Figures and figure supplements

The right hippocampus leads the bilateral integration of gamma-parsed lateralized information

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Figure 1. Experimental paradigm and clean out of the Schaffer and CA3som activities. (A) Functional characteristics of the bilateral CA3→CA1 segment: (1) an intrinsic gamma oscillator fueled by inhibition in each CA3 region produces gamma output from PCs; (2) The left and right CA3-PCs are interconnected through the ventral hippocampal commissure (VHC, maroon arrows), enabling the coupling of CA3 gamma oscillators; (3) The excitatory outputs of CA3-PCs from both sides converge in each CA1 (Schaffer and Commissural pathways). (B) Experimental setup. Two-shank linear arrays were located at homotopic sites of the dorsal left and right hippocampi. Recordings were acquired simultaneously and each group was analyzed separately by an Independent Component Analysis (ICA). (C) ICA of a sample epoch across the CA1 and CA3/DG layers. In raw LFPs (black traces), several bands of coherent voltage fluctuations are observed that indicate multiple activation in different synaptic territories (three are outlined by filled ovals spanning the CA1 and the Dentate subfields, while small maroon ovals mark activity in the st. pyramidale of the CA3). The ICA returns the spatially-coherent components and provides readout of the temporal dynamics free of a contribution by the others. A set of components or LFP-generators was obtained per shank, each with a characteristic spatial distribution or voltage weight ($V_{wt}$) that enabled matching between shanks. Details of the extraction are in Figure 1—figure supplement 1. Colored traces from top to bottom: Schaffer (cyan), CA3som (maroon), lacunosum-moleculare (green), and GCsom (purple). The amplitudes are normalized (0.37:0.25:0.84:1). In other figures voltage units are employed that were estimated for the sites with maximum power (triangles in $V_{wt}$ plots).

Figure 1 continued on next page
Figure 1—figure supplement 1. Details of the extraction and ICA performance. To illustrate the performance of the ICA, we chose sample epochs in which two nearby sources produce rhythmic LFP waves of similar duration that makes the respective time courses hardly recognizable by the naked eye: Black, LFPs; color, ICA components. (A) Mixed contributions by the Schaffer (cyan) and lacunosum-moleculare (l-m) components (green). A phase mismatch of LFP waves recorded in contiguous sites (vertical lines) indicates pathway co-activation (recall that a single pathway produces proportional LFPs in all sites). The differences between time courses of LFP and ICA waves denote the net volume-conducted contribution that each pathway entered on the other’s site: this is removed by the ICA (bicolor arrows). (B) Example of LFPs in the CA3/Dentate Hilus containing CA3som waves and DG-contributed potentials. Only the first CA3som wave, a, is visible as it does not coincide with any other, but the waves b and c overlap in space and time with Hilar waves. The respective spatial distributions are however different. Hilar waves are nearly identical in all recording sites and hence, deviations from the time course in some sites indicate the presence of additional sources. CA3som wave b occurs at a negative hilar deflection (arrowheads: the difference of LFP and the dashed time courses mark the site-specific contribution of the CA3som wave), while wave c does so on a positive-going hilar wave, modifying the slope of LFPs at CA3som specific sites.

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Figure 2. Functional asymmetry in the bilateral CA3-CA1 system. (A) Sample string of Schaffer-gamma obtained from four sites. Individual waves coincide regardless of their amplitude. Globally, Schaffer-gamma is larger on the right side. The scheme shows the location of recordings from a coronal view (Figure 2—figure supplement 1). (B–E) Representative experiment showing the features of individual waves compared pairwise within (La, Lp) and between hippocampi (La,Ra) (n = 6623 pairs of waves in 167 s). The blue and red dots belong to the pairs when L or R waves were longer, respectively. The population statistics and additional examples are in Figure 2—figure supplements 2–3. (B) Waves co-vary closely in the same side (left) and much less so between sides (right): a, best fit tangent; r, correlation coefficient. The insets show superimposed averaged waves (cal: 20 ms and 100 μV). (C) A string of Schaffer gamma shows unilateral waves in both sides (triangles). In paired bilateral waves, either side may lead (ovals). (D) Bilateral synchronization was measured from the start of the waves (time lag). The positive and negative values indicate that L or R waves led, respectively. R waves preceded more often (black bars), the bilateral lag being larger when R-waves were longer (line subplot in blue). (E) The amplitude difference between paired waves in the right and left sides is plotted against their time lag. Larger waves on any side had a tendency to lead.

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The following source data is available for figure 2:

Source data 1. Spreadsheet containing measurements of the LFP generators and extracted waves for each experiment.
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Source data 2. Schaffer LFP generators and extracted waves for the experiments used in Figures 2 and 4.
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Figure 2—figure supplement 1. Histological and electrophysiological localization of recording sites. (A) The location of recording sites was reconstructed from histological sections in six animals. The tracks left by the twin-

Figure 2—figure supplement 1 continued on next page
shank linear probes were recognized by Dil marks in the tissue (pictures of one illustrative experiment are shown below), and drawn on sagittal representations of the rat hippocampus taken from the atlas of Paxinos and Watson. The indicated lateral coordinate is only an approximation to actual site. The extent of recordings across the CA1 and CA3/Dentate subfields (colored bars) has been scaled and adjusted by the location of cell body layers in the CA1 and CA3 using the characteristic evoked potentials recorded simultaneously from all four shanks (star: stimulus in the left CA3b soma layer). The st. pyramidal of the CA1 and CA3 are marked by filled and open triangles, respectively. Dots mark the stimulus artefact. (B) An epoch containing spontaneous LFPs and an evoked potential (color code indicates the recording sites in A). The black traces belong to the CA3 soma layer where CA3som waves appear (arrows). Cyan ovals mark the Schaffer potentials in the CA1 st. radiatum (note that stimulation in the left CA3 also activates Schaffer fibers in the right-hand side through antidromic firing of the CA3). Black ovals mark recurrent excitatory waves in the st. radiatum of the CA3. Note also the correspondence of amplitude differences of equivalent waves originated in different subfields to recording sites: closer to the CA3 (CA3som and st. radiatum CA3 waves) or to the DG (asterisks). DOI: 10.7554/eLife.16658.008
**Figure 2—figure supplement 2.** Additional data and population statistics for the comparison of intra and interhippocampal CA3→CA1 Schaffer activity. (A) Intra (upper row) and interhippocampal (lower row) wide band spectral coherences between Schaffer-LFPs. Δt is the length of the epoch analyzed. SPWs were excluded manually to avoid adding an excessive weight of slow frequencies to the analysis. Blue areas correspond to statistically significant coherences (gray areas mark the level of statistical significance; surrogate test, n=1000). Interhippocampal Schaffer coherence was lower in all animals and centered in 40–45 Hz gamma frequency (arrows). (B,C) Population statistics for the comparisons as in the representative experiment shown in Figure 1B and D of the main text. (B) Cross-correlation coefficient (CC) for the co-variance of amplitude between the paired waves in all seven experiments. The diagonal red line marks equal CC for intra than interhippocampal comparisons. All values lie below the diagonal, indicating a lower CC between L and R homotopic sites compared to the intrahippocampal sites. In a t-test of the data all values were significant (p<0.001) except one (blue square, p<0.05). (C) Population statistics for the lag between the paired waves in the two hippocampal hemispheres (L,Ra). Negative values indicate that waves in the R led to L. Black symbols stand for all pairs, while the blue and red symbols belong to the pair subclasses when R or L led, respectively. The mean confidence intervals at α = 0.01 are shown.

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Additional sample traces of Schaffer activity simultaneously obtained from CA1 homotopic sites. R and L traces are depicted in black and cyan, respectively. The upper and lower fragments correspond to 1 s epochs (taken 2 s apart) of tight and loose bilateral co-variation, respectively. Note the coarse (slow waves/groups of gamma waves) and the fine (individual gamma waves) bilateral amplitude co-variation of the gamma oscillations in the upper traces, and the frequent mismatch of amplitude in paired (bilateral) waves in the lower traces, which however maintained tight L-R synchrony. Such epochs of tight and loose co-variation were intermingled and occurred unpredictably. Since individual Schaffer gamma waves reflect the size and firing synchronization of CA3 pyramidal cells forming a functional assembly, tight bilateral covariation indicates a sequence of CA3 assemblies that are parallel in both hemispheres of the hippocampus, while loose bilateral co-variation indicates lateralized strings of CA3 assemblies that notwithstanding, beat at a similar pace.

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Figure 3. Assessment of functional asymmetry with Granger causality and phase relations. (A) A short epoch of activations of the right and left Schaffer pathways. (B) F-statistics for Granger Causality (GC) test revealing significant reciprocal influence from R to L and from L to R sides. (C) Frequency dependence of GC. R to L relation exhibits a peak at gamma frequency. (D) Time-frequency display of the GC index. R to L relationship is stronger and more persistent. (E) Distribution of phases in the L side with onsets related to zero phases in the R side, i.e., when field events begin. The mean phase lag of 0.22 rad (corresponding to 0.95 ms time lag) is highly significant. The population data is indicated in the text.

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Figure 4. CA3soma gamma activity has weak bilateral coherence but is coupled to ipsilateral Schaffer. (A) Comparison of CA3soma activities between pairs of sites. The histograms of spectral coherence only show significant values (blue) for ipsilateral comparisons. The sample traces show tight matching in superimposed activities at a-p sites (upper traces) and frequent mismatch in bilateral comparisons in the same epoch (lower traces). Cyan and black traces correspond to the left and right sides. (B) Comparisons between Schaffer and CA3soma activities (blue and maroon traces, respectively). The spectral coherence showed significant values only at gamma frequency at all four sites. Sample traces show strong wave-to-wave coupling despite the poor amplitude covariation. The CC was strong and showed a marked left-shift that mostly originates from the different waveform of individual waves. All data were taken from the same animal (see population statistics in the text, and additional analyses in Figure 4—figure supplement 1).

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Figure 4—figure supplement 1. Additional features of the CA3\textsubscript{som} activity and waves. (A) Statistics of extracted bilateral CA3\textsubscript{som} waves from a representative experiment. Waves co-vary closely in the same side (left panel) and much less so between sides (middle panel): a, best fit tangent; r, correlation coefficient. The panel on the right shows the quantification of time lags between bilateral paired waves. Same color coding as in Figure 2. See population statistics in the text. (B) Correlation between Schaffer and CA3\textsubscript{som} activities at the same site shows distinct dynamics over different time scales. The upper pairs of superimposed plots represents the time envelope of Schaffer (cyan) and CA3\textsubscript{som} activities (maroon) calculated with a different sliding windows (1 or 0.1 s). A notable reduction in the CC for the smaller time scale denotes mismatch of the convolved waves, as noted in Figure 4—figure supplement 1 continued on next page