

Left–right dissociation of hippocampal memory processes in mice

Olivia A. Shipton^{a,b}, Mohamady El-Gaby^a, John Apergis-Schoute^c, Karl Deisseroth^d, David M. Bannerman^{b,e}, Ole Paulsen^{a,b,1}, and Michael M. Kohl^{a,b,1}

^aDepartment of Physiology, Development and Neuroscience, University of Cambridge, Cambridge CB2 3EG, United Kingdom; ^bOXION Initiative, Department of Physiology, Anatomy and Genetics, University of Oxford, Oxford OX1 3PT, United Kingdom; ^cDepartment of Pharmacology, University of Cambridge, Cambridge CB2 1PD, United Kingdom; ^dDepartment of Bioengineering, Stanford University, Stanford, CA 94305; and ^eDepartment of Experimental Psychology, University of Oxford, Oxford OX1 3UD, United Kingdom

Edited by Charles F. Stevens, The Salk Institute for Biological Studies, La Jolla, CA, and approved August 25, 2014 (received for review March 26, 2014)

Left–right asymmetries have likely evolved to make optimal use of bilaterian nervous systems; however, little is known about the synaptic and circuit mechanisms that support divergence of function between equivalent structures in each hemisphere. Here we examined whether lateralized hippocampal memory processing is present in mice, where hemispheric asymmetry at the CA3–CA1 pyramidal neuron synapse has recently been demonstrated, with different spine morphology, glutamate receptor content, and synaptic plasticity, depending on whether afferents originate in the left or right CA3. To address this question, we used optogenetics to acutely silence CA3 pyramidal neurons in either the left or right dorsal hippocampus while mice performed hippocampus-dependent memory tasks. We found that unilateral silencing of either the left or right CA3 was sufficient to impair short-term memory. However, a striking asymmetry emerged in long-term memory, wherein only left CA3 silencing impaired performance on an associative spatial long-term memory task, whereas right CA3 silencing had no effect. To explore whether synaptic properties intrinsic to the hippocampus might contribute to this left–right behavioral asymmetry, we investigated the expression of hippocampal long-term potentiation. Following the induction of long-term potentiation by high-frequency electrical stimulation, synapses between CA3 and CA1 pyramidal neurons were strengthened only when presynaptic input originated in the left CA3, confirming an asymmetry in synaptic properties. The dissociation of hippocampal long-term memory function between hemispheres suggests that memory is routed via distinct left–right pathways within the mouse hippocampus, and provides a promising approach to help elucidate the synaptic basis of long-term memory.

Unilateral specializations may facilitate greater processing power in bilateral brain structures by using the available neuronal circuitry more effectively. Nevertheless, the nature of the mechanisms that can act within the confines of duplicate neural structures to support different cognitive functions in each hemisphere remains elusive.

The hippocampus is essential for certain forms of learning and memory, both in humans (1) and in rodents (2, 3), and also plays an important role in navigation (4). The left and right mammalian hippocampi comprise the same anatomical areas and directional connectivity, and yet in the human hippocampus, task-related activity may be localized to only one hemisphere (5). This lateralization may enable the left and right hippocampus to support complementary functions in human episodic memory, with left hippocampal activity associated with an egocentric, sequential representation of space but greater activity in the right hippocampus when an allocentric representation is used (6). It has been suggested that human hippocampal asymmetry is primarily dictated by external asymmetry—namely, the left hemispheric involvement in language processing and the stronger contribution of the right hemisphere to visuospatial attention (7), supported by observations of left hippocampal dominance when semantic information is most task-relevant, compared with right hippocampal dominance when spatial information becomes

more pertinent (8). However, a seminal discovery in the mouse brain suggests that left–right asymmetry may actually be a fundamental property of the mammalian hippocampus: it was found that the postsynaptic spine morphology and receptor distribution in CA1 pyramidal neurons is determined by whether the presynaptic input originates in the left or right CA3 (9, 10). Specifically, apical CA1 postsynaptic spines receiving input from the left CA3 are primarily thin and rich in GluN2B subunit-containing NMDA receptors (NMDARs); in contrast, there is a higher proportion of mushroom-shaped spines receiving right CA3 projection, and these larger spines have a lower density of GluN2B subunit-containing NMDARs (9, 10). Interestingly, synaptic plasticity also shows hemispheric asymmetry: irrespective of the hemispheric location of the CA1 neuron, GluN2B NMDAR-requiring spike timing-dependent long-term potentiation (LTP) was induced at synapses where presynaptic input originates in the left CA3, but not in the right CA3 (11).

These left–right synaptic differences raise the question as to whether memory processing in mice, as in humans, might differ between the left and right hippocampus. Therefore, in this study, we asked whether acutely inactivating one part of the asymmetric CA3–CA1 network unilaterally would affect learning and memory differentially between hemispheres. To test this, we silenced excitatory cells of CA3 in either the left or the right hippocampus, and consequently also both their ipsilateral and

Significance

The hippocampus is implicated in memory and spatial navigation. In rodents, in which this bilateral brain structure has been studied extensively, the left and right hippocampi have generally been considered functionally equivalent. However, recent work has revealed unexpected asymmetries in the molecular and morphological characteristics of neuronal connections according to brain hemisphere. To investigate whether this left–right difference has implications for hippocampal function, we acutely inhibited activity in an area-specific and genetically-defined population of hippocampal neurons during various behavioral tasks. We found that silencing the CA3 area of the left hippocampus impaired associative spatial long-term memory, whereas the equivalent manipulation in the right hippocampus did not. Thus, our data show that hippocampal long-term memory processing is lateralized in mice.

Author contributions: O.A.S., K.D., D.M.B., O.P., and M.M.K. designed research; O.A.S., M.E., J.A.-S., and M.M.K. performed research; K.D. contributed new reagents/analytic tools; O.A.S., D.M.B., and M.M.K. analyzed data; and O.A.S., D.M.B., O.P., and M.M.K. wrote the paper.

The authors declare no conflict of interest.

This article is a PNAS Direct Submission.

Freely available online through the PNAS open access option.

¹To whom correspondence may be addressed. Email: op210@cam.ac.uk or michael.kohl@dpag.ox.ac.uk.

This article contains supporting information online at www.pnas.org/lookup/suppl/doi:10.1073/pnas.1405648111/-DCSupplemental.

effect of hemisphere: $F_{(1,82)} = 5.37$; $P = 0.023$, but no transgene by hemisphere interaction: $P = 0.23$].

We also tested mice on a different short-term memory task, the spatial novelty preference Y-maze task, in which extramaze spatial cues are important to generate novel arm preference (Fig. 2C) (15). The effect of light delivery was similar to that in the spontaneous alternation short-term memory task, with an impairment arising from unilateral CA3 silencing irrespective of whether it was the left or right CA3 that was silenced [Fig. 2D; left-NpHR = 6 mice, right-NpHR = 5 mice, left-YFP = 7 mice, right-YFP = 4 mice; two-way ANOVA; main effect of transgene: $F_{(1,18)} = 14.91$; $P = 0.001$].

Overall, these results show that a unilateral manipulation can impair hippocampus-dependent short-term memory, and that silencing of either the left or the right CA3 reduces performance on short-term memory tasks.

Acute Silencing of Left CA3 Impairs Hippocampus-Dependent Long-Term Memory, but Silencing the Right CA3 Has No Effect. We next wanted to investigate whether unilateral dorsal CA3 silencing could also impair hippocampus-dependent long-term memory. We tested the same mice on an appetitively motivated task where they had to learn which arm of an elevated Y-maze was rewarded using extramaze spatial cues. The rewarded location remained constant for each mouse across consecutive days of testing. We verified that this task generated a long-term memory of the rewarded arm because a separate cohort of mice showed stable performance upon retesting 1 wk after the end of the acquisition period with no exposure to the apparatus in the intervening period (83% correct choices on both last trial before and first trial after the 7-d retention interval; $n = 12$), which extended to the whole trial block ($85 \pm 6\%$ correct arm choices on final block before retention interval and $85 \pm 5\%$ after retention interval; $n = 12$). A pseudorandom order of arm starts and periodic maze rotation between trials meant that intramaze cues provided no information that mice could use to perform the task successfully (Fig. 3A) (13, 16). Short-term memory errors could affect the acquisition of a spatial long-term memory task, but preventing arm reentry during a single trial removes this contribution to learning deficits (17). Therefore, to isolate long-term memory in this experiment, mice were only allowed to make one arm choice per trial and thus could not self-correct. Mice received blocks of 10 trials a day for 11 consecutive days, with five starts from the arm to the left of the designated rewarded arm, and 5 from the right in a pseudorandom order. Light was delivered for all mice during every trial, and was limited to the trial duration (10–40 s). To confirm that mice were not using olfactory cues from the reward to solve the task, the food was delivered after the arm choice was made on the final day of testing; this postchoice baiting did not cause performance to deteriorate.

Mice in the two control groups (left-YFP and right-YFP) acquired the task over the course of testing, reaching 90–100% accuracy. The right-NpHR group performed equivalent to the control mice. Strikingly, however, silencing the left CA3 did impair performance on this long-term memory task, and the deficit was not overcome even by the end of testing [Fig. 3B and C; left-NpHR = 21 mice, right-NpHR = 19 mice, left-YFP = 18 mice, right-YFP = 22 mice; two-way ANOVA; main effect of transgene (NpHR/YFP): $F_{(1,76)} = 6.01$, $P = 0.017$; transgene by hemisphere interaction: $F_{(1,76)} = 11.46$, $P = 0.001$; analysis of simple main effects showed a significant effect of transgene on the left hemisphere: $F_{(1,76)} = 16.62$, $P < 0.001$ and a significant effect of hemisphere for NpHR: $F_{(1,76)} = 13.29$, $P < 0.001$]. The absence of an effect on task performance by silencing the right CA3 indicates that this network is dispensable for associative spatial long-term memory. Moreover, the acute nature of the manipulation, which limits compensatory changes associated with longer-term manipulations (18), further suggests the right CA3 is

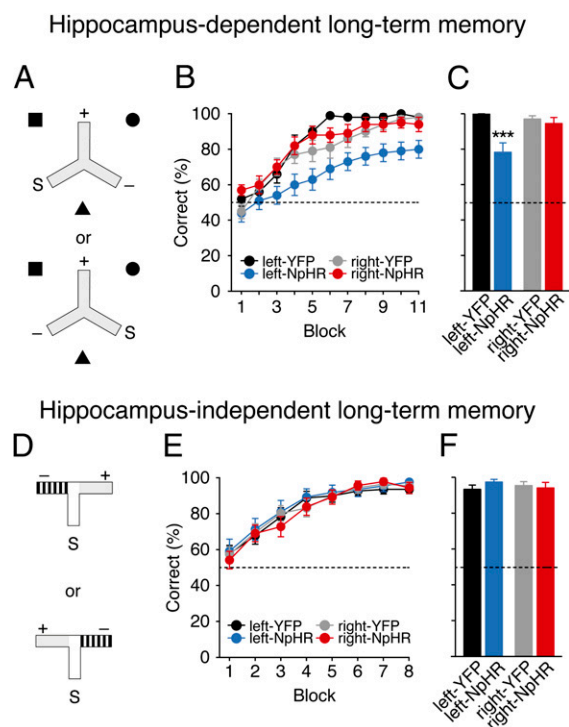


Fig. 3. Hippocampus-dependent associative spatial long-term memory uniquely requires the left CA3. (A) Mice were trained on a hippocampus-dependent long-term memory task where they had to associate a reward location that was fixed with respect to allocentric extramaze spatial cues (black square, circle, and triangle), and remained constant for each mouse across consecutive days of testing. Mice received arm starts (S) to the left or the right of the rewarded arm (+) in a pseudorandom order. Mice entering the nonrewarded arm (–) were not allowed to self-correct. (B) Light delivery in mice expressing eNpHR3.0 in the left CA3 (left-NpHR, blue) impairs but does not affect learning in right-NpHR mice (red) and control groups (left-YFP: black, right-YFP: gray) in this hippocampus-dependent long-term memory task. (C) Average performance on penultimate day. (D) Mice were trained on a hippocampus-independent visual-discrimination long-term memory task where they had to associate arm floor and wall color (gray vs. black-and-white stripes) with a reward; this was fixed for each mouse across consecutive days of testing. Rewarded (+) and nonrewarded (–) arms were pseudorandomly interchanged so that reward location was learnt independent of the spatial position of the arms of the maze. (E) Mice in all groups successfully learned this task at an equivalent rate. (F) Average performance on penultimate day. In both tasks, on the last day of testing, reward was delivered after the animal had chosen to control for the possibility of mice smelling the milk (postchoice baiting). Broken lines represent chance performance. Mean percentage correct choices \pm SEM. *** $P < 0.001$.

not required even under normal learning conditions. In contrast, the left CA3 appears to form an important part of the network that supports associative spatial long-term memory performance.

Acute Silencing of Either Left or Right CA3 Does Not Affect Performance on a Hippocampus-Independent Visual (Nonspatial) Long-Term Memory Task. To ensure that unilateral optogenetic silencing does not cause a generalized sensorimotor or motivational behavioral impairment that could account for the deficit in the left-NpHR group on the spatial long-term memory task, a subset of the same mice, as well as a group of experimentally naïve mice, were trained on an associative, nonspatial visual discrimination T-maze task (16, 19) with trial-limited light delivery, as before (10–40 s). Mice had to learn to associate either a gray or a black/white-striped goal arm with reward (Fig. 3D). As with the previous long-term memory task, mice received training over consecutive days with 10 trials per block and were prevented from self-correcting within

a trial. However, in contrast to the associative spatial Y-maze task, the positions of the target arms were interchanged in a pseudo-random order so that, within each block, mice received a total of five starts with the rewarded arm to the left of the start arm and five starts with it to the right (Fig. 3D). Consequently, there was no extramaze spatial information that could be used to solve the task.

In contrast to the asymmetric effect of silencing on the spatial long-term memory task, all four groups of mice learnt this nonspatial control task successfully (90–100% correct) and at an equivalent rate [Fig. 3E and F; left-NpHR = 15 mice, right-NpHR = 16 mice, left-YFP = 17 mice, right-YFP = 17 mice; two-way ANOVA; main effect of block: $F_{(7,427)} = 80.27$, $P < 0.001$, but no main effect of hemisphere: $F_{(1,161)} = 0.43$, $P = 0.51$, no main effect of transgene: $F_{(1,161)} = 0.09$, $P = 0.76$, no hemisphere by transgene interaction: $F_{(1,161)} = 0.43$, $P = 0.51$; and also no interaction between block and transgene $F_{(7,427)} = 0.19$, $P = 0.99$, nor between block and hemisphere: $F_{(7,427)} = 1.14$, $P = 0.34$ and no triple interaction: $F_{(7,427)} = 0.36$, $P = 0.93$]. Thus, the effect of optogenetic manipulation of the CA3 is limited to hippocampus-dependent tasks; furthermore, it implies that the impairment in the left-NpHR group during the associative spatial long-term memory task was not due a gross asymmetric disruption of sensorimotor or motivational aspects of task performance as a result of silencing of the left CA3.

High Frequency Stimulation-Induced LTP Is Present at CA3–CA1 Synapses Where Afferents Originate in the Left CA3, but Not in the Right CA3. Although their precise roles are debated, NMDAR-dependent synaptic plasticity processes are likely to be involved during performance on hippocampus-dependent spatial memory tasks (20–23). It has previously been reported that there is an asymmetry in the induction of hippocampal spike timing-dependent LTP (tLTP), such that tLTP can only be induced in CA3–CA1 synapses where the presynaptic input originates in the left CA3 via a GluN2B-dependent mechanism (11). However, conventional high-frequency stimulation (HFS)-induced LTP is not blocked by pharmacological GluN2B antagonism (24). Here we investigated whether the expression of HFS-LTP might also be asymmetric. Because hippocampal pyramidal neurons could not be driven at 100 Hz with optogenetic tools, we induced LTP

with nonselective electrical HFS and sampled the left and right CA3–CA1 synapses selectively with optical stimulation to monitor any changes in synaptic weights.

Adult male wild-type mice were injected in the CA3 of one hemisphere with a viral construct containing channelrhodopsin-2 (hChR2) under control of the CaMKII α promoter [AAV5-CaMKII α -hChR2(E123T/T159C)-eYFP; Fig. 4A]. At 4–6 wk later, coronal slices were prepared for plasticity experiments, which were performed blind to injection side. We performed field recordings from CA1 with one electrically and one optically stimulated input pathway, and maximized the overlap between these two pathways by electrode and optical fiber placement (Fig. 4A). We recorded a stable baseline of both optically and electrically stimulated field excitatory postsynaptic potentials (fEPSPs), then induced LTP with high-frequency electrical stimulation (100 stimuli at 100 Hz). Following this induction protocol, we monitored the optical and electrical pathways to determine whether there was a difference in the response of synapses receiving input from either the left or right CA3. Despite equivalent potentiation in the electrical pathway in both left- and right-injected mice (left: $154 \pm 6\%$, $n = 14$; right: $149 \pm 6\%$, $n = 11$; $P = 0.50$), the optical pathway showed a significant increase in synaptic strength only in left-injected mice, irrespective of whether the slice was ipsilateral or contralateral to the injection side, and the fEPSP increase was significantly greater in left-injected compared with right-injected mice (Fig. 4B and C; left: $145 \pm 7\%$; right: $113 \pm 7\%$; $P = 0.004$). This result held when the change in the optical pathway was normalized to the magnitude of electrical LTP (left: $84 \pm 11\%$ of electrical; right: $19 \pm 15\%$; $P = 0.002$). Thus, the expression of HFS-LTP depends on whether the input originates in the left or right CA3; this suggests that these two inputs may perform different functions in vivo and provides one possible mechanistic explanation for the observed functional lateralization in long-term memory.

Discussion

Using trial-limited optogenetic silencing of excitatory neurons in either the left or right CA3, we have found a left–right functional dissociation in hippocampal memory performance in the mouse. Silencing of the left CA3 alone impairs performance on

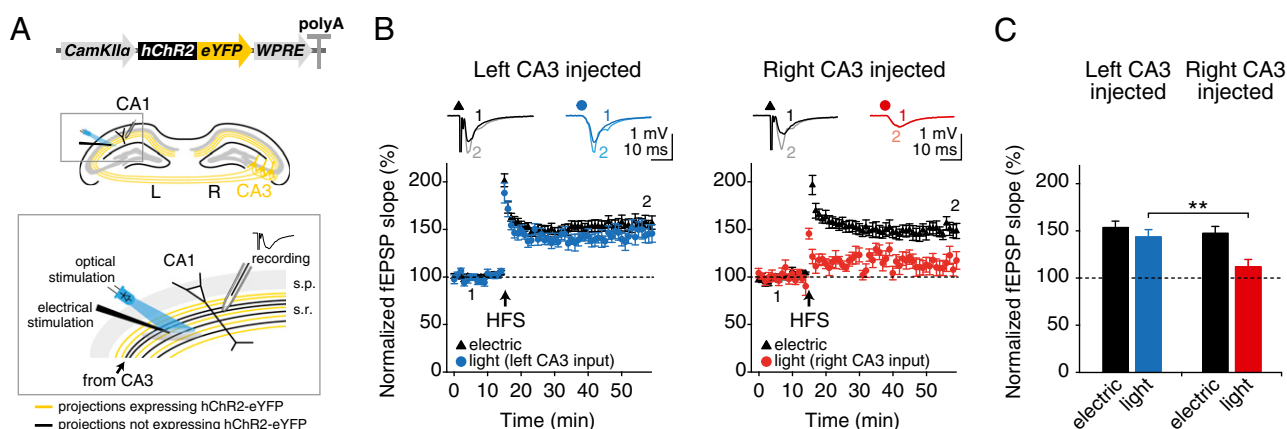


Fig. 4. High-frequency stimulation-induced LTP is asymmetrically expressed at the CA3–CA1 pyramidal cell synapse. (A, Upper) Adeno-associated virus containing hChR2-eYFP construct under the control of a CaMKII α promoter was unilaterally injected into the dorsal CA3 area of C57BL/6J mice. (Lower) An electrode to deliver nonselective electrical stimulation was placed in the stratum radiatum and a high-power 470-nm LED was arranged to recruit an overlapping population of projections. Optical stimulation only recruits projections originating in the CA3 of the injected hemisphere (yellow), whereas electrical stimulation is nonselective (black and yellow). Electrical stimulation was used to deliver the high-frequency LTP induction protocol and the effects were monitored via field recording of EPSPs evoked by electrical or optical stimulation. (B) HFS produces robust LTP in the electrical pathway (black triangles), but LTP is only expressed in the optical pathway (circles) when projections originate in the left CA3. (Insets) Representative field EPSPs at the indicated time points (1, 2). (C) Significantly more LTP is observed in left-injected mice than in right-injected mice in the optical pathway. Broken lines represent baseline. Error bars represent SEM. ** $P < 0.01$, Student's t test.

a hippocampus-dependent long-term memory task. In contrast, unilateral silencing of either the left or the right CA3 causes a short-term memory deficit on hippocampus-dependent tasks. Together, these results show that there is a dissociation between the hemispheric involvement in short-term memory and long-term memory. We also found that high-frequency stimulation-induced LTP is only expressed at CA3–CA1 synapses when presynaptic input originates in the left CA3.

Unilateral hippocampal lesions in mice have not revealed a distinct hemispheric contribution to long-term memory (25), although split-brain mice with left eye deprivation showed greater spatial memory accuracy than those with right eye deprivation when the environmental complexity increased (26). Studies in rats have either shown no effect of unilateral lesions (27, 28) or no asymmetry of hippocampal function (27, 29), or have produced inconsistent findings (30–32). However, the chronic nature of surgical, and even pharmacological, manipulations can allow compensatory changes to develop. Acute optogenetic silencing can circumvent such adaption, which may explain why our unilateral silencing of a relatively small volume of cells in the mouse hippocampus produced considerable memory deficits; nevertheless, there may also be a larger indirect silencing effect from our manipulation at the CA3 network level, given its recurrent connectivity.

Optogenetic manipulations can provide new insights into the networks normally engaged during memory tasks (18), and thus enable a precise dissection of the functional roles of the areas within the hippocampus. Here we have found that the left CA3 is a key component in the hippocampal circuitry that supports long-term memory. Synaptic plasticity has been proposed as a cellular model for learning and memory (21), and it is likely that LTP or other NMDAR-dependent processes are important for accurate performance on spatial long-term memory tasks, although a causal relationship remains elusive. Therefore, it is tempting to speculate that the functional asymmetry relates to the synaptic asymmetry in the mouse hippocampus; CA3–CA1 synapses originating in the left CA3 have a high density of postsynaptic GluN2B subunit-containing NMDARs and show LTP, whereas CA1 spines that receive right CA3 input have a low density of GluN2B subunits, and do not exhibit LTP (9–11). In support of the interpretation that plastic synapses typical of left CA3–CA1 are required, a mutant mouse line that lacks synaptic asymmetry (homozygous *inversus viscerum* mice), instead having only synapses characteristic of those receiving right CA3 input in wild-types (33), is impaired on hippocampus-dependent short- and long-term memory tasks relative to heterozygous controls (34), whereas overexpression of GluN2B enhances LTP and improves hippocampus-dependent memory performance (35). Thus, our findings could be accounted for by a hippocampus-intrinsic mechanism, whereby these two types of synapse receive equivalent information but perform distinct information processing or storage functions. Our manipulation affects both the ipsilateral and contralateral CA3–CA1 projections originating in one hemisphere; although both ipsilateral and contralateral projections do show equivalent LTP in rats (36) and mice (11), we currently cannot exclude the possibility that they play independent roles. It is also conceivable that the asymmetry in long-term memory is explained either completely or in part because the left and right CA3 receive different information, akin to how the distinct functional contributions of dorsal and ventral hippocampus might arise through differences in first- and second-order inputs (37). One possible source of asymmetry before the hippocampus might be the

lateral entorhinal cortex (LEC) input to dorsal hippocampus; the left LEC exhibits a higher metabolic demand than the right LEC (38), which may be indicative of distinct computational demands present in the neuronal circuitry. Asymmetry may even exist at the level of sensory inputs (30). These explanations are not mutually exclusive, however, because the different types of synapses receiving left compared with right CA3 input may have evolved in concert with such nonhippocampal asymmetries to optimally process different types of incoming information.

In contrast to the unique requirement for the left CA3 in a long-term memory task, unilateral silencing of the CA3 in either hemisphere was sufficient to impair hippocampus-dependent short-term memory. Thus, left CA3 silencing is not always more disruptive to hippocampal function than right CA3 silencing, which rules out trivial surgical or technical explanations for the left-NpHR deficit on the hippocampus-dependent long-term memory task, a conclusion supported by the equivalent implant placements between behavioral groups. This result further suggests that asymmetry does not arise from a different efficacy of silencing between hemispheres. Moreover, it corroborates the supposition that mechanisms supporting short- and long-term memory are dissociable (23). The reason why left or right CA3 silencing can cause an impairment in short-term memory may be because short-term memory requires a higher proportion of the hippocampal circuitry for effective performance, or necessitates communication between the CA3 in each hemisphere. Alternatively, the same result could arise if the left and right CA3 play independent, but equally necessary, roles in the activity required for short-term memory. One such role could relate to gamma oscillations, which have been closely linked to short-term memory (39), and, interestingly, a left–right asymmetry of gamma power was recently reported in the CA1 of the rat hippocampus following environmental enrichment (40).

The functional division of labor in memory processes that we have uncovered in the mouse suggests there could be parallels with the hippocampal asymmetry found in humans. Thus, left–right human hippocampal differences may not be a simple reflection of the lateralization in language processing (41) but, instead, asymmetry could be a fundamental characteristic of mammalian hippocampal function. In humans, a higher level of lateralization is associated with increased cognitive performance (42). Thus, hippocampal asymmetry may have arisen early in evolution and has been maintained to facilitate more efficient use of bilateral neural substrates. Such asymmetry might enable the hippocampus to support functions both in memory and in navigation (43), and could provide a synaptic mechanism by which the two can interact to underlie spatial long-term memory performance.

Materials and Methods

We used a total of 138 male C57BL/6J mice in this study. All procedures were performed in accordance with UK Home Office Regulations and approved by the License Review Committee at the University of Cambridge. For detailed methods and experimental procedures, see *SI Materials and Methods*.

ACKNOWLEDGMENTS. We thank R. Deacon for advice on behavioral testing; I. Goshen, L. Gunaydin, and T. Davidson for optogenetic advice; G. W. Y. Ang for helpful discussion; and R. Jude Samulski and the University of North Carolina Vector Core for manufacture of viral constructs. This research was made possible by grants from Alzheimer's Research UK and the Biotechnology and Biological Sciences Research Council (BBSRC), and additionally supported by an OXION Wellcome Trust Prize Studentship (to O.A.S.), a BBSRC Studentship (to M.E.), and a Royal Society Travel Grant (to M.M.K.).

1. Squire LR, Zola-Morgan S (1991) The medial temporal lobe memory system. *Science* 253(5026):1380–1386.
2. Morris RG, Garrud P, Rawlins JN, O'Keefe J (1982) Place navigation impaired in rats with hippocampal lesions. *Nature* 297(5868):681–683.
3. Eichenbaum H, Sauvage M, Fortin N, Komorowski R, Lipton P (2012) Towards a functional organization of episodic memory in the medial temporal lobe. *Neurosci Biobehav Rev* 36(7):1597–1608.

4. O'Keefe J, Dostrovsky J (1971) The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat. *Brain Res* 34(1):171–175.
5. Squire LR, et al. (1992) Activation of the hippocampus in normal humans: a functional anatomical study of memory. *Proc Natl Acad Sci USA* 89(5):1837–1841.
6. Igloi K, Doeller CF, Berthoz A, Rondi-Reig L, Burgess N (2010) Lateralized human hippocampal activity predicts navigation based on sequence or place memory. *Proc Natl Acad Sci USA* 107(32):14466–14471.

7. Hutslar J, Galuske RAW (2003) Hemispheric asymmetries in cerebral cortical networks. *Trends Neurosci* 26(8):429–435.
8. Motley SE, Kirwan CB (2012) A parametric investigation of pattern separation processes in the medial temporal lobe. *J Neurosci* 32(38):13076–13085.
9. Kawakami R, et al. (2003) Asymmetrical allocation of NMDA receptor epsilon2 subunits in hippocampal circuitry. *Science* 300(5621):990–994.
10. Shinohara Y, et al. (2008) Left-right asymmetry of the hippocampal synapses with differential subunit allocation of glutamate receptors. *Proc Natl Acad Sci USA* 105(49):19498–19503.
11. Kohl MM, et al. (2011) Hemisphere-specific optogenetic stimulation reveals left-right asymmetry of hippocampal plasticity. *Nat Neurosci* 14(11):1413–1415.
12. Gradinaru V, et al. (2010) Molecular and cellular approaches for diversifying and extending optogenetics. *Cell* 141(1):154–165.
13. Deacon RMJ, Bannerman DM, Kirby BP, Croucher A, Rawlins JNP (2002) Effects of cytotoxic hippocampal lesions in mice on a cognitive test battery. *Behav Brain Res* 133(1):57–68.
14. Deacon RMJ, Rawlins JNP (2006) T-maze alternation in the rodent. *Nat Protoc* 1(1):7–12.
15. Sanderson DJ, et al. (2007) Deletion of glutamate receptor-A (GluR-A) AMPA receptor subunits impairs one-trial spatial memory. *Behav Neurosci* 121(3):559–569.
16. Reisel D, et al. (2002) Spatial memory dissociations in mice lacking GluR1. *Nat Neurosci* 5(9):868–873.
17. Schmitt WB, Deacon RMJ, Seeburg PH, Rawlins JNP, Bannerman DM (2003) A within-subjects, within-task demonstration of intact spatial reference memory and impaired spatial working memory in glutamate receptor-A-deficient mice. *J Neurosci* 23(9):3953–3959.
18. Goshen I, et al. (2011) Dynamics of retrieval strategies for remote memories. *Cell* 147(3):678–689.
19. Lyon L, et al. (2011) Fractionation of spatial memory in GRM2/3 (mGlu2/mGlu3) double knockout mice reveals a role for group II metabotropic glutamate receptors at the interface between arousal and cognition. *Neuropsychopharmacology* 36(13):2616–2628.
20. Bliss TV, Collingridge GL (1993) A synaptic model of memory: Long-term potentiation in the hippocampus. *Nature* 361(6407):31–39.
21. Martin SJ, Grimwood PD, Morris RG (2000) Synaptic plasticity and memory: An evaluation of the hypothesis. *Annu Rev Neurosci* 23:649–711.
22. Ramirez S, Tonegawa S, Liu X (2013) Identification and optogenetic manipulation of memory engrams in the hippocampus. *Front Behav Neurosci* 7:226.
23. Bannerman DM, et al. (2014) Hippocampal synaptic plasticity, spatial memory and anxiety. *Nat Rev Neurosci* 15(3):181–192.
24. Shipton OA, Paulsen O (2014) GluN2A and GluN2B subunit-containing NMDA receptors in hippocampal plasticity. *Philos Trans R Soc Lond B Biol Sci* 369(1633):20130163.
25. Gerlai RT, McNamara A, Williams S, Phillips HS (2002) Hippocampal dysfunction and behavioral deficit in the water maze in mice: An unresolved issue? *Brain Res Bull* 57(1):3–9.
26. Shinohara Y, et al. (2012) Right-hemispheric dominance of spatial memory in split-brain mice. *Hippocampus* 22(2):117–121.
27. Li H, Matsumoto K, Watanabe H (1999) Different effects of unilateral and bilateral hippocampal lesions in rats on the performance of radial maze and odor-paired association tasks. *Brain Res Bull* 48(1):113–119.
28. Jerman T, Kesner RP, Hunsaker MR (2006) Disconnection analysis of CA3 and DG in mediating encoding but not retrieval in a spatial maze learning task. *Learn Mem* 13(4):458–464.
29. 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(4):552–564.
30. LaMendola NP, Bever TG (1997) Peripheral and cerebral asymmetries in the rat. *Science* 278(5337):483–486.
31. Poe GR, et al. (2000) Partial hippocampal inactivation: Effects on spatial memory performance in aged and young rats. *Behav Neurosci* 114(5):940–949.
32. Klur S, et al. (2009) Hippocampal-dependent spatial memory functions might be lateralized in rats: An approach combining gene expression profiling and reversible inactivation. *Hippocampus* 19(9):800–816.
33. Kawakami R, Dobi A, Shigemoto R, Ito I (2008) Right isomerism of the brain in *inversus viscerum* mutant mice. *PLoS ONE* 3(4):e1945.
34. Goto K, et al. (2010) Left-right asymmetry defect in the hippocampal circuitry impairs spatial learning and working memory in iv mice. *PLoS ONE* 5(11):e15468.
35. Tang YP, et al. (1999) Genetic enhancement of learning and memory in mice. *Nature* 401(6748):63–69.
36. Bliss TV, Lancaster B, Wheal HV (1983) Long-term potentiation in commissural and Schaffer projections to hippocampal CA1 cells: An in vivo study in the rat. *J Physiol* 341(1):617–626.
37. Ohara S, Sato S, Tsutsui K, Witter MP, Iijima T (2013) Organization of multisynaptic inputs to the dorsal and ventral dentate gyrus: Retrograde trans-synaptic tracing with rabies virus vector in the rat. *PLoS ONE* 8(11):e78928.
38. Khan UA, et al. (2014) Molecular drivers and cortical spread of lateral entorhinal cortex dysfunction in preclinical Alzheimer's disease. *Nat Neurosci* 17(2):304–311.
39. Fuchs EC, et al. (2007) Recruitment of parvalbumin-positive interneurons determines hippocampal function and associated behavior. *Neuron* 53(4):591–604.
40. Shinohara Y, Hosoya A, Hirase H (2013) Experience enhances gamma oscillations and interhemispheric asymmetry in the hippocampus. *Nat Commun* 4:1652.
41. Bishop DVM (2013) Cerebral asymmetry and language development: Cause, correlate, or consequence? *Science* 340(6138):1230531.
42. Gotts SJ, et al. (2013) Two distinct forms of functional lateralization in the human brain. *Proc Natl Acad Sci USA* 110(36):E3435–E3444.
43. Eichenbaum H, Cohen NJ (2014) Can we reconcile the declarative memory and spatial navigation views on hippocampal function? *Neuron* 83(4):764–770.