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Functional diversity along the transverse axis of hippocampal area CA1

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Abstract

Decades of neuroscience research have shed lights on the hippocampus as a key structure for the formation of episodic memory. The hippocampus is divided into distinct subfields – CA1, CA2 and CA3. Whereas accumulating evidence points to cellular and synaptic heterogeneity within each subfield, this heterogeneity has not received much attention in computational and behavioural studies and subfields have until recently been considered functionally uniform. However, a couple of recent studies have demonstrated prominent functional differences along the proximodistal axis of the CA1 subfield. Here, we review anatomical and physiological differences that might give rise to heterogeneity along the proximodistal axis of CA1 as well as the functional implications of such heterogeneity. We suggest that such heterogeneity in CA1 operates dynamically in the sense that the CA1 network alternates, on a subsecond scale, between a state where the network is primarily

responsive to functionally segregated direct inputs from entorhinal cortex and a state where cells predominantly are controlled by more integrated inputs from CA3.

Introduction

The Cornu Ammonis (CA) of the hippocampus is typically divided into three subfields, CA1, CA2 and CA3, based on cellular morphology and synaptic inputs [1]. Each subfield has its own functional characteristics, with the uniqueness of each area being particularly prominent in the way information is represented at the neural ensemble level [2,3]. These CA subfields are connected by excitatory connections through the trisynaptic pathway, which for decades was thought to be the main pathway for transmission of information in the hippocampus [4]. The description of the trisynaptic circuit led to the idea that the CA subfields, especially the CA1 and CA3 regions, correspond to successive processing stages in a major feed-forward loop through the hippocampus. Later work has shown that cortical inputs reach each of the subfields directly [5-8] but the unidirectionality of the loop still makes the hippocampal circuit simple enough to be attractive to anyone interested in understanding circuit interactions in the mammalian cortex.

The most striking functional correlate of pyramidal cells in the CA regions is their tendency to fire at specific locations in the environment. The study of such cells began with O'Keefe and Dostrovsky's (1971) discovery of 'place cells' in the CA1 subfield. Place cells are cells that fire specifically when an animal is at a certain location. Different place cells fire at different locations, such that, as a population, place cells provide an accurate map of where the animal is at any given time [9]. Later studies, however, also reported a prominent representation of a number of other features of the environment in CA1 neurons, such as floor texture [10], odours [11-13], colour or shapes of experimental setups [14], passage of time [15,16] or motivational states [17,18]. It was not clear from the early studies whether those non-spatial features were represented by a separate class of neurons, or whether spatial and non-spatial features were encoded conjunctively in the same cells.

Is the CA1 population uniform, with place as a fundamental property on top of which other features are associated [19]? Or does CA1 have discrete sets of neurons dedicated for the processing of different types of information about the environment, possibly with a subset encoding mixtures of the two [20]? Recent studies have compared functional correlates in distinct parts of CA1. The results point to functional heterogeneity among CA1 neurons, although the observations do not rule out conjunctive coding of place and discrete object or event features. In this review, we first summarize these results and subsequently discuss its potential anatomical mechanisms and functional implications. We shall focus our discussion on CA1 because of the richness of the experimental data in this subfield.

Distinct coding in proximal and distal parts of CA1

The CA1 region of the rat hippocampus is large. In rats, CA1 spans ~3.2 mm x 3.5 mm of the antero-positerior and lateral-medial plane and almost ~6.0 mm of the dorso-ventral axis (Fig. 1A). Is there any functional distinction inside this wide area? In his original report, Lorente de Nó introduced subdivisions CA1a, CA1b and CA1c along the transverse axis based on the difference of connection to extrahippocampal regions [1]. To explore the possibility that representation of space varies along the transverse axis of CA1, Henriksen et al. (2010) recorded simultaneously from proximal CA1 (near CA3) and distal CA1 (near subiculum) using electrodes that spanned the entire axis [21]. The rats foraged randomly for cookie crumbs in open-field environments (Fig. 1C and D). The study showed that proximal CA1 cells have higher spatial specificity, with only one or few narrow place fields in a 2-m wide environment. By contrast, place cells in distal CA1 have more (up to 7) place fields in the same environment and the fields are wider, thus making the representation of space in each individual cell less specific.

The distinction between place cells in proximal CA1 and distal CA1 is consistent with functional gene-expression data. Hartzell et al. (2013) examined mRNA expression in CA1 of the immediate early gene *Arc* in animals exposed to different environments [22]. One group of animals explored one environment with the same object on two occasions; a second group explored two different environments with the same object. The authors performed fluorescence in situ hybridization for *Arc* mRNA and analysed its subcellular localization, which provides an estimate of neuronal activity in each of two environmental exposures [23]. The overlap of neuronal activity between environments, expressed by the subset of *Arc*-transcribing neurons, was significantly higher in distal CA1 than in proximal CA1. The results suggest that the difference between representations for the two environments is larger in proximal than distal CA1 [24]. Together with the unit recordings of Henriksen et al., these data suggest that proximal CA1 has a more crucial role than distal CA1 in distinguishing spatial environments and retaining such distinctions in memory [24,25].

What kind of information do neurons in the distal part of CA1 represent then? Burke et al. (2011) demonstrated that the firing rate and size of place cells in distal CA1 are sensitive to object manipulations, suggesting that distal CA1 cells respond to information about the properties of discrete objects [26], much in the same way as object-responsive neurons in the lateral entorhinal cortex [27,28], although it remains to be determined which properties of the objects control this activity. In a recent study, we asked whether simultaneously recorded distal and proximal CA1 cells exhibit different representation for odours – another non-spatial property of the environment – in a cued spatial memory task that requires odour-place associations [13]. The task is likely to require the hippocampus for acquisition [29]. The choice of an odour task in this study was motivated by the fact that CA1 has ‘odour cells’ that represent types of odour irrespective of the location where the odours were presented [11]. The odour input to CA1 is thought to provide a basis for storage of odour-based memory, and may come from olfactory regions such as the olfactory bulb and the olfactory cortex, via the lateral entorhinal cortex [30,31]. We recorded and compared spike activity of a population of

cells in distal and proximal CA1 when rats were sampling odour cues. The identity of the odour was predictive of where food was subsequently available. We found that, in distal CA1, a substantial fraction of cells gradually developed selective firing for one of the odours as the rats learned the odour-place association. By contrast, cell in proximal CA1 did not exhibit any selectivity for the odours, consistent with the notion that olfactory information is primarily represented in the distal part of CA1.

However, although cells in proximal CA1 and distal CA1 may have distinct coding properties, it is unlikely that there is a sharp border between proximal and distal CA1. As indicated, space is represented throughout CA1 but more accurately, or at higher information rates, in proximal than distal CA1, whereas information about object or odour identity, as well as its association with spatial location, is expressed primarily in the distal region. Because spatial information is present across the entire transverse axis, it comes as no surprise that, spatial and non-spatial information is combined in the activity of a large number of CA1 cells, giving rise to cells with conjunctive firing properties [12,32,33].

Proximal and distal CA1 differ in functional connectivity with entorhinal cortex

The diversity in spatial coding properties along the transverse axis in CA1 may reflect the differential connectivity of these regions with the entorhinal cortex (EC). The EC provides most of the input to the hippocampus, receives much of its output, and interfaces the hippocampus with a number of cortical regions (Fig. 2) [34,35]. In general, superficial layers of EC project to the hippocampus, whereas output from the hippocampus is sent back to the deep layers of the EC, which in turn project to the superficial layers of EC [36,37], forming a loop. The CA1 subfield receives entorhinal input via two major routes, often referred to as the direct and indirect pathways [35]. In the direct pathway, layer III neurons in EC have direct synapses onto CA1 pyramidal cells and

interneurons. In the indirect pathway, layer II cells in EC reach CA1 cells via synapses in the dentate gyrus and the CA3.

EC is anatomically divided into two distinct parts, lateral entorhinal cortex (LEC) and medial entorhinal cortex (MEC, Fig. 1C) [35]. Although these two regions are located next to each other and share the properties of an allocortical-neocortical transition cortex with four principal cell layers, they process distinct information. Principal cells in LEC exhibit less spatial modulation [38] but are instead strongly modulated by odours [10,13] or present or past encounters with discrete objects [27,28]. By contrast, the activity of a large proportion of the principal cells in MEC reflects the animal's location relative to the geometry of the environment. The largest class of spatial MEC neurons is the grid cells, which exhibit spike activity in a triangular grid-like pattern across the environment (Fig. 2B) [39]. The MEC network also contains head direction cells [40] and border cells [41]. Although the presence of object-related information in MEC data needs further investigation, the fact that MEC cells do not exhibit changes in firing rates (rate remapping) after environmental change [42] speaks against a major role for MEC in representation of discrete non-geometric environmental information. These putative functional LEC-MEC differences are thought to emerge from the differential cortical input of the two regions [30], as well as differences in the intrinsic firing properties of cells in these regions that may result from distinct biophysical properties and different intrinsic synaptic connectivity [43-46]. The differential representations of the two regions are further transferred to the hippocampus via separate projections [47].

In the direct pathway, LEC and MEC neurons project to different parts of CA1. LEC axons primarily project to distal CA1, whereas MEC projects to proximal CA1 [5,47,48]. The more prominent spatial representation of proximal CA1 cells compared to distal CA1 cells matches this anatomical distinction. Proximal CA1 cells have sharper place fields than distal CA1 cells presumably because proximal CA1 receives direct input from only from the medial part of EC. Representations in distal CA1 are more strongly modulated by objects likely because this part of

CA1 receives direct input only from the lateral part of EC. In contrast to this scheme, in the indirect pathway, axons from MEC and LEC converge on the same population of cells in DG and CA3, enabling integration of spatial and non-spatial information in the target neurons. The integration of spatial and non-spatial information in the DG and CA3 circuits may be essential for encoding and retrieval of episodic memory, which almost without exception has both spatial and non-spatial components [25]. The integrated representation of the DG and CA3 regions is likely projected to the CA1 region, across the entire transverse axis due to the termination pattern of the CA3 Schaffer collaterals. This implies that CA1 cells receive two sets of inputs – functionally segregated impulses through the direct pathway and functionally integrated impulses through the indirect pathway. The fact that CA1 cells toggle several times per second between a state of high coherence with slow gamma oscillations in CA3 and a state of coherence with fast gamma oscillations in MEC (Colgin et al 2009) suggests that the balance between the two sets of projections is dynamic, with direct and indirect influences potentially associated with different sets of computational operations.

However, while entorhinal cortex definitely provides the major cortical input to the hippocampus, it should not be forgotten that there are some additional connections that might also give rise to some of the functional distinction along the transverse axis of CA1. The postrhinal cortex has direct inputs to the most proximal part of CA1[49], whereas the perirhinal cortex innervates the distal-most part of CA1 [50,51]. Considering a role for the postrhinal cortex in visual- or spatial information processing [52,53] and that of the perirhinal cortex in object recognition [54,55], these two regions may contribute to the difference in functional correlates between proximal and distal CA1.

Dual recordings from entorhinal cortex and CA1

The idea that parallel pathways from MEC and LEC underlie some of the proximal-distal functional diversity in CA1 is further supported by dual recording experiments in CA1 and EC. Henriksen et al. (2010) compared not only firing fields but also spike timing of proximal CA1 and distal CA1 cells. It is known that spike timing of MEC neurons is modulated more strongly by theta oscillations than activity in LEC [56]. When spike timing of CA1 place cells in the Henriksen study was measured relative to the phase of theta oscillations recorded simultaneously in MEC, cells in proximal CA1 showed stronger modulation to the specific phase of MEC theta oscillations than cells in distal CA1 (Fig. 1C and D), as expected if MEC cells control also the temporal aspects of proximal CA1 cells.

In a recent study where we recorded neural activity in proximal and distal CA1 as animals learned an odour-place association task, we also asked whether characteristics of distal CA1 activity are discernible in the LEC, and whether coherent activity between LEC and distal CA1 is necessary for successful encoding and retrieval of odour information [13]. We found that local field potentials (LFP) in LEC exhibited strong oscillations in the 20 – 40 Hz band during the cue sampling period (Fig. 3B and C). This activation did not exist in MEC, which instead showed 65-100 Hz fast gamma oscillations during running [57]. In the hippocampus, the distal CA1 exhibited strong 20-40 Hz oscillations during cue sampling, as in LEC, whereas oscillatory activity in proximal CA1 occurred in a higher frequency band, between 30 and 50 Hz (Fig. 3D). Because communication between mutually connected brain areas is thought to be facilitated by synchronized oscillatory activity, we performed a coherence analysis to probe the degree of synchronization between activity in CA1 and EC. Only oscillations in LEC and distal CA1 (not proximal CA1, not MEC) showed strong coherence in the 20-40 Hz band during the cue interval, suggesting that LEC during this time window primarily communicates with distal CA1 in this frequency band (Fig. 3E). Spike activity during cue sampling that differentiated trials with different odour-place associations was more

prominent in LEC and distal CA1 than in MEC or proximal CA1, further supporting the idea that characteristics of LEC activity are reflected in distal CA1.

Neuromodulatory input to proximal and distal CA1

We have discussed data that point to a major role for differential MEC and LEC inputs in generating functional differences along the proximodistal axis of CA1. But is there also a difference in neuromodulatory input to proximal and distal CA1? Ito and Schuman (2012) used immediate-early gene *c-Fos* to test whether information about novel spatial context and novel objects is differentially processed along the proximodistal axis of CA1 [58]. They observed that, while exposure to novel objects primarily enhanced protein expression of c-Fos in distal CA1, exposure to a novel spatial context enhanced expression uniformly across proximal and distal CA1. The preferential c-Fos activation in distal CA1 following novel object exposure was largely abolished by blockers of dopamine (DA) receptors, indicating a crucial role of this neuromodulatory system in the preferential activation of distal CA1. The authors also tested the effect of DA modulation on synaptic efficacy on CA1 in a hippocampal slice preparation and showed that DA has a selective modulatory effect on LEC terminals in distal CA1 but not on MEC terminals in proximal CA1. As the release of DA in the brain is likely to reflect incentive value or novelty of external stimuli [59], the differential effects on distal and proximal CA1 cells may be critical for encoding of new information in the hippocampus. Differences in modulatory input may thus contribute to the functional heterogeneity of the CA1 subfield.

Differences in intrinsic cellular properties

Proximal and distal CA1 differ in connectivity with external brain areas but is there any difference in the intrinsic cellular properties of proximal and distal CA1 neurons? A recent study on gene expression in the hippocampus described a gradient expression of several genes along the proximodistal axis of CA1, implying that intrinsic physiological properties may be different in proximal and distal CA1. In whole-cell patch clamp experiments, Jarsky and colleagues (2008) explored this question [60]. One important physiological feature of pyramidal neurons in the hippocampus is their bursting property. Many studies have reported that bursting properties can be used to define two distinct populations of CA1 pyramidal neurons: bursting (or early bursting) and non-bursting (or late bursting). These two populations exhibit several morphological and physiological differences and comprise clearly isolated, not continuous, clusters [61]. Jarsky et al. observed a gradient in the proportion of bursting neurons along the proximodistal axis of CA1. The percentage of bursting pyramidal neurons was 10% in proximal CA1and 24% at the distal end of CA1. A similar gradient could be observed along the proximodistal axis of the subiculum (low in proximal and high in distal). Another study demonstrated that bursting and non-bursting populations are differentially modulated via metabotropic glutamate and acetylcholine receptors [61]. Since spike bursting may enhance salient information or novel events [62], the abundance of bursting neurons and their modulation in distal CA1 may support the representation of transient tactile, olfactory or object-related information in this area.

Why are there direct and indirect pathways from EC to CA1?

We have highlighted the roles of EC-CA1 direct input in the expression of proximodistal functional differences. However, representation in CA1 neurons is likely a result of interactions between the direct and indirect pathways from EC to CA1 (Fig. 2A). What are the functional contributions of direct and indirect pathways, and how do they interact? In the indirect pathway, the

axons from MEC neurons project to the middle third of the apical dendrites of DG, or the deep part of the stratum lacunosum moleculare (SLM) of CA3, whereas LEC cells send their axons to the distal most part of the molecular layer of DG, or the superficial SLM of CA3 [35]. Thus, each neuron in DG and CA3 may in principle receive inputs from both MEC and LEC, pointing to a possible integration of spatial and sensory-related information within each neuron.

While CA1 receives inputs from both the direct and the indirect pathway, the impact of each pathway is likely to be controlled by behavioural demand. [57,63,64]. For example, in an odour-place association task, the activity of neurons in proximal CA1 is predominated by the position of the animal, with minimal selectivity to odour identity [13], despite the fact that proximal CA1 neurons can in principle receive such inputs from LEC via the indirect pathway. The spatial bias of these neurons points to a major role of the direct pathway under many behavioural circumstances. On the other hand, neurons in distal CA1 exhibit selective activation to different odour cues in the same task but they also exhibit location-specific activity, although less than place cells in proximal CA1 [21]. The clear presence of spatial information in distal CA1 cells implies an influence of the indirect pathway on distal CA1 most of the time; LEC input alone might not be sufficient to maintain spatial firing since neurons in LEC express little spatial information [38]. Firing properties of CA1 cells may thus reflect inputs from both EC and CA3 but the contribution of each input may vary over time.

What kind of mechanism controls selection of information from direct and indirect inputs to the CA1? As indicated before, a plausible candidate for the selection process is the instantaneous frequency of neuronal oscillations in CA1. Changes in the frequency of neural oscillations may determine the efficiency of communication between CA1 cells and other brain regions [13,57,65,66]. Momentary coherence of oscillations between distal CA1 and LEC, for example, may create a window of opportunity for transmission of odour-related signals between those structures. Coherence between CA1 cells on one hand and CA3 or EC cells on the other may change several times per

second, modulated by the theta rhythm [57]. When coherence is stronger with EC than CA3, proximal and distal parts of CA1 may be functionally segregated due to the different nature of those two inputs. When coherence is stronger with CA3, inputs may be more integrated, considering that individual CA3 cells are likely to combine inputs from MEC and LEC. The coherence between CA1 cells and external networks may be dependent on behaviourally relevant factors such as running speed [67], odour sampling [13], or behavioural decision [68]. The function of rapid switches between CA1 and outside networks remains to be determined and there is currently no answer as to why temporal segregation would be advantageous or whether and how the two states interact with each other.

Neuromodulators, such as acetylcholine, DA or NE, may play a role in selecting inputs that oscillate coherently with CA1 cell assemblies. While acetylcholine is known to modulate CA3-CA1 synapses [69], DA and NE exhibit largely selective modulation of the terminals of LEC neurons in CA1 [58]. As cue-reward association tasks are typically accompanied by a temporally-controlled release of neuromodulators [59], it is of interest to determine how neuromodulators control the direct and indirect pathways in CA1 to enable functional coupling with other areas via neuronal oscillations.

Why are MEC and LEC inputs integrated in dentate gyrus and CA3 but segregated along the proximodistal axis in CA1? While the CA3 circuit is often thought to integrate inputs from a variety of sources, such as MEC and LEC, the circuit also has the capacity to generate representations internally, depending on previous experiences [2,3,70-72] as well as hardwired subcircuits [73]. It is, however, still unclear how such internal representations influence downstream brain regions. The CA1 region has long been thought to function as a comparator [69,74,75], representing mismatches between internally generated representations and external stimuli, originating, respectively, from CA3 and EC inputs. At some stage, these mismatch signals may need to be decomposed into modalities and be sent back to the brain areas from which the information was derived. Although

direct evidence is yet missing, we propose that proximodistal differentiation in CA1 may play, at least in part, a crucial role in this process, because it will allow prediction errors to be transmitted back to functionally distinct areas of the EC, including the main divisions, MEC and LEC.

Future direction

We have discussed experimental data that collectively point to CA1 as a heterogeneous structure, with larger spatial information in the proximal part of the area and expression of olfactory and discrete object-related information primarily in the distal part. We have also argued that despite the proximodistal gradient in spatial representation, location is represented at all levels, enabling cells in particularly the distal part to represent conjunctions of spatial and non-spatial information. We have further discussed that direct inputs from EC likely differ from those mediated through CA3 in that cells in the latter integrate signals from MEC and LEC. The response to direct and indirect inputs in CA1 may vary over time, both across behavioural situations and at a faster time scale within behaviours. The details of this dynamics are among the key questions to be settled as researchers now dig into the functions and mechanistic operations of the CA1 area.

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Figure Legends

Figure 1

Distinct representation between proximal and distal CA1. (A) Dorsal view of the right hippocampus (HPC) in the rat brain. (Inset) Proximal CA1 (prox) and distal CA1 (dist) are portions of CA1 that are adjacent to CA2 and subiculum (SUB), respectively (green and red). FC, fasciola cinereum. (B) Coronal section of the right hippocampus showing proximal CA1 (prox) and distal CA1 (dist). DG, dentate gyrus. (C) (Top) Rate maps for three representative place cells in proximal CA1 recorded from rats performing a random foraging task in a 2m-diameter environment. Peak rates (Hz) are indicated on top right and shown in red colour. (Bottom) Relationship between CA1 spike times and theta phase simultaneously recorded in medial entorhinal cortex (MEC). Left: spike times for a place cell in proximal CA1 (red) superimposed on theta oscillations simultaneously recorded from layer III of MEC. The x and y axis bars indicate 200 ms and 25 mV, respectively. Right: distributions of spike times across phases of theta in layer III of MEC. (D) Same panel as in (C), but for cells in distal CA1. While most of place cells in proximal CA1 have a single confined firing field, those in distal CA1 typically have multiple place fields, indicating low special information content in these cells. Spikes of proximal CA1 cells exhibit strong phase-locking to MEC theta occurring near the trough of theta. Distal CA1 cells exhibit weaker phase locking. (C) and (D), modified from [21], with permission.

Figure 2

(A) Schematic diagram of the major connections of the rat hippocampal formation. The hippocampus receives and sends information with neocortex via entorhinal cortex. Medial and lateral entorhinal cortex (MEC and LEC) project to CA1 through direct and indirect pathways. In the direct pathway (1), layer III cells in MEC largely project to proximal CA1 (prox), whereas layer III cells in LEC to distal CA1 (dist). By contrast, in the indirect pathway, axons of layer II cells in MEC and LEC (2) converge on the same population of cells in the dentate gyrus (DG) and CA3. This mixed information in DG and CA3 are conveyed to CA1 via mossy fibres (3) and Schaffer collaterals (4). Output form CA1 is conveyed to entorhinal cortex mainly via subiculum (SUB). In this output, information in proximal CA1 is conveyed to MEC via distal subiculum, whereas distal CA1 send information to LEC via proximal subiculum ((5) and (6)). See text for details.

(B) An example grid cell in MEC (left) and a representative cell with low spatial information in LEC (right). Rate maps of spikes recorded in 1 m square box are shown. Peak rates (Hz) are indicated on top right and shown in red colour.

Figure 3

Coupled 20-40 Hz oscillations between distal CA1 and LEC during odour-place association memory. (A) Time-resolved power spectrum during cue sampling. (Left) In this task, 20-40 Hz oscillatory activity was observed in LEC but not in MEC when rats are making odour cue sampling (orange bar). (Right) In CA1, similar 20-40 Hz oscillations were observed in distal part (dCA1), but not in proximal part (pCA1). Anatomical evidence for LEC – distal CA1 and MEC – proximal CA1 connection is schematically shown in thick arrows in the middle. (B) To test coupling of the oscillatory activities, coherence was measured for pairs between (1) LEC – distal CA1, (2) MEC –

distal CA1, and (3) LEC – proximal CA1. Only the LEC – distal CA1 pair showed coherence in 20-40 Hz, suggesting selective coupling for this pair during cue sampling. Modified from [13].

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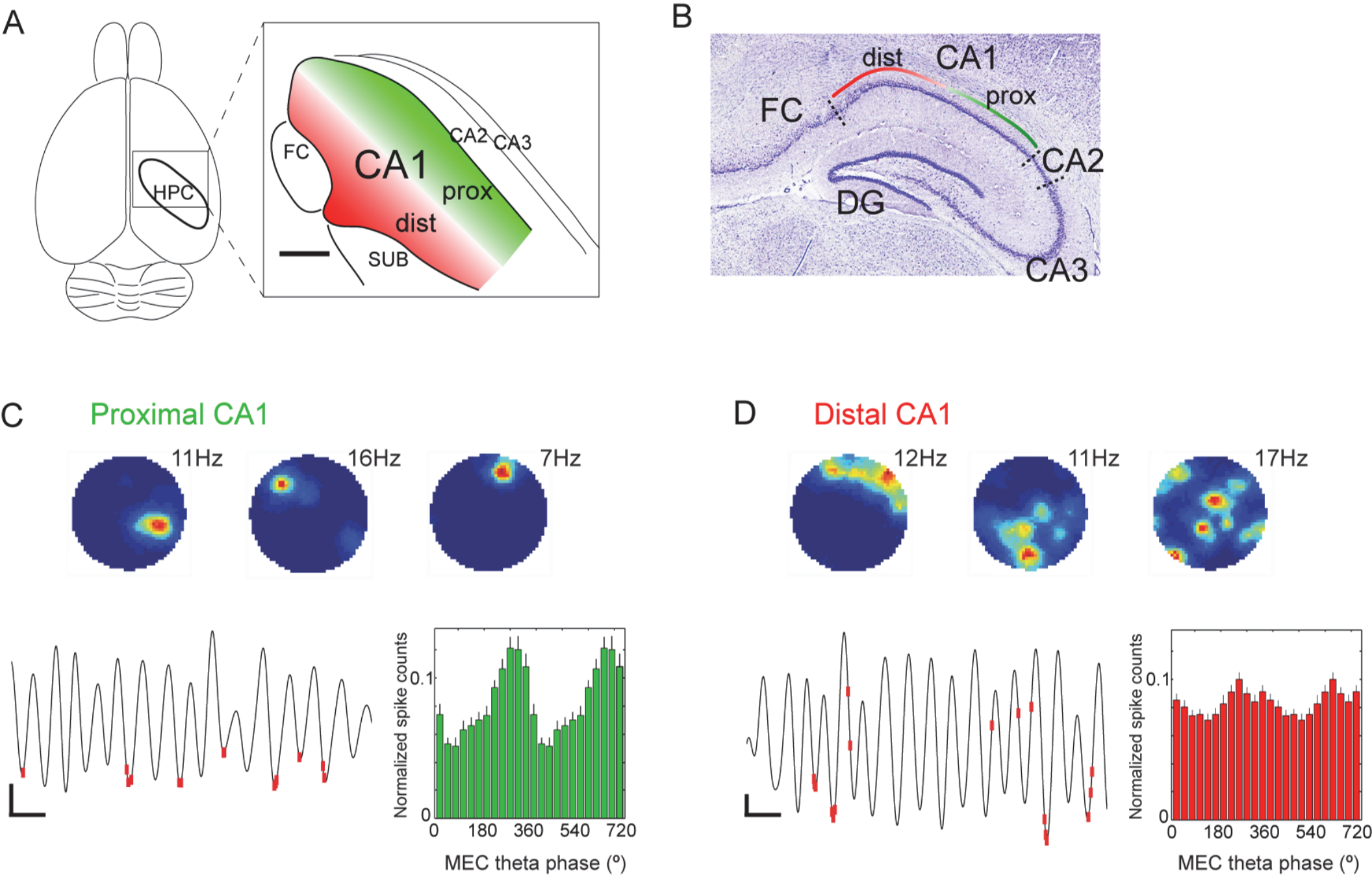
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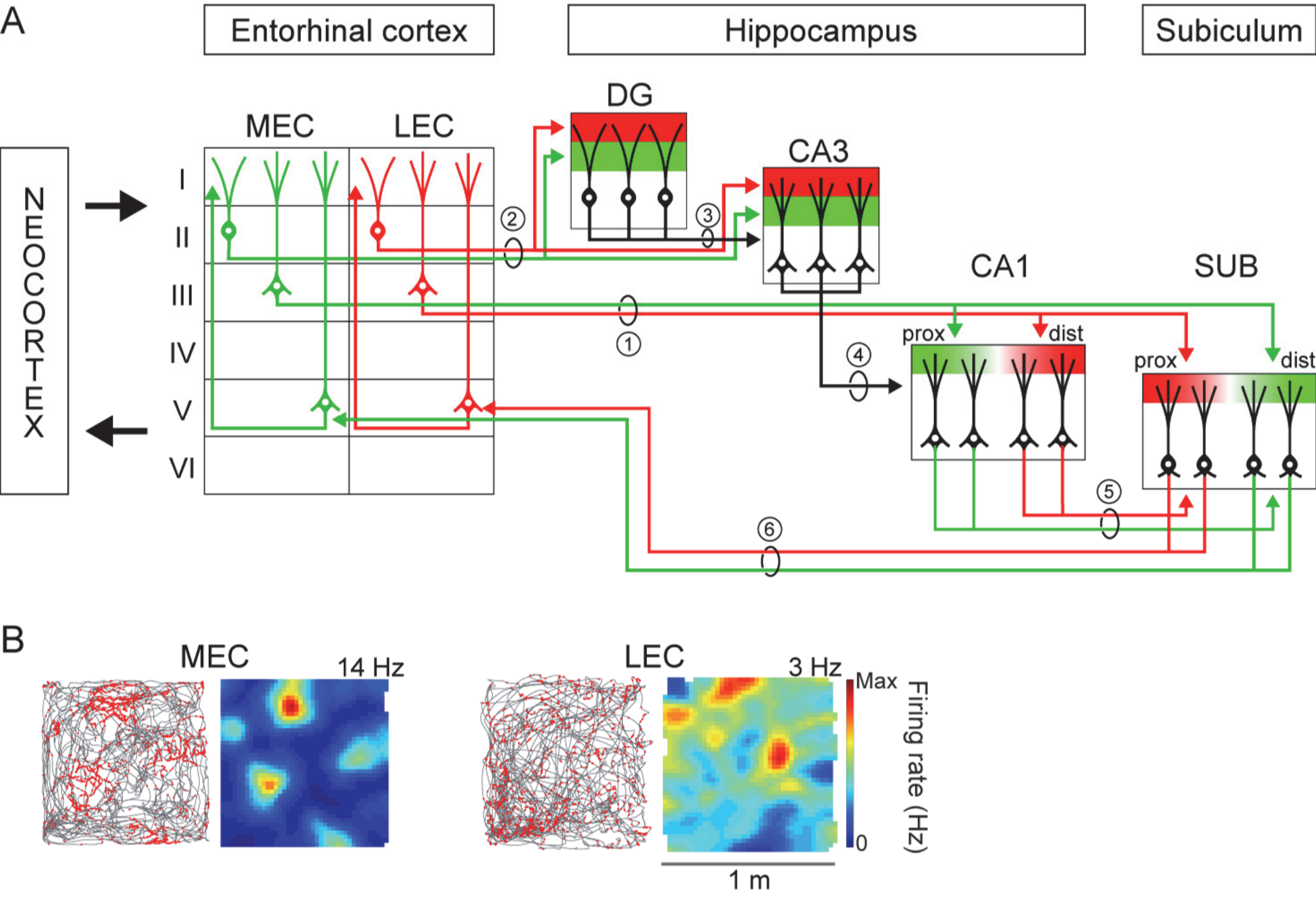
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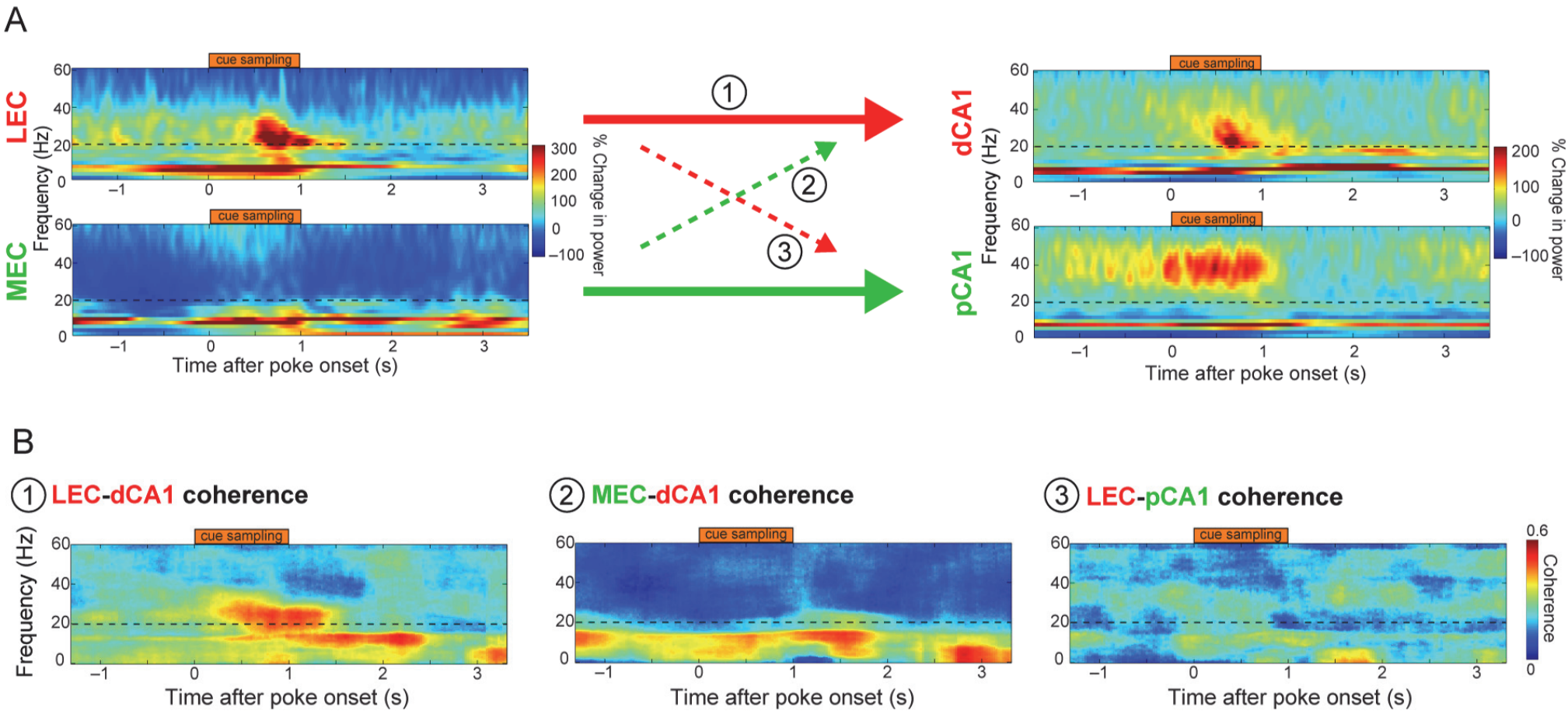
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