

Review

Functional features of the rat subicular microcircuits studied in vitro

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Abstract

The subiculum has a strategic position in controlling hippocampal activity and is now receiving much experimental attention. However, information regarding this structure remains fragmented and there are important gaps in our knowledge between what we know about the subicular architecture and its biological function. In recent years a substantial amount of in vitro experimentation has explored many aspects of the functional organization of the subicular microcircuits. Here we review these recent findings. We aim to identify the rules that govern the operation of subicular microcircuits in vitro and to relate these to the role of the subiculum in the intact brain.

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1. Introduction

The subiculum is a pivotal structure that controls the output and input activity to the hippocampus. An accumulating body of evidence now suggests that this structure has a decisive role in both normal and pathological brain function. Specifically, it is crucially involved in spatial encoding [3,70,79,80], mnemonic functions [25,31,32,59,87] and in devastating human conditions such as Alzheimer's disease [16,20,46], schizophrenia [1,26,27,61,62] and temporal lobe epilepsy [2,10]. In most cases, the role of the subiculum is different but complementary

to that of the hippocampus [17,68]. During spatial navigation for instance, subicular cells exhibit place fields that are modulated by the animal's head-direction and are insensitive to environmental landmarks, in contrast to hippocampal place cells [65,66,80,81]. It has been suggested that subicular cells encode a universal location-specific map that assists the hippocampus to form context-specific representations [67].

Most of the remarkable functions of the subiculum derive from its unique properties. Not only is it strategically placed to relate hippocampal, cortical and subcortical activity, but it also exhibits particular cellular and network features. However, until relatively recently the subiculum has been demoted to a secondary place compared with the hippocampus. Here, we review recent findings on the intrinsic organization of subicular microcircuits studied in vitro. We aim to delineate functional subicular

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networks and to put these in relation with their role in the normal brain.

2. Principal cell types

The subiculum is a three-layered allocortex composed of a range of electrophysiological neuronal types. Early studies in the 1990s showed that principal glutamatergic neurons can be classified as bursting and regular-spiking cells [47,48,76,78]. Bursting cells respond with a burst of 2–5 action potentials during the initial 50–60 ms of a supra-threshold current injection. Following this initial firing, some bursting cells can burst again while others fire single action potentials or remain silent (Fig. 1). These two firing patterns are sub-classified as strong and weak bursting, respectively [55,73].

Regular-spiking subicular neurons respond to supra-threshold current pulses by firing of single action potentials (Fig. 1). Some regular-spiking cells exhibit prominent adaptation while others fire in a tonic fashion [55]. Interestingly, some bursting cells switch to a regular-spiking pattern upon membrane depolarization [47,55,76]. However, a regular-spiking cell cannot be transformed into a bursting cell by changing resting membrane potential.

Electrophysiologically, bursting cells have lower input resistance compared to adapting regular-spiking cells but not to tonic cells [30,55]. Bursting cells exhibit prominent sags and rebounds in response to long hyperpolarizing current pulses [76]. Sags seem to be produced by I_H whereas low- (LVA) and high-voltage activated (HVA) Ca^{2+} currents together with I_H shape rebounds induced by depolarization of the membrane potential from hyperpolarized levels [49,55]. Another prominent feature of bursting cells is the presence of an after-depolarization (ADP) following single spikes [37,55]. It seems that regular-spiking, but not bursting subicular cells show NADPH-diaphorase activity and a lower effect of the neuropeptide somatostatin [28,29].

Some data suggests that the bursting and regular-spiking cells may project to different brain regions. By combining antidromic and orthodromic stimulation with sharp recordings in vitro, Stewart [75] explored this issue in the ventral subiculum. He found that bursting cells are likely to project to the presubiculum and that regular-spiking cells project to the entorhinal cortex. Different subcortical targets of bursting and regular-spiking cells have been also suggested based on their spatial distribu-

tion [30,55] and the topography of subicular projections to the anteroventral thalamic nucleus, the mammillary bodies and the nucleus accumbens [36].

The proportion of bursting and regular-spiking cells of the subiculum has been a matter of debate. It was initially reported that between 70 and 100% cells were of the bursting type [47,48,76,78]. This led to the general assumption that the subiculum is a bursting structure (in contrast to its CA1 input area). However, subsequent data suggested that only about 50% of cells were bursters [5]. Greene and Totterdell [30] helped to clarify this apparent discrepancy by showing that there are different deep-to-superficial and proximo-to-distal distributions of bursting and regular-spiking cells in the subiculum (see also Refs. [34,55]). It was also reported that there is a difference in somatic size and shape between these two groups [30,55], and this may significantly affect cell sampling during visual-assisted patch recordings [54].

But, do subicular bursting cells actually burst? Using cell-attached recordings, which do not alter the cell firing capability, we recently showed that the majority of the strong (~75%) but not weak (~22%) bursting cells fire bursts in response to local synaptic activation [51]. Near 55% of the weak bursting subicular cells were not synaptically activated and the remaining 20% responded with single action potentials. This was similar to the regular-spiking group which remained silent in most cases (~87%) or fired single spikes. Therefore, at least under the in vitro conditions, it is the strong bursting phenotype that has a functional bursting capacity.

It is likely that the different synaptic responsiveness of strong versus weak bursting cells is related to the ionic mechanisms underlying subicular bursting, as synaptic inputs were found to be similar for all cell types [44,51]. There is data suggesting that Na^+ currents boost EPSPs elicited by hippocampal afferent stimulation, and that this mechanism could differentially affect regular-spiking and bursting cells [15]. Both Ca^{2+} [76,78] and Na^+ persistent currents [47,55] were suggested to underlie burst firing. Recent work has suggested that a Ca^{2+} tail current but not a Ca^{2+} spike could shape the ADP that drives subicular bursting [37]. According to this data, the strong and the weak bursting phenotypes would result from different amount of Ca^{2+} tail currents, which are differently contributed by multiple Ca^{2+} channel subtypes. A relatively small fraction of the HVA Ca^{2+} tail current appears to be mediated by the L-type current whereas the

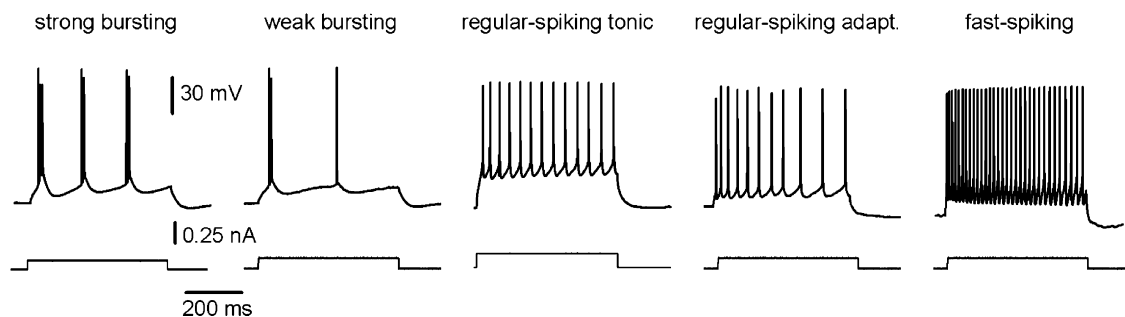


Fig. 1. Electrophysiological heterogeneity of subicular cell types. Glutamatergic cells of the subiculum are either intrinsic bursters or regular-spiking neurons. Bursting cells can be divided in strong and weak bursting cells according to the number of bursts elicited by depolarizing current pulses. Regular-spiking cells can fire with different degree of adaptation. Putative GABAergic interneurons of the subiculum exhibit a fast-spiking firing pattern.

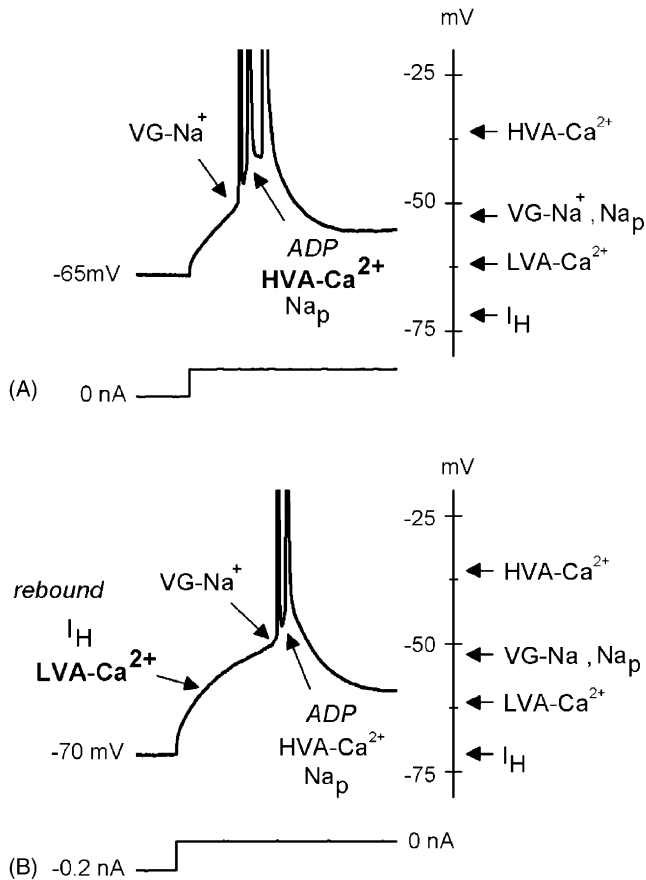


Fig. 2. Different ionic currents may participate in bursting depending on the voltage ranges: (A) bursts elicited by current pulses applied at resting or slightly depolarized membrane potential levels. At this voltage levels the low-voltage activated (LVA) Ca^{2+} current is inactivated and the I_{H} current is de-activated and poorly contribute to bursting. Arrows in the voltage scale at right indicate the relative threshold of aperture of different ionic channels; (B) same cell as in (A). Burst elicited by a rebound from hyperpolarized membrane potential is more likely to be contributed by LVA and I_{H} currents.

P/Q and N subtypes contribute a larger fraction. The nimodipine and ω -conotoxin MVIIC resistant R-type channels have a major contribution to tail currents [37]. Still, a fraction of tail current is mediated by LVA T-type channels as suggested by pharmacological experiments.

However, different ionic currents may participate in the above depending on the voltage range over which bursts are being induced. The I_{H} , for example, is de-activated by depolarization from hyperpolarized levels of the membrane potential, which together with the activation of LVA Ca^{2+} currents could shape bursts induced by current injection from hyperpolarized levels [55,62,76] (Fig. 2). I_{H} and LVA Ca^{2+} components would have a smaller contribution to bursts induced from more depolarized membrane potentials. It is possible that in such circumstances HVA, but not LVA, Ca^{2+} channels contribute a larger fraction to ADP and bursting (Fig. 2). According to this scenario, subicular bursting may critically depend on the recent past history of the membrane potential. Additional information on the kinetics of the different currents involved may help to further understand bursting mechanisms in subicular neurons.

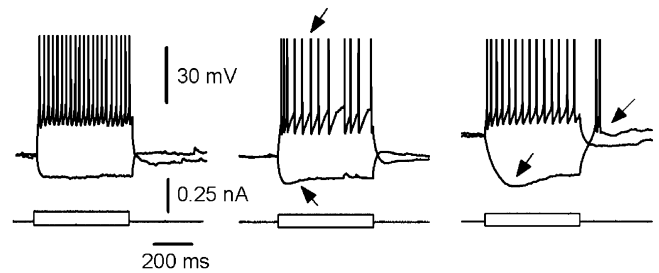


Fig. 3. Electrophysiological heterogeneity of interneurons from the subiculum. Firing responses from three different interneurons to depolarizing and hyperpolarizing current pulses. Note the different degree of firing adaptation, sags and rebounds (arrows).

3. Local circuit interneurons

In contrast to principal glutamatergic neurons, much less is known about subicular GABAergic cells. There are few data on their electrophysiological, morphological and neurochemical properties [30,38,43,55,64,72]. Most of the assumption of their GABAergic nature derives from their typical fast-spiking firing pattern (>200 Hz), small non-pyramidal somata and local axon collateral field (but see next section). However, local circuit cells of the subiculum appear to be more electrophysiologically heterogeneous than originally thought (Fig. 3; Gal and Menendez de la Prida, unpublished data). Fast-spiking subicular cells have a larger input resistance compared to principal cells, a slightly more depolarized resting membrane potential and larger membrane time constants [55].

4. Subicular microcircuits

Subicular microcircuits can be directly activated by inputs from the entorhinal cortex [74] and the CA1 region of the hippocampus [1,4,86]. In addition, afferents from the amygdala [21,45], the anteroventral and the reuniens thalamic nuclei have been described [71,83]. The most conspicuous feature of the subicular response to afferent stimulation *in vivo* is a brief excitatory period followed by prominent firing suppression that lasts more than 100 ms [11,18,24]. Early evidence hinted at the possibility of a feedforward activation of local GABAergic circuits mediating this effect [19].

Further support derived from *in vitro* studies. Intracellular sharp recordings showed the presence of biphasic GABA_A- and GABA_B-dependent IPSPs following the hippocampal- and cortical-evoked EPSP [6,78]. In addition, firing could be evoked in subicular interneurons in response to afferent stimulation [19,24]. The local nature of this inhibition was further assessed by microapplication experiments [78,51]. However, feedback inhibition can also operate at this level. We recently showed that local non-NMDA-mediated synaptic activation of fast-spiking cells reliably elicits single spikes in more than 70% interneurons [51].

It seems clear that the reliable recruitment of GABAergic circuits of the subiculum has a profound impact on bursting. Even a single GABA_A receptor mediated IPSP can delay or prevent bursting [51] and reset spontaneous firing [76]. This suggests

that there is probably no need for synchronous fast inhibition to modulate the output of subicular principal cells. Antidromic-elicited bursting for instance [75], is released after removing feedback inhibition, which suggests that under *in vitro* conditions the firing of most subicular bursting cells is under a strong inhibitory control [51]. As to the hippocampus [57], removing the fast GABAergic inhibition uncovers local glutamatergic circuits [76,53].

There is substantial lack of data on the microanatomical organization of subicular circuits. The divergence and convergence ratio of inhibitory and excitatory connections is unknown, and there are no quantitative estimates of synaptic connectivity between distinct cell types. To address this issue we recently carried out recordings from pairs of subicular cells (Gal and Menendez de la Prida, unpublished data). Approximately 10% of cells recorded within 150–200 μm of a fast-spiking cell were found to be synaptically connected. No reciprocal connections or gap-junctions were encountered. The response in post-synaptic cells consisted of an IPSP of 0.4–1.2 mV amplitude at resting membrane potentials of -52 to -58 mV (Fig. 4A and B). Synaptic conductances were on the range of 5.4–6.6 nS and reversal potential was consistent with a GABA_A mediated chloride current. This further supports the proposal that the subicular fast-spiking cell has a GABAergic phenotype.

We failed to detect excitatory synaptic connections after more than 25 pairs recorded under the same conditions. This suggests a lower connectivity density compared with that of the inhibitory plexus at 150–200 μm radius. However, local polysynaptic circuits can be activated by discharging single bursting neurons (Fig. 4C), consistent with the existence of columnar and laminar glutamatergic networks [22,34,58,77]. Moreover, a variety of small glutamatergic circuits are described at the short-range scale, i.e. subiculum–presubiculum [22,23,42], subiculum–CA1 [9,12,33,63] and subiculum–entorhinal cortex [39,40,82].

It is known that most of the local glutamatergic transmission in the subiculum is non-NMDA dependent. However, NMDA-mediated neurotransmission increases single EPSC amplitude

and duration by 15–30% and 20–50%, respectively, in a cell type independent manner [51]. These excitatory glutamatergic connections constitute the substrate for the diverse forms of population activity that can be induced in the isolated subiculum (see next section). The NMDA component for instance, appears to be essential for the formation of functional cell ensembles *in vitro* [52].

EPSPs evoked in subicular cells by CA1 and entorhinal cortex stimulation are also glutamatergic, with different AMPA and NMDA components [6,78]. Nevertheless, these two subicular inputs are differentially modulated. The CA1-activated EPSPs are the main targets of a dopaminergic control that depresses glutamate release via presynaptic D1 receptors [7], in contrast to the weakly modulated perforant path. Subicular EPSPs activated by CA1 stimulation also exhibit diverse forms of plasticity such as LTP [13,14], which do not depend on NMDA receptors [35,44] (but see also Ref. [61]).

5. Lessons from the isolated subiculum *in vitro*

In order to understand the role of subicular circuits it is essential to identify those neurons and networks that produce activity within this structure. The spontaneous activity of a neuronal circuit in the absence of external stimuli is likely to reflect its intrinsic architecture. This intrinsic organization will critically shape the output of that circuit in response to complex patterns of incoming inputs.

One of the most reliable manipulations to activate the isolated subicular circuits *in vitro* is the use of nominally zero Mg^{2+} media [8,84] or NMDA [33]. Disinhibition-induced spontaneous hyperexcitability is less consistently present in the isolated subiculum and is highly dependent on recording conditions, i.e. interface or submerged chambers (Menendez de la Prida, unpublished observations). This probably reflects the important role of NMDA-mediated currents in amplifying AMPA-mediated EPSPs in the subiculum, even under conditions of intact inhibition.

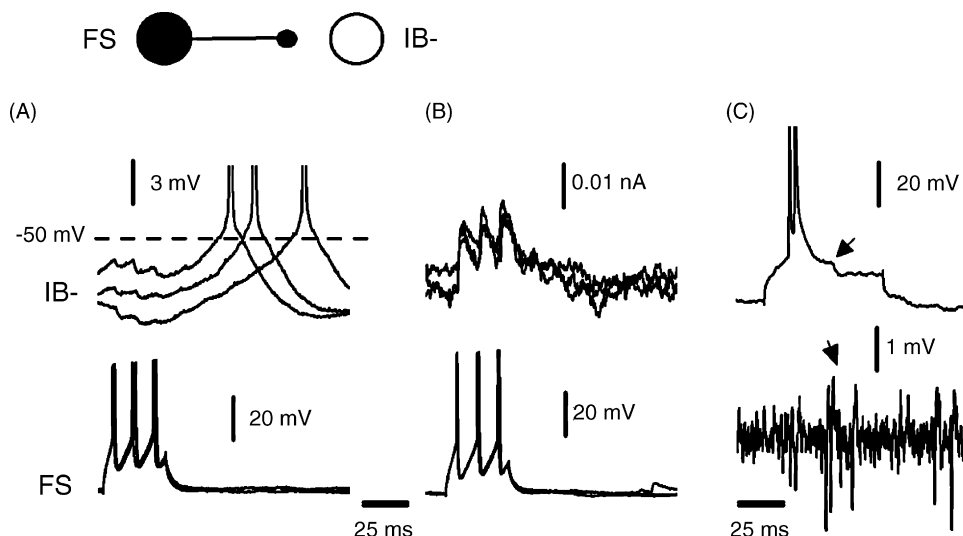


Fig. 4. IPSPs (A) and IPSCs (B) initiated by a presynaptic fast-spiking (FS) cell onto a postsynaptic weak bursting neuron (IB-). (C) Local circuit interactions were explored by combining whole-cell and multi-unit recordings. Discharging single bursting cells in the subiculum result in the polysynaptic activation of local circuits.

Using the zero Mg^{2+} approach and intracellular sharp recordings, Harris and Stewart [33] suggested a role for subicular bursting cells in generating spontaneous network activity. They found that some of these cells burst during periods when field activity is absent. This would suggest that bursting neurons serve as initiators of population firing by injecting activity into the network and subsequently driving the recruitment of their targets [56] (see Fig. 4C). However, intrinsic bursting switched to regular-spiking upon depolarization [33,76,78]. It is therefore essential to use recordings conditions that do not alter the intrinsic firing pattern. There is another potential problem when studying single cell firing and population activity. Because of the firing of a given cell is not preserved from episode to episode of population activity, the neuronal code is dynamic and should be examined statistically.

To overcome these problems we recently combined cell-attached and field recordings during spontaneous population activity in subicular minislices [52]. After completing the examination of firing dynamics from several consecutive episodes of field activity, we switched to whole-cell configuration to classify cells. This allowed us to statistically evaluate the cell type specific firing dynamics. We found that a subset of bursting cells were drivers of the network activity, preceding the later by 13–100 ms. Interestingly, not all bursting cells were found to fire before the field event and therefore they do not define a leader group per se. Leader cells, which represent almost 45% of either strong and weak bursting neurons, were spontaneously active, had lower firing thresholds and more numerous apical dendrites [52].

All the regular-spiking cells examined fired after field activity already started or remained silent [52]. This supports the idea that subicular regular-spiking cells may sustain network activity once it has been initiated [75,76]. Because these cells exhibited a very low spontaneous firing rate they may largely contribute to accentuate activity differences between ensembles.

Regarding inhibitory events, a major feature was that fast-spiking interneurons fired at high frequencies 10–12 ms after the population event [52]. This is consistent with the idea that interneurons are reliably recruited by subicular principal cells, and supports the possibility that feedback inhibition also contributes to firing suppression following afferent stimulation *in vivo* [11,18]. This cell type specific interaction determines a precise synaptic sequence of excitation and inhibition. The fast conductance changes generated by GABAergic synapses were occasionally large enough (>100% resting conductance) and appropriately timed to shunt the initial excitatory wave generated by leader bursting cell firing. As a result activity remained restricted to only a few cells. On other occasions, synchronous population activity spread throughout [52]. It is unknown which mechanisms account for the transition from local to widespread population activity.

6. Building blocks of subicular microcircuits

It is now clear that subgroups of subicular bursting cells are able to initiate a local recruitment process. These leader cells

will activate additional glutamatergic neurons, both bursting and regular-spiking cells, together with fast-spiking GABAergic interneurons. The secondary activation of GABAergic cells will in turn inhibit leader and follower cells and spatially constrain the activity. Consequently a functional unit is defined (Fig. 5).

One can postulate that many of these functional units can together control the subicular output. The firing dynamics of these modules provides a mechanism to preserve both temporally and spatially the firing specificity of subicular microcircuits. Accordingly, when inputs reach the subiculum either from the CA1 region or from the entorhinal cortex, those leader cells reliably recruited will pass on the activity to their targets throughout the subiculum. Recurrent inhibition will act locally to limit further recruitment [52]. A subicular ensemble is therefore activated. Here, an ensemble is defined as a group of subicular cells that transiently fire together. Note that this does not necessarily mean that cells belonging to one ensemble are physically close. Instead the ‘spatial domain’ of the ensemble is likely to be defined from the connections of a number of leader cells and the local inhibitory circuits they concurrently activate. Note also that a given cell could participate in different ensembles since it can be driven by different leaders (Fig. 5).

This functional architecture fits well into the path integration scheme that is proposed to account for the continuous tracking of animal’s location and head-direction [50,60]. According to this view, cells representing a particular position or head-direction are linked together through several leader cells in a particular ensemble. This ensemble results from inputs from the CA1 (place maps), the entorhinal cortex (environmental information) and also subicular interconnections (current place and head-direction information). When some relevant external information about the animal’s movement reaches the subiculum via the afferent system [69] it activates a different set of leader cells. Because the extinction of activity in a functional block of the subiculum takes 100–150 ms [52], firing from the former ensemble is still present. Therefore, new ensemble activity could

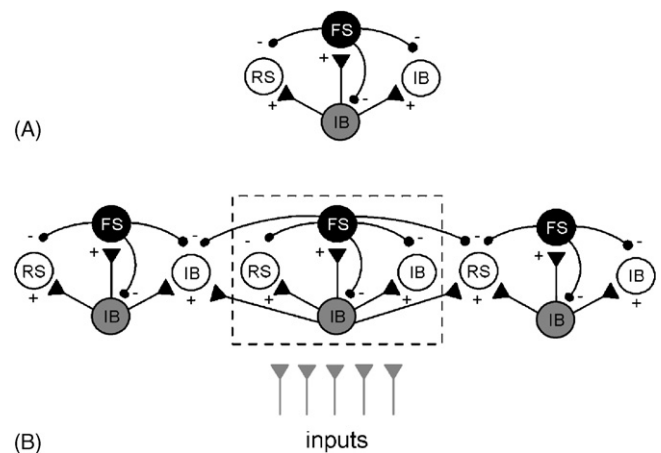


Fig. 5. Proposed functional modules of subicular circuits: (A) leader bursting cells (IB) recruit firing from follower glutamatergic (either regular-spiking, RS, and bursting cells) and GABAergic (FS) neurons. GABAergic follower cells feedback onto leader and follower glutamatergic neurons to attenuate their activity. This firing sequence defines a functional ensemble of active cells; (B) the subicular microcircuits can be formed by several of these modules.

be initially shaped by previous place and head-direction information. Consequently, a new ensemble develops progressively carrying information about the recent past history.

A major conflict between this view and the *in vitro* experimental data is that in the absence of external influences ensemble activity should remain stable, i.e. persistent activity (see [85] for review). Nevertheless, this was not the case *in vitro*. The fact that fast-spiking inhibitory cells are always recruited by leader cells causes a window of inhibition which prevents firing [52]. Therefore, leader cells should be activated by specific temporally patterned inputs to keep them firing. If this were the case, ensemble activity at the subiculum should reflect somehow this temporal sequence.

7. What next?

The conceptual model discussed above still lacks more experimental support. At present, we only have small pieces of the puzzle. *In vitro* studies can decipher basic information about subicular microcircuits but cannot provide data on their participation in elaborated cognitive tasks. *In vivo* data has been collected ‘blindly’ with important gaps about the functional organization of the subiculum and its related structures. What is needed is a combination of approaches to link subicular microcircuits with behavior. It would be essential to detect elementary behavioral processes where the subiculum plays a critical role. This would allow us to specifically target those circuits and look for their related structures and function. Several aspects such as synaptic plasticity, microanatomical organization and the short-range pathways (CA1–subiculum, presubiculum–subiculum, etc.) need to be further explored. They constitute essential pieces of information to build a comprehensive picture of the role of this structure in the intact brain.

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