



HAL
open science

Plasticity of intrinsic neuronal excitability

Dominique Debanne, Yanis Inglebert, Michaël Russier

► **To cite this version:**

Dominique Debanne, Yanis Inglebert, Michaël Russier. Plasticity of intrinsic neuronal excitability. Current Opinion in Neurobiology, 2019, 54, pp.73-82. 10.1016/j.conb.2018.09.001 . hal-01963474

HAL Id: hal-01963474

<https://amu.hal.science/hal-01963474>

Submitted on 21 Dec 2018

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License



Plasticity of intrinsic neuronal excitability

Dominique Debanne, Yanis Inglebert and Michaël Russier

Long-term synaptic modification is not the exclusive mode of memory storage, and persistent regulation of voltage-gated ion channels also participates in memory formation. Intrinsic plasticity is expressed in virtually all neuronal types including principal cells and interneurons. Activation of synaptic glutamate receptors initiates long-lasting changes in neuronal excitability at presynaptic and postsynaptic side. As synaptic plasticity, intrinsic plasticity is bi-directional and expresses a certain level of input-specificity or cell-specificity. We discuss here the nature of the learning rules shared by intrinsic and synaptic plasticity and the impact of intrinsic plasticity on temporal processing.

Address

UNIS, UMR1072 INSERM – AMU, Marseille, France

Corresponding author: Debanne, Dominique (dominique.debanne@inserm.fr)

Current Opinion in Neurobiology 2019, **54**:73–82

This review comes from a themed issue on **Neurobiology of learning and plasticity**

Edited by **Scott Waddell** and **Jesper Sjöström**

<https://doi.org/10.1016/j.conb.2018.09.001>

0959-4388/© 2018 Elsevier Ltd. All rights reserved.

Introduction

Long-lasting plasticity of chemical synaptic transmission is usually considered as the main mechanism accounting for information storage in the brain. Synapse-specific changes in transmission from a large array of inputs appears particularly appealing for maintaining a high computational capacity in the brain. However, this appears not to be the whole story and many other factors involved in the transfer of neuronal information occupy today a key position in functional plasticity. Voltage-gated channels located at the input or output side of neurons are involved in a form of activity-dependent plasticity called intrinsic plasticity (for review, see Refs. [1–5]).

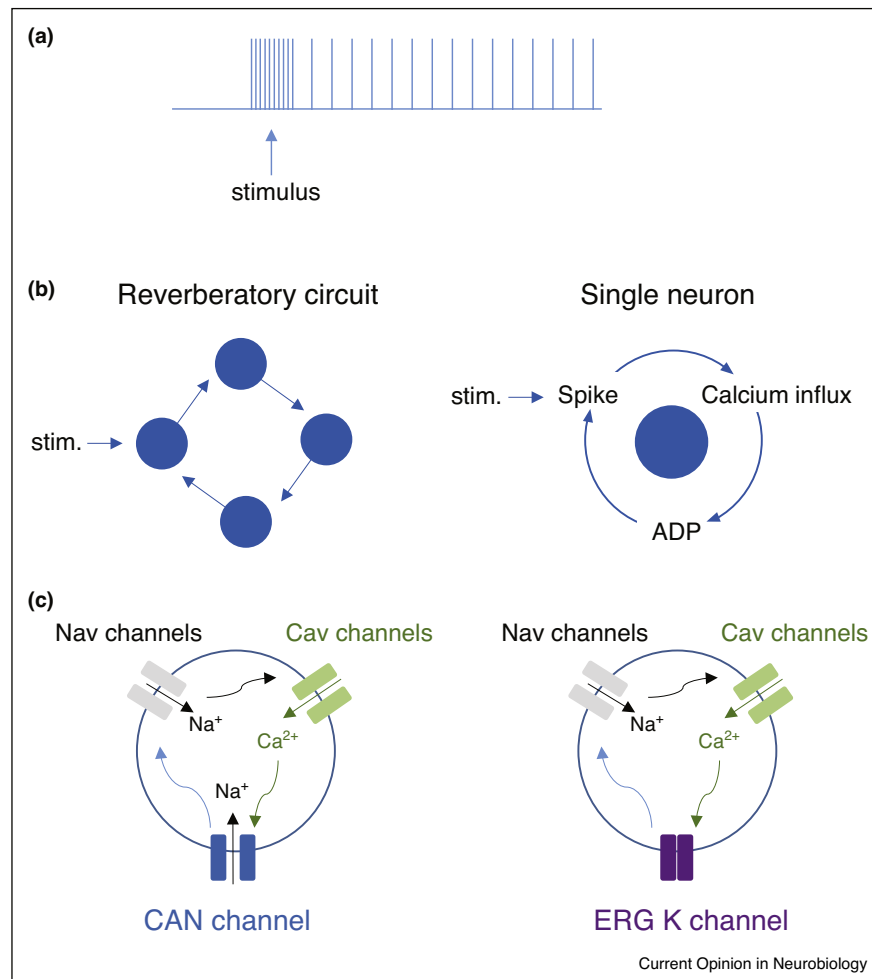
Here, we review recent *in vitro* works devoted to the study of intrinsic plasticity in mammalian neurons. First, we will discuss new expression mechanisms of graded persistent firing, a form of short-term plasticity that may account for working memory. Second, we review some recent findings

that illustrate cellular correlates of learning mediated by changes in intrinsic excitability. Next, we will describe different ways of modulating input–output function at the neuronal scale. Then, we will consider the learning rules of intrinsic plasticity on the basis of those defined for synaptic modifications. Next, we will review recently identified mechanisms of intrinsic plasticity in GABAergic interneurons. Finally, we will discuss the consequences of intrinsic plasticity on temporal processing.

Graded firing: a cellular analog of working memory

Working memory is an ephemeral retention of information whose neurobiological substrate can be seen as a stimulus-specific modulation of neural activity that lasts until a new stimulus is presented (Figure 1a). The neuronal basis for this form of memory was first identified in associative cortices of the monkey (for review, see Ref. [6]). In the prefrontal cortex, the posterior parietal cortex or the inferotemporal cortex, a subset of neurons called ‘memory neurons’ show persistent activity during a delayed response task, in which the animal is required to retain information of a sensory cue across a delay period between the stimulus and the behavioral response. In contrast with long-lasting forms of memory requiring molecular and/or structural changes, this form of short-term memory (or working memory) is a dynamic and ephemeral process. According to the classical view, the stimulation is memorized through reverberating activity within interconnected groups of neurons (Figure 1b). Inhibition of one of the neurons may stop activity within interconnected neurons. Egorov *et al.* [7] discovered that single isolated neurons are able to memorize the stimulus that was transiently applied (Figure 1b). During basal stimulation of muscarinic acetylcholine receptors (mAChR), neurons from the entorhinal cortex may, upon brief stimulation, generate sustained increases in their electrical activity that are graded in frequency and reversible by hyperpolarization. Persistent firing is cell-specific [8] and it has been also reported in CA3 [9] and CA1 [10] hippocampal pyramidal neurons, mitral cells from the olfactory bulb [11] and L5 cortical pyramidal neurons [8,12**] under stimulation of mAChR. Graded persistent firing requires postsynaptic calcium influx mediated by spiking activity. The original mechanism of graded firing was thought to be mediated by calcium-activated non-selective (CAN) cationic current that in turn depolarizes the cell [7] (Figure 1c). But, the molecular identity of CAN channels remains elusive and alternative mechanisms have been considered. The inversion of the Na⁺/Ca²⁺ exchanger activity by accumulation of intracellular Na⁺ has been proposed to account for persistent firing in

Figure 1



Persistent firing as a cellular model of working memory.

(a) Brief excitation of the neuron by the stimulus leads to persistent firing that is persistently maintained at the same rate. Adapted from Ref. [7] **(b)** Reverberatory circuit versus single neuron mnemonics. In both cases, an external stimulation leads to persistent activity through synaptic connections (reverberatory circuit) or through a calcium-dependent afterdepolarization (ADP). Left, the opening of CAN channel leads to sustained firing through Na^+ influx (adapted from Ref. [7]). Right, the closure of an ether-à-gogo related gene (ERG) channel leads to persistent firing through a depolarization of the membrane conjugated with an increase in input resistance (adapted from Ref. [12**]).

mitral cells of the olfactory bulb [11]. Although attractive, this mechanism seems unable to explain all forms of persistent firing since in neocortical pyramidal neurons, persistent firing is still observed in the presence of tetrodotoxin, a potent Nav channel blocker [12**] (in this case, calcium spikes replace sodium spikes). In this study, persistent firing is mediated by the modulation of ether-à-Go-Go related gene (ERG) K^+ channel [12**]. ERG channels mediate a leak potassium current that is downregulated by calcium entry induced with repetitive spiking (Figure 1c).

Cellular correlates of learning

The search for cellular excitability correlates of learning and memory in the mammalian brain has focused on neurons that

are thought to be active during learning. Since the pioneering work of C. Woody, many studies have shown that classical conditioning alters intrinsic excitability (IE) in neurons from the pericruciate cortex [13], hippocampus [14,15] or cerebellum [16]. All these studies indicate that intrinsic plasticity occurs in neurons following learning but the activity of the recorded cell was not accurately controlled during learning. A recent study went a step further by showing using a fluorescent activity-reporter that intrinsic excitability is altered only in cells that are active during learning [17**].

Regulations of neuronal excitability have been involved in others forms of learning such as spatial learning [18], fear conditioning [19–22], odor discrimination [23–25].

Experiencing new or enriched environment is also known to affect intrinsic excitability [26,27]. Following learning, usually after-hyperpolarization (AHP), AP threshold and accommodation are decreased resulting in an enhancement of AP firing and neuronal IE in the hippocampus (spatial and fear conditioning), amygdala (fear conditioning and odor discrimination), or prefrontal cortex (fear conditioning). While most of excitability changes discussed so far corresponds to enhanced IE, *decrease* in IE has been observed in mitral cells of the accessory olfactory bulb following social learning [17**]. In fact, mitral cells showed an unusual reduction in cell firing during repetitive stimulation. The reason why polarity is changes in this particular case is not yet elucidated but it may act to filter sustained or repetitive signals.

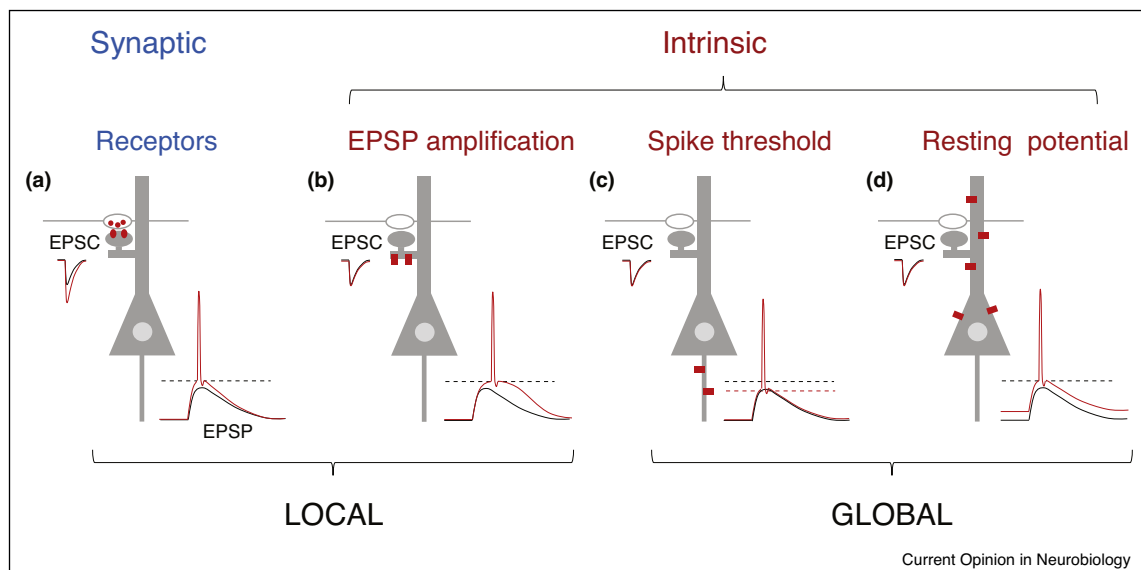
Multiple mechanisms for modulating input–output function

Input–output function is a critical operation achieved by synaptic and intrinsic mechanisms. Whereas expression mechanisms of synaptic plasticity are rather simple and involve either presynaptic change in neurotransmitter release or postsynaptic change in glutamate receptor density or function, plasticity of IE can be expressed through at least three different types of

functional modulation (Figure 2). Ion channels located in dendrites shape EPSP waveform by either boosting or attenuating the synaptic response. Thus, a given EPSP may lead to an action potential if the net amplification is enhanced. Two ion channels located in the dendrites, the hyperpolarization-activated cyclic nucleotide-gated (HCN) channel and the voltage-gated potassium channel (Kv4.2) attenuate the EPSP amplitude. Their downregulation following induction of synaptic potentiation enhances input–output function [28–31]. As synaptic plasticity, the modulation of EPSP amplification is generally *local* as other inputs remain unchanged [28,32].

Input–output function may be altered via modulation of spike threshold (Figure 2). The spike threshold is determined by voltage-gated Na⁺ (Nav) and K⁺ (Kv) channels. Shift of Nav activation towards hyperpolarized values lowers the spike threshold and increases excitability following induction of synaptic potentiation in CA1 pyramidal neurons [33]. Similarly, downregulation of Kv1 channels, as observed in auditory neurons following cochlea removal, lowers the spike threshold and increases intrinsic excitability [34**]. This type of modulation is *global* since it may affect all incoming inputs.

Figure 2



Mechanisms of input–output function modulation.

(a) Synaptic modification of input–output function. Local potentiation of synaptic transmission by increase in transmitter release and/or postsynaptic receptor density is characterized by an enhanced excitatory post-synaptic current (EPSC). At the initial segment, the excitatory post-synaptic potential (EPSP) becomes large enough to cross the action potential (AP) threshold and to elicit a postsynaptic spike. Note the larger EPSP slope. **(b)** Change in EPSP amplification. When dendritic channels (red) are regulated, the resulting EPSP is amplified and crosses the spike threshold. Note that here the synaptic current (EPSC) is kept constant to clearly distinguish intrinsic from synaptic changes and the initial EPSP slope remains unchanged. These first two modifications are *local* because they do not affect all synaptic inputs. **(c)** Change in spike threshold. An increase in spike firing is obtained when the AP threshold is hyperpolarized through the regulation of voltage-gated ion channels located at the axon initial segment. Here again, synaptic current (EPSC) remains unchanged. **(d)** Change in resting membrane potential. Following modulation of voltage-gated channels, the resting membrane potential of the neuron is depolarized leading to the triggering of an action potential by the EPSP. Note that here again, synaptic current (EPSC) remains unchanged. These last two modifications are *global* because they affect all synaptic inputs.

Input–output function can be modulated by changing the resting membrane potential (RMP) of the neuron (Figure 2). Hippocampal granule cells display long-term depolarization (LT-Depol) of the RMP by approximately 8–10 mV following high frequency firing [35]. LT-Depol in granule cells is mediated by a protein kinase A-dependent upregulation of HCN channels. While, the regulation of HCN channels leads to attenuated EPSP amplitude and therefore to a reduction in intrinsic excitability (see above), the net effect here is however an increase in excitability. In fact, the large depolarization of resting membrane potential (8–10 mV) largely dominates the excitability reduction caused by the attenuation of excitatory synaptic inputs. This sustained depolarization may not only lead to granule cell firing in response to incoming excitatory inputs but also to the facilitation of

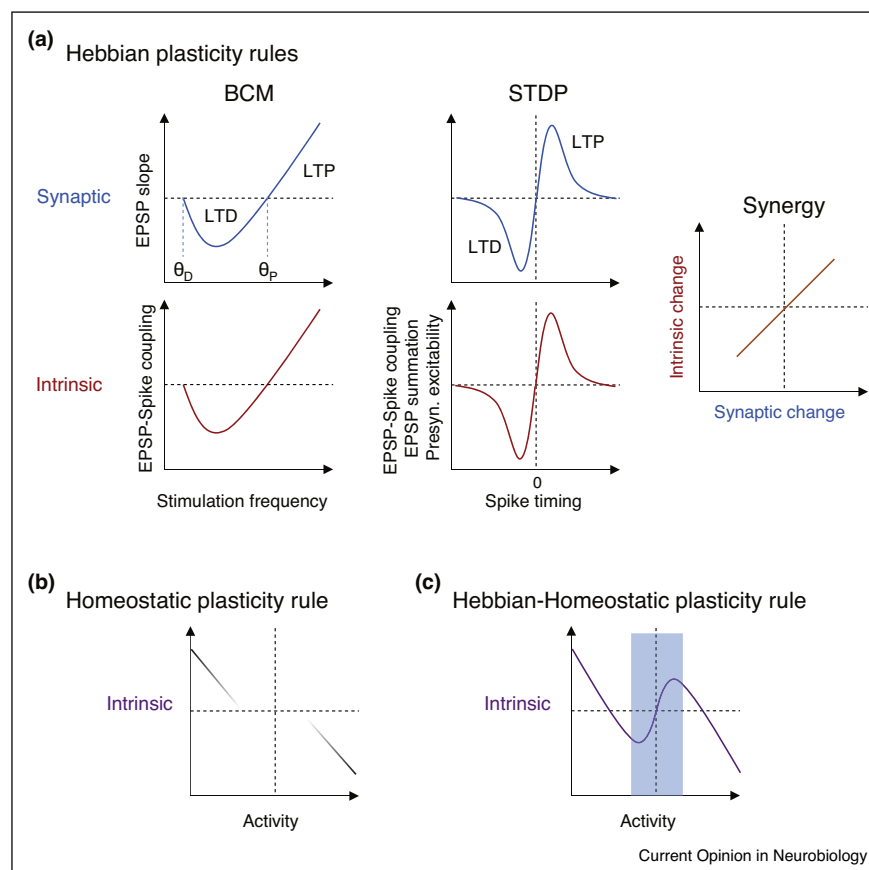
transmission at their mossy-fiber boutons through an analog-digital signaling mechanism [36]. Here again, this modulation is *global* as all inputs will be equally affected.

Learning rules of intrinsic plasticity

Hebbian changes in IE

Hebbian plasticity has been first defined for synaptic transmission in the form of the Bienenstock-Cooper-Munro (BCM) rule. BCM rule stipulates that synaptic modification correlates with the activity modulation during learning (for a recent review, see Ref. [37]; Figure 3a). Hebbian synaptic modification in the hippocampus and neocortex is also induced by the degree of correlation between presynaptic and postsynaptic activity and is referred to as spike-timing dependent plasticity or STDP [38]. Both types of Hebbian plasticity are associated with

Figure 3



Cooperation between synaptic and intrinsic plasticity rules.

(a) Synergistic changes in synaptic and intrinsic plasticity (Hebbian). Left, BCM (Bienenstock-Cooper-Munro) rule defines synergistic synaptic and intrinsic modification following low ($\theta_D < \text{frequency} < \theta_P$) or high ($> \theta_P$) stimulation frequency. θ_D = LTD threshold, θ_P = LTP threshold. Adapted from Ref. [41]. Middle, STDP (spike-timing dependent plasticity) rule defines synergistic synaptic and intrinsic modification following negative or positive spike timing. Adapted from Refs. [28,32,50,51]. Right, synaptic and intrinsic plasticity change synergistically. Adapted from Refs. [32,41]. **(b)** Homeostatic plasticity rule. Increase in synaptic activity induces an opposite decrease in excitability whereas reduction in synaptic drive induces an elevation in excitability. Note that homeostatic plasticity rule only accounts for intrinsic excitability changes following low or high, but not for intermediate changes in synaptic activity. Adapted from Refs. [56,63,64]. **(c)** Hebbian-homeostatic plasticity rule. This plasticity rule links homeostatic plasticity as defined in panel (b) to Hebbian changes in intrinsic excitability as defined in panel (a). Adapted from Refs. [29,69].

intrinsic plasticity that are synergistic to the induced synaptic changes (Figure 3a).

At the postsynaptic side, synaptic modifications are associated with synergistic plasticity of IE that affects the input–output function of the neuron (i.e. excitatory post-synaptic potential-spike (or EPSP-spike) coupling; see for review Refs. [1,39]). In CA1 pyramidal neurons, long-term synaptic potentiation (LTP) is associated with an increased firing probability in response to the tetanized or paired input [32,40,41] whereas long-term synaptic depression (LTD) is associated with a decreased firing probability in response to the stimulated input [32,41]. EPSP summation is changed synergistically with synaptic modifications induced by STDP protocols [28] (Figure 3a). All these Hebbian modifications in IE require NMDA-receptor activation and are input-specific, that is no modification occurs on other inputs. Hebbian intrinsic plasticity is not specific to hippocampal neurons and long-lasting increase in IE has been induced in neocortical neurons following synaptic [42] or intrinsic [43,44,45*] activation paradigms.

Intrinsic plasticity has been reported in at least three different types of cerebellar neurons. In deep cerebellar nuclei, granule and Purkinje neurons, IE is enhanced following high frequency stimulation that induces LTP [46–48]. Here again, NMDA-receptor activation is required for induction of intrinsic plasticity. In Purkinje cells, enhanced IE is mediated by the downregulation of SK channels and requires activation of PKA and casein kinase 2 (CK2). As in cortical neurons, the reciprocal is true and long-lasting decrease in IE is observed following LTD induction [49]. This LTD-IE is mediated by the upregulation of HCN channels.

Synergistic changes in IE have been also identified at the presynaptic side when LTP or LTD is induced by STDP protocols in hippocampal and neocortical neurons [50,51] (Figure 3a). IE in the presynaptic neuron was found to be enhanced following induction of synaptic LTP by positive correlation whereas IE of the presynaptic cell was decreased following induction of LTD by negative correlation. Presynaptic intrinsic plasticity involves yet unidentified retrograde messengers and might be of great importance for the dynamics of neural circuits by creating privileged pathways of activity in the brain where presynaptic and postsynaptic excitability as well as synaptic transmission change harmoniously.

Homeostatic plasticity of IE

Hebbian mechanisms appear insufficient to explain activity-dependent plasticity during development because they tend to reinforce active circuits and depress inactive ones and are thus destabilizing. In fact, stability in neural circuits can be achieved by introducing homeostatic plasticity that adjust synaptic strength and intrinsic

excitability [52]. Initially reported in cultured visual cortical neurons [53], homeostatic plasticity of IE has been observed in virtually all neuronal types. IE is enhanced in response to chronic activity deprivation induced pharmacologically [54–57] or by sensory deprivation [34**,58,59], whereas it is reduced in response to elevated network activity [54,56,60], leading to a homeostatic plasticity rule that is globally anti-Hebbian (Figure 3b).

While many ion channels are regulated in parallel [61], two inhibitory channels have recently retained attention: Kv1 channels located in the axon that determine spike threshold and intrinsic excitability [62], and HCN channels located in the dendrites that dampens all depolarizing events such as EPSPs. Downregulation of Kv1 channel activity has been identified as a major mechanism for the increased excitability observed in CA3 pyramidal neurons after chronic blockade of glutamate receptors [55] and in auditory neurons following cochlear removal [34**]. Conversely, Kv1 currents are upregulated following epileptiform activity [60], indicating that Kv1 channel activity is bi-directionally regulated. In CA1 pyramidal neurons, HCN channels are homeostatically regulated following bidirectional chronic manipulation of network activity [56] or following induction of large synaptic modification [63,64].

Whereas homeostatic plasticity in cortical pyramidal cells is usually induced by persistent modulation of activity lasting few tens of hours [53–56], homeostatic potentiation of IE can be induced by a transient hyperpolarization (20–300 s) in vestibular neurons [65] and cerebellar Golgi cells [66]. Both forms of plasticity involve the downregulation of BK channel activity. It should be noted that in contrast to pyramidal cells that are silent at rest, these cells correspond to pacemaker neurons that continuously fire at 5–10 Hz. Interestingly, vestibular sensory loss triggers rapid potentiation of excitability in vestibular neurons thus enabling adaptive compensatory increases in optokinetic reflex gain [67*].

Linking Hebbian and homeostatic intrinsic plasticity

Despite their apparent antagonistic feature, Hebbian and homeostatic plasticity are thought to work hand-in-hand [68]. The modulation of HCN channel following induction of synaptic modification provides a good example for such interaction. Whereas large LTP is associated with decreased IE due to the upregulation of HCN channel activity [63], small LTP is combined with increased IE resulting from downregulation of HCN channel [32]. The opposite is true for LTD with a HCN-dependent increase in IE induced in parallel of large LTD [64] and a HCN-dependent decrease in IE for small LTD [69*]. The multiple regulation of HCN channel implies distinct induction and expression pathways [63,64,69*,70]. Thus,

IE follows a single plasticity rule linking Hebbian and homeostatic plasticity (Figure 3c).

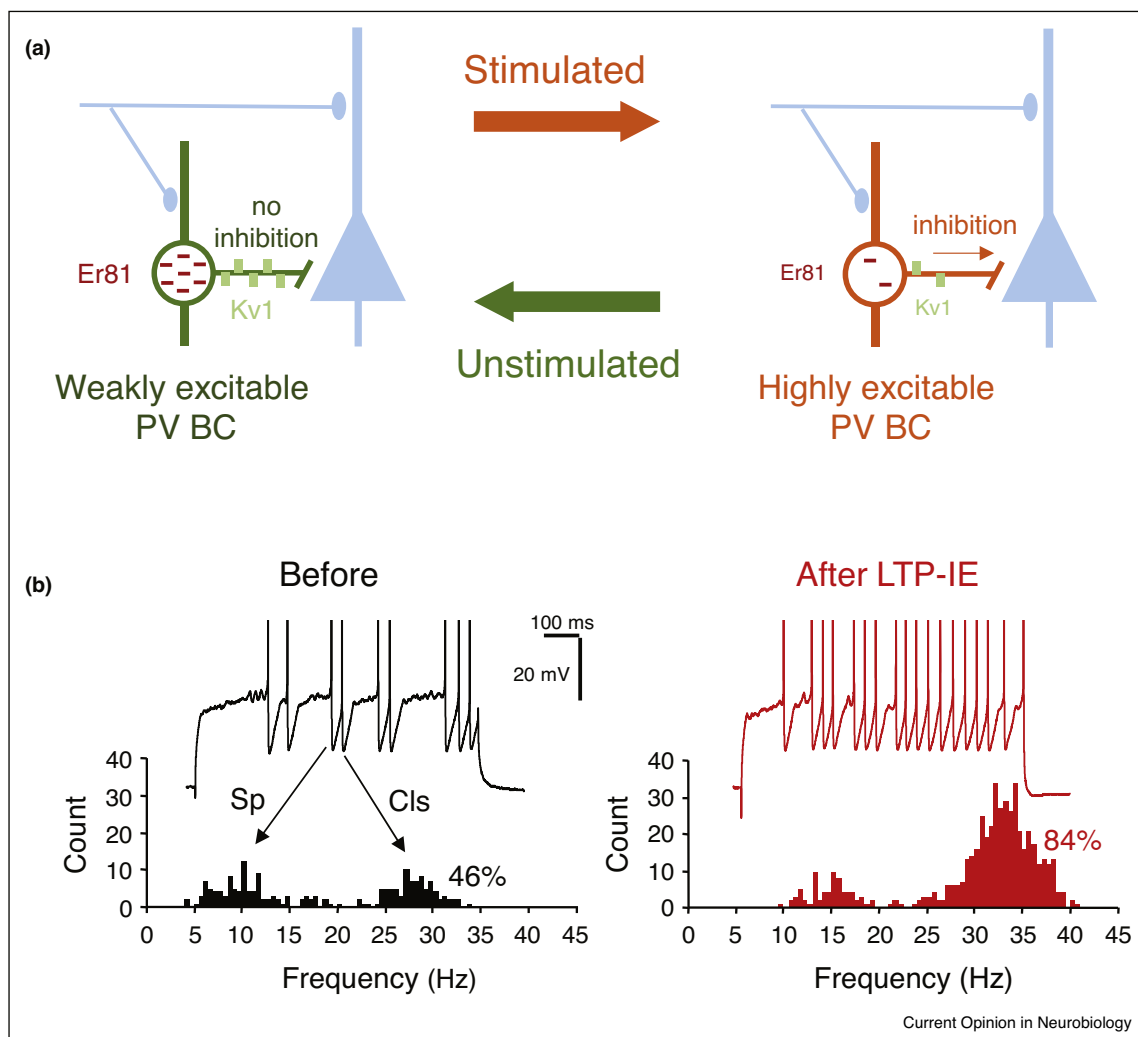
Intrinsic plasticity in GABAergic interneurons

Intrinsic plasticity is not exclusively expressed in principal neurons and GABAergic interneurons also display several forms of long-term intrinsic plasticity. Basket cells of the dentate gyrus exhibit LT-Depol of their resting membrane potential following high-frequency stimulation of the glutamatergic inputs [71]. As in granule cells, LT-Depol

enhances the efficacy of EPSPs to fire the interneuron but in basket cells LT-Depol results from changes in the Na^+/K^+ ATPase pump function and requires the activation of calcium-permeable AMPA receptor.

Voltage-dependent excitability is also finely tuned in basket cells by Kv1-dependent modulation of the spike threshold to adjust inhibition levels in cortical circuits. Stimulation of the Neuregulin 1 receptor ErbB4 has been shown to strongly regulate Kv1 channel activity and

Figure 4



Intrinsic plasticity in GABAergic interneurons.

(a) Bidirectional regulation of intrinsic excitability in parvalbumin positive basket cells (PV-BC). Left, in unstimulated conditions, no inhibition is observed because the PV-BC is not recruited by the circuit as the consequence of elevated levels of Kv1 channels in the axon through activity-dependent elevation of the transcription factor Er81. Right, in stimulated conditions, PV-BC is recruited because of reduced levels Kv1 channels through activity-dependent reduction in Er81, leading to functional inhibition that counterbalance enhanced excitation. Adapted from Refs. [73**,74*,75*].

(b) Modulation of temporal processing in PV-BC. In control conditions, PV-BC display a specific mode of firing composed of sparse spikes (Sp) typically occurring after a slow depolarizing ramp of potential at an instantaneous frequency of ~10 Hz (i.e. theta frequency) and clustered spikes (Cl) that immediately follow a spike at an instantaneous frequency of ~30 Hz (i.e. gamma frequency). After induction of long-term potentiation of intrinsic excitability (LTP-IE), the proportion of Cls increases from 46 to 84% indicating a gain of spiking activity in the gamma frequency range. Adapted from Ref. [73**].

intrinsic excitability in parvalbumin positive basket cells (PV-BC) [72]. Likewise, PV-BCs exhibit potentiation of IE mediated by the downregulation of Kv1 channel activity and induced by synaptic activation of metabotropic glutamate receptor subtype 5 (mGluR5) [73^{••}] (Figure 4a). This facilitation is responsible for most of the increased firing and is thought to compensate enhanced synaptic and intrinsic excitation in pyramidal neurons. The reciprocal modulation has been recently observed in somatosensory PV interneuron following activity-deprivation [74[•]], indicating that Kv1-dependent regulation of neuronal excitability is bidirectional (Figure 4a). In the cortex, most PV interneurons express Er81, a transcription factor involved in the activation pathway of Ca²⁺/calmodulin-dependent kinase I [75[•]]. Noteworthy, Er81 is highly regulated by activity and controls levels of Kv1.1 channel in PV interneurons [75[•]]. In fact, Er81 level is high in weakly active circuits whereas it is low in highly active circuits (Figure 4a).

Incidence of intrinsic plasticity on temporal processing

Temporal processing is thought to represent a key factor in brain function and is controlled by synaptic circuits and by intrinsic properties [76,77]. For example, during initial storage of fear learning, spiking activity among adjacent CA1 pyramidal neurons becomes more synchronized [78]. At a cellular scale, spike-timing, membrane resonance and pacemaker activity are all controlled by voltage-gated ion channels including those involved in intrinsic plasticity [55,79,80]. Both Hebbian and homeostatic regulations of IE are associated with improved spike-time precision [42,45[•],55]. In all cases, improved precision results from an ion channel-dependent enhancement of the voltage rising-slope preceding the action potential.

HCN channels set resonance frequency in hippocampal CA1 neurons in the θ range. Following large synaptic modifications, the resonance frequency is modulated as the sign of the induced synaptic change through modifications in HCN channel properties [64,81]. This shows that oscillatory intrinsic dynamics in the hippocampus can be finely tuned under homeostatic plasticity of IE.

Modulation of the temporal structure of firing has been described in two cell types. In Purkinje cells, SK-dependent enhancement of intrinsic excitability leads to increased burst firing in response to climbing fiber discharge and shortening of spike pauses [82[•]]. As Purkinje cells inhibit deep cerebellar nuclei, these briefer spike pauses are seen as enhanced excitation at the output side of the cerebellum. Likewise, enhanced IE in PV-BC promotes clustered spiking activity in the gamma-frequency range [73^{••}] (Figure 4b). As PV-BC represents the main cell-type orchestrating network oscillations in the hippocampus, this modulation in the temporal

structure of PV-BC firing suggests use-dependent modulation of gamma oscillations [83].

Conclusion and perspective

Remarkable progress in understanding learning rules and in identifying mechanisms of intrinsic plasticity has been made these recent years. However, many issues remain. For instance, most studies reported in this review comes from *in vitro* works and very few studies have been performed *in vivo* [44,45[•]] with physiologically realistic induction protocols. One may dream in the nearest future of monitoring IE in cortical or cerebellar neurons during the acquisition of a simple behavioral task. To achieve this goal, development of new tools will be required. Another challenge will consist in identifying why opposite changes in intrinsic excitability is observed in different types of neuron within the same structure following sensory deprivation [58,84]. Whereas changes in IE are clearly homeostatic in layer 2/3 principal neurons [58], they are Hebbian in layer five pyramidal cells [84]. The future will probably help to answer all these questions.

Conflict of interest statement

Nothing declared.

Acknowledgements

Supported by INSERM, CNRS, AMU, FRM (FDT2170437059 & DVS20131228768) and ANR NEUC 2014 (ANR-14-NEUC-0004).

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as

- of special interest
 - of outstanding interest
1. Zhang W, Linden DJ: **The other side of the engram: experience-driven changes in neuronal intrinsic excitability.** *Nat Rev Neurosci* 2003, **4**:885-900.
 2. Daoudal G, Debanne D: **Long-term plasticity of intrinsic excitability: learning rules and mechanisms.** *Learn Mem* 2003, **10**:456-465.
 3. Sjostrom PJ, Rancz EA, Roth A, Hausser M: **Dendritic excitability and synaptic plasticity.** *Physiol Rev* 2008, **88**:769-840.
 4. Tittley HK, Brunel N, Hansel C: **Toward a neurocentric view of learning.** *Neuron* 2017, **95**:19-32.
 5. Lisman J, Cooper K, Sehgal M, Silva AJ: **Memory formation depends on both synapse-specific modifications of synaptic strength and cell-specific increases in excitability.** *Nat Neurosci* 2018, **21**:309-314.
 6. Zylberberg J, Strowbridge BW: **Mechanisms of persistent activity in cortical circuits: possible neural substrates for working memory.** *Annu Rev Neurosci* 2017, **40**:603-627.
 7. Egorov AV, Hamam BN, Franssen E, Hasselmo ME, Alonso AA: **Graded persistent activity in entorhinal cortex neurons.** *Nature* 2002, **420**:173-178.
 8. Rahman J, Berger T: **Persistent activity in layer 5 pyramidal neurons following cholinergic activation of mouse primary cortices.** *Eur J Neurosci* 2011, **34**:22-30.
 9. Jochems A, Yoshida M: **Persistent firing supported by an intrinsic cellular mechanism in hippocampal CA3 pyramidal cells.** *Eur J Neurosci* 2013, **38**:2250-2259.

10. Knauer B, Jochems A, Valero-Aracama MJ, Yoshida M: **Long-lasting intrinsic persistent firing in rat CA1 pyramidal cells: a possible mechanism for active maintenance of memory.** *Hippocampus* 2013, **23**:820-831.
11. Zylbertal A, Kahan A, Ben-Shaul Y, Yarom Y, Wagner S: **Prolonged intracellular Na⁺ dynamics govern electrical activity in accessory olfactory bulb mitral cells.** *PLoS Biol* 2015, **13**e1002319.
12. Cui ED, Strowbridge BW: **Modulation of ether-a-go-go related gene (ERG) current governs intrinsic persistent activity in rodent neocortical pyramidal cells.** *J Neurosci* 2018, **38**:423-440.
- This study shows that persistent firing in neocortical pyramidal neurons is mediated by the reduction of the ether-à-gogo related gene (ERG) K⁺ channel. Calcium accumulation during triggering stimuli appears to attenuate ERG currents, leading to depolarization of the membrane potential and increased input resistance.
13. Woody CD, Black-Cleworth P: **Differences in excitability of cortical neurons as a function of motor projection in conditioned cats.** *J Neurophysiol* 1973, **36**:1104-1116.
14. Disterhoft JF, Coulter DA, Alkon DL: **Conditioning-specific membrane changes of rabbit hippocampal neurons measured in vitro.** *Proc Natl Acad Sci U S A* 1986, **83**:2733-2737.
15. Coulter DA, Lo Turco JJ, Kubota M, Disterhoft JF, Moore JW, Alkon DL: **Classical conditioning reduces amplitude and duration of calcium-dependent afterhyperpolarization in rabbit hippocampal pyramidal cells.** *J Neurophysiol* 1989, **61**:971-981.
16. Schreurs BG, Tomsic D, Gusev PA, Alkon DL: **Dendritic excitability microzones and occluded long-term depression after classical conditioning of the rabbit's nictitating membrane response.** *J Neurophysiol* 1997, **77**:86-92.
17. Gao Y, Budlong C, Durlacher E, Davison IG: **Neural mechanisms of social learning in the female mouse.** *Elife* 2017, **6**.
- This study shows how social learning affects intrinsic excitability in two cell types of the accessory olfactory bulb. Mitral cells show an unusual attenuation of IE during repetitive firing whereas inhibitory interneurons display an enhanced IE.
18. Oh MM, Kuo AG, Wu WW, Sametsky EA, Disterhoft JF: **Watermaze learning enhances excitability of CA1 pyramidal neurons.** *J Neurophysiol* 2003, **90**:2171-2179.
19. Rosenkranz JA, Grace AA: **Dopamine-mediated modulation of odour-evoked amygdala potentials during pavlovian conditioning.** *Nature* 2002, **417**:282-287.
20. Santini E, Quirk GJ, Porter JT: **Fear conditioning and extinction differentially modify the intrinsic excitability of infralimbic neurons.** *J Neurosci* 2008, **28**:4028-4036.
21. Kaczorowski CC, Disterhoft JF: **Memory deficits are associated with impaired ability to modulate neuronal excitability in middle-aged mice.** *Learn Mem* 2009, **16**:362-366.
22. Song C, Ehlers VL, Moyer JR Jr: **Trace fear conditioning differentially modulates intrinsic excitability of medial prefrontal cortex-basolateral complex of amygdala projection neurons in infralimbic and prelimbic cortices.** *J Neurosci* 2015, **35**:13511-13524.
23. Saar D, Grossman Y, Barkai E: **Reduced after-hyperpolarization in rat piriform cortex pyramidal neurons is associated with increased learning capability during operant conditioning.** *Eur J Neurosci* 1998, **10**:1518-1523.
24. Zelcer I, Cohen H, Richter-Levin G, Lebiosn T, Grossberger T, Barkai E: **A cellular correlate of learning-induced metaplasticity in the hippocampus.** *Cereb Cortex* 2006, **16**:460-468.
25. Motanis H, Maroun M, Barkai E: **Learning-induced bidirectional plasticity of intrinsic neuronal excitability reflects the valence of the outcome.** *Cereb Cortex* 2014, **24**:1075-1087.
26. Malik R, Chattarji S: **Enhanced intrinsic excitability and EPSP-spike coupling accompany enriched environment-induced facilitation of LTP in hippocampal CA1 pyramidal neurons.** *J Neurophysiol* 2012, **107**:1366-1378.
27. Valero-Aracama MJ, Sauvage MM, Yoshida M: **Environmental enrichment modulates intrinsic cellular excitability of hippocampal CA1 pyramidal cells in a housing duration and anatomical location-dependent manner.** *Behav Brain Res* 2015, **292**:209-218.
28. Wang Z, Xu NL, Wu CP, Duan S, Poo MM: **Bidirectional changes in spatial dendritic integration accompanying long-term synaptic modifications.** *Neuron* 2003, **37**:463-472.
29. Campanac E, Daoudal G, Ankri N, Debanne D: **Downregulation of dendritic I(h) in CA1 pyramidal neurons after LTP.** *J Neurosci* 2008, **28**:8635-8643.
30. Frick A, Magee J, Johnston D: **LTP is accompanied by an enhanced local excitability of pyramidal neuron dendrites.** *Nat Neurosci* 2004, **7**:126-135.
31. Losonczy A, Makara JK, Magee JC: **Compartmentalized dendritic plasticity and input feature storage in neurons.** *Nature* 2008, **452**:436-441.
32. Campanac E, Debanne D: **Spike timing-dependent plasticity: a learning rule for dendritic integration in rat CA1 pyramidal neurons.** *J Physiol* 2008, **586**:779-793.
33. Xu J, Kang N, Jiang L, Nedergaard M, Kang J: **Activity-dependent long-term potentiation of intrinsic excitability in hippocampal CA1 pyramidal neurons.** *J Neurosci* 2005, **25**:1750-1760.
34. Kuba H, Yamada R, Ishiguro G, Adachi R: **Redistribution of Kv1 and Kv7 enhances neuronal excitability during structural axon initial segment plasticity.** *Nat Commun* 2015, **6**:8815.
- The authors show that auditory deprivation by removing the cochlea in the chick leads to the elongation of the axon initial segment associated to the switch from Kv1 to Kv7 channels.
35. Mellor J, Nicoll RA, Schmitz D: **Mediation of hippocampal mossy fiber long-term potentiation by presynaptic Ih channels.** *Science* 2002, **295**:143-147.
36. Alle H, Geiger JR: **Combined analog and action potential coding in hippocampal mossy fibers.** *Science* 2006, **311**:1290-1293.
37. Cooper LN, Bear MF: **The BCM theory of synapse modification at 30: interaction of theory with experiment.** *Nat Rev Neurosci* 2012, **13**:798-810.
38. Feldman DE: **The spike-timing dependence of plasticity.** *Neuron* 2012, **75**:556-571.
39. Debanne D, Poo MM: **Spike-timing dependent plasticity beyond synapse - pre- and post-synaptic plasticity of intrinsic neuronal excitability.** *Front Synaptic Neurosci* 2010, **2**:21.
40. Andersen P, Sundberg SH, Sveen O, Swann JW, Wigstrom H: **Possible mechanisms for long-lasting potentiation of synaptic transmission in hippocampal slices from guinea-pigs.** *J Physiol* 1980, **302**:463-482.
41. Daoudal G, Hanada Y, Debanne D: **Bidirectional plasticity of excitatory postsynaptic potential (EPSP)-spike coupling in CA1 hippocampal pyramidal neurons.** *Proc Natl Acad Sci U S A* 2002, **99**:14512-14517.
42. Sourdet V, Russier M, Daoudal G, Ankri N, Debanne D: **Long-term enhancement of neuronal excitability and temporal fidelity mediated by metabotropic glutamate receptor subtype 5.** *J Neurosci* 2003, **23**:10238-10248.
43. Cudmore RH, Turrigiano GG: **Long-term potentiation of intrinsic excitability in LV visual cortical neurons.** *J Neurophysiol* 2004, **92**:341-348.
44. Paz JT, Mahon S, Tiret P, Genet S, Delord B, Charpier S: **Multiple forms of activity-dependent intrinsic plasticity in layer V cortical neurones in vivo.** *J Physiol* 2009, **587**:3189-3205.
45. Mahon S, Charpier S: **Bidirectional plasticity of intrinsic excitability controls sensory inputs efficiency in layer 5 barrel cortex neurons in vivo.** *J Neurosci* 2012, **32**:11377-11389.
- The authors show that rhythmic firing can trigger long-lasting increase or decrease in intrinsic excitability in layer five pyramidal neurons of the rat barrel cortex *in vivo*. The direction of plasticity depends on initial cell excitability.

46. Aizenman CD, Linden DJ: **Rapid, synaptically driven increases in the intrinsic excitability of cerebellar deep nuclear neurons.** *Nat Neurosci* 2000, **3**:109-111.
47. Armano S, Rossi P, Taglietti V, D'Angelo E: **Long-term potentiation of intrinsic excitability at the mossy fiber-granule cell synapse of rat cerebellum.** *J Neurosci* 2000, **20**:5208-5216.
48. Belmuguenai A, Hossy E, Bengtsson F, Pedroarena CM, Piochon C, Teuling E, He Q, Ohtsuki G, De Jeu MT, Elgersma Y *et al.*: **Intrinsic plasticity complements long-term potentiation in parallel fiber input gain control in cerebellar Purkinje cells.** *J Neurosci* 2010, **30**:13630-13643.
49. Shim HG, Jang DC, Lee J, Chung G, Lee S, Kim YG, Jeon DE, Kim SJ: **Long-term depression of intrinsic excitability accompanied by synaptic depression in cerebellar Purkinje cells.** *J Neurosci* 2017, **37**:5659-5669.
50. Ganguly K, Kiss L, Poo M: **Enhancement of presynaptic neuronal excitability by correlated presynaptic and postsynaptic spiking.** *Nat Neurosci* 2000, **3**:1018-1026.
51. Li CY, Lu JT, Wu CP, Duan SM, Poo MM: **Bidirectional modification of presynaptic neuronal excitability accompanying spike timing-dependent synaptic plasticity.** *Neuron* 2004, **41**:257-268.
52. Turrigiano GG, Nelson SB: **Homeostatic plasticity in the developing nervous system.** *Nat Rev Neurosci* 2004, **5**:97-107.
53. Desai NS, Rutherford LC, Turrigiano GG: **Plasticity in the intrinsic excitability of cortical pyramidal neurons.** *Nat Neurosci* 1999, **2**:515-520.
54. Karmarkar UR, Buonomano DV: **Different forms of homeostatic plasticity are engaged with distinct temporal profiles.** *Eur J Neurosci* 2006, **23**:1575-1584.
55. Cudmore RH, Fronzaroli-Molinieres L, Giraud P, Debanne D: **Spike-time precision and network synchrony are controlled by the homeostatic regulation of the D-type potassium current.** *J Neurosci* 2010, **30**:12885-12895.
56. Gasselín C, Inglebert Y, Debanne D: **Homeostatic regulation of h-conductance controls intrinsic excitability and stabilizes the threshold for synaptic modification in CA1 neurons.** *J Physiol* 2015, **593**:4855-4869.
57. Shim HG, Jang SS, Jang DC, Jin Y, Chang W, Park JM, Kim SJ: **mGlu1 receptor mediates homeostatic control of intrinsic excitability through Ih in cerebellar Purkinje cells.** *J Neurophysiol* 2016, **115**:2446-2455.
58. Maffei A, Turrigiano GG: **Multiple modes of network homeostasis in visual cortical layer 2/3.** *J Neurosci* 2008, **28**:4377-4384.
59. Milshstein-Parush H, Frere S, Regev L, Lahav C, Benbenishty A, Ben-Eliyahu S, Goshen I, Slutsky I: **Sensory deprivation triggers synaptic and intrinsic plasticity in the hippocampus.** *Cereb Cortex* 2017, **27**:3457-3470.
60. Kirchheim F, Tinnes S, Haas CA, Stegen M, Wolfart J: **Regulation of action potential delays via voltage-gated potassium Kv1.1 channels in dentate granule cells during hippocampal epilepsy.** *Front Cell Neurosci* 2013, **7**:248.
61. Marder E, Goaillard JM: **Variability, compensation and homeostasis in neuron and network function.** *Nat Rev Neurosci* 2006, **7**:563-574.
62. Rama S, Zbili M, Fekete A, Tapia M, Benitez MJ, Boumedine N, Garrido JJ, Debanne D: **The role of axonal Kv1 channels in CA3 pyramidal cell excitability.** *Sci Rep* 2017, **7**:315.
63. Fan Y, Fricker D, Brager DH, Chen X, Lu HC, Chitwood RA, Johnston D: **Activity-dependent decrease of excitability in rat hippocampal neurons through increases in I(h).** *Nat Neurosci* 2005, **8**:1542-1551.
64. Brager DH, Johnston D: **Plasticity of intrinsic excitability during long-term depression is mediated through mGluR-dependent changes in I(h) in hippocampal CA1 pyramidal neurons.** *J Neurosci* 2007, **27**:13926-13937.
65. Nelson AB, Krispel CM, Sekirnjak C, du Lac S: **Long-lasting increases in intrinsic excitability triggered by inhibition.** *Neuron* 2003, **40**:609-620.
66. Hull CA, Chu Y, Thanawala M, Regehr WG: **Hyperpolarization induces a long-term increase in the spontaneous firing rate of cerebellar Golgi cells.** *J Neurosci* 2013, **33**:5895-5902.
67. Nelson AB, Faulstich M, Moghadam S, Onori K, Meredith A, du Lac S: **BK channels are required for multisensory plasticity in the oculomotor system.** *Neuron* 2017, **93**:211-220.
- This paper shows that unilateral vestibular deafferentation triggers rapid potentiation of IE in vestibular neurons and occludes induction of intrinsic plasticity, concomitant with an increase in the gain of the optokinetic reflex.
68. Zenke F, Gerstner W: **Hebbian plasticity requires compensatory processes on multiple timescales.** *Philos Trans R Soc Lond B Biol Sci* 2017, **372**.
69. Gasselín C, Inglebert Y, Ankri N, Debanne D: **Plasticity of intrinsic excitability during LTD is mediated by bidirectional changes in h-channel activity.** *Sci Rep* 2017, **7**:14418.
- This study shows that the magnitude of LTD determines the polarity of intrinsic changes in CA1 pyramidal neurons, thus providing support to a continuum rule linking synergistic (Hebbian) and compensatory (homeostatic) changes in excitability.
70. Santoro B, Piskorowski RA, Pian P, Hu L, Liu H, Siegelbaum SA: **TRIP8b splice variants form a family of auxiliary subunits that regulate gating and trafficking of HCN channels in the brain.** *Neuron* 2009, **62**:802-813.
71. Ross ST, Soltesz I: **Long-term plasticity in interneurons of the dentate gyrus.** *Proc Natl Acad Sci U S A* 2001, **98**:8874-8879.
72. Li KX, Lu YM, Xu ZH, Zhang J, Zhu JM, Zhang JM, Cao SX, Chen XJ, Chen Z, Luo JH *et al.*: **Neuregulin 1 regulates excitability of fast-spiking neurons through Kv1.1 and acts in epilepsy.** *Nat Neurosci* 2011, **15**:267-273.
73. Campanac E, Gasselín C, Baude A, Rama S, Ankri N, Debanne D: **Enhanced intrinsic excitability in basket cells maintains excitatory-inhibitory balance in hippocampal circuits.** *Neuron* 2013, **77**:712-722.
- This study shows that high frequency stimulation of the Schaffer collaterals that induces LTP and intrinsic excitability in CA1 pyramidal cells also enhances intrinsic excitability in PV-BC through an mGluR5-dependent reduction of Kv1 channel activity. Enhanced intrinsic excitability promotes spiking activity at the gamma frequency.
74. Gainey MA, Aman JW, Feldman DE: **Rapid disinhibition by adjustment of PV intrinsic excitability during whisker map plasticity in mouse S1.** *J Neurosci* 2018, **38**:4749-4761.
- The authors show that brief sensory deprivation rapidly weakens excitability of PV interneurons in the barrel cortex through the upregulation of Kv1 channel activity.
75. Dehorter N, Ciceri G, Bartolini G, Lim L, del Pino I, Marin O: **Tuning of fast-spiking interneuron properties by an activity-dependent transcriptional switch.** *Science* 2015, **349**:1216-1220.
- The authors show that network activity modulates intrinsic excitability of neocortical PV-BC through the post-mitotic expression of the transcriptional regulator Er81 and the regulation of Kv1.1 channels.
76. Eichenbaum H: **Time cells in the hippocampus: a new dimension for mapping memories.** *Nat Rev Neurosci* 2014, **15**:732-744.
77. Paton JJ, Buonomano DV: **The neural basis of timing: distributed mechanisms for diverse functions.** *Neuron* 2018, **98**:687-705.
78. Liu YZ, Wang Y, Shen W, Wang Z: **Enhancement of synchronized activity between hippocampal CA1 neurons during initial storage of associative fear memory.** *J Physiol* 2017, **595**:5327-5340.
79. Fricker D, Miles R: **EPSP amplification and the precision of spike timing in hippocampal neurons.** *Neuron* 2000, **28**:559-569.
80. Gastrein P, Campanac E, Gasselín C, Cudmore RH, Bialowas A, Carlier E, Fronzaroli-Molinieres L, Ankri N, Debanne D: **The role of hyperpolarization-activated cationic current in spike-time**

precision and intrinsic resonance in cortical neurons in vitro. *J Physiol* 2011, **589**:3753-3773.

81. Narayanan R, Johnston D: **Long-term potentiation in rat hippocampal neurons is accompanied by spatially widespread changes in intrinsic oscillatory dynamics and excitability.** *Neuron* 2007, **56**:1061-1075.
82. Grasselli G, He Q, Wan V, Adelman JP, Ohtsuki G, Hansel C:
• **Activity-dependent plasticity of spike pauses in cerebellar Purkinje cells.** *Cell Rep* 2016, **14**:2546-2553.

This study demonstrates that in cerebellar Purkinje cells the pauses following spike bursts can be modulated by the activity-dependent regulation of SK2, thus altering the spike output pattern of these neurons.

83. Whittington MA, Traub RD, Jefferys JG: **Synchronized oscillations in interneuron networks driven by metabotropic glutamate receptor activation.** *Nature* 1995, **373**:612-615.
84. Nataraj K, Le Roux N, Nahmani M, Lefort S, Turrigiano G: **Visual deprivation suppresses L5 pyramidal neuron excitability by preventing the induction of intrinsic plasticity.** *Neuron* 2010, **68**:750-762.