Phasic Boosting of Medial Perforant Path-Evoked Granule Cell Output Time-Locked to Spontaneous Dentate EEG Spikes in Awake Rats

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INTRODUCTION

The hippocampal network of freely moving rats exhibits two major types of synchronized population activity: rhythmic oscillations and transient field events. The best characterized of these are the hippocampal theta rhythm and hippocampal sharp waves (SPWs). Both patterns are evident in extracellular field recordings. The theta rhythm is recorded throughout the hippocampus as a 6–10 Hz sinusoidal wave and reflects local membrane potential oscillations driven by rhythmic afferent input, most critically from medial septal neurons (Bland and Colom 1993; Buzsaki et al. 1983; Green and Arduini 1954; Petsche et al. 1954; Stewart and Fox 1990; Ylinen et al. 1995b). SPWs are recorded as negative field potential transients in stratum radiatum of field CA1 and are generated by synchronous firing of excitatory Schaffer collateral input from CA3 pyramidal cells (Buzsaki 1986; Chrobak and Buzsaki 1994; Suzuki and Smith 1987, 1988a, b; Ylinen et al. 1995a). Recently, Bragin et al. (1995) described a novel type of field event, the dentate spike (DS). DSSs are recorded as large (1–3 mV), positive-going field potentials of short duration (15–40 ms) in the hilar region of the dentate gyrus and are associated with synchronous firing of hilar interneurons.

These patterns of neuronal population activity are expressed during distinct stereotypic behaviors or behavioral states. Whereas the theta rhythm occurs during exploration, consummatory behaviors, and rapid-eye movement sleep (Bland and Colom 1993; Green and Arduini 1954), SPWs and DSSs occur aperiodically during still-alert wakefulness (SAL, or awake immobility), drowsiness, and slow-wave sleep (SWS) (Bragin et al. 1995; Buzsaki et al. 1983; Suzuki and Smith 1987). Thus with ongoing changes in behavioral state, the hippocampal network oscillates more or less continuously between a theta and SPW/DS mode of population activity. Studies on the theta rhythm suggest that neuronal excitability and synaptic plasticity are modulated by the timing of synaptic input relative to the phase of the rhythm (Huerta and Lisman 1995; Pavlova et al. 1988; Rudell et al. 1980). In this regard, much less is known about the functions of aperiodically occurring SPWs, and, in particular, DSSs.

The efficacy of neuronal transmission in the perforant path-granule cell pathway and the ability to induce long-term potentiation (LTP) at this site are both subject to state-dependent modulation (Austin et al. 1989; Buzsaki and Srebro 1989; Bramham and Srebro 1989; Cain et al. 1994; Green et al. 1993; Leonard et al. 1987; Winson and Abzug 1978). We have reported further that LTP induction is regulated in an all-or-none manner within behavioral states associated with DSSs (Bramham and Srebro 1989; Bramham et al. 1994). For example, during SWS (but not rapid-eye movement sleep), high-frequency stimulation induces either full LTP or no change in MPP responses. Given the phasic nature of the regulation, the possibility emerges that DSSs gate neuronal transmission and/or the ability to induce LTP. In previous studies, electrical stimulation of afferents was applied manually at random time points relative to spontaneously occurring population events. In the present study, we have used a method for DS-triggered stimulation to directly examine modulation of medial perforant path-granule cell transmission during DSSs in freely moving rats.

Synchronous firing of hilar interneurons during DSSs is...
considered to be triggered by synchronous activation of the perforant path (Bragin et al. 1995). The perforant path arises in the entorhinal cortex and provides monosynaptic excitatory input to granule cells, mossy cells, and various types of interneurons (Andersen et al. 1966; Han et al. 1993; Scharffman 1991). Granule cells, in turn, provide a major excitatory input to CA3 pyramidal cells through the mossy fiber pathway (Amaral and Witter 1989; Andersen et al. 1971; Blackstad et al. 1970). Despite the existence of a powerful disynaptic excitatory relay from the entorhinal cortex through granule cells to CA3, DSs are associated with a decrease or no change in CA3 pyramidal cell firing. Thus during DSs, the dominant action of the dentate gyrus on CA3 appears to be inhibitory, possibly due to feedforward inhibition by hilar interneurons (Sik et al. 1997). Here we demonstrate enhanced excitability of granule cells to MPP input, time-locked to DSs. DS events therefore may function to intermittently boost excitatory transmission to CA3 while simultaneously silencing CA3 output. Part of this work has been published in abstract form (Bramham 1996).

METHODS

Subjects

Eleven male Mol:SD rats (Møllegaards Avls-Laboratorium, Denmark) weighing between 250 and 300 g at the time of surgery were used as experimental subjects. Animals were housed in a temperature- and light-controlled vivarium (23°C), lights on 0700 h, lights off 1900 h] and supplied with food and water ad libitum.

Electrode implantation

Rats were anesthetized (chloral hydrate/pentobarbital, 17 mg and 3.9 mg/kg ip, respectively) and placed in a stereotaxic apparatus in the skull flat position, and burr holes of 1.5-mm diam were drilled on one side of the skull to accommodate electrodes placed at the following coordinates relative to bregma: 7.9 mm A-P, 4.2 mm M-L for stimulation of the MPP, and 3.9 mm A-P, 2.3 mm M-L for recording in the dentate gyrus. Rectal temperature was maintained at 37°C by a servo-heating pad. A bipolar twisted-wire stimulating electrode (Teflon-insulated stainless steel, 140-μm diam, 500-μm vertical tip separation) was lowered into the dorsomedial aspect of the angular bundle for selective stimulation of the MPP. After making a small slit in the dura, a vertical recording electrode array (6 tips, 120- to 150-μm vertical tip separation) was lowered slowly into the dorsal hippocampus until a positive-going field excitatory postsynaptic potential (f EPSP) of maximum slope was obtained from the bottom electrode in the dentate hilus. Both sharpened tungsten matrix-electrodes (75-μm diam, FHC, Brunswick, ME) and formvar-coated nichrome wires (65-μm diam; A-M systems, Everett, WA) were used for recording. The depth of the bottom electrode ranged between 200 and 300 μm below the level of the maximum negative-going f EPSP sink recorded in the middle-third of the dentate molecular layer. Electrophysiological criteria for assessing selective stimulation of the MPP were based on properties of the f EPSP waveform and the population spike evoked at different depths in the angular bundle, as previously described (Bramham et al. 1991). Two stainless steel jeweler’s screws threaded into burr holes in the frontal bones served as ground and reference electrodes. The electrode lead pins were inserted into a multichannel plastic connector socket and the assembly was secured in place with dental cement.

Experimental protocol

After implantation, rats were housed individually and allowed ≥10 days in their home cages to recover from surgery. Animals then were handled for 10 min and acclimated to the recording cage (30 cm square × 40 cm high) over two consecutive days. Preliminary electrophysiological recordings were carried out on the next 2 days. During recording, the rat’s headplug was connected to the electrophysiological apparatus via a light-weight, counterbalanced cable leading to a commutator mounted on the cage ceiling.

Rats were transferred from their home cages into the recording cage and allowed ≥30 min to habituate before starting data collection. Nine stimulus intensity levels ranging from subspike threshold to the maximum population spike were used for constructing input-output curves. These intensity levels were determined using manual stimulation in the SAL state as follows: level 1 was ≥60 μA below the population spike threshold and evoked a positive f EPSP wave, level 2 was 30 μA below spike threshold, level 3 was at the spike threshold, and levels 3–9 were incremented in steps of 40–80 μA with level 9 giving the maximal population spike response. Current intensities across all rats ranged from 20 to 600 μA. Pulses were biphasic of 150-μs pulse duration.

Input-output curves were collected using DS-triggered stimulation or random, manual stimulation. Stimulus delay ranges relative to the DS peak were 0–5, 40–50, 100–120, and 500–520 ms. These delays will be referred to as 0, 50, 100, and 500 ms. The order in which the delay data were collected was random. Data for each rat were collected during a period of 10–14 days. Two rats with unstable responses were discarded from further testing.

Behavioral state

All recordings were carried out during the light cycle between 0930 and 1500 h. Behavioral states were defined on the basis of the animal’s activity and hippocampal EEG. Field potential data were collected during the still-alert (SAL, or awake immobility) state. In this state, the rat is sitting or lying motionless with its eyes open and the electroencephalogram (EEG) shows low-voltage activity and irregularly occurring DSs. Evoked responses were collected only during spontaneous still-alertness as opposed to a stimulus-induced immobility or freezing. It was observed that DSs do not occur during the first few seconds after a startle response. Cain et al. (1994) have identified a state in which rats appear to be awake behaviorally yet exhibit an SWS-like EEG. To avoid collecting data in this state, the cage sometimes was rocked gently to ascertain if the rat was awake. Rats that were obviously drowsy were allowed to sleep. Field potentials also were collected in deep, stage 3/4 SWS in some rats. During SWS, the rat was lying down with its eyes closed, respiration was slow and regular, and the EEG was dominated by high-voltage, irregular delta waves (1–4 Hz).

DS detection and DS-triggered collection of evoked potentials

A computer program for DS-triggered stimulation was developed using DataWave Technologies WorkBench software (Longmont, CO). MPP stimulation was triggered when the hilar EEG signal crossed a positive threshold set at 5 ms before the mean DS peak. Stimulus delays were set at 0, 50, 100, 300, and 500 ms. Three-hundred–millisecond EEG segments extracted around the DS peak and stimulus artifact were stored to disk, allowing offline confirmation of DS detection and stimulus timing. Collection of the EEG events was carried out independently of the DS detection/stimulation routine. The latter routine was automatically shut off for 10 s after detection of an event. DS-triggered and manually triggered field potentials were eliminated from analysis if they
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FIG. 1. A and B: averaged traces of dentate spikes (27 events) and medial perforant path (MPP)-evoked field potentials (4 responses) recorded from the dentate hilus and molecular layer during still-alert wakefulness. Recordings were made using a vertical electrode array with 6 tips staggered at 120- to 150-μm steps from the dentate hilus into the CA1 field. Traces from the deepest electrode (in the dentate hilus) and the site of maximum MPP-evoked negativity are shown. Dentate spikes (DSs) were identified by their characteristic dipole across the 2 recording sites as well as their amplitude, waveform, and state dependency. Two of the 27 DS events averaged here were classified as type 2, the rest were type 1. Sampling rate is 3.3 kHz for the electroencephalogram (EEG) and 20 kHz for the evoked field potentials. Wide band-pass filter was 1 Hz to 10 kHz. DS traces were filtered digitally off-line (1 ± 200 Hz). MPP responses were collected using manual stimulation. Depth of the multielectrode array was positioned for optimal recording of field excitatory postsynaptic potentials (fEPSPs) in the dentate hilus. Because the recording sites in the molecular layer were separated by ~125 μm, the negativity recorded may not correspond to the site of maximal medial perforant-evoked negativity in the middle molecular layer.

 occurred within 500 ms of a DS. Manual stimulation therefore refers to random and explicitly non-DS-associated stimulation. DSs occasionally had several (2–5) distinct peaks. Responses triggered off of multiple-peak events were eliminated from analysis.

Because DSs and SPWs occur in the same behavioral states, the occurrence of overlapping events may complicate isolation of DS effects. In preliminary experiments, two electrode arrays were implanted in the dentate gyrus and CA1 region for dual recording of SPWs and DSs. Confirming an early report (Bragin et al. 1995), the two events rarely occurred together within a 150-ms time window (n = 2). Furthermore, in hilar EEG recordings, SPWs are either not discernible or they appear as low-amplitude slow waves that are readily distinguished from DSs.

Data analysis

Recorded signals were amplified, wide band-pass filtered (1 Hz to 10 kHz), digitized (20 kHz for field potentials; 3.3 kHz for the EEG), and stored to computer disk. Analysis of evoked field potentials was accomplished using DataWave Technologies WorkBench software. Standard measurements of dentate field potentials were obtained, including the maximum slope of the fEPSP, the height of the population spike measured from the negative apex to a tangent line between the two positive peaks, and the spike onset latency measured from the stimulus artifact to the first positive peak. Averages of four responses were obtained off-line. Analysis of variance (ANOVA) for repeated measures followed by a post hoc Scheffé’s test was used for statistical analysis of group input-output curves based on the raw data values (STATISTICA package, StatSoft, Tulsa, OK).

RESULTS

Identification of dentate spikes

Dentate spikes (DSs) were identified readily by their characteristic voltage-versus-depth profile, amplitude, duration, and state dependency. Figure 1 shows a typical averaged DS and a MPP-evoked field potential evoked by manual stimulation during SAL. DSs were recorded from the deepest electrode in the dentate hilus as positive-going spikes of 1- to 3-mV amplitude and 20- to 45-ms duration at the base. All DSs exhibited a dipole across recording sites in the hilus and dentate molecular layer. Two main types of DSs were identified on the basis of their depth profiles. The first type of DS, by far the most common, was either isoelectric or showed a small negativity at the level of the MPP-evoked negativity (Fig. 1A). A second type of DS showed a polarity reversal and much stronger negativity in the molecular layer. These two variants of DSs closely resembled the type 1 and type 2 DS described by Bragin et al. (1995). Type 2 DSs were very rare, however, comprising <10% of the total number of events. No attempt was made to distinguish between these two events in the subsequent stimulation experiments.

DS-associated enhancement of MPP-evoked transmission

Figure 2 shows EEG segments collected during manual and DS-triggered stimulation and the corresponding evoked field potentials. The timing of stimuli relative to the DS peak, and absence of a DS within a 500-ms time window

FIG. 2. Example traces showing DS-triggered stimulation and the effect on MPP-evoked field potentials. A: averaged (n = 4) 300-ms EEG traces collected during manual and DS-triggered stimulation in still-alert wakefulness. Stimulation was delivered on the positive peak of the DS (marked by the arrow). Manually evoked responses were accepted when they occurred in the absence of a DS within 500 ms of the stimulus. B: corresponding MPP-evoked field potentials. Note the large enhancement in the MPP-evoked population spike during DS-triggered stimulation. Signals were wide band-pass filtered (1 Hz to 10 kHz).
FIG. 3. A: averaged group input-output curves of the population spike (pop spike) amplitude, latency, and fEPSP slope obtained using DS-triggered stimulation (○) and manual stimulation (●) of the MPP. Values were normalized relative to the value obtained at the highest stimulus intensity (intensity level 9) on the input-output curve. Plots are means ± SE (n = 6). B: representative fEPSP-spike plot obtained using DS-triggered (○) and manual stimulation (●). DSs were associated with a marked increase in granule cell excitability to synaptic input. C: bar graph of population spike amplitude after DS-triggered and manual stimulation in still-alert wakefulness (SAL) and slow-wave sleep (SWS). DS-associated enhancement was obtained in both behavioral states.

on either side of the peak, were confirmed off-line. Stimulation on the peak DS was associated with a significant increase in the population spike amplitude and a reduction in population spike latency relative to manual stimulation, as can be seen from the field potentials in Fig. 2B and the group input-output curves of normalized response values in Fig. 3A (n = 6, P < 0.05, ANOVA of raw data for each response measure). A decrease in the fEPSP slope also was observed, but only at stimulus intensities well above the population spike threshold. Plots of the individual data revealed a marked leftward shift in the fEPSP-spike relation at all amplitudes of the fEPSP, indicating an increase in granule cell excitability to synaptic input (Fig. 3B). This pattern of effects was observed in six of six rats and was repeated readily in subsequent experiments examining the time course of DS enhancement.

In previous studies using manual stimulation, the perforant path-evoked population spike was found to be larger in SWS compared with SAL. This difference may be due to the higher incidence of DSs in SWS resulting in a greater probability of stimulating during a DS. We therefore compared DS-triggered and manual, non-DS–triggered responses in SWS. In SWS, as in SAL, DSs were associated with a larger amplitude of the population spike. This enhancement was superimposed on a state-dependent increase in the population spike amplitude (Fig. 3C; similar effects were obtained in 3 rats). The results confirm a state-dependent increase in granule cell excitability in SWS and dissociate this effect from DS enhancement.

**Time course of DS-associated enhancement**

We then assessed the time course of DS enhancement by varying the stimulus delay relative to the DS peak. Standard delays used were 0, 50, 100, and 500 ms. As shown in Fig. 4A, maximal effects on all response measures were obtained at zero delay, followed by a decline to nonsignificant, manual stimulation levels within 100 ms for the population spike amplitude, 50 ms for the spike latency, and 500 ms for the fEPSP slope (P < 0.05, n = 6). Field potentials from a representative experiment and EEG traces obtained at the time of stimulation are shown in Fig. 4, B and C, respectively. At 300-ms post-DS, the field potential waveform was essentially identical to the manually evoked response. Thus field potentials changes were time-locked to the DS yet clearly outlasted the fast spike component of the event.

**Paired-pulse inhibition**

Increased firing of hilar GABAergic interneurons during DSs would be expected to reduce, not enhance, granule cell excitability (Bragin et al. 1995). However, the circuitry within the hilus is complex and the little is known about the activity of specific classes of interneurons (Freund and Buzsaki 1996). Here we asked whether the enhancement of granule cell excitability was associated with a reduction of recurrent inhibition on granule cells. Paired-pulse inhibition of the population spike as obtained using a 15-ms interval between the conditioning and test pulses was assessed in two rats across a range of stimulus intensities. The effect of DS-triggered (0 delay) conditioning was compared with manual stimulation. As shown in Fig. 5, the population spike was inhibited completely in both manual and DS-triggered conditions, suggesting that enhancement of granule cell excitability is not due to a loss of recurrent inhibition.

**DISCUSSION**

The main results of the present study demonstrate that DSs are associated with enhanced excitability of granule
A: bar graphs show time course of DS-related enhancement. Values are expressed in percent of responses obtained using manual stimulation. Plots are means ± SE. DS-associated facilitation of the population spike (pop spike) is maximal on the positive peak and persists for ≈50 ms. At 500 ms, all field potential measures have returned to manual stimulation levels. *Significant difference relative to manual stimulation (P < 0.05, t-test dependent samples). B: MPP-evoked field potentials (mean of 4 responses) evoked at various delays after the DS peak. At 300 ms, field potentials had returned to the manual stimulation level. C: EEG traces (mean of 4 events) obtained at the time point of stimulation. Wide band-pass filter was 1 Hz to 10 kHz. Arrows mark the DS. *, late negative-wave component of the evoked field potential, likely representing disynaptic activation of hilar neurons and/or CA3 pyramidal cells (Berger and Yeckel 1991; Buzsaki 1988). EEG traces were averaged around the stimulus artifact. Averaged DS at 50 ms is wider than the individual DS events used in creating the average because of a 10-ms jitter in stimulus delay timing.

Dentate spike enhancement of granule cell excitability: specificity of the effect

Behavioral state-dependent gating of perforant path-granule cell-evoked responses was first demonstrated by Winson and Abzug (1978) and since has been replicated by a number of laboratories (Bramham and Srebro 1989; Cain et al. 1994; Hargreaves et al. 1990; Moser et al. 1994). For example, SWS is associated with enhancement of the population spike amplitude, a reduction in spike onset latency, and a reduction in fEPSP slope, relative to responses obtained using random, manual stimulation in the SAL state. This pattern of changes during SWS is similar to the DS-associated changes observed here, raising the possibility that the effect may be due to a behavioral state bias during collection of manual and DS-triggered responses rather than a true effect of DSs. For example, a “drowsy” behavioral state has been identified during which rats appear to be awake behaviorally (eyes open, lying flat), yet exhibit an SWS-like EEG (Cain et al. 1994; Pavlides and Winson 1989). Such a bias was excluded in the present study, most conclusively by virtue of the temporal relationship found between DSs and changes in MPP responses; maximum effects were obtained at the DS peak, after which they rapidly declined (<300 ms) to the manual stimulation level. By the same token, a state-related decrease in brain temperature, suggested to partly mediate the increase in granule cell excitability in SWS (Cain et al. 1994; Moser et al. 1993), cannot explain the present findings. We therefore conclude that neuronal transmission...
in the dentate gyrus is enhanced phasically in relation to single DSs in SAL.

**Mechanism and function of DS-associated enhancement**

The mechanism of DS generation and the associated increase in perforant path-granule cell excitability is unknown. Single-unit recordings have shown increased firing of putative dentate hilar interneurons during DSs (Bragin et al. 1995). This presents a paradox inasmuch as the firing of GABAergic interneurons would be expected to decrease, not increase, granule cell excitability.

Two main mechanisms seem plausible for the increased perforant path-granule cell excitability during DSs. 1) Perforant path activation of granule cells. This could be monosynaptic and/or disynaptic through perforant path activation of hilar mossy cells providing excitatory input to granule cells (Scharfman 1991, 1995). Current-source density analysis has suggested that the perforant path is activated during DS (Bragin et al. 1995). Furthermore, using intracellular recording in urethan-anesthetized rats, Penttonen et al. (1997) showed recently that granule cells are depolarized during DSs. The time course of the depolarization parallels the time course of enhanced MPP-granule cell excitability observed here, with decay to baseline outlasting the extracellularly recorded DS by ~200 ms. 2) Inhibition of inhibitory hilar interneurons, i.e., “disinhibition” of granule cells. Hajos et al. (1996) have identified a population of GABAergic hilar interneurons that contains vasoactive intestinal polypeptide (VIP) and calretinin and that innervates other nonprincipal hilar neurons, including GABAergic interneurons targeting granule cell dendrites. Increased firing of these VIP-containing interneurons have been postulated to play a major role in disinhibiting granule cells; they also may be driven by the perforant path as they have extensive dendritic arbors within the dentate molecular layer. Sik et al. (1997) have identified a population of interneurons that discharges preferentially during DSs and targets other hilar interneurons as well as granule cells. These interneurons also could be involved in a disynaptic inhibitory circuit. The fact that paired-pulse inhibition of the population spike was intact in the present study suggests only that the increased excitability of granule cells is not due to a loss of basket cell-mediated recurrent inhibition (Hajos et al. 1996; Ramón y Cajal 1893; Ribak et al. 1990; Sik et al. 1997); it does not exclude effects on other types of interneurons or multisynaptic effects in the interneuronal network. The circuitry is complex and incompletely understood: any direct inhibition of granule cells associated with interneuronal bursts may be counterbalanced by perforant path activation and disinhibition. The net effect, however, at least with regard to the MPP input, is enhanced granule cell excitability.

What is the function of DSs? Bragin et al. (1995) showed that DSs are associated with inhibition of CA3 pyramidal cell firing. DS events therefore are associated with boosting of perforant path-evoked granule cell transmission to CA3 in parallel with a powerful inhibition of CA3 pyramidal cells. By boosting excitatory input from the entorhinal cortex to CA3, DSs may represent a natural mechanism for generating plastic changes such as LTP at mossy fiber-CA3 synapses. Although the mechanism of CA3 inhibition is unclear, evidence suggests that it could be driven feedforwardly by hilar neurons projecting to CA3 pyramidal cells and interneurons (Frotscher 1989; Michelson and Wong 1991; Muller and Misgeld 1990, 1991; Sik et al. 1997). Silencing of CA3 pyramidal cells could prevent propagation of synchronous mossy fiber input, effectively uncoupling this circuit from downstream processing. As a provisional hypothesis, we suggest that DSs allow plastic changes to be induced in the CA3 region in isolation from events occurring elsewhere in the network, such as hippocampal SPWs.

Buzsaki and colleagues (Buzsaki 1989; Chrobak and Buzsaki 1994) have suggested previously that SPW bursts may represent a natural mechanism for generating LTP. A silencing mechanism, similar to that proposed here for DSs, also may exist for SPWs. SPWs are observed along a circuit of excitatory connections from the CA1 region, to subiculum, to deep layer (V–VI) entorhinal cortex. SPWs in the deep entorhinal cortex do not, however, have any immediate impact on superficial layer (II–III) entorhinal neurons (which give rise to the perforant path), although excitatory connections between these regions have been demonstrated (Bartesaghi et al. 1989; Chrobak and Buzsaki 1994, 1996; Pare et al. 1995). Perhaps DSs and SPWs mediate plastic changes in separate, yet interconnecting, segments of the entorhinal-hippocampal-entorhinal loop. Whereas DSs are triggered in the superficial entorhinal cortex and silenced in CA3, SPWs are triggered in CA3 and silenced in the superficial entorhinal cortex. As junctions between SPW and DS segments of the loop, the entorhinal cortex and CA3 regions may be critical sites for DS-SPW interactions.

Modulation of neuronal transmission and synaptic plasticity by state-dependent population activity only has been studied in detail for the theta rhythm. Studies in anesthetized rats and hippocampal slices have shown that synaptic excitability as well as the threshold and direction of plastic changes (long-term potentiation or depression) are determined by the timing of the synaptic input relative to the peak and trough of the theta wave (Huerta and Lisman...
1995; Pavlides et al. 1988; Rudell et al. 1980). The present findings are significant in demonstrating that neuronal transmission in the dentate gyrus is modulated powerfully in relation to an aperiodic population event in the dentate gyrus network of freely moving rats. Our previous studies have shown that, during behavioral states associated with DSs, LTP is induced in an all-or-none manner (Bramham and Srebro 1989; Bramham et al. 1994). This suggested the idea that DSs may actively modulate LTP induction as a function of the timing of stimulus trains relative to DS events. The method of event-controlled stimulation used in the present study will allow a direct test of the role of DSs and other network events in modulating synaptic plasticity in behaving rats.

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