Bimodal dendritic processing in basket cells drives distinct memory-related oscillations

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Abstract

Hippocampal oscillations regulate distinct memory stages and behavioral states, yet the mechanisms by which interneurons contribute to these rhythms remain elusive. Here, we establish a novel link between the bimodal nonlinear dendritic processing of PV+ fast-spiking basket cells (FSBCs) and hippocampal oscillations. Our model predicts that FSBCs can flexibly adjust their activity without changes in synaptic input quantity, leveraging their supralinear and sublinear dendritic branches to selectively shape network dynamics. Supralinear dendritic activation enhances high-frequency oscillations, while sublinear dendritic activation amplifies slow oscillatory power, dynamically modulating the excitation/inhibition (E/I) balance. These findings reveal a previously unrecognized role of FSBC dendritic integration in memory-related oscillatory dynamics, offering new insights into the cellular mechanisms governing hippocampal rhythm generation.

Significance Statement

Hippocampal oscillations play a crucial role in memory processes, yet how interneurons dynamically regulate these rhythms remains unresolved. Our study reveals that fast-spiking basket cells (FSBCs) exploit bimodal nonlinear dendritic processing to selectively shape slow and fast oscillatory components, independently of synaptic input quantity. This energy-efficient mechanism allows FSBCs to fine-tune the excitation-inhibition balance, modulating network dynamics essential for learning and consolidation. By challenging the conventional view of interneuron function, our findings redefine how inhibitory circuits contribute to hippocampal rhythm generation, providing new insights into the cellular basis of memory-related oscillations.

Main

Hippocampal oscillations exhibit a variety of distinct frequency bands (Buzsáki and Draguhn, 2004). For example, neuronal activity often associates with a slow local field potential (LFP) component, known as theta activity, which ranges from 3 to 10 Hz (Buzsáki and Draguhn, 2004; Jackson and Skinner, 2018; Lisman and Jensen, 2013). Additionally, hippocampal activity includes fast-frequency oscillations spanning from 30 to 200 Hz (Buzsáki and Draguhn, 2004; Griffiths and Jensen, 2023; Jackson and Skinner, 2018; Lisman and Jensen, 2013; Tort et al., 2013). Both experimental and computational studies have linked these slow and fast components to different stages of hippocampal memory formation and distinct behavioral states (Buzsáki, 1989; Buzsáki and Wang, 2012; Lisman and Jensen, 2013). Specifically, slow 3-10 Hz oscillations correlate with memory encoding, spatial navigation, and sensory processing (Lisman and Jensen, 2013). Conversely, fast oscillations are associated with memory encoding and consolidation (Buzsáki and Wang, 2012; Lisman and Jensen, 2013). Notably, these fast and slow components often occur together in a phenomenon known as oscillation coupling (Jackson et al., 2011; Schomburg et al., 2014; Tort et al., 2013; Wulff et al., 2009; Zhang et al., 2016; Zhong et al., 2017) which has been proposed as a signature of working memory processing and various behavioral states (**Figure.1a**) (Lisman and Jensen, 2013; Tort et al., 2013). To understand the cellular mechanisms behind these oscillatory events, significant efforts have been made to delineate the effects of various subclasses of both excitatory and inhibitory hippocampal populations. Among these, PV+ GABAergic interneurons play a crucial role in both slow and fast oscillations as well as in coupled oscillatory activity (Allen and Monyer, 2015; Cardin et al., 2009; Lucas and Clem, 2018; Pelkey et al., 2017a; Topolnik and Tamboli, 2022; Tzilivaki et al., 2023; Wulff et al., 2009). However, most research has focused on manipulating PV+ interneurons through optogenetic and computational approaches, primarily investigating their activation or silencing during oscillatory activity. While these studies have significantly advanced our understanding of the importance of PV+ interneurons in hippocampal oscillations, they have provided little insight into the specific subcellular properties that enable these interneurons to exert such precise control over distinct oscillatory states and memory processes.

For many years, a prevailing dogma dominated the field of interneuron research, suggesting that interneurons possessed passive, linear dendrites incapable of integrating synaptic inputs in a nonlinear manner. According to this view, interneurons were thought to exert inhibition based purely on the quantity of synaptic inputs they received. This simplistic framework assumed that the inhibitory regulation of a network's activity across distinct oscillatory activity depends solely on the synaptic input amount that interneurons receive, disregarding the potential influence of potential complex nonlinear dendritic integration rules. Contrary to this linear model, recent experimental findings have revealed that hippocampal PV+ interneurons exhibit complex nonlinear dendritic computations, significantly enhancing their computational capabilities and shaping their input-output (I/O) transformations (Chiovini et al., 2014; Cornford et al., 2019; Hu and Vervaeke, 2018a; Judák et al., 2022; Katona et al., 2011; Morabito, 2024; Tzilivaki et al., 2019, 2022). Nonlinear dendrites allow neurons to function as intrinsic computational units, enabling them to differentially respond to incoming synaptic inputs (Tran-Van-Minh et al., 2015). While nonlinear dendritic integration has long been recognized in pyramidal cells and is known to optimize their role in memory formation, its presence in interneurons has only recently gained attention. To date, most available data come from studies on hippocampal PV+ interneurons (Cornford et al., 2019; Katona et al., 2011), a highly diverse class that includes distinct subtypes, such as aspiny fast-spiking basket cells (FSBCs), which primarily target the somata of pyramidal neurons and other interneurons (Pelkey et al., 2017b; Topolnik and Tamboli, 2022; Tzilivaki et al., 2023).

In the case of hippocampal FSBCs, biophysical computational modeling has proposed that their dendritic trees exhibit two distinct modes of nonlinear integration, both coexisting within the same dendritic tree (Tzilivaki et al., 2019, 2022). Specifically, multicompartmental biophysical simulations indicate that FSBCs possess two types of nonlinear dendrites: supralinear dendrites, capable of generating local dendritic spikes, and sublinear dendrites, which integrate excitatory synaptic input passively (**Figures. 1b-c, S2a-d**). This model suggests that FSBCs engage in bimodal nonlinear dendritic processing, leveraging both supralinear and sublinear integration mechanisms. Although both types of nonlinear dendrites coexist within the same dendritic tree (**Figure. 1b-c, S2**) and share similar active properties, they differ in morphology and function (Tzilivaki et al., 2019). Supralinear branches exhibit larger volumes and lower input resistance, allowing them to generate local sodium spikes (**Figure. S2a-e**). In contrast, sublinear branches found to have smaller volumes and higher input resistance. Given their small volume and high input resistance (**Figure S2**), sublinear dendrites are structurally constrained from generating spikes. When coincident synaptic inputs arrive at these branches, they produce large, rapidly rising excitatory postsynaptic potentials (EPSPs). However, the presence of A-type potassium channels facilitates rapid membrane repolarization, effectively preventing local spike initiation.

Notably, the theoretical prediction of bimodal nonlinear dendritic integration in FSBCs, a major subclass of hippocampal PV+ interneurons, was later supported experimentally. Specifically, studies in CA1 PV+ interneurons provided direct evidence of bimodal nonlinear dendritic processing, demonstrating the presence of both supralinear and sublinear dendrites (Cornford et al., 2019). This discovery challenges traditional assumptions about interneuron function, emphasizing the critical role of dendritic nonlinearities in shaping hippocampal network dynamics. While further research is needed to fully unravel the dendritic processing patterns of other interneuron subtypes, existing evidence strongly supports the idea that the complex nonlinear dendritic behavior of PV+ FSBCs serves functions beyond the traditional view of simply regulating network excitation.

A fundamental question that arises—and one that inspired this study—is: How do FSBCs leverage their bimodal nonlinear dendrites at the network level during memory encoding and recall related oscillations? Why are these cells equipped with two distinct types of nonlinear dendrites rather than just one? What are the network-level implications of supralinear and sublinear activation during different memory-related oscillations? Given the involvement of FSBCs in both slow (e.g., theta-frequency) and fast oscillations (Chamberland and Topolnik, 2012; Klausberger and Somogyi, 2008; Tzilivaki et al., 2023), we employed state-of-the-art biophysical modeling to test our hypothesis: that the supralinear and sublinear branches of FSBCs differentially modulate their activity and, consequently, orchestrate local field potentials (LFPs) during mnemonic functions. Specifically, we hypothesized that FSBCs exploit their bimodal dendritic processing to selectively shape fast and slow oscillatory activity within a hippocampal circuit **(Figures 1-2)**. This mechanism could allow FSBCs to fine-tune the excitation-inhibition (E/I) balance and modulate both slow and fast oscillatory signals without requiring changes in synaptic input quantity **(Figure 3)**. Such a strategy would maximize the flexibility of this interneuron subtype, enabling it to engage with distinct memory-related rhythms in an energy-efficient manner.

To test our hypothesis, we utilized a published biologically plausible hippocampal microcircuit model (Hadler et al., 2024), which incorporates compartmental biophysical models of pyramidal cells (PCs) with simplified morphologies (Hadler et al., 2024) and FSBCs with anatomically reconstructed bimodal nonlinear dendritic trees (Tzilivaki et al., 2019) (**Tables S1–S5, Figures. 1a, S1, S2**). Both neuronal types were extensively calibrated based on

electrophysiological data (**Tables S1-S5, Figure S1**). Given that, to our knowledge, experimental evidence on dendritic integration in other interneuron subtypes (e.g., SOM+ or VIP+) remains insufficient, we sought to avoid assumptions. Therefore, we exclusively modelled FSBCs with bimodal nonlinear dendritic trees as the only inhibitory component of our microcircuit model.

Upon activation with a theta-like input (as per Park et al., 2020; Turi et al., 2019), our model recapitulated the experimentally observed coupling of slow and fast oscillations (Schomburg et al., 2014; Tort et al., 2008; Wulff et al., 2009), generating a slow oscillatory component alongside a fast oscillatory component (**Figure. 1a, d**). To systematically investigate how FSBC dendritic integration modes influence network dynamics, we designed three distinct activation conditions while ensuring that the total number of synaptic inputs remained constant across all simulations: 1. *Bimodal Activation* (Control Condition): Synapses onto FSBCs were randomly distributed across both supralinear and sublinear dendritic branches (**Figures. 1a, d, 2a**). This represents a balanced scenario where inputs arrive at both dendritic types. 2. *Supralinear Activation*: To understand the effects of supralinear dendrites in these cells, we restricted all synaptic inputs exclusively to supralinear branches (**Figures. 1e, 2b**). 3. *Sublinear Activation*: Similarly, to examine the role of sublinear dendritic processing, we constrained all synaptic inputs to only sublinear branches (**Figures. 1f, 2c**). In all three conditions, the total number of synaptic inputs remained the same and identical, and all other network parameters and simulation settings were kept unchanged to ensure a controlled comparison of how the two types of nonlinear dendrites shape FSBCs firing patterns and network oscillatory behavior.

Our model predicts that supralinear dendritic activation in FSBCs preferentially amplifies the fast oscillatory component of our LFP signal, whereas sublinear dendritic activation enhances the slow LFP (**Figures 1-2**). Specifically, when supralinear dendrites are activated, the network exhibits higher fast peak-frequency values as well as higher fast peak-frequency power values compared to both bimodal and sublinear activation conditions (**Figures. 1e, 2b, 2d, 2e**). In sharp contrast, sublinear FSBCs dendritic activation significantly reduces the fast peak-frequency power relative to both bimodal and supralinear activation (**Figure. 2d**), while simultaneously increasing slow LFP power values (**Figures. 1f, 2c, 2e, 2f**). These predictions suggest that FSBCs leverage their bimodal dendritic architecture to selectively regulate distinct oscillatory components, dynamically shaping hippocampal network activity based on input distribution.

To assess the robustness of the differential impact of supralinear versus sublinear dendritic activation on LFP oscillations, we performed a sensitivity analysis on synaptic parameters and input characteristics. In all cases, supralinear activation enhanced both peak power and peak frequency power of the fast LFP component, whereas sublinear activation consistently resulted in stronger slow oscillatory power compared to supralinear activation (**Figure, S3**).

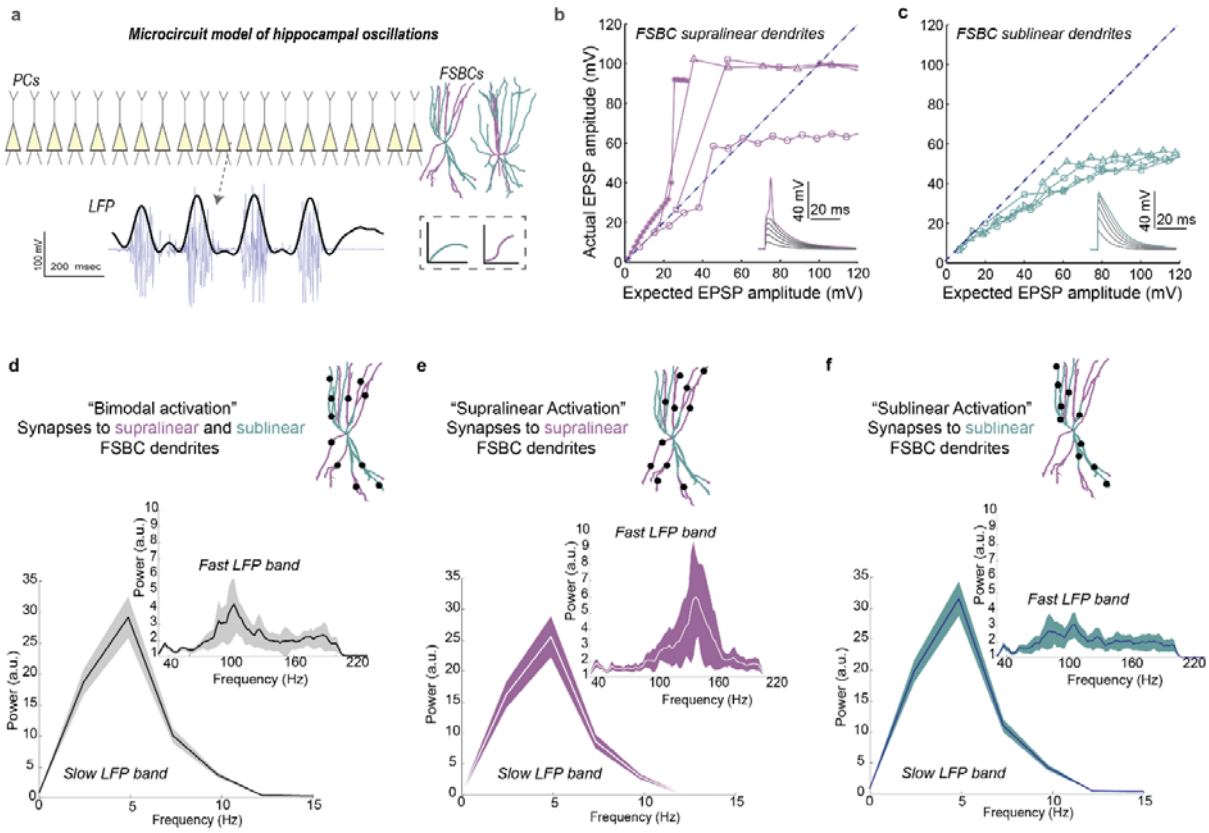

Figure 1. Supralinear and Sublinear branches of FSBCs differentially modulate memory-related hippocampal oscillations. *Schematic Illustration of the hippocampal microcircuit model. Pyramidal Cells (PCs) and FSBCs populations are activated by a theta (4 Hz) input for 1000 msec. An LFP electrode is positioned nearby the PCs somata. Upon activation the model exhibits slow (bandpassed at 3-10 Hz) and fast (bandpassed at 30-200 Hz) LFP bands. The arrow indicated the in-silico electrode position. FSBCs are equipped with bimodal nonlinear trees as per* (Cornford et al., 2019; Tzilivaki et al., 2019)*.* ***(b-c).*** *Representative input-output curves from supralinear (**b**) and sublinear (**c**) dendritic branches in FSBC models, in response to synaptic stimulation. Increasing numbers of synapses (from 1 to 20 with step□=□1) are uniformly distributed in every stimulated branch and are activated with a single pulse. The y-axis shows the amplitude of the dendritic EPSP caused by synaptic activation while the x-axis shows the expected EPSP amplitude that would result from the linear summation of synaptic EPSPs. The dashed line indicates linear summation. Insets show representative traces. Panels were adopted from Tzilivaki et al., 2019.* ***(d-f).*** *Power Spectrum Density (PSD) plots under 3 synaptic placement configurations: when both supralinear and sublinear dendrites of the FSBCs receive synapses (bimodal activation) (**d**), when only the supralinear branches receive synapses (supralinear activation) (**e**), and when only the sublinear branches receive synapses (sublinear activation) (**f**). The number of activated synapses remain identical for all 3 configurations. Activation of the supralinear dendrites (**e**) supports the fast LFP signature while sublinear activation (**f**) promotes slow LFP power. Data from 30 random simulation trials.*

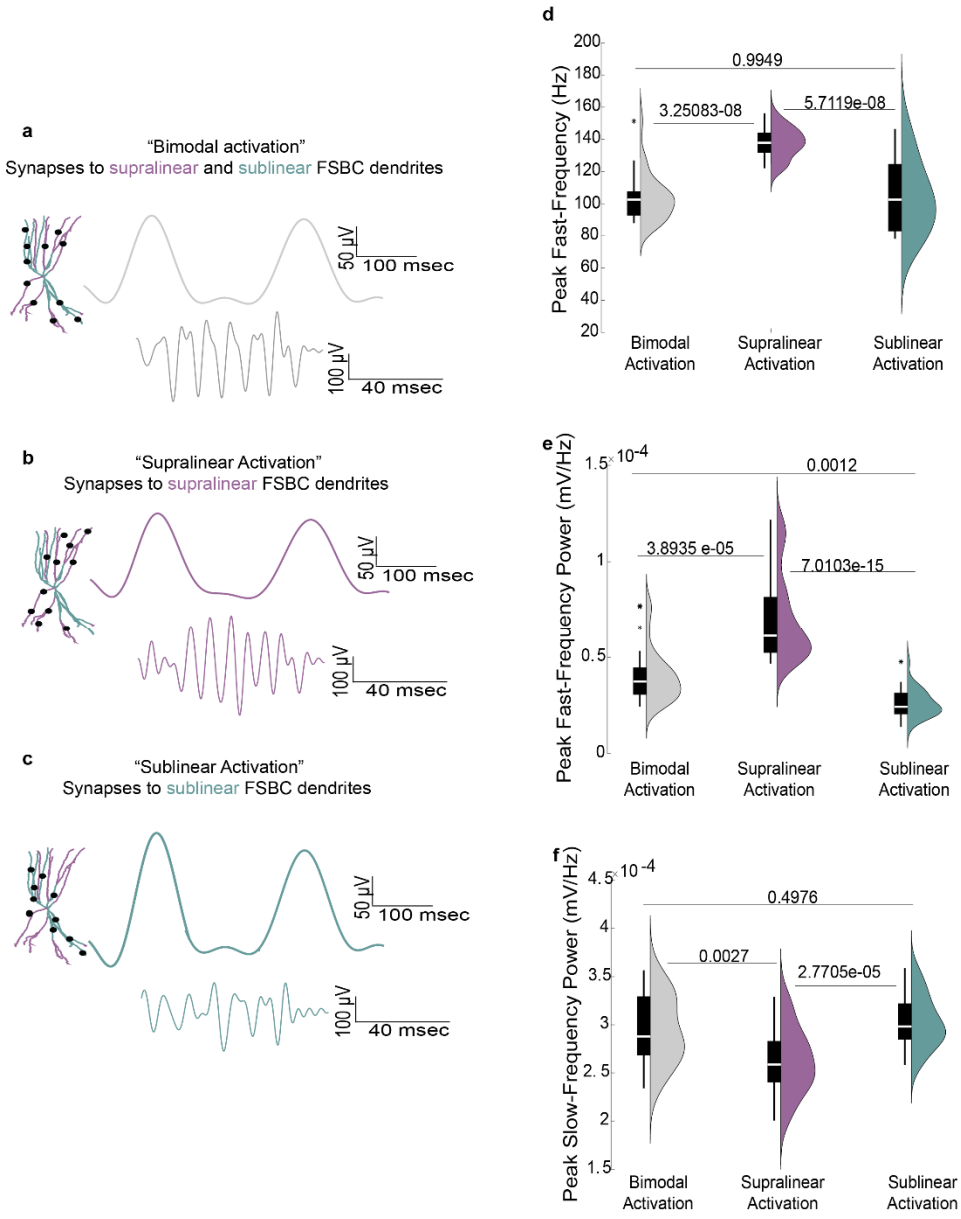

Figure 2. LFP frequency and power are regulated by FSBC nonlinear dendritic activation. *(**a-c**) Schematic illustration of the activation protocols and representative traces of the evoked LFP bandpassed at slow (theta 3-10 Hz) and fast (30-200 Hz) frequences. The same number of synapses targets either both types of nonlinear dendrites (bimodal activation) (**a**) or only supralinear (**b**) or only sublinear (**c**). (**d-f**) Comparison of the peak fast-frequency (**d**) and the peak powers of the fast (**e**) and slow (**f**) LFP components. Data from 30 random simulation trials. Synaptic activation of supralinear dendrites of the FSBCs bimodal trees results in a higher peak fast-frequency and increased fast-frequency peak power, while reducing the peak power of slow oscillations compared to sublinear dendrite activation. Statistical comparisons across multiple groups were performed using the Kruskal-Wallis test followed by a post-hoc correction for multiple comparisons, suitable for data with unequal variance.*

Given that the total number of synapses was identical across all three activation conditions (bimodal, supralinear, and sublinear), we sought to understand the factors driving the observed LFP modulation. To achieve this, we analyzed the spiking activity of both pyramidal cells (PCs) and FSBCs under these conditions (**Figure. 3a-c**). Our analysis showed that under supralinear activation, FSBCs exhibited significantly higher firing rates compared to the bimodal and sublinear conditions (**Figure. 3a, c**). This increase in FSBC activity led to a suppression of PC firing, as observed in the lower firing frequencies of PCs under this condition (**Figure. 3b, c**). Conversely, under sublinear activation, FSBC firing rates were reduced, resulting in disinhibition of the PCs and subsequently higher PC firing frequencies compared to the supralinear condition (**Figure. 3a, b, c**). The bimodal activation condition, in which synapses were distributed across both dendritic types, displayed intermediate firing rates for both FSBCs and PCs, reflecting a balance between the effects observed in the supralinear and sublinear conditions (**Figure. 3c**). These results demonstrate that dendritic nonlinearities in FSBCs enable differential modulation of network activity, with supralinear dendrites suppressing PC activity via enhanced FSBCs firing and sublinear dendrites facilitating PC activity through reduced FSBC firing. This dynamic regulation of the E/I balance highlights the functional significance of FSBCs' bimodal nonlinear dendritic architecture in shaping hippocampal network oscillatory dynamics.

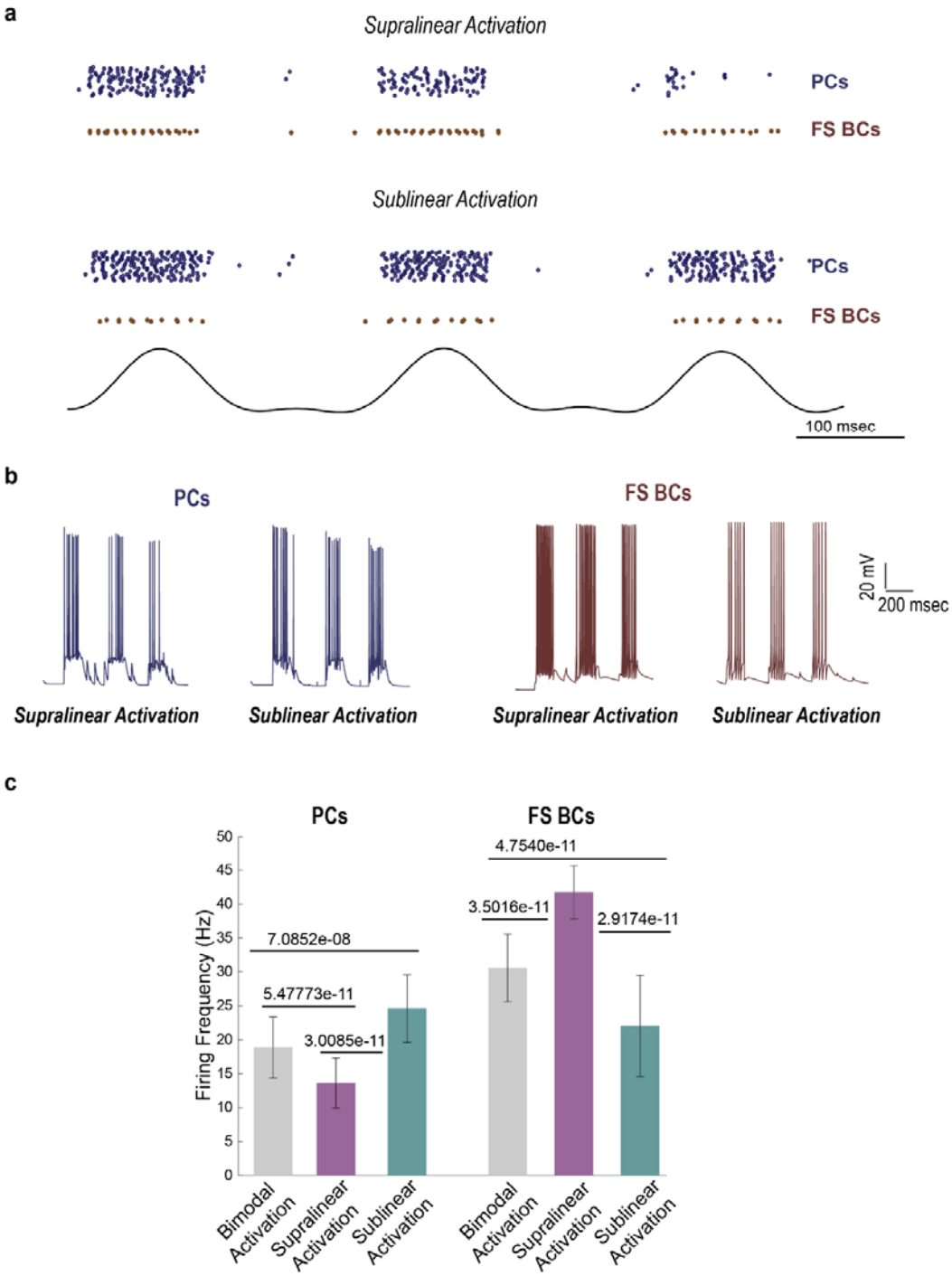

Figure 3 **Supralinear and sublinear FSBC dendrites differentially modulate the E/I balance in the microcircuit under identical synaptic activation conditions.** (a) Representative raster plots depicting the spiking activity of pyramidal cells (PCs) (blue) and FSBCs (brown) across theta cycles when synaptic inputs are selectively targeted to either supralinear dendrites (upper panel) or sublinear dendrites (lower panel) of FSBCs. (b) Representative spike trains of pyramidal cells (left) and FSBCs (right). When FSBCs receive synaptic input in their supralinear branches, their firing rates increase across theta cycles, leading to a decrease in PC spiking. Conversely, when synaptic inputs are restricted to

sublinear dendrites, FSBC firing rates decrease, resulting in increased pyramidal cell activity. (c) *Activation of a fixed number of synapses on randomly selected supralinear dendrites significantly increases the firing frequency of FSBCs, leading to a reduction in the activity of PCs when compared to bimodal (supralinear and sublinear) or purely sublinear activation. Conversely, activation of randomly selected sublinear dendrites decreases the firing frequency of FSBCs, resulting in disinhibition of the PCs. Data are based on 30 random simulation trials. Pairwise comparisons were performed using the Mann–Whitney U test.*

These observations demonstrate that FSBCs can dynamically adapt their firing patterns depending on whether synaptic input is received by their supralinear or sublinear dendritic branches, despite the total synaptic input remaining constant. Supralinear branches, characterized by larger volumes and lower input resistance (Tzilivaki et al., 2019), facilitate enhanced forward propagation of synaptic signals (**Figure S2g**). In contrast, sublinear branches, which have smaller volumes and higher input resistance (Tzilivaki et al., 2019), limit forward propagation (**Figure. S2f**), leading to a decrease in FSBCs firing rates. Consequently, this differential activation modulates the E/I balance in the network, directly shaping the oscillatory activity observed in the LFP. These findings indicate that PV+ FSBCs leverage their bimodal nonlinear dendrites to differentially process incoming synaptic inputs, even when the total synaptic input remains unchanged. This mechanism not only modulates FSBC firing responses at the cellular level (**Figure 3**) but also plays a crucial role in determining the network's oscillatory state, thereby influencing hippocampal rhythm dynamics.

We further explored how altering the dendritic integration profile of FSBCs, specifically by manipulating them to possess purely supralinear or sublinear trees, impacts network behavior compared to the control (bimodal) trees (**Figure. S4a-b**). Leveraging the distinct morphological features of supralinear and sublinear branches in our bimodal FSBCs reconstructions, we adjusted the dendritic morphologies as per (Tzilivaki et al., 2019). When FSBCs were equipped with purely supralinear dendritic trees, we observed enhanced fast frequency and power compared to both bimodal and sublinear tree configurations. This configuration also maximized the firing response of FSBCs (**Figure S4a, c-h**). Conversely, FSBCs with purely sublinear dendritic trees present a reduced spike rate which increased the PCs activity (**Figure. S4h**). Sublinear FSBC trees exhibited increased slow power and decreased fast power and lower fast power compared to supralinear trees (**Figure. S4b-g**).

These simulations underscore that FSBCs take advantage of their bimodal nonlinear dendritic trees by dynamically utilizing their supralinear and sublinear dendrites to regulate the E/I balance within the network, thereby orchestrating distinct oscillatory behaviors under equivalent synaptic input conditions. Importantly, activating either only supralinear or only sublinear branches of a bimodal tree (**Figs.1-2**) exhibits similar phenotypic responses to hypothetical configurations of purely supralinear or purely sublinear trees (**Fig.S3**). This further supports the notion that the bimodal nonlinear nature of FSBCs dendrites allows for flexible modulation of network activity and oscillatory patterns crucial for hippocampal mnemonic functions.

Apart from the type of dendritic integration, the spatial arrangement of synapses also influences the firing characteristics (Kastellakis et al., 2015). It's well-established that supralinear dendrites tend to enhance clustered synaptic allocation, whereas sublinear dendrites prefer dispersed activation. For FSBCs, it has been observed that dispersed synaptic activation leads to higher firing frequencies compared to clustered (Hu et al., 2014; Tzilivaki et al., 2019, 2022). This phenomenon is influenced by the co-existence of sublinear

along with supralinear branches, coupled with their small size and the presence of A-type potassium channels(Hu and Vervaeke, 2018b; Hu et al., 2014; Tzilivaki et al., 2019), which discourages preference for clustered inputs. To investigate how synaptic clustering affects the oscillatory behavior of our network, we simulated the activation of the same number of synapses as in our disperse protocols (as in **Figure. S4**) but now clustered in a few randomly chosen dendrites (**Figure. S5**). As anticipated, clustered activation of sublinear FSBC trees significantly reduced their firing rates while maximizing the E/I balance in the network. Conversely, clustering synapses in supralinear trees enhanced FSBC firing rates compared to both bimodal and sublinear clustering configurations, while also decreasing the firing rates of the PCs (**Figure. S5j**). At the oscillatory level, akin to our simulations with dispersed synaptic activation, clustered synapses in supralinear FSBC trees enhanced fast LFP components, whereas synaptic clustering in sublinear trees boosted the slow LFP power (**Figure. S5a-i**). These findings underscore the dual impact of dendritic morphology and synaptic spatial arrangement on neuronal firing patterns and network oscillatory dynamics. They highlight the intricate mechanisms by which FSBCs can dynamically modulate their responses and contribute to the regulation of network excitability and oscillatory activity crucial for hippocampal function. An important consideration for future experimental studies is whether supralinear and sublinear dendrites receive synaptic inputs from distinct hippocampal or cortical regions. Such compartmentalization or segregation of inputs could profoundly influence FSBC activity across different oscillatory and behavioral states (see Discussion).

Finally, we analyzed the Phase-Amplitude Coupling (PAC),(Tort et al., 2010) to check the slow-fast oscillation coupling in the LFP across all cases (**Figure. S6**). Indeed, the LFP response aligns with experimental findings, indicating that slow activity entrains hippocampal networks to slow-fast coupling (**Figure .S6a**)(Belluscio et al., 2012; Canolty et al., 2006; Park et al., 2020; Scheffer-Teixeira et al., 2012; Scheffzük et al., 2011; Tort et al., 2013; Zhang et al., 2016). Activation of either supralinear or sublinear branches did not alter the coupling between the two oscillatory components (**Figure. S6b-f**). However, coupling was enhanced when synapses were clustered on fully sublinear dendritic trees of FSBCs. Conversely, coupling was reduced when similar clustering occurred on supralinear FSBC dendritic trees (**Figure. S6g-j**). These results indicate that as the power and frequency of the fast component decrease, it becomes more synchronized with the slower component.

Discussion

While the role of interneurons in hippocampal memory-related oscillations is well established (Allen and Monyer, 2015; Klausberger and Somogyi, 2008; Pelkey et al., 2017b; Topolnik and Tamboli, 2022; Tzilivaki et al., 2023), a significant gap remains in understanding the cellular and subcellular mechanisms that enable these neurons to flexibly control memory-related rhythms. Recent studies have highlighted the involvement of PV+ interneuron dendrites in fast oscillations (Chiovini et al., 2014; Judák et al., 2022; Kriener et al., 2022), and suggest the potential advantage of supralinear dendritic integration (Memmesheimer, 2010), yet a direct link between interneuronal dendritic integration and its impact on slow and fast hippocampal memory-related rhythms remains unexplored. In particular, our biophysical modeling predictions reveal that hippocampal FSBCs, a prominent subtype of PV+ interneurons, exhibit distinct firing patterns that modulate the E/I balance independently of synaptic input quantity. Specifically, activation of supralinear dendritic branches in bimodal FSBCs (**Figures 1-2**) reduces the E/I balance (**Figure. 3**), thereby promoting fast oscillatory activity associated with memory consolidation (**Figures. 1-2**). In contrast, activation of

sublinear dendritic branches increases the E/I balance (**Figure. 3**), leading to an enhanced slow LFP signature (**Figures. 1- 2**), which is linked to memory encoding. These new findings redefine our understanding of FSBCs contributions to hippocampal memory oscillations, by shedding light on how these interneurons exploit their intricate and highly adaptive nonlinear dendritic trees. This work also sets the foundation for future experimental efforts aimed at linking dendritic processing at the subcellular level to its broader effects on cellular and network computations, particularly under the influence of GABAergic inhibition.

Despite significant progress in understanding interneuron function, we are still far from fully linking subcellular properties of interneurons not only to memory states but also to behavioral states, such as learning during spatial navigation and memory consolidation during sleep. To comprehensively investigate how interneuron dendrites influence memory-related oscillations, it is essential to explore the diversity of hippocampal interneurons. Within the hippocampal formation alone, over 20 distinct interneuron subtypes have been identified, each classified based on biophysical, morphological, developmental, and connectivity profiles. Beyond FSBCs, other PV+ interneuron subclasses and different inhibitory neuron classes (e.g., SOM+ and VIP+ interneurons) are known to participate in distinct memory-related rhythms (Ascoli et al., 2008; Pelkey et al., 2017a; Sanchez-Aguilera et al., 2021). However, a major gap remains in characterizing the dendritic integration mechanisms of these diverse interneuron subtypes. To bridge this gap, experimental approaches such as glutamate uncaging, dendritic patch clamp recordings and detailed biophysical modeling are needed to determine the precise dendritic processing mechanisms and their corresponding biophysical underpinnings. Expanding our knowledge in this area will enable the refinement of computational models, such as the one presented in this study, to provide a detailed framework for understanding how dendritic function across inhibitory and excitatory neuronal subtypes shapes the oscillatory activity of the networks during different memory stages.

Additionally, future studies should investigate whether specific interneuron dendritic compartments receive distinct synaptic inputs from different hippocampal and cortical areas, as this could provide a critical link between dendritic function, interneuron activity, and network oscillations associated with learning and memory. A critical unresolved question is where and when nonlinear dendrites receive inputs during distinct behavioral and memory stages. Specifically, in the case of bimodal nonlinear dendritic trees in PV+ FSBCs, it remains unknown whether supralinear and sublinear branches are activated by different axons originating from local hippocampal neurons or extrahippocampal sources, such as the entorhinal cortex, septum, or locus coeruleus (Fernández-Ruiz et al., 2021; Pelkey et al., 2017b; Topolnik and Tamboli, 2022; Tzilivaki et al., 2023). Given that functional connectivity patterns within and beyond the hippocampus are thought to underlie distinct behavioral states (e.g., active navigation vs. sleep-related consolidation), we believe it would be of great interest to map the precise origins of these inputs. Our modeling results indicate that PV+ FSBCs respond differently depending on whether their supralinear or sublinear dendritic branches are targeted—regardless of the total synaptic input. This raises the intriguing possibility that PV+ FSBCs might exploit their bimodal nonlinear dendrites to interpret inputs from different sources across distinct memory stages (encoding/learning and consolidation) and behavioral states. Could supralinear branches preferentially process inputs from one brain region while sublinear branches receive signals from another, dynamically tuning FSBC responses during learning versus consolidation? Could the activation of inhibitory sublinear branches facilitate a shift in the network into a "learning mode" by promoting disinhibition? Similarly, could inhibitory supralinear activation function as a mechanism to transition the network into a "consolidation mode" for processing and stabilizing learned information? To address these questions, future experimental studies should employ advanced, *in vivo* approaches to identify the origins of synaptic inputs targeting supralinear

and sublinear dendrites during distinct memory stages. Computational models, like the one presented here, can then be refined to incorporate this knowledge, allowing for predictions of how connectivity patterns and input sources influence dendritic computations in PV+ FSBCs. Ultimately, unraveling these mechanisms will provide a deeper understanding of how complex dendritic architectures contribute to hippocampal network function across different memory and behavioral states.

Author contributions: AT and DS conceived the study. AT designed and ran the simulations, analyzed the data, and prepared the figures. MEL and DS provided senior conceptual input on the study and methodology. AT wrote the manuscript. DS funded and supervised the project. All authors edited and approved the final version of the manuscript.

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Code and Data availability

All codes/scripts and datasets required to reproduce the results and figures, as well as all statistical analyses, are accessible in the ModelDB database. https://modeldb.science/2018008 *Access code:* 280621Interneurons! They are also available on Github: https://github.com/AlexandraTzilivaki/Tzilivakietal2024

Competing interests

The authors declare no competing interests.

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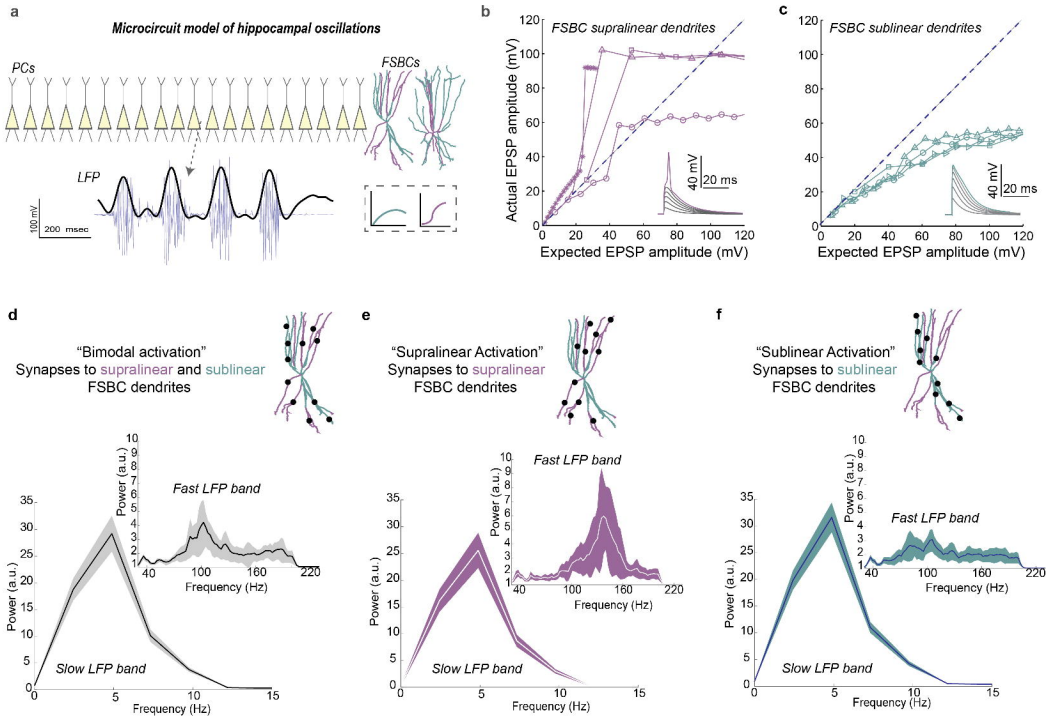
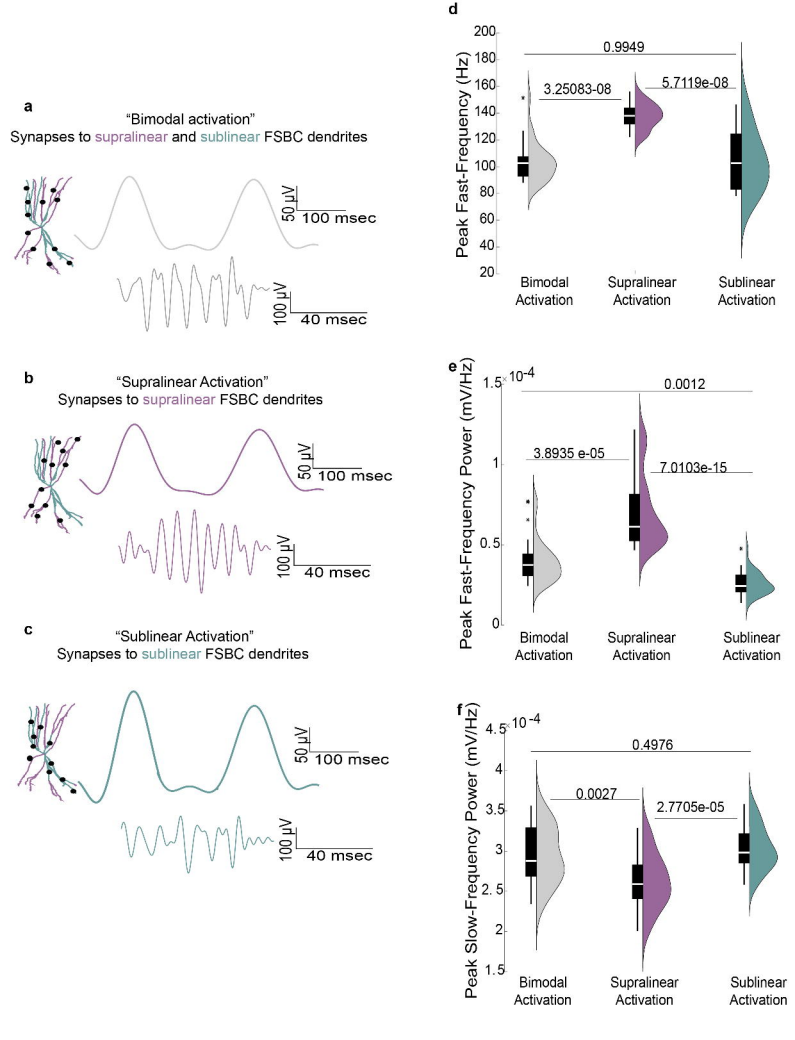
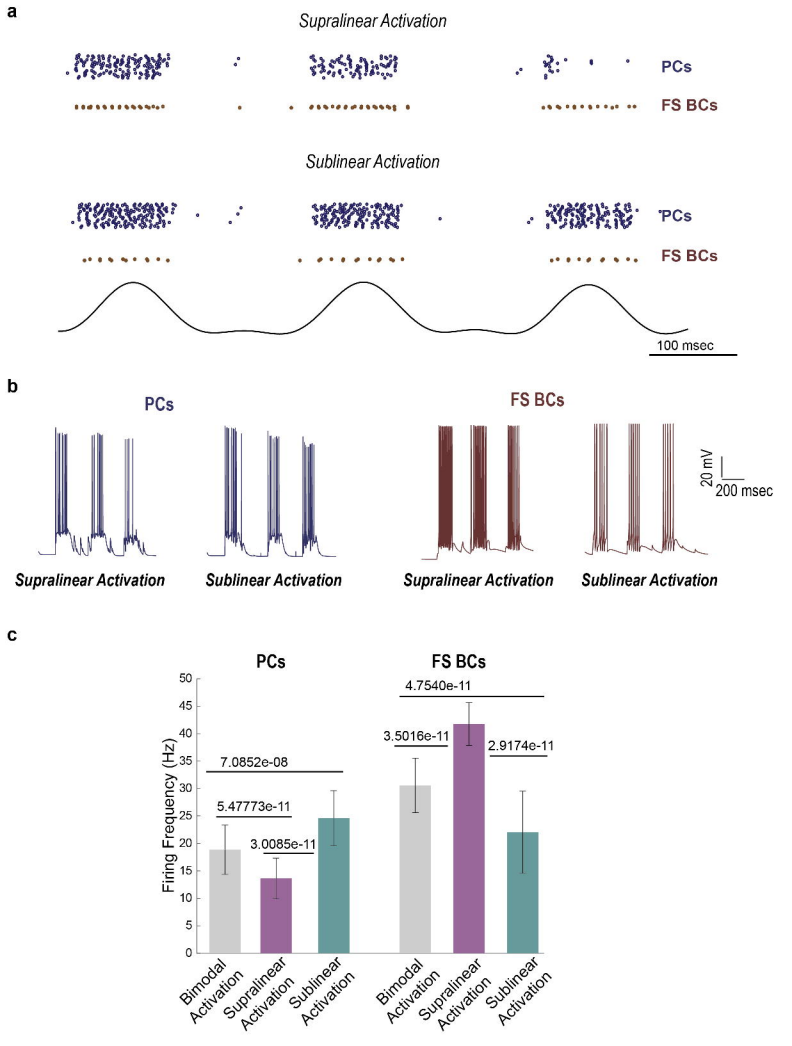

a
Microcircuit model of hippocampal oscillations
PCs
FSBCs
LFP
100 mV
200 msec
b
FSBC supralinear dendrites
Actual EPSP amplitude (mV)
Expected EPSP amplitude (mV)
40 mV
20 ms
c
FSBC sublinear dendrites
Expected EPSP amplitude (mV)
40 mV
20 ms
d
"Bimodal activation"
Synapses to supralinear and sublinear
FSBC dendrites
Fast LFP band
Slow LFP band
Power (a.u.)
Frequency (Hz)
e
"Supralinear Activation"
Synapses to supralinear
FSBC dendrites
Fast LFP band
Slow LFP band
Power (a.u.)
Frequency (Hz)
f
"Sublinear Activation"
Synapses to sublinear
FSBC dendrites
Fast LFP band
Slow LFP band
Power (a.u.)
Frequency (Hz)


a
"Bimodal activation"
Synapses to supralinear and sublinear FSBC dendrites
50 µV
100 msec
100 µV
40 msec
b
"Supralinear Activation"
Synapses to supralinear FSBC dendrites
50 µV
100 msec
100 µV
40 msec
c
"Sublinear Activation"
Synapses to sublinear FSBC dendrites
50 µV
100 msec
100 µV
40 msec
d
Peak Fast-Frequency (Hz)
0.9949
3.25083-08
5.7119e-08
Bimodal Activation
Supralinear Activation
Sublinear Activation
e
Peak Fast-Frequency Power (mV/Hz)
10-4
0.0012
3.8935 e-05
7.0103e-15
Bimodal Activation
Supralinear Activation
Sublinear Activation
f
Peak Slow-Frequency Power (mV/Hz)
10-4
0.4976
0.0027
2.7705e-05
Bimodal Activation
Supralinear Activation
Sublinear Activation


a
Supralinear Activation
PCs
FS BCs
Sublinear Activation
PCs
FS BCs
100 msec
b
PCs
FS BCs
20 mV
200 msec
Supralinear Activation
Sublinear Activation
Supralinear Activation
Sublinear Activation
c
PCs
FS BCs
Firing Frequency (Hz)
0
5
10
15
20
25
30
35
40
45
50
7.0852e-08
5.47773e-11
3.0085e-11
4.7540e-11
3.5016e-11
2.9174e-11
Bimodal Activation
Supralinear Activation
Sublinear Activation
Bimodal Activation
Supralinear Activation
Sublinear Activation