1
2 **Bimodal dendritic processing in basket cells drives distinct memory-related oscillations.**

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15

16 **Abstract**

17 Hippocampal oscillations span from slow to high-frequency bands that are linked to different
18 memory stages and behavioral states. We show that fast spiking basket cells (FSBCs) with
19 bimodal nonlinear dendritic trees modulate these oscillations. Supralinear FSBC dendritic
20 activation enhances high-frequency oscillations, while sublinear activation increases slow
21 oscillatory power, adjusting the Excitation/Inhibition balance in the network. This underscores
22 a new link between FSBCs nonlinear dendritic integration and memory-related oscillations.

23

24 **Main**

25 Hippocampal oscillations exhibit a variety of distinct frequency bands[1]. For example,
26 neuronal activity often associates with a slow local field potential (LFP) component, known
27 as theta activity, which ranges from 3 to 10 Hz[1–3]. Additionally, hippocampal activity includes
28 fast-frequency oscillations spanning from 30 to 200 Hz[1–5]. Both experimental and
29 computational studies have linked these slow and fast components to different stages of
30 hippocampal memory formation and distinct behavioral states[3,6,7]. Specifically, slow 3-10 Hz
31 oscillations correlate with memory encoding, spatial navigation, and sensory processing[3].
32 Conversely, fast oscillations are associated with memory encoding and consolidation[3,6].
33 Notably, these fast and slow components often occur together in a phenomenon known as
34 oscillation coupling[5,8–11] which has been proposed as a signature of working memory
35 processing and various behavioral states (**Fig.1a**) [3,5].

36 To understand the cellular mechanisms behind these oscillatory events, significant efforts
37 have been made to delineate the effects of various subclasses of both excitatory and
38 inhibitory hippocampal populations. Among these, PV+ GABAergic interneurons play a
39 crucial role in both slow and fast oscillations as well as in coupled oscillatory activity[10,12–17].
40 However, the vast majority of research has traditionally focused on the activation or silencing
41 of PV+ interneurons during oscillations through optogenetic and modeling approaches.

42   Recent computational and experimental studies reveal that PV+ interneurons exhibit diverse
43   nonlinear dendritic computations, significantly enhancing their computational capabilities and
44   shaping their input-output (I/O) configurations[18–23]. Notably, a subtype of PV+ interneurons,
45   the Fast-Spiking Basket Cells (FSBCs), possesses bimodal nonlinear dendritic
46   integration[18,19,24]. Specifically, multicompartmental biophysical modeling has shown that
47   FSBCs have two types of co-existing nonlinear dendrites: supralinear dendrites, which can
48   generate local dendritic spikes, and sublinear dendrites, which integrate excitatory synaptic
49   input passively (**Figs.1b-c,S1a-d**). While both types of nonlinear dendrites co-exist in the
50   same tree (**Fig.1b-c,S1**), and share similar active properties, they differ morphologically[19].
51   Supralinear branches have higher volume, and lower input resistance, enabling local sodium
52   spikes (**Fig.S1a-e**). Conversely, sublinear branches have lower volume, and higher input
53   resistance. Thus, coincident synaptic input induces large, fast rising EPSPs that in turn
54   activate A-type potassium channels leading to a fast repolarization of the membrane, thus
55   preventing the generation of local sodium spikes (**Fig.S1a-d**). These modeling predictions[19]
56   are supported by recent experimental findings in PV+ interneurons across different
57   hippocampal areas[18,20,21].

58   However, it remains unknown whether the bimodal nonlinear nature of FSBCs dendrites
59   affects network function by modulating different memory-related oscillations. Given the
60   involvement of FSBCs in both slow (e.g. theta-frequencies) and fast oscillations[12,25,26], we
61   hypothesized that the supralinear or sublinear branches of FSBCs would differentially
62   modulate FSBCs activity and, consequently, their impact on orchestrating the LFP during
63   mnemonic functions.

64   To test our hypothesis, we used a previously published biologically plausible hippocampal
65   microcircuit model[27] that includes compartmental biophysical models of pyramidal cells
66   (PCs) with reduced morphology[27] and FSBCs with anatomical reconstructions of bimodal
67   nonlinear dendritic trees, as in[19,27] (**TablesS1-5**, **Fig.1a**). Upon activation with a theta-like
68   input as per[28,29], our microcircuit exhibited a slow oscillatory component coupled with a fast
69   one (**Fig.1a,d**). In our control experiment (bimodal activation), synapses to FSBCs were
70   placed in randomly chosen both supralinear and sublinear branches (**Fig.1a,d, 2a**). We
71   investigated how the network would respond when keeping the amount of synaptic contacts
72   constant but activating either only randomly chosen supralinear branches (**Fig.1e, 2b**) or
73   only sublinear branches (**Figs.1f, 2c**) of FSBCs trees. Our model predicts that activation of
74   the supralinear branches of the FSBCs trees supports the fast oscillatory component
75   (**Fig.1e,2b**). In sharp contrast, activation of only sublinear branches enhances the power of
76   the slow LFP band (**Figs 1f, 2c**). Specifically, supralinear activation results in a higher fast
77   frequency and fast peak-frequency power compared to both bimodal and sublinear activation
78   conditions (**Fig.2d, e**). In contrast, sublinear activation massively decreases the fast peak-
79   frequency power compared to both bimodal and supralinear activation (**Fig.2d**), as well as
80   the fast peak-frequency and slow power compared to supralinear activation (**Fig.2e,f**). To
81   assess the robustness of the differential impact of supralinear vs sublinear dendritic
82   activation in the LFP bands, we performed a sensitivity analysis on the synaptic parameters
83   and input features. In all cases supralinear activation enhanced the peak power and peak
84   frequency power of the fast LFP component whereas sublinear activation resulted in higher
85   slow power compared to supralinear activation (**Fig.S2**).

86

87   ***Figure 1. Bimodal dendritic integration in FBCs modulate memory-related***
88   ***hippocampal oscillations.*** *Schematic Illustration of the hippocampal microcircuit model. A*
89   *population of 20 PCs and 2 FSBCs is activated by a theta (4 Hz) input for 1000 msec. An*
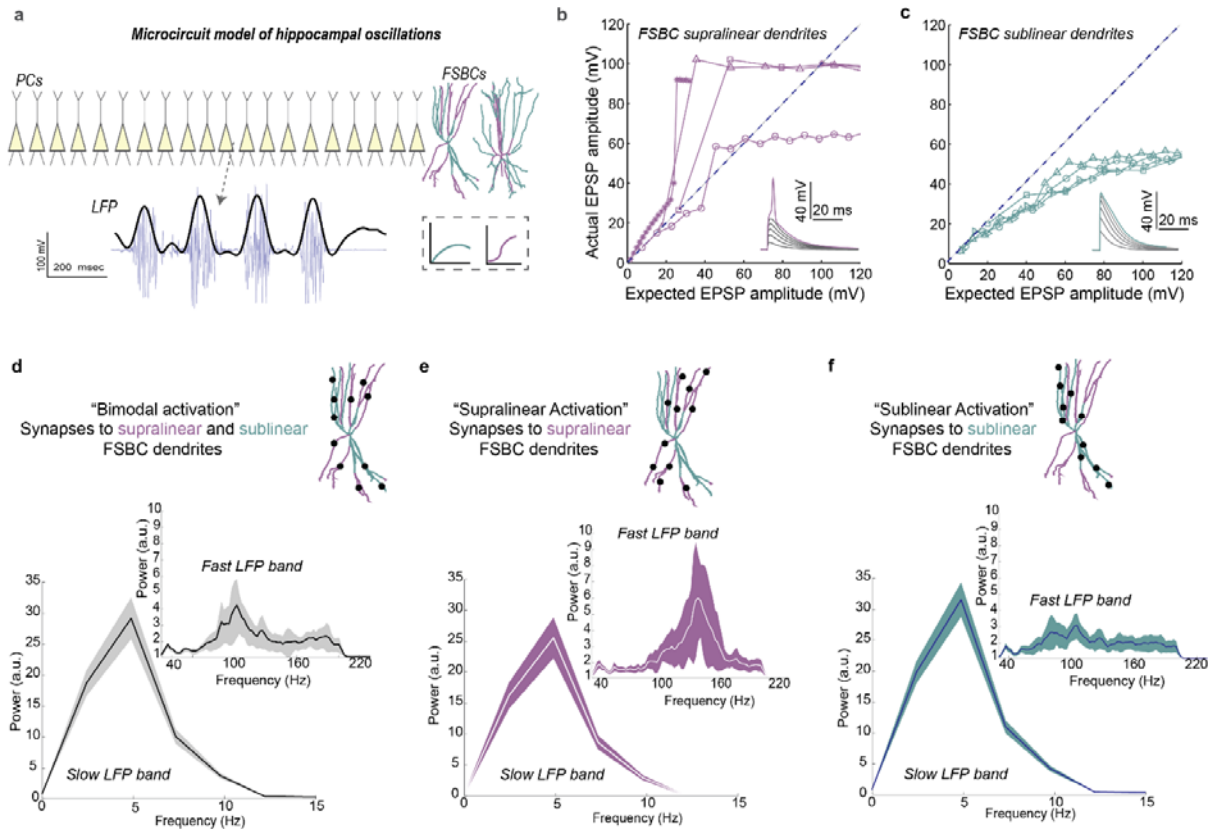
90   *LFP electrode is positioned nearby the PCs somata. Upon activation the model exhibits slow*
91   *(bandpassed at 3-10 Hz) and fast (bandpassed at 30-200 Hz) LFP bands. The arrow*
92   *indicated the in-silico electrode position. FSBCs are equipped with bimodal nonlinear trees*
93   *as per Tzilivaki et al., 2019. **b-c.** Representative input-output curves from supralinear (**b**) and*
94   *sublinear (**c**) dendritic branches in FSBC models, in response to synaptic stimulation.*
95   *Increasing numbers of synapses (from 1 to 20 with step□=□1) are uniformly distributed in*
96   *every stimulated branch and are activated with a single pulse. The y-axis shows the*
97   *amplitude of the dendritic EPSP caused by synaptic activation while the x-axis shows the*
98   *expected EPSP amplitude that would result from the linear summation of synaptic EPSPs.*
99   *The dashed line indicates linear summation. Insets show representative traces. Panels were*
100 *adopted from Tzilivaki et al., 2019. **d-f.** Power Spectrum Density (PSD) plots upon bimodal*
101 *(**d**), supralinear (**e**) and sublinear (**f**) activation. The number of activated synapses remain*
102 *identical for all conditions. Synapses were placed in randomly chosen supralinear and*
103 *sublinear branches (**d**) or in either randomly chosen supralinear (**e**) or sublinear (**f**)*
104 *branches. Activation of the supralinear dendrites (**e**) supports the fast LFP signature while*
105 *sublinear activation (**f**) promotes slow LFP power. Data from 30 random simulation trials.*
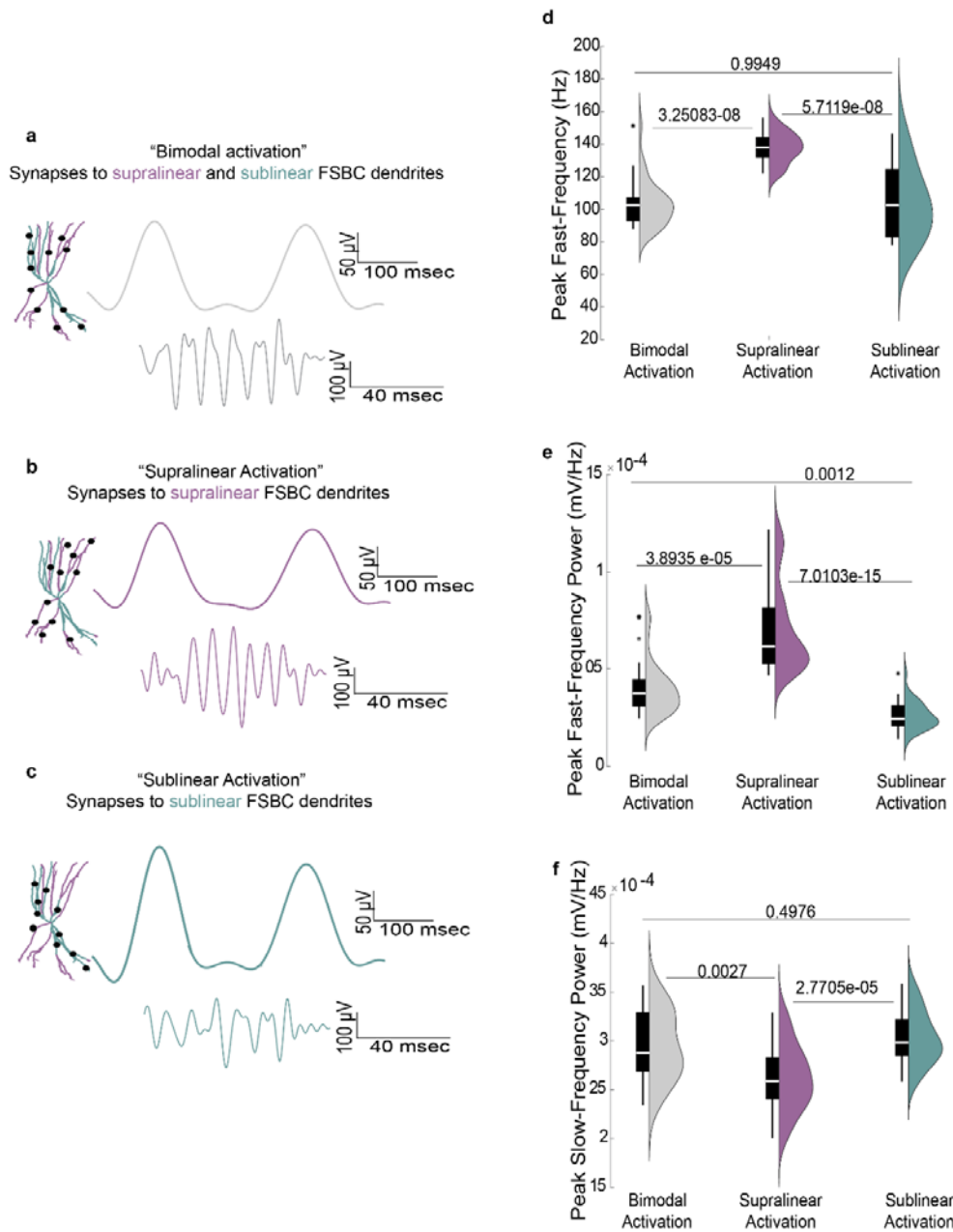
Figure 2. LFP frequency and power are regulated by FSBC nonlinear dendritic activation. *(a-c) Schematic illustration of the activation protocols and representative traces of the evoked LFP bandpassed at slow (theta 3-10 Hz) and fast (30-200 Hz) frequences. The same number of synapses targets either 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.*

142 Given that the number of synapses remains consistent across all three activation scenarios
143 (bimodal, supralinear, and sublinear), we sought to understand the factors driving the
144 observed LFP modulation. To achieve this, we analyzed the spiking activity of both the PC
145 and FSBC populations under these conditions. Our analysis revealed that supralinear
146 activation led to higher spike rates in FSBCs, resulting in decreased firing of the PC
147 population compared to both bimodal and sublinear activation conditions. Conversely,
148 activation of sublinear branches in FSBCs reduced their firing rates, thereby disinhibiting the
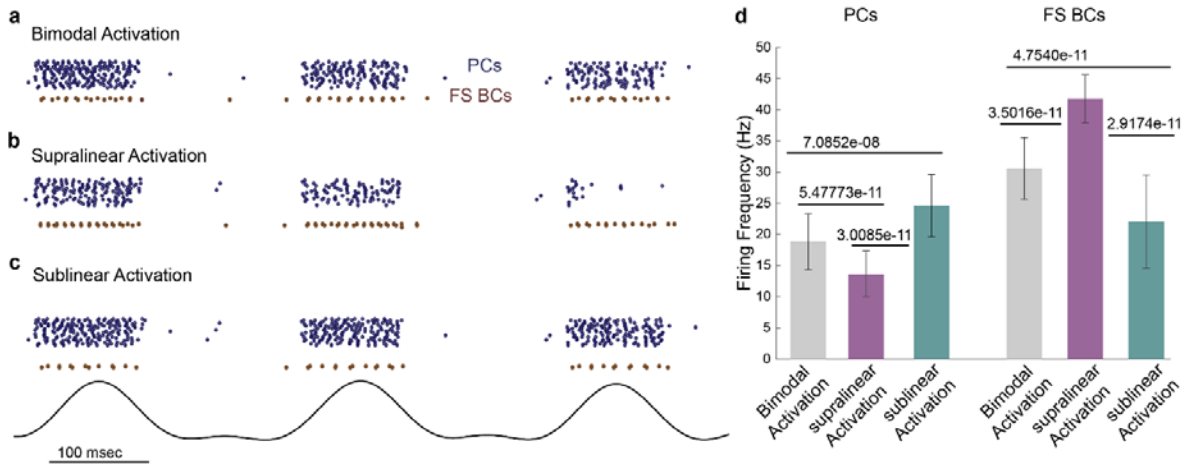
149 PC population (**Fig.3**).

150

151 *Figure 3. Supralinear and Sublinear FSBC dendrites differentially modulate the E/I*
152 *balance in the microcircuit. (a-c). Representative raster plots showing the spiking activity*
153 *of PCs (blue) and FSBCs (brown) across indicative theta cycles under different dendritic*
154 *activation conditions: bimodal (a), supralinear (b), or sublinear (c). (d) Activation of a fixed*
155 *number of synapses on randomly selected supralinear dendrites significantly increases the*
156 *firing frequency of FSBCs, leading to a reduction in the activity of PCs when compared to*
157 *bimodal (supralinear and sublinear) or purely sublinear activation. Conversely, activation of*
158 *randomly selected sublinear dendrites decreases the firing frequency of FSBCs, resulting in*
159 *disinhibition of the PCs. Data are based on 30 random simulation trials. Pairwise*
160 *comparisons were performed using the Mann–Whitney U test.*

161

162 These observations demonstrate that FSBCs can adapt their firing patterns when activated
163 through either supralinear or sublinear branches, despite receiving an equivalent synaptic
164 input. Supralinear dendritic branches are characterized by larger volumes and lower input
165 resistance[19] which facilitates enhanced forward propagation of signals. In contrast, activation
166 of sublinear branches, which have smaller volumes and therefore higher input resistance[19],
167 restricts forward propagation (**Fig.S1f-g**), leading to decreased firing rates of FSBCs.
168 Consequently, this modulation alters the excitation to inhibition (E/I) balance within the
169 network, thereby influencing the characteristic oscillatory activity observed in the LFP.

170 We further explored how altering the dendritic integration profile of FSBCs, specifically by
171 manipulating them to possess purely supralinear or sublinear trees, impacts network
172 behavior compared to the control (bimodal) trees (**Fig.S3a-b**). Leveraging the distinct
173 morphological features of supralinear and sublinear branches in our bimodal FSBCs
174 reconstructions, we adjusted the dendritic morphologies as per[19]. When FSBCs were

175 equipped with purely supralinear dendritic trees, we observed enhanced fast frequency and
176 power compared to both bimodal and sublinear tree configurations. This configuration also
177 maximized the firing response of FSBCs (**Fig.S3a,c-h**). Conversely, FSBCs with purely
178 sublinear dendritic trees present reduced spike rate which increased the PCs activity
179 (**Fig.S3h**). Sublinear FSBC trees exhibited increased slow power and decreased fast power
180 and lower fast power compared to supralinear trees (**Fig.S3b-g**).

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

190 Apart from the type of dendritic integration, the spatial arrangement of synapses also
191 influences the firing characteristics[30]. It's well-established that supralinear dendrites tend to
192 enhance clustered synaptic allocation, whereas sublinear dendrites prefer dispersed
193 activation. For FSBCs, it has been observed that dispersed synaptic activation leads to
194 higher firing frequencies compared to clustered[18,19,31]. This phenomenon is influenced by the
195 co-existence of sublinear along with supralinear branches, coupled with their small size and
196 the presence of A-type potassium channels[19,22,31], which discourages preference for
197 clustered inputs. To investigate how synaptic clustering affects the oscillatory behavior of our
198 network, we simulated the activation of the same number of synapses as in our disperse
199 protocols (as in **Fig.S3**) but now clustered in a few randomly chosen dendrites (**Fig.S4**). As
200 anticipated, clustered activation of sublinear FSBC trees significantly reduced their firing
201 rates while maximizing the E/I balance in the network. Conversely, clustering synapses in
202 supralinear trees enhanced FSBC firing rates compared to both bimodal and sublinear
203 clustering configurations, while also decreasing the firing rates of the PCs (**Fig.S4j**). At the
204 oscillatory level, akin to our simulations with dispersed synaptic activation, clustered
205 synapses in supralinear FSBC trees enhanced fast LFP components, whereas synaptic
206 clustering in sublinear trees boosted the slow LFP power (**Fig.S4a-i**). These findings
207 underscore the dual impact of dendritic morphology and synaptic spatial arrangement on
208 neuronal firing patterns and network oscillatory dynamics. They highlight the intricate
209 mechanisms by which FBCs can dynamically modulate their responses and contribute to the
210 regulation of network excitability and oscillatory activity crucial for hippocampal function.

211 Finally, we analyzed the Phase-Amplitude Coupling (PAC),[32] to check the slow-fast
212 oscillation coupling in the LFP across all cases (**Fig.S5**). Indeed, the LFP response aligns
213 with experimental findings, indicating that slow activity entrains hippocampal networks to
214 slow-fast coupling (**Fig.S5a**)[5,9,28,33–36]. Activation of either supralinear or sublinear branches
215 did not alter the coupling between the two oscillatory components (**Fig.S5b-f**). However,
216 coupling was enhanced when synapses were clustered on fully sublinear dendritic trees of
217 FSBCs. Conversely, coupling was reduced when similar clustering occurred on supralinear
218 FSBC dendritic trees (**Fig.S5g-j**). These results indicate that as the power and frequency of
219 the fast component decrease, it becomes more synchronized with the slower component.

220 Overall, while the role of interneurons in hippocampal memory-related oscillations is
221 established[13,16,18,26], there remains a significant gap in understanding the cellular and
222 subcellular mechanisms that enable these neurons to flexibly control memory-related
223 rhythms. Recent studies suggest the involvement of PV+ interneuron dendrites in fast

224   oscillations[20,37,38], yet a direct link between interneuronal dendritic integration and their
225   impact on slow and fast hippocampal memory-related rhythms is lacking. Our biophysical
226   modeling provides novel insights showing that hippocampal FSBCs, a prominent subtype of
227   PV+-positive interneurons, exhibit distinct firing patterns that modulate the excitatory-
228   inhibitory (E/I) balance in networks independent of synaptic input quantity. Specifically,
229   activation of supralinear dendritic branches in bimodal FSBCs (**Fig.1,2,S1**) reduces the E/I
230   balance (**Fig.3**), thereby promoting fast oscillatory activity associated with memory
231   consolidation (**Fig.1,2**). In contrast, activation of sublinear dendritic branches increases the
232   E/I balance (**Fig.3**), enhancing the slow LFP signature (**Figs.1,2**), linked to memory
233   encoding. To fully explore the impact of interneuron dendrites on memory-related
234   oscillations, it is crucial to investigate the diversity among hippocampal interneurons[12,13,15,26].
235   Beyond FSBCs, other subclasses of PV+ interneurons and different inhibitory classes (e.g.
236   SOM+ and VIP+ interneurons) are active during distinct memory-related rhythms[12,13], yet
237   their specific dendritic integration profiles remain poorly characterized. Future studies should
238   thus aim to dissect how dendritic nonlinear integration across different interneuron
239   types[12,13,15,16] and PCs[39] modulate memory-related oscillations. Future experimental efforts
240   should aim to elucidate whether distinct hippocampal and cortical inputs selectively target
241   the supralinear or sublinear branches of bimodal FSBCs trees. Although connectivity
242   patterns between hippocampal (e.g. CA3) and extrahippocampal (e.g. entorhinal
243   cortices)populations to FSBCs are documented during fast oscillations[12,13,31,40], it remains
244   unclear whether neurons from the same or different regions preferentially target these two
245   types of nonlinear dendrites. Investigating the potential differential targeting of FSBCs'
246   supralinear and sublinear branches during distinct memory stages, such as encoding versus
247   consolidation, could significantly enhance our understanding of how FSBCs dynamically
248   regulate memory-related rhythms by leveraging their diverse dendritic architectures across
249   different oscillatory activity patterns. Our simulations suggest that bimodal nonlinear dendritic
250   processing in FSBCs could be critical to drive different memory stages and, therefore,
251   influence behavioral states.

252

270

271   **Code and Data availability**

272 Scripts and datasets required to reproduce the results and figures, as well as all statistical
273 analyses, are publicly accessible in www.github.com/AlexandraTzilivaki/Tzilivakietal2024

Competing interests

275 The authors declare no competing interests.

276

Methods

Model implementation and availability

279 Simulations were conducted using NEURON (v7.6)[41] on a High-Performance Computing
280 Cluster, utilizing 111 CPU cores on a 64-bit CentOS Linux operating system. All
281 codes/scripts and datasets required to reproduce the results and figures, as well as all
282 statistical analyses, are publicly accessible in
283 www.github.com/AlexandraTzilivaki/Tzilivakietal2024

284

285

Neuronal populations

287   1. Fast Spiking Basket Cells (FSBCs)

288   Two multi-compartmental biophysical models of CA3 FSBCs were employed, adopted
289   from Tzilivaki et al. (2019)[19]. These FSBCs models include detailed anatomical
290   reconstructions of somata and dendritic trees taken from Neuromorpho database
291   (originally published in Tukker et al. 2007[42]), (**Figure S1**). Both FSBCs feature bimodal
292   nonlinear dendritic branches, characterized by both supralinear and sublinear branches.
293   They are equipped with fast voltage-dependent sodium channels (gnafin), delayed
294   rectifier potassium channels (gkdrin), slow inactivation potassium channels (gslowin),
295   slow calcium-dependent potassium channels (gkcain), A-type potassium channels in
296   proximal and distal dendritic regions (gkadin, gkapin), h-currents (ghin), and L-, N-, and
297   T-type voltage-activated calcium channels (gcal, gcan, and gcat, respectively). These
298   models have been extensively validated against experimental data and accurately
299   capture the intrinsic features and electrophysiological responses of hippocampal FSBCs
300   (See original reference[19] and Supplementary Information). The mean dendritic diameter
301   and total dendritic length were measured for the supralinear and sublinear dendrites of
302   the two FSBCs morphological reconstructions. Dendritic volume was calculated as per
303   Tzilivaki et al. (2019)[19] using the following formula:

$$V = \pi * \left(\frac{diameter}{2}\right)^2 * length \ (\mu m^3)$$

304 To causally manipulate the dendritic morphologies of FSBCs to generate fully supralinear or
305 sublinear trees (Figure S2), we performed causal manipulations according to the approach
306 described in Tzilivaki et al. (2019)[19]. We fixed the diameter and length of all dendrites to
307 create trees with average supralinear or sublinear dendritic volume (**Figure S1B**), which
308 dictated the integration mode as shown in the original modeling publication. Dendritic Input
309 Resistance was calculated using the following formula:

310

$$Rin = \frac{DV}{I} \left(\frac{mV}{nA}\right)$$

311 where I = −100 pA injected in each dendritic branch and DV is the generated
312 IPSP.

313

314 For more detailed information about the FSBC models, please refer to the relevant
315 publication[19] and **Tables S1-2, 4-5**.

316

317   2. Pyramidal Cells (PCs)

318 Biophysically relevant hippocampal PC models (n = 20) were adopted from Hadler et al.
319 (2024)[27]. These models consist of somata and proximal, distal, and basal dendritic branches.
320 PCs include a Ca2+ pump and buffering mechanism, Ca2+ activated slow AHP and medium
321 AHP potassium (K+) currents, an HVA L-type calcium (Ca2+) current, an HVA R-type
322 Ca2+current, an LVA T-type Ca2+ current, an h-current, a fast sodium (Na+) current, a
323 delayed rectifier K+ current, a slowly inactivating K+ M-type current, and a fast inactivating
324 K+ A-type current. These current mechanisms were non-uniformly distributed along the
325 somatodendritic compartments. They were validated based on *in vitro* data to replicate the
326 electrophysiological profile and basic dendritic architecture of hippocampal CA3 PCs[27,43].
327 The PC models do not include detailed nonlinear dendritic trees, as this was beyond the
328 scope of this study. Incorporating realistic anatomical reconstructions for PCs would have
329 significantly increased computational complexity and reduced simulation speed. For more
330 information, see Hadler et al. (2024)[27] and **Tables S3-5**.

331 **Synaptic properties**

332 The PC models were equipped with AMPA, NMDA, and γ-aminobutyric acid type A (GABAA)
333 synapses, while the FSBCs included Ca2+ permeable AMPA (CP-AMPA), NMDA, GABAA,
334 and autaptic GABAA synapses. The synaptic conductance values for every connection type
335 were calibrated based on experimental[44–47] and modelling studies[19] and are listed in **Table
336 S5**
337 To ensure the robustness of our finding we repeated the simulations upon increased or
338 decreased synaptic conductance values (15% change) (see sensitivity analysis Figure S2)

339 **Hippocampal Microcircuit**

340 The hippocampal microcircuit configuration was adopted from Hadler et al. (2024)[27]. The
341 model consists of 20 PCs and 2 FSBCs. In each random simulation trial (n = 30), each PC
342 contacted up to seven (7) randomly chosen PCs with one AMPA and one NMDA synapse
343 activation per contact. Each FSBC received synaptic input from fifteen (15) randomly chosen
344 PCs in each simulation trial. Additionally, each PC received thirteen (13) feedback inhibitory
345 GABAergic inputs from each FSBC per simulation trial. Each FSBC formed five (5)
346 GABAergic synapses per simulation trial and was self-inhibited through autapses. For further
347 details, see the Simulation Paradigms chapter and Hadler et al. (2024)[27].

348 **Simulation Paradigms**

349 Input

350   The microcircuit is activated by a theta entrained presynaptic population as per Turi
351   et al., 2018[48]. The input was modeled as an artificial presynaptic population (N=22)
352   using NEURON's VecStim function. The spike times of the presynaptic population
353   were generated using a sinusoidal theta like filter that was applied so to account for
354   theta like modulated spike times.

355   Thata like probability formula (as per [48]):

$$p(t) = (\sin\left(2.0 * pi * \frac{f_{theta*spike}}{1000.0} + phi_{theta}\right) + 1.0)/2.0$$

356   Where:

357   •   spike = the spike time in msec (float)

358   •   f_theta = theta-cycle frequency in Hz. (float)

359 For the simulations shown in Figures 1-3 and Supplementary Figures 3-5, f_theta=4
360 Hz. For the sensitivity analysis simulations as shown in Supplementary Figure 2, we
361 changed the input the theta frequency to f_theta=5Hz.

362   •   phi_theta= theta cycle phase in radians.

363 For the simulations shown in Figures 1-3 and Supplementary Figures 3-5,
364 phi_theta=0 (equal to 0 radians). For the sensitivity analysis simulations as shown in
365 Supplementary Figure 2, we shifted the input phase so phi_theta=0.5 (equal to 180
366 radians).

367

368 If the probability p(t) is greater than 0.7 a spike is generated for the specific artificial
369 neuron (n=22). Every input neuron has its own theta modulated spike train.

370

371 Each PC received input from 5 artificial presynaptic neurons, while each FSBC
372 received input from 7 artificial presynaptic neurons. Although the input was sufficient
373 to activate the PC population due to its reduced morphology, 7 artificial presynaptic
374 neurons were insufficient to evoke spiking activity in the FSBC models, given their
375 realistic complex anatomical reconstructions. This subthreshold activation was
376 selected to ensure that FSBCs were primarily engaged in the network due to the
377 local inputs they received from PCs.

378

379   1. **Simulations**
380 The microcircuit model was simulated for approximately 12,000 milliseconds (ms)
381 with a time step of 0.1 ms. The first 200 ms were excluded from the analysis to allow
382 the model to reach an equilibrium state. For the dispersed protocols, synapses to
383 FSBCs (both input and local PC-to-FSBC synapses) were randomly assigned to
384 dendrites, meaning one randomly chosen dendrite received one pair of NMDA and
385 CP-AMPA synapses. For the clustered protocol (Supplementary Figure S4), the
386 same total amount of synapses was placed in 4 randomly chosen dendrites (cluster
387 size: 5-7 synapses (per dendrite) Data represent the results (mean and standard
388 deviation values (std)) of thirty (30) random simulation trials for each protocol. In
389 every trial, the total number of synaptic contacts and the connectivity ratios remained
390 identical, but different randomly chosen neurons (from both PC and FSBC
391 populations) were connected to different random neurons. Additionally, in each trial,
392 different dendrites from both PCs and FSBCs were randomly chosen and synapses
393 were activated at different parts of the chosen dendrites. This approach ensured that
394 the results reflected the diversity, especially of the FSBCs trees, in bimodal activation
395 protocols. Furthermore, two different anatomical reconstructions were used for our
396 FSBC models to account for FSBCs morphological variability (see relevant chapter).

397

398   2. **LFP simulation and Spectral analysis**

399 To record the Local Field Potential (LFP), an *in silico* electrode was simulated based on
400 NEURON's extracellular function, following the modelling approach of Vladimirov et al.
401 (2013)[49]. The electrode was placed close to the PCs somata and remained in the exact
402 same position throughout the execution of all protocols and simulation trials. The

403 sampling frequency was set at 10 kHz. Despite the microcircuit model's small size, it
404 efficiently generated fast and slow oscillations comparable to experimental
405 observations[5,11,32,35] while maintaining low computational complexity and demands.

406 The *in silico* LFP datasets were band-passed at two respective bands: slow (3 – 10 Hz)
407 and fast (30-200 Hz). Slow and fast Peak-Frequency powers and peak Fast frequency
408 were determined using custom-made MATLAB scripts (MATLAB, The MathWorks Inc.,
409 Natick, MA; Torrence and Compo 1998) utilizing the p-welch function (0.4 Hz resolution)
410 and visualized as Power-Frequency plots. Phase-Amplitude Coupling (PAC) analysis
411 was conducted using Comodulogram generation and the calculation of the modulation
412 index (MI) metric that were adopted from Tort et al. (2008)[50]. Wavelet phase was
413 calculated at 15 levels from 1-15 Hz, and the amplitude at 50 levels from 30-180 Hz. The
414 MI was obtained by measuring the divergence of the observed amplitude distribution
415 from the uniform distribution.

416 **Statistical Analysis**

417 Statistical analyses for multigroup comparisons were performed using the Kruskal-Wallis
418 test, followed by a post-hoc correction for multiple comparisons (multcompare function
419 Matlab). For pairwise comparisons where data exhibited unequal variance, p-values
420 were calculated using the Mann-Whitney U test.

421 <u>**Supplementary Information**</u>
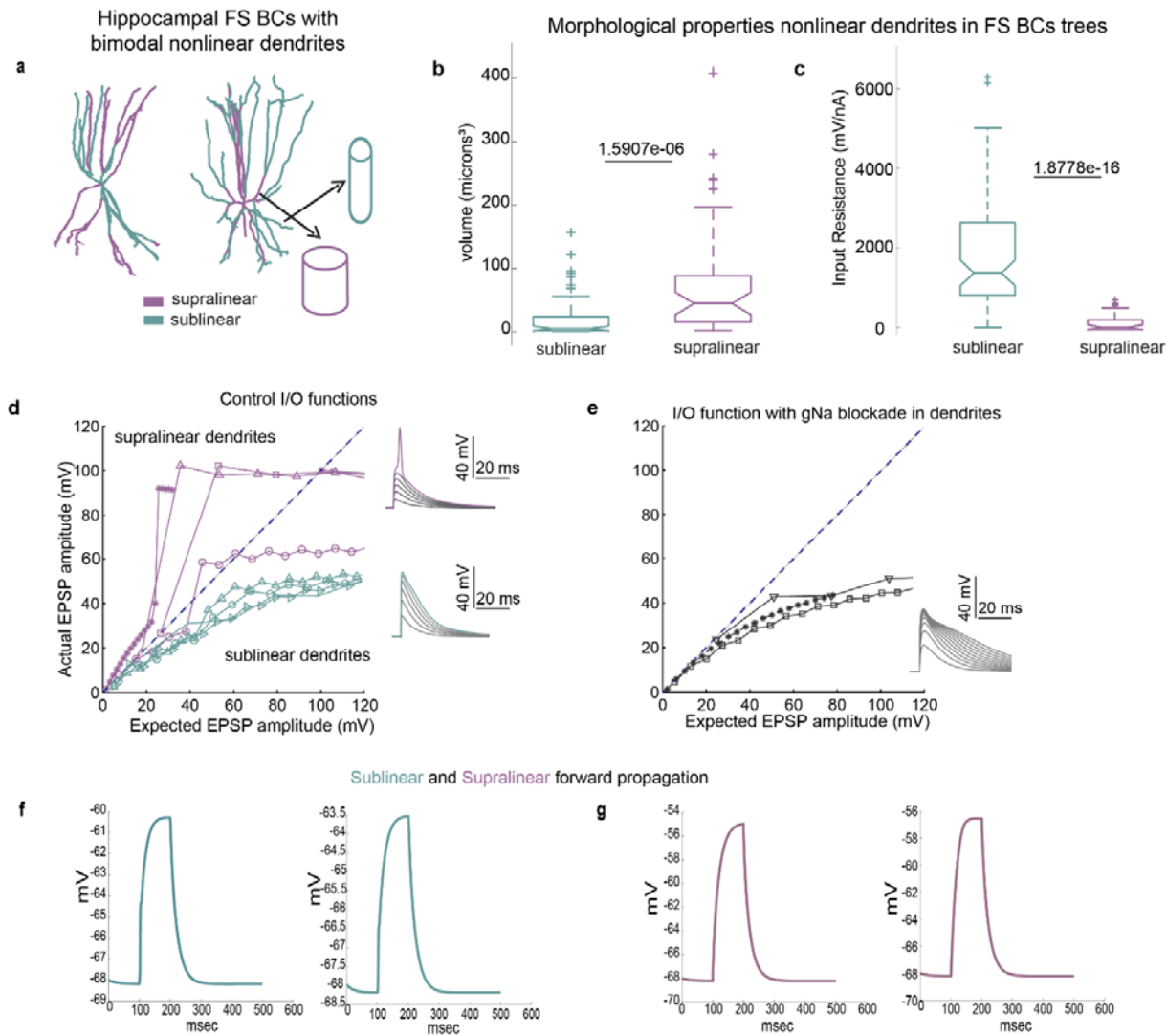
Figure S1. Mechanisms of bimodal nonlinear dendritic integration in Multicompartmental Models of Hippocampal FSBCs.

a. Illustration of the morphological characteristics of supralinear and sublinear dendrites in bimodal FSBC models. Supralinear dendrites (purple) are larger, whereas sublinear dendrites (blue) are longer and thinner. **b-c**. Discriminative features between dendrite types: supralinear dendrites have larger volumes (b) and lower input resistance (c) compared to sublinear dendrites. Statistical significance was determined using the Mann–Whitney U test. **d-e**. Supralinear dendrites (purple) are capable of generating local sodium-dependent spikes, whereas sublinear dendrites (blue) cannot (d). Blocking active sodium conductances in FSBC dendrites completely abolishes the supralinear mode (e). **f-g**. Forward propagation efficiency in bimodal nonlinear dendrites of FSBCs: Current injection (100 pA) at randomly selected dendrites and recording at the soma show that sublinear branches (f) propagate signals less effectively compared to supralinear branches (g). Panels a,d,e were adopted from [19]

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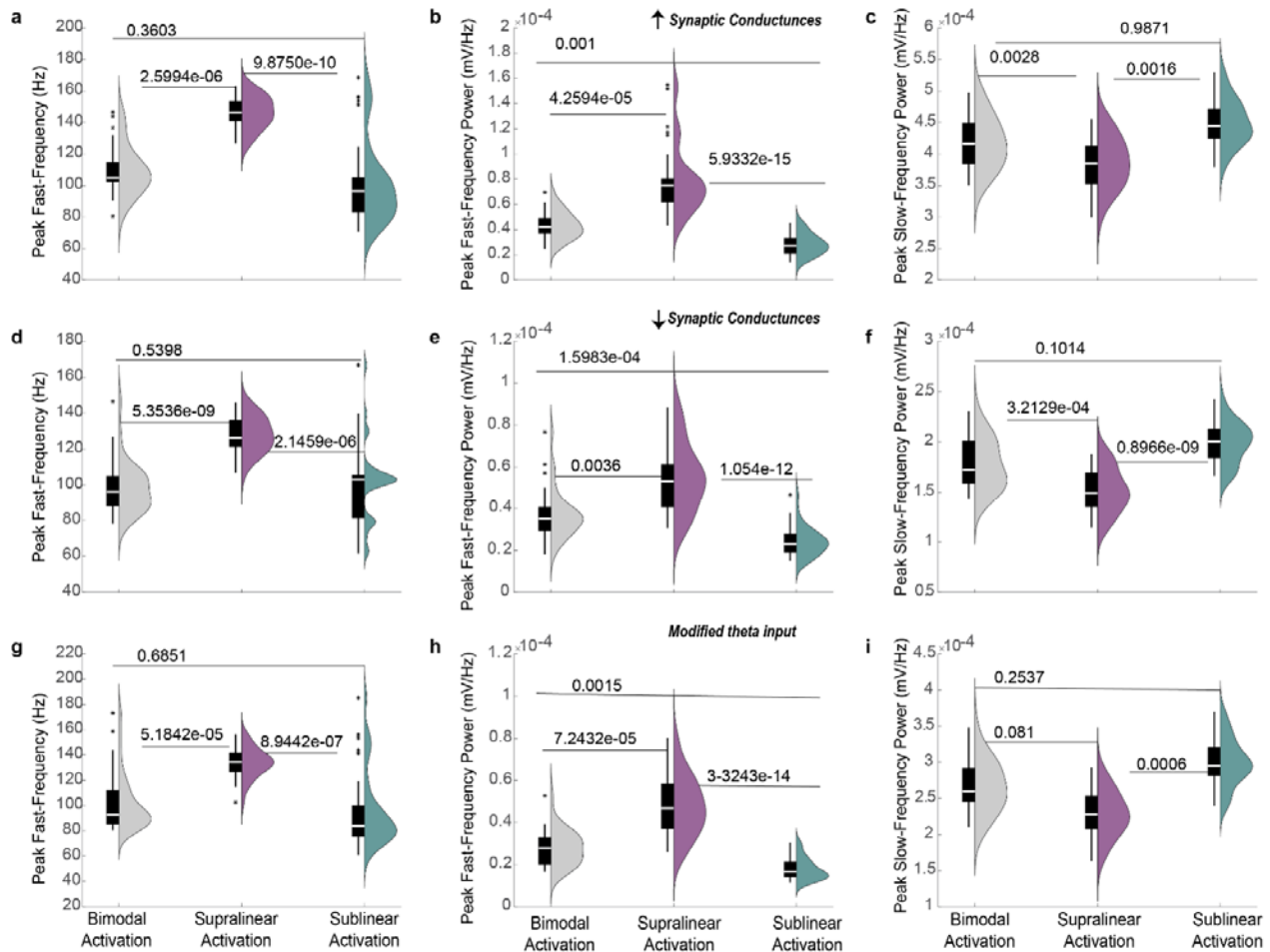
Figure S2. Sensitivity Analysis on Synaptic and Input Parameters (Related to Figure 2). a-c. 15% increase in the synaptic conductance values (applied to both input and network synapses for/from both PCs and FSBCs) do not alter the enhancement of fast peak frequency and power observed with supralinear activation. **d-f**. 15% reduction of the synaptic conductance values (for both input and network synapses involving PCs and FSBCs) also maintain the observed increase in fast peak frequency and power upon supralinear activation. **g-i**. Modifications to input parameters (input phase shifted 180°, peak frequency 5 Hz) similarly do not affect the enhancement of fast peak frequency and power driven by supralinear activation. Statistical analyses for multigroup comparisons were performed using the Kruskal-Wallis test, followed by a post-hoc correction for multiple comparisons.

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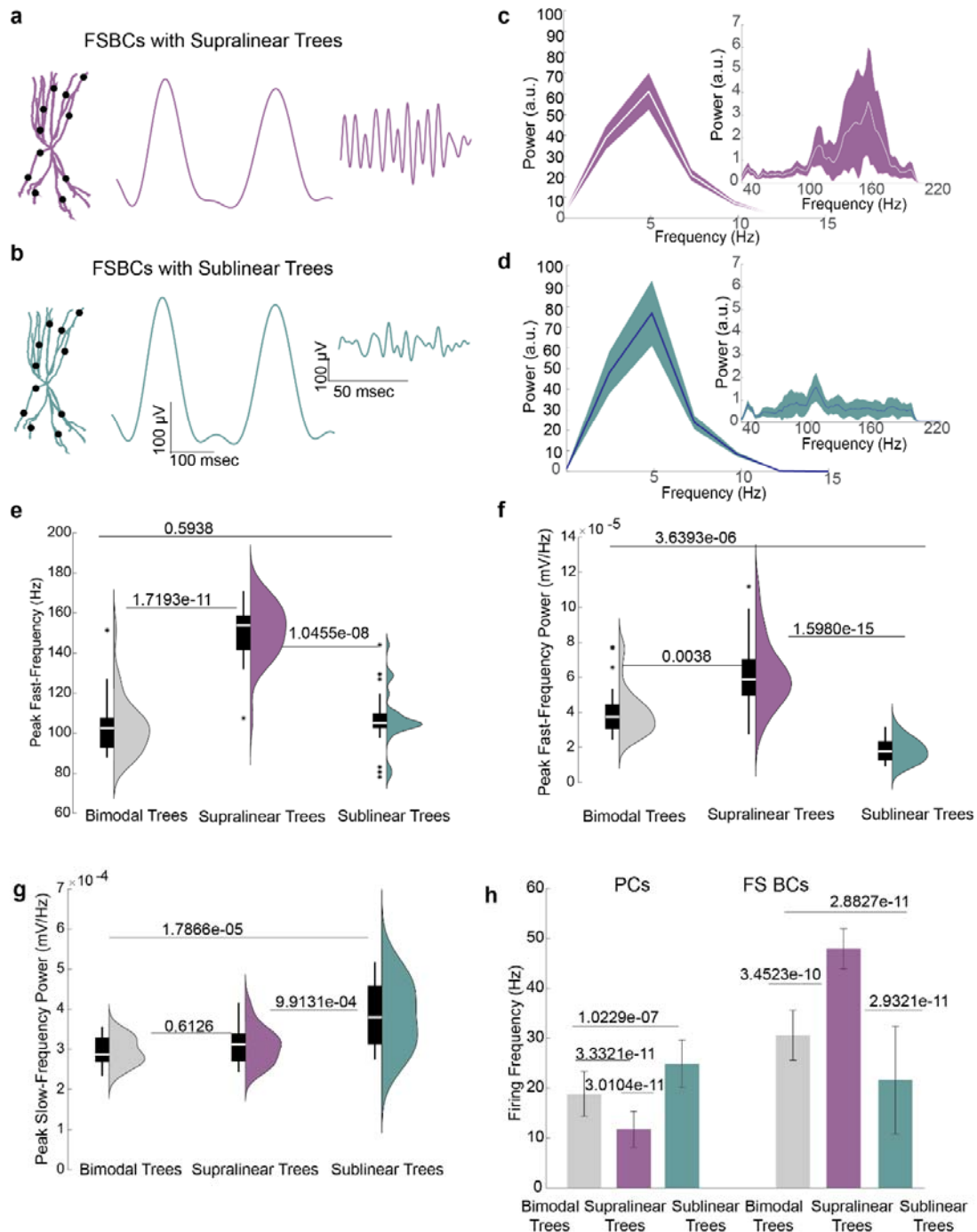
Figure S3. Differential Modulation of Slow and Fast LFP Components by Supralinear and Sublinear FSBC Dendritic Trees.

a. Activation of FSBCs equipped with purely supralinear dendritic trees, showcasing representative LFP traces bandpassed at slow (3-10 Hz) and high (30-200 Hz) frequencies. **b**. Similar to **a** but displaying activation of FSBCs with purely sublinear dendritic trees. **c-d**. Power Spectrum Density (PSD) plots of the LFP evoked when FSBCs are equipped with

455   purely supralinear (c) or purely sublinear (d) dendritic trees, highlighting differences in
456   frequency response. **e-g**. Comparative analysis of the peak fast-frequency (e) and peak
457   power of fast (f) and slow (g) oscillations for FSBCs with bimodal (grey), supralinear (purple),
458   or sublinear (blue) dendritic trees. Data are derived from 30 random simulation trials. **h**.
459   Firing activity of the PCs and FSBCs populations within the microcircuit network across 30
460   random simulation trials. Activation of supralinear FSBC dendritic trees results in a
461   decreased E/I balance compared to both bimodal (control) and sublinear trees. Statistical
462   analyses for multigroup comparisons were conducted using the Kruskal-Wallis test followed
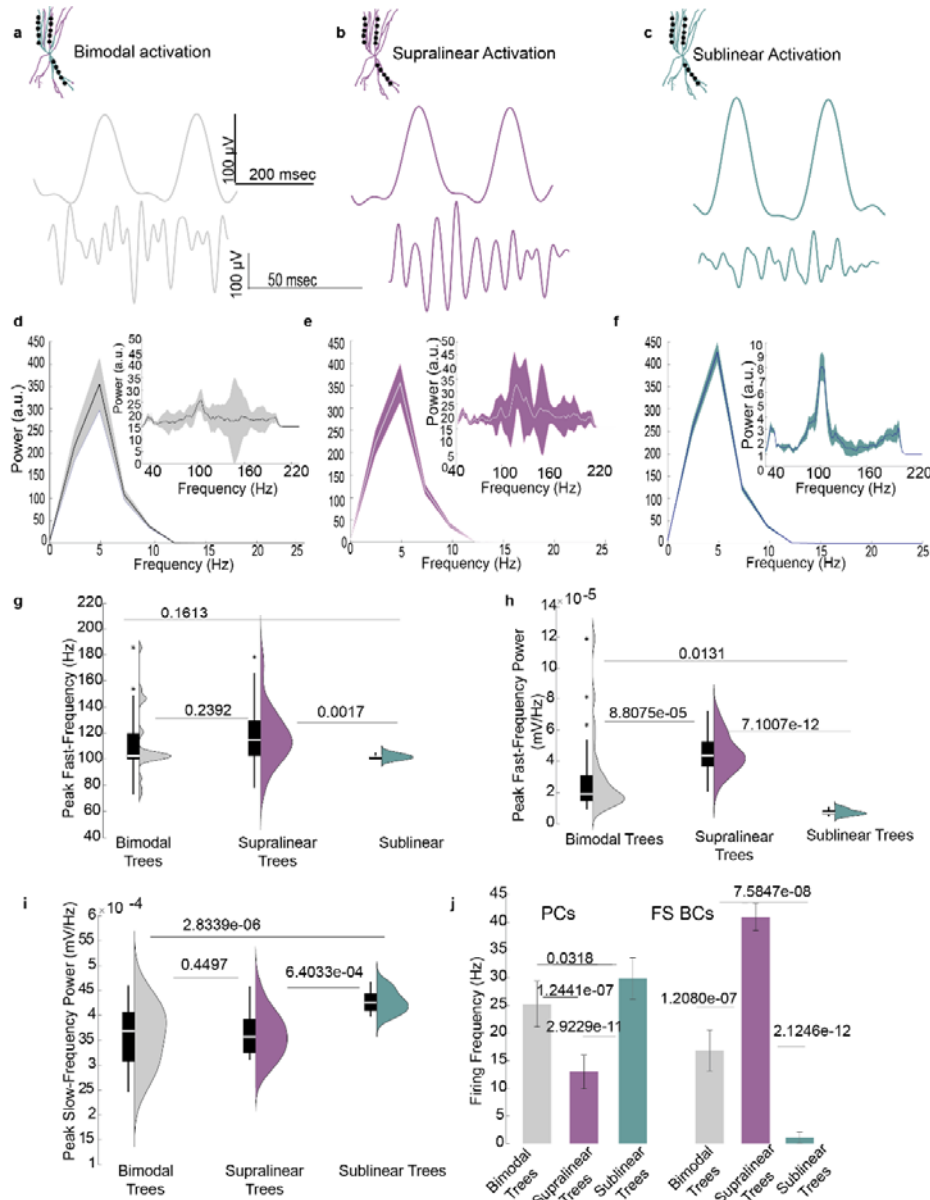463   by a post-hoc correction for multiple comparisons. Paired comparisons and p-values were
464   calculated using the Mann-Whitney U test for data with unequal variance.

465

Figure S4. Impact of Clustered Synaptic Activation on LFP and E/I Balance in Bimodal, Supralinear, and Sublinear FSBC Dendritic Configurations. a. Activation of FSBCs with bimodal nonlinear dendrites (control configuration), showing representative LFP traces for slow (3-10 Hz) and fast (30-200 Hz) frequencies. Synapses are clustered in a few randomly chosen supralinear or sublinear branches. **b**. Activation of FSBCs with purely supralinear dendritic trees, showing LFP traces under clustered synaptic activation. **c**. Activation of FSBCs with purely sublinear dendritic trees, similar to conditions in a and b, illustrating the effect of clustered synaptic activation on LFP traces. **d-f**. Power Spectrum Density (PSD) plots for LFPs under clustered synaptic conditions in FSBCs with bimodal (d), supralinear (e), and sublinear (f) dendritic configurations. **g-i**. Comparison of peak frequency (g) and peak power for the fast LFP component (30-200 Hz) (h), and peak power for the slow LFP component (i), across dendritic configurations. **j**. Firing activity of PC and FSBC populations in the microcircuit network from 30 random simulation trials. Clustering in supralinear FSBC dendritic trees decreases the E/I balance in the network compared to bimodal (control) or sublinear trees. Statistical analyses for multigroup comparisons were conducted using the Kruskal-Wallis test followed by a post-hoc correction for multiple comparisons. Paired comparisons and p-values were calculated using the Mann-Whitney U test for data with
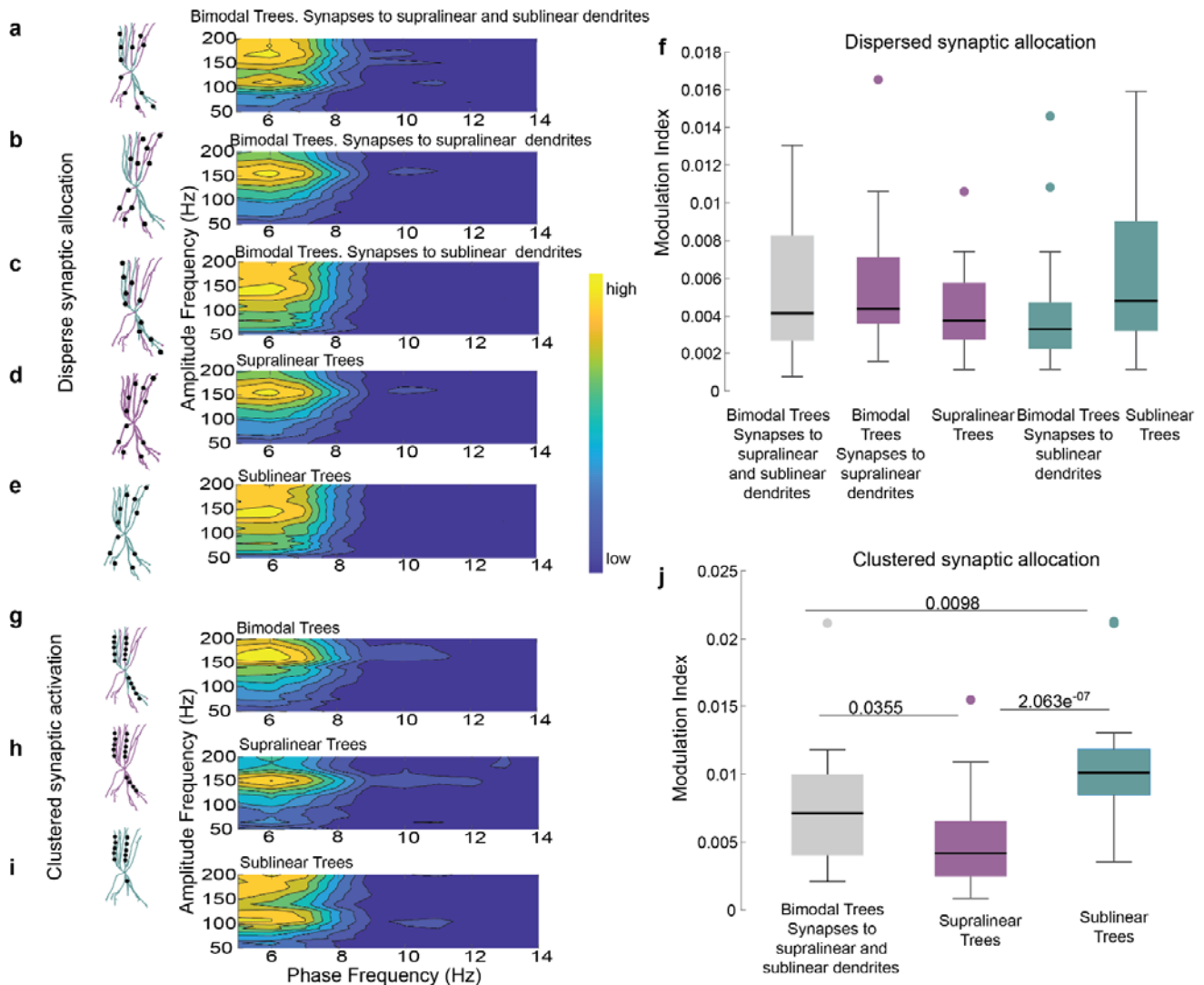
unequal variance.

484

Figure S5. Slow-Fast Oscillation Coupling in the Microcircuit Model Under Various Dendritic and Synaptic Configurations in FSBCs. a-e. Representative comodulograms illustrating the slow-fast coupling for the protocols detailed in Figures 2 and S3. These visualizations provide insights into the phase-amplitude coupling dynamics under different synaptic and dendritic configurations. Data from 30 random simulation trials are represented. **f**. Coupling analysis shows that synaptic distribution in a dispersed configuration across bimodal, purely supralinear, or purely sublinear FSBC dendritic trees does not affect slow-fast oscillation coupling. **g-i**. Similar to a-e but showcasing comodulograms for a clustered synaptic arrangement (detailed in Figure S4), using the same number of synapses as in the dispersed experiments. **j.** MI indicates that slow-fast oscillation coupling decreases when synapses are clustered in purely sublinear dendritic trees compared to other configurations. Multigroup comparisons were performed using the Kruskal-Wallis test followed by a post-hoc correction for multiple comparisons for multi-group data with unequal variance. This statistical approach was chosen to accommodate the diversity in the data from 30 random simulation trials.

500

501

Table S1. Active properties of Fast Spiking Basket Cell (FSBC) Models

Ion channel (S/cm^2)	Soma	Axon	Proximal dendrites	Distal Dendrites
Na_v	0.396	1.296	0.018	0.014
H_v	0.00001	X	x	X

*values as per [19,51,52]

Table S2. Passive properties of FSBCs

	Soma	Axon	Proximal dendrites	Distal Dendrites
Leak conductance (g_pas)[53]	1.315e-4 S/cm^2	3.55e-6 S/cm^2	1.315e-4 S/cm^2	1.34e-5 S/cm^2
Resting Membrane Potential (e_pas)[53,54]	-68 mV	-68 mV	-68 mV	-68 mV
Membrane capacitance (cm)[53]	1.2 uf/cm^{-2}	1.2 uf/cm^{-2}	1.2 uf/cm^{-2}	1.2 uf/cm^{-2} 0.00216
Axial Resistance (Ra)[53]	172 ohm/ cm	172 ohm/ cm	142 ohm/ cm	142 ohm/ cm
		X	0.00003	0.00003
Can_v	x	X	0.00003	0.00003
Cat_v	x	X	0.0002	0.0002
Calcium buffering dynamics	Yes	No	Yes	Yes

*values as per [19,53,54]

513

514

Table S3. Passive Parameters and Active Conductance Values of the Pyramidal Cell (PC) Model

Mechanism	Soma	Proximal Apical	Distal Apical	Basal

		Dendrite(n=1)	Dendrites (n=2)	Dendrites (n=2)
Leak conductance [S/cm2]	0,0002	0,0002	0,0002	0,0002
Na+ conductance [S/cm2]	0,0105	0,0084	0,0084	0,0084
Delayed rectifier K+ conductance [S/cm2]	0,00086	0,00086	0,00086	0,00086
Proximal A-type K+ conductance [S/cm2]	0,0075	0,015	-	0,0075
Distal A-type K+ conductance [S/cm2]	-	-	0,04875	-
M-type K+ conductance [S/cm2]	0.06	0.06	-	0.06
Ih conductance [S/cm2]	0.00005	0.0001	-	0.00005
L-type Ca2+ conductance [S/cm2]	0.0007	0.00003	-	0.00003
R-type Ca2+ conductance [S/cm2]	0.0003	0.00003	-	-
T-type Ca2+ conductance [S/cm2]	0.00005	0.0001	-	0.0001
Ca2+ -dependent sAHP K+ conductance [S/cm2]	0.0015	0.001	-	0.0005
Ca2+-dependent mAHP K+ conductance [S/cm2]	0,9	0,03	-	0,08
Membrane capacitance Cm [μF/cm2]	1	1	1	1
Membrane resistance Rm [Ohm cm2]	6000	6000	6000	6000
Axial resistance Ra [Ohm cm]	150	150	150	150

515 *values as per [27]

516

Table S4. Electrophysiological properties of the PCs and FSBCs models

	Value
Rheobase (pA)	200 (PC) / 150 +/- 10 (FSBC)
Input Resistance (MΩ)	142 (PC) / 97+/- 30 (FSBC)
Spike Threshold (mV)	-43,11 (PC) / -37 +/-1 (FSBC)
Spike Overshoot (mV)	30 (PC) / 48 +/- 1 (FSBC)
Resting Membrane Potential (mV)	-70 (PC) / -68 (FSBC)

517

Table S5. Synaptic conductance weight values of the PC and FSBC models.

Synapse Type	Pyramidal model	FSBC model
INPUT AMPA	0,00272	-
INPUT NMDA	0,0053	0.00032
INPUT CA++ PERMEABLE (CP)-AMPA	-	0.00075
AMPA	0,0017	-
CP-AMPA	-	0,0034

NMDA	0,0051	0.00144
GABA	0,0068	0,0051
Autapse GABA	-	0,007

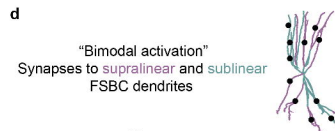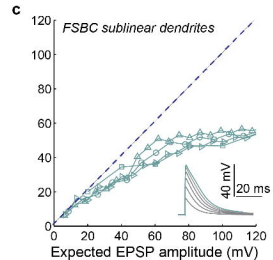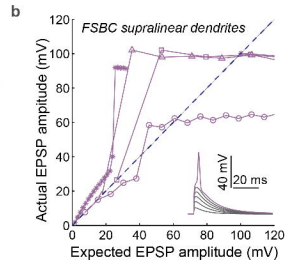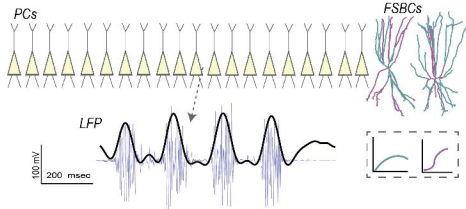518 *values based on[19,27,44,45,47,55]

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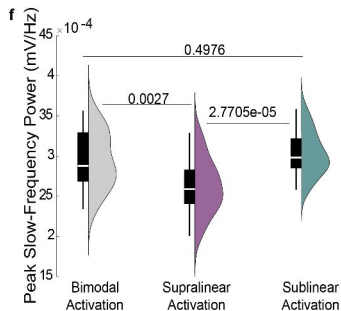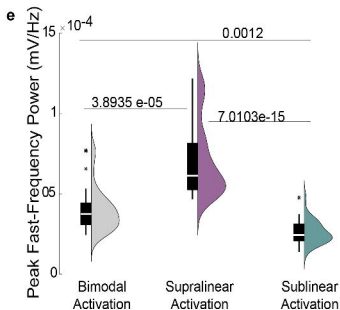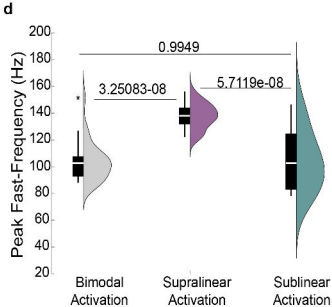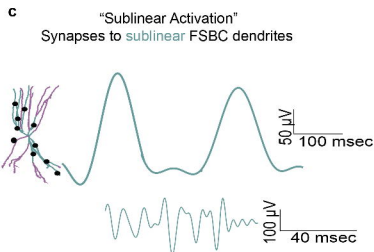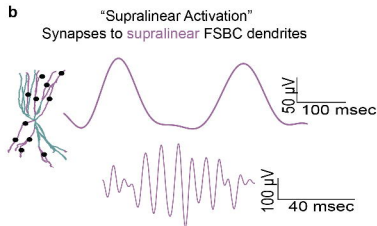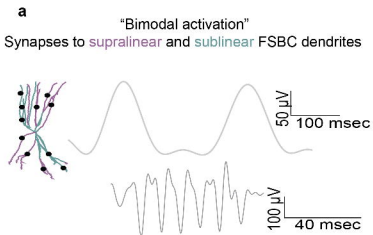556   *Neurobiol.* **31**, 81–87 (2015).

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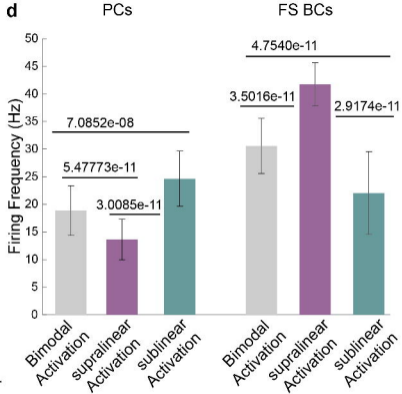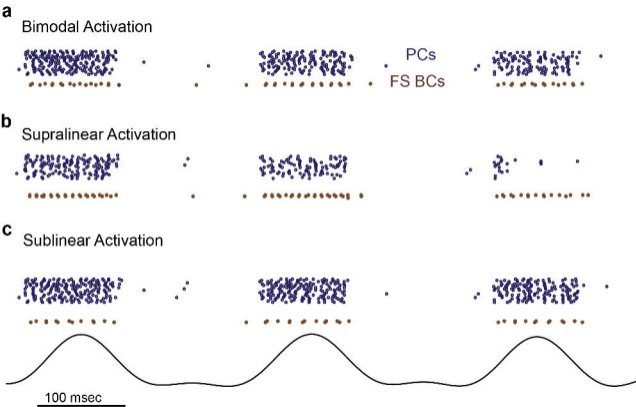
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653

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*

Actual EPSP amplitude (mV)

Expected EPSP amplitude (mV)

40 mV

20 ms

d "Bimodal activation"
Synapses to supralinear and sublinear FSBC dendrites

Power (a.u.)

Fast LFP band

Slow LFP band

Frequency (Hz)

e "Supralinear Activation"
Synapses to supralinear FSBC dendrites

Power (a.u.)

Fast LFP band

Slow LFP band

Frequency (Hz)

f "Sublinear Activation"
Synapses to sublinear FSBC dendrites

Power (a.u.)

Fast LFP band

Slow LFP band

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 Bimodal Activation

PCs
FS BCs

b Supralinear Activation

c Sublinear Activation

100 msec

d

PCs

FS BCs

Firing Frequency (Hz)

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

Hippocampal FS BCs with bimodal nonlinear dendrites

a

supralinear
sublinear
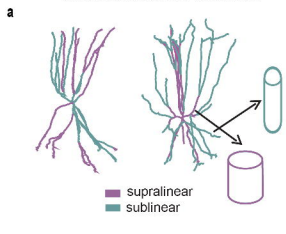
Morphological properties nonlinear dendrites in FS BCs trees

b

volume (microns³)

1.5907e-06

sublinear   supralinear

c

Input Resistance (mV/nA)

1.8778e-16

sublinear   supralinear

d

Control I/O functions

supralinear dendrites

Actual EPSP amplitude (mV)

sublinear dendrites

Expected EPSP amplitude (mV)

40 mV
20 ms
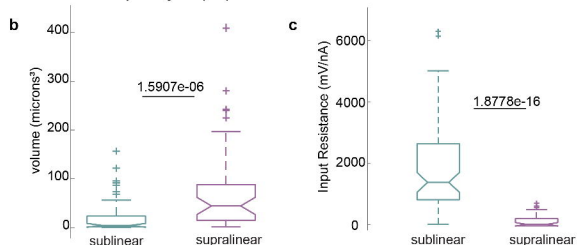
40 mV
20 ms
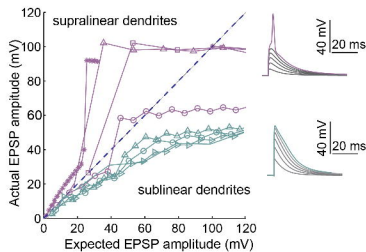
e

I/O function with gNa blockade in dendrites

Actual EPSP amplitude (mV)

Expected EPSP amplitude (mV)

40 mV
20 ms
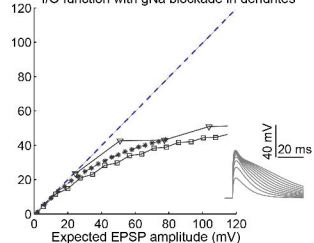
Sublinear and Supralinear forward propagation

f

mV

msec

mV

msec

g

mV

msec

mV

msec

a FSBCs with Supralinear Trees

b FSBCs with Sublinear Trees

c

d

e

f

g

h PCs   FS BCs

a Bimodal Trees. Synapses to supralinear and sublinear dendrites

b Bimodal Trees. Synapses to supralinear dendrites

c Bimodal Trees. Synapses to sublinear dendrites

d Supralinear Trees

e Sublinear Trees

Disperse synaptic allocation

f Dispersed synaptic allocation

Modulation Index

Bimodal Trees Synapses to supralinear and sublinear dendrites | Bimodal Trees Synapses to supralinear dendrites | Supralinear Trees | Bimodal Trees Synapses to sublinear dendrites | Sublinear Trees

g Bimodal Trees

h Supralinear Trees

i Sublinear Trees

Clustered synaptic activation

j Clustered synaptic allocation

Modulation Index

0.0098

0.0355   2.063e^{-07}

Bimodal Trees Synapses to supralinear and sublinear dendrites | Supralinear Trees | Sublinear Trees

Phase Frequency (Hz)

Amplitude Frequency (Hz)