1 **GABAergic Interneurons with nonlinear dendrites: from neuronal computations**
2 **to memory engrams.**

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11 Abstract: GABAergic interneurons are a highly diverse class of neurons in the mammalian brain
12 with a critical role in orchestrating multiple cognitive functions and maintaining the balance of
13 excitation/ inhibition across neuronal circuitries. In this perspective, we discuss recent findings
14 regarding the ability of some interneuron subtypes to integrate incoming inputs in nonlinear
15 ways within their dendritic branches. These recently discovered features may endow the specific
16 interneurons with advanced computing capabilities, whose breadth and functional contributions
17 remain an open question. Along these lines, we discuss theoretical and experimental evidence
18 regarding the potential role of nonlinear interneuron dendrites in advancing single neuron
19 computations and contributing to memory formation.
20 Keywords: Interneurons, Nonlinear Dendrites, Memory engrams

21

22 **Introduction:**

23 Interneurons (INs) constitute a highly heterogeneous class of neurons in the mammalian central
24 nervous system(Defelipe et al., 2013; Maffei, 2017).They are characterized by significant
25 variability in their anatomical, biophysical and molecular features(Ascoli et al., 2008). Numerous
26 studies have investigated the extent of this variability and suggested new roles for multiple
27 subtypes in brain circuits (reviewed in (Buzsáki et al., 2004; Maffei, 2017)). For example, several
28 studies highlight the crucial role of INs in orchestrating the activity of neural ensembles in
29 multiple brain areas and across various tasks, mainly via the flexible control of excitation-
30 inhibition balance(Campanac et al., 2013; Isaacson and Scanziani, 2011; Lucas and Clem, 2018).
31 Moreover, interneuron contributions to cognitive abilities such as sensory processing, learning
32 and memory, attention *etc.,* have recently started to be unveiled(Feldmeyer et al., 2018; Holly et
33 al., 2019; Kim et al., 2016; Xia et al., 2017; Xu et al., 2019).Despite their documented complexity
34 and key role in normal brain functioning, little is known about the ways in which incoming inputs
35 are integrated within the dendrites of most IN types. Currently, the most widely accepted
36 conceptual model of how INs integrate incoming signals is that of a simple summing device (*point*

1   *neuron*), according to which synaptic integration is essentially linear and independent of any
2   local, dendritic influences.

3   However, recent experimental and modeling studies suggest that the dendrites of some IN
4   subtypes are anatomically and biophysically complex(Hu and Vervaeke, 2018) and can support
5   localized, non-linear integration of incoming signals through the generation of dendritic
6   spikes(Chiovini et al., 2014; Cornford et al., 2019; Katona et al., 2011; Tran-Van-Minh et al., 2016;
7   Tzilivaki et al., 2019).(**Figure 1, Table 1**). These non-linear dendritic events were recently
8   predicted to enable INs to act as multi-stage nonlinear integrators (**Figure 2**)(Tzilivaki et al., 2019),
9   in ways that resemble their excitatory neuron counterparts (Losonczy and Magee, 2006; Poirazi
10 et al., 2003a; Polsky et al., 2004). Such multi-stage integration was previously shown to expand
11 the information processing capabilities of individual neurons well beyond those of a point
12 neuron(Jadi et al., 2014; Poirazi and Mel, 2001; Poirazi et al., 2003b). Moreover, INs were shown
13 to support plasticity induction, especially in subclasses with spiny dendrites(Abs et al., 2018;
14 Galván et al., 2015; Kullmann and Lamsa, 2011; Tran-Van-Minh et al., 2016) and influence both
15 the induction and the properties of oscillatory rhythms (Allen and Monyer, 2015; Klausberger
16 and Somogyi, 2008). For example, dendritic activity in fast spiking basket cells (FS BCs) was
17 suggested to underlie the induction of Sharp Wave Ripples (SWRs) (Chiovini et al., 2014) in the
18 hippocampus, a rhythm associated with memory consolidation and retrieval (Joo and Frank,
19 2018). The above suggest that specific IN subtypes, especially those that support nonlinear
20 dendritic events, may exhibit advanced processing capabilities at the single neuron level and play
21 important roles in high level functions such as learning and memory.

22 Memories are generally thought to emerge via the storage of information within specific
23 excitatory neuronal sub-populations, known as *memory engrams*(Tonegawa et al., 2015).These
24 memory engrams-although regulated by INs (Morrison et al., 2016; Stefanelli et al., 2016; Tzilivaki
25 et al., 2019)- are typically ascribed to excitatory neurons(Wu and Mel, 2009; Wu et al., 2019).
26 Recent findings, however, reveal that interneurons also undergo plasticity in response to learning
27 and may thus play important roles in memory functions, presumably through the formation of
28 inhibitory assemblies termed *inhibitory engrams*(Barron et al., 2017; Cummings and Clem, 2019;
29 Froemke, 2015; Lamsa and Lau, 2019a). In this article, we summarize recent evidence regarding
30 the nonlinear processing capabilities of IN dendrites and suggest that these features could allow
31 INs to perform complex functions that go beyond the balancing of excitation. We also discuss
32 how plasticity and nonlinear integration within IN dendrites can contribute to the formation of
33 memory engrams, in ways that facilitate resource utilization. Finally, we adapted a previously
34 published circuit model (Kastellakis et al., 2016; Tzilivaki et al., 2019) to investigate the formation
35 of inhibitory engrams and highlight their potential role in memory formation (**Figure 3**).

36 **Going beyond the point (inter-)neuron dogma**

37 According to the point neuron conceptual model, incoming inputs integrate linearly at the soma,
38 independent of their (dendritic) location. Dendritic integration is not explicitly modeled in this
39 schema, thus the term "point neuron". A suitable mathematical formalism for this type of

1 computation is a single-layer artificial neural network (ANN), whereby synaptic inputs are
2 weighted and linearly summed at the somatic node, before going through a non-linear activation
3 function(McCulloch and Pitts, W., 1943).
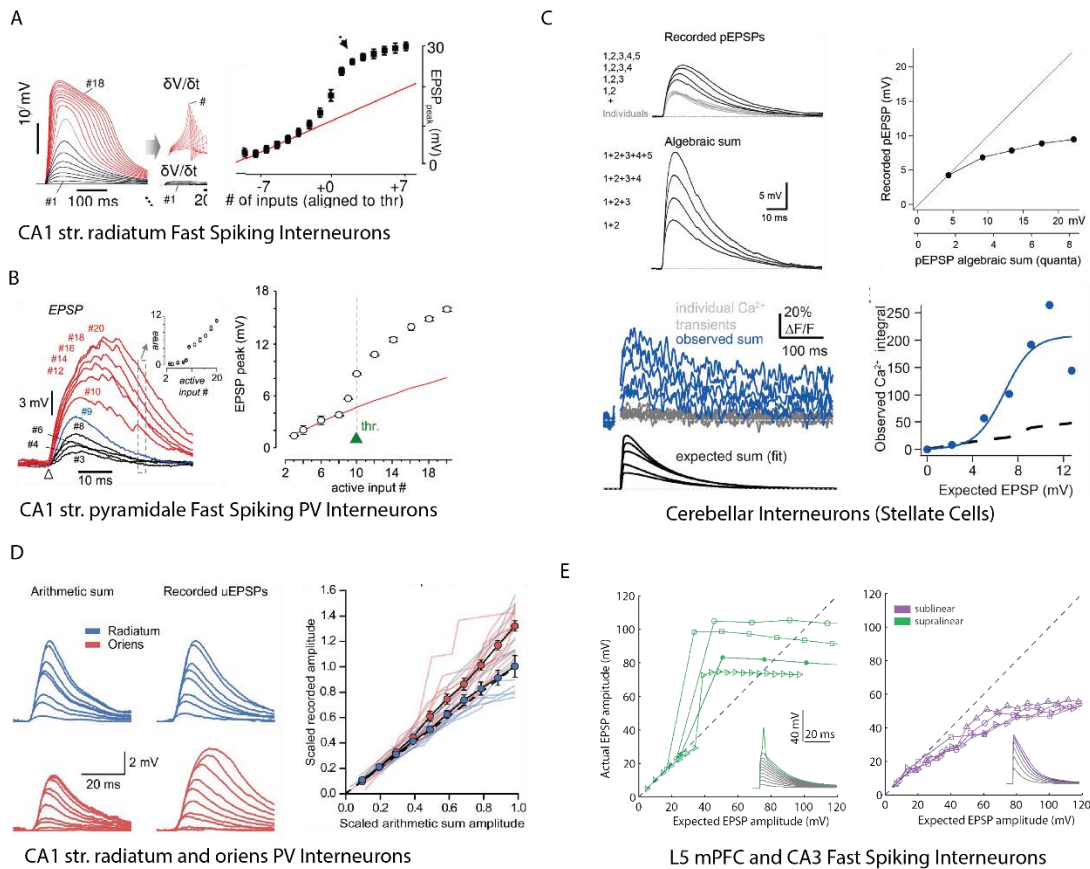
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5 *Figure 1: Nonlinear dendritic integration in Interneurons.*

6 **A.** CA1 Fast Spiking PV+ INs exhibit supralinear EPSP summation during SWRs (adopted from
7 Chiovini et al 2014). **B.** CA1 str. Radiatum Fast spiking INs exhibit NMDA-dependent supralinear
8 EPSP summation (adopted from Katona et all., 2011). **C.** Cerebellar INs exhibit sublinear EPSP
9 summation (upper panels adopted from Abrahamsson et al 2012) and supralinear calcium
10 accumulation (bottom panels adopted from Tran van Minh et al 2016) **D.** CA1 PV+ INs have two
11 types of dendrites: those integrating inputs in a supralinear manner and those summating their
12 inputs linearly (adopted from Cornford et al., 2019) **E.** Biophysical models predict that Fast
13 Spiking Basket Cells in both L5 mPFC and CA3 have dendrites that integrate synaptic inputs in
14 either a supralinear or a sublinear manner. Both types of dendrites co-exist within individual FS
15 BC models (adopted from Tzilivaki et al., 2019).

16

17 Interneurons were traditionally described as point neurons, mostly due to the lack of information
18 regarding their dendritic physiology. The complex arborization patterns of INs subtypes (Ascoli

et al., 2008; Hu and Vervaeke, 2018), made it challenging to investigate dendritic integration with widely-used experimental techniques. Currently, the scarce data that exist suggest a sublinear integration of inputs within the dendrites of some IN subtypes(Abrahamsson et al., 2012; Hu and Vervaeke, 2018; Vervaeke et al., 2012). For example, parvalbumin positive (PV+) FS BCs in the Dentate Gyrus (DG) have considerably lower somato-dendritic input resistance values compared to pyramidal neurons, a characteristic thought to dampen distal inputs and prevent the induction of local dendritic events (Nörenberg et al., 2010). In addition, the high potassium-to-sodium current ratio in the dendrites of the same INs was shown to hinder the active backpropagation of APs(Hu et al., 2010). Finally, the calcium dynamics of PV+ Basket Cells (BC), Calretinin-positive Irregular Spikers (IS) and Adapting Cells (AD) in the V1 supragranular layer result from a variety of ionic channels, making it difficult to infer their dendritic integration modes. Specifically, PV+ BCs exhibit supralinear calcium accumulation in their dendrites, mediated by CP-AMPA receptors and VGCCs while the other types exhibit NMDA-dependent calcium dynamics. Importantly, while both sodium and potassium currents were found in PV+ BCs in V1, A-type potassium channels were highly expressed in distal dendritic compartments(Goldberg et al., 2003b, 2003a). Taken together, for PV+ INs in particular, the high conductance of A-type potassium channels(Goldberg et al., 2003a; Hu et al., 2014), the relatively low density of sodium channels, especially in distal dendritic compartments(Hu et al., 2010), the low density of NMDA receptors(Camire and Topolnik, 2014; Goldberg et al., 2003b; Wang and Gao, 2009) and the weak back propagation of action potentials(Hu et al., 2010)are all strong indicators that PV+INs act as point neurons.

In light of conflicting findings in the literature, however, the issue of dendritic integration in interneurons remains unsettled. For example, active backpropagation of APs has been reported in Calretinin positive irregular spikers and Adaptive cells (Goldberg et al., 2003a) while supralinear calcium accumulation was found in the dendrites of the same neurons (Goldberg et al., 2003a), in CA1 INs -driven by the GLuR2 lacking calcium permeable (CP) AMPA receptor (Camire and Topolnik, 2014) and in the thin dendrites of cerebellar INs (Tran-Van-Minh et al., 2016). Moreover, NMDA-dependent (Cornford et al., 2019; Katona et al., 2011) and sodium-mediated (Chiovini et al., 2014) supralinear integration of synaptic inputs, especially when activated in clusters, has also been reported in different subtypes of PV+INs (Figure 1A). The various types of dendritic integration reported thus far for INs are listed in **Table 1**.

Interestingly, different modes of synaptic integration can also coexist within the same dendritic tree. Using computational modelling, Tzilivaki et al (Tzilivaki et al., 2019), recently predicted that dendrites of both cortical (from the Prefrontal Cortex, PFC) and hippocampal (CA3) FS BCs operate in one of two modes: supralinear or sublinear (**Figure 1E**). In these detailed biophysical model neurons, supralinear integration was due to the generation of local dendritic sodium spikes is some but not all dendritic branches. Specifically, while the distribution of sodium channels was uniform throughout the dendritic tree of all model neurons, dendritic spikes occurred selectively in branches with a larger volume (determined by their diameter and length) and not in thin branches, where integration was sublinear. This bimodal integration was robust to fluctuations in the conductance of voltage-gated channels, including sodium. Of note, bimodal

1 dendritic integration was also seen experimentally in CA1 PV+INs, although in this case synaptic
2 inputs were integrated either linearly or slightly supralinearly (Figure 1D)(Cornford et al., 2019).
3 Having dendrites with different types of nonlinearities is important because the exact same input
4 would lead to different dendritic response if it projects to a sublinear (suppressed) or a
5 supralinear (enhanced) dendrite. Combinations of such dendritic responses would further
6 expand the repertoire of outputs produced by a given IN. Importantly, the presence of dendrites
7 that integrate inputs linearly would not hinder this possibility, assuming they are not the
8 majority. Finally, cerebellar INs were found to support sublinear EPSP summation (Abrahamsson
9 et al., 2012; Vervaeke et al., 2012)but supralinear calcium accumulation(Tran-Van-Minh et al.,
10 2016), presenting an even more diverse behavior (Figure 1C).

11 Overall, both experimental and modelling studies indicate that the dendrites of several IN types
12 can integrate inputs in nonlinear ways. Consequently, the point neuron abstraction may not be
13 a very accurate representation of how interneurons process incoming signals.

14

Interneuron type	Region	Nonlinearity type	Mechanism	Reference
FS interneurons	CA1 str. radiatum	Supralinear EPSP summation	NMDAcurrents	Experimental(Katona et al., 2011)
PV Interneurons	CA1 str. radiatum	Linear EPSP summation	-	Experimental (Cornford et al., 2019)
PV Interneurons	CA1 str. Oriens	Supralinear EPSP summation	NMDA currents	Experimental (Cornford et al., 2019)
PV interneurons	CA1 str.pyramidale	Supralinear Ca^{++} & EPSP summation	L type Ca^{++} currents	Experimental (Chiovini et al., 2014)
FS Basket Cells	L5 mPFC	Supralinear & sublinear EPSP summation	Na^+ currents	Modelling(Tzilivaki et al., 2019)
FS Basket Cells	CA3	Supralinear & sublinear EPSP summation	Na^+ currents	Modelling(Tzilivaki et al., 2019)
Stellate Cells	Cerebellum	Sublinear EPSP summation & Supralinear Ca^{++} summation	Ca^{++} currents	Experimental & modeling(Abrahamsson et al., 2012; Tran-Van-Minh et al., 2016)
Golgi Interneurons	Cerebellum	Sublinear EPSP summation	Dendritic Gap junctions	Experimental(Vervaeke et al., 2012)

15 **Table 1. Dendritic integration in various interneuron subtypes.**

16 **Reducing interneurons to Artificial Neural Networks (ANNs)**

17 To assess the validity of the point neuron abstraction for FS BCs, Tzilivaki et al used a combination
18 of biophysical modelling and machine learning(Tzilivaki et al., 2019)(**Figure 2**). PV+ FS BCs from

two brain areas (PFC and CA3) were simulated as anatomically and electrophysiologically detailed single neurons; their response characteristics were assessed across an extensive dataset of synaptic stimuli, varying in strength and/or spatial arrangement. It was found that responses to synaptic stimuli -measured as the mean firing rate of the biophysical model cells- is best approximated by a two-stage nonlinear ANN rather than a point neuron abstraction, for all neurons tested. In these 2-stage ANN abstractions, both types of dendritic nonlinearities were incorporated as parallel hidden layers (**Figure 2**). While this study focused on PV+ FS BCs, it is likely that similar reductions apply to other IN subtypes. For example, Cerebellum interneurons, which are believed to be furnished with sublinear dendrites(Abrahamsson et al., 2012; Vervaeke et al., 2012),could be represented by ANNs with logarithmic activation functions in their hidden nodes. Similarly, interneurons with supralinear dendrites (Katona et al., 2011)could be described by ANNs with sigmoidal hidden units, along the lines of pyramidal neuron reductions(Häusser and Mel, 2003; Jadi et al., 2014; Poirazi et al., 2003b).

Whether this or another reductionist approach is applicable to all interneuron types, remains unclear; primarily because the integrative properties of most interneuron subtypes are largely unknown. Dendritic integration depends on both anatomical and electrophysiological features, which vary among interneuron subtypes(Defelipe et al., 2013). Thus, the first step towards an accurate mathematical reduction of interneurons, is the detailed characterization of their dendritic integration modes. Dendritic compartmentalization is also critical for understanding how a neuron computes under conditions of widespread, *in vivo* like synaptic input that is distributed over multiple branches. Pyramidal neurons, for example, are highly compartmentalized, with their dendrites acting largely as independent integration units(Losonczy and Magee, 2006; Poirazi et al., 2003b; Polsky et al., 2004). A similar analysis has yet to be performed for most interneuron types and will certainly influence the choice of mathematical reduction. If the dendrites of an IN sub-type communicate with one another, e.g. due to diffusion phenomena or the presence of gap junctions(Hu and Vervaeke, 2018; Tamas et al., 2000; Vervaeke et al., 2012), the ANN reduction will have to be adjusted to include interconnections among hidden layers/nodes. Finally, dendritic excitability is not static. During different developmental stages, INs undergo changes in their morphology, connectivity, membrane properties *etc.,* which can greatly alter their integration profiles (Hu et al., 2017).Thus, a mathematical reduction for a given IN subtype may need to be specific to the developmental stage of the animal(Biane et al., 2021).

1 Overall, appropriate ANN reductions for interneurons can be generated given sufficient
2 information about the modes of dendritic integration and the extent of intercommunication
3 between dendrites, under defined developmental stages. Experimental approaches are critical
4 for providing such information and assessing whether and which interneuron subtypes could
5 express a nonlinear arithmetic in the awake, behaving animal.
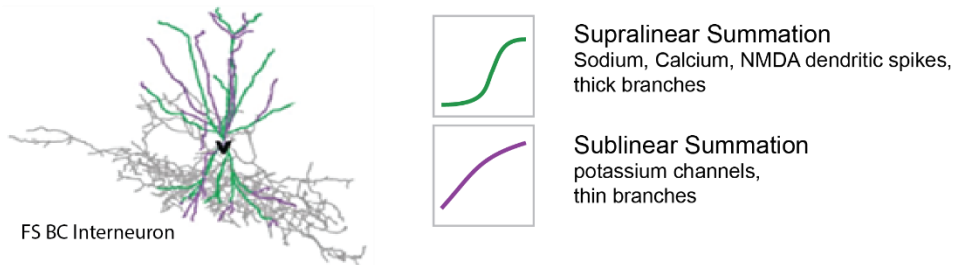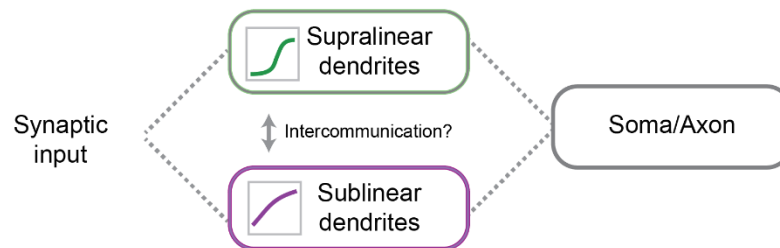
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7 *Figure 2: Nonlinear dendritic integration in PV+ FS BCs, as predicted by computational models.*
8 **A.** Hippocampal FS BCs were recently predicted by biophysical modelling to consists of two types
9 of dendrites: large-diameter ones that integrate synaptic inputs supralinearly, via the induction
10 of sodium spikes and thin-diameter ones that integrate inputs sublinearly, mainly due to the
11 dampening effects of potassium channels. **B.** Because of their dendritic nonlinearities, FS BC can
12 be reduced to a 2-stage Artificial Neural Network (ANN) abstraction, whereby the two types of
13 dendrites are described as parallel hidden layers. This reduction was shown to capture the
14 responses of detailed biophysical models of FS BCs to thousands of synaptic inputs much better
15 than a linear ANN. Figure adapted from (Tzilivaki et al, 2019).

16

17 **Next steps in dissecting the interneuron arithmetic**

18 Technical advances have now made it possible to dissect the nonlinear arithmetic profile of
19 different types of INs, *in vitro* and/or *in vivo*. Towards this goal, experimental approaches such as
20 glutamate uncaging(Abrahamsson et al., 2012), coupled to calcium and/or voltage

1 recordings(Tran-Van-Minh et al., 2016) can be used to map the dendritic integration mode in
2 response to targeted stimulation. Patch clamp techniques can also be used to characterize the
3 electrophysiological properties and spatial distribution of the different conductances found
4 within interneuron dendrites, while the arborization profile of dendrites and their
5 synapses/spines can be mapped with electron microscopy techniques.

6 It remains challenging, however, to experimentally assess how different arrangements of inputs
7 would affect dendritic and neuronal integration in either individual neurons or neurons emended
8 into circuits. Such stimulation patterns can be achieved via the use of holographic laser
9 stimulation(Yang et al., 2018). When applied *in vivo,* where numerous other factors can influence
10 responses, even such advanced techniques cannot delineate specific contributions. Detailed
11 biophysical modelling, heavily constrained by experimental data, can be used to address such
12 technically challenging questions.

13 Finally, the extensive variability among different IN types should be considered when assessing
14 the generality of experimental findings and their utilization in building models. As previously
15 mentioned, interneuron families like PV+ interneurons(Que et al., 2021) consist of multiple
16 subtypes with potentially very different active membrane properties and consequently
17 arithmetic profiles. Thus, apart from categorizing interneurons based on their postsynaptic target
18 groups (namely perisomatic, axonal or dendritic targeting), the dendritic integration mode could
19 also serve as a feature for a more accurate cell-type classification.

20 **The added value of nonlinear dendrites in interneuron arithmetic**

21 While the above studies suggest that certain types of INs can integrate synaptic inputs in
22 nonlinear ways and these ways can be described by abstract mathematical models, their
23 potential contribution to neuronal and circuit function remains largely unexplored. One frequent
24 misconception is that linear and sublinear dendritic integration are essentially equivalent and
25 that only supralinear dendrites advance neuronal computations. This is far from the truth.
26 Dendrites with sublinear activation functions are also quite powerful: they are theoretically
27 predicted to solve numerous non-linearly separable functions and have been associated with the
28 effective integration of coincident inputs (Cazé et al., 2013; Tran-Van-Minh et al., 2015, 2016).
29 Supralinear integration in the dendrites of PV+ neurons on the other hand was recently shown
30 to stabilize the formation and function of CA1 cell assemblies (Cornford et al., 2019).

31 According to biophysical modelling, dendritic nonlinearities underlie the preference of FS BCs to
32 distributed rather than spatially clustered synaptic inputs (Tzilivaki et al., 2019). This unintuitive
33 finding is opposite to that seen in pyramidal model neurons, whereby clustered synaptic input
34 drives stronger somatic responses (Poirazi et al, 2003b). This discrepancy can be explained by the
35 very small dendritic diameter, the high conductance of A type potassium channels and the
36 presence of both sub- and supralinear dendrites in FS BCs (Hu et al., 2014; Tzilivaki et al., 2019).
37 Of note, preference to disperse synaptic input was also seen in Cerebellar INs (Abrahamsson et

al., 2012) while increased responses to clustered synaptic input were seen in Entorhinal cortex INs(Schmidt et al., 2017).

Overall, these findings suggest that dendritic nonlinearities may underlie the expression of different types of input-sensitivity to distinct IN subtypes. Regardless of the exact way in which dendritic nonlinearities influence neuronal output, their presence suggests important processing advantages like the ability to solve non-linear computations (Jadi et al., 2014; Poirazi and Mel, 2001; Tran-Van-Minh et al., 2015).

Plasticity in interneurons with nonlinear dendrites and possible contributions to memory engrams

Nonlinear dendritic integration is maximally exploited by neuronal circuits when used in conjunction with localized plasticity rules, as the latter tunes responses to stimuli of behavioral relevance. Evidence for synaptic plasticity in INs dates back to 1982, when Long-Term-Potentiation (LTP) was successfully induced by tetanic stimulation in CA1 INs *in vivo* (Buzsaki and Eidelberg, 1982) and in the Dentate Gyrus (DG) (Kairiss et al., 1987; Tomasulo and Steward, 1996). This interest was recently renewed for INs in the hippocampus and cortical areas in rodents (for further reading see (Abs et al., 2018; Chistiakova et al., 2019; Lamsa and Lau, 2019b), including the confirmation of plasticity in DG INs (Hainmüller et al., 2014; Ross and Soltesz, 2001). Several of these studies highlighted the diversity of IN plasticity, stemming from the variety of active conductances and their heterogeneous distribution across different subtypes (Ascoli et al., 2008; Kullmann and Lamsa, 2007; Lamsa et al., 2007).

In addition to the plasticity of synaptic connections, the intrinsic excitability of inhibitory neurons is also plastic (Ross and Soltesz, 2001). Basket cells in the DG, for example, exhibit long-term increases in their resting membrane potential following high-frequency stimulation of their glutamatergic inputs. This long-lasting depolarization, which enhances the efficacy of EPSPs to fire the interneuron, results from changes in the Na+ /K+ ATPase pump function and requires the activation of calcium-permeable AMPA receptor. Similarly, brief repetitive stimulation of the CA3 Schaffer collaterals causes long-term increase in the intrinsic excitability of PV+ basket cells in CA1 (Campanac et al., 2013). Whether such an increase in intrinsic excitability can be localized within specific dendrites, as in pyramidal cells (Losonczy et al., 2008), remains unknown.

The above establish the presence of plasticity mechanisms in INs but do not explain how nonlinear dendrites and plasticity may work together to advance circuit computations.

Effects of interneuron dendrites on excitatory and inhibitory memory engrams

Memories are typically thought to be stored in excitatory neuronal engrams(Tonegawa et al., 2015), often consisting of multiple cell assemblies (Ghandour et al., 2019; Sun et al., 2020). However, recent studies suggest that INs can also form strongly connected engram populations(Barron et al., 2017). These *inhibitory engrams* are proposed to emerge as balancing replicas of the excitatory populations, aiming to: a) prevent excessive activation of excitatory

engram cells and b) make memories quiescent, namely stored in a "latent" form that can be available upon context-relevant activation (Barron et al., 2017). In line with this hypothesis, inhibitory engrams in the human hippocampus were suggested to protect from memory interference (Koolschijn et al., 2019). Yet, a well-defined theory on the role of inhibitory engram cells in memory formation is missing. Moreover, the cellular and sub-cellular mechanisms underlying the formation of these inhibitory engrams, their cell-type composition, input characteristics and wiring configurations, all remain unclear. It has been suggested that induction of LTP in IN dendrites and decreased disinhibitory input may underlie the creation and stabilization of inhibitory engrams (Barron et al., 2017) while gap junctions(Fukuda and Kosaka, 2003), through their role as network synchronizers (Tamas et al., 2000; Traub et al., 2001), are another candidate mechanism. Finally, PV+INs were shown to control the size of excitatory engrams in the lateral amygdala (Morrison et al., 2016), whereas SST+ INs were proposed to do the job in the Dentate Gyrus(Stefanelli et al., 2016). Overall, these findings call for a deeper investigation of the mechanistic underpinnings of inhibitory engram neurons and their contributions to memory processes. Given that nonlinear dendrites and synaptic plasticity are key players in memory processes(Kastellakis et al., 2015), these phenomena should be extensively studied not only in excitatory but also in inhibitory neurons.

Towards this goal, we can draw inspiration from studies that revealed strong links between subcellular dendritic processes in pyramidal neurons and the properties of excitatory memory engrams. Modelling and experiments for example, suggest that nonlinear dendrites and structural plasticity underlie the binding of associated information (Legenstein and Maass, 2011) and the linking of information across time (Kastellakis et al., 2016). Increased synapse clustering within nonlinear dendrites has also been associated with faster learning and increased sparsity of excitatory engrams(Frank et al., 2018). The respective role of IN dendrites in memory engrams has recently started to be investigated: FS BCs with nonlinear dendrites were predicted to enable the encoding of new memories within a smaller, sparser and less excitable excitatory neuronal population, thus increasing sparsity and storage capacity(Tzilivaki et al., 2019). These nonlinearities were also predicted to reduce the overlap between the excitatory population engrams of memories formed close in time. This reduction in population overlap is thought to decrease the probability of interference, in line with experiments (Koolschijn et al., 2019).

To motivate further research exploring the potential contributions of nonlinear IN dendrites in memory engrams, we adapted the (Tzilivaki et al., 2019) model to account for calcium and protein-dependent plasticity in excitatory and inhibitory synapses impinging on pyramidal and interneuron models. We then trained the network model to encode a single associative memory, comprised of two input streams projecting randomly to excitatory model neurons. After learning, we assessed the properties of engram neurons, namely those excitatory and inhibitory neurons that responded to the presentation of one of the two input streams. Engram populations were studied under two conditions: when FS BCs were equipped with linear dendrites vs. Nonlinear dendrites (as in Tzilivaki et al, 2019). Results shown in **Figure 3** reveal that, in network configurations where FS BCs are equipped with nonlinear dendrites, the size of the excitatory

1   engram population is smaller (**Figure 3B, top left**) while the size of the respective inhibitory
2   assembly is larger (**Figure 3B, middle left**), compared to network configurations with linear
3   dendrites in FS BCs. However, the combined engram population, consisting of both excitatory
4   and inhibitory neuronal assemblies is significantly smaller in the nonlinear vs. the linear
5   configuration (**Figure 3B, bottom left**). On the contrary, the sparsity of all engram populations
6   (**Figure 3B, right**) is significantly higher in the nonlinear compared to the linear case. Overall,
7   these simulations suggest that nonlinearities in the dendrites of FS BCs can affect the size of both
8   excitatory and inhibitory engram populations in opposite ways, with the net effect being the
9   storage of memories within fewer neurons, in significantly sparser networks. Moreover, these
10 simulations predict a tight link between subcellular features (i.e. dendritic nonlinearities) and
11 network-level computations (in this case memory formation) and call for a more detailed
12 investigation of how IN dendrites can contribute to higher order functions. Whether the
13 abovementioned predictions hold true in real neurons remains an open question, which we hope
14 will be addressed by future experimental investigations.

16 *Figure 3: Properties of excitatory and inhibitory engrams in a network model of associative*
17 *memory encoding*. **A.** We adapted a previously published model (Tzilivaki et al, 2019) to account
18 for inhibitory calcium and protein-dependent plasticity, and assessed the properties of memory
19 engrams during recall of the memory separately for inhibitory and excitatory populations (See
20 supplementary information). **B Left column:** Size of the engram population for excitatory,

inhibitory and combined (both excitatory and inhibitory) populations of neurons. **Right column:** Firing rate sparsity measured according to the Treves-Rolls sparsity metric for each type of engram population (higher is sparser). **: p <0.005, ***: p < 0.005 t-test. 10 simulation trials are shown in box plots.

Concluding remarks

In conclusion, accumulating new evidence shows that the dendrites of some IN subtypes support nonlinear integration of incoming signals. These nonlinearities, in conjunction with a variety of plasticity processes, endow specific subtypes with the ability to integrate inputs as multilayer artificial neural networks. As such, it is possible that interneurons can undertake new roles: like their excitatory neuron counterparts, they too can learn to solve challenging computational tasks and contribute to efficient learning and information storage. The extent to which interneurons act as powerful information processing players in the behaving animal remains unknown. This is largely because the computations that take part inside their dendritic trees have yet to be described. Are interneurons the alter egos of excitatory cells, implementing similar computations with the goal of balancing the two opposite forces that dominate brain functioning? Or do they have additional new roles that are just beginning to be addressed? Do their dendrites drive rhythm generation in ways that facilitate learning and memory functions, or do they simply tune in to network-level effects? In the quest of finding answers to these questions, targeted characterization of dendritic processing in combination with computational modelling and mathematical reductions can get to the core of what it is that interneurons compute.

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