Title: Interhemispheric specialization in the rodent hippocampus: Implications for storage and retrieval of short- and long-term memories.

Author: Jake Jordan[1]*, Carolyn Pytte[1,2]

Affiliation: 1 – Biology PhD Program, The Graduate Center, City University of New York, New York, NY 10016; 2 – Psychology Department, Queens College, City University of New York, Flushing, NY 11367

*Correspondence: Correspondence should be addressed to: Jake Jordan, 65-30 Kissena Blvd, Razran Hall 272, Flushing, NY 11367; jake.jordan@qc.cuny.edu

Abstract

Lateralization is an organizing principle of nervous systems across taxa. The human hippocampus is known to be lateralized with respect to memory and spatial navigation. In contrast, the rodent hippocampus has been traditionally thought of as a bilaterally symmetric structure, as early studies did not uncover functional differences between the left and right hemispheres. Moreover, it is a common view that the primate hippocampus lacks strong, interhemispheric projections between the bilateral hippocampi, which are present in the rodent brain. Advances in experimental technology have resulted in discoveries of hemispheric asymmetries in the rodent hippocampus, which have led to more sophisticated hypotheses of bilateral hippocampal function. Here, we review studies on hippocampal lateralization with a particular focus on the rodent brain, and suggest that there are more similarities between the human and rodent hippocampus than previously thought. We propose novel hypotheses to uncover the contributions of the left and right hemisphere to hippocampal processing and cognition.

1. Introduction

For over a hundred years, the hippocampus has been one of the most intensively studied structures in the brain. The discovery of permanent amnesia resulting from hippocampectomy (Scoville & Milner, 1957) gave birth to an entirely new field of study, known today as cognitive neuroscience. Single unit recordings in behaving animals led to the finding of place cells (O'Keefe & Dostrovsky, 1971), undermining the behaviorist approach, which had so heavily influenced psychological theory. Long-term potentiation, perhaps a cellular signature of memory (Bliss & Collingridge, 1993), was first seen at hippocampal synapses (Bliss & Lømo, 1973). Finally, oscillations of the local field potential, which are thought to bind perceived and stored information together, have been extensively studied in the hippocampus (Buzsáki, 2015). Despite the wealth of attention directed toward understanding how this system works and what it does, the hippocampus remains a goldmine of novel and fascinating discoveries. Moreover, in recent years, hippocampal research has reliably lead to remarkable insights regarding the cellular basis of cognition more broadly (Dragoi & Tonegawa, 2011; Kohl et al., 2011; Liu et al., 2012; Akers et al., 2014; Aronov et al., 2017; Sarel et al., 2017), continuously opening new avenues of inquiry.

Among the many alluring discoveries of hippocampal function, has been the lateralization of synaptic plasticity in rodents (Kohl et al., 2011; Shipton et al., 2014). Lateralization is an asymmetry of, or presence in one cerebral hemisphere, but not in the other, of a particular neural substrate (Concha et al., 2012). The hippocampus has been shown to be strongly lateralized with respect to cognitive function in humans (Maguire et al., 1998; O'Keefe et al., 1998; Spiers et al., 2001; Burgess et al., 2002; Maguire & Frith, 2003; Howard et al., 2014). Specifically, the left hippocampus is specialized for episodic, contextual, and autobiographical memory (Spiers et al., 2001; Maguire & Frith, 2003), while the right hippocampus is specialized for navigation (Maguire et al., 1998; Spiers et al., 2001; Howard et al., 2014). Despite recent findings of lateralized synaptic plasticity (Kohl et al., 2011; Shipton et al., 2014), a vast majority of studies on the rodent hippocampus do not take lateralization into account. This is perhaps because the rodent hippocampus has substantial bilateral projections between hippocampal subfields, which are thought to be absent or considerably weaker in primates (Wilson et al., 1987; Amaral & Lavenex, 2007). Further, the Morris Water Maze, the most widely used behavioral test to assess rodent hippocampal function, relies equally on both hippocampi for optimal performance (Fenton & Bures, 1993). For these reasons, it is thought that the rodent hippocampus is not lateralized, or at least not to the same degree as the human hippocampus. As discussed below, bilateral hippocampal projections in rodents mask certain interhemispheric asymmetries under typical experimental conditions. These asymmetries were only recently uncovered using advanced methodologies. Additionally, some have suggested that there may indeed be functional, clinically relevant bilateral projections in the human hippocampus (Gloor et al., 1993; Rosenzweig et al., 2011), suggesting that human hippocampal lateralization may not be a consequence of hemispheric isolation.

In this review, we will summarize studies on rodent hippocampal lateralization. Our first goal is to describe the major findings regarding rodent hippocampal lateralization. Our second goal is to describe the methods leading to discoveries of hippocampal asymmetries and to explain how lateralization is difficult to detect using classic experimental protocols. Third, we argue that lateralization in primates and rodents may be more similar than traditionally thought, and that rodent models may lead to novel insights regarding interhemispheric contribution to

hippocampal function. Finally, we will review theories of the cognitive contribution of the left and right hippocampi, including novel hypotheses characterized by wild speculation, which is, of course, what makes science fun (Pytte et al., 2009).

2. Lateralization of Hippocampal Synaptic Physiology

2.1 NMDA Receptor Subunits

Shigemoto, Ito, and colleagues made a discovery of momentous consequence for understanding asymmetries in the rodent hippocampus. In a landmark study, Kawakami et al. (2003) transected the ventral hippocampal commissure (VHC), which consists of fibers projecting from CA3 to the contralateral CA1 in mice. Five days following VHC transection, commissural projections were absent, meaning that after VHC transection, CA1 only received ipsilateral projections. In VHC-transected (VHCT) mice, GluN2B was expressed more densely in left CA1 dendritic spines that received input from only left CA3 Schaffer collaterals than those in right CA1 that received input from only right CA3 Schaffer collaterals. NMDA EPSC's were recorded these mice, and it was found that spines receiving left CA3 input showed a greater sensitivity to GluN2B antagonism than those receiving right CA3 input, but only in VHCT mice. This asymmetry was not seen in intact mice (no VHC transection), and thus left-lateralization of GluN2B density was solely dependent on the hemispheric origin of presynaptic input and not on which hemisphere the postsynaptic spine was located in. I.e., CA1 spines in both the left and right hemisphere receiving left CA3 input were similarly GluN2B-rich, whereas left and right CA1 spines receiving right CA3 input were similarly GluN2B-scarce. A follow-up study determined that this asymmetry of postsynaptic GluN2B density in CA1 was specific to pyramidal neurons as interneurons showed no such laterality (Wu et al., 2005).

In addition to a left-dominance of GluN2B density, Shinohara et al. (2008) found that in VHCT mice, there was also a complementary right-dominance of GluR1 density, an AMPA receptor subunit associated with LTP saturation, in CA1 spines. Interestingly, there was no observed asymmetry in NR2A. Additionally, the authors injected a viral vector to drive expression of axonal GFP into either the left or right CA3 of intact mice. They then identified projections arising from left or right CA3 at the CA1 synapse in electron micrographs and digitally reconstructed postsynaptic spines. CA1 spines targeted by right CA3 axons had a larger volume and synaptic surface area than CA1 spines targeted by left CA3 axons. Further, a greater proportion of right CA3-targeted CA1 spines displayed the mushroom head phenotype, which indicate synaptic maturity. These initial studies on molecular and microanatomical asymmetries in the rodent hippocampus were crucial for the formulation of novel, fruitful hypotheses regarding functional dissociations between the left and right hippocampus.

2.2 Synaptic Physiology at Schaffer Collateral Synapses

The synaptic memory hypothesis suggests that memory may be stored via activity-dependent changes in the strength of synaptic transmission (Bliss & Collingridge, 1993). Though recent data has called this idea into question (Chen et al., 2014; Ryan et al., 2015), it is clear that synaptic plasticity and memory are intimately linked. Long-term potentiation (LTP) is a long-lasting form of synaptic plasticity in which synaptic transmission is enhanced on the timescale of hours to days. LTP at Schaffer collateral synapses between CA3 and CA1 is important for

hippocampus-dependent memory (Wong et al., 1999). As GluN2B is lateralized with respect to presynaptic fibers (Kawakami et al., 2003), and as GluN2B is associated with the potential for LTP induction (Lisman et al., 2002), these early studies led to the hypothesis that LTP at Schaffer collateral synapses may be left-lateralized.

Paulsen, Kohl, and colleagues have used recently developed optogenetic methods to overcome previous experimental limitations and examine the left/contribution of CA3 to plasticity in the CA1 region. CA1 receives Schaffer collateral input from both left and right CA3. Therefore, using an electrical source to stimulate Schaffer collaterals can mask any potential presynaptic lateralization because CA3 terminals from either hemisphere are too proximal too each other to selectively target (Kawakami et al., 2003; Kohl et al., 2011; Shipton et al., 2014). To overcome this limitation, Kohl et al. (2011) injected either the left or right CA3 with a viral vector carrying the gene for channelrhodopsin-2, a light-gated cation channel. This ensured that they could selectively stimulate the fibers originating from CA3 in only one hemisphere when using an optical stimulus. Once ChR2 expression occurred, slices from either hemisphere were prepared for physiological recording. A protocol for the induction of t-LTP, a form of LTP in which presynaptic stimulation is followed closely by a train of postsynaptic action potentials, was performed on slices from either hemisphere. Optical stimulation of only the left CA3 resulted in t-LTP at Schaffer collateral synapses. Electrical stimulation of either hemisphere induced t-LTP, confirming that the asymmetry had been masked using traditional methodologies. The authors found no lateralization of NMDA:AMPA receptor ratios, but did find that GluN2B antagonists blocked a greater percentage of NMDA currents at Schaffer synapses with left CA3 input than those with right CA3 input, in line with a study by Kawakami et al. (2003) suggesting an input-specific left-dominance of GluN2B density (discussed above).

Using a similar approach, Shipton et al. (2014) examined whether high frequency stimulus (HFS) LTP, which does not depend on GluN2B action, is also lateralized. To do this, they injected left or right CA3 with a ChR2-containing virus as done previously (Kohl et al., 2011). Since optical stimulation cannot produce a response frequency comparable to standard HFS induction protocols, an electrical stimulus of 100Hz was used for HFS. Potentiation was tested using optical or electrical pulses to CA3 while recording field potentials in CA1. Optical stimuli revealed a greater potentiation of left CA3 inputs to CA1 than of right inputs. This effect was again masked when using electrical stimuli. Thus, both an GluN2B-sensitive (t-LTP) and an GluN2B-insensitive form of LTP have shown a left-dominance at Schaffer collateral synapses.

3. Goal-Directed Navigation

3.1 Engram Storage and Retrieval in Spatial Tasks

Lesions of either the left or right hippocampus equally impair water maze performance in rodents (Fenton & Bures, 1993). However, following the discovery of left-lateralized GluN2B, a new hypothesis emerged that suggested a possible left-lateralization of long-term memory storage. In an elegant study, Klur et al. (2009) examined how the timing of unilateral hippocampal inactivation may affect water maze retrieval in rats. In their first series of experiments, rats were tested on their ability to retrieve the location of a well-learned escape platform. After 6 days of training a probe trial was conducted during which the escape platform was removed from the pool and either the left, right, both, or neither hippocampus was

inactivated prior to the probe. Inactivation of either the right or both hippocampi impaired selective searching for the escape platform (measured by duration spend in the correct quadrant), while left inactivation had no effect. Thus, after 6 days of learning, only the right hippocampus was necessary to perform the water maze. In a parallel series of experiments, the authors examined how hippocampal inactivation during acquisition impaired later recall of the escape platform location. The authors found that if either the left or both hippocampi were inactivated during the 6 days of training, performance on the probe trial was impaired. However, inactivation of the right hippocampus during training produced no such effect. The authors interpreted these data as a right hippocampal dominance for memory retrieval and a left hippocampal dominance for memory storage.

Shinohara et al. (2012) tested the spatial memory abilities of the left and right hippocampus by severing the VHC and corpus callosum, thereby eliminating interhemispheric information transfer. Either the left or right eye was stitched shut, forcing usage of only the ipsilateral hippocampus, i.e. right-eye deprived mice processed a majority of visual input in the right hemisphere and vice versa for left-eye deprived mice. Performance on the Barnes Maze was better in mice that used their right hippocampus than those that used only their left hippocampus. Notably, mice using their left hippocampus still searched selectively near the escape hole, just not as selectively as mice using their right hippocampus. Follow-up experiments showed that both hippocampi were capable of spatial processing as there was no difference between the two groups on a T-Maze task. Finally, there was no difference between groups following contextual fear conditioning, though it is not clear that sensory modalities other than visual input may have played a role in contextual recall. Thus, with respect to goal-directed navigation, Klur et al. (2009) suggested an interhemispheric asymmetry related to storage and retrieval, while Shinohara et al. (2012) suggested a right-dominance of spatial memory.

3.2 Memory and Navigation in Humans

Maguire, Spiers and colleagues have used a range of imaging techniques along with studies of patients with unilateral medial temporal lobe lesions to study the contributions of the left and right hemispheres to hippocampal function. In a PET imaging study, Maguire et al. (1998) found that both the left and right hippocampi demonstrated increased activity during goal-oriented virtual navigation. However, activity in only the right hippocampus positively correlated with navigation accuracy. Interestingly, activity in only the right caudate nucleus significantly correlated with virtual navigation speed. Thus, they hypothesized that the left hippocampus may store an episodic or contextual representation of particular goal locations, while the right hippocampus may process how to navigate to that goal. The authors concisely summarized this hypothesis with the phrase “Knowing where and getting there”, i.e. the left hippocampus “knows where” and the right hippocampus “gets you there.” In a subsequent study of patients with temporal lobe lesions, Spiers et al. (2001) found that left hippocampal damage resulted in deficits of contextual memory while patients with right hippocampal damage were impaired in navigation. In an fMRI study, signals in the right, but not in the left hippocampus were found to convey information regarding the distance to a goal location (Howard et al., 2014). In summary, human studies have suggested that the left hippocampus stores representations of important locations, while the right hippocampus specializes in route computation (O’Keefe et al., 1998; Burgess et al., 2002).

3.3 Comparison of Rodent and Human Hippocampal Lateralization in Goal-Directed Navigation

The “knowing where and getting there” framework may quite accurately describe data from the rodent studies discussed above. For example, the Morris Water Maze task requires both “knowing where” and “getting there”. Therefore, it is no surprise that both are required for optimal performance (Fenton & Bures, 1993). Klur et al. (2009) concluded that the left hippocampus was necessary for storage of the water maze engram, while the right hippocampus was necessary for retrieval of the stored engram. An alternative explanation may be that in order to perform the water maze, the left hippocampus stores a representation of the location of the goal location (knowing where), while the right hippocampus is necessary for computing the route to navigate towards the stage (getting there). In the case of a well-learned water maze, only the right hippocampus was necessary for recall (Klur et al., 2009). This may be because the right hippocampus is essential for computing the route to the escape platform. On the other hand, the platform location, which may initially have been stored in the left hippocampus could have been consolidated into the cortex due to time and extensive training. In the case of inhibition during learning, blocking the left hippocampus may impair storage of the platform location so that it cannot be recalled during the probe trial. On the other hand, blocking the right hippocampus during acquisition results in no such impairment during recall. Thus, rather than left-hippocampal memory storage which is then transferred to the right hippocampus, as Klur et al. (2009) suggested, data from human hippocampal literature suggests that the platform location may indeed be stored in the left hippocampus (or even in the cortex following extensive training), while the right computes a route for escape. Additionally, Shinohara et al. (2012) suggested that spatial memory as measured by the Barnes Maze is a right-dominant process. However, mice using the left hippocampus still searched near the escape hole. Thus, mice using the left hippocampus may still remember in general where the escape hole is (knowing where), but the right hippocampus is required for accurate navigation (getting there).

4. Short- and Long-Term Memory in the Left and Right Hippocampus

Left-lateralization of GluN2B and LTP suggested that long-term memory may also be left-dominant. Klur et al. (2009) provided evidence supporting the hypothesis that long-term spatial memories are stored in the left hippocampus, but also suggested that these memories are transferred to the right hippocampus. Recently, Shipton et al. (2014) tested the hypothesis that long-term memory is left-dominant using *in vivo* optogenetic inactivation of unilateral CA3 in mice. The authors tested how unilateral CA3 inactivation affected performance on a goal-driven long-term spatial memory Y-Maze task. *Left, but not right inactivation impaired performance of this task.* Surprisingly, left-inactivated mice did not reach control levels of performance even after 11 days of training. Finally, control experiments showed no effect of unilateral hippocampal inactivation in either hemisphere on a hippocampus-independent long-term memory task. To be sure that deficits were due to inactivation of left CA3 input to bilateral CA1 rather than synapses between left CA3 and another structure, El-Gaby et al. (2016) injected left or right CA3 with a virus that drove Archaerhodopsin expression in CA3 neurons. Archaerhodopsin is a light-activated proton pump that silences neuronal activity when stimulated. The authors bilaterally implanted optical fibers into CA1, and thus were able to inactivate left- or right-originating CA3 axons in CA1. Inactivation of left, but not right CA3 axons impaired performance long-term memory retrieval on the Y-Maze, while right inactivation did not impair performance, replicating findings by Shipton et al. (2014). Results from these rodent studies appear consistent with a human fMRI study which found that autobiographical

memories recruited the left hippocampus, no matter how remote, while activation in the right hippocampus decreased as time since encoding increased (Maguire & Frith, 2003). However, if a bilateral division of labor is beneficial for hippocampal processing, it is not yet clear why the right hippocampus is required for short-term memory storage, if the left hippocampus stores the memory in the long-term (discussed below).

Shipton et al. (2014) also tested unilateral contributions to short-term hippocampus-dependent memory. The left or right CA3 was inactivated during a spontaneous alternation in the T-Maze, designed to test hippocampal-dependent short-term spatial memory. Mice started from the bottom of the T-Maze and were allowed to explore whichever arm they chose first for 30 seconds. After exploration, they were *immediately* placed back into the start arm and allowed to again choose an arm to explore. Inactivation of either left or right CA3 impaired performance on this short-term memory task. Interestingly, right inactivation led to even more impairment than left inactivation. In another test of hippocampal-dependent short-term spatial memory, mice explored two arms of a Y-Maze during an encoding trial. On the retrieval trial, occurring 1 minute after the end of the encoding trial, mice were allowed access to the novel arm. Inactivation of either the left or right CA3 impaired preference for the novel arm. Thus, hippocampus-dependent short-term memory requires both the left and right CA3. However, the T-Maze alternation task was more greatly impaired by right CA3 inactivation than by left CA3 inactivation, perhaps because there was no delay between trials. It may be that while long-term memory is lateralized to the left hippocampus, working memory is lateralized to the right hippocampus. Interestingly, β2 microglobulin-deficient mice, whose hippocampal synapses lack the GluN2B-scarce synapses found to be dominant at right CA3 terminals (Shinohara et al., 2008), were impaired in a spatial working memory task. Perhaps large, stable synapses in the right hippocampus may favor working memory. In humans, spatial working memory has indeed been reported to be impaired in human patients with damage to the right hippocampus (Abrahams et al., 1999). Thus, it appears that in rodents, the left hippocampus may be dominant for long-term memory storage, the right hippocampus may be dominant for spatial working memory, and that both are required for short-term recall.

5. A Novel Mechanism for Interhemispheric Contributions to Hippocampal Memory

5.1 Hippocampal Oscillations and Memory

Colgin and colleagues have studied how neural oscillations contribute to memory encoding and retrieval. Measurements of the hippocampal local field potential (LFP) oscillate at certain frequencies depending on behavioral state. Colgin et al. (2009) reported that gamma waves, which oscillate at a frequency of 25-100 Hz, could be parsed into fast gamma and slow gamma. One the one hand, when CA1 oscillates in the upper frequencies of the gamma range (i.e. fast gamma), it tends to be coupled with fast gamma in the medial entorhinal cortex (MEC). However, when CA1 oscillates in the slow gamma range, it tends to be coupled with slow gamma in upstream CA3. It has been hypothesized that fast gamma coupling of the MEC and CA1 is associated with memory encoding, while slow gamma coupling of CA3 and CA1 is associated with retrieval of memories stored in CA3 (Colgin, 2016). Thus, studying interhemispheric dynamics of gamma oscillations may provide important clues for how memories are stored and retrieved.

Benito et al. (2016) recorded gamma wave activity bilaterally from the Schaffer CA3 to CA1 pathway of anesthetized animals. They noted that wave amplitude was significantly larger on the right side. Further, they characterized gamma wave that were present either bilaterally or unilaterally. By comparing the time course for wave initiation between hemispheres, they found that the right hemisphere preceded the left in roughly two thirds of waves that were bilaterally synchronized, while the left preceded the right in the other third. Further, unilateral waves occurred more frequently in the right than in the left hippocampus. The amplitude of unilateral waves in the right hippocampus was smaller than the amplitude of bilateral waves in the right hippocampus, while there was no difference in amplitude between unilateral or bilateral waves recorded in the left hippocampus. Perhaps gamma waves may be generated frequently in the right hemisphere as a consequence of strong, efficient synaptic connectivity. Thus, consolidation of left-lateralized hippocampal memory traces (Maguire & Frith, 2003; Klur et al., 2009; Shipton et al., 2014; El-Gaby et al., 2016) may result in an increase in unilateral waves, particularly in the left hemisphere. If CA3-CA1 gamma-mediated coupling is associated with retrieval, and these events most often originate in the right hemisphere, it should be considered how these events are associated with left-lateralized long-term memory (discussed below).

In addition to gamma oscillations, sharp wave-ripple complexes, events which contain extremely high frequency oscillations of the LFP, are thought to be important for memory consolidation (Buzsáki, 2015). A recent study found that these events may be dissociated across hemispheres and may exhibit several interhemispheric asymmetries, such as higher frequency oscillations in the left hippocampus and longer intervals between events in the right hippocampus (Villalobos et al., 2017). The significance of these results is not yet clear. Future studies should examine the dynamics of interhemispheric oscillations in awake animals encoding, retrieving, or consolidating hippocampus-dependent memory tasks.

5.2 Right Hemisphere-Led Consolidation

Patients with interhemispheric connections severed demonstrate impairments in memory, despite a lack of damage to either hippocampus (Zaidel & Sperry, 1974), suggesting that interhemispheric communication is required for memory consolidation. Interestingly, while both GluN2B-dependent and GluN2B-independent forms of LTP at Schaffer synapses in either hemisphere only occurs when input originates from left CA3 (Kohl et al., 2011; Shipton et al., 2014) right-originating SC synapses appear to be briefly potentiated, decaying to baseline within minutes of induction (Shipton et al., 2014). Further, though both short- and long-term memory are impaired by left hippocampal inactivation, only short-term memory is impaired by right hippocampal inactivation (Shipton et al., 2014). Thus, hippocampal memory is only briefly dependent on the bilateral hippocampi, before becoming dependent solely on the left hippocampus.

Shinohara et al. (2008) found that CA1 spines receiving left CA3 input have an immature microanatomical phenotype while CA1 spines receiving right CA3 input show mature phenotypes. Further, Wu et al. (2005) found that NMDAR-mediated EPSC's are larger in CA1 spines receiving right CA3 input than those receiving left CA3 input. Both of these studies were performed in experimentally naïve (no learning task or spatial experience) mice. Thus, it is perhaps possible that memory is stored in the left hippocampus (Klur et al., 2009), but that left hippocampal circuits initially have immature synapses (Shinohara et al., 2008) which take time to potentiate, thus preventing efficient retrieval before LTP is induced. Large-amplitude gamma

waves originating in the right hippocampus, which then spread to the left hippocampus via connections between bilateral CA3 (Benito et al., 2017), may promote synaptic modification of the circuit that is storing the memory in the left hemisphere. Attractor networks, which sustain activity within a certain neural population (Hopfield, 1982; Zipser et al., 1993) in the right hemisphere (Colgin et al., 2010) may temporarily favor activity in those neurons active at encoding, thereby allowing right CA3 to drive consolidation in left CA3. This consistent with a right hippocampal dominance in working memory (proposed above) and a necessity of the right hemisphere in short-term memory. Once left CA3 synapses are modified, the right hippocampus is no longer required for recall, consistent with a left-dominance in recall of more remote memories (Maguire & Frith, 2003; Shipton et al., 2014; El-Gaby et al., 2016). Such attractor properties for working memory may be intrinsic to the right hippocampus, but is likely to heavily involve the prefrontal cortex (Pucak et al., 1996; Melchitzky et al., 1998; Miller & Cohen, 2001).

It is important to note that in this model, right inactivation should impair long-term memory acquisition, as memories would not be consolidated in the left hemisphere. Of course, previous studies have seen no impairment of right CA3 inactivation on long-term memory retrieval (Klur et al., 2009; Shipton et al., 2014; El-Gaby et al., 2016). However, these studies used the Morris Water Maze (Klur et al., 2009) and the Y-Maze (Shipton et al., 2014; El-Gaby et al., 2016), both of which require many training trials over many days. As ensembles encoding memories that are close in time are more similar than ensembles that encode memories that are far apart in time (Cai et al., 2016), repeated training on the same day may promote consolidation in the left hippocampus without the need for the right hippocampus. Thus, extensive practice may compensate for a loss of right hemisphere function.

6. Is CA1 Lateralized?

One major question remaining with respect to hippocampal lateralization is whether lateralization in function of CA3 extends to CA1 – is the output of the hippocampus lateralized? Though there are clear asymmetries at Schaffer synapses between CA3 axons and CA1 dendrites (Kawakami et al., 203; Wu et al., 2005; Shinohara et al., 2008; Kohl et al., 2001; Shipton et al., 2014; Benito et al., 2016), both CA3 fields project bilaterally. Therefore, any asymmetries upstream of CA1 may be lost in CA1. Klur et al. (2009) studied the effects of spatial learning on gene expression in the left and right CA1 and found that gene expression was heavily modulated in the right CA1 (623 genes), and modulated very little in left CA1 (74 genes). It will be important to identify the function of genes that are upregulated or downregulated in one hemisphere and not the other following spatial learning. Doing so may lead to novel insight regarding the function of left and right CA1.

CA1 place cells are the most studied cell class of the hippocampus *in vivo*. To date, no form of lateralization has been reported with respect to place cell activity or to the activity of other hippocampal cell types. However, circumstantial evidence indicates there may indeed be interhemispheric differences. O'Keefe (2007) discusses an interesting debate in the hippocampal literature concerning how place cells represent an environment. It is pointed out that many studies have reported that place cells are uniformly distributed across an environment (Muller et al., 1987), while few studies have shown that they may actually cluster around salient cues (Hetherington & Shapiro, 1997) or goal locations (Hollup et al., 2001). While many of the studies reporting uniform distribution do not report which hemisphere was recorded, Muller et al.

(1987) reported right CA1 recordings to be distributed across the recording to their chamber, and noted their surprise that the position or shape of place fields did not appear to be influenced by salient environmental cues. This was not the case in a study by Hetherington & Shapiro (1997) which found that place fields recorded in left CA1 appeared to cluster near salient environmental cues. Further, many place fields remapped following the removal of such cues. Similarly, Hollup et al. (2001) found that place fields of left CA1 neurons clustered around the goal platform in an annular water maze, even when this goal was moved to a new location. A recent study found that internally generated schemas serve as a template for CA1 place field generation, which are then tuned by experience (Dragoi & Tonegawa, 2013). El-Gaby et al. (2015) have suggested that these schemas may originate in the right hippocampus, allowing for the rapid emergence of a spatial map in a novel environment, which is then modified by experience, which over time will be stored in the left hippocampus. An interesting point made by El-Gaby et al. (2015) is that we do not yet know whether plastic synapses with left CA3 input and rigid synapses with right CA3 input are on the same CA1 pyramidal cells. Does plasticity in the left hippocampus simply fine-tune CA1 place cells, or does it recruit new place cells at learned locations, as seen in Hollup et al. (2001)? These possibilities are not mutually exclusive.

Recently a new class of hippocampal pyramidal neurons were described in the bat hippocampus which were sensitive to the distance from or direction to a goal location (Sarel et al., 2017). Some of these goal-distance and goal-direction cells were shown to be distinct from either place cells or head direction cells. These recordings were taken from right CA1 (see Supplemental Materials for Sarel et al., 2017). Interestingly, goal-distance signals were originally reported in a human fMRI study where they occurred in the right, but not left hippocampus (Howard et al., 2014). Thus, goal-distance and -direction cells may represent a lateralized form of CA1 output.

7. Comparisons of Bilateral Hippocampal Projections in Rodents and Humans

Above, we have discussed potential similarities between functional lateralization between human and rodent studies. Of critical importance in comparing hippocampal lateralization in humans and in rodents is the degree to which hippocampal anatomy allows for the sharing of information between the bilateral hippocampi. However, the existence of strong interhemispheric projections between the bilateral rodent hippocampi, and lack of such connections in humans has led many to conclude that hippocampal asymmetries in humans and rodents are incongruous. The anatomy of the human, and more generally, of the primate bilateral hippocampus is considerably different from the rodent hippocampus. In fact, anatomical and physiological studies have indicated that primates have a very small, perhaps even non-existent fiber pathway between the left and right hippocampi (Wilson et al., 1987; Amaral & Lavenex, 2007). This pathway is often referred to as the psalterium (Amaral & Lavenex, 2007), though we will refer to it here as the dorsal hippocampal commissure (DHC; Gloor et al., 1993) to facilitate the comparison of this primate structure to the rodent bilateral pathway known as the ventral hippocampal commissure (VHC). It should be noted that in monkeys, in addition to the DHC, there is also a VHC as well as a hippocampal decussation (Demeter et al., 1985). The rodent VHC contains strong, extensive bilateral projections. In contrast, early studies on the human DHC suggested that this pathway is extremely weak and allows for the sharing of very little if any information bilaterally within the hippocampus. Such isolation may result in enhanced

lateralization of primate hippocampal function. However, studies on the spread of epileptic waveforms in humans suggest that activity spreading from one hemisphere to another may in fact spread via a direct projection from one hippocampus to the other (Gloor et al., 1993). This is because the arrival of epileptic activity in the contralateral hippocampus occurs too rapidly to have been routed through another pathway, e.g. the corpus callosum, and activity is seen in the contralateral hippocampus before being seen in other structures, suggesting a direct pathway. In fact, it is even thought that this pathway may be responsible for false lateralization of seizure localization in epileptic patients (Rosenzweig et al., 2011).

8.1 Future Directions

El-Gaby et al. (2015, 2017) have proposed a number of open questions regarding the nature of hippocampal lateralization, including the importance to understanding how rodent hippocampal lateralization relates to the human brain. We stress the importance of comparative studies of hippocampal lateralization across mammals. Although the traditional view of the rodent hippocampus as a non-lateralized, homogenous structure has received significant challenges in recent years, it is still possible that primates (or humans specifically) may be unique in that the *degree* of hippocampal lateralization may be greatest. Therefore, as hippocampal asymmetries become known in rodents, they should be examined in other mammals to determine the generalizability of these phenomena. A recently popular animal model is the Egyptian fruit bat, which allows for the recording of three-dimensional place cells (Yartsev & Ulanovsky, 2013) and even three-dimensional head-direction cells (Kinelstein et al., 2015). Bats belong to the order Chiroptera, and thus are distinct from both primates and rodents. The unique behavior and sensory processing capabilities of bats in comparison to other mammals suggests that these animals will be a useful measure to determine how widespread a certain neural phenomenon is within mammals. Indeed, just as Howard et al. (2014) found goal-distance signals in the right human hippocampus, Sarel et al. (2017) found similar signals in right CA1. This also suggests the need for interhemispheric comparisons of the types of codes in the left and right hippocampi. While inactivation studies are able to distinguish the role of the left and right hippocampus in memory processing (Spiers et al., 2001; Klur et al., 2009; Shipton et al., 2014; El-Gaby et al., 2016), goal-directed spatial navigation has been shown to recruit both hippocampi in humans (Maguire et al., 1998) and require both hippocampi in rodents (Fenton & Bures, 1993). However, the task-relevant computations performed are thought to distinct and complementary (Maguire et al., 1998). Thus, hypotheses regarding the contributions of the left and right hippocampi (e.g., “knowing where and getting there”) to goal-driven spatial navigation may lead to the discoveries of complementary coding motifs across hemispheres.

9.1 Conclusions

A majority of studies on the rodent hippocampus do not take hemispheric differences into account. However, recent studies have suggested that the rodent hippocampus may indeed be lateralized, perhaps in a manner similar to the human hippocampus. While studying the human hippocampus has the obvious advantage of verbal attestation to episodic memories, the rodent hippocampus allows electrophysiological, transgenic, and molecular and cellular approaches to studying the contribution of the hippocampus to cognition in freely moving animals. Further,

impairments in hippocampal lateralization has been seen in disease (Medina et al., 2007). Thus, future studies should examine the relationship between hippocampal lateralization in human and rodents. Understanding the contribution of the left and right hemisphere to hippocampal processing my lead to novel insights regarding the neural mechanisms of cognition.

Acknowledgments

We wish to thank Sana Ahsan, Jake Aronowitz, Mohamady El-Gaby, and Allison Winter for helpful comments on drafts of this manuscript. We thank Jeff Beeler for discussions related to this manuscript.

References

1. Akers KG et al. 2014. Hippocampal neurogenesis regulates forgetting during adulthood and infancy. Science, 344(6184): 598-602
2. Amaral D, Lavenex P. 2007. Hippocampal Neuroanatomy. In: Andersen P, Morris R, Amaral D, Bliss T, O'Keefe J, eds. The Hippocampus Book. Oxford University Press, Oxford.
3. Aronov D, Nevers R, Tank D, 2017. Mapping of a non-spatial dimension by the hippocampal–entorhinal circuit. Nature, 543: 719-722
4. Benito N, Martín-Vázquez G, Makarova J, Makarov VA, Herreras O, 2016. The right hippocampus leads the bilateral integration of gamma-parsed lateralized information. eLife, 5:e16658.
5. Bliss TVP & Collingridge GL, 1993. A synaptic model of memory: long-term potentiation in the hippocampus. Nature, 361: 31-39
6. Bliss TVP & Lømo T, 1973. Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the performant path. Journal of Physiology, 232: 331-356
7. Burgess N, Maguire EA, O'Keefe J, 2002. The human hippocampus and spatial and episodic memory. Neuron, 35: 625-641.
8. Buzsáki G, 2015. Hippocampal sharp wave-ripple: A cognitive biomarker for episodic memory and planning. Hippocampus, 25: 1073-1188.
9. Chen S, Cai D, Pearce K, Sun PY, Roberts AC, Glanzman DL, 2014. Reinstatement of long-term memory following erasure of its behavioral and synaptic expression in Aplysia. eLife, 3:e03896.
10. Colgin LL, 2016. Rhythms of the hippocampal network. Nature Reviews Neuroscience, 17: 239-249
11. Colgin LL et al., 2009. Frequency of gamma oscillations routes flow of information in the hippocampus. Nature, 462: 353-357.
12. Colgin LL, Moser EI, 2010. Gamma oscillations in the hippocampus. Physiology, 25: 319–329.
13. Concha ML, Bianco IH, Wilson SW, 2012. Encoding asymmetry within neural circuits. Nature Reviews Neuroscience, 13:832-843.
14. Demeter S, Rosene DL, Van Hoesen GW, 1985. Interhemispheric pathways of the hippocampal formation, presubiculum, and entorhinal and posterior parahippocampal cortices in the rhesus monkey: the structure and organization of the hippocampal commissures. Journal of Comparative Neurology, 233(1):30-47.
15. Dragoi G, Tonegawa S, 2011. Preplay of future place cell sequences by hippocampal cellular assemblies. Nature, 469:397-401.
16. El-Gaby M, Kohl MM, Paulsen O, 2017. Optogenetic methods to study lateralized synaptic function. In: Rogers LJ, Vallortigara G. Lateralized Brain Functions: Methods in Humans and Non-Human Species. Springer, New York.
17. El-Gaby M, Shipton OA, Paulsen O, 2015. Synaptic plasticity and memory: New insights from hippocampal left–right asymmetries. Neuroscientist, 21(5): 490-502.
18. El-Gaby M, Zhang Y, Wolf K, Schwiening CJ, Paulsen O, Shipton OA, 2016. Archaerhodopsin selectively and selectively and reversibly silences synaptic transmission though altered pH. Cell Reports, 16: 2259-2268.
19. Fenton AA, Bures J, 1993. Place navigation in rats with unilateral tetrodotoxin inactivation of the dorsal hippocampus: Place but not procedural learning can be lateralized to one hippocampus. Behav Neurosci 107:552–564.
20. Hetherington PA, Shapiro ML, 1997. Hippocampal place fields are altered by removal of single visual cues in a distance-dependent manner. Behavioral Neuroscience, 111(1): 20-34
21. Hollup SA, Molden S, Donnett JG, Moser MB, Moser EI, 2001. Accumulation of hippocampal place fields at the goal location in an annular water maze task. Journal of Neuroscience, 21(5): 1635-1644

22. Hopfield JJ, 1982. Neural networks and physical systems with emergent collective computational abilities. Proceedings of the National Academy of Sciences, 79: 2554-2558
23. Howard LR, Javadi HR, Yu Y, Mill RD, Morrison LC, Knight R, Loftus MM, Staskute L, Spiers HJ, 2014. The hippocampus and entorhinal cortex encode path and Euclidean distances to goals during navigation. Current Biology, 24:1331-1330.
24. Kawakami R, Shinohara Y, Kato Y, Sugiyama H, Shigemoto R, Ito I, 2003. Asymmetric allocation of NMDA receptor ε2 subunits in hippocampal circuitry. Science, 300: 990-994
25. Klur S, Muller C, Pereira de Vasconcelos A, Ballard T, Lopez J, Galani R, Certa U, Cassel JC, 2009. Hippocampal-dependent spatial memory functions might be lateralized in rats: An approach combining gene expression profiling and reversible inactivation. Hippocampus 19, 800–816.
26. Kohl M, Shipton OA, Deacon RM, Rawlins JNP, Deisseroth K, Paulsen O, 2011. Hemisphere-specific optogenetic stimulation reveals left-right asymmetry of hippocampal plasticity. Nature Neuroscience, 14: 1413-1415
27. Lisman JE, Schulman H, Cline H, 2002. The molecular basis of CaMKII function in synaptic and behavioral memory, Nature Reviews Neuroscience, 3: 175-190.
28. Liu X, Ramirez S, et al., 2012. Optogenetic stimulation of a hippocampal engram activates fear memory recall. Nature, 484: 381-385
29. Maguire EA, Burgess N, Donnett JG, Frackowiack RSJ, Frith CD, O'Keefe J, 1998. Knowing where and getting there: A human navigational framework. Science, 280: 921 – 924
30. Maguire EA, Frith CD, 2003. Lateral asymmetry in the hippocampal response to the remoteness of autobiographical memories. Journal of Neuroscience, 23(12): 5302 – 5307
31. Melchitzky DS, Sesack SR, Pucak ML, Lewis DA. 1998. Synaptic targets of pyramidal neurons providing intrinsic horizontal connections in monkey prefrontal cortex. Journal of Comparative Neurology, 390:211–24.
32. Miller EK, Cohen JD, 2001. An integrative theory of prefrontal cortex function. Annual Reviews of Neuroscience, 24: 167-202.
33. Muller RU, Kubie JL, Ranck Jr JB, 1987. Spatial firing patterns in hippocampal complex-spike cells in a fixed environment. Journal of Neuroscience, 7(7): 1935-1950
34. O'Keefe J, Dostrovsky J, 1971. The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat. Brain Research, 34(1): 171-175
35. O'Keefe J, Burgess N, Donnett JG, Jeffrey KJ, Maguire EA, 1998. Place cells, navigational accuracy and the human hippocampus. Phil. Trans. R. Soc. Lond. B, 353, 1333 – 1340
36. O'Keefe J. 2007. Hippocampal Neurophysiology in the Behaving Animal. In: Andersen P, Morris R, Amaral D, Bliss T, O'Keefe J, eds. The Hippocampus Book. Oxford University Press, Oxford.
37. Pucak ML, Levitt JB, Lund JS, Lewis DA. 1996. Patterns of intrinsic and associational circuitry in monkey prefrontal cortex. Journal of Comparative Neurology, 376:614–30.
38. Pytte C, Wilbrecht L, Kirn J. 2009. Regulation and function of neuronal replacement in the avian song system. In: Zeigler HP, Marler P, eds. Neuroscience of Birdsong. Cambridge University Press, Cambridge.
39. Ryan TJ, Roy DS, Pignatelli M, Arons A, Tonegawa S, 2015. Engram cells retain memory under retrograde amnesia. Science, 348(6238): 1007-1013.
40. Sarel A, Finkelstein A, Las L, Ulanovsky N, 2017.Vectorial representation of spatial goals in the hippocampus of bats. Science, 355:176-180.
41. Scoville W and Milner B, 1957. Loss of recent memory after bilateral hippocampal lesions. J Neurol Neurosurg Psychiatry, 20(1):11-21)
42. Shinohara Y, Hirase H, Watanabe M, Itakura M, Takahashi M, Shigemoto R, 2008. Left-right asymmetry of the hippocampal synapses with differential subunit allocation of glutamate receptors. Proceedings of the National Academy of Sciences, 105(49):19498-503.

43. Shinohara Y, Hosoya A, Yamasaki N, Ahmed H, Hattori S, Eguchi M, Yamaguchi S, Miyakawa T, Hirase H, Shigemoto R, 2012. Right hemispheric dominance of spatial memory in split-brain mice. Hippocampus 22, 117–121.
44. Shipton OA, El-Gaby M, Apergis-Schoute J, Deisseroth K, Bannerman DM, Paulsen O, Kohl MM, 2014. Left-right dissociation of hippocampal memory processes in mice. Proceedings of the National Academy of Sciences, 111(42): 15238-15243.
45. Spiers HJ, Burgess N, Maguire EA, Baxendale SA, Hartley T, Thompson PJ, O'Keefe J, 2001. Unilateral temporal lobectomy patients show lateralized topographical and episodic memory deficits in a virtual town. Brain, 124: 2476 - 2489
46. Villalobos C, Maldonado PE, Valdés JL, 2017. Asynchronous ripple oscillations between left and right hippocampi during slow wave sleep. PLoS One, DOI:10.1371/journal.pone.0171304.
47. Wilson CL, Isokawa-Akesson M, Babb TL, et al: A comparative view of local and interhemispheric limbic pathways in humans: an evoked potential analysis, in Fundamental Mechanisms of Human Brain Function: Opportunities for Direct Investigation in Association With the Surgical Treatment of Epilepsy. Edited by Engel JJ, Ojemann GA, Lüders HO, et al. Stuttgart, Germany, London, UK, Raven, 1987, pp 27–38.
48. Wong ST, Athos J, Figueroa XA, Pineda VV, Schaefer ML, Chavkin CC, Muglia LJ, Storm DR, 1999. Calcium-stimulated adenylyl cyclase activity is critical for hippocampus-dependent long-term memory and late phase LTP. Neuron, 23:787–798
49. Wu Y, Kawakami R, Shinohara S, Fukaya M, Sakimura K, Mishina M, Watanabe M, Ito I, Shigemoto R, 2005. Target-cell-specific left-right asymmetry of NMDA receptor content in Schaffer collateral synapses in ε1/NR2A knock-out mice. Journal of Neuroscience, 25(40): 9213 – 9226.
50. Zaidel D, Sperry RW, 1974. Memory impairment after commissurotomy in man. Brain, 97: 263-272.
51. Zipser D, Kehoe B, Littlewort G, Fuster J, 1993. A spiking network model of short-term active memory. Journal of Neuroscience, 13: 3406–20.