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DIFFERENTIAL BEHAVIORAL STATE-DEPENDENCE IN THE BURST PROPERTIES OF CA3 AND CA1 NEURONS

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Abstract—Brief bursts of fast high-frequency action potentials are a signature characteristic of CA3 and CA1 pyramidal neurons. Understanding the factors determining burst and single spiking is potentially significant for sensory representation, synaptic plasticity and epileptogenesis. A variety of models suggest distinct functional roles for burst discharge, and for specific characteristics of the burst in neural coding. However, little *in vivo* data demonstrate how often and under what conditions CA3 and CA1 actually exhibit burst and single spike discharges.

The present study examined burst discharge and single spiking of CA3 and CA1 neurons across distinct behavioral states (awake-immobility and maze-running) in rats. In both CA3 and CA1 spike bursts accounted for less than 20% of all spike events. CA3 neurons exhibited more spikes per burst, greater spike frequency, larger amplitude spikes and more spike amplitude attenuation than CA1 neurons.

A major finding of the present study is that the propensity of CA1 neurons to burst was affected by behavioral state, while the propensity of CA3 to burst was not. CA1 neurons exhibited fewer bursts during maze running compared with awake-immobility. In contrast, there were no differences in burst discharge of CA3 neurons. Neurons in both subregions exhibited smaller spike amplitude, fewer spikes per burst, longer inter-spike intervals and greater spike amplitude attenuation within a burst during awake-immobility compared with maze running. These findings demonstrate that the CA1 network is under greater behavioral state-dependent regulation than CA3. The present findings should inform both theoretic and computational models of CA3 and CA1 function.

Key words: hippocampus, place cell, theta, learning, plasticity, epilepsy.

The hippocampal formation plays an important role in spatial navigation and the formation of certain types of memories (Scoville and Milner, 1957; O'Keefe and Nadel, 1978; Sutherland and Rudy, 1989; Cohen and Eichenbaum, 1993; Vargha-Khadem et al., 1997). To understand how the hippocampus processes information one needs to examine the manner in which hippocampal neurons respond to hippocampal and extra-hippocampal inputs. In addition to location-specific discharge (O'Keefe and Dostrovsky, 1971), CA1 and CA3 pyramidal "place cells" can fire single spikes or a fast series of spikes commonly referred to as a burst. Typically bursts contain two to six spikes at short intervals, with a progressive attenuation in the amplitude of the spikes within the burst (Kandel and Spencer, 1961; Ranck, 1973; Quirk and Wilson, 1999; Quirk et al., 2001). Both the burst and attenuation phenomena have been postulated to play an important role in information processing (Buzsáki et al., 1996; Lisman, 1997; Quirk et al., 2001; Harris et al., 2002). Hippocampal bursts are often assumed to have distinct physiological (Pike et al., 1999; Buzsáki et al., 2002) and/or computational functions (Lisman, 1997; Kepecs et al., 2002). Thus, bursts may enhance plasticity at both the pre-synaptic inputs that initiate a burst (Magee and Johnston, 1997; Pike et al., 1999) as well as cause supra-linear summation of excitatory postsynaptic potentials (EPSPs) at postsynaptic targets that would enhance postsynaptic potentiation (Cousens and Otto, 1998; Williams and Stuart, 1999; Thompson, 2000). Further the distinct temporal characteristics of a burst in contrast to a single spike may serve unique computational (neural coding) significance. Burst duration, the number of spikes per burst, or burst frequency could each serve specific coding functions (Harris et al., 2001; Kepecs et al., 2002).

The functional significance of CA3 and CA1 bursts however is not clear. Harris and colleagues (2001) analyzed the relationship between single spikes and bursts in CA1 during locomotor activity (theta) and slow wave sleep. CA1 bursting conveyed no unique information about spatial position as compared with single spikes, and the propensity to burst was most dependent on prior periods of neuronal silence during both behavioral states (Harris et al., 2001).

Both CA1 and CA3 pyramidal neurons exhibit burst discharges during locomotion associated with hippocampal theta, as well as during immobility and slow-wave sleep when the hippocampus exhibits sharp wave bursts (Buzsáki, 1989). Data however are quite limited about differences in the burst characteristics across behavioral states. Are there unique characteristics of the burst associated with distinct behavioral states? Further, since CA3 and CA1 pyramidal neurons have distinct cellular properties and receive quite distinct inputs (Fig. 1), does this lead to differences in their bursts characteristics as a function of behavior?

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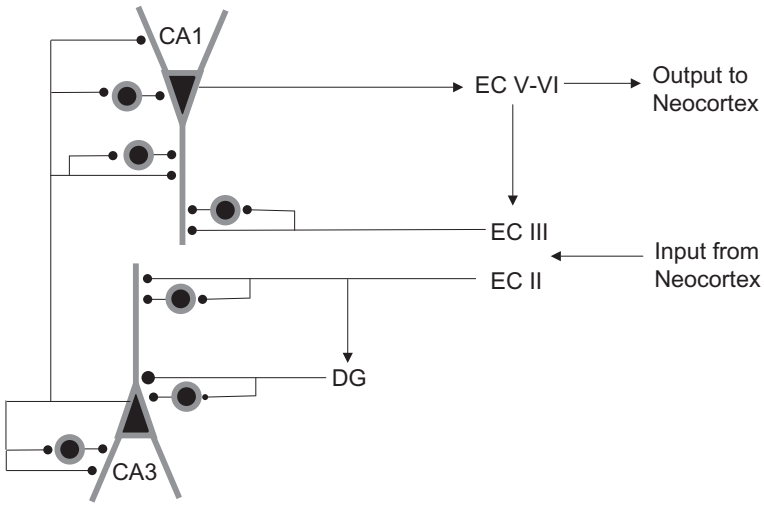

Fig. 1. The organization of EC inputs to the main subfields of the dorsal HPC (DG, CA3 and CA1) and the interconnections among these subfields. The principal glutamatergic drive onto CA3 pyramids (large pyramids) arises from the direct layer II input, the mossy fiber input from the DG and a massive recurrent input from CA3. The principal glutamatergic drive onto CA1 neurons arises from the direct layer III input and the Schaffer collateral input from CA3. Each major afferent input is associated with different classes of GABAergic neurons (shown as smaller circles innervating somatic or dendritic compartments) that can be activated in a feed-forward manner and which regulate bursting in somatodendritic compartments. The excitatory inputs to the GABAergic interneurons are illustrated to the somatic compartment for illustration purposes only. The bursting capacity of CA3 and CA1 pyramids is regulated by intrinsic membrane currents that can be altered by the dynamic interplay of glutamatergic and GABAergic input. Additional glutamatergic input to the DG, CA3 and CA1 arises from the amygdala and the nucleus reuniens of the thalamus. These inputs are largely absent from the dorsal hippocampus pyramids recorded in the present study. CA3 and CA1 neurons also receive a number of subcortical neuromodulatory inputs from the medial septum, hypothalamic nuclei and brain stem nuclei.

The present study examined differences in bursting properties of CA1 and CA3 neurons in awake-behaving rats. In an effort to inform theoretic discussion of hippocampal bursting and its role in sensory representation, memory consolidation and epileptogenesis, the present report details the similarities and differences in the burst discharge of CA3 and CA1 neurons during distinct behavioral states (awake-immobility and maze performance).

EXPERIMENTAL PROCEDURES

Subjects

Thirteen female Sprague–Dawley rats (approximately 6–8 months of age; Harlan, Indianapolis, IN, USA) were used in this experiment. This research was approved by the University of Connecticut Institutional Animal Care and Use Committee and conformed to all American Psychological Association ethical standards for the treatment and care of animals. The experimental procedures included measures to reduce the number of animals used and their suffering. Rats were singly housed in transparent plastic tubs, in a room with a 12-h light/dark cycle. All animals were weighed daily and extensively handled before any behavioral training. The recordings were conducted across the estrous cycle of these rats. No effects of the cycle were found on the burst firing characteristics of the cells (Tropp et al., 2005).

Apparatus and training procedure

All animals were mildly food deprived to 90–95% of their *ad libitum* body weights (Tropp and Markus, 2001). The testing environment consisted of a small room (2.1 m×2.1 m), which was dimly lit by lights from an open doorway. A "U" shaped runway was located in the center of the room and was raised 96 cm off the floor. The runway consisted of three black Plexiglas arms (width=10 cm). The total path length of the runway was 228 cm. Rats were pre-trained to alternate on the "U" shaped runway (Fig. 2) for food reinforcement (Noyes pellets; Research Diets, Inc., New Brunswick, NJ, USA) on an automated system (custom software A. Kuzin, University of Connecticut, Stoyes, CT, USA). The rats were given a 30-minute session each day to learn to alternate in the apparatus (from Feeder A to Feeder B). The animals were trained until they reached a criterion of 80 alternations for at least 4 days of training.

Surgery

After reaching criterion levels of performance, the animals received surgical implantation of an electrode microdrive for single unit recordings. Animals were anesthetized with a 4 ml/kg dose

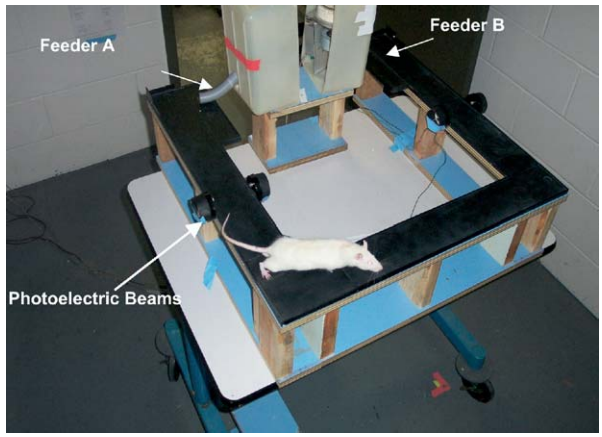

Fig. 2. Behavioral apparatus and training procedure. Animals were trained to alternate (from Feeder A to Feeder B) on a "U" shaped runway to receive a food reward. The animal made a total of 40 alternations during a recording session usually within 15 min.