Neuroscience 130 (2005) 519–526

A TEST OF THE REVERBERATORY ACTIVITY HYPOTHESIS FOR HIPPOCAMPAL 'PLACE' CELLS

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Abstract—One of several tenable hypotheses that can be proposed to explain the complex dynamics of spatially selective hippocampal neural activity postulates that the region of space over which a given cell receives its external input is actually much smaller than the classical 'place field.' According to this notion, the later portions of the field reflect some form of network hysteresis resulting from 'reverberatory' activity within reentrant, synaptically coupled cell assemblies within the hippocampus. This hypothesis predicts that transient, global inhibition, induced after the onset of firing, might truncate the remainder of the place field. To test this hypothesis, principal afferents to the hippocampus were stimulated bilaterally in rats running on a circular track, evoking widespread inhibition throughout the hippocampus, and abolishing all spike activity from simultaneously recorded populations of CA1 pyramidal cells for periods of 150–300 ms. Stimulation at any point within the place field of a given cell suppressed firing only for such brief intervals, followed by an immediate resumption for the remainder of the field. These results suggest that without additional cellular and/or synaptic mechanisms, reverberatory activity alone within the hippocampus does not account for the shape and spatial extent of place fields.

Key words: memory, place cell, cell assemblies, inhibition, network, theta.

Despite decades of study, the cellular and network level dynamics underlying the expression of location-specific firing in hippocampal neurons ('place cells'; O'Keefe and Dostrovsky, 1971) remain poorly understood. The simplest explanation is that the classical place field is shaped directly by external sensory input (McNaughton et al., 1983a; Eichenbaum et al., 1989; O'Keefe and Burgess, 1996). Abundant evidence against the sufficiency of such a model exists (O'Keefe and Conway, 1978; Muller et al., 1987, 1994; McNaughton et al., 1989; Quirk et al., 1990; Sharp et al., 1990; Bostock et al., 1991; Markus et al., 1994; Gothard et al., 1996a,b; Barnes et al., 1997; Knierim et al., 1998; Skaggs and McNaughton, 1998; Wood et al., 2000; Bower et al., 2002; Ferbinteanu and Shapiro, 2003). In particular, which hippocampal cells fire in a given sensory context depends strongly on internal state variables such as distance moved from the last known reference point, the state of the head direction system, behavioral set, and recent memory.

A second class of models suggests that place cell firing is in some sense predictive of future locations (Muller and Kubie, 1989). Several models (Jensen and Lisman, 1996; Tsodyks et al., 1996; Wallenstein and Hasselmo, 1997) suggest that the phenomenon of phase precession (O'Keefe and Recce, 1993; Skaggs et al., 1996) is accounted for by asymmetric connections in the network (Mehta et al., 1997), through which activity is propagated forward from the current location representation during each θ cycle. In such models, most of the classical place field reflects a network-based prediction of the rat's arrival at a point near the end of the place field and is not the result of direct sensory input.

A third class of model can be proposed in which the classical place field is shaped largely by some form of 'reverberatory' network dynamics (e.g. Hebb, 1949). The most general form of such a model would be that the determination of which cells fire at a given location is governed by an interaction between the current state of network activity and the current input to the hippocampus from elsewhere in the brain. External information may trigger the initial firing as the rat enters the field, but, according to this hypothesis, subsequent firing represents some form of reverberation, which could be due to either network effects or intrinsic cellular dynamics. For example, Koulakov et al. (2002) have invoked such mechanisms to model neural integrator circuits whose activity could persist following a discrete input. It is possible that, in the hippocampus, a short history of recent experience would be replayed during each θ cycle. As the rat moves in space, new information would be added to the top of the reverberation stack and old information would drop off the bottom, resulting in the gradual phase shift. Evidence consistent with such a model comes from the observation that, if a rat exits from a variably located start-box, the firing pattern for the first few seconds is independent of the location of the box in the room or of the direction the rat turns upon leaving the box (Gothard et al., 1996a,b; Redish et al., 2000), indicating that the firing is determined entirely by inputs that occurred at an earlier time. Similarly, although firing patterns while running in two directions on a simple linear track are normally uncorrelated (McNaughton et al., 1983a), if the rat changes direction abruptly in the midportion of the track, the currently active cells continue to fire while the rat begins to move in the opposite direction

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0306-4522/05$30.00+0.00
doi:10.1016/j.neuroscience.2004.09.044

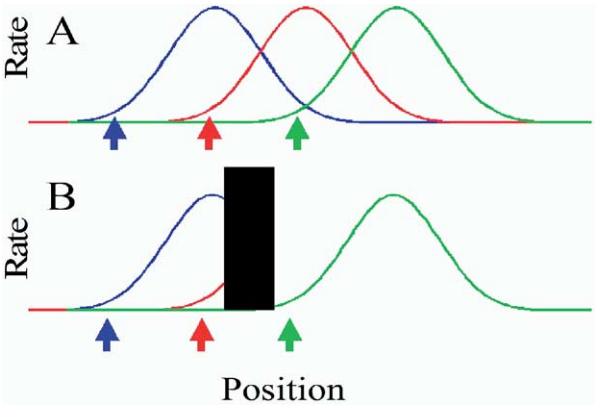

Fig. 1. Diagrammatic representation of the prediction of the recurrent activity hypothesis in its simplest form. (A) Information (colored arrows) leading to the activation of specific hippocampal neurons arrives near the beginning of the place field (colored Gaussians). The remainder of the place field is a consequence of network and/or intrinsic cellular dynamics which cause the firing to persist beyond the initial point. (B) Induction of brief but strong inhibition (black rectangle) abolishes all firing. According to the simplest form of the reverberation hypothesis (see introduction and Discussion), this should terminate the firing of place cells responding to earlier inputs, thus truncating the place field.

where the cell normally does not fire (Redish et al., 2000). An extreme variant of such models is the 'path integration' scheme, in which the selection of which cells fire at a given position can be completely independent of external input per se, but may depend only on the earlier state of the hippocampal network, the pattern of intrinsic connections, and the distance and direction that the rat moves (O'Keefe and Speakman, 1987; Redish and Touretzky, 1997; Samsonovich and McNaughton, 1997).

A recurrent activity-based model would depend either on some form of LTP-like associative synaptic coupling of sequential network states (e.g. Samsonovich and McNaughton, 1997) or on some form of persistent membrane current specific to the currently active cell assembly (Lisman et al., 1998; Wang, 1999) that would bias the active population such that it might recover spontaneously and selectively after a period of inhibition. In the absence of such effects, such a model predicts that transient but complete inhibition of spike activity in the network could abolish information about its recent history. Thus, when the network is allowed to recover from inhibition, the nascent activity might either be random, or at least depend only on the current input. In other words, either a 'remapping' might be expected as the system recovers, or at the very least, the cells that were firing in the latter portions of their place fields at the onset of inhibition would not recover. The latter hypothesis is illustrated in Fig. 1. A method of testing this prediction arises from the fact that electrical stimulation of the hippocampus or its major afferents evokes powerful, widespread inhibition through feed-forward and feedback inhibitory pathways (Andersen et al., 1963, 1964; Alger and Nicoll, 1982; Douglas et al., 1983; Buzsáki, 1984; Mizumori et al., 1989). The present experiment was designed to exploit this phenomenon to test the reverberatory activity hypothesis.

EXPERIMENTAL PROCEDURES

Surgical procedures

Data were obtained from three male Fisher-344 rats (20–24 months old, approximately 350 g) that underwent bilateral implantation of bipolar teflon-insulated stainless-steel electrodes (coated diameter 0.0045 inch) for stimulation of the perforant pathway (8.1 mm posterior to bregma, 4.4 mm lateral to the midline, approximately 2.5–3 mm ventral to brain surface). The stimulus field included entorhinal cortical layer II inputs to CA3 and the dentate gyrus as well as direct inputs to CA1 from entorhinal layer III. A 'hyperdrive' containing 12 tetrodes each consisting of four Teflon-coated 13 μm nichrome wires (McNaughton et al., 1983b; Wilson and McNaughton, 1993; Gothard et al., 1996a) was implanted unilaterally for recording from multiple CA1 neurons in the right dorsal hippocampus (approximately 3.8 mm posterior to bregma and 2.5 mm lateral to the midline). Two additional tetrodes served to record a neutral reference signal in the corpus callosum and an EEG signal from the vicinity of the hippocampal fissure (optimized for θ amplitude). Rats were anesthetized with Nembutal (sodium pentobarbital, 40 mg/kg). Surgeries were conducted according to NIH guidelines and IACUC approved protocols. Efforts were made to minimize the number of animals used as well as any suffering potentially associated with the surgery or the experiments.

Behavior and recording procedures

Prior to and after surgery, the animals were placed on food restriction to approximately 85–90% of their *ad libitum* weight, and trained to walk around a circular track 1.2 m in diameter, for food reinforcement delivered at random locations, once per lap. The track was located in a 4×4 m, sound-attenuating room containing multiple visual cues. The track was cleaned between trials. The recording instrumentation and computers were located in the adjacent room. During recording, the hyperdrive was connected to a multichannel, impedance matching, unity gain headstage (Neuralynx Inc., Tucson, AZ, USA). The output of the headstage was conducted via a lightweight multiwire tether and commutator to the signal processing amplifiers and Neuralynx 'Cheetah' data acquisition system. Light emitting diodes on the headstage were tracked at 60 Hz using a video system (approximately 0.3 cm/pixel). Unit activity was filtered with a bandpass of 600 Hz–6 kHz. Spike waveforms above a 40 μV threshold were timestamped and digitized at 32 kHz for 1 ms beginning near spike onset, and EEG activity from the hippocampal fissure was recorded continuously in the 1–350 Hz band.

Recording sessions included a period of track running flanked on either side by periods of 15–30 min rest in a nest placed in the center of the track. Animals were allowed to run for 40 laps around the track. During laps 11–20 and 31–40, bilateral perforant path stimulation was delivered every 4 s. The stimulus intensity was selected so as to maximize the amplitude of the monosynaptically evoked population spikes in the dentate gyrus whose currents can be detected at the hippocampal fissure and CA1 pyramidal layers due to volume conduction. For the first several sessions, stimuli consisted of single, 100 μs, 500–800 μA, constant current, cathodal pulses that evoked the maximum short-latency population spike. In later sessions, two-pulse bursts were delivered with an inter-pulse interval of 60 ms in order to maximize and prolong the duration of inhibition. In order to reduce the possible contribution of external sensory input to the recovery of firing after inhibition, some sessions were conducted in complete darkness, under the control of an experimenter wearing night vision goggles.

Single unit spike trains were extracted from the tetrode spike waveform data using a combination of BBCLUST (P. Lipa, University of Arizona) and MCLUST (A. D. Redish, University of Minnesota) clustering software. During the period of approximately 30 ms following each electrically evoked synaptic response

it was not possible reliably to isolate single units, due to the synchronous nature of the population spikes. Although some of the highest amplitude spike clusters did exhibit some spike events during the 10–20 ms time-windows of the population spikes (Fig. 2), no reliable estimate of overall unit firing probabilities could be obtained during these epochs.

RESULTS

Analysis of the data from freely moving rats was conducted both at the population level and at the level of single units. For population analysis, spikes from all isolated cells were pooled and perievent histograms of total pyramidal cell activity were constructed around the perforant path stimulus events (Fig. 2). Single pulse stimulation resulted in a transient elevation of pyramidal cell firing in the window of the population spike, followed by complete cessation of all recorded pyramidal cell discharge for periods of 130–200 ms, followed by gradual recovery. Double-pulse stimulation produced a more prolonged inhibition of spontaneous activity (Fig. 2B, C). Spontaneous activity was suppressed for periods substantially exceeding the typical duration of $GABA_A$ IPSPs (Dingledine and Langmoen, 1980), including the period from about 40 to about 100 ms, during which evoked population spikes typically exhibit a post-inhibitory facilitation (Austin et al., 1989; Green et al., 1993). Recovery was complete after 500–1000 ms, both when room lights were on and in total darkness (Fig. 2B vs. C). Because a large majority of spontaneous spikes occur within a cell's place field, the data in Fig. 2 reflect the average recovery time of place fields irrespective of the position in the field at which the stimuli were delivered.

A total of 96 of the most well-isolated pyramidal cells exhibiting clear and stable place fields on the circular track were selected for detailed, lap-by-lap analysis. Spike rasters with independent variables of space (Fig. 3) or time (Fig. 4) were constructed on a lap-by-lap basis centered on the midpoint of the place-field or its crossing time respectively. Those laps in which one or more stimuli occurred within the overall average place field were sorted according to the position of the stimulus within the field on each lap. This enabled the determination of whether there was any effect on the recovery time of unit firing depending on where in the field the stimuli were delivered. The reverberatory activity hypothesis elaborated in the introduction predicts that stimulation might result in either termination of the place field or a complete 'remapping' of the place field distributions. Stimulation at any point within the place fields resulted in a clear, but transient hiatus in cell firing, but in none of the recorded cells, including those recorded in darkness, was there any evidence for either truncation of the place field after stimulation within it, or remapping. As long as the stimulation was delivered within about 200 ms of the end of the average place field, place-specific firing typically resumed within about 200 ms. Recovery of firing was always observed under these conditions (96/96 neurons). The illustrations in Figs. 3 and 4 are from double-pulse experiments in which inhibition was maximal.

DISCUSSION

Abundant previous evidence, based on both anatomy and physiology, indicates that perforant path or direct hippocampal stimulation evokes widespread inhibition throughout the hippocampus. First, many hippocampal interneurons have very extensive axonal arbors, that spread for several millimeters in the rostrocaudal axis of the hippocampus (Freund and Buzsáki, 1996) and, in some cases, into the contralateral hippocampus (Seress and Ribak, 1984; Goodman and Sloviter, 1992). These interneurons receive direct projections from excitatory afferents and are activated with far lower stimulus intensities than those required to evoke population spikes (Buzsáki and Eidelberg, 1981; Fox and Ranck, 1981; Mizumori et al., 1989). Second, both CA3 pyramidal cells (Henze et al., 1997) and hilar mossy cells (Scharfman et al., 1990; Scharfman, 1991), which project for long distances in the longitudinal axis of the hippocampus, are activated by granule cell output at low threshold and, in turn, activate inhibitory interneurons at low threshold, providing strong feed-forward inhibition (Douglas et al., 1983; Buzsáki, 1984) over widespread areas of the hippocampus (Lømo, 1968). Unilateral perforant path stimulation that evokes an ipsilateral population spike results in commissural field potentials and strong inhibition of perforant path evoked population spikes in the contralateral hippocampus (B. L. McNaughton, unpublished observations), and stimulation at the same coordinates and intensities as those used for the unit recording experiments evokes paired pulse inhibition in both dorsal and ventral hippocampus (M.-B. Moser, E. I. Moser, C. A. Barnes, and B. L. McNaughton, unpublished observations), suggesting that the inhibition is widespread.

In the freely moving animals, bilateral stimulation of the major hippocampal afferent pathway from the entorhinal cortex evoked strong postsynaptic inhibition that was sufficient to abolish all spontaneous activity in pyramidal cells recorded in the dorsal CA1 region, for periods of 130–300 ms. Stimulation within the place field of a given cell, however, failed to disrupt the continuation of location-related firing more than transiently. In no case was there any evidence for either a failure of resumption of firing within the field or a remapping of the place field distribution, even when the experiment was conducted in total darkness. The present results thus fail to support the simplest form of the reverberatory activity hypothesis, which postulates that firing in the latter portions of a place field may reflect persistent spiking activity in the hippocampal network related to information received near the beginning of the place field, but no longer present at the input stage. We conclude that the spatial extent of place fields is not disrupted by effectively silencing the network for approximately one θ cycle. Thus, in the absence of additional mechanisms discussed below, the shape of the place field is unlikely to depend on a simple, short term, reverberatory memory mechanism, at least not within the hippocampus per se.

Two slightly more complex mechanisms of persistent activity should be considered, which might be more robust against transient inhibition than simple reverberation. A transient form of associative synaptic potentiation, lasting a few

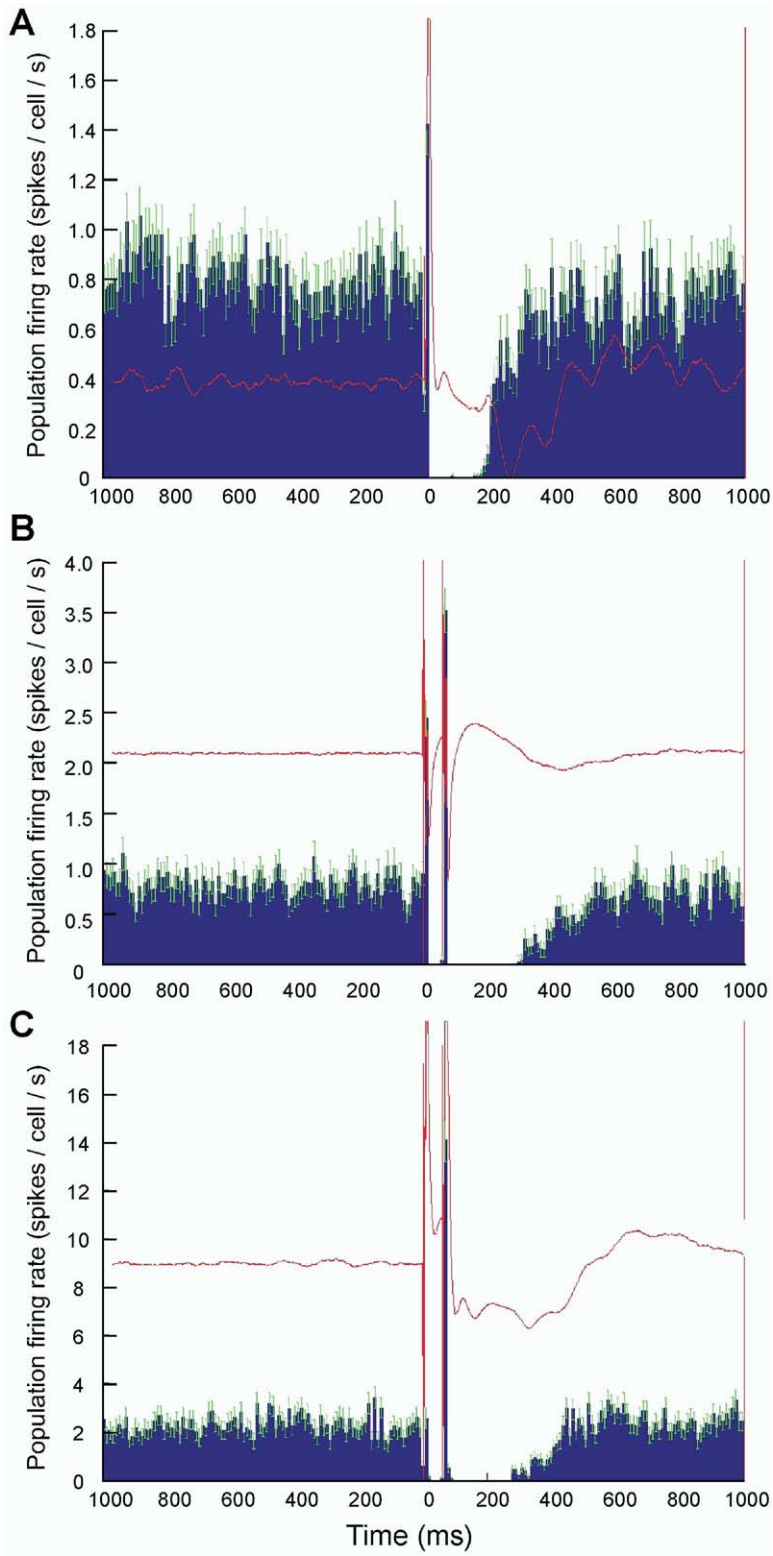

Fig. 2. Representative perievent histograms showing the population average of CA1 pyramidal cell firing rate (dark blue bars; means±S.E.M.) and EEG (red trace) before and after bilateral stimulation of the perforant pathway with single pulses (A) or double pulses at a 60 ms interval (B, C). The data are aligned to the onset of the first stimulus pulse (Time 0). A and B were performed with room lights on; C was performed in total darkness. Stimuli evoked large short latency population spike discharges followed by prolonged, complete inhibition of pyramidal cell discharge. Because virtually all of the spontaneous firing of the included cells occurs within the cells' place fields, this population average represents the average recovery time of the place fields following stimulation at any point within them. Examples from individual cells are given in Figs. 3 and 4. These results show that CA1 place

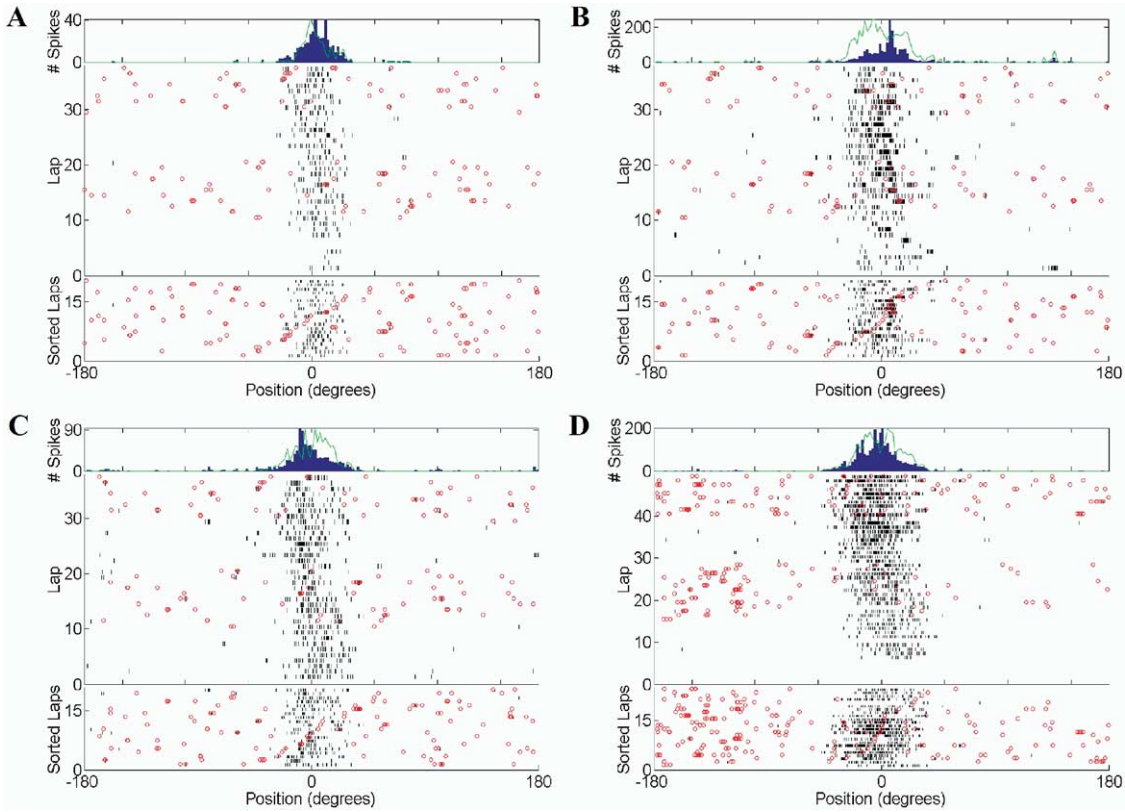

Fig. 3. Illustrations of stimulation effects on spatial firing of individual cells. The firing is illustrated with respect to position on the circular track in angular units, centered on the peak firing location. Total spikes (blue histograms) and occupancy normalized firing rates (green curves) are shown at the top. The middle portion of each figure shows lap-by-lap firing, with spikes indicated by black tic marks and stimuli as red circles. At the bottom of each example, laps with stimuli are sorted with respect to the position of the stimulus within the place field. Data in D in this and the following figure were collected in total darkness. These plots show that spatially specific firing within each lap is not abolished following the period of inhibition.

hundred milliseconds, might bias the network to return to its preceding state following inhibition, even in the absence of specific sensory information. All forms of such transient potentiation in hippocampus observed to date, however, involve non-associative changes in transmitter release probability and hence are non-selective (McNaughton, 1980, 1982) and could not support the formation of new cell assemblies. Nevertheless, one can postulate a scenario by which non-selective changes in release probability might bias the network to reactivate existing cell assemblies that were active prior to inhibition. If the synapses that support the recurrent activity have undergone a form of LTP that magnifies the effect of changes in presynaptic transmitter release (McNaughton, 1982), then a recurrent network might be statistically biased to reactivate the most recently active cell assembly because its members would have more short-term-facilitated synapses on average than non-members, and would thus be more likely to respond to any random input. To our knowledge, such a non-associative mechanism for maintaining reverberatory activity in a pre-existing cell assembly has not been carefully explored through simulation. An additional possible mechanism that has been studied (Lisman et al., 1998) is the possibility of a persistent depolarization due to voltage dependent activation of ion channels with long time constants, such as the NMDA receptor channel. This mechanism was postulated as a solution to the problem of maintaining reverberatory activity in recurrent networks with sparse connectivity and sparse activity. It is difficult to find parameters for such realistic networks that sustain reverberation using synapses with time constants comparable to AMPA receptor channels. The non-linearity of the NMDA channel (or other voltage-gated, long lasting channel) generates a persistent depolarization only in those cells that were recently activated, biasing them to respond preferentially to subsequent inputs. As the authors have pointed out, such a mechanism would also provide a basis for Hebb's (1949) initial assumption that reverberation facilitates the formation of cell assemblies. There are two arguments against a role of the NMDA channels underlying the recovery of place fields from inhibition in the present case, however. First, at least in

fields are not significantly truncated by transient, global inhibition and hence the results do not support the reverberatory activity hypothesis as presented. Note the appearance of θ waves in the averaged EEG trace after stimulation in A, suggesting that θ activity may have been reset at the time of stimulation in some cases (Givens, 1996). The data in A, B and C are based on averages of 45, 25, and 18 simultaneously recorded pyramidal cells, respectively.

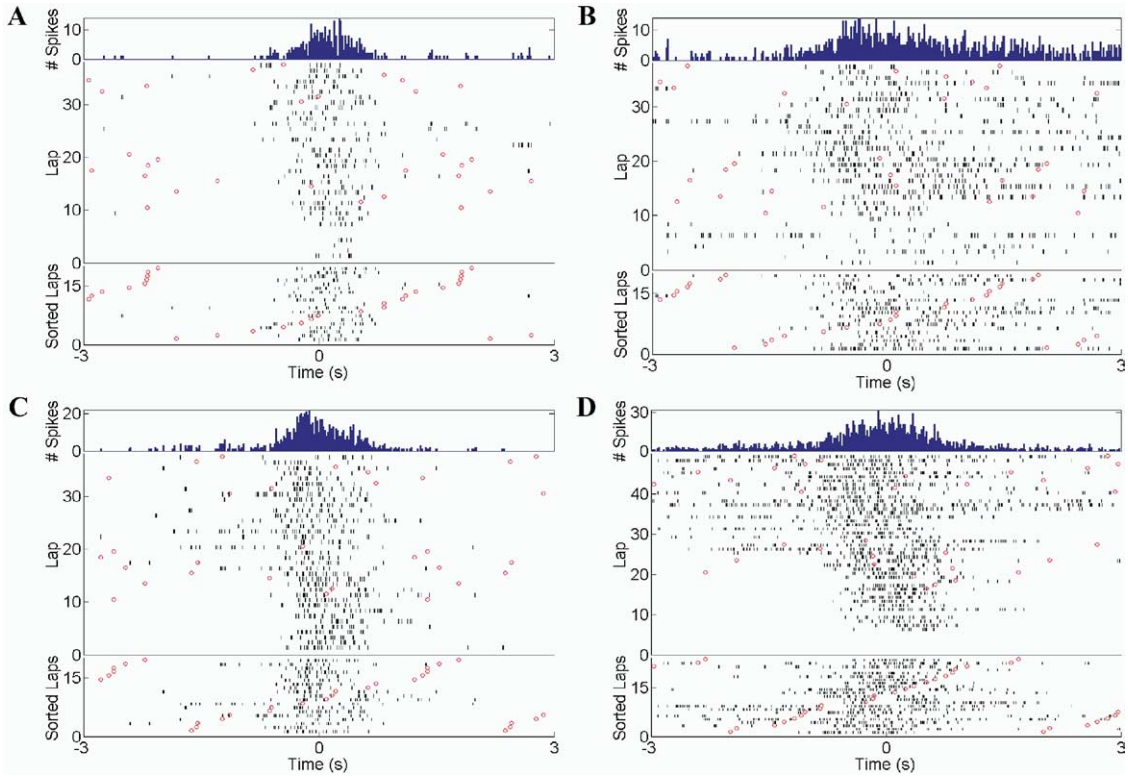

Fig. 4. Stimulation effects on temporal firing dynamics for the same individual cells illustrated in Fig. 3. The firing is illustrated with respect to time (±3 s), centered on the moment the rat passed the center of the place field on each lap. Total spikes (blue histograms) are shown at the top. The middle portion of each figure shows lap by lap firing, with spikes indicated by black tic marks and stimuli as red circles. At the bottom of each example, laps with stimuli are sorted with respect to the timing of the nearest stimulus to the crossing time of the place field center on each lap. These plots show that firing within each lap is only transiently abolished by the period of inhibition, recovering within less than 300 ms, as long as the rat remained within the average place field.

the presence of external cues, place fields are not truncated by doses of NMDA receptor activity that block LTP and associative learning (Kentros et al., 1998; Ekstrom et al., 2001), and second, the time constant of the hippocampal NMDA channel does not appear long enough to sustain excitability for 150 ms or more.

The 150–300 ms required for the recovery of spontaneous activity (Fig. 2) is of interest given the observation, based on evoked population spikes, that the hippocampus is actually in a hyperexcitable state (Green et al., 1993) during this period. Presumably, the prolonged silence of hippocampal principal cells reflects the time necessary for the propagation of excitatory information to the hippocampus from other brain regions. It cannot be ruled out that some of these regions may sustain persistent neural activity that might lead to restoration of hippocampal place fields without further external sensory input. Thus, although in the absence of the additional synaptic mechanisms just discussed, recurrent dynamics within the hippocampus itself do not appear to account for the spatial extent of place fields, persistent activity propagated from other sites cannot presently be excluded. In particular, given the equally rapid recovery of spatially selective firing in total darkness, the present results are consistent with the hypothesis proposed by Redish and Touretzky (1997) that there is a path integration system which is external to the hippocampus and which does not necessarily rely on information from it. This appears certainly to be true in the case of angular path integration. In the present case, due to the circular nature of the apparatus, position could have been uniquely predicted from head orientation, and thus information arriving from the head-direction cells (Taube et al., 1990) may have been sufficient to restore the hippocampal spatial correlate. Nevertheless, the present data support the idea that if the spatial extent of place fields is determined by recurrent activity mechanism within the hippocampus itself there must be additional mechanisms involved besides mere spike activity.

Acknowledgments—Supported by PHS grants NS20331, AG03376 and MH01565, and a Centre of Excellence grant from the Norwegian Research Council (grant no. 145993/310). We thank the anonymous reviewers of a previous version of the ms for helpful suggestions.

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(Accepted 20 September 2004)
(Available online 13 November 2004)