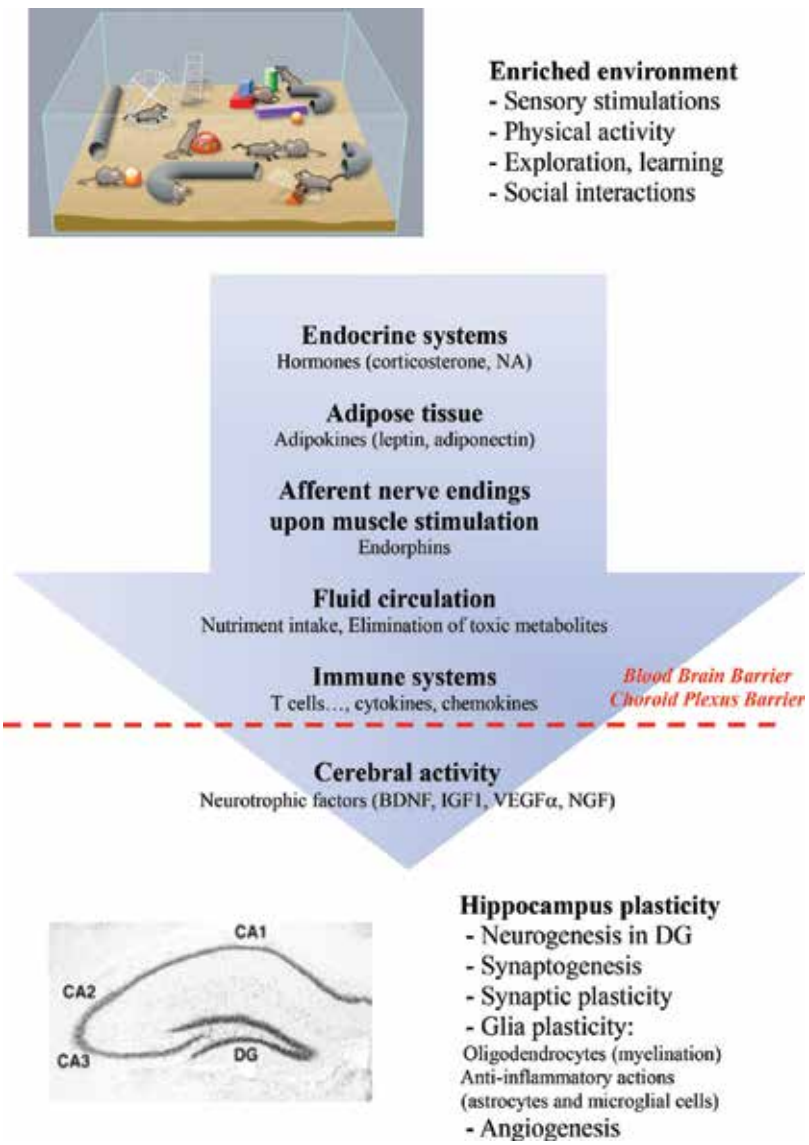


**Figure 1.** Enriched environment can modulate hippocampus plasticity through multiple pathways.

hippocampus and throughout the whole body, including muscles, bones, adipose tissue, endocrine, immune, and circulatory systems. Dysfunction in any of these components could subsequently reduce or impair the beneficial effects of EE. However, the pleiotropic effects of EE contribute to the prevention of vascular and neurodegenerative brain diseases. How does one define an EE for humans? It probably includes activities associated with spatial learning and motor coordination, such as sport, artistic and creative activities (for example, music or dance), learning new skills, training memory, playing games, and the presence of a developed social life, whereas life as a recluse, a prisoner, in temporary or permanent isolation could undermine the cognitive and learning abilities of the hippocampus. Elderly citizens are at particular risk of such decline. Conversely, a stimulating environment, such as that associated with a balanced lifestyle, should favor hippocampus activity, leading to enhanced learning aptitudes and improved adaptability to new situations.

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Chapter 2

# Factors Regulating Neurogenesis in the Adult Dentate Gyrus

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Additional information is available at the end of the chapter

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**Abstract**

The dentate gyrus (DG), an important part of the hippocampus, plays a critical role in consolidation of information from short-term to long-term memory, and also in spatial navigation. Neural stem/progenitor cells (NSPCs) exist throughout life in the subgranular zone (SGZ) of the DG, where they develop into granular cells and establish synaptic connections with nearby cells. Granular cells of the DG sprout axons targeting neurons in the cornu ammonis 3 (CA3) area of the hippocampus, forming a neural trisynaptic circuit, an important part of the neural network in the hippocampus. Thus, the DG and the neurogenic cells it contains are of importance in controlling formation of memories, learned behaviors, and also in the maintenance and restoration of functions of the hippocampus. According to reports, both *in vivo* and *in vitro* neurogenesis in the DG are regulated by a variety of endogenous and exogenous factors at different stages. Therefore, a better understanding of the factors in NSPC niches and the intracellular molecules regulating/directing adult DG neurogenesis is needed to fully realize the potential of NSPCs in the treatment of hippocampal-related disorders. This chapter systematically summarizes the factors reported in regulating adult DG neurogenesis in mammals. Specifically, neurotransmitters, hormones, trophic factors, and others will be discussed.

**Keywords:** dentate gyrus, hippocampus, neurogenesis, neural stem and progenitor cell, regulation

## 1. Introduction

The dentate gyrus (DG) is an important structure within the hippocampus and plays critical roles in consolidation of information from short-term memory to long-term memory, as well as spatial navigation. Neural stem/progenitor cells (NSPCs), which undergo neurogenesis,

are present throughout life in the subgranular zone (SGZ) of the DG. Approximately 700 newborn granular neurons are formed every day in the adult human DG [1]. NSPCs in the SGZ, which differentiate into granular cells, are anchored within the granular layer of the DG, and following differentiation, establish synaptic connections with neighboring neurons, and maintain the function of the hippocampus. Granular cells in the DG sprout axons targeting neurons in the cornu ammonis 3 (CA3) area of the hippocampus, forming a neural trisynaptic circuit, an important part of the neural network in the hippocampus. Thus, the DG and the neurogenic cells it contains are of importance in controlling the formation of memories and learned behaviors. A better understanding of the factors regulating neurogenesis in the DG is therefore needed to fully understand the mechanisms involved in the differentiation of NSPCs in the hippocampus. Indeed, adult DG neurogenesis is regulated by a variety of endogenous and exogenous factors at different stages of differentiation. This chapter reviews the effect of regulation factors, including chemical cytokines, signals, and also of physiological and pathological factors on the neurogenic potential of NSPCs in the adult DG.

## 2. Neurotransmitters

Neurotransmitters are specific chemicals that act as a "messenger" in synaptic transmission. As neurobiology has developed, a large number of neurotransmitters have been found in the nervous system. It was shown that the presence of many neurotransmitters influences neurogenic niche.

### 2.1. Serotonin (5-hydroxytryptamine, 5-HT)

The 5-HT is a monoamine neurotransmitter of the central nervous system (CNS) and is synthesized primarily by the lower midbrain and the raphe nuclei of the medulla oblongata (reviewed in [2]) from the amino acid tryptophan. Fibers of serotonergic neurons project throughout the brain, including afferent to the hippocampus. A role for 5-HT in the enhancement of adult hippocampal neurogenesis was first identified through the use of selective serotonin reuptake inhibitors (SSRIs), which were used as antidepressant drugs [3]. Chronic administration of SSRIs was shown to markedly increase adult neurogenesis [4, 5], but interestingly, was reduced or blocked in aged models [6]; this suggests that actions of SSRIs on neurogenesis may depend on the age of the treated individual and that the therapeutic effects of antidepressants in elderly patients are not mediated by neurogenesis modulation. Furthermore, neurogenesis in the adult hippocampus in aged mice was enhanced when central 5-HT levels were reduced specifically in adulthood (reviewed in [7]). These findings collectively suggested that aging was a key factor affecting adult hippocampal neurogenesis and that this is important in effect of serotonin. With regard to 5-HT receptors, several studies showed that 5-HT1A and 5-HT4 receptor agonists increased adult cell proliferation in the DG [8–12], while 5-HT1A receptor antagonists decreased proliferation and survival of newborn cells in the DG [13, 14]. Interestingly, both receptors have been shown to have putative antidepressant activity [15, 16], possibly partially depending on the receptor mediating hippocampal neurogenesis [12]. These reports also found that brain-derived neurotrophic factor

(BDNF) isoforms may act as a bridge between serotonin and its pro-neurogenic effects in the DG, because BDNF has the ability to enhance neurogenesis and its level can be up-regulated by serotonin ([17]; as reviewed below).

### 2.2. Dopamine (DA)

CNS-derived DA is mainly secreted by dopaminergic neurons in the substantia nigra pars compacta (SNc) and the ventral tegmental area (VTA). Dopaminergic fibers from the SNc and VTA have been shown to partially target the hippocampal subventricular zone (SVZ) [18, 19]. In addition, ultrastructural evidence showed that highly proliferative precursors in the adult brain express dopamine receptors and receive dopaminergic afferents [20]. Together, these results implicate that DA participated in regulating adult neurogenesis. Moreover, evidence indicated that destruction of DA neurons in SNc and VTA, or deletion of dopamine through neurotoxic 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) or 6-hydroxydopamine (6-OHDA) injection, all reduced proliferation of NSPCs in both the SVZ and SGZ [18, 20]. It has also been demonstrated that pramipexole, a D2-like selective DA agonist, enhanced the proliferation of hippocampal NSPCs and also enhanced the proportion of neuronal differentiation in the DG of adult mice [21]. In contrast, Egeland et al. found that pharmacological or genetic blockade of the D3 receptor increased neurogenesis in the hippocampus of adult mice [22]. Taken together, these studies showed that the DA system plays an important role in adult hippocampus neurogenesis.

### 2.3. γ-Aminobutyric acid (GABA)

GABA, the major inhibitory neurotransmitter in the adult brain, exerts its roles via two main receptor types, GABA-A and GABA-B [23]. GABAergic signaling modulates the spatially and temporally regulated network activities underling hippocampus-dependent memory [24]. The previous studies have shown that the GABA-A receptor is expressed in NSPCs *in vitro* [25, 26]. In addition to findings that GABA influences postnatal neurogenesis in the SVZ and striatum [27, 28], a role in hippocampal neurogenesis has also been suggested. Deletion of distinct GABA-A receptor subunits, γ2 and α4, reduced adult hippocampal neurogenesis [29, 30]. In contrast, pharmacological inhibition of the GABA-B receptor stimulated NSPC proliferation, and genetic deletion of the GABA-B receptor increased NSPC proliferation and also differentiation of neuroblasts *in vivo* [23]. These findings propose that the GABAergic system is an important regulator of adult neurogenesis in the DG, and that different GABA receptor subtypes provide different or opposing effects on neurogenesis and neuronal maturation in the adult hippocampus.

### 2.4. Acetylcholine (ACh)

ACh is an important transmitter in the basal forebrain cholinergic system, located primarily in the medial septum, nucleus basalis of Meynert, vertical limbs of the diagonal band of Broca, and substantia innominate, which project their fibers to the hippocampus, thalamus, olfactory bulb, and cortical regions (reviewed in [31]). In particular, the septo-hippocampal pathway from the medial septal nucleus and diagonal band to the hippocampus plays a significant role in both learning and in cognitive deficits that are associated with aging and Alzheimer's disease

(AD) [32]. Neurons in the DG and olfactory bulb abundantly express nicotinic acetylcholine receptors (nAChRs) and metabotropic muscarinic acetylcholine receptors [33, 34]. It was shown that cholinergic fibers innervated and synapsed on immature neurons in the DG [35]. Thus, it is possible that cholinergic afferent fibers in the DG contribute to the control of neurogenesis as well as neuronal activity. Previous studies reported that deletion of forebrain cholinergic input using the selective neurotoxic, 192 IgG-saporin, reduced DG neurogenesis, whereas administration of physostigmine, the cholinergic agonist, increased DG neurogenesis in adult and aged rodents [36, 37]. Furthermore, deletion of the β-2 subunit of nAChRs reduced cell proliferation by ~43% in the DG, and was accompanied by a significant decrease in both DG area and granule cell layer length [38]. Similarly, stimulation of α-7nAChRs promoted hippocampal neurogenesis, including neuronal differentiation, maturation, integration, and survival [39, 40]. ACh released in synapses is usually removed through hydrolysis by acetylcholinesterase (AChE) and both pharmacological inhibition of AChE activities and transgenic deletion of AChE increased proliferating cells and the survival of newborn neurons in the DG, while increased AChE levels induced apoptosis [41]. Interestingly, pharmacological activation of muscarinic receptors reversed the deficits in hippocampal neurogenesis following cholinergic denervation [42]. These data suggested that in the cholinergic system, the levels of ACh and its interactions with AChRs are important in controlling adult neurogenesis in the hippocampus.

### 2.5. Glutamate

Another neurotransmitter associated with hippocampal neurogenesis is glutamate, an important excitatory neurotransmitter. Previous studies indicated that glutamate can regulate adult neurogenesis in the DG [43, 44]. Among the eight metabotropic glutamate receptors (mGluRs), mGluR5 is highly expressed in NSPCs [45, 46]. The mGluR5-induced neurogenesis may contribute to the markedly ameliorated cognitive impairment through stimulating mGluR5 receptors, but not mGluR2/3 [47]. Although the mechanism of these pro-cognitive effects of mGluR5 was not elucidated, mGluR5 activation most likely partially contributed to the increased neurogenesis found in these studies.

## 3. Hormones

### 3.1. Ghrelin

Ghrelin, a unique 28-amino acid peptide hormone synthesized primarily in the stomach, has various physiological actions such as stimulating growth hormone release and regulating the function of the gastrointestinal tract [48–51]. Recent studies have shown that the ghrelin receptor mRNA is widely expressed in the brain, including the CA2 and CA3 areas of the hippocampus, as well as in the DG [52–54]. Furthermore, researchers found that exogenous ghrelin passes through the blood-brain barrier and binds to neurons located in areas of the hippocampus [55] where NSPCs expressed ghrelin receptors [56]. Interestingly, hippocampal neurogenesis was shown to be enhanced in adult rodents treated with systemic delivery of ghrelin [57–59]. Furthermore, ghrelin knockout decreased the number of NSPCs in the DG of mice [60]. Of more

significance was the discovery that ghrelin restored impaired hippocampal neurogenesis in an AD animal model, 5× FAD mice [61], indicating that it is a potential candidate for treatment of AD. However, unlike systemic administration that exerted positive neurogenic effects, local intra-hippocampus ghrelin infusion showed no effects on adult neurogenesis, and even impaired spatial memory formation [58]. Although causes for this phenomenon remain unclear, it is proposed that systemic administration of ghrelin is more like the physiological condition; therefore, the effect of ghrelin may be mediated by different mechanisms compared to local administration.

### 3.2. Thyroid hormone

Thyroid hormone is synthesized by the follicular cells of thyroid gland and is released into blood as the precursor thyroxine (3,30,5,50-tetraiodothyronine; T4), and also as the active form of thyroid hormone (3,30,5-triiodothyronine; T3) [62, 63]. The process of transporting thyroid hormones into the brain is regulated by the transporters, monocarboxylate transporter-8 and transthyretin, among others [64–67]. Reports indicated that thyroid hormone perturbations resulted in decreased hippocampal progenitor proliferation and survival, while the adult hippocampal progenitors exhibited enhancement of proliferation, survival in response to thyroid hormone in adult rat [68–70]. The thyroid hormone receptors (TRs), TR$\alpha$ and TR$\beta$ comprise distinct isoforms, TR$\alpha$1 and TR$\alpha$2, TR$\beta$1, and TR$\beta$2 [71]. Research has indicated that TRs also influence adult hippocampal neurogenesis. TR$\alpha$1 receptors are involved in regulating survival and differentiation of post-mitotic progenitors in adult hippocampus [72], while loss of TR$\beta$ may contribute to the increased progenitor proliferation and differentiation in adult hippocampus [73]. These data suggested that the thyroid hormone system plays a role in the regulation of adult hippocampal neurogenesis.

### 3.3. Sex hormones

Several studies have shown that there are differences in hippocampal neurogenesis in adult rodents depending on sex. For example, adult female rodents had higher levels of cell proliferation than males in the DG [74, 75]. These sex differences in hippocampal neurogenesis may be dependent on the natural fluctuations of gonadal hormones.

#### *3.3.1. Androgens*

Androgens, the predominant gonadal hormones in males, include testosterone, and rostenedione, and 5a-dihydrotestosterone (DHT). They are primarily produced in the testes Leydig cells and carried elsewhere through the blood system. Androgen receptors (ARs) are expressed throughout the male and female rat brain, including the hippocampus [76–78]. Within the rat hippocampus, ARs are expressed primarily in the pyramidal cell layer of CA1 and stratum lucidum of CA3, but not in the adult DG [78–80]. Several studies have shown that androgens influence DG neurogenesis. Long-term exposure to androgens increased neurogenesis in the DG of adult male rodents [81], whereas removal of testicular hormones resulted in the reduction of newly generated neurons in the DG [80, 82, 83]. Androgenic regulation of neurogenesis in the DG may be associated with the activation of ARs in rodents. Administration of testosterone metabolite DHT with higher affinity for ARs than testosterone, resulted in increased neurogenesis, which was subsequently blocked by the AR antagonist, flutamide. Moreover,

testosterone treatment did not enhance neurogenesis in rats with a mutation in the AR gene [80]. Mahmoud et al. speculated that androgens binding with ARs in the CA3 region may induce retrograde signaling of survival factors from CA3 and promote neurogenesis in the adult DG [84].

*3.3.2. Estrogen*

Estrogen is secreted primarily by follicular cells of the ovary (but also from the testis, placenta, and adrenal gland), and promotes the development of primary and secondary sexual organs in women and maintains normal sexual and reproductive functions. Three forms of estrogens exist, estradiol, estrone, and estriol, with estradiol being the most abundant. Reports have confirmed that estrogen, especially estradiol, regulates adult neurogenesis in the hippocampus [81, 85]. Estradiol carries out its physiological effects by binding to the classical estrogen receptors (ER), ER$\alpha$ and ER$\beta$, and the G protein-coupled estrogen receptor (GPER) [86–88]. The fact that ER$\alpha$ and ER$\beta$ receptors are both expressed in the hippocampus [89–91] indicates that hippocampus is the important target of estrogens. Treatment with the ER$\alpha$- or ER$\beta$-selective agonists resulted in an increase of cell proliferation in the hippocampus of adult ovariectomized female rats, while it was shown that estrogen receptor antagonists reversed estradiol-induced increase in cell proliferation [92, 93]. Interestingly, treatment with a GPER agonist G1 and antagonist G15, respectively, decreased and increased cell proliferation in adult ovariectomized rats [94], indicating the estradiol independent role of GPER on hippocampal neurogenesis. Taken together, these studies suggested that the estrogen system participates in the process of neurogenesis in the adult hippocampus.

## 4. Trophic factors

### 4.1. BDNF

It has been reported that BDNF modulates neuronal development in the hippocampus and participates in the maturation of GABAergic inhibitory networks in the cortex [95–97]. In adult macaque brains, the highest levels of BDNF were shown to be in the hippocampus [98]. Further studies found that neurogenesis was attenuated by BDNF knockdown in the adult DG [99], but was increased in response to exogenous BDNF injection [100]. Dendritic growth in adult hippocampal neurons was also decreased by BDNF deletion and increased by BDNF overexpression [101]. Increases in proliferation were reported in heterozygous BDNF knockout mice [102, 103]. Specifically, it was shown that proliferation of SGZ NSPCs increased in mice with BDNF conditional knockout in hippocampal neurons [104]. These conflicting results have not yet been fully reconciled, although it was suggested that developmental and/or behavioral differences between the strains used in these studies may have contributed to the divergent findings [105].

### 4.2. Neurotrophic growth factor (NGF)

Early studies confirmed that NGF is crucial for neuronal survival and growth [106], especially for cholinergic neurons and neurotransmission in both CNS and peripheral nervous system [107, 108]. Recent reports indicated that continuous NGF infusion promotes proliferation and synaptogenesis in the hippocampus and enhanced survival of new neurons in the DG granule

cell layer of young adult rats [109, 110]. Neurogenic conditions in the hippocampus may be enhanced by the synergistic interactions of NGF and its receptor, TrkA, as well as by NGF-mediated cholinergic regulation. Finally, intracerebroventricular NGF infusion rescued hippocampal neurogenesis deficiencies in a transgenic mouse model of Huntington's disease [111], suggesting that NGF may be a valuable therapy in treatment of this disease.

### 4.3. Vascular endothelial growth factor (VEGF)

VEGF is an angiogenesis factor with neurotrophic and neuroprotective effects [112–115]. Additionally, it is increasingly clear that VEGF plays a crucial role in neurogenesis in the adult hippocampus. Jin et al. found that intracerebroventricular administration of VEGF into adult rat brains increased proliferation and neuronal differentiation in the SVZ and SGZ [114]. In addition, adult hippocampal NSPCs are known to secrete large quantities of VEGF, which functionally maintains the neurogenic niche [116]. Specific loss of VEGF in NSPC resulted in impairment of stem cell maintenance although VEGF produced from other cell types was still present [116]. Evidence from knockout mice indicated that hippocampal neurogenesis was impaired in VEGF B-KO mice, whereas intraventricular administration of VEGF B restored neurogenesis to control levels [117]. Moreover, delivery of VEGF via VEGF-secreted cells in microcapsules or VEGF-loaded poly (lactic co-glycolic acid) nanospheres increased the proliferation of neuronal progenitors [118, 119]. These findings suggested that VEGF is involved in neurogenesis in the adult hippocampus. Indeed, increasing evidence has shown that VEGF acts as a molecular mediator for adult hippocampal neurogenesis and is upregulated by antidepressant treatments including drugs, electroconvulsive seizure [120, 121], exercise, and enriched environments [122, 123], indicating that VEGF is a promising target for treatment of neural disorders.

### 4.4. Fibroblast growth factor-2 (FGF-2)

In the adult CNS, FGF-2 and its receptors (FGFR) are expressed by astrocytes and neurons located in the SVZ and SGZ, although their expression is also found in many other brain regions [124, 125]. After birth, FGF-2 is concentrated primarily in the hippocampal subfields CA1-3, and in neurons of the medial septum and the vertical limb of the diagonal band nuclei. The adult pattern of neuronal FGF-2 is restricted to particular populations, such as those in the cingulate cortex and hippocampus. Within the mature hippocampus, the CA2 region is the primary area of neuron-derived FGF-2 expression [126], suggesting that FGF-2 may play a role in the development and function of the adult hippocampus. In particular, use of FGF-2 knockout mice showed that loss of FGF-2 caused decreases in adult hippocampal neurogenesis and that these defects could not be rescued by exogenous FGF-2 [127]. Yoshimura et al. reported that hippocampal neurogenesis increased in normal adult mice after brain injury, but this phenomenon did not appear in FGF-2 knockout adult mice [128]. These results indicated that endogenous FGF-2 is necessary and sufficient to stimulate NSPC proliferation and differentiation in the adult hippocampus. In the adult rat CNS, FGF-2 receptors, FGFR1 and FGFR4, were shown to be predominantly expressed on neurons, whereas FGFR2 and FGFR3 were more highly expressed on oligodendrocytes and astrocytes, respectively [129, 130]. Genetic deletion of FGFR1 resulted in reduced proliferation of hippocampal NSPCs and reduced hippocampal volume during embryonic and postnatal development [131]. These studies suggested that the functions of the FGF-2/FGFR system may promote neurogenesis in the adult hippocampus.

## 5. Signaling pathways

### 5.1. Wingless (Wnt)

The Wnt pathway is one of the principal developmental pathways and is involved in body axis specification, morphogenesis, and stem cell proliferation, and differentiation [132]. To date, 19 Wnt proteins have been confirmed in mammals. Studies by Lie et al. showed that Wnt signaling components and their respective receptors have been shown to be expressed in the adult hippocampus. When Wnt3 was overexpressed, neurogenesis was increased, while blockade of Wnt signaling was reduced [133]. Evidence also suggested that β-catenin plays an important role in the dendritic development of adult hippocampal neurons [134]. These data suggested that Wnt signaling may be a regulator of adult hippocampal neurogenesis.

### 5.2. Notch

Studies have shown that Notch molecules (four in mammals) and their associated signaling pathway are crucial for the maintenance, proliferation, and differentiation of stem cells [135]. In adult mice, overexpression of Notch1 increases hippocampal cell proliferation and maintenance of GFAP-expressing NSPCs [136]. Abrogation of Notch signaling leads to a decrease in cell proliferation and a shift in differentiation of newly born cells toward a neuronal lineage [137]. This evidence suggested that, in particular, Notch1 signaling is required to maintain a reservoir of undifferentiated cells and ensure continuity of adult hippocampal neurogenesis. In addition, Notch1 signaling modulates the dendritic morphology of newborn granule cells by increasing dendritic arborization [137]. Furthermore, the expression of Notch1 signaling components (including Jag1, NICD, Hes1, and Hes5) are increased in parallel with hippocampal neurogenesis in adult rats after chronic fluoxetine (antidepressant) administration [138]. These findings suggested that Notch1 signaling is involved in adult hippocampal neurogenesis.

### 5.3. Bone morphogenetic protein (BMP)

BMP, an extracellular signaling molecule, regulates cell proliferation and fate commitment throughout development and in the postnatal SVZ and SGZ neurogenic niches [139, 140]. It has been shown that BMP signaling inhibits neurogenesis and promotes NSPC glial differentiation in the adult SVZ [140]. However, in the adult hippocampus, BMP signaling inhibits NSPC proliferation and promotes their maintenance in an undifferentiated and quiescent state [141]. Specifically, Gobeske et al. found that exercise reduced levels of BMP signaling in hippocampus, and that blockade of BMP signaling reproduced the effects of exercise on learning and neurogenesis in adult mice [142]. These studies showed that BMP decreases adult neurogenesis and that inhibition of BMP can partially rescue neurogenesis in the adult hippocampus.

### 5.4. Sonic hedgehog (Shh)

Shh is crucial for the expansion and establishment of postnatal hippocampal progenitors [143]. The Shh receptors, patched (Ptc) and smoothened (Smo), were detected in the DG, including

the neurogenic niche of the SGZ and NSPCs derived from adult hippocampus [144, 145]. In adult rats, overexpression of Shh in the DG increased cell proliferation and survival [145]. However, inhibition of Shh signaling with the inhibitor, cyclopamine, reduced cell proliferation [145, 146]. In addition, the loss of Shh signaling results in SVZ cells undergoing programmed cell death [147]. These studies emphasized the importance of the Shh signaling pathway in adult neurogenesis. Furthermore, in electroconvulsive seizure-mediated adult rat hippocampal neurogenesis, the Shh signaling cascade was found to be activated [146].

### 5.5. PI3K-Akt

The PI3K-Akt signaling pathway is a downstream pathway of neurotrophic and growth factor receptors, as well as monoamine receptors [148]. It has been potentially implicated in a number of different functions and is especially associated with cell survival through inhibition of the activation of proapoptotic proteins and transcription factors [149]. It was shown that Akt1 and Akt2 (two members of the Akt protein kinase family) knockout mice had lower levels of hippocampal cell proliferation compared to wild-type animals, but only Akt2 knockout mice had impaired survival of adult born hippocampal progenitors [150]. Reports also showed that PI3K/Akt participated in the enhancement of adult hippocampal neurogenesis via activation by other factors [151], VEGF [152] and intermittent hypoxia after ischemia [153].

### 5.6. Reelin

Reelin is an extracellular matrix glycoprotein and aides in neural migration and brain development [154–156]. It is preferentially secreted by GABAergic interneurons located in the cortex and hippocampus of the mammalian brain [157]. Gain and loss of function studies indicated that the reelin pathway regulated adult hippocampal neurogenesis and dendritic maturation orientation [158]. In addition, using retroviral tracing and 3D-EM, it was shown that the reelin/Dab1 pathway controlled adult granular cell spinogenesis and synaptogenesis [159]. Recent studies suggested that changes in reelin expression contribute to the pathogenesis of several neurological diseases that display abnormalities in granule cell neurogenesis and organization [160–162]. These studies indicated that reelin signaling participates not only in the development of the embryonic brain, but also in multiple processes of adult hippocampal neurogenesis, and enhanced cognitive ability [163].

## 6. Physiological and pathological factors

### 6.1. Exercise

Exercise exerts many effects on brain functions, including enhancement of adult hippocampal neurogenesis [164]. Increased blood flow due to exercises most likely facilitates delivery of trophic factors to the neurogenic niche. Furthermore, running has been shown to influence all aspects of hippocampal neurogenesis, including cell proliferation, survival, differentiation, and recruitment in the DG [165–167]. Studies suggested that exercise increases peripheral and central levels of BDNF and FGF-2 [168–171], which were both reported to be involved in neurogenesis

in the developing and adult brain [170, 172]. Peripheral VEGF produced by skeletal muscles after exercise may also play an important role in exercise-induced adult hippocampal neurogenesis, because the increased number of newborn neuronal precursor cells in the hippocampus were not present in adult conditional skeletal myofiber-specific VEGF gene-ablated mice [173, 174], suggesting that VEGF expressed by skeletal myofibers may directly or indirectly regulate hippocampal neurogenesis, as well as blood flow.

### 6.2. Enriched environment (EE)

Running and exposure to an enriched environment (EE) are two of the most common ways to increase adult neurogenesis, which provide sensory, social, and motor stimulation. Researchers discovered that there was no effect on cell proliferation in mice exposed to EE, but these mice showed significantly higher numbers of total granule neurons in hippocampus compared with controls [175]. In order to determine the long-term effects of EE, 10-month-old mice were housed in an EE for 10 months (roughly half of their life) [176] and consistent with the above results, neuronal differentiation of newborn cells significantly increased in these mice, but not proliferating cells. More recently, several reports suggested that the notable EE-induced increase in adult neurogenesis was attributed to physical activity associated with exercise [177, 178].

### 6.3. Aging

Aging is a natural process associated with cognitive decline and functional and social impairments, and is also very closely associated with changes to hippocampal formation. Indeed, the number of newborn neurons in the SGZ declines with age [179–181]. During the aging process, reduction of hippocampal volume [182], degeneration of hippocampal vessels, [183] and decrease in hippocampal blood flow [184] may all contribute to the reduced neurogenesis seen in the aged hippocampus. In addition, increase in microglial activation with age was observed in the hippocampus of both rats and humans [185, 186]. This microglia-mediated neuroinflammation and subsequent neuronal damage also likely contribute to decline neurogenesis with age. Furthermore, several neurotrophic factors such as FGF-2 [187], BDNF [188, 189], VEGF [187, 190], and NGF [191] exhibit considerable decline with age, all of which play an important role in hippocampal neurogenesis (as reviewed above). Therefore, an overall reduction of these factors may also contribute to deficits in hippocampal neurogenesis with age. Interestingly, although hippocampal neurogenesis declines with age, it persists in certain pathological conditions. Darsalia et al. reported that hippocampal neurogenesis was observed in aged rats with stroke, but maturation and survival of these newborn neurons in the DG were approximately one-third less compared to the young DG [192]. As the decline of hippocampal neurogenesis with age cannot be explained by only one factor, there is likely a complex regulation of different factors associated with this decline.

### 6.4. Stress

Stress is a threat-induced response associated with the homeostasis of an organism and subsequent physiological and behavioral responses. Individuals experiencing this phenomenon exhibit differential responses to various stress-inducing factors (stressors). Increasing evidence

suggested that exposure to stress at different life stages leads to distinct alterations in hippocampal neurogenesis. Studies have shown that chronic and acute stressors reduce cell proliferation, survival, and neuronal differentiation in the adult DG [193–196]. Yet, the correlation between stress and reduced neurogenesis is more complex. Changes induced by prenatal stress may depend upon genetic background [197, 198]. Susceptibility and resilience to stress highlight that gene-environment interactions may modulate adult stress-altered hippocampal neurogenesis. Using animals with different genetic backgrounds, it was shown that they could be segregated into subgroups of stress-susceptible animals that showed depression-like behaviors, stress behaviors, and stress-resilient behaviors that showed no or little response to stressors [199]. Interestingly, this difference in the stress response has been linked to hippocampal volume. Hippocampal volume increased in resilient animals after stress, while susceptible animals exhibited a decrease in volume [200]. Whether adult hippocampal neurogenesis occurred specifically in animals that were more resilient or more susceptible to stress remains unclear, but susceptible behaviors were reversed by increased hippocampal neurogenesis [201, 202]. It will be important to carefully examine how adult hippocampal neurogenesis contributes to stress resilience or susceptibility and to the process of developing effective treatments for stress-related psychiatric disorders according to individual genetic backgrounds.

### 6.5. Ischemia

Ischemia has been noted to produce enhanced neurogenesis in neural proliferative regions of the adult rodent brain. The first description, in 1998, showed that transient global ischemia in adult gerbils increased neurogenesis in the DG [203]. Subsequent findings in adult mouse and rat also proved that transient focal or global ischemia enhanced hippocampal neurogenesis [204–207]. Tsai et al. indicated that post-ischemia intermittent hypoxia in adult rats induced hippocampal neurogenesis and synaptic alterations, and actually alleviated long-term memory impairment, which may be contributed by the increased neurogenesis [152]. All of these studies suggested that neurogenesis may be a compensatory, adaptive mechanism mediating functional recovery after ischemia in adult mammals.

### 6.6. Traumatic brain injury (TBI)

As the hippocampus is particularly vulnerable to brain trauma, TBI can induce immature neuronal death in the DG and result in learning and memory dysfunctions [208–210]. However, many studies have confirmed that NSPC proliferation is actually increased after TBI in the adult hippocampus of both rodents and humans [211–213], indicating an innate repair may be occurring in the hippocampus [212–215]. As expected, levels of neurogenesis after TBI correlated with injury severity [215]. This innate repair cannot always completely compensate for cell loss, resulting in permanent functional deficits in numerous TBI survivors [216]. Further research is needed to fully understand the mechanisms involved in TBI-related hippocampal neurogenesis.

### 6.7. Seizures

Seizures are characterized as the periodic and unpredictable occurrences of epilepsy. Studies have shown that acute seizures abnormally increased the amount of hippocampal neurogenesis

and induced aberrant migration of newly born neurons into the DG hilus and molecular layer [217–220]. Furthermore, recurrent spontaneous seizures also led to dramatically reduced neurogenesis [219, 221], which is concurrent with learning and memory impairments and depression in epilepsy patients. However, a modest increase in neurogenesis was observed 2 months post status epilepticus in a lithium-pilocarpine model of epilepsy using postnatal day 20 rats [222]. These data suggested that seizures can not only disrupt both the structure and the function of the hippocampus, but also increase neurogenesis in the hippocampus. These seemingly contradictory results may be related to the type and severity of epileptic seizures.

## 7. Conclusions

Differentiation of static radial glial cells (RGC) to mature granular cells occurs in a series of morphologically and genetically identifiable stages, including the slowly dividing RGC stage, the rapidly proliferating NSPC stage, commitment to a neuronal fate, immature to mature neuronal progression, and finally, survival and projection of axons to target cells. Findings also indicated that the regulatory effects of different factors are defined at different steps in the overall differentiation process. For example, the transmitter serotonin exerts its effects at the proliferation stage, while GABA and DA are known to induce neuronal commitment, and glutamate and ACh play positive roles in the survival of newborn neurons. With regard to extrinsic factors, exercise may enhance proliferation of NSPCs, although this process is likely inhibited by stress. Learning and EE induce neuronal differentiation and survival. Taken together, a more complete understanding of the intrinsic and extrinsic factors regulating/directing different stages of adult hippocampal neurogenesis will aide in the development of exogenous and endogenous NSPCs as a therapeutic tool in the treatment of neural disorders. In addition, these findings have increased the likelihood of using hippocampal neurogenesis in the treatment of adult mammalian neurological diseases. Although the exact mechanisms involved in adult neurogenesis have not been identified, emerging technology will likely advance our understanding of the processes involved.

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## Abbreviations

| | |
|---|---|
| 5-HT | serotonin or 5-hydroxytryptamine |
| ACh | acetylcholine |

| | |
|---|---|
| AChE | acetylcholinesterase |
| AD | Alzheimer's disease |
| BDNF | brain derived neurotrophic factor |
| BMP | bone morphogenetic protein |
| CA | cornu ammonis |
| CNS | central nervous system |
| DA | dopamine |
| DG | dentate gyrus |
| DHT | dihydrotestosterone |
| ER | estrogen receptor |
| FGF-2 | fibroblast growth factor-2 |
| GABA | γ-aminobutyric acid |
| GFAP | glial fibrillary acidic protein |
| GPER | G protein-coupled estrogen receptor |
| NGF | neurotrophic growth factors |
| NSPC | neural stem/progenitor cell |
| SGZ | subgranular zone |
| Shh | sonic hedgehog |
| SVZ | subventricular zone |
| TBI | traumatic brain injury |
| VEGF | vascular endothelial growth factor |
| VTA | ventral tegmental area |
| Wnt | wingless |

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Chapter 3

# Long-Term Potentiation-Associated Gene Expression: Involvement of the Tumour Protein p53

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Additional information is available at the end of the chapter

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**Abstract**

Long-term potentiation of synaptic transmission (LTP) is one of the most studied manifestations of neuroplasticity and hippocampus is a classic object for the study of LTP mechanisms. The early phase of LTP depends on modifications of pre-existing synaptic proteins and the late phase of LTP needs *de novo* protein synthesis and gene expression. LTP-associated dynamics of the transcriptome and mechanisms of coupling synaptic activity with gene expression are intensively studied, but due to the vast complexity of the issue, abundance of unresolved questions remains in this field. The diversity of brain cell types is one of the main challenges. Until relatively recently, the analysis of molecular and genetic aspects of neuroplasticity has usually been confined to neuronal populations. Meanwhile, glia substantially contributes to synaptic transmission regulation. Astrocytes release various gliotransmitters, which modulate synaptic transmission and plasticity. S100B is one of those glia-derived regulatory factors. Learning in rats is accompanied by an increase in S100B expression in various brain regions including the hippocampus. The present study is focused on the neuroplasticity-associated *S100B* expression upregulation using long-term post-tetanic potentiation in rat hippocampal slices. In this chapter, we present a short review of published articles devoted to the analysis of gene expression during LTP formation including studies of the mechanism of LTP-associated *S100B* upregulation in hippocampus.

**Keywords:** hippocampus, CA1, long-term potentiation, gene expression, p53, *S100B*, *Bax*

## 1. Introduction

Long-term alterations in the strength of synaptic transmission are a key physiological mechanism of learning and memory. To explain the formation of conditioned reflexes, Donald Hebb

proposed that simultaneous or quasi-simultaneous discharge of two neuronal populations leads to the establishment of a functional connection between them [1]. The first attempts to find "Hebbian synapses" were undertaken by Jan Bureš [2, 3]. In his experimental model, sound or tactile sensory conditioned stimulus (CS), which slightly changed a frequency of neuronal discharges, was reinforced by a depolarizing current delivered through a recording microelectrode (unconditioned stimulus, US), which caused a strong neuronal discharge. In some neurons, responses to CS essentially increased after appropriate combination of CS and US. Interestingly, most significant effects were observed in the hippocampus [4], which is critical for acquisition and retrieval of some forms of memory [5, 6]. However, the persistence of plastic changes in this and other similar experimental models (tens of minutes) was relatively low in comparison with memory traces (reviewed in [7]).

The discovery of LTP in the hippocampus was a next essential step in the research of cellular and molecular mechanisms of synaptic plasticity [8]. LTP is the most studied form of plasticity associated with alterations in synaptic strength. A fairly common model of LTP is the increase in responses of postsynaptic neurons to stimulation of presynaptic fibers after high frequency stimulation (HFS)—tetanization or theta-stimulation—of the afferents. LTP is widely accepted as a neuronal mechanism of learning [9–11]. LTP that is dependent on glutamate receptors of NMDA type (NMDAR) is the most widespread in CNS and the most studied. LTP of perforant fiber-granular cell synapses in the dentate gyrus (DG) and LTP of Schaffer collateral (SC)-pyramidal cells in the area CA1 of the hippocampus are classic examples of this kind of LTP.

There are two main phases of LTP: the early phase lasting usually less than 1 hour and the late phase lasting several hours or longer (months). The early phase of LTP is based on post-translational modifications of pre-existing synaptic proteins and the late phase of LTP requires *de novo* protein synthesis and gene expression [12–14]. According to varying estimates, within 4–8 h after induction, LTP is maintained due to the translation of pre-existing mRNAs, while transcription is necessary for later stages [15–17]. However, the disturbance of CREB-dependent gene expression due to inhibition of CREB coactivator TORC1 leads to a decline in LTP maintenance, which became evident as early as 75 min after induction of LTP [18]. Such contradictions might reflect varying demand for gene expression in different experimental conditions or difficulties in accounting for the side effects of intracellular signalling network disturbance. As a rule, the later inhibitors of translation or transcription are applied after the induction of LTP, the less they influence the maintenance of the late phase of LTP [19]. Transcription and translation within a time window ≤2 h after the induction of LTP are most critical for the persistence of LTP [20].

## 2. LTP and neural activity-regulated genes

Identification of genes regulated by neuronal activity (ARGs) and clarification of the mechanisms of this regulation is an intensively developing research area. The families of transcription factors (TFs) thus far found to be critically involved in synaptic plasticity and memory formation include CREB, C/EBP, AP-1, Egr, and Rel/NFκB [21, 22]. Important advances in this

field have been achieved by using microarrays and high-throughput sequencing. Hundreds of ARGs have been identified with complex expression dynamics after various kinds of stimulation: seizures, chemical stimulations, behavioural tasks, and HFS [20, 22–24]. Among transcriptomic studies of LTP in the hippocampus, works with induction of LTP in DG *in vivo* prevail. Exceptions include HFS-induced LTP in DG mini-slices [25] and chemically induced LTP in CA3/CA1 mini-slices [20] in mice.

Remarkably, the ARG lists from different authors showed little overlap [22]. One of the multiple reasons of this is a highly dynamic temporal regulation of the neuronal activity-regulated gene expression. For example, the level of *Fos* mRNA increased 30 min after tetanization, then returned to the initial level after 60 min, and again increased 120 min after LTP induction in the CA1 field of rat hippocampal slices [26]. Only 8 genes were overlapping from 226 and 190 genes differentially expressed 20 min and 5 h, correspondingly, after LTP induction in DG *in vivo* [24, 27]. Rapid dynamics of transcriptional profiles was demonstrated also in the hippocampus after learning [28] and in mice hippocampal mini-slices after induction of LTP [20, 25]. Therefore, the duration of LTP-inducing stimulation is of special significance for reproducibility of gene expression data, particularly when early stages of the transcriptional response are examined. Meanwhile, the duration of LTP-inducing stimulation in different works varies from 1.5 min [25] to 45 min [23]. Moreover, analysed time points are quite diverse in different experiments.

Temperature is also a factor influencing gene expression dynamics in brain slices. For example, differential expression of *Egr1* was not detected in the CA1 region of hippocampal slices after induction of LTP at room temperature [29], while at a temperature of ≥30°C, LTP induction led to the increase in the level of *Egr1* mRNA in the area CA1 [20, 26, 30, 31].

In addition, the comparison of datasets generated in different studies is complicated by the limited access to original data. Only partial lists of ARGs, which passed arbitrarily designed significance filters, were often presented by authors. Nevertheless, differential expression of some genes is reproduced quite frequently. This is particularly true for early genes, association of which with LTP was already demonstrated in earlier works on this issue, such as *Fos, Jun, Egr1, Arc, Homer1,* and *Bdnf* [32, 33], which are well known.

One of the most serious problems is a great diversity of the brain cell types, which is reflected in the diversity of their transcriptomes [34, 35]. For example, granular cells of the DG and pyramidal cells of the CA1-CA4 regions of the hippocampus differ in their transcriptomes [36], which can exhibit distinct dynamics after LTP induction [29]. Dorsal and ventral subregions of the rodent area CA1 also differ in their transcriptomes [37]. LTP induction alters gene expression not only in neurons but also in glial cells [20, 38, 39]. The role of glia in a structural, metabolic, and trophic support of neurons is well known. Undoubtedly, neuron life support is crucial for all brain functions including learning. For example, learning in rats is associated with an increase in extracellular lactate concentration in the brain, and disruption of lactate export out of astrocytes or import into neurons disturbs long-term memory and LTP in hippocampus [40]. In addition, glial cells directly participate in synaptic transmission [41, 42]. Astrocytes respond to neurotransmitters by an increase in intracellular calcium concentration followed by secretion of gliotransmitters modulating synaptic transmission and plasticity.

Therefore, adequate research of LTP-associated gene expression must include an analysis of the cellular localization of observed phenomena, which is quite laborious. The task is somewhat easier, when ARGs are cell-specific.

One of such relatively cell-specific genes is *S100B*. In the adult brain, S100B protein is synthesized mainly in astrocytes. It is constitutively secreted and its secretion can be regulated by a number of factors [43] including neuronal activity [44]. In physiological (nanomolar) concentrations, it possesses neurotrophic activities [43] and modulates neuronal activity [44] and synaptic plasticity [45]. *S100B*-knockout mice have enhanced LTP in the area CA1 of the hippocampus, enhanced spatial memory in the Morris water maze test, and enhanced fear memory in the contextual fear conditioning [45].

However, *S100B*-knockout animals are more prone to seizures during kindling, than wild-type controls [46], which can be, in part, a consequence of enhanced LTP, since there are parallels between kindling and LTP [47]. Disturbed calcium homeostasis in glial cells of mutant mice [48] is also a possible reason of their susceptibility to seizures, since calcium waves in astrocytes play an important role in epileptogenesis [49]. Thus, normal S100B expression is necessary for proper functioning of neuroglial networks. However, at high (micromolar) doses, S100B is toxic [43]. S100B is used as a marker of brain damage, since it can cross the blood-brain barrier and several brain pathologies are associated with elevated levels of S100B in the serum [50]. The *S100B* allele with increased gene expression is a putative risk variant for bipolar disorder [51]. Therefore, chronically increased *S100B* expression, in combination with additional adverse factors, can be harmful. In this context, the fact that learning in rats can increase S100B level in the hippocampus and other brain regions [52, 53] is of special interest.

To study the mechanisms of the neuroplasticity-associated *S100B* expression upregulation, we have modelled this phenomenon using long-term post-tetanic potentiation in rat hippocampal slices [39, 54–60].

## 3. LTP-associated expression of *S100B* and other p53 target genes in rat hippocampal slices

The increase in *S100B* mRNA level was detected in area CA1 of slices prepared from rat dorsal hippocampus as soon as 10 min after tetanization of Schaffer collaterals, and the maximal increase in *S100B* mRNA level occurred 20–30 min after tetanization [39, 59]. Low frequency stimulation, which does not induce LTP, does not alter *S100B* expression [54]. The level of S100B protein increased significantly 20 min after tetanization [59] and remained elevated up to 240 min after tetanization.

Transcription factor p53, well known as a key regulator of apoptosis, proved to be one of the TFs determining *S100B* mRNA dynamics after LTP induction. We analysed a 2 kb promoter region proximal to the first of the two alternative transcription starts of the rat *S100B* gene and identified putative p53-responsive elements (pREs) partially matching the canonical p53 binding sequence RRRCWWGYYY$(n)_{0\text{-}13}$RRRCWWGYYY [61, 62]. One example is presented in **Figure 1**. This is the only pRE we recovered, which apparently resembles one of the pREs

identified in a similar promoter region of the human gene *S100B* [63]. The mouse *S100B* promoter also contains a pRE, which is similar to the rat pRE (**Figure 1**). It is tempting to speculate that this conserved site is particularly important for *S100B* regulation in rodents and humans. We used chromatin immunoprecipitation to study p53 binding to three loci in *S100B* promoter with pREs within them (**Figure 1**). The p53 binding to all these sites in *S100B* promoter strongly correlated with *S100B* mRNA dynamics in a time window 10–40 min after SC tetanization [60]. Interestingly, the p53 binding to the conserved site was most expressed.

The increase in p53 DNA-bound fraction was not associated with the increase in total p53 protein, which suggests p53 activation was due to post-translational modifications. The total p53 protein level even decreased in the area CA1 20 min after LTP induction, while *p53* mRNA level did not change [60]. Therefore, the p53 protein degradation accelerated or/and *p53* mRNA translation slowed in the early phase of LTP.

To confirm that LTP-associated p53 binding to *S100B* promoter is functional, we carried out experiments [57, 58] with the inhibitor of p53-dependent transcription, pifithrin-β and p53 activators, nutlin-3 and EX-527, which are inhibitors of p53 negative regulators ubiquitin ligase Mdm2 and deacetylase Sirt1, correspondingly. The two p53 activators increased the basal level of *S100B* mRNA. However, LTP induction in their presence led to further significant increase in *S100B* mRNA level. Moreover, p53 inhibitor pifithrin-β incompletely suppressed tetanization-induced *S100B* upregulation [57]. This suggests that some additional factors contributed to *S100B* transactivation in our experiments, besides p53.

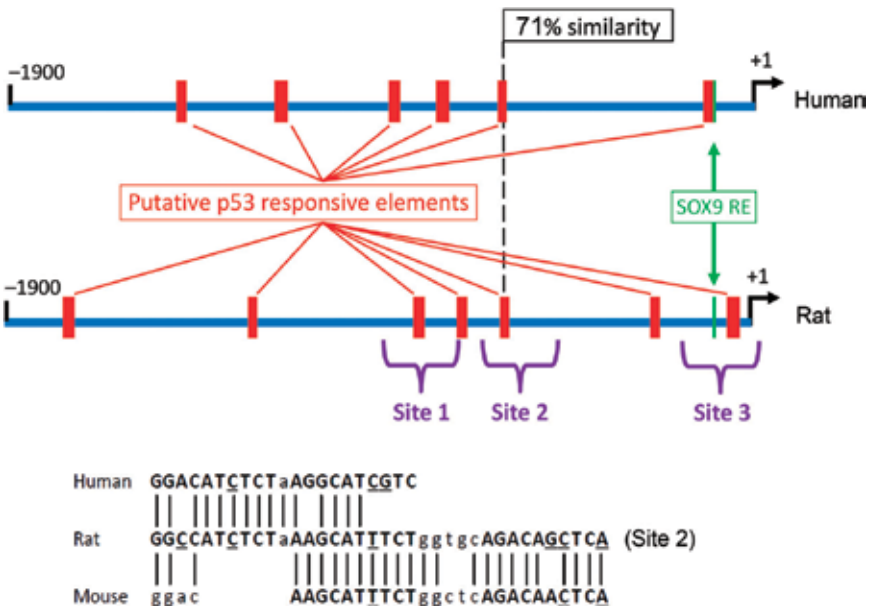


**Figure 1.** Putative p53 responsive elements in the promoters of rat, human, and mouse genes *S100B*. Top—Schematic representation of human and rat *S100B* promoters, which are aligned relative to conserved SOX9 responsive elements. "+1"— Transcription starts. Boxes indicate positions of pREs. Sites 1/3 were tested for p53 binding. Bottom—Sequences of pRE in the rat *S100B* site 2 and homologous pREs of human and mouse *S100B* promoters. Capitalized letters denote sequences partially matching to the consensus RRRCWWGYYY. Mismatches are underlined. Vertical lines indicate nucleotides conserved among rat and human or rat and mouse genes *S100B*.

Thus, LTP in the area CA1 of the hippocampus is associated with transient p53 activation, which is one of the reasons of increased S100B synthesis. The decrease in p53 protein level after SC tetanization indicates that p53 negative regulators are activated soon after LTP induction. As mentioned above, p53 negative regulators include ubiquitin ligase Mdm2 and deacetylase Sirt1. Mdm2 negatively modulates p53 transcription activity, protein stability, and mRNA translation [64, 65]. Ubiquitination of lysine residues of p53 promotes its export from the nuclei followed by its degradation in proteasomes [66]. Thus, acetylation of lysine residues is an important element of p53 activation promoting its stabilization and import into the nucleus, while deacetylation decreases this activity and facilitates ubiquitination of lysine residues. Deacetylases controlling p53 acetylation status include NAD-dependent deacetylases, Sirt1 and Sirt2 [67, 68], and nonselective inhibitor of sirtuins tenovin-1 inhibits Mdm2-dependent degradation of p53 [69].

For evaluation of the contribution of Mdm2 and Sirt1 in tetanization-induced p53 protein downregulation, we studied the effects of Mdm2 inhibitor nutlin-3 and Sirt1 selective inhibitor EX-527 on the level of p53 protein after LTP induction. Inhibition of Mdm2 or Sirt1 fully prevented tetanization-induced decrease in p53 protein level [56, 57]. Therefore, Sirt1/Mdm2 tandem plays a key role in the p53 protein level decrease after LTP induction in the area CA1 of the hippocampus.

To reveal mechanisms of *S100B* expression regulation in more detail, we studied the influence of inhibitors of several intracellular regulatory network elements on tetanization-induced *S100B* expression [55, 57, 58]. **Figure 2** illustrates our current hypothesis concerning mechanisms of LTP-associated *S100B* upregulation. The obtained results indicate that NMDAR and

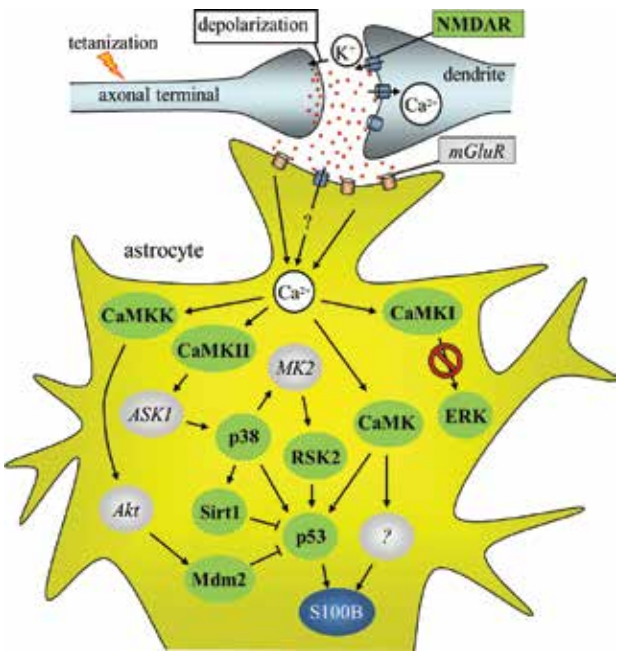


**Figure 2.** Putative mechanism of *S100B* regulation during LTP. Dots in synaptic cleft— glutamate. mGluR—metabotropic glutamate receptors; Akt, ASK1—protein kinases; and CaMKK—CaMK kinase. Involvement of the factors shown in bold was tested in experiments with appropriate inhibitors; hypothetical intermediates are shown in italics.

$Ca^{2+}$/calmodulin-dependent protein kinases (CaMKs) are essentially involved in neuronal activity-regulated *S100B* expression. However, contributions of separate CaMKs were not determined, since pan-CaMK inhibitor was used.

It is an open question, furthermore, where NMDARs participating in *S100B* regulation are located. The presence of functional NMDARs in adult rodent astrocytes has not been evidenced reliably. However, neuronal NMDAR activation could lead to an increase in extracellular potassium concentration (due to potassium efflux through postsynaptic NMDARs) followed by presynaptic terminal depolarization and enhanced glutamate release [70], which can increase intracellular calcium levels through activation of metabotropic glutamate receptors and induction of gene expression in astrocytes.

Mitogen-activated protein kinase (MAPK) p38 and 90 kDa ribosomal S6 kinases (RSKs) are also involved in *S100B* expression induction, while participation of MAPK/ERK and protein kinases C is unlikely [58]. MAPK/ERK plays an important role in LTP-associated gene regulation, and RSKs are believed to mediate its long-term effects [19, 71]. Nevertheless, the fact that inhibition of ERK cascade did not suppress tetanization-induced *S100B* transactivation [58] is not surprising. It seems that neurons and astrocytes differ in their mechanisms of $Ca^{2+}$-dependent MAPK/ERK activation, since glutamate application did not activate MAPK/ERK in cultured astrocytes, in contrast to neurons [72].

Then, how are RSKs activated during LTP in astrocytes in this case? There are alternative ways of RSK regulation. For example, in dendritic cells, RSKs can be activated through MAPK p38–MK2 [73]. Protein kinase MK2 is also expressed in microglia, neurons, and astrocytes [74]. Therefore, theoretically, $Ca^{2+}$-dependent *S100B* transactivation through the CaMK–ASK1–p38–MK2–RSK2–p53 pathway is possible (**Figure 2**).

Further, we questioned to what extent the short-term p53 activation in the early stage of LTP contributes to transcriptome dynamics. To estimate this contribution, we have studied the expression of several tens of genes that are directly or indirectly regulated by p53 30 min after induction of LTP [60]. The p53 activator nutlin-3 was used for the preliminary assessment of a putative participation of p53 in LTP-associated regulation of these genes. If p53 contribution to tetanization-induced expression of a gene is significant, nutlin-3 would be expected to occlude the effect of tetanization.

Based on this approach, we conclude that expression of several established p53 target genes is altered after LTP induction in a p53-independent way. They include *Apaf1, Bbc3, Bid, Cdkn1a, Dnmt1, Egfr, Egr1, Mdm2, Mlh1, Pcna*, and *Tp73*. However, some genes might be regulated by p53: *Bax, Bcl2, Btg2, Ccnb1, Check2, Dapk1, Gadd45a, Prkca*, and *Pten*. Sometimes, p53 contribution is shadowed by other factors, which act in the same (*Btg2*) or in the opposite (*Ccnb1, Check2, Dapk1*, and *Prkca*) direction as p53. It remains to be determined, whether p53 interacts with other factors within the same cells, or LTP-associated regulation of *Btg2*, *Ccnb1*, *Check2*, *Dapk1*, and *Prkca* in the hippocampus is cell-specific.

Some of these results are consistent with the data obtained previously by other researchers. For example, a neuronal activity-dependent decrease in the level of mRNA of the proapoptotic protein Bbc3 was observed in neuronal cultures [75, 76] and in mini-slices of areas CA3/CA1 of the hippocampus [20]. Moreover, Léveillé et al. [76] also concluded that this decrease did not

depend on p53. Similarly, an increase in *Btg2* mRNA level was often reproduced in LTP models [20, 25, 27, 77] and observed in neuronal cultures [75]. Since *Btg2* is a target gene of the TF CREB, which plays a key role in neuroplasticity, the neuronal activity-driven increase in *Btg2* expression is usually *a priori* associated with the CREB activity. However, our results demonstrate a complex regulation of *Btg2* after LTP induction, and perhaps p53 takes part in it.

It should be noted, however, that our suggestion that p53 participates in LTP-associated regulation of *Bax*, *Btg2*, and some other genes mentioned above is preliminary and needs more direct evidence such as provided by chromatin immunoprecipitation.

## 4. Conclusion

*De novo* transcription plays an important role in long-term neuroplasticity underlying memory formation. Synaptic rearrangement is associated with substantial shifts in the brain transcriptome, analysis of which is necessary for the clarification of neuroplasticity mechanisms. The functional outcome of transcription in memory stabilization and storage was thoroughly discussed recently [21]. Here, we propose a hypothesis about a possible function of the p53-dependent transcription in LTP-associated processes.

Although p53 is known mostly as a key factor of apoptosis, its function is really much broader [78, 79] and sometimes prosurvival [80]. Intracellular regulatory cascades associated with LTP formation overlap with pathways regulating p53 activity, which indicates that, theoretically, p53 can be activated after LTP induction [58]. For example, active (phosphorylated) CREB directly interacts with p53, thus increasing its transcriptional activity [81].

During LTP formation in the area CA1 of the hippocampus, the increase in p53 transcriptional activity leads to *S100B* upregulation [59]. Taking into consideration that S100B suppresses LTP [45], we suggest that the increase in *S100B* expression is a part of the mechanism of synaptic scaling, a goal of which is to keep synaptic connection strengths within an optimal range necessary for proper functioning of a neuronal network. Heterodendritic metaplasticity [82] can be one of the manifestations of this mechanism. In the area CA1 of the hippocampus, priming stimulation delivered to inputs to the basal dendrites of pyramidal cells generates metaplastic inhibition of LTP and facilitates long-term depression (LTD) at inputs to the apical dendrites, hundreds of microns away and on the other side of the soma. Interestingly, astrocytes are involved in this form of metaplasticity. Thus, we proposed that an increase in S100B level associated with LTP [39] or learning [52, 53] prevents excessive enhancement of excitatory synaptic connections and reduces a risk of seizures.

In addition, LTP-associated upregulation (perhaps, also p53-dependent) of the proapoptotic protein of Bcl2 family Bax is of special interest in the context of neuroplasticity. This protein is involved in a mechanism of NMDAR-dependent LTD in the area CA1 of the hippocampus. Bax-mediated limited activation of caspases leads to the internalization of AMPA-type glutamate receptors, thus weakening synaptic strength [83]. Therefore, as in the case with *S100B*, *Bax* upregulation after LTP induction might reflect the formation of a negative feedback, which makes excitatory glutamatergic connections prone to LTD. This hypothesis suggests that the

Bax level increases in neurons. As shown in **Figure 3**, Bax is really expressed mainly in pyramidal cells of the area CA1 and it is rarely detectable in S100B-producing cells in acute rat hippocampal slices.

Finally, at physiological doses, S100B possesses trophic and protective properties [43]. Btg2 is also capable of rendering neurons more resistant against excitotoxicity and promoting neuronal survival under stress [75]. Thus, LTP-associated alterations in the expression of p53 target genes are capable of mediating neuroprotective and trophic effects of neuronal activity.

Indeed, the answer to the question of how nuclear activity alters brain functioning will only be achieved by using a systems biology approach, in which the focus moves from single genes to

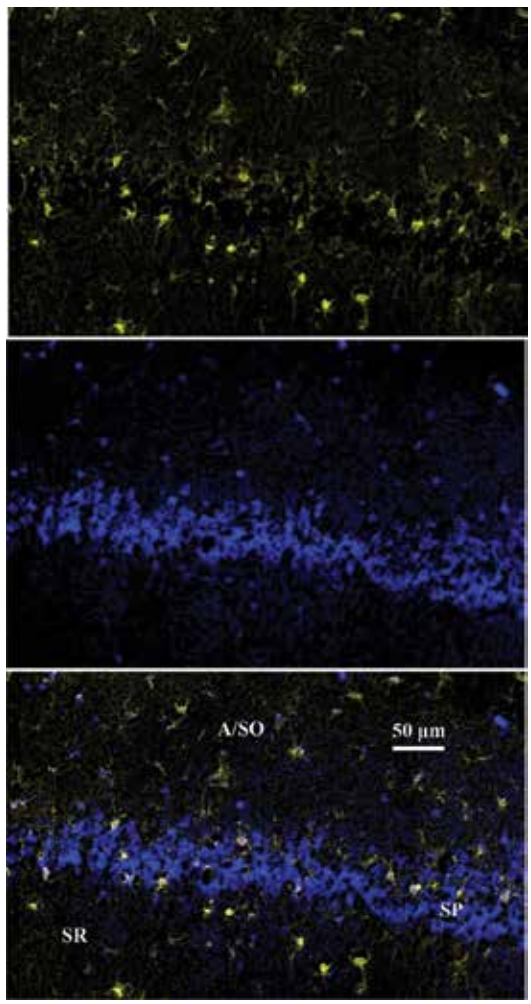


**Figure 3.** S100B and Bax immunoreactivity in the area CA1 of a rat hippocampal slice 30 min after tetanization of Schaffer collaterals. The same area is presented in all frames. Top—S100B-positive cells; middle—Bax immunoreactivity, bottom—the above images are merged. The section thickness is 30 μm. A/SO, alveus/stratum oriens; SP, stratum pyramidale, SR, stratum radiatum.

gene network interactions [22]. Moreover, profound molecular changes following hippocampal slice preparation suggest the need for careful interpretation of gene expression regulation results when using the acute slice as a model to study physiological responses [38, 84]. In particular, it needs to be determined whether p53 is activated in the brain after LTP induction in vivo or in behavioural tasks such as learning. Further investigation of p53 and its target gene roles in neuroplasticity should be undertaken to improve existing knowledge of the regulation of gene expression in the brain and its role in plasticity and neuropathology.

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Section 2

# The Hippocampus Functions in Health and Disease

Chapter 4

# A Role for the Longitudinal Axis of the Hippocampus in Multiscale Representations of Large and Complex Spatial Environments and Mnemonic Hierarchies

Bruce Harland, Marcos Contreras and
Jean-Marc Fellous

Additional information is available at the end of the chapter

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**Abstract**

The hippocampus is involved in spatial navigation and memory in rodents and humans. Anatomically, the hippocampus extends along a longitudinal axis that shows a combination of graded and specific interconnections with neocortical and subcortical brain areas. Functionally, place cells are found all along the longitudinal axis and exhibit gradients of properties including an increasing dorsal-to-ventral place field size. We propose a view of hippocampal function in which fine-dorsal to coarse-ventral overlapping representations collaborate to form a multi-level representation of spatial and episodic memory that is dominant during navigation in large and complex environments or when encoding complex memories. This view is supported by the fact that the effects of ventral hippocampal damage are generally only found in larger laboratory-scale environments, and by the finding that human virtual navigation studies associate ventral hippocampal involvement with increased environmental complexity. Other mechanisms such as the ability of place cells to exhibit multiple fields and their ability to scale their fields with changes in environment size may be utilized when forming large-scale cognitive maps. Coarse-grained ventral representations may overlap with and provide multi-modal global contexts to finer-grained intermediate and dorsal representations, a mechanism that may support mnemonic hierarchies of autobiographical memory in humans.

**Keywords:** hippocampus, longitudinal axis, dorsoventral, ventral, place cell, grid cell, multiple place fields, interneuron, gamma oscillations, large environment, complexity, spatial navigation, spatial memory, multi-scale representations, CA3, memory hierarchies

## 1. Introduction

The hippocampus is one of the most studied brain structures in humans and animals. Most work has focused on its dorsal subdivision and little is known, functionally and theoretically, of the entire structure along its longitudinal, dorsoventral axis. In this chapter, we review the recent literature and propose that the longitudinal axis of the hippocampus may be crucial to support multi-scale mnemonic hierarchies. We further propose that, in the rodent, this axis may be crucially involved in spatial navigation in large and complex environments.

The hippocampus is an elongated bilateral C-shaped structure with a dorsal to ventral longitudinal axis which corresponds to some extent to the posterior to anterior axis in humans [1]. Cell structure and function, and intrinsic trisynaptic circuitry, are conserved along the longitudinal axis, although there are differences in subfield composition. Patterns of gene expressions along the axis suggest molecularly defined dorsal, intermediate, and ventral domains each containing further subdomains showing gradual or sharp transitions. The dorsal and ventral regions of the structure exhibit differing cortical and subcortical connectivity. For example, the dorsal hippocampus receives visual and spatial information from the anterior cingulate and retrosplenial cortices via the medial entorhinal cortex, whereas the ventral hippocampus has major connections with the prefrontal cortex, amygdala, and hypothalamus (**Figure 1**). Interestingly, most of this connectivity is gradated, and in the case of structures with which dorsal and ventral connect contiguously, such as the medial entorhinal or prefrontal cortices, there can be transitional areas of overlapping inputs from both poles. The demarcated genetic domains and differing connectivity of the long axis have led to the hypothesis that the dorsal and ventral regions may be functionally distinct. In this model, the dorsal region mediates spatial and declarative memory, while the ventral region is involved in regulating emotional responses (see [2] for review). However, the presence of smooth graded transitions of connectivity within the long axis may suggest a more complex functional gradient.

Spatially-tuned "place cells" involved in navigation are found all along the dorsal to ventral axis with gradually increasing place field sizes. Compared to the wealth of knowledge available on dorsal hippocampal place fields, relatively few studies have examined the functional correlates of place fields in the intermediate and ventral hippocampus. Most lesion, electrophysiological, and pharmacological studies have found a role for dorsal but not ventral hippocampus in spatial navigation. It is clear however that the computations involved in small visually-accessible spaces may be fundamentally different from that in larger, more complex memory-based spaces (see [3] for Review). Interestingly, however, as will be reviewed below, spatial deficits associated with the rodent ventral hippocampus have been mostly observed in open environments such as the water maze. In addition, several human studies involving spatial navigation or scene recollection using fMRI showed that the posterior hippocampus (dorsal) is always activated, whereas the anterior hippocampus (ventral) is mostly activated in more complex tasks. Taken together, the rodent and human literature suggest that although the dorsal hippocampus alone is sufficient for simple spatial processing, more complex spatial processing, such as navigating in larger or cluttered environments, requires coordination along the entire hippocampal long itudinal axis.

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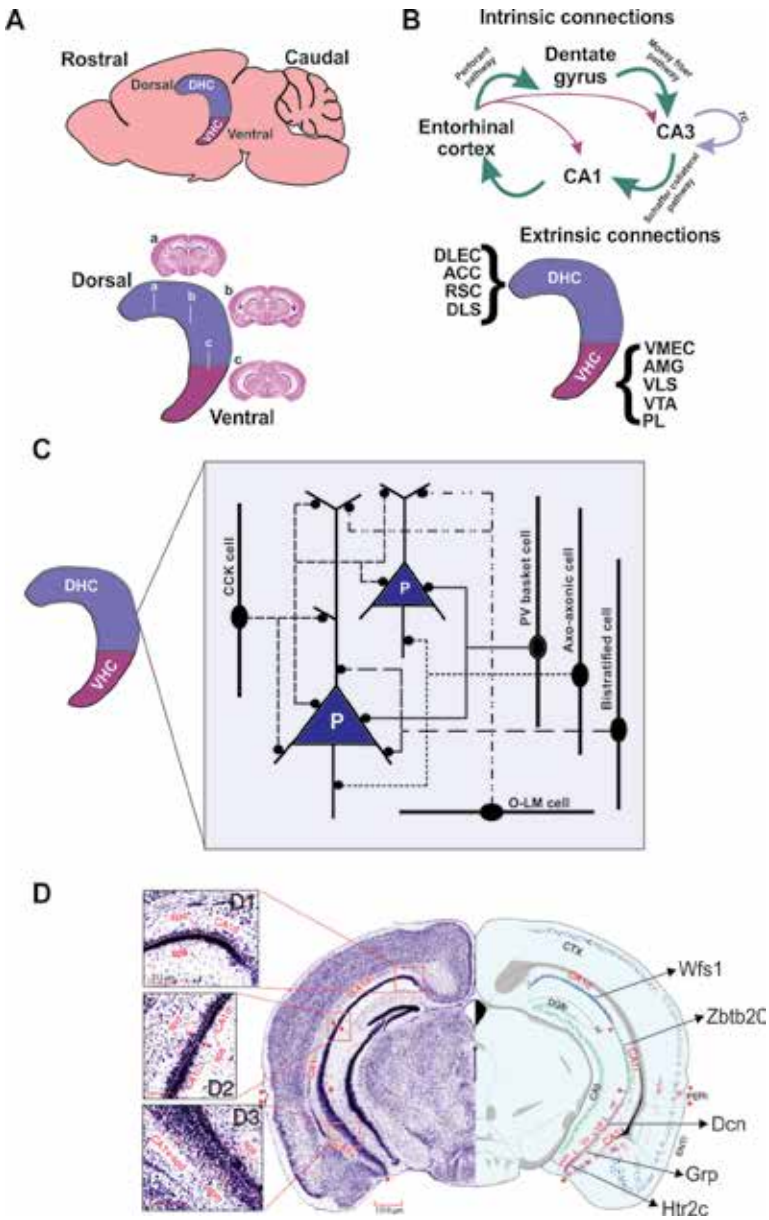


**Figure 1.** A) Schematic representation and photomicrographs of cresyl violet-stained coronal sections along the longitudinal axis of the hippocampus in rodents. The most rostral sections (e.g. a) contain the dorsal hippocampus (DHC) only. In contrast, more caudal sections contain ventral (VHC) and intermediate (not shown) subdivisions of the hippocampus. B) Simplified representation of intrinsic (upper panel) and extrinsic (lower panel) connectivity along the dorsoventral axis of the hippocampus. Abbreviations: entorhinal cortex (EC), dorsolateral band of the entorhinal cortex (DLEC), anterior cingulate cortex (ACC), retrosplenial cortex (RSP), dorsal part of the lateral septum (DLS), ventromedial band of the entorhinal cortex (VMEC), amygdala (AMG), ventral part of the lateral septum (VLS), ventral tegmental area (VTA), prelimbic cortex (PL). C) Schematic summary of the main synaptic connections between pyramidal cells (P) and several classes of interneuron, see ref. [83]. D) Distributions of five marker genes (arrows), Wfs1, Zbtb20, Dcn, Htr2c, and Grp reveal three molecular domains of the CA1 subfield (CA1d, dorsal; CA1i, intermediate; and CA1v, ventral HC), adapted from Ref. [8].

There is currently very little known about how spatial cells generate a cognitive map of large, cue rich, natural environments in which cues are functionally relevant. Such navigation is likely supported by a multi-scale memory system in the hippocampus and associated structures. In this view, finer grain dorsal place fields preferentially encode important locations such as burrows or reward sites with enhanced details, whereas global representations, as well as less important spatial areas, encode broader ventral place fields. Dynamic scaling of place fields in response to changes in environment size, and increased density of place fields at important locations or landmarks would also be important mechanisms contributing to such a multi-scale representation (See [4] for Review). Moreover, because dorsal place cells can exhibit multiple fields in larger environments their representation of the larger space may include robust redundancies that can be disambiguated by specific overlapping large ventral place fields. In this fashion, different sub-populations of place cells along the longitudinal axis may be involved in tracking and triangulating multiple goal positions in large environments containing multiple sub-regions.

Several human studies proposed a role for the dorsoventral axis in declarative memory [5]. The dorsal hippocampus is involved in recollection of specific details of an event, whereas ventral areas are involved in the global essence, schema, or "gist" of the event. This is consistent with the idea of "nested hierarchies" or memory "chapters" in which more global / general events and lifetime periods (ventral) overlay and confer meaning to more specific episodic events and details (dorsal). However, we will argue below that while specialization may result from the longitudinal organization of the hippocampus, it is not its primary purpose. Rather, we propose that complexity (as applied to memory or space) determines the extent to which specific levels of the structure are involved and how they interact.

## 2. Hippocampal long-axis anatomy and connectivity

Since its first anatomical description by Julius Caesar Arantius in 1587 [6], the hippocampus (HC) has been shown to have a rich and well-structured anatomical organization and specific connectivity pattern with distinct brain areas. Based on differences in its inputs, Cajal and Lorente de Nó suggested that the structure could be subdivided into functionally distinct subregions along its longitudinal axis [7]. Subsequent studies using modern tracing techniques have demonstrated that the connections between the HC and other brain areas were indeed topographically organized, supporting the idea of a modular organization. The dorsoventral axis of the HC (also referred to as septo-temporal or longitudinal axis in the rodent) can be subdivided into dorsal (septal), intermediate and ventral (temporal) portions based on variation in entorhinal inputs, subcortical projections, and gene expression. A number of excellent reviews describe the details of this organization [1, 2, 8–10]. Historically, significant emphasis has been placed on the notion that the dorsal hippocampus (DHC) supports spatial learning and that the ventral hippocampus (VHC) is primarily involved in emotional and motivational processes [1, 2, 5]. However, evidence for multiple levels of anatomical and functional organization along the longitudinal axis may change this dichotomous view towards an integrated, more holistic theory of the hippocampal function, as is reviewed below.

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### 2.1. Intrinsic connectivity

The HC is a dorsoventrally elongated structure (**Figure 1A**) that includes the dentate gyrus (DG), the cornu ammonis (CA) fields CA1, CA2, and CA3, or HC proper, and the subiculum (Sub). The main excitatory synaptic pathway within the HC, referred to as the trisynaptic circuit (**Figure 1B**), receives its inputs from the superficial layers of the entorhinal cortex via the perforant path to the DG. The DG projects to the CA3 region, which in turn projects to CA1. The CA1 region projects back to the deep layers of the entorhinal cortex, closing the circuit [7]. As such, the hippocampus may be seen as a computational cul-de-sac receiving, processing and returning information from and to the entorhinal cortex. Strong experimental evidence has implicated the trisynaptic circuit in spatial navigation and memory processing, but how exactly the HC encodes locations and events at the network level along the long axis is not yet fully understood. Seminal studies have shown that the entorhinal cortex provided a first level of short-range longitudinal integration through its connection with DG [11].

The CA1 projection to the subiculum follows a transverse topography. In an arrangement that minimizes axonal overlaps, CA1 pyramidal neurons located close to CA2 send projections to the most distal portion of the subiculum, whereas CA1 cells further away from CA2 project across the CA1/subicular border to more proximal portions of the subiculum [12]. Evidence for local connections within CA1 revealed that the majority of the projections from pyramidal neurons travel a relatively short distance along the dorsoventral axis, suggesting that distant dorsal and ventral CA1 levels may not have robust intrinsic associational excitatory connections [13, 14]. However, this does not exclude the possibility for significant multi-synaptic interactions between CA1 neurons along the longitudinal axis. For example, CA1 neurons that project to the subiculum send axon collaterals to the stratum oriens of longitudinally nearby CA1 cells. Importantly, CA1 neurons project longitudinally broadly to the subiculum, making this structure another site for dorsoventral integration [14]. Further studies are needed to clarify whether these fibers make contact with CA1 pyramidal neurons.

CA3 pyramidal neurons are connected with the ipsilateral CA1 field through Schaffer collaterals, and with contralateral CA1 and CA3 neurons through commissural fibers. Postsynaptic targets from CA3 to CA1 comprise both interneurons and pyramidal cells [15]. CA3 projections to CA1 significantly extend dorsoventrally, both in rats and monkeys, providing a strong opportunity for longitudinal integration [16]. Interestingly this pattern of projection seem to be ordered: CA3 neurons located close to the DG (proximal) preferentially project to dorsal portions of CA1, distal CA3 neurons tend to project to ventral CA1 [17]. CA3 neurons also project heavily to each other, forming an associational recurrent network (**Figure 1B**). Specifically, CA3 pyramidal cells located close to CA1 (mid and distal portions of CA3) project prominent fibers along the dorsoventral axis of CA3 [17, 18]. These studies suggest that the longitudinal component of the CA3 to CA1 projection and associational connections within CA3 may provide a significant means for integration of information along the dorsoventral axis of the HC. This raises the possibility that CA3 could coordinate the activity of dorsal and ventral CA1 networks that are activated during spatial navigation and memory.

Oscillatory activity patterns are thought to be involved in the transmission and integration of information. It has been reported that gamma oscillations dynamically coordinate the activity of CA3-CA1 networks in DHC during performance of a hippocampus-dependent memory task, and gamma waves are coherent along the dorsoventral axis [19]. Gamma rhythms could also coordinate the activity between HC and entorhinal cortex along the axis [20] and may serve to control the timing of information flow throughout the HC. Evidence suggests that gamma rhythm generation in the CA3-CA1 regions does not require external inputs and results from the interaction between CA3 pyramidal neurons and interneurons [21]. This conclusion holds for sharp wave ripple oscillations as well [22]. Although GABAergic interneurons represent only about 10% of the total hippocampal neuronal population, they strongly influence the activity of the pyramidal cells (**Figure 1C**). The parvalbumin (PV)-expressing basket cells, which innervate perisomatic regions, proximal dendrites, and axon initial segments of pyramidal neurons, represent about 20% of all GABA-containing interneurons [23] and are key to the generation of gamma oscillations [24]. They are unevenly distributed along the longitudinal axis [25] but form an extensive, mutually interconnected interneuron network along that axis. For instance, a PV-containing basket cell in the CA1 region labeled with biocytin can provide divergent outputs to 60 other PV-expressing basket cells [15]. In contrast, a single inhibitory cell in CA3 contacts about 1000 postsynaptic pyramidal cells within a limited zone of innervation, suggesting that it can synchronize the activity of many local pyramidal cells [26]. In addition to the PV-expressing basket cells, the HC also contains basket cells expressing vasoactive intestinal polypeptide (VIP) and/or cholecystokinin (CCK). Note that the CA1 subfield contains more than 21 types of interneurons in addition to pyramidal cells. CCK-expressing basket cells share similar features to PV-expressing basket cells, however, most CCK cells are regular-spiking and form much smaller intrahippocampal networks than PV cells [27, 28]. CCK-containing cell ensembles are highly sensitive to neuromodulators and the disruption of this system has been associated with disorders such as anxiety [29]. These studies indicate that the inhibitory networks along the dorsoventral axis of the HC can support large-scale oscillations (e.g. gamma, sharp wave ripple, theta) and long-range information gating [25, 30]. This may provide the precise temporal structure necessary for dorsoventral ensembles of pyramidal neurons to perform specific functions, such as memory formation and complex spatial navigation [31]. However, although our understanding of the physiology of interneurons has advanced substantially, the exact longitudinal connectivity within and across different classes of interneurons is not yet well understood. A comprehensive understanding of the dialog between interneuron networks and pyramidal neurons along the longitudinal axis of HC may provide important insights into its function.

### 2.2. Extrinsic connectivity

It is generally thought that the dorsal-ventral organization of the HC corresponds to that of the entorhinal cortex (reviewed in Ref. [32]). DHC is preferentially connected to the dorsolateral portion of the medial entorhinal cortex, which conveys proprioceptive information to the HC, a modality thought to be critical for spatial navigation [33, 34]. In contrast, VHC has strong connections to the ventromedial part of the medial entorhinal cortex, which is modestly modulated by spatial information [35] (**Figure 1B**). Both lateral (LEC) and medial (MEC)

entorhinal cortex feature 3 bands (medial, intermediate and lateral) which further differentiate their interactions along the longitudinal axis of HC. The medial band of the LEC receives strong inputs from VHC, while the medial band of the MEC receives projections from both DHC and VHC. The lateral band of the LEC projects to the DHC. Unlike the medial entorhinal cortex, which contains grid cells, the lateral entorhinal cortex does not display spatial tuning and is thought to provide multi-sensory contextual inputs to spatial navigation computations [36, 37]. Overall, these observations indicate that the MEC provides spatial information to the DHC, whereas the LEC provides non-spatial information to the VHC. It also shows that the band-like structure of the entorhinal cortex and its non-uniform interactions with the longitudinal axis of HC may act as a site of interaction and integration along that axis. However, it is important to emphasize that the organization of HC-entorhinal cortex connectivity follows a gradual transition along the longitudinal axis, which does not support the often dichotomous view of a dorsal-ventral functional differentiation.

Prefrontal cortex projections to the entorhinal cortex are also topographically organized [38]. Infralimbic (IL) and prelimbic (PL) areas of prefrontal cortex influence the VHC via projections to the ventromedial parts of the entorhinal cortex. In contrast, anterior cingulate and retrosplenial cortices influence the DHC through their projections to the dorsolateral parts of the entorhinal cortex. The IL and PL are involved in emotional regulation and memory [39, 40] while the retrosplenial cortex is involved in spatial navigation [41] (**Figure 1B**). Generally, studies have shown that the medial prefrontal cortex is involved in predictive and adaptive behavior [42]. Some neurons in the PL/IL area represent the motivational salience of places and have place cell-like spatial activity, while others reflect the specifics of the rat trajectory [43]. Ventral CA1 is directly connected to the PL as shown by retrograde labeling, indicating that VHC is able to directly influence neural activity in PL. Importantly, transient deactivation of the PL-VHC circuit impairs spatial learning in the water maze [44, 45]. Anterior insula, the high-order interoceptive cortex, is also connected with the VHC [46]. It is has been reported that the anterior insula is involved in context-drug association [47] indicating that VHC may also play a role in drug addiction.

The connections between the different dorsoventral levels of the hippocampus and subcortical areas have been described in detail. For instance, most of the projections from the amygdala to the hippocampal formation terminate in the VHC and in entorhinal regions that are interconnected with VHC rather than in the DHC [48]. Moreover, VHC is connected predominantly to the caudomedial part of the nucleus accumbens whereas DHC is connected to the lateral and rostral portions of this nucleus [49]. The dorsal part of the lateral septum is mainly connected to DHC whereas its ventral part is more connected to VHC [50]. The amygdala, ventral striatum, and lateral septum are involved in motivation and emotional processing [51–53]. Interestingly, it has been reported that striatal neural ensembles reactivated during post-learning sleep, which may contribute to learning and memory consolidation [54, 55].

Altogether, these studies point to a complex heterogeneous pattern of inputs and outputs that led some to propose that the longitudinal axis is composed of "modular" sections, specialized for specific functions. An alternative hypothesis is that, in fact, there are no specialized modules

along the longitudinal axis, at least not computationally. The longitudinal axis may be a site of interaction between various streams of information emanating from the processing of complex information, with longitudinal interneurons "orchestrating" the information flow.

### 2.3. Neurochemical and genetic differences

The differential connectivity seen along the longitudinal axis of the HC is also mirrored neurochemically (**Figure 1D**). For instance, the monoamine systems tend to primarily project to the VHC. Serotonin and norepinephrine innervation are greater in VHC than DHC [56–59]. Dopaminergic input of the ventral tegmental area (VTA) to the HC is stronger in VHC [60–62]. Recent evidence shows that the VTA reactivates during sleep, suggesting that it may continue to modulate the HC during memory consolidation [63]. It is well-known that dopaminergic signaling plays an important role in novelty-related modulation of hippocampal memory. For example, dopamine D1/D5 receptor activity in DHC regulates synaptic plasticity and memory consolidation [64] and dopamine released from the locus coeruleus into the DHC promotes spatial learning and memory [62, 65]. Other differences have been established. Parvocellular vasopressin neurons of the suprachiasmatic nucleus project mainly to the VHC [66]. Cholinergic input from the fornix innervates more strongly DHC [67]. VHC, *in vitro*, has a weaker GABAergic synaptic inhibition response to Schaffer collateral stimulation when compared to DHC [68]. Interneurons containing calretinin, nitric oxide synthase, and somatostatin are more common in VHC than DHC [69]. Interneurons containing calretinin play a crucial role in the generation of rhythmic hippocampal activity by controlling other interneurons terminating on different dendritic and somatic compartments of pyramidal cells [70]. Molecular studies performed in the HC have also revealed differential gene expression along its dorsoventral axis. For example, the expression of neurotrophin-3, which is associated with neurogenesis, is higher in DHC than VHC; while VIP-positive interneurons are more common in the VHC [71]. Similarly to interneurons containing calretinin, VIP-expressing interneurons can be subdivided into distinct classes depending on the selectivity of their projections to other cells [72]. Serotonin receptors are more numerous in the VHC [73], in particular serotonin receptor 3A (5-HT3AR) [74]. In contrast, histidine decarboxylase, the enzyme responsible for the synthesis of histamine, is predominant in DHC, but not in VHC [74]. Functionally, the infusion of histamine into DHC improved both reference and working memory, while histamine in VHC produced only a working memory improvement [75].

Functional differentiation along the dorsoventral axis of the HC could be related to a corresponding differentiation in the glutamatergic system's function. Studies have indeed found a lower expression of both NMDA receptor and AMPA receptor subunits in VHC compared to DHC [76]. A dorsoventral differential expression in GABAA receptor subunits has also been reported. The expression for $\alpha$1, $\beta$2, and $\gamma$2 subunits was lower, whereas $\alpha$2 and $\beta$1 subunits were higher, in the VHC compared to DHC [77]. These functional differences of the glutamatergic and GABAergic systems could explain differences in long term potentiation (LTP, a cellular correlate of learning and memory) induction observed along the septotemporal axis. In VHC, the magnitude of LTP in response to afferent stimulation is smaller

than LTP elicited in the DHC [78]. Interestingly, exposure to acute stress or increased corticosterone levels enhanced LTP in the VHC through the activation of a mineralocorticoid receptor [79]. Finally, interesting variation in the expression of HCN1 and HCN2 channel subunits across the dorsal-ventral hippocampal axis have been observed in CA1 pyramidal neurons [80]. The expression for HCN2 subunit in dendrites was lower in VHC, whereas HCN1 was higher, compared with DHC. In addition, the differential expression for HCN subunits was correlated with the functionally augmented H-conductance gradient observed in VHC neurons, which could explain why CA1 neurons in VHC are more excitable than DHC CA1 neurons [81, 82].

Overall, these findings suggest that the HC exhibits multiple micro and macro domains distributed along its longitudinal axis. The VHC, but not DHC, seems to be strongly modulated by diverse neurotransmitter systems that can influence numerous neural processes involved, for instance, in learning and memory. Moreover, the ventral CA1 neurons target cortical and subcortical brain areas that mediate a variety of functions such as cognitive control, decision making, motivation, reward processing and hormonal regulation. The VHC is thus well positioned to play a broader role than DHC in interfacing hippocampus-related functions with other computations in the brain. We postulate that this interface, and hence dorsoventral coordination, is likely to be more active when tasks are complex and heavily rely on memory. More studies on hippocampal architecture are needed to advance our understanding of how different hippocampal domains process information and can be coordinated during behavior and memory-related processes.

## 3. Functional organization of the hippocampal long-axis

All levels of the longitudinal axis of the HC include place cells exhibiting firing fields at specific locations within the environment. We will first review the properties of these cells, we will then examine how manipulations of the dorsal and ventral regions of the HC impact spatial navigation and memory in different types of environments.

### 3.1. Place cell properties and gradated field size along the longitudinal axis

Place cells, discovered by O'Keefe and Dostrovsky in 1971, are pyramidal neurons within the HC that exhibit so called "complex spikes" and become active when an animal moves through a particular place within a given environment. The regions in which a place cell fires is that cell's "firing field" or "place field." Place cells are non-topographic in that neighboring cells are as likely to have nearby place fields as distant ones [18, 19]. Although place fields will remain stable when an animal is removed and then later replaced in an environment, only about half of them will still exhibit spatial firing in a new environment, often at positions unrelated to their former locations [84]. This shift in place field locations is known as "global remapping" and also occurs if all cues are removed from a familiar environment [85]. It is important to note that spatial cues can be multimodal i.e. visual, olfactory, auditory [86], and if only some cues are removed or other subtle changes are made to the environment, place fields remain spatially stable but exhibit changes in their

overall firing rate ("rate-remapping"). Accordingly, a subpopulation of place cells can be thought to form a dynamic cognitive map of an environment [87]. Place cells are present in all parts of the trisynaptic circuit (CA1-3, and DG) and although they are traditionally thought to possess a single place field, they may exhibit multiple fields [24, 88–90]; see **Figure 2A**. For example, DG place cells have multiple fields even in small environments (~1 meter) and the firing rates of these cells are sensitive to even small changes in the environment. CA1 and CA3 cells generally have a single field in small environments, although around 20% are thought to exhibit two fields [7]. Interestingly, in a larger than usual open-field environment (180 × 140 cm), dorsal CA1 and CA3 place cells exhibited multiple fields [88], although CA3 fields were generally singular on an 18 m linear track [91]. This finding suggests that space may be coded differently in a narrow 1D walkway than in an open 2D field, an idea that is supported by the fact that many CA1 place cells fire in only one direction when an animal traverses a 1D walkway, but are omnidirectional in an open 2D space [92]. In another study, dorsal CA1, CA3, and DG cells generally had multiple fields in a large 4 × 4 m environment, but not as many as would be predicted for such a large space [93]. This may be due to the exact proximal-distal DHC locations from which these cells were recorded suggesting that this proximal-distal axis may represent an additional functional gradient within the HC related to the number of fields a place cell exhibits [21].

Grid cells in the medial entorhinal cortex also possess multiple fields, however, these fields are evenly distributed in a hexagonal lattice and the scale, relative orientation, and offset of grid firing patterns are generally conserved across environments [94]. It has often been suggested that with the extensive hippocampal to entorhinal cortex connections, there may be a role for grid cells in shaping the spatial selectivity of place fields along the dorsoventral axis [20, 95]. However, studies demonstrating that medial septum inactivation as well as lesions to the head direction system disrupt grid cell but not place cell functions, suggest that this is not entirely the case [23, 70]. Moreover, place fields mature before grid cell firing patterns are established, suggesting that place cells may be established in the absence of grid-like firing [96]. Instead, place cells and grid cells are likely complementary and interacting representations that work in concert to support the reliable coding of large-scale space [12, 32]. Grid field size and spacing increases along the dorsoventral axis of the medial entorhinal cortex in several discrete steps, in contrast to the apparently smooth gradient of increasing place field sizes found along the dorsoventral axis of CA1/CA3.

Seminal studies identified place fields in both DHC and VHC, although ventral place cells were less common and had larger and less spatially selective place fields [26, 97] (**Figure 2A**). More than 20 years later, relatively few studies have further compared dorsal and ventral place fields. A recent study revealed a gradient of increasing place field size from the dorsal through intermediate to ventral regions of the longitudinal axis in CA3 in an 18 meter long one-dimensional track [91]. In this study, place field diameters ranged quasi-linearly from smaller than 1 meter in dorsal CA3 to about 10 meters near its ventral pole. Ventral place fields were often less defined than dorsal fields in terms of shape and in-field firing rate. Whereas dorsal firing fields were generally ovoid with symmetrical bands of diminishing firing rate, ventral fields show irregular edges and multiple firing rate peaks. However, the increased size and reduced spatial selectivity of ventral place cells do not necessarily indicate

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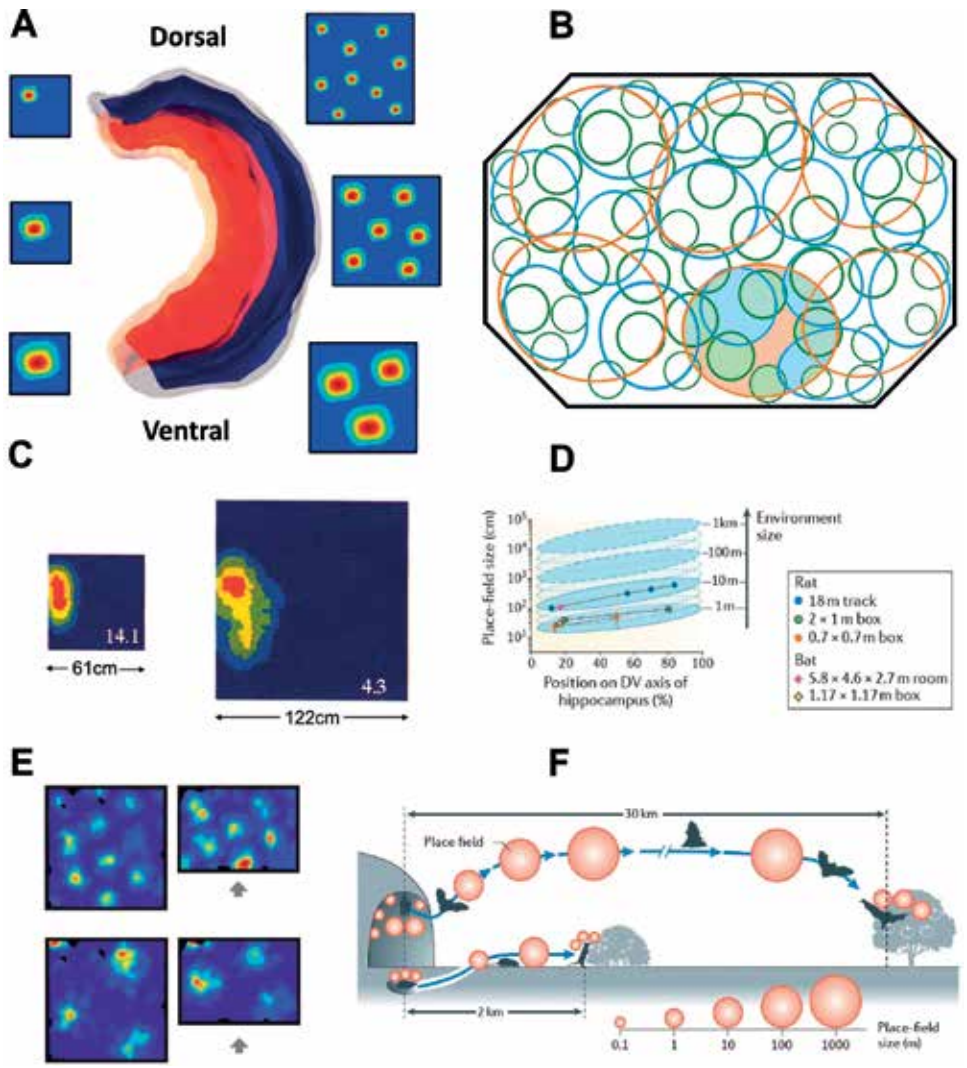


**Figure 2.** Possible mechanisms involved in a spatial representation of large-scale space. A) a 3D rendering of the hippocampal longitudinal axis. An individual place cell from the dorsal, intermediate, and ventral regions exhibits a single place field in a small environment (left), and multiple place fields in a large environment (right) see Ref. [127]. B) Large environment populated with overlapping small, medium and large place fields from the dorsal, intermediate, and ventral regions respectively. The shaded area shows a large ventral place field overlapping multiple intermediate and dorsal fields. C) Experimental data showing that an individual place field increases in size when the environment dimensions are enlarged, adapted from Ref. [128]. D) Data pooled from multiple experimental studies is extrapolated to predict that the up-scaling of place fields along the hippocampal long axis will hold over a continuum of environmental sizes. The ellipses depict a 10-fold gradient of spatial scales found along the dorsoventral hippocampal axis (x-axis) plotted against place field size (left y-axis) in different sized environments (right y-axis). The vertical-shift between the different ellipses represents the place field of the same neuron increasing with environment size, adapted from Ref. [4]. E) Experimental data showing that smaller-scale dorsolateral grid cells in the medial entorhinal cortex only show minimal rescaling associated with environmental compression (upper panel), whereas larger-scale ventromedial grid cells re-scaled completely to cover the re-sized environment (lower panel), adapted from Ref. [129]. F) Depiction of how the home range of a bat or rat may be represented at multiple spatial scales. Smaller more dorsal place fields encode a higher-resolution representation of important locations such as the home area or food sites. Larger more ventral place fields encode a lower-resolution representation of less important "travel" areas, adapted from Ref. [4].

a reduction in spatial precision. Instead, the gradient of place field size along the longitudinal hippocampal axis may signal a shift from sparse to distributed coding and may suggest a role for ventral cells in spatial context processing and generalization [13]. This may explain why aged rats and humans, who are thought to rely more on DHC than VHC, perform poorly in memory tasks that require contextual reminders [98, 99].

We propose a functional organization of the hippocampal long axis in which a continuous gradient of place field size implements a representation of space at multiple scales and levels of detail. Each environment may be mapped and landmarks triangulated by ensembles of overlapping place fields located at all levels along the axis, each with different remapping properties, size, and number of irregularly spaced subfields. Grid cell and border cell inputs would provide a metric framework on which these ensembles would depend, helping to anchor place fields and reduce drift in open areas of the environment [28]. These ensembles may be strengthened and consolidated during sleep. Individual place cells would be involved in multiple ensembles, and it is likely that multiple ensembles would be active simultaneously, adding redundancy as well as potentially coding different aspects of an environment. Concurrently, larger ventral place fields would overlap with and bind together smaller dorsal fields and may play a particularly important role in navigating through larger, more complex environments.

### 3.2. Dorsal and ventral hippocampal functions

The traditional view has been that lesions or inactivation of the DHC but not VHC result in spatial learning and memory deficits, whereas targeted disruption of the VHC but not DHC attenuates fear responses in anxiogenic paradigms [9, 10, 17, 31]. However, most laboratory-scale environments used for testing spatial learning and memory in rodents may lack the size and complexity to properly engage the VHC. For example, lesions to the DHC but not the VHC consistently impaired spatial memory performance in radial-arm and T-maze tasks which consist predominantly of narrow bidirectional walkways [17, 64, 100, 101]. Interestingly, VHC inactivation produced a spatial performance deficit in a circular open field (1.8 m diameter) in which the rat had to learn sequences of reward locations, but only when small or large obstacles were introduced to the maze [102]. The obstacles are likely to have increased the complexity of the environment requiring greater involvement of the hippocampal circuitry, especially the ventral levels. Effects of ventral lesions have also been reported, albeit inconsistently, in the water maze, an open circular environment of about 1.5 to 2 meters in diameter. Although the water maze is relatively large, it still could be in sufficient to require the engagement of ventral place fields most of which may be about 5.5 meters in diameter [91]. Also, because swimming is generally stressful to rodents, the spatial navigation involvement of the VHC in this task cannot easily be dissociated from its involvement in fear. Moreover, the water maze constitutes a “vista space” in which the entire environment, spatial cues, and target destination can be perceived at all times. The VHC may be more involved in spatial navigation in more complex “environmental spaces” which contain multiple regions that cannot be visually apprehended without considerable movements and require more planning, decision points, and integration of information over time (see [3] for review). Clearly, more studies in positively rewarded large-scale and complex environments are necessary to further understand the respective roles of the dorsal and ventral hippocampal poles.

In earlier work, DHC lesions were shown to produce a spatial deficit comparable to total hippocampal lesions in both the working memory and reference memory versions of the water maze, whereas VHC lesions had no effect. In addition, retrieval of a spatial memory could be achieved with about 70% of the DHC in normal rats, whereas 20% of the dorsal region was sufficient for acquisition [29, 31, 103, 104]. In another study, lesions of DHC but not VHC mildly impaired both working memory and reference memory in the water maze, compared to full HC lesions, suggesting that spatial learning and memory in this task may engage both the dorsal and ventral regions [15, 17]. Further evidence for the involvement of the entire axis in navigation comes from a study in which reversible inactivation of either DHC or VHC produced comparable retrieval deficits when delivered just before a probe trial, however only dorsal inactivation had an effect when delivered before training [105]. These results suggest that although spatial memory can be acquired by dorsal circuits, it can be less efficiently acquired with ventral ones, and retrieval of such a memory engages both DHC and VHC if it was acquired with a fully functional HC. Two more studies found similarly that VHC lesions produced spatial deficits in the water maze, although not as severe as those associated with dorsal lesions [106, 107]. Finally, a recent study found that large DHC and VHC lesions which each included at least part of the intermediate hippocampus resulted in a double dissociation in the water maze [108]. When the lesions were made before any experience, rats with ventral lesions could learn the position of a platform both in the original pool, and in a second novel pool, whereas rats with dorsal lesions could not. Intriguingly, when the lesions were made after training in the original pool, only rats with dorsal lesions could learn the platform position in the new environment. This suggests that the VHC may have a specific role in spatial learning in a novel environment. Together these studies suggest that the VHC may be involved in storing, retrieving, and comparing memories of varying sized and shaped environments.

These finding in rats may be closely related to findings in humans that suggest that the anterior hippocampus, the human analogue of VHC, is important for spatial context differentiation [109]. Indeed, human navigation studies often involve larger and more complex environments than the mazes traditionally used in rodent experiments. Although responses to spatial manipulations usually involve the posterior hippocampus (PHC), the human analogue to the dorsal hippocampus, the anterior hippocampus (AHC) is often also involved. For example, accurate wayfinding activated PHC in subjects navigating a route through a virtual town, but subjects that navigated best also activated AHC [110]. Another study involved learning to navigate through three virtual mazes consisting of interconnected corridors of increasing sizes followed by recalling which images of landmarks belonged to which of the three mazes [111]. While the PHC was activated during the traversal of all three mazes, the AHC was only involved when navigating through the largest and most intricate maze. A number of seminal human fMRI studies have measured hippocampal activation in licensed London taxi drivers, who are required to train over 4 years to learn the complex layout of London's streets [112–115]. Interestingly, these drivers had greater gray matter volume in PHC and less in AHC compared to matched controls [112, 113]. Taxi drivers were significantly more knowledgeable about London landmarks and their spatial relationships than controls. However, they were significantly worse at forming and retaining new associations involving visuo-spatial information, suggesting that these may involve the AHC [113, 114]. A follow-up study demonstrated that

the taxi driver's ability to form associations between visual stimuli was intact, the impairment being specific to acquiring new information containing a spatial component [115]. Another study has shown that both imagination and 1-week recall of scenes engage AHC, suggesting its role in scene construction [116]. In contrast, recall of scenes after a 30-minute delay elicited significantly less activation of the AHC and was more associated with PHC activation. Recall of longer-term spatial memories may require activation of more "global" levels of autobiographical memory (see Section 5), which may explain the involvement of the AHC.

There is strong evidence that lesioning VHC in rodents attenuates fear response in a number of anxiogenic paradigms including light/dark exploration, hyponeophagia, open field exploration, and the elevated plus maze [10, 117, 118]. It is therefore possible that VHC lesions could attenuate anxiety in the water maze resulting in improved performance which may compensate for any spatial impairments resulting from the lesions. In fear conditioning experiments, dorsal lesions impair the retention of contextual fear but not cued fear [119, 120]. Ventral lesions attenuate conditioned freezing in response to cued fear as well as contextual fear, although a more consistent response to contextual fear is observed after dorsal lesions [120–123]. Subsets of neurons in CA1 of the VHC fire differently in places associated with elevated anxiety or during goal approach [124]. Ventral neurons that show anxiety-related firing typically project to the prefrontal cortex, whereas neurons that show goal-directed firing usually target the nucleus accumbens. Ventral hippocampal neurons that are most active during behavioral tasks and sharp wave ripples triple-project to prefrontal cortex, amygdala, and nucleus accumbens. This last finding suggests that VHC cells may be conjunctive, with the potential to encode both spatial and affective properties of an environment.

In sum, both human and rodent studies suggest that spatial processing involves the activation of the DHC, and that the VHC becomes involved when more spatial processing is required, for example in larger and more complex spaces or when forming new spatial associations. Moreover, the widespread connectivity of the VHC to regions such as the medial prefrontal cortex may be critical for processes involved in navigating large-scale space such as route planning and wayfinding. The ability of ventral place cells to encode both spatial and affective components may suggest its role in sensing and avoiding danger. It is therefore important that more studies examine the properties and function of these larger ventral place fields while simultaneously recording dorsal place fields during spatial navigation through large and complex environments (see [125, 126] for example environments). Similarly, the effects of DHC and VHC lesions or inactivation need to be examined in the context of much larger and more complex spatial navigation tasks. In the next section we will argue that a multi-scale memory system incorporating the entire longitudinal axis of the hippocampus is critical for supporting spatial representations in such large-scale complex environments.

## 4. Navigating in large-scale complex space

Wild animals often traverse large and sometimes dynamic expanses of complex cue-rich space. We next examine what is currently known about navigating in such large natural environments. Mechanisms such as the dynamic scaling of place and grid fields in response to environment

size and level of details may play a role in forming efficient large-scale representations of space. An environmental-scale representation may consist of a collection of smaller detailed spatial maps linked together through a coarser more global representation. The ability of grid cells to form a contiguous pattern between environments may be involved in forming this global map. Additionally, ventral place fields or specialized subsets of goal-sensitive neurons may facilitate the transition between sub-sections of the larger environment. The ability of place cells to exhibit multiple place fields in larger environments may be a critical mechanism for forming a multi-scale representation of complex large space. Important locations such as burrows or reward sites may be preferentially encoded with finer grained dorsal place fields, whereas large ventral fields with their connectivity to brain areas involved in fight or flight may be preferred in more exposed travel areas. However, the overlapping of dorsal to ventral representations in both small and large environments may facilitate different kinds of spatial processing. The multiple fields exhibited by hippocampal place cells could be flexibly recombined to form a complex spatial representation similar to that of a "megamap" which could simultaneously encode non-spatial information [130]. We propose that multiple overlapping megamaps consisting of different place-field scales along the hippocampal long axis simultaneously encode an animal's environment.

### 4.1. Differences between laboratory-style and natural environments

Most of what is known about spatially-tuned cells in the brain has been learned while recording from rodents moving through small, highly controlled, and often highly symmetrical environments. Most unit-recordings are made while an animal explores or forages in small otherwise empty boxes or cylinders typically between 40 cm and 1.5 m across [13, 97, 131], or on linear tracks [90, 91]. As discussed in the previous sections, most hippocampal lesion or inactivation studies also take place on narrow walkways or in relatively small open environments [17, 108]. The advantage of such environments is that they allow the experimenter to study sub-components of behavior by controlling the information that is available to solve the task. However, these environments, most of which are vista-space paradigms where the entire environment, cues, and target destination can be perceived at all times, limit our understanding of more complex large-scale navigation. It has been established that place cells, border cells, grid cells and head direction cells are all active in these types of environment and together facilitate the creation and maintenance of cognitive maps. However, how these neuronal mechanisms operate in larger spaces, such as rodents natural habitats is unknown. For example, Norway rats typically have a home range of around 250 $m^2$ [132] but have been reported to roam up to 2 km in a night [133]. Environmental spaces of that scale will contain large numbers of vista areas that cannot be simultaneously perceived. Navigating between different areas would require a number of processes that are not recruited in laboratory settings such as planning and maintaining routes out of sensory range, being able to take unplanned shortcuts, and wayfinding new routes around obstacles or other changes in the environment [3]. The vastly increased spatial scale involved in this type of navigation likely means that the VHC would be much more involved. Larger ventral place fields may therefore have a role both in covering spaces with its large place fields as well as overlapping and giving context to more-dorsal smaller fields (See **Figure 2B**).

In addition to an increase in spatial scale, the fundamental structure of natural space is vastly different from that found within the mazes and environments typically used in the laboratory. Whereas experimental settings generally contain a relatively small number of highly controlled distal and/or local visual cues, natural environments are comparatively cue-rich with an abundance of visual, auditory, and olfactory cues as well as irregular terrain. These differences could have profound effects on the way hippocampal place cells function. For example, dorsal place fields were shown to be significantly smaller when rats ran along a track that contained a rich set of somatosensory and olfactory cues compared to the same cells recorded on a featureless running track [134]. Consequently, place cells may function quite differently in a natural setting, in fact, dorsal place cells recorded in the laboratory may be larger than they would be in natural settings because of a lack of fine details to encode. In addition, the environments used in laboratories are almost always symmetrical whereas perfect symmetry is less common in natural environments. Grid cells fire in regular hexagonal bands in boxes and cylinders but non-hexagonal firing patterns have been shown in irregularly shaped environments [135]. Natural environments often have very asymmetrical and complex boundaries and it is unclear how grid and border cells would function in these conditions. Furthermore, HC cells may also respond to environmental changes. For examples, dorsal place fields have been shown to enlarge as well as drift when recorded in darkness [136]. Animals likely build up detailed cognitive maps of their habitat over the course of their lifetime and can undoubtedly use other navigation strategies when traversing less familiar regions (see [4, 137]).

Electrophysiology in freely moving rodents has historically been limited to small laboratory-style environments because data transmission has required a ceiling mounted tether. One technical innovation that may open the door to larger-scale recordings is the emergence of wireless electrophysiological recording systems. Although the current generation of wireless devices has some limitations, such as battery life, overheating, and the combined weight of the drive and implant which often is carried on the animal's head, these devices will undoubtedly help elucidate the role of dorsal and ventral place fields in navigating larger-scale and complex environments. An interesting question is whether laboratory rodents born and raised in small home-cages have the full capability to encode and navigate in large environments. Wild-born animals may have the ability to more rapidly and comprehensively form large-scale spatial representations and may be better candidates for these types of studies [4]. It is currently unknown how animals generate a cognitive map of large complex environments, although some pertinent work will be reviewed next.

### 4.2. Potential mechanisms involved in a large-scale spatial representation

The dynamic nature of individual place cells is likely to play a role in creating a large-scale spatial representation. A number of studies have shown that place field size scales with environment size. Place fields recorded in a 60 $cm^2$ environment were 60% larger in a 120 $cm^2$ environment [128] (**Figure 2C**). In another study, place field size increased by 30% on average when rats were transferred from a 68 cm diameter cylinder to a 150 × 140 $cm^2$ square box. This also resulted in the place cells exhibiting multiple fields [131]. It has been suggested that this

re-scaling of place fields would hold over a continuum of environmental sizes, and that all neurons along the hippocampal longitudinal axis may scale their place-field sizes simultaneously as environmental size changes [4] (**Figure 2D**). Place cells in DHC also respond to environmental parameters such as the amount of local detail and the position of their field relative to environmental features [134, 136]. Place field size changes have also been reported when objects or cues are added to, removed from, or shifted within an environment. For example, place cells become larger and less stable when visual and odor cues are removed from a familiar environment [138]. Adding or removing objects from the environment led to partial remapping of place fields, and the size of place fields decreased when objects were present [139]. Finally, place fields tended to be smaller at locations close to the walls or local cues during exploration of an open-field [140]. This flexibility in matching place field size to environment size and to the density of local spatial details may be even more pronounced in larger, more cue-rich environments and may constitute an important mechanism for representing space at that scale. Moreover, although these studies exclusively looked at dorsal place cells, it is likely that ventral place fields also exhibit similar properties especially considering their connectivity to grid cells in the ventromedial entorhinal cortex which have also been shown to exhibit environmental compression.

The dorsal to ventral hippocampal long axis has topographical connections originating from the dorsolateral to ventromedial extent of the medial entorhinal cortex [141]. Grid cells exhibit hexagonal lattices of firing fields which, unlike place cells, occur in several modules of discretized field size and spacing [129]. Smaller scale grid cells are found more dorsolaterally in the medial entorhinal cortex and share connections with the DHC, whereas larger scale grid cells, shown to be up to 10 ten times larger, are found more ventromedially and share connections with the VHC [142]. Individual grid cells exhibit similarly sized fields when recorded in different environments [143]. In contrast, when an environment increases in size in the presence of an animal, grid spacing was shown to increase transiently, perhaps as a consequence of grid cells being anchored to environmental boundaries, but then reverted to the original grid spacing shortly thereafter [144, 145]. In addition, a study that included recordings of grid cells along the dorsolateral to ventromedial extent of the medial entorhinal cortex showed a functional dissociation with environmental compression [129]. Smaller-scale grid cells showed minimal rescaling of about 20% when the environment was reduced in size. In contrast, the larger-scale grid cells rescaled completely so that the same fields exhibited in the original environment were maintained, albeit with reduced grid-field distances in the compressed direction (See **Figure 2E**). This result suggests that these larger-scale grid cells may have a role in facilitating the formation of new and unique representations for novel environments. Another possibility is that these cells, in concert with the larger ventral place fields, may preferentially encode larger and more complex environments. VHC place fields may also share this property so that rather than re-scaling to 30–60% of the extension of an environment as reported in DHC cells [128, 131] they may rescale completely with changes in the environment size. The ability to dynamically change grid field size could be particularly useful when traversing natural environments which often contain regions of different sizes. Several models have suggested that grid cells could play a central role in a large-scale spatial representation. Theoretically, two grid cells with different scales could together represent a

coding range that is much larger than the individual grid wavelengths producing a highly precise estimate of position [146, 147]. This combinatorial grid code hypothesis proposes that the function of grid cells is to efficiently encode very large environments. However, although possible, it seems unlikely that the medial entorhinal cortex would circumvent the hippocampus in situations involving large-scale navigation given that fMRI studies consistently demonstrate robust hippocampal activation in large-scale spatial navigation paradigms [110, 111, 148]. Therefore it is more likely that place and grid cells have complementary roles in supporting the reliable encoding of large-scale space [12]. Environments that contain multiple interconnected compartments can be used to compare local and global representations. Dorsolateral grid cells initially represented two identical and connected maze compartments with identical but disjointed sets of fields. However, with repeated experience in the maze the grid cell representation spanned both compartments, and thus provided a global representation of the apparatus [149]. In contrast, dorsal place fields continued to exhibit fragmentation across multiple interconnected identical compartments arranged in parallel even when tested for a comparatively larger number of sessions [150]. A different subset of place cells may encode each locality within a larger environmental space, whereas grid fields may be contiguous between localities representing both the environment and a metric of the movement of the animal through space.

When thought about in these terms, spatial representations of very large environments may be a collection of DHC-bound detailed spatial maps linked together by coarser more global representations involving the VHC. There is indeed some evidence for compartmentalization of larger spaces from studies with humans. For example, participants in a virtual reality navigation study performed better at pointing to previously learned targets if their body or pointing targets were aligned with the local reference frame [151]. Interestingly, performance was further increased when the participant's body or current corridor was parallel or orthogonal to a global reference frame instead of oblique. These findings suggest an influence of both local and global frames of reference on recall of a multi-scale spatial environment.

*Graph theory* has provided an interesting set of tools to formalize the integration of interconnected representations of space [152, 153]. In graph-like structures, local positional information is represented by nodes that are interconnected with edges. The *Network of Reference Frames* theory [153] expands this concept and proposes that graphs are superseded by reference frames that each represents a vista space of variable size with an independent coordinate system and orientation. Reference frames are interconnected by edges that describe the perspective shift required to move between them. These theories very effectively model tasks such as traversing rooms and corridors in a building, or streets in a city. Larger open spaces such as a field or park would have to be represented by multiple overlapping graphs or reference frames. While interesting, the neural representation of graph-like structures is still unclear. As previously mentioned, grid cells may form a global representation responsible for connecting smaller detailed spatial maps. Grid cell's connection and conjunction with head direction and border cells may enable them to make the translation and rotations necessary for connecting nodes. Another possibility is that the VHC forms a coarser representation that overlaps with different independent local DHC representations. Alternatively, specialized route and goal- distance and

direction cells may have a role in connecting independent representations. For example, neurons in the parietal cortex fire in relation to route traversals in rats [154]. Route- and goal-sensitive neurons have also been demonstrated in the hippocampus of both rats and bats. In rats traversing a maze in which two partially overlapping routes led to the same goal location, 95.8% of dorsal place cells that fired were active on only one of the routes [155]. Goal-directed firing has also been shown in a subset of ventral CA1 neurons [124]. A subpopulation of CA1 neurons exhibited angular tuning to goal direction and/or goal distance in bats flying in complex trajectories towards a spatial goal [156]. Goal direction cells also fired towards a familiar but hidden goal, and this tuning did not change if the bat flew different routes to the goal. It would be interesting to record CA1 neurons along the extent of the hippocampal long axis while rats explored a large open space containing multiple "cities" each consisting of a different arrangement of interconnected local compartments. This paradigm would allow for a comparison of global and local representations, and rewards sites located within the cities would enable the examination of the route- and goal- tuning of neurons. Such a multi-scale task may help assess whether the mechanisms discussed in this section are involved in a large-scale spatial representations.

### 4.3. A multi-scale memory system for representing complex large-scale space

A multi-scale memory system utilizing the entire hippocampal longitudinal axis may use finer grained dorsal place fields to encode important locations such as burrows or reward sites with enhanced spatial details, whereas ventral place cells may be used to represent less important travel areas and to form a coarser, overlapping global representation [4] (**Figure 2E**). Several studies have reported increased density of dorsal place cells at salient reward-related locations within an environment [157–159]. For example, some DHC cells tend to cluster around the location of the hidden platform in the water maze [159] and respond to a shock-associated tone only when the animal is in that cell's place field [160]. Additionally, a subset of VHC CA1 neurons showed increased firing rate with increased anxiety in the open arms of an elevated plus maze [124]. These results in the rodent suggest that multiple overlapping dorsal and ventral representations would enable both fine- and coarse-grained representations to be simultaneously utilized in the same space, together with saliency and emotional information. The fine/coarse grain encoding of space is supported in humans by a fMRI study in which participants learned the positions of objects in relation to room geometry in a virtual environment [148]. The subjects were then required to position the objects onto a 2D overview of the environment and were given a positional granularity assessment of fine-, medium-, or coarse–grained, or failed, dependent on distance between their placement and the true positional pattern of the objects. The highest activation in the PHC (analogous to DHC in rats) was for fine-grained representations, and in the intermediate hippocampus for medium-grained representations. Although activation of the AHC (analogous to VHC in rats) did not significantly differ across fine-, medium-, or coarse-grained representations, it was significantly correlated with the number of coarse environmental representations encoded. This study suggests that dorsal, intermediate, and ventral representations occur simultaneously fulfilling the particular spatial processing needs as required.

A number of studies have demonstrated that hippocampal place cells exhibit multiple irregularly–spaced place fields in larger environments (see 3.1). One possibility is that at least some of these irregular fields may be dynamic, potentially changing their position, size, or firing rate in response to familiarization or changes to the environment. In addition, there may be some inherent interaction between the multiple fields exhibited by individual place cells and the phenomenon of "preplay" of future trajectories of the animal over short distances [161, 162]. Many attractor models have provided useful insights into how place cells represent an environment [163–165] but these models have been largely based on the assumption of a single spatial field per place cell. However, a recent model accounts for place cells exhibiting multiple fields and introduced the concept of a "megamap," in which place cells are flexibly recombined to represent a large space [130]. This flexibility gives the megamap a large representational capacity while enabling the hippocampus to represent multiple learned memories. Importantly, non-spatial information can be simultaneously encoded at no additional cost. Another feature of the megamap is that an underlying network of place cells is able to robustly encode any location in a large environment given a weak or incomplete input signal. We propose that any spatial environment is a priori represented by multiple megamaps consisting of different ensembles of place cells along the hippocampal longitudinal axis. These maps would encode different types of spatial and non-spatial information, and would be selectively activated by the demands of each task. For each map, ventral place fields would overlap with many dorsal place fields providing specific contextual and affective information to the map as well as facilitating a coarser representation of space when required (see **Figure 2B**). Dorsal place fields would cluster around task specific objects and cues increasing spatial resolution in these regions. Together, the dorsal-to-ventral components of a megamap would allow for its use in complex and large environments.

Although little is known about how the extended hippocampal system supports spatial representations of large-scale and complex space, some of the mechanisms discussed in this section, such as multiple place fields per neuron, are likely involved. It remains to be determined whether the multiple fields exhibited by place cells differ from each other in some quantitative manner such as in firing rate, size, or modulation by theta or sharp wave ripple oscillations. Do ventral place cells provide a secondary level of spatial processing when more complex spatial navigation or recollection are required, or are they specifically active when a coarse-grained representation is needed? Are grid cells part of a more global cognitive map which connects separate spatial reference frames? Are dorsal place fields more functionally important when navigating corridors and small rooms than during exploration of a large open space? Recording dorsoventral hippocampal place cells as well as grid cells while an animal navigates between discretized local spatial representations, such as small single-entrance mazes, nested within a larger more open environment may answer some of these questions. Studies that simultaneously record from the dorsal and ventral hippocampus during different types of experiences may also be critical. It may be that, to truly understand hippocampal function, some new recording probes are needed, capable of simultaneously recording from multiple points along its longitudinal axis. Moreover, although some studies have produced computational models of spatial representation and memory consolidation that include both DHC and VHC [32, 37, 166, 167], more work in this area is also required.

Finally, the gradated spatial representations along the dorsoventral axis of the hippocampus may go beyond purely spatial processes and help explain the mechanisms of mnemonic hierarchies in declarative memory.

## 5. Mnemonic hierarchies in declarative memory

The human hippocampus is critical for the encoding and recall of episodic memories. Humans with hippocampal damage exhibit anterograde and temporally graded retrograde amnesias. There is evidence from human studies that episodic memory is encoded in complex mnemonic hierarchies in which lower-order categorical and specific events are nested within multiple layers of higher-order memories of extended lifetime periods (See [168]). The AHC has been associated with recollection of more global, "gist-like," higher order episodic memory, whereas the PHC has been associated with retrieving more categorical and specific episodes. Augmenting this view, we suggest that global and specific memories are not encoded within one particular segment of the axis but instead are distributed along the entire HC, as will be reviewed below.

### 5.1. Functional segregation of the hippocampal long axis in humans

In addition to the spatial studies already discussed in this chapter [110, 111, 148, 151], human fMRI studies have also shown other types of posterior and anterior hippocampal dissociations related to novelty [169, 170], encoding and retrieval [171], and vestibular and visual processing (see [5] for a review). Of specific relevance are findings that show PHC activation associated with recall of detailed or localized information, and AHC activation associated with more schematic, or "gist" recollection. One measure of gist memory consists in abstracting over large sets of items to create category-consistent false alarms which have been associated with activation of the AHC [172]. In contrast, recollection of detailed contextual information has been associated with PHC activation [173]. Additional indirect evidence comes from studies in participants with Post Traumatic Stress Syndrome who exhibit volume loss in the PHC and an increased reliance on AHC-dependent gist memory for more detailed recollection [174, 175].

There is also evidence that the recollection of detailed individual events is associated with PHC activation, whereas more comprehensive "global" multi-event narratives require AHC activation. In one study, participants watched realistic, life-like videos showing individual events that could be integrated into narratives in order to experimentally simulate processes involved in episodic memory formation [176]. These narratives were gradually built up by presenting seemingly unrelated events which were linked by subsequent events enabling both direct and inferred associations. Recollection of individual event-pairs was associated with PHC activation. When multiple event-pair associations were recalled, the intermediate hippocampus was involved if the events were not connected via inference, whereas recall of the same events pairs that included all the possible associations preferentially activated the AHC. Intriguingly, these findings suggest that the multi-event narrative was simultaneously

represented at multiple "narrative scales" along the hippocampal long axis. Other studies have also reported intermediate and AHC activation during inference or as a result of making new connections between associations [177, 178]. The simultaneous hierarchical encoding of memory along the hippocampal long axis would provide both the ability to recall separate events as well as to integrate multiple experiences into a more global memory representation. The AHC would maintain this more global representation and would therefore be involved in integrating new inferences or connections between events. Representing events at multiple scales may provide an effective way for a context or schema to improve recall and protect against loss of event details [176]. Similarly, a spatial representation encoded at multiple scales along the hippocampal long axis may improve navigation performance and help to prevent the loss of local spatial details.

### 5.2. Multi-scale models of declarative memory

Some have proposed a model of hippocampal long axis function in which the PHC and AHC have separate specializations [5]. In this view, the AHC and PHC constantly index information from different regions with which they are connected, each interaction changing the dynamics of the circuit. The relatively low volume of the DG in AHC would bias it towards pattern completion, whereas its higher relative volume in PHC would promote pattern separation. These biases, as well as the influence of graded entorhinal cortex connectivity would produce sharp PHC representations (high match specificity) and broader AHC representations (low match specificity). In this model, the AHC might retain links between principals, actions and setting of an event, whereas the PHC might retain the exact spatial and temporal context of the event even if this information is tangential to the episode's theme. This division of hippocampal function is compatible with the concept of "nested hierarchies" in autobiographical memory in which more abstract and longer lasting life periods (anterior) nest with less abstract and shorter autobiographical episodes (posterior).

It is likely that the relationships between autobiographical periods and specific episodes are characterized by many associations so that a given memory could be part of multiple autobiographic periods which themselves could be contained in multiple "Life Chapters" [168, 179]. Life chapters are major components in this hierarchical autobiographical knowledge structure that reflect extended time periods, typically spanning months to years, such as an individual's childhood or career [168, 179, 180]. As with nested hierarchies, one could predict that the AHC would have a functional role in the recollection of broader-scaled life chapters and the PHC would be more involved in recalling finer-grained episodes. However, it has been shown that the AHC is activated during the search and retrieval of specific episodic memories and that the PHC is associated with subsequent elaboration and reliving of the memory [181]. Although the memories accessed in this study were prompted by simple thematic cues such as "kiss" or "party", it is thought that the first level of entry of searching autobiographical knowledge is by searching more general and abstract autobiographical knowledge of extended life events. However, because the recollection of a memory was shown to involve both the AHC and PHC, the different scales of memory may not be restricted to specific sections of the longitudinal axis. This idea is further supported by the

fact that recollection of two-week-old as well as 10-year-old memories activated both the PHC and AHC [182].

To summarize, autobiographical memory in humans, similar to spatial representation in rodents, may consist of simultaneous overlapping fine- to coarse-grained representations along the hippocampal longitudinal axis. These graded representations may relate to a multi-layer memory hierarchy in which lower-order categorical and specific memory episodes are nested within multiple higher-order life chapters. There is evidence that the PHC and AHC may be more active when retrieving and encoding lower-order and higher-order components of this memory hierarchy, respectively. However, additional evidence of whole-hippocampal activation during recall in general suggests that autobiographical memory may be distributed along the entire hippocampus.

## 6. Conclusion/summary

The hippocampal long axis consists of multiple interacting levels working together to generate complementary representations along a functional fine to coarse gradient. In this integrated model of hippocampal function, the extrinsic connectivity along the longitudinal axis enables the hippocampus to incorporate input from a wide range of brain regions. It is likely that the intrinsic interactions between the longitudinal regions of the hippocampus occur via selective excitatory connections, such as in CA3, and via interneuronal connections, especially during oscillatory episodes and it is important that more work be done to elucidate this inter-region connectivity within the long axis. Although there is compelling evidence that the VHC becomes more active during spatial navigation in larger and more complex environments, more work also needs to be done to record simultaneously at different longitudinal levels in tasks in which complexity and environmental size are systematically varied. This type of realistic navigation may rely on a number of additional mechanisms such as re-scaling of place and grid field representations with environment size, increased number of active place fields per neuron, the clustering of finer-scale place cells in important regions of the environment, and the existence of overlapping fine-to-coarse scale representations in all environments. Multi-scale models of autobiographical memory in humans describe a similar hierarchy of overlapping fine-to-coarse representations along the hippocampal longitudinal axis. Although the PHC and AHC may perhaps specialize in encoding and retrieving information from the lower- and higher-order divisions of these memory hierarchies respectively, there is evidence that encoding and recollection involves the entire extent of the hippocampus.

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Chapter 5

# The Importance of Distinguishing Allocentric and Egocentric Search Strategies in Rodent Hippocampal-Dependent Spatial Memory Paradigms: Getting More Out of Your Data

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Additional information is available at the end of the chapter

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**Abstract**

While the brain works as a dynamic network, with no brain region solely responsible for any particular function, it is generally accepted that the hippocampus plays a major role in memory. Spatial memory operates through the hippocampus with communication with the prefrontal and parietal cortices. This chapter will focus on two separate reference frames involved in spatial memory, egocentric and allocentric, and outline the differences of these reference frames and associated search strategies with relevance to behavioural neuroscience. The importance of dissociating these search strategies is put forward, and steps researchers can take to do so are suggested. Neurophysiological and clinical differences between these spatial reference frames are outlined to further support the view that distinguishing them would be beneficial.

**Keywords:** allocentric, egocentric, hippocampus, maze, navigation, networks, spatial memory

## 1. Introduction

Spatial memory is the cognitive process of noticing, encoding, and retrieving landmarks in the surrounding environment, to allow an organism to navigate and exist in the world. It is important for survival, by enabling searching and finding safety and food and being able to return to found places without issue. It is the domain of the hippocampus and medial temporal lobe,

with links to the retrosplenial cortex and parietal cortex [1]. Seminal studies in humans and animals have demonstrated the important role that the hippocampus plays in navigating the world around us [2, 3]. In humans, damage to the temporal lobe causes disturbances to spatial navigation [4], and similarly, humans employed in roles that require fantastic spatial navigation skills have enlargement of the hippocampus and its connections [5, 6]. In parallel, through multiple manipulations such as lesion, electrophysiological and optogenetic studies, the hippocampus has been shown to be equally important to animal spatial memory. Disruptions to hippocampal tissue or silencing of neurons in the hippocampus leads to spatial memory deficits [7, 8]. This parallel role of the hippocampus in both humans and animals allows research to be performed on these animals with the insights gained able to be extrapolated to humans.

## 2. Spatial memory in behavioural testing

Behaviourally characterising an animal model of disease often involves a battery of tests that investigate the animal's motivation, locomotor activity, startle reflex, anxiety, fear response, social behaviour, learning, memory and other emotional and cognitive traits. Dysfunctions in these behaviours are used to infer structural and functional changes in the brain, and the recovery of performance on these tests is used to evaluate the effectiveness of potential therapeutics. These inferences are only accurate with the use of appropriate tests with high specificity both for the behaviour in question and in terms of the specific brain regions recruited during test performance. Therefore, behavioural tests that are specific to one domain or behavioural tests that can correctly dissociate multiple domains should be used. Rodent spatial memory tests, often mazes, are commonly used in preclinical drug development and fundamental science experiments. The use of these behavioural tests dates back over a century, and a plethora of maze designs have been developed since then to probe different aspects of learning and memory [9]. Complex networks of brain regions and neuron populations are required to orientate and navigate using information such as environmental, vestibular and proprioceptive cues [10]. The current general consensus is that spatial memory encompasses two distinct but related reference frames, egocentric and allocentric. Here, we outline the differences between these reference frames and their relevance in behavioural neuroscience and discuss the merits of placing a stronger emphasis on distinguishing egocentric and allocentric search strategies in spatial memory tests.

## 3. What are allocentric and egocentric search strategies?

The egocentric reference frame is also referred to as a fixed, self-centred or first-person perspective. Egocentric navigation is based on direction (left-right) responses and actions independent of environmental cues. Directional decisions are made at single or sequential choice points; however, these locations are not used as cues and are therefore still egocentric in nature [11]. For example, memorising routes based on sequential turns would employ a mostly egocentric strategy (**Figure 1A**). Path integration, the summation of travelled vectors to deduce current position, is an example of an egocentric strategy that can navigate through

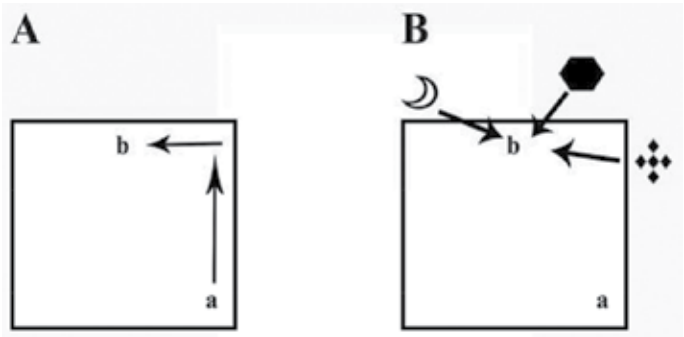


**Figure 1.** Schematic of egocentric (A) and allocentric (B) frames in a spatial memory task. Within each arena, (a) is the start position and (b) is the goal location. Egocentric strategies are referenced from self with set directions and distances to the goal (shown indirect here but may also be direct). Note that if the start position (Aa) is changed, the strategy would fail to reach the goal (Ab). Allocentric strategies relate the location of the goal to visual cues. Note that if the start position (Ba) is changed, the strategy would still successfully locate goal (Bb). If the visual cues are moved, the strategy would fail to reach the goal (Bb).

novel paths. The allocentric reference frame, on the other hand, can be thought of as a third-person perspective. Allocentric navigation utilises external cues or landmarks in relation to each other to navigate and is independent of self (**Figure 1B**). Utilising compass directions (north, south, east, west) is an example of allocentric reference frame use as these directions are relative to the Earth and do not change depending on the orientation of the navigator [12]. An advantage of allocentric navigation is the flexibility of being able to locate novel points from various start locations as long as the external cues remain the same. In situations where external cues are changing, minimal or absent, egocentric strategies become more salient [1].

Navigating environments outside of experimental settings requires the use of both allocentric and egocentric reference frames, with relative saliencies falling within a spectrum [1]. Experiments in controlled settings with specifically designed spatial memory tasks aim to dissociate these reference frames; however, it is argued that complete dissociation is not achieved [1]. Nevertheless, the employment of more precise tasks as well as the use of more rigorous analytical techniques allows greater dissociation and investigation into navigational strategy preference and specific dysfunctions in reference frames. Nonspatial strategies such as random or serial searches can often be successful in that they result in lower latencies to a goal. These, however, are not indicative of spatial memory, and measures should be put in place to detect such strategy use. The following section provides an overview of the various spatial memory tasks currently used in behavioural neuroscience and their ability to effectively probe egocentric and allocentric search strategies.

## 4. Spatial memory and navigation paradigms

There are a large variety of behavioural tests for both rodents and humans that provide a measure of spatial memory and navigation [9, 13, 14]. Generally, rodent spatial memory tests

utilise maze apparatus that have a goal area that the animals must find, learn and remember. These goals can be positive reinforcements such as food rewards, escapes from negative stimuli such as water or bright light or a result of instinctive behaviour such as exploratory drive. Human spatial memory testing, on the other hand, is mostly conducted on virtual reality setups that create controlled three-dimensional environments with goals usually being explained to the subject by the researcher. More recently, steps have been taken to combine aspects from both animal and human tests to increase the similarity and therefore translatability of these tests. Virtual reality versions of rodent tests have been developed for humans [15], and virtual reality and touchscreen setups for rodents that were developed from human equivalents have also become popular [16, 17]. Distinguishing allocentric and egocentric reference frames and search strategies used in spatial memory tasks for rodents differs depending on the type of test. Some tasks are designed to encourage employment of a single strategy, and so performance on that task is reflective of the saliency of that particular reference frame. Other tasks can be completed with a combination of allocentric and egocentric strategies, and subsequent analysis or probe tests are needed to infer deficits or preferences in these reference frames. Consideration of what types of spatial navigation are being tested, and extra steps to dissociate these strategies are often overlooked, despite the relative ease of implementing such measures. Below we discuss popular maze apparatus used to investigate spatial memory and various tests, controls and analyses that can help distinguish egocentric and allocentric navigation.

Spatial memory can be investigated through a variety of tests on mazes such as the Y-maze, cheeseboard maze, Morris water maze, Star maze, Barnes maze, radial arm maze and T-maze. These mazes encompass investigation of a range of spatial memory, including long-term, short-term and working memory, as well as cognitive flexibility. Tests that probe allocentric reference frames include the use of static visual cues which the rodent can use to develop a cognitive map. Efforts are made to minimise proximal cues and create open, unobstructed spaces to avoid non-allocentric strategies. The opposite is true for egocentric tasks where visual cues are minimised or made irrelevant (incorrect or random). The most accurate way of testing for egocentric strategies is to perform a test in the dark, which ensures removal of visual distal cues that could be used for allocentric strategies [18]. Many apparatus that are used to investigate egocentric navigation restrict movements to narrow channels or arms to create distinct choice points where egocentric strategies are encouraged [19].

Constructed in the shape of a capitalised 'T', the **T-maze** (**Figure 2A**) is a simple apparatus used to probe working and short-term spatial memory. Due to the shape of the maze, only two options, a 90-degree left or right turns, are available to the rodent when leaving the start arm. The T-maze can be unbaited, baited or use negative stimuli to drive exploration of the maze [20]. Generally, one of the arms is correct (unexplored, food/water rewarded, containing escape platform) and is learnt in the presence of intact memory. Internal and external visual cues can be used to probe navigational strategy [21]. Briefly, animals can be trained with the presence of extra-maze visual cues and an intra-maze visual cue. Reaching the goal arm can be achieved by either remembering to turn in the correct direction, move towards or avoid the intra-maze cue or move to the correct area in relation to the static external cues. Following successful acquisition of the task, animals can be tested on probe trials which involve systematically switching the cues or correct turn direction so that they are now incorrect. Indeed,

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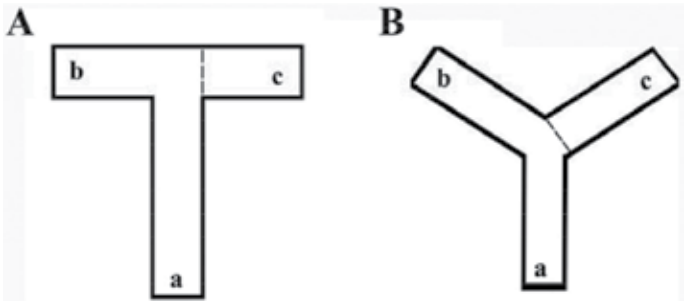


**Figure 2.** Schematic of a T-maze and Y-maze. (A) is the start location and the (B) and (C) arms are the choice arms. One choice arm (C shown here) may be physically blocked during the first phase of unbaited tests to create a novelty seeking drive to that arm when made accessible in the second phase.

rats were shown to have an overall preference for a direction-based strategy on the T-maze, suggesting that this apparatus encourages egocentric navigation [21]. Using similar visual cue manipulations on the T-maze, transgenic mice expressing an Alzheimer's disease-related mutation were shown to have specific allocentric place learning deficits in the absence of a general disruption in learning and memory, highlighting the importance of including these probe tests when possible [22].

The **Y-maze** (**Figure 2B**) works much in the same way as a T-maze; however, the apparatus is designed in a Y shape with three equal arms at 120 degrees from each other. Unbaited tests are popular on this apparatus, relying on the animal's innate preference to explore previously unexplored areas. Short-term memory can be tested by blocking access to one of the arms in the first phase of the test and observing the time spent in that arm in the second phase where all three arms can be accessed. There is a variable delay between phases to control short-term memory load of the task. This novel arm preference task is a test for allocentric spatial memory as rodents use both intra- and extra-maze cues to remember the location of the novel arm. Working memory can also be tested by allowing the animal to freely explore all three arms and observing if they chose to enter the arm most recently explored or they alternate and enter the more novel arm—this is called spontaneous alternation. Spontaneous alternation can also be investigated on the T-maze; however, because the arms of the Y-maze are equal (and can each become new start arms), alternation can be continuously measured without constant investigator interaction. Modifying the protocol to include baited arms and including or removing the use of proximal and distal cues allows for the investigation of allocentric and egocentric strategies [23–25].

**The Biel water maze** was developed by William Biel [26] and is constructed of multiple T-mazes that interconnect to create a labyrinth in which rodents must navigate from the 'Start' to 'Goal' to escape the maze. The maze is run in visible light, and no explicit distal cues are provided; in addition, the maze is covered by a large container to minimise access to both distal and proximal cues. Parameters that are used to measure egocentric navigation include errors across trials and escape latency. However, this maze had limitations in design and level of difficulty, most importantly that it was run in visible light which could provide distal or proximal cues from the box overhead [19]. The **Cincinnati water maze (CWM)** is an extension of the Biel water maze. It is a complex labyrinth water maze consisting of nine interconnecting

T-mazes (**Figure 3**). An experimental rodent must get from position A to position B and is motivated by its survival instinct to leave the water. It is designed to employ egocentric search strategies based on the physical dimensions and design of the maze that creates nine choice points (rather than six in the Biel water maze) at intersections where rodents are required to make a left or right turn. The CWM is constructed using an acrylic material so that the walls are smooth, and no proximal cues are available. The width of the channels ensures the rodent cannot climb the walls of the maze, and running the test in the dark under infrared light can act as a double insurance against the use of visual cues [19]. Generally, the number of errors, number of start return and latency to escape are the main parameters reported for this maze.

**The radial arm maze** (RAM) consists of a central circular area from which multiple arms radiate outwards. Rodent spatial memory is measured by the ability to remember the location of baited arms through the use of salient cues around the maze room (allocentric) [27] or an egocentric-focused paradigm that employs forced arm entry. An example of an egocentric paradigm using the RAM follows. In this instance the maze has automated doors that open and close to allow entry for the animal. The animal starts in one arm, and once the experiment starts, two adjacent arms to the start arm are opened to construct a Y shape. There will be a food reward at the end of one arm, determined for each mouse to be either left or right. The maze arm entered by the animal becomes the new start arm, which the animal is restricted to during an intertrial interval. Following an intertrial interval, two arms adjacent to the new start arm are opened, with the direction of arm (left or right) being correct with a food reward. The experiment continues in this fashion and requires the animal to navigate the maze in reference to its own position [28]. By limiting access to only three arms (in addition to the original start arm) at a time, this insures against a non-egocentric strategy to be used by the

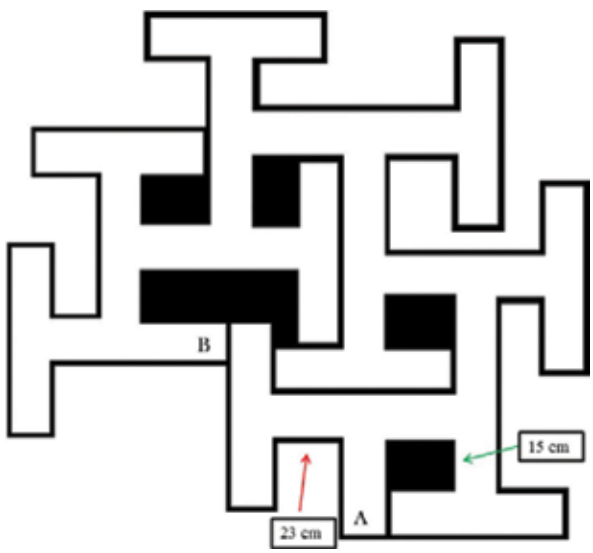


**Figure 3.** The Cincinnati water maze (CWM), original image from Vorhees and Williams [19], is a labyrinth-like maze that is performed in the dark. The forced left or right choice in addition to the lack of visual cues promotes egocentric strategies. (A) Is the start location and (B) is the escape platform.

animal. For example, if all arms of the RAM were available, the animal could use the serial strategy of entering each arm sequentially in order to find the food reward. For the RAM, measurements such as number of errors and rank of the first error [27] are reported to indicate memory performance. While the RAM can be used to investigate both egocentric and allocentric search strategies, the armless Morris water maze became the standard for allocentric testing [13], with the open opaque water acting as a mask for both choice points to learn a set sequence, and olfaction. In contrast to the armed designs of egocentric tests, mazes that target allocentric spatial strategies are designed to be open and free from intra-maze objects/edges that may act as choice points [13].

**The Barnes maze** is based upon the preference for dark, enclosed spaces by rodents. It is an open circular maze with holes around the perimeter (**Figure 4**). Underneath one of these holes is the 'target box' goal, which provides a small enclosed space for the rodent. During testing the maze is flooded with bright lights, sounds and/or air jets to provide motivation to find the goal. Distal cues are provided around the room to help the rodent navigate. Number of errors, escape latency and search strategies are commonly reported as a measure of spatial memory performance [20]. Visual cue manipulations on the Barnes maze show that distal cues are more salient than proximal cues, with animals trained without distal cues (with a marker at the goal location) showing decreased performance [29]. Thus this task tends to encourage allocentric strategies.

**The Morris water maze (MWM)** has been an integral part of neuroscience research as a gold standard when testing spatial memory in rodents since its introduction (Morris et al. [38]). The MWM utilises a large, circular pool with opaque water and a hidden escape platform (**Figure 5A**). Multiple distal cues are placed around the maze to aid the rodent to reach the

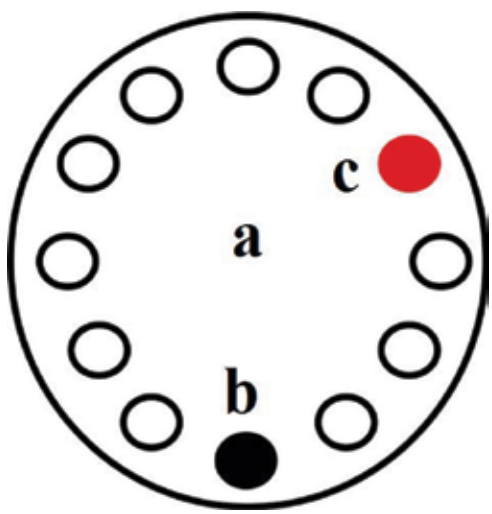


**Figure 4.** Schematic of the Barnes maze. Animals start in the Centre of the maze (A) and must find and remember the location of the hidden escape box (B). After acquisition, the correct location can be changed (C) to investigate cognitive flexibility.

hidden platform they use to escape. Most protocols are performed over multiple days, with multiple trials per day, and while the hidden platform position remains the same, starting position for the research animal is often changed to minimise egocentric strategies. However, if the start location is kept consistent, and the test is performed in the dark without external cues, rodents can complete the MWM using an egocentric strategy [30]. After training, the escape platform is removed, and reference memory is tested. Animals are expected to spend an increased amount of time in the quadrant where the goal previously was. The location of the goal can also be changed to investigate reversal learning and cognitive flexibility. The main motivation for the rodent to navigate the maze is to escape the water. The main advantage of the MWM when testing allocentric search strategies is the removal of intra-maze visual and olfactory cues with the use of opaque water. Indeed, the masking of any available olfactory cues is imperative due to the rodents' powerful sense of smell and the use of olfaction in their navigation [31]. However, the water in the MWM can also be a disadvantage, especially when working with mice because they are not natural swimmers in the wild and become stressed in the water [32].

**The cheeseboard maze (CBM)** (**Figure 5B**) is a dry version of the MWM and is similarly a long-term spatial memory test as well as a measure of cognitive flexibility. The CBM is a uniform circular arena with wells that can be baited. The wells radiate in lines evenly from the centre of the board. Spatial cues are placed around the CBM. Rodents are food deprived for the duration of the experiment to provide motivation to find the food reward. The location of the baited well is different for each animal and is kept constant across trials and days for each individual mouse. Animals should learn to use the spatial cues placed around the maze to find the baited well from the start area in the centre to receive the reward and are expected to use allocentric search strategies. Following acquisition of the goal location, the location of the food reward is changed, and the animal then must adopt a new learning strategy (reversal). This is a measure of cognitive flexibility and is testing the ability of the animal to ignore the initial position of the reward and learn the new location of the second reward. Compared to the MWM which relies on survival motivation, the CBM relies on hunger drive. Both tasks involve distal cues to guide the mouse to its goal, be it the platform of the MWM or the food reward of the CBM. These different motivations could influence the cognitive processing of

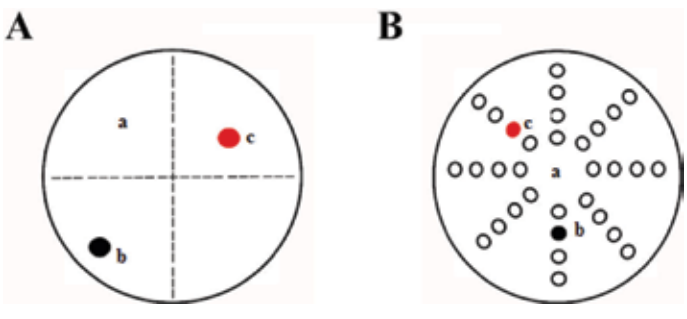


**Figure 5.** The Morris water maze (A) and the dry cheeseboard maze (B). (a) is the start location, (b) is the goal location, and (c) is a new goal location used to investigate cognitive flexibility. Both apparatus are circular, open-arena mazes that can contain goal locations in a range of xy coordinates.

the rodents. MWM has been criticised as unduly stressful [13], with the research animal having to employ avoidance learning. The CBM, while food deprivation may provide a similar stress [13], involves positive reinforcement through the food reward. There are some arguments that positive reinforcement may not be sufficient enough [13] to encourage the research animals to learn, in comparison to a test such as MWM where negative consequences must be avoided. It may be that each test provides a different angle to the study of cognition. Panicked stress may be detrimental to effective learning or a stronger drive compared to food deprivation. The main advantage of the MWM in terms of teasing out allocentric and egocentric strategies is that it is a cleaner allocentric maze. In the MWM, the use of opaque water that the rodents must swim through minimises the availability of choice points and olfactory cues. In comparison, the CBM is a maze that requires rodents to not only navigate using the distal cues but also around the wells. Hence, rodents may incorporate these wells into their navigation strategy—something that cannot be done in the MWM. This could provide an opportunity for the rodents to employ non-allocentric strategies, such as the serial strategy. This issue of detecting said egocentric versus allocentric search strategies is further discussed in the following section.

**The Star maze** (**Figure 6**), designed by Rondi-Reig et al. [33], is a purpose-built water maze that allows for the distinction of allocentric and egocentric search strategies. It is a circular water maze consisting of five water channels that form a central pentagon, and five water channels radiate out from this pentagon. The walls of the maze have a uniform colour, and the water is made opaque. The goal of the maze is to find the hidden platform in order to escape. Extra-maze cues on the walls are made available when analysing allocentric navigation. The setup of this maze allows for multiple protocols to test allocentric or egocentric navigation.

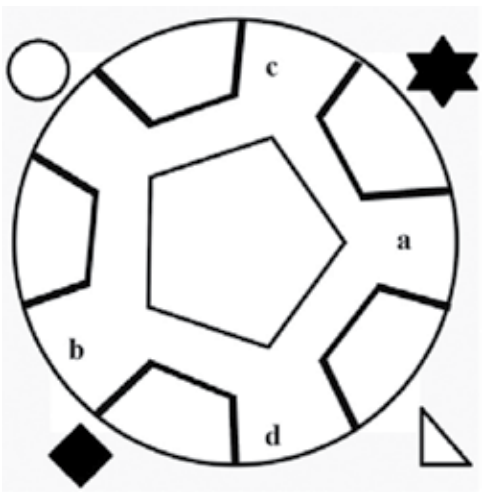


**Figure 6.** The Star maze, adapted from Rondi-Reig et al. [33], which is a water maze that allows for the investigation of spontaneous search strategy used by rodents. The design of the Star maze is such that either egocentric route learning or allocentric navigation can be analysed. For example, animals are trained from start position (a) to goal (b) until a threshold performance is reach. The start position is then moved to (c). An egocentric strategy would lead the animals to (d), whereas an allocentric strategy would continue to navigate to (b).

The first protocol, 'the multiple strategies version', is set up to investigate spontaneous navigation strategy that is employed by the rodent. The second protocol investigates egocentric navigation by setting up the maze so that a sequence of direction movements sends the rodent to the escape platform. The final protocol requires rodents to use the spatial cues provided in order to escape from randomly assigned start points [33]. This maze is a great setup as it allows the elucidation of individual search strategies, and given that it is a water maze, it controls for equal motivation and opportunity [13].

## 5. Analysing search strategies to compare the use of egocentric or allocentric search strategies

Spatial memory proficiency is commonly measured through a range of parameters in the above-mentioned mazes including latency, distance and time spent in target quadrants. However, evidence suggests that these analyses are not providing sophisticated enough insights into cognition and behaviour [34]. The Current trend is a deeper analysis of spatial navigation in order to produce more efficient research and more efficient use of research animals [34], moving beyond the well-known parameters of latency and distance. Research is now interested in the search strategy employed by research subjects and animals (**Figure 7**). Search strategy analysis can observe the complexity and dynamic nature of cognition employed in spatial memory mazes. For example, while different genotypes may have no significant differences in the typical parameters of latency, distance or target quadrant, a difference in approach to goal could exist and demonstrate changed cognition as a result of genotype. This may be more reflective of the innate differences that can exist in individual cognition despite similar anatomy. Of particular interest is the path trace analysis of allocentric tests in open field-type mazes, where movement is not restricted by walls (such as the MWM, CBM or Barnes maze). Although the absence of choice points aims to encourage allocentric strategies in these mazes, evidence suggests egocentric strategies can still be used; view-matching on distal cues can lead to egocentric cue guidance (e.g. face the star and then turn left) [35], which can successfully complete the task. Non-allocentric strategies such as serial strategies (visit all locations) and chaining (knowing distance from the edge of the maze) can also be successful strategies that also cannot be seen using traditional metrics (see **Figure 7**). These search strategies can be manually assigned through blinded categorisation or be analysed using automated algorithms. While historically latency and distance have been used as measures of cognitive disturbance in the MWM, time spent in the target quadrant on the probe day and search strategy are adjunct parameters that can provide a deeper analysis. Indeed, Rogers et al. [34] elegantly put forth how imperative investigating search strategy and setting up a high-powered experiment can be. Their study demonstrated not only the importance of high saliency cues but also the depth and breadth of information available through the analysis of search strategy.

The adoption of an allocentric search strategy is completely dependent on the quality of landmarks available [34]. This adds another consideration to the design of experiments for researchers; the setup of the maze must be carefully considered. Additionally, Rogers et al.

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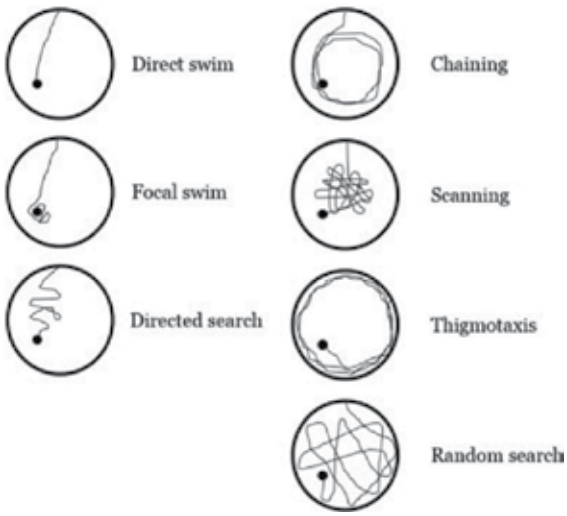


**Figure 7.** Selection of search strategies employed by rodents on the Morris water maze, adapted from Rogers et al. [34].

[34] demonstrated that the latency and path length parameters do not provide differentiation between the different search strategies and in fact do not provide a reliable analysis of spatial memory formation. From this arises the argument that not only does investigating search strategy allow for the elucidation of egocentric versus allocentric search strategies but that the saliency of distal cues allows the research animal to employ these strategies in the first place. It is important to note that more thorough methods for evaluating MWM performance have been suggested for a long time. The proximity measure, introduced in 1993, measures distance to the goal at a frequency of 10 Hz to get an average proximity throughout the trial. This measure was seen to be more sensitive than latency to the goal and was able to pick up subtle and otherwise masked effects [36]. Unfortunately, this measure is still currently under-reported and highlights the need to actively encourage extended analysis beyond latency, distance and time.

Building upon this, the study by Suzuki and Imayoshi [37] deftly investigated and presented a novel method of analysing navigation in the Barnes maze. The authors titled this 'network analysis method', which allowed for the visualisation of a rodent's exploratory patterns. The method involves several algorithms which initially determine the search strategy employed by a rodent (spatial, serial or random). Following this analysis, Suzuki and Imayoshi [37] were interested in determining if particular networks were associated with particular search strategies. A local network is the exploratory behaviour pattern of one mouse of one experimental group. Once local networks are established for all mice of an experimental group, a global network can be created from this data and demonstrates the exploratory behaviour of the whole experimental group. For this study, Suzuki and Imayoshi [37] focused on eight different exploratory behaviours that formed dynamic nodes. Following algorithmic analysis, links between the different nodes (i.e. exploratory behaviours) were established. The authors observed that as spatial learning is established across the experimental days, the global network is simplified,

and nodes surrounding the target area are stronger than indirect nodes with indirect links. Most importantly, as highlighted by Suzuki and Imayoshi [37], although significant differences in cognitions were subtle, these spatial navigation behaviours were able to be recognised and quantitatively analysed using the 'network analysis method'. The capacity to apply quantitative statistics to patterns of behaviour provides a fantastic opportunity to apply strong, scientific investigation into higher cognitive processing. This is a strong example of utilising search strategy analysis in order to identify the more dynamic substrates of the cognitive underpinnings of navigation. The successful identification of strengthened spatial memory by Suzuki and Imayoshi [37] using the 'network analysis method' demonstrates the brevity of utilising similar approaches when investigating spatial memory.

## 6. Neurophysiology of allocentric and egocentric strategies

Studies investigating the neurological correlates of egocentric and allocentric navigation have utilised lesion, electrophysiological and optogenetic techniques to better understand the distinct mechanisms underlying them. In many experimental and clinical settings, specific deficits in one reference frame but not the other are observed, further indicating separate mechanisms.

### 6.1. Lesion studies for identification of allocentric and egocentric brain networks

A number of studies have investigated the cognitive consequences of lesioning the hippocampus using spatial memory tests such as the MWM. The overwhelming consensus is that allocentric learning is impaired after hippocampal lesioning. One of the first studies to demonstrate this was by Morris et al. [38] in rats. They demonstrated that lesioning the hippocampus of rats resulted in an inability to navigate the MWM. This is supported by numerous other studies [7, 39, 40], which all found significant deficits in traditional spatial memory measurements such as time to platform, distance to platform and time spent in target quadrant (probe trial). Other lesion studies indicate the perirhinal cortex, entorhinal cortex and parietal cortices to be involved in allocentric search navigation [41–43]. Maze apparatus that can be utilised to test egocentric search strategies include RAM [44], Cincinnati water maze and Star maze [33]. While allocentric search strategies appear to be dependent majorly upon the temporal lobe components, egocentric navigation appears to have a broader network. A study using the RAM observed deficits in egocentric navigation after lesioning medial agranular cortices [44]. Comparatively, a fascinating study by Wolff et al. [45] demonstrated that region-specific lesions of the thalamus impaired egocentric and allocentric navigation independently. They postulated that lateral thalamic lesions interrupt communication between the striatum and frontal cortex, by destruction of the intralaminar nuclei. This interrupted pathway manifested as deficits in egocentric navigation. Indeed, studies have indicated that the dorsal striatum and head direction cells are involved in egocentric navigation [18]. The cerebellar-dentate nucleus has also been implicated in egocentric processes [46], demonstrating the complexity of the networks involved in these search strategies. While we have so far attempted to separate these two navigation strategies, they are not mutually exclusive. A fantastic review by

Ekstrom, Arnold and Iaria [1] goes into detail on theories that describe transitions between allocentric and egocentric strategies, as well as the overlap between them.

### 6.2. Electrophysiological studies for identification of allocentric and egocentric brain networks

There has been extensive research into the neural correlates of spatial memory and navigation. In the seminal book, *The Hippocampus as a Cognitive Map* [47, 48], O'Keefe and Nadel put forward evidence for a cognitive map of space in the hippocampus. A neural model for a spatial map was proposed, built by specialised populations of cells in the hippocampal formation that fire with direct relation to place (place cells). The flow of spatial information in this model begins with sensory and contextual stimuli from the neocortex moving through the entorhinal cortex where egocentric information is encoded. The signal then moves to the fascia dentata of the hippocampus where is it thought that this mix of information is organised and sent to the CA3 and CA1 field of the hippocampus. It is here that the construction of the spatial map is thought to be accommodated with place and misplace cell systems. This model paved the way for future research and identification of other specialised cell types such as head direction cells located between the entorhinal cortex and CA1 in the postsubiculum [49], boundary cells in the subiculum [50], grid cells in the entorhinal cortex [51] and speed cells in the medial entorhinal cortex [52]. Edvard and May-Britt Moser (grid cells), along with John O'Keefe (place cells), were awarded the Nobel prize in Physiology or Medicine in 2014 for their work in investigating these cells underlying the spatial representations of space in the brain. Grid cells, similar to place cells, fire in response to changing position in an environment [51]. These cells differ, however, in their response to a change in environment [53]. When exposed to a new environment, grid cells maintain their representation of space and can therefore represent universal metrics such as distance and direction. These properties suggest that grid cells are involved in path integration [54], a navigational method that integrates movement, direction and speed to compute location. Importantly, path integration primarily relies on an egocentric reference frame because the abovementioned movement, direction and speed are all relative to self [12]. On the other hand, place cells undergo remapping and adopt new, unrelated representations when exposed to novel environments. The resulting allocentric map includes locations predominantly independent of the path taken to get there [55].

Mechanistic differences between egocentric and allocentric reference frames are also observed in electrophysiological recordings. Theta oscillations, or the theta rhythm, are low-frequency (~7–9 Hz) local field potential oscillations that function as a temporal frame in which neurons fire action potentials [56]. Both place and grid cells demonstrate theta phase precession effects to differing levels during navigation. That is, as an animal travels closer to the peak firing field of a certain place or grid cell, that cell will fire earlier in the theta phase [57]. This adds an additional layer of encoded information that contributes to navigation. Furthermore, oscillatory activity has been shown to facilitate the coherency between brain regions involved in egocentric and allocentric navigation [58]. Specifically, low-gamma oscillations (25–50 Hz) between the CA1 and CA3 and high-gamma oscillations (65–140 Hz) between the CA1 and

entorhinal cortex. Indeed, these oscillatory frequency ranges in the CA1 are associated with changes in egocentric and allocentric behaviour [59].

### 6.3. Optogenetic studies for identification of allocentric and egocentric brain networks

Optogenetics is an outstanding technique to elucidate the functional relevance of particular neuron populations in specific brain regions and areas. A study by Andrews-Zwilling et al. [60] optogenetically inhibited hilar GABAergic neurons which led to a spatial memory retrieval impairment in the MWM. This study used the parameters escape latency and percentage time spent in target quadrant. However, there was no reported analysis of search strategy. As outlined by Rogers et al. [34], search strategy analysis is imperative to confirm spatial memory learning. For this study, it would be interesting to know the strategies employed by the mice and compare to controls, to see exactly how the optogenetic inhibition is affecting navigation. By knowing the effects upon search strategy, it provides further depth and breadth to understanding the cognitive processes occurring. Yamamoto et al. [8] further confirm a role for the hippocampus in spatial memory with their optogenetic inhibition of medial entorhinal cortex layer III (MEC) inputs to the CA1 of the hippocampus. This was demonstrated using the delayed nonmatch-to-place T-maze task, a working memory task that is based upon egocentric navigation, that is, it is based upon the successful alternation of turning left or right at a junction [61]. Building upon this, the study by Perusini et al. [62] demonstrated that optogentically stimulating the dentate gyrus in aged mice improved memory retrieval in the contextual fear conditioning paradigm. This has great implications for the current problem of the world's extended life span and associated neurodegenerative diseases such as dementias. The hippocampus is a hub for memory and is linked to multiple networks, as demonstrated especially by Ito et al. [63]. Optogenetic inhibition of cells in the nucleus reuniens of the thalamus resulted in reduced trajectory-dependent firing of the CA1 region of the hippocampus. Projections from the medial prefrontal cortex to the nucleus reuniens which end in the CA1 hippocampus region are imperative to goal-directed map representation.

The studies examined above indicate that some regional differentiation exists between the individual networks involved in allocentric and egocentric navigation. Taken together, it would appear that the hippocampus and surrounding areas are strongly involved in spatial memory and in particular the allocentric search and egocentric navigation strategies. Understanding the effects upon spatial memory and navigation is enhanced by analysing the search strategies employed by research animals. Disruptions to normal functioning could result in compensatory mechanisms that disguise impairments to spatial memory, if the appropriate analyses are not performed. Future studies should use techniques such as optogenetics to specifically investigate cell populations in the hippocampus and associated areas and their role in spatial memory and allocentric and egocentric navigation strategies using specifically designed mazes such as the Star maze. It is widely accepted that the hippocampus has a role in spatial memory, but we are now starting to understand how disrupting spatial memory alters navigational pathways.

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## 7. Search strategies and their relevance to ageing and disease

Further incentive to differentiate egocentric and allocentric navigation in spatial memory tests arises from evidence in studies of human ageing and disease showing that deficits are observed in specific search strategies. Studies in real-world environments such as supermarkets [64] and roads [65] confirm the anecdotally long-held belief that spatial memory performance worsens with normal ageing. Elderly humans also perform worse in virtual reality versions of mazes designed to investigate spatial memory [66] accompanied by changes in electrophysiological event-related potentials [67]. Allocentric navigation seems to be affected more so than egocentric navigation [25, 67], and specific deficits arising only when switching to an allocentric from an egocentric strategy have also been observed [68]. These behavioural changes may be a result of age-related changes in the hippocampus including decreased synapse function and long-term potentiation [69]. Declines in other domains such as working memory and sensory perception most likely also contribute to the decreased spatial memory performance seen in ageing; however, the vulnerability of allocentric over egocentric strategies prompts the need for further investigation into the mechanism behind this deficit. Interestingly, allocentric-specific deficits also seem to manifest in the young (6–7 years old) as well as the elderly [70], suggesting the deficit may be related to cognitive load.

Alongside ageing is an increase in risk for neurodegenerative disorders such as Alzheimer's disease (AD) and associated decline in memory. Topographical disorientation is an early symptom of AD that involves the inability to orientate in the environment and often leads to patients being prone to getting lost. A systematic review of egocentric and allocentric spatial ability in AD by Serino and colleagues [71] observed an allocentric deficit in both mild cognitive impairment and AD. Furthermore, a later study by Allison and colleagues showed allocentric-specific deficits can also be seen in asymptomatic preclinical AD, suggesting allocentric spatial memory tasks may be useful in the early diagnosis of AD [72]. Similar allocentric-specific deficits are also observed in neurodevelopmental disorders such as attention deficit hyperactivity disorder [73]. Although the ability to learn locations from allocentric representations has been shown to be decreased in patients with autism spectrum disorder (ASD) as well [74], there is sparse literature and agreement on this topic [75]. Cognitive symptoms are an untreated aspect of schizophrenia, and allocentric-specific deficits have been observed [76].

Many spatial memory deficits in cognitive decline and disease seem to preferentially affect the allocentric reference frame and navigational strategy. Constructing an allocentric cognitive map of an environment would allow navigation from any start point to a goal location compared to an egocentric sequence, which would only be viable from a single start point to reach a goal. Intuitively, allocentric search strategies are more complex than egocentric strategies and therefore may experience loss of function before the onset of more severe deficits that then go on to affect the egocentric reference frame. In a similar vein, there is also evidence to suggest that perhaps the allocentric reference frame is a culmination of many egocentric frames, meaning egocentric frames are likely to exist without allocentric frames but not vice versa [77]. This could explain the disproportionate dysfunction in allocentric abilities and the relative persistence of

egocentric ones. Another possibility is that specific navigational deficits are a reflection of inaccurate (unconscious) selection of the search strategy most suited for the task at hand [78].

## 8. Why is the distinction important?

Animal models allow the investigation of specific forms of memory and dysfunctional neurocomponents, as a way to parallel human illness. Since humans and animals have analogous brain regions with similar functions, it is helpful to the expansion of biological knowledge to investigate possible disruptions in order to understand the fundamental neuroscience.

Distinguishing egocentric and allocentric search strategies in spatial memory tests is important because:

1. Accuracy and integrity of experimental results would be stronger. Due to the fact that one strategy may be preferentially affected over the other, not considering the distinction has a similar effect to not measuring the effect of an unknown variable. Results may become skewed, diluted or even completely masked.
2. There is a potential to discover novel therapeutic targets. Coupling behavioural data with known physiological and molecular pathways underlying these search strategies could elucidate specific deficits in disease.
3. They can function as more precise outcome variables that can potentially be utilised in early diagnosis of cognitive impairments. Detection of subtle deficits may also be improved.
4. Understanding the inner workings of our brains will be advanced.

## 9. Conclusions

Reviewed here is evidence supporting the distinction of egocentric and allocentric reference frames in spatial memory. These reference frames and their respective search strategies are closely related and are often used in combination when navigating. We argue that because these reference frames involve different mechanisms and they are differentially affected by experimental manipulations and disease, they should be appropriately dissociated when investigated. Rodent mazes such as the Star maze have been developed to tackle this issue by directly probing egocentric and allocentric strategies. Other, more widely used mazes such as the Y-maze and RAM are able to probe these strategies with slightly modified protocols. Open arena apparatus such as the MWM, CBM and Barnes maze can provide different insights on spatial memory performance, but an often overlooked and informative parameter is the qualitative measurement of path traces and investigation of search strategies. Not only has the investigation of search strategy been shown to be required to confirm the creation of an allocentric map, it provides a depth and breadth to understanding the cognitive processes occurring post-experimental intervention or modification. We strongly encourage and recommend the adoption of search strategy analysis and comparison between experimental groups, in order to gain the most from your data.

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Chapter 6

# The Hippocampus as a Neural Link between Negative Affect and Vulnerability for Psychostimulant Relapse

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Additional information is available at the end of the chapter

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**Abstract**

Psychostimulant dependence (including cocaine, amphetamine, and methamphetamine) is a chronic relapsing disorder with significant personal, health, and financial burdens. Attempts at abstinence produce a severe and protracted withdrawal syndrome characterized by stress hypersensitivity that can facilitate drug craving, anxiety, and dysphoria. These negative withdrawal symptoms can induce relapse, maintaining the addiction cycle. The hippocampus mediates cognitive, emotional, and endocrine responses to stressors. The ventral hippocampus is in a pivotal position to regulate the mesoaccumbal dopamine reward system, and interacts with serotonergic and glucocorticoid systems that mediate anxiety and stress responsiveness. Psychostimulant actions on the hippocampus induce long-term changes to these systems and impact the process of adult neurogenesis in the hippocampus, which may facilitate drug dependence by altering drug-cue learning and emotional regulation. Multiple studies indicate that psychostimulant-induced hippocampal neuroadaptations heighten hippocampal-mesoaccumbal activity to amplify drug- and drug-cue responses while persistent dysregulation of hippocampal emotional systems potentiate negative affect. Understanding how psychostimulants modulate the hippocampus to alter hippocampal-mesoaccumbal activity—and how hippocampal neurogenesis influences drug-related memories and reward—is important for identifying novel treatment strategies that can ameliorate negative affect and relapse vulnerability in psychostimulant addiction.

**Keywords:** psychostimulant, hippocampus, stress, withdrawal, serotonin, corticosterone, neurogenesis

# 1. Introduction

## 1.1. The problem of stimulant abuse

Abuse of psychostimulants such as cocaine and amphetamines affects millions of people worldwide, as psychostimulants are the second most widely abused class of illicit drug globally behind marijuana [1–5]. In general, drug addiction and subsequent relapse vulnerability are thought to occur through counter-adaptive neurochemical changes within brain circuits that normally conserve an emotional homeostasis [6–8]. Dysregulation of the homeostatic system—through genetics, environment (stress), history of drug taking, or current emotive states—produces susceptibility to become dependent and to relapse during long-term abstinence [9, 10]. Psychostimulants produce a severe and protracted withdrawal syndrome which includes symptoms of stress hypersensitivity, intense drug craving, anxiety, and dysphoria [11–16]. These symptoms are reproduced in animal models [17–21], and can induce craving and relapse in humans [13, 22, 23], thus maintaining the addiction cycle [24–27]. The underlying mechanisms that enable stress-sensitive and dysphoric states in withdrawal to induce relapse are thought to involve alterations to the mesolimbic dopamine reward system and anti-reward/stress systems [9, 26, 28] that include the hippocampus [28–30]. Currently, no medications have proven effective for treating psychostimulant withdrawal [13, 16, 31]. Thus, understanding the neurobiology underlying the aversive states during psychostimulant withdrawal is an essential component of relapse prevention [32].

## 1.2. The hippocampus, stress and addiction

The hippocampus, a brain region associated with spatial learning and memory, has been established as a critical region for reward- and stress-associated responses and drug-seeking behaviors [30, 33–37]. Exposure to conditioned contextual cues and aversive or stressful stimuli are powerful triggers of drug cravings [38–41] and are associated with activation of limbic brain regions, including the hippocampus, in both human and rodent models [42–46]. Dorsal and ventral subdivisions of the rodent hippocampus have been proposed based on anatomical connectivity and behavioral output [47–51]. The rodent dorsal hippocampus, analogous to the human posterior hippocampus, receives *exteroceptive* information from the entorhinal cortex and has a major role in rapid spatial learning (**Figure 1**) [52]. The ventral hippocampus, analogous to the human anterior hippocampus, receives *interoceptive* information through reciprocal connections to limbic regions that modulate motivational and affective states; the other limbic brain regions involved include the nucleus accumbens, amygdala, medial prefrontal cortex, and hypothalamus (**Figure 1**) [50–54]. Notably, both regions of the hippocampus are involved in memory formation [55]; dorsal neurons form contextual representations of specific single events while ventral neurons form representations of multiple events (related by a distinct context) over time [56].

The subiculum, the major output structure of the hippocampus, provides projections to the nucleus accumbens, which also receives input from ventral tegmental area (VTA) dopamine terminals [34, 57–59]. The nucleus accumbens integrates affective and motivational information

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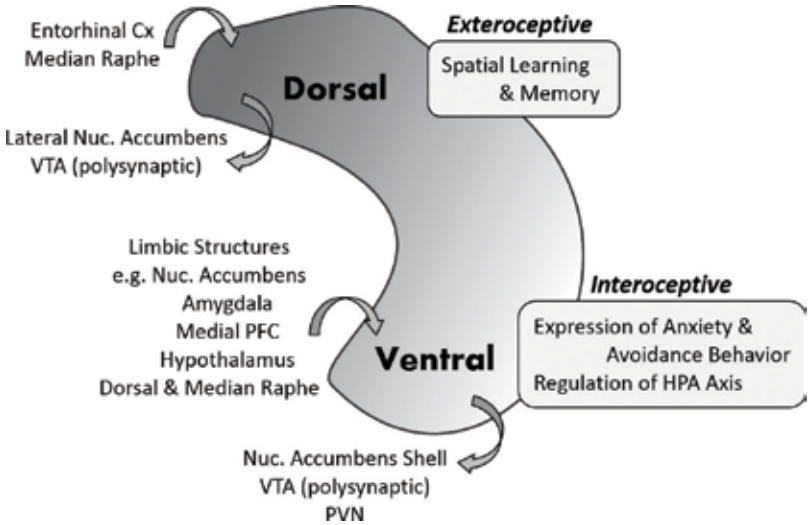


**Figure 1.** Schematic of afferent/efferent connections and functions of the dorsal and ventral hippocampus related to reward and stress processes. Abbreviations: Cx, cortex; HPA, hypothalamic-pituitary-adrenal; PFC, prefrontal cortex; PVN, paraventricular nucleus of the hypothalamus; VTA, ventral tegmental area.

to produce goal-directed behavioral output [60–62]. Thus, the hippocampus is poised to play an important role in mediating the effects of drugs of abuse (e.g., psychostimulants) through its interactions with the mesoaccumbal dopamine system. Importantly, the dorsal and ventral hippocampus may differentially regulate accumbal activity [60, 63], since the ventral subiculum projects to the medial shell of the nucleus accumbens while the dorsal subiculum projects to the more lateral accumbens and core (**Figure 1**) [51, 54, 64]. The dorsal and ventral hippocampus also influences accumbal activity indirectly, via multi-synaptic projections to the VTA (**Figure 1**) [65–67]. Consequently, glutamatergic output from the hippocampus facilitates dopaminergic activity in the mesolimbic dopamine pathway [34, 57, 68, 69]. In the nucleus accumbens shell, this communication is vital for forming place-reward associations [70–72] and mediating reward salience [63]. Thus, context-related processing within the hippocampus may drive reward-related processes mediated by the nucleus accumbens.

The hippocampus also regulates anxiety and avoidance behaviors. Anxiety is an innate response coordinated to protect an animal from potential harm, which is linked to maximizing chances of reward in approach-avoidance conflict situations. The hippocampus has been proposed to underlie anxiety behaviors by detecting novelty or uncertainty [73, 74] and then increasing attention and behavioral inhibition [75, 76]. However, maladaptive changes to the circuits underlying this response can constrain normal functioning and lead to a disruptive pathological state.

The *ventral* hippocampus in particular plays a predominant role in mediating anxiety/avoidance behaviors. For example, glutamatergic activation of the ventral hippocampus is important for expressing anxiety-like behaviors [77, 78] and lesioning the ventral—but not dorsal—hippocampus reduces innate avoidance behavior in unconditioned anxiety tests, and reduces

conditioned responding to anxiogenic cues [79–84]. Moreover, a recent study in humans found that the anterior (ventral) hippocampus is necessary for passive avoidance behavior [85], and studies in rats and humans have shown that increased activity between the ventral/anterior hippocampus and the medial prefrontal cortex is necessary for expressing anxiety in anxiogenic environments [86–89]. Also, activating basolateral amygdala (BLA) inputs to the ventral hippocampus increases—while inhibition decreases—anxiety-like behaviors [90]. Together, these findings suggest that activation of the ventral hippocampus by glutamatergic input from the BLA and its subsequent communication with regions like the prefrontal cortex is essential for the appropriate expression of anxiety/avoidance behaviors.

Related to its involvement in emotional regulation, the ventral hippocampus also exerts influence on the hypothalamic-pituitary-adrenal (HPA) axis and coordinates stress responses (**Figure 1**) [36, 91, 92]. The HPA axis organizes neuroendocrine responses to physical and psychogenic stressors through release of the glucocorticoid hormone cortisol (humans) or corticosterone (rodents) [92]. The hippocampus is the primary target for glucocorticoids in the brain [93] and the ventral subiculum is thought to be the primary limbic region that utilizes glucocorticoid feedback to inhibit HPA axis activity [91, 94–96]. This feedback inhibition is mediated through corticosteroid activation of corticosterone's mineralocorticoid (MR) and glucocorticoid (GR) receptors that are both cytosolic (genomic) and membrane-bound (non-genomic) [96–99].

Cytosolic MRs (cMRs), with restricted expression (highest in the hippocampus), have 10-fold higher affinity for corticosterone than GRs, and are ~90% occupied under basal conditions [100–103]. They are attributed with regulating HPA inhibition at basal corticosterone levels, and thus determine HPA "set point" [96, 104–108]. cMRs also sustain cellular stability, which maintains stress sensitivity thresholds and preserves limbic network communication [97, 103, 107, 109, 110]. Cytosolic GRs (cGRs) are ubiquitously expressed, with high expression in the hippocampus [95], and regulate delayed feedback inhibition of HPA activity after diurnal corticosterone peaks and acute stress [92, 96, 104, 105]. cGRs are also attributed with normalizing neuronal excitability in response to stress and normalizing network activity, which dampens initial stress responses, and promotes adaptive stress coping [107, 109, 110].

Corticosterone stress responses that occur too quickly to attribute to genomic effects are credited to activation of non-genomic membrane-bound receptors (mMRs/mGRs) in the hippocampus (and other regions). These membrane receptors have ≥10-fold lower affinity for corticosterone than their cytosolic counterparts [97, 103, 108] and thus act as hippocampal "cortico-sensors" [99, 111]. mMRs rapidly and reversibly enhance excitatory glutamatergic transmission in the hippocampus [97, 99, 107]; they contribute to rapid inhibition of HPA activity and activate rapid and reversible behavioral stress responses important for appraisal and coping [99, 110]. mGRs have lower corticosterone affinity than mMRs and augment inhibitory GABAergic interneuronal transmission [112] to suppress excitability; they also promote spinogenesis [97, 113]. Alterations in these receptors' expression, function, and ratios relative to one another—especially within the hippocampus—can diminish stress responsiveness and coping ability, which is associated with multiple disease states, including depression and psychostimulant withdrawal [113, 114].

Glucocorticoid stress responses in the hippocampus also vary based on hippocampal region (dorsal vs. ventral): acute foot shock rapidly increases corticosterone levels in the dorsal hippocampus, followed by a more delayed elevation in the ventral hippocampus [115]. Also, acute swim stress *decreases* long-term potentiation (LTP) in the *dorsal* hippocampus, but *increases* LTP in the *ventral* hippocampus [116]. This differential response may temporarily suppress the dorsal hippocampus' cognitive cortical communication and facilitate ventral hippocampal transmission of emotional information [117].

### 1.3. Goals of this review

Overall, the ventral hippocampus is in a pivotal position to play a key role in addictive processes via its role in modulating activity of reward and stress pathways such as the mesoaccumbal dopamine system and HPA axis respectively. This review will provide evidence for psychostimulant-induced changes in the hippocampus leading to negative affect that promotes psychological withdrawal symptoms and maintains the cycle of psychostimulant dependence. Specifically, this review will evaluate and integrate various studies concerning alterations of hippocampal activity and structural plasticity due to chronic drug exposure that contribute to the pathophysiology of drug abuse through maladaptive reward responses and/or the promotion of dysphoric states. In doing so, potential mechanisms underlying psychostimulant withdrawal symptoms and relapse to drug-seeking will be revealed and future directions identified.

## 2. Psychostimulants and hippocampal-mesoaccumbens circuitry

The mesoaccumbal dopaminergic system (VTA to nucleus accumbens) is involved in reinforcement learning and motivated behavior. Dopamine release in the nucleus accumbens shell is associated with reward salience [63] and drug/reward context conditioning [118], and is enhanced by drug use [42, 118], drug-predictive contexts [118, 119], and during novel environment exploration [120]. In line with its role as a novelty detector, the ventral hippocampus controls the novelty-induced dopamine response in the nucleus accumbens [73]. Novelty-induced activation of the ventral hippocampal-nucleus accumbens pathway is thought to be important for long-term memory formation [121]. In support of this, place-reward associations depend on communication between the ventral hippocampus and the nucleus accumbens shell [68, 69]. Likewise, neuronal activity between the nucleus accumbens, hippocampus, and prefrontal cortex during goal-directed behavior learning is believed to contribute to reward-context memory consolidation and strengthening [122–125]. Finally, co-activation of the anterior (ventral) hippocampus and VTA dopamine neurons is linked to long-term reward-related memory enhancement [126, 127]. Thus, reward enhances memory formation, and this effect is closely linked to reward-context engagement of the hippocampal-mesoaccumbal pathway.

The dopamine system has long been associated with stress/aversion as well as reward-related behaviors [128, 129]. For example, stress increases dopamine levels in the nucleus accumbens shell (but not core) [130]. Preliminary studies in rats suggest that mimicking the hippocampal

glucocorticoid stress response [131–134] by infusing corticosterone into the ventral subiculum stimulates dopamine efflux in the nucleus accumbens shell [29], thus indicating a role for the ventral hippocampus in enabling stress to enhance accumbal dopamine output. Stressors also increase VTA dopamine activity, and this increase is dependent upon ventral hippocampal activity [135]. The ventral hippocampus-VTA dopamine pathway is also potentiated in mice with increased social avoidance after chronic social defeat stress, and is necessary for this behavioral outcome [136]. Thus, it is suggested that the ventral hippocampus uses prior experience to bias the responsive state of accumbal dopamine [135]. In line with this suggestion, mice with increased avoidance behavior following chronic stress also display increased VTA dopamine neuron burst firing [137, 138]. Therefore, a behaviorally salient stimulus (aversive or rewarding) within a given context would heightened activation of the ventral hippocampus-accumbens pathway.

The ventral hippocampal-nucleus accumbens pathway also influences psychostimulant responses. Rats with greater dopaminergic responses to novelty will self-administer psychostimulants more readily [139, 140] and rats with repeated cocaine exposure display enhanced accumbal dopamine responses to glutamatergic stimulation of the ventral hippocampus [141]. This is likely reflective of the finding that repeated cocaine exposure and withdrawal selectively potentiates ventral hippocampal input to the nucleus accumbens shell [142, 143]. Furthermore, rats that exhibit behavioral sensitization to amphetamine display enhanced VTA neuronal firing and accumbal dopamine output, and these behavioral and neurophysiological effects are dependent on ventral hippocampal input [144, 145]. Hippocampal activity is also associated with psychostimulant-induced conditioned place preference (CPP) acquisition and expression [146, 147]. For example, lesions or inactivation of the hippocampus inhibit CPP acquisition and context-induced drug-seeking behavior [148–152]. Specifically, interactions between ventral hippocampal glutamatergic projections to neurons expressing postsynaptic D1 dopamine receptors in the nucleus accumbens shell contribute to drug-context memory formation and subsequent drug-seeking reinstatement [37, 153, 154]. Thus, ventral hippocampal facilitation of accumbal dopamine may generate drug-seeking behavior. Further, ventral hippocampal inhibition reduces cocaine- cue- or context-induced reinstatement of drug-seeking behavior [37, 148, 149, 155, 156] and its activity primes context-dependent relapse to drug-seeking for cocaine or d-amphetamine [37, 154, 157]. Overall, it appears that ventral hippocampal enhancement of accumbal dopamine activity likely promotes storage and retrieval of drug-reward information that underlies drug-seeking behaviors (**Figure 2**).

The mechanisms by which psychostimulants enhance ventral-hippocampal-regulated dopamine activity are not fully understood. Stress and repeated cocaine exposure independently increase LTP in the ventral hippocampus [116, 158]. Interestingly, acute *stress-induced* hippocampal plasticity is mediated by MRs and GRs in the ventral hippocampus; whereas *cocaine-induced* hippocampal plasticity seems to instead involve D2 dopamine receptors [116, 158, 159]. Related, repeated cocaine increases trafficking of glutamate receptors toward the membrane in the rat hippocampus [160], suggesting that psychostimulant-induced changes in hippocampal glutamate receptor availability contribute to increased hippocampal excitability and enhanced elevation of accumbal dopamine [141]. Repeated amphetamine exposure

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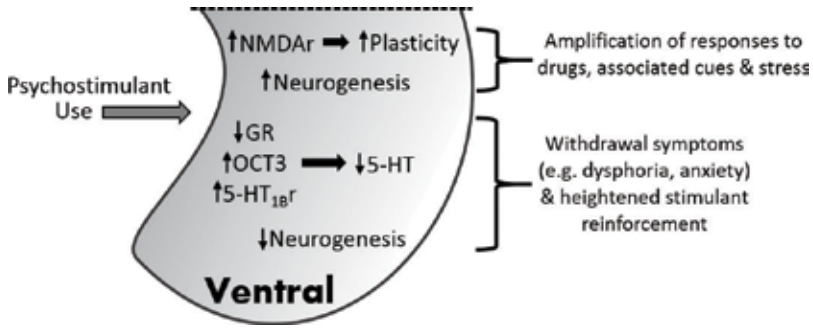


**Figure 2.** Overview of the effects of psychostimulant use on the ventral hippocampus that lead to increased sensitivity to psychostimulants, cues, stress and withdrawal symptoms**.** As discussed in the text, repeated psychostimulant exposure may either increase or decrease neurogenesis in the hippocampus under differing conditions, with either outcome contributing to the symptoms of dependence. Abbreviations: 5-HT, serotonin; GR, glucocorticoid receptor; OCT3, organic cation transporter 3.

also results in a reduced GR to MR ratio in the ventral hippocampus [114], which could further alter hippocampal excitability [97, 108] and hippocampal-accumbens activity. Further, repeated psychostimulant exposure alters neurotransmitter and endogenous neuropeptide levels in the hippocampus. For example, intrahippocampal oxytocin is decreased following chronic cocaine, whereas exogenous administration inhibits psychostimulant-induced behaviors [161]. Oxytocin alters hippocampal excitability by increasing the firing rate of inhibitory interneurons, likely influencing hippocampal terminal regions including the mesoaccumbal dopaminergic system [162]. Together, these findings suggest that psychostimulants can alter synaptic plasticity in the ventral hippocampus, facilitating hippocampal-accumbal pathways to amplify responses to drug reward- or stressor-associated cues (**Figure 2**).

## 3. Psychostimulants and hippocampal affect regulation: spotlight on serotonin and glucocorticoids

A critical modulator of hippocampal activity is serotonin (5-HT). The serotonergic median raphe nucleus innervates the entire dorsal-ventral axis of the hippocampus while the ventral hippocampus receives additional projections from the dorsal raphe nucleus (**Figure 1**) [161, 162]. Thus, the ventral hippocampus receives a higher density of serotoninergic innervations than the dorsal hippocampus [163]. The expression of 5-HT receptors is also differentiated along the dorsal-ventral axis of the hippocampus [164], which supports distinct 5-HT contributions to regionally distinct hippocampal functions.

Various stressors increase extracellular 5-HT levels in the hippocampus [165–172], and this is thought to be mediated by GR activation [114, 172, 173]. In rats, total brain 5-HT depletion increases stress sensitivity and abolishes stress adaptation [174], while specific 5-HT depletion in the ventral hippocampus increases anxiety-like behavior [175]. This supports the role of the ventral hippocampus as regulating anxiety behavior, and comports findings that suggest 5-HT acts as an inhibitory modulator in the hippocampus by activating inhibitory

5-$HT_{1A}$ receptors [176–182]. For example, 5-$HT_{1A}$ receptor activation in the hippocampal dentate gyrus inhibits LTP and impairs fear-related memory acquisition and consolidation [183–185]. Also, post-stress injection of a selective 5-HT reuptake inhibitor or activation of 5-$HT_{1A}$ receptors in the hippocampus prevents stress-induced behavioral deficits [186–188]. Overall, increased 5-HT in the hippocampus seems to be important for repeated stress habituation, while reduced ventral hippocampal 5-HT heightens anxiety [172, 175, 189, 190].

A reciprocal and regulatory interaction exists between the serotonergic and glucocorticoid systems [191–193]. Systemic corticosterone enhances—and blocking corticosterone synthesis or GRs reduces—hippocampal 5-HT turnover and release [114, 194, 195]. These and other findings suggest that hippocampal GR activation in response to stress enhances hippocampal 5-HT transmission [114, 174], which may hold implications for behavioral and emotive stress responses such as anxiety [172, 175]. For example, many antidepressants that decrease anxiety states increase GR expression and 5-HT transmission [196]. In relation to psychostimulant use, chronic amphetamine pretreatment reduces GR protein expression in the ventral hippocampus and abolishes the 5-HT response to physiologically relevant hippocampal corticosterone levels after 24 hours of withdrawal [114], when heightened anxiety states emerge [197]. Overall, blunted stress-induced 5-HT signaling in the ventral hippocampus may contribute to negative affect during psychostimulant withdrawal.

Interestingly, rats with high anxiety behavior and diminished stress-induced 5-HT release also have increased levels of 5-HT transporter (SERT) in the raphe and hippocampus, suggesting enhanced 5-HT clearance from the synaptic cleft also contributes to a reduced serotonergic stress response [189]. Acute amphetamine administration can increase SERT activity at the membrane [198]; however, repeated administration of amphetamine or its derivatives consistently fails to alter SERT expression or function in the hippocampus [199–204]. Therefore, while psychostimulants interact acutely with SERT, chronic psychostimulant exposure does not appear to alter SERT expression or function in the hippocampus to alter 5-HT activity during withdrawal.

The organic cation transporter 3 (OCT3) is a low affinity, high capacity transporter that contributes to 5-HT clearance, and a high density of OCT3 is present in the hippocampus [205–210]. OCT3 is directly linked to anxiety behavior, as OCT3 knockout mice display an anxiolytic phenotype [211] and OCT3 inhibition has antidepressant-like effects in rats [210]. Similarly, *SERT* knockout mice consistently display heightened OCT3 activity in the hippocampus [212, 213] and increased anxiety-like behavior [214, 215], as well as increased OCT3 mRNA in the hippocampus (but not other brain regions) [213]. This suggests that OCT3 may have a region-specific role for 5-HT reuptake in the hippocampus [209, 211, 213, 216]. Accordingly, amphetamine inhibits OCT3 monoamines transport [208, 217] (although see [218]) and withdrawal from methamphetamine is associated with decreased OCT3 mRNA in *whole brain* homogenates [212]. However, OCT3 expression and function are *increased* in the ventral hippocampus of rats at 24 hours of withdrawal from chronic amphetamine, resulting in increased 5-HT clearance in this region [203, 204]. Thus, psychostimulant exposure may enhance OCT3-mediated serotonin uptake in the hippocampus to produce the heighten anxiety states observed in these animals.

In addition, chronic cocaine administration increases $5HT_{1B}$ autoreceptors [219], which regulate serotonin release and anxiety-like behavior in the ventral hippocampus [220, 221]. Thus, psychostimulant-induced increases of $5HT_{1B}$- and OCT3 expression in the ventral hippocampus may reduce ventral hippocampal 5-HT levels and enhance anxiety/avoidance behavior during withdrawal (**Figure 2**) [175, 197, 222–225]. Furthermore, reductions in evoked 5-HT release in the ventral hippocampus have been linked to augmented reinforcing properties of cocaine and ecstasy (MDMA) [226, 227]. Overall, psychostimulant exposure can induce multiple detrimental effects on serotonin signaling during withdrawal that can alter hippocampal activity, disrupt hippocampal communication with reward processing regions (nucleus accumbens), and may culminate in maladaptive behaviors (**Figure 2**).

The hippocampal *glucocorticoid stress* system may play a key role in anhedonia and dysphoria that drive relapse during psychostimulant withdrawal. In support of this suggestion, major depressive disorder—with core features of anhedonia and dysphoria—is associated with reduced hippocampal GR to MR ratio (GR/MR) [228] and reduced GR expression and function [229–231]. Knocking out central GR expression (except in the hypothalamus) produces a reliable depression-like phenotype in rodents, which is restored with tricyclic antidepressant treatment [232]. Antidepressants also increase hippocampal GR/MR ratio, expression, and function [233–236], and short-term treatment with the GR antagonist mifepristone improves depressive symptoms in hypercortisolemic patients [237, 238].

Repeated psychostimulant exposure—which produces dysphoric states in withdrawal [13, 16, 239, 240]—also results in reduced GR expression—and a reduced GR/MR ratio—in the ventral hippocampus (in rats) [114]. The reduced GR/MR ratio may result in MRs having a more pronounced effect in the ventral hippocampus [114], which may function to preserve HPA regulation and homeostasis, since MRs are thought to preserve basal HPA tone [103, 104]. In support of this possibility, neither plasma nor hippocampal corticosterone levels are altered under basal conditions after repeated amphetamine exposure [114]. However, reduced GR/MR ratio is associated with depression [228], and may thus contribute to the dysphoric states that cause relapse during psychostimulant withdrawal. Further, the reduced GR/MR ratio may alter hippocampal excitability and result in dysregulated serotonin- and dopamine responses to stress (Section 2 and [114]).

Interestingly, *protracted* amphetamine withdrawal (2 weeks) results in an enhanced corticosterone stress response in the ventral hippocampus, without altering basal hippocampal or plasma corticosterone levels, or *stress-induced* plasma corticosterone levels [134]. This enhanced hippocampal corticosterone stress response—paired with the possible persistence of lower GR/MR ratio in the ventral hippocampus [114]—may affect hippocampal regulation of accumbal dopamine output and drug salience (Section 2 and [29]). For example, preliminary findings suggest that a stress-relevant concentration of corticosterone infused into the ventral hippocampus rapidly enhances accumbal shell dopamine output (Section 2 and [29]), which may enable stress to enhance reward value [63] and promote goal-oriented behavior [60]. In amphetamine withdrawal, infusing corticosterone into the ventral hippocampus may *reduce* accumbal dopamine output [29]. Thus, corticosterone in the ventral hippocampus may enable stress to *reduce* reward value during psychostimulant withdrawal, thereby contributing

to anhedonia and dysphoria that can prompt relapse [13, 16]. Overall, these recent findings support a role for hippocampal corticosterone in mediating reward responses to stress, and suggest that dysregulated corticosterone signaling in the ventral hippocampus may contribute to stress-induced relapse during psychostimulant withdrawal.

Acute stress exposure has also been found to produce an immediate 3-fold increase of free corticosterone levels in the dorsal hippocampus [241]. GR/MR ratio is also altered in the dorsal hippocampus during psychostimulant withdrawal [114, 241]. In Ref. [241] an *increase* in GR/MR mRNA ratio was observed in the dorsal dentate and CA1 in response to withdrawal from extended access to daily cocaine self-administration, accompanied by increased GR mRNA in the dentate and CA3, and increased MR mRNA in the dentate. In contrast, others have shown that repeated amphetamine administration selectively *down*-regulates GR mRNA in the dorsal hippocampus (when sampled as a whole) [242–245]. Furthermore, in Ref. [114] a *reduction* in dorsal hippocampal GR/MR protein ratio was observed in response to repeated amphetamine exposure during acute (24 h) withdrawal, even though neither GR nor MR protein expression were significantly reduced [114]. The lack of change in GR protein expression was also observed after cocaine self-administration [246]. These differences suggest a possible dissociation between mRNA and protein expression, and may also suggest that psychostimulant exposure has differential effects on GR/MR regulation, dependent upon the exposure model, duration of drug abstinence, and hippocampal sub-region assessed.

Overall, the effects of psychostimulant exposure in the dorsal hippocampus seem to alter GR/MR protein ratio as well as GR and MR mRNA levels. The reduced GR/MR ratio in the dorsal hippocampus could reduce corticosterone-induced serotonin activity in that region [195], similar to the reduction observed in the ventral hippocampus [114]. This has not yet been tested; however, if present, reduced corticosterone-induced serotonin activity in the dorsal hippocampus could impair serotonin-mediated processing of stress-related memories [186] and thus disrupt stress adaptation. The resultant reduced stress coping ability could contribute to stress-induced relapse during psychostimulant withdrawal, as has been reported in humans [13]. Furthermore, the dorsal hippocampus sends excitatory projections to the nucleus accumbens core [51], where dopamine release is associated with coordinating motor programs necessary for drug-seeking [63]. However, dorsal hippocampal stimulation reduces extracellular dopamine in the accumbens core [247] where differential dopaminergic responses are observed in response to appetitive stimuli (increased dopamine) and aversive stimuli (decreased dopamine), while the dopaminergic response in the shell is enhanced regardless of stimulus type [248, 249]. Thus, future research should further dissect the differential roles of the dorsal and ventral hippocampus in contributing to psychostimulant abuse and withdrawal pathology through interactions with the mesolimbic dopamine system and stress responsivity.

## 4. Psychostimulant regulation of hippocampal structural plasticity: drug-context and negative affect

Psychostimulants dramatically alter structural plasticity; inducing long-term changes to dendrite and dendritic spine morphology [250], and potently altering adult neurogenesis, the

process by which new neurons are generated in adulthood. Adult neurogenesis enables experience to alter neuronal circuitry (structural plasticity) in the hippocampus and other regions [251–254]. Adult neurogenesis in the dentate gyrus sub-region of the hippocampus, an essential region for drug-reward-memory formation [152], plays a role in hippocampal-dependent learning and memory [253, 255, 256], as well as hippocampal regulation of stress responses [257, 258] and anxiety-like behaviors [259].

Learning processes increase long-term survival of new neurons [260, 261] and contextual learning and remembering (novel object recognition) depend upon neuron survival for the ability to rearrange circuits (structural plasticity) [262–265]. Interestingly, removing new neurons after contextual fear- or water maze- training degrades memory [266]; however, increasing neurogenesis after training promotes *forgetting* of hippocampal-dependent recent memory, but not remote- or hippocampus-*independent* memory [267, 268]. Thus, augmented hippocampal neurogenesis can weaken existing memories and facilitate encoding of new experiences, whereas diminished neurogenesis can stabilize existing memories and impede new memory encoding. Similarly, adult neurogenesis promotes cognitive flexibility and inhibitory control, behaviors regulated by the ventral hippocampus, suggesting ventral hippocampal neurogenesis significantly contributes to these behaviors [269–272].

Importantly, dorsal-ventral differences are distinguished in hippocampal neurogenesis processes. Several studies indicate predominant neurogenesis in the *dorsal*- compared to the *ventral*- dentate gyrus [224, 273–277]. However, new neurons mature more slowly in the ventral dentate than in the dorsal, suggesting a prolonged period in which immature neurons could be influenced by activity and incorporated or removed from local circuitry [278, 279]. Therefore, a larger pool of potential new neurons in the *dorsal* dentate gyrus might contribute to rapid spatial memory formation, whereas slower maturation in the *ventral* dentate gyrus may support the regulation of affective states. In support of this notion, an enriched environment preferentially increases neurogenesis in the *dorsal* dentate, whereas antidepressant treatment increases neurogenesis and chronic stress decreases neurogenesis to a greater degree in the *ventral* dentate gyrus [280–284].

The specific role of dentate gyrus neurogenesis in regulating anxiety and negative affect remains unclear [285]. Several studies correlate reduced neurogenesis with increased anxiety-like behaviors [259, 286–288]. For example, antidepressants that reduce anxiety states stimulate neurogenesis in the rodent and human hippocampus [289–292]; however, suppressing neurogenesis alone does not seem to be sufficient to induce anxiety-like behaviors [293–296]. Events that induce negative affect—such as chronic stress—also suppress adult hippocampal neurogenesis [297] and increasing adult neurogenesis reduces anxiety and depression-like behaviors in mice treated chronically with corticosterone [298], supporting a role for neurogenesis in mediating hippocampal responses to stress. Stress-induced suppression of cell proliferation in the hippocampus may occur through GRs, which are expressed on proliferating cells [299]. Further, impaired neurogenesis is associated with weakened HPA axis feedback inhibition and increased glucocorticoid levels after acute stress [257, 258]. This suggests that neurogenesis may maintain hippocampal regulation of HPA activity. Thus, impaired neurogenesis may intensify subsequent glucocorticoid effects on hippocampal function, in part through altered serotonergic neurotransmission (see Section 3). This may induce long-term stress sensitivity and negative affect.

Psychostimulants directly regulate the process of adult hippocampal neurogenesis. In rats, chronic but not acute cocaine exposure reduces proliferation rates in the dentate gyrus, but does not alter newborn cell survival rates [300–302]. However, in mice, cocaine seems to increase proliferation [303], and its effects on neuron survival appear to depend on existing vulnerability and drug dosage [304, 305]. Amphetamines have less of an impact on proliferation rates (relative to cocaine), but a greater tendency to reduce the long-term survival of newborn cells [224, 306, 307]. However, methamphetamine exposure reduces both proliferation and survival of new neurons [308, 309]. While most research has focused on the negative regulation of neurogenesis by drugs of abuse, multiple positive effects on neurogenesis have also been observed, particularly during withdrawal. These include increased markers of immature neurons during withdrawal [302, 303, 310, 311] and increased survival of hippocampal progenitors [312, 313]. It appears that drug-seeking behaviors persist independent of recovery from initial drug-induced decreases in new neuron proliferation [302]. However, altered hippocampal neurogenesis impacts drug-taking behaviors. When hippocampal neurogenesis is impaired prior to cocaine self-administration training, rats take greater amounts of cocaine and display higher breakpoints (vs controls), suggesting an intensification of drug reward [314]. Natural reward (sucrose administration) is not altered by this process [314], although transgenic mice with impaired neurogenesis exhibit no sucrose preference, which is an indication of anhedonia [258]. Further, impairing neurogenesis prior to cocaine self-administration training does *not* alter relapse to drug-seeking [314], yet impairing neurogenesis *after* self-administration training—or before CPP—increases context-induced drug-seeking behavior and impedes extinction [314, 315]. This suggests that impaired neurogenesis enhances potency of drug-associated environmental cues in a time-dependent fashion, and *enhancing* neurogenesis may promote *forgetting* of recent hippocampal-dependent drug-reward memory [267]. Increased neurogenesis elicited by voluntary wheel-running or environmental enrichment *before* conditioning also delays extinction of cocaine CPP, whereas running that occurs *after* conditioning accelerates cocaine CPP extinction [316, 317] (although see [318]). Together, these studies suggest that hippocampal neurogenesis may play a role in drug-reward-context memory formation and relapse to drug-seeking.

Psychostimulants may alter neurogenesis processes at least partially through their interactions with the hippocampal dopamine system. Dopamine is known to selectively modulate neurogenesis and immature neuron activity [319], and the ventral hippocampus receives a higher density of dopaminergic inputs than the dorsal hippocampus [320], which may contribute to the dorsa-ventral differences observed in hippocampal neurogenesis processes (described above). Interestingly, dopamine receptor activation promotes adult hippocampal neurogenesis [321, 322], but dopamine can also decrease the capacity of young neurons to express LTP by persistently attenuating young neuron inputs [319]. Psychostimulant-induced alterations to hippocampal dopamine output could then selectively modulate the activity of immature neurons and dictate their subsequent integration into hippocampal circuitry. In support of this suggestion, cocaine enhances LTP magnitude selectively in the ventral hippocampus (where dopamine innervation is highest) in a dopamine-receptor-dependent fashion [158]. Likewise, cocaine-induced CPP stimulates context-dependent activation of adult-born neurons to a greater extend in the ventral dentate gyrus [323]. Altogether, these findings suggest that psychostimulants may exert dynamic effects on

hippocampal neurogenesis, promoting functional integration or reducing proliferation or survival, depending upon hippocampal region and age of the newly-generated cells at the time of drug experience (**Figure 2**) [324]. This preferential activation could promote formation and incubation of drug-context associations. Additionally, altered neurogenesis—perhaps through changes in immature neurons—could indirectly influence hippocampal networks involved in mediating anxiety states—including those induced by drug use and withdrawal—depending upon individual susceptibility, experience, and withdrawal state (**Figure 2**). Overall, more studies are necessary to determine the long-term impact of psychostimulants and withdrawal on new neuron integration along the dorsal-ventral extent of the hippocampus. Specifically, it will be important to uncover the subsequent impact of psychostimulant-induced neurogenesis on drug memory reinstatement, and further identify the underlying mechanisms at play, to develop new therapeutic strategies.

## 5. Conclusions

Together, the literature reviewed indicates that the hippocampus contributes to drug-reward processes, drug-related memory formation, and drug-induced anxiety and dysphoria. Neuroadaptations following repeated drug administration lead to heightened hippocampal-mesoaccumbal activity, thus amplifying responses to psychostimulants and associated cues. At the same time, a persistent dysregulation of the hippocampal component of the brain's emotional system produces a bias toward negative affect-like responses (**Figure 2**). Moreover, long-term alterations of neurogenesis within the hippocampus may contribute to relapse vulnerability through enhanced drug sensitivity, enhanced drug memory, or anxiogenic stimuli. However, further study is necessary to determine how psychostimulants modulate the hippocampus to heighten hippocampal-mesoaccumbal activity, and particularly how hippocampal neurogenesis functions to influence drug-reward and drug-related memories. Future studies should also explore the functional implications of the impact of drugs of abuse and withdrawal on the hippocampus regarding its dorsal-ventral axis. A better understanding of regional differences may help clarify the roles of neurogenesis in changes induced by psychostimulants on different types of hippocampus-dependent behavior. Taking into consideration the activity of these hippocampal systems under drug naïve conditions, chronic psychostimulant-induced alterations to the hippocampus produce ineffective maladaptive behavioral responses to stress and environmental challenges. Restoration of these abnormalities within the hippocampus, either in neuronal activity, neurochemical levels, or neurogenesis could provide an effective therapeutic option to ameliorate negative affect and relapse vulnerability in psychostimulant addiction.

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The hippocampus is an important brain region, a true central hub for memory of various kinds and other processes. Neuropsychiatric disorders such as Alzheimer's disease, drug addiction, and schizophrenia are characterized by hippocampal alterations. The dentate gyrus of the hippocampus is a site exhibiting adult neurogenesis. This book covers the topic of the hippocampus from various perspectives. It discusses adult neurogenesis, effect of enriched environments on hippocampal plasticity, and long-term potentiation-associated gene expression. The book also addresses multiscale representations of complex environments and strategies in the hippocampus-dependent spatial tasks. Finally, insight into the hippocampus as a link between negative affect and relapse to psychostimulants is provided. The book collects evidence of various hippocampal functions in healthy and disordered brain.

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