A Composite Sketch of Fast-Spiking Parvalbumin-Positive Neurons

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Abstract

Parvalbumin-positive neurons are inhibitory neurons that release GABA and are mostly represented by fast-spiking basket or chandelier cells. They constitute a minor neuronal population, yet their peculiar profiles allow them to react quickly to any event in the brain under normal or pathological conditions. In this review, we will summarize the current knowledge about the fundamentals of fast-spiking parvalbumin-positive neurons, focusing on their morphology and specific channel/protein content. Next, we will explore their development, maturation, and migration in the brain. Finally, we will unravel their potential contribution to the physiopathology of epilepsy.

Key words: basket cell, epilepsy, fast-spiking cell, parvalbumin neuron

Introduction

The brain is constituted of several cell types, interacting together in a fine-tuned network to allow individuals to perform complex tasks. Novel cellular and molecular actors in this neuronal network are continuously brought to light, increasing the complexity of the yarn we are trying to unravel. The human brain contains approximately one hundred billion neurons and roughly as many glial cells (von Bartheld et al. 2016). In mice, the balance is more tilted towards neurons (Herculano-Houzel et al. 2006). Although it is challenging to assess the proportion of each cell population of the brain, it is considered that 80% of neurons in the mouse brain are excitatory and 15% of them are inhibitory (Keller et al. 2018). The remaining 5% fall into several specific neuronal populations, whose description is beyond the scope of this review.

The considerable heterogeneity of the brain has been known for over a century, and inhibitory neurons have been particularly targeted by many classification attempts based on markers, electrophysiological profile(s), connectivity, morphology or other characteristics. These various endeavors indicate in fact that their identification and classification remain unsatisfactory. None of the aforementioned features is sufficient to distinguish an interneuron per se, and inhibitory neurons are more intricate than excitatory neurons. Thanks to single-cell RNA sequencing, efforts to sort inhibitory neurons by gene expression recently resulted in even more molecular subclasses than previously suggested (Zeisel et al. 2015; Tasic et al. 2016; Tasic et al. 2018). Interestingly, these subclasses seem universal as they can be found almost in all areas of the brain, whereas many
glutamatergic neuronal groups differ from one brain region to another (Zeisel et al. 2015; Tasic et al. 2018). Inhibitory neurons are usually divided into 3 subpopulations, based on molecular markers: they are either positive for parvalbumin (PV—a calcium-binding protein), somatostatin (SOM—a neuropeptide), or 5HT1a (a serotonin receptor). Besides, inhibitory interneurons can be distinguished by the expression of other calcium-binding proteins such as calbindin (CB) or calretinin (CR), other neuropeptides as cholecystokinin (CCK), vasoactive intestinal peptide (VIP), or neuropeptide Y (NPY) (DeFelipe et al. 2013). In this review, we will focus on the parvalbumin-positive neurons (PV+ neurons), and more specifically on PV+ neurons from the cortex and the hippocampus.

Discussion
General Features of Fast-Spiking PV+ GABAergic Interneurons
PV+ neurons are one of the most abundant subtypes of GABAergic interneurons, accounting for 30%–40% of them (Tremblay et al. 2016). These neurons are usually characterized by fast-spiking profile and can be found almost everywhere in the brain. The term “fast-spiking” (FS) refers to the firing pattern of those cells. It is associated with short-action potentials and the capability to sustain a high firing frequency. Having a closer look at the available tools for studying PV+ neurons, one could notice that those cells are built for speed in almost every aspect of the transmission.

Based on their axonal arborization, PV+ interneurons of the cortex are morphologically described either as “basket cell” (BC) or “chandelier cell” (ChC, also named axo-axonic cell) (Katsumaru et al. 1988a; DeFelipe et al. 1989; Hendry et al. 1989). While almost all fast-spiking BCs are PV+, things are more complicated for ChCs. With their typical morphology and low number, ChCs rarely required any specific labeling, so the observation that a fraction of ChCs is PV+ was made quite recently (Taniguchi et al. 2013). In the cortex, PV+–ChCs seem to express vasoactive intestinal peptide receptor 2 (Vipr2) as a secondary marker and a recent study identified the protein Fgf13 as an additional marker (Tasic et al. 2018; Favuzzi et al. 2019). Vipr2 is a G protein-coupled receptor for the corresponding neuropeptide, while Fgf13 is a multifunctional protein implicated in microtubule stabilization for instance.

BCs and ChCs are also found in the hippocampus, along with a few other PV+ populations: oriens-lacunosum moleculare cells (O-LM) and bistratified cells (BiO) (Halasy et al. 2002). BCs, ChCs, and BiCs can be observed mainly in stratum pyramidale (Fig. 1), while O-LMs are found in the stratum oriens of the hippocampus (Yamada and Jinno 2017). However, as O-LMs and BiCs also express other markers, we will not go into further details about them (Somogyi and Klausberger 2005; Jinno and Kosaka 2006).

Mode of Action of PV+ Neurons
Recruitment Mechanisms: The Dendritic Tree
PV+ cells display one of the most extensive dendritic trees among interneurons, as well as the largest number of received inputs, most of them being excitatory (Fig. 2). In the hippocampus, PV+ cells receive between 16,000 and 35,000 contacts mainly originating from pyramidal cells (PC) or granular cells (GC), only around 10% are inhibitory (Gulyás et al. 1999; Tukker et al. 2013). The dendritic tree of cortical PV+ neurons displays a low density of spines with excitatory synapses (Sancho and Bloodgood 2018), the majority of inputs being received on dendritic shafts (i.e., axo-dendritic contact). A small proportion of those axo-dendritic inputs come from SOM+ or other PV+ interneurons. Inhibitory axo-somatic inputs are mainly coming from VIP+ interneurons, whereas axo-axonic contacts are probably arising from ChCs (Hioki et al. 2013; Tukker et al. 2013). One recent study has reported that PV+ neurons with local high spine density, associated with few perineuronal nets (PNN, see Maturation), could be found in the dentate gyrus. (Foggetti et al. 2019).

In terms of glutamate receptors, it has been shown that the post-synaptic compartment of PV+ neurons presents different types of NMDA and AMPA receptors (NMDAR and AMPAR) to suit their specific electrophysiological profile. NMDARs differ from each other in their diverse subunits and therefore exhibit different decay kinetics (Tovar and Westbrook 2017). Adult cortical and hippocampal PV+ neurons mainly rely on the GluN1 and GluN2A NMDAR subunits, the duo with the fastest decay kinetics, but the association of GluN1-GluN2B and GluN1-GluN2D (in the hippocampus only) can also be found (Monyer et al. 1994; Geiger et al. 1997; von Engelhardt et al. 2015; Mierau et al. 2016). NMDARs are involved in calcium influx when Mg2+ blockade is alleviated and may be linked to PV and GAD67 expression in the cortex (Kinney 2006). Interestingly, NMDARs tend to be concentrated in spiny synapses, in contrast to AMPARs, which are uniformly distributed along the dendrites of cortical PV+ neurons (Sancho and Bloodgood 2018).

AMPARs are also made of different subunits, conferring specific gating and kinetics to the complex (Lee 2012). In cortical and hippocampal PV+ neurons, it has been shown that the majority of AMPARs lacks the GluA2 subunit, making it permeable to Ca2+ (Jonas et al. 1994; Geiger et al. 1995; Talos et al. 2006). These calcium-permeable AMPARs are largely responsible for Ca2+ influx into the postsynaptic compartment. They also ensure NMDAR activation through the clearance of Mg2+ (Goldberg et al. 2003b; Camiré and Topolnik 2014). AMPARs allow PV+ neurons to quickly generate excitatory post-synaptic potential (EPSP) during a short period following excitatory inputs. Because one EPSP is rarely enough to induce an AP generation, this system allows PV+ neurons to fire only if they received several
synchronous EPSPs. Indeed, AMPARs’ conductance, rapid rise, and decay parameters associated with strong desensitization and small recovery time make them particularly suitable to the task (Geiger et al. 1997; Traynelis et al. 2010).

Aside from these glutamate receptors, EPSPs are also shaped by ions channels in PV+ neurons. At least 2 L-type Ca^{2+} voltage-gated channels can be found in hippocampal PV+ neurons, which also influence their firing properties (Jiang and Swann 2005; Xu et al. 2006). Besides, voltage-gated K+ channels type 3 (Kv3) are highly concentrated in cortical and hippocampal PV+ dendrites (Rudy and McBain 2001). Kv3 channels contribute to the propagation and the quick decay time of EPSP, ensuring a tight summation window for generating action potential (AP) (Fricker and Miles 2000; Hu et al. 2010). Besides, the concentration of Na+ channel is relatively low, specifically at the apical dendrite. This particular cocktail of ion channels explains why cortical and hippocampal BCs are unable to produce dendritic spikes. Different teams showed that short high-intensity somatic currents fail to trigger an AP in the dendrite of FS neurons, contrary to the situation observed in PCs. Upon long somatic current pulse, an AP can be observed in the basal dendrite but fails to ascend further (Goldberg et al. 2003a; Hu et al. 2010). The ascension of APs is also called “backpropagation” and probably participates to synaptic plasticity, which we will approach in the section The long-term Plasticity in PV+ Neurons. Finally, cortical and hippocampal dendrites of PV+ neurons are connected by gap junctions, further contributing to the high synchronic power of this neuronal network (Katsumaru et al. 1988b; Galarreta and Hestrin 1999).

Action Potential Generation: The Axonal Compartment
The signature of PV+ interneurons lies in their axonal thickness and ramifications. In cortical BCs, the axon usually originates from the apical part of the soma and extends mainly around it, targeting proximal dendrites and soma of postsynaptic cells. In cortical ChCs, the axon arises from the basal part of the soma and has a typical candlesticks-like shape, connecting to the axon of their target (Markram et al. 2004; Jiang et al. 2015).

The location of synapses that connect PV+ interneurons with their targets improves their efficiency: the closer it is to the AP generation site, the stronger the synapse is (Kubota et al. 2015). The location of synapses that connect PV+ interneurons with their targets improves their efficiency: the closer it is to the AP generation site, the stronger the synapse is (Kubota et al. 2015). Recent studies have demonstrated that most cortical BC neurons present patches of myelin sheets on their axon, both in mice and humans. Authors suggest an effect on the energy needed for the AP propagation (rather than the classical role in AP velocity),
but pieces of supporting evidence are scarce (Micheva et al. 2016; Micheva et al. 2018).

All PV+ neurons initiate the AP in a structure particularly close to the soma, called the Axon Initial Segment (AIS) and characterized by a specific cocktail of ions channels that are in high densities (Hu et al. 2015; Hu and Jonas 2014; Höflin et al. 2017). The AIS of PV+ neurons contains classical voltage-gated channels (Kv1.1, 1.2 and Nav1.6), along with some other channels (Lorincz and Nusser 2008). Indeed, the voltage-gated sodium channel Nav1.1, enriched in the AIS of all FS cells, contributes to AP generation by sustaining high-frequency firing, while Kv3.2 channels complete the AP during repolarization at least in the cortical PV+ neurons (Lau et al. 2000; Ogwara et al. 2007). A comparison between CCX+ and PV+ neurons revealed that they use different types of channels to trigger Ca\(^{2+}\) entry into the pre-synapse. Cortical and hippocampal BCs mainly rely on Cav2.1 (also called P/Q-type) channels to release neurotransmitter rapidly following APs, in a synchronous manner. Neurons in which fusion events can occur several seconds after APs mediate Ca\(^{2+}\) entry partly or entirely using Cav2.2 (N-type) channels (Hefft and Jonas 2005; Zaitsev et al. 2007; Rossignol et al. 2013).

Similar to dendrites, axons of cortical and hippocampal PV+ neurons are connected by gap junctions, allowing them to propagate newly generated AP (Kosaka and Hama 1985; Tamás et al. 2000). Interestingly, a recent study notably reports that simultaneous or sequential excitation of several connected cerebellar BCs increased the probability of AP generation and reduced their latency (Alcami 2018).

**Signal Transmission: Pre-Synapses and Synapses**

The synapses of PV+ neurons also contribute to their ability to fire very rapidly following an input. All hippocampal interneurons apparently display a similar presynaptic terminal density (i.e., 21–28 synapses/100 µm), which means that 1 BC innervates around 1500 cells (with an average of 6 contacts per target) (Gulyás et al. 1993; Buhl et al. 1994; Sik et al. 1995). Their synapses also present a low failure rate and a rapid release of GABA following to AP arrival, again stressing out the need for synchronous communication (Kraushaar et al. 2000). Hippocampal BCs organize their synaptic machinery into small boutons, bearing a small number of active zones, considered as “nanodomains.” As a result of their spatial promiscuity, 2 or 3 Ca\(^{2+}\) channels are sufficient to induce the vesicle release via Ca\(^{2+}\) sensor protein-dependent exocytosis (Bucurenciu et al. 2008; Bucurenciu et al. 2010). These well-organized nanodomains also facilitate Ca\(^{2+}\) clearance following neurotransmitter release and save energy, as less ion exocytosis is needed to return to the resting condition.

Besides, the parvalbumin protein has a buffering ability and helps to rapidly decrease the Ca\(^{2+}\) concentration. PV is a calcium-binding protein with 3 EF-hand domain also found in muscle cells (Bottoms et al. 2004). Even if the dissociation constant of PV and Ca\(^{2+}\) is very low, this protein presents rather slow binding kinetics. Indeed, the binding capacity of PV to Mg\(^{2+}\) at physiological concentration makes it the favored partner, impeding or slowing the reaction with Ca\(^{2+}\) (Schwaller 2009). As a result, PV co-exists in 3 states: free of ions, bound to Mg\(^{2+}\) or Ca\(^{2+}\). It turns out that this three-state organization could contribute to the buffering capacity of PV. Indeed, computational studies performed on cerebellar BCs revealed that free PV is replenished only from the Mg\(^{2+}\)-bound fraction, thus ensuring a constant buffer capacity during stimulation (Eggermann and Jonas 2012). The high mobility of this protein combined with the organization in nanodomains could, therefore, contribute to easier maintenance of buffering capacity, as even small changes in the absolute number of ions could impact their total concentrations (Schwaller 2009; Eggermann et al. 2012). PV could also participate in the depressing profile of BCs synapses, as suggested by the facilitation phenotype of cerebellar and hippocampal BCs in PV-deficient mice (Vreugdenhil et al. 2006; Eggermann and Jonas 2012). A depressing synapse, in contrast with a facilitated one, presents a reduced amplitude of post-synaptic current following a train of APs. Neurons with a high probability of release usually harbor depressing synapses, as their efficient machinery rapidly clear transient Ca\(^{2+}\) and/or they will use the majority of their readily releasable pool (RRP) of vesicles faster than its replenishment potential (Jackman and Regge 2017).

**The Synaptotagmins in PV+ Neurons**

Synaptotagmins (Syt) also take part in the peculiar profile of PV+ neurons. This family of proteins includes 17 members, divided into 3 groups according to their ability to bind 0, 5, or 10 Ca\(^{2+}\) ions. Syt also differ by their binding kinetics. A majority of them are also able to bind SNARE proteins, a complex responsible for synaptic vesicles docking to the plasma membrane of neurons (Chen and Jonas 2017; Wu et al. 2019). Hippocampal PV+ neurons express 9 paralogs of the synaptotagmin family (i.e., 1–5, 7, and 11–13), although their genuine role in inhibitory neurons is unclear (Kerr et al. 2008). The fast-release sensors Syt1 and Syt2 are found in cortical and cerebellar PV+ neurons (as well as in a fraction of hippocampal BC) and ensure a fast and synchronous neurotransmitter release, contributing to the depressing profile of PV+ neurons’ synapses (Sommenje and Levelt 2012; Bouhours et al. 2017; Borsneich and Schmidt 2019). Contrary to Syt1 and Syt2, Syt7 is not located in the vesicle membrane but at the plasma membrane of cerebellar and hippocampal PV+ neurons and is implicated in an asynchronous release, facilitation, and managing of the RRP (Jackman et al. 2016; Li et al. 2017). Even though asynchronous release and facilitation are not typical characteristics for PV+ neurons, Syt7 ensures sustainable neurotransmitter release by spreading vesicle release over time following one or several APs, thus prolonging inhibition (Chen et al. 2017). Besides, Syt1 and Syt7 may contribute to vesicle recycling through clathrin-mediated endocytosis (CME) and a slower calcium-independent mechanism, respectively, (Haucke et al. 2000; Li et al. 2017).

Syt11 could play a balancing role by inhibiting the CME in hippocampal and ganglionic neurons, thereby maintaining a reasonable number of active endocytosis sites in a calcium-independent manner (Wang et al. 2016; Wang et al. 2018). Other teams reported the presence of Syt11 in dendritic endosome-like structures, linking the protein to long-term potentiation (LTP, see below) rather than vesicle recycling. Indeed, Syt11 knock-out (KO) neurons display a normal secretion of neurotransmitters and peptides (Dean et al. 2012; Shimojo et al. 2019). The role of Syt4 seems to be subtler, as several experiments on neurons and neuroendocrine cells showed that Syt4 can impair vesicle fusion by unproductively competing for SNARE binding with other Syt. In contrast, it enhances exocytosis under high Ca\(^{2+}\) concentration (Wang et al. 2001; Wang et al. 2003; Bhalla et al. 2008; Zhang et al. 2009; Huang et al. 2018). These concentration-dependent opposite effects of Syt4 is surprising given its inability to bind ions (Dai et al. 2004) but could be associated with its interaction with other calcium-dependent Syt members. The absence of effects following Syt4 overexpression in hippocampal neurons may argue against its putative fusion-impairing role or
highlight a failsafe mechanism preventing the system from over-inhibiting fusion (Ting et al. 2006). Another paper has shown that the absence of Syt4 in presynaptic terminals increases the spontaneous release of vesicles via BDNF, thus confirming the inhibitory effect of Syt4 on vesicle fusion (Dean et al. 2009). The same team has also reported a link between Syt4 and LTD, as observed for Syt11.

Syt12 also seems able to compete with Syt1 for SNARE binding, potentially acting as another inhibitory protein (to a lesser extent compared to Syt4, likely not biologically relevant) (Bhalla et al. 2008). By contrast, it was reported that Syt12 could support spontaneous release when phosphorylated after binding to Syt1 in an SNARE-independent manner (Maximov et al. 2007). Finally, Syt3 has recently been linked to AMPAR internalization following NMDA or AMPA activation in hippocampal neurons primary cultures (Dean et al. 2012; Awasthi et al. 2019). Removing Syt3 in mice leads to a lack of forgetting ability, but since its activity is mainly mediated by GluA2 binding (a subunit of AMPA receptor weakly expressed in BC), its effect in PV+ neurons could be limited.

Most of the information about Syt5 functions is inferred from its activity in secretory cells. Syt5 has been found in peptide-containing, dense-core vesicles from the adrenal medulla or pancreatic-derived cell lines. Syt5 could act as a positive modulator of calcium-dependent exocytosis (Saegusa et al. 2002; Iezzi 2004). To date, no genuine evidence for a defined function of Syt13 in the brain has been generated. However, the glucose-induced secretion of insulin is significantly reduced in pancreatic cells with lower expression of Syt13 (Andersson et al. 2012). Together, all these studies show the wide variety of molecular tools that PV+ neurons can use to fine tune their activity and ensure fast and efficient responses.

The Long-Term Plasticity in PV+ Neurons

Once generated in the AIS, the AP can backpropagate towards the proximal dendrite and usually fails to reach to the distal dendrites, probably due to the lack of Na channels. In cortical BCs, this phenomenon has minimal impact on Ca2+ accumulation and is regulated by A-type K+ channel (Goldberg et al. 2003b; Cho et al. 2010). Nonetheless, recent findings indicate that sharp wave oscillations and nicotinic cholinergic receptors (nAChR) could carry the AP further into the distal dendrite and sustain high Ca2+ concentrations in dendrites of hippocampal BCs (Chiovini et al. 2010). Moreover, type I metabotropic glutamate receptors (mGlur) are reported on PV+ neuron membranes and could also contribute to Ca2+ accumulation in the post-synaptic compartment (Muly et al. 2003; Sun et al. 2009; van Hooft et al. 2018). Unlike axons, Ca2+ concentration in dendrites of hippocampal BC is mainly managed by a fixed rather than a mobile buffer. A fixed buffer should induce a slow Ca2+ release close to the source, elongating the decay time of transient Ca2+. This could provide an efficient summation of Ca2+ influx between 2 events and explain why successive inputs are able to accumulate Ca2+ in dendrite and support AP backpropagation (Aponte et al. 2008).

Once accumulated in the post-synaptic compartment, the calcium contributes to the synaptic plasticity of the neuron. The phenomenon has been mainly studied in the hippocampus, and it was shown that yet again PV+ neurons have several tools available to modulate their activity. In vivo experiments showed that theta burst stimulation (TBS) in rat hippocampi can either induce long-term potentiation (LTP), facilitating the next AP generation or long-term depression (LTD), inhibiting the next burst of AP generation (Lau et al. 2017). Unlike PCs, interneurons of the CA1 showed a special Hebbian LTP that is independent of NMDAR but involve group I mGlur and AMPAR (Perez et al. 2001). Further ex vivo experiments on mice hippocampal slices showed that subthreshold TBS (thus triggering no AP) can induce anti-Hebbian LTP through CP-AMPAR-driven Ca2+ accumulation (Lamsa et al. 2007; Camiré and Topolnik 2014). On the contrary, suprathreshold TBS (thus producing a signal) creates LTD, weakening the next input. In this case, the transient Ca2+ increase is higher and relies on internal storage in addition to CP-AMPAR contribution (Camiré and Topolnik 2014). Moreover, group I mGlur and cannabinoid receptors have also been implicated in LTD of hippocampal FS neurons (Péterfi et al. 2012). A computational study revealed that internal stores, clearance mechanisms and the specific morphology of the dendrite have a major impact on the calcium summation system of the neuron (Camiré et al. 2018).

Development of PV+ Neurons

Migration

During mouse development (Fig. 3), the majority of PV+ interneurons populating the cortex and the hippocampus comes from the rostral part of the medial ganglionic eminence (MGE), with weakened Wnt signaling (McKenzie et al. 2019). MGE is present from mouse embryonic day 9 (E9) to E16 and generates interneurons from E13.5, which migrate through the marginal or subventricular zone to reach their final destination (Wichterle et al. 2001; Xu 2004). A smaller proportion of fast-spiking BCs arises at E11.5 from the preoptic area (POA), after migration through the marginal zone, the subplate to the cortex and the hippocampus (Gelman et al. 2009; Gelman et al. 2011). Each population begins to migrate tangentially around E14 to E18, then switch to radial migration to invade the cortical plate between E18 and postnatal day 2 (P2) and finally reach the correct layer at P2 to P6.

Several waves of interneurons follow these steps, the first ones settling in deep layers of the cortex while the late ones invading the superficial layers (Bartolini et al. 2013). The existence and the relevance of these diverse paths are not clearly understood yet. Nonetheless, results obtained in a sub-class of SOM+ interneurons indicate that future interneurons could choose one road or another based on their mature morphology and final destinations (Lim et al. 2018b). On the other hand, neurons assigned to the hippocampus preferentially migrate tangentially through the marginal zone towards the stratum lacunosum moleculare and populate all layers of the hippocampus (Ticoire et al. 2011). Recent results suggest that the final concentration of intracellular PV decreases with each wave of interneurons, as early-born PV+ neurons display stronger PV signal than late-born PV+ neurons in the hippocampus, somatosensory cortex, and dorsal striatum (Donato et al. 2015).

After the disappearance of the MGE around E16, the ventral germinal zone of the lateral ventricle (VZ) continues to generate interneurons, including the majority of ChC (even though a small fraction of them were generated earlier by the MGE) (Inan et al. 2012; Taniguchi et al. 2013). After the tangential migration around P0, neurons will cross the cortical plate around P2 to spread a little more at the cortical surface between P4 and P6 and finally invade cortical layers around P7 (Fig. 3) (Taniguchi et al. 2013). If some other subtypes of interneurons have postnatal sources to replenish their ranks (Inta et al. 2008; Wu et al. 2011; Riccio et al. 2012), it is yet to be proven for PV+ neurons. The migration of interneurons and their early diversification is a well-orchestrated mechanism that we are slowly beginning to grasp. As 2 recent reviews have dissected them in detail (Peyre et al. 2015; Lim et al. 2018a), we will not linger on those phenomena.
As reported by several authors, the first 2 postnatal weeks are characterized by a 40%–50% decrease in the density of different cell types, including interneurons (either in cortical or hippocampal structures) (López-Bendito et al. 2004; Tricoire et al. 2011). This phase corresponds to an increase in the whole brain volume, but stainings have proven that programmed cell death is also at play (Verney et al. 2000; Southwell et al. 2012; Denaxa et al. 2018; Priya et al. 2018). Indeed, the number of interneurons is to be tightly regulated: the loss of specific inhibitory cortical subpopulations is compensated by other subtypes or grafted interneurons to preserve the ratio of excitatory versus inhibitory neurons (Azim et al. 2009; Batista-Brito et al. 2009; Lodato et al. 2011; Denaxa et al. 2018). This reduction of inhibitory neuron density could be linked to network activity, as blocking NMDA receptors increases the number of apoptotic cells in the cortex (Roux et al. 2015). Also, brain regions showing higher network activities present reduced apoptosis of cortical neurons (Blanquie et al. 2017). A recent report shows that, in most interneurons, the network activity reduces postnatal cell death through activation of the Calcineurin protein (Priya et al. 2018).

**Maturation**

Regarding PV+ neurons, the first weeks of life are also marked by profound changes and maturations. Different studies have found that the fast profile of cortical and hippocampal BCs is reached between P7 and P25 (Itami et al. 2007; Doischer et al. 2008), after the switch from excitatory to inhibitory GABAergic signal (Rivera et al. 1999).

In the cortex, this modification of the firing profile is accompanied by changes in gene expression that could explain some electrophysiological parameters, e.g., 1) the down-regulation of Kcnm2, encoding for the small conductance Ca^{2+}-activated K⁺ channel, which could favor the depressing profile observed from P10 or 2 the up-regulation of Kcn1 and Kcn2 genes (corresponding to the Kv3 potassium channel type) could account for the increased firing rates and reduced spikes from P10 (Okaty et al. 2009). Indeed, the blockade of Kv3 channels at P10 has little effect in PV+ neurons, whereas inducing a massive increase in IPSC in PCs at P18, confirming the upregulation of Kv3 channels and their effect on synaptic depression (Goldberg et al. 2011). Between P10 and P18, a K⁺ leak current appears, influencing the resting membrane potential (RMP) and the membrane resistance (Rm).
of PV+ neurons. At least K_{v}2 and K_{v}3 channels participate, as RMP and R_A are modified upon application of specific blockers (Goldberg et al. 2011).

This critical period also corresponds to the settling of the Ca^{2+} managing system. Several Ca^{2+} channel subunits, which form low-voltage threshold (T-type: Cacna1g) or long-lasting activation (L-type: Cacna4, Cacnb1) channels, are down-regulated, presuming narrower regulation of Ca^{2+} flux. Indeed, the PV protein and the plasma membrane Ca^{2+}-ATPase are also upregulated, inducing a tighter control of intracytoplasmic Ca^{2+} concentration (Okaty et al. 2009). The fastest calcium-sensor Syt2, used as BC marker in the visual cortex, is also upregulated from P10 to P18 (Sommeijer and Levelt 2012). Interestingly, electrical synapses between PV+ neurons can already be observed at P10, even if the arborization is not yet fully matured (Goldberg et al. 2011).

As for apoptosis, the correct maturation of PV+ interneuron also relies on network activity. In the cortex, GluN2C and D sub-units of NMDA receptors help to establish the neuronal arborization (Hanson et al. 2019), whereas the GluN2A subunit is needed to face oxidative reactions and to establish the perineuronal net (PNN) (Cardis et al. 2018). The PNN is a specific type of extracellular matrix that surrounds several neurons and their dendrites. The PNN is composed of proteoglycan (PG), hyaluronan and smaller molecules synthesized by neurons and neighboring glial cells (John et al. 2006; Carulli et al. 2007). Different associations of PG can form these PNNs. PNNs in cortical BCs, (but not in ChCs), are composed of chondroitin sulfate, keratan sulfate, and brevican PG (Wegner et al. 2003; Takeda-Uchimura et al. 2015; Favuzzi et al. 2017; Yamada and Jinno 2017). The PNN is settled from P10 to P30, mostly around cortical PV+ neurons and its establishment is influenced by received inputs and stimuli (McRae et al. 2007; Ye and Miao 2013; Ueno, Suemitsu, Murakami et al. 2017a). Some studies demonstrated that the magnitude, shape, and content of PNN associated with PV+ neurons can vary between the regions of the brain (Yamada and Jinno 2013; Ueno, Suemitsu, Okamoto et al. 2017b). PNNs are well known to influence synaptic plasticity and may have a subtler role than only a physical barrier preventing synapse establishment. PNNs can bind molecules such as β-Integrin in the hippocampus or Sema3A in the cortex, respectively, preventing their promoting role in spine formation (Orlando et al. 2012) or enabling their inhibitory action (Ve et al. 2013). Indeed, the PNN may impact the cortical neuron without complete network digestion, but rather via the change of sulfation pattern involved in protein binding (Miyata et al. 2012; Miyata and Kitagawa 2016). PNNs also modulate receptor activity by acting 1) directly as a physical fence, as demonstrated for the AMPAR GluA1 and 2 receptors (Frischknecht et al. 2009), or 2) indirectly by sequestering or accumulating partners. For example, the neuronal-pentraxin 2 (NP2 encoded by the Narp gene) modulates GluA4 in hippocampal PV+ neurons after being secreted, only in the presence of PNN (Chang et al. 2011). Finally, PNNs are also involved in the trafficking and the clustering of K+ channel Kv1.1 and 3.1 in the hippocampus (Favuzzi et al. 2017).

Concerning maturation, less information is known about ChCs. Some papers have highlighted a slower establishment of synapses and FS properties in mouse cortical ChCs, compared to BCs (Miyamae et al. 2017; Pan-Vazquez et al. 2020). Nonetheless, one specific feature of maturing ChCs is still under debate: ChCs may remain excitatory longer than other inhibitory neurons. At first, the high intraneuronal Cl− concentration makes GABA inputs depolarizing, and consequently all “inhibitory” neurons remain excitatory. Around P7 in mouse, the expression of symporter KCC2 rises and shifts the Cl− gradient to induce the hyperpolarizing effect of inhibitory neurons (Rivera et al. 1999; Ben-ari 2002). Yet, several teams have observed depolarizing input coming from ChCs in cortices and hippocampi of rodent between P15 and P35 (Szabadics et al. 2006; Khirug et al. 2008; Woodruff et al. 2011). As interneurons connect to different parts of their targets, those observations could be explained by local change of Cl− concentration gradient. In mouse cortical neurons, KCC2 expression rises later in the AIS, which could explain why ChCs would remain depolarizing longer than BCs (Rinetti-Vargas et al. 2017; Pan-Vazquez et al. 2020).

The late maturation of PV+ neurons, simultaneous to the establishment of the synaptic network, makes them a pivotal actor in neurodevelopmental and neurodegeneration diseases (van Bokhoven et al. 2018; Ferguson and Gao 2018; Wen et al. 2018).

Parvalbumin Neurons in Epilepsy

PV+ neurons display a strong ability to decrease the global brain excitability and are thought to play a role in epilepsy. Epilepsy is a group of disorders commonly characterized by the recurrent appearance of seizures, which consist of abnormal and highly synchronous brain activity and AP discharges. The cause of these diseases can sometimes be identified (i.e., genetic, traumatic, hemorrhagic . . .), but is unknown in most cases (i.e., idopathic or cryptogenic epilepsy). Epilepsy is a chronic disease with very acute expression, and patients suffering from epilepsy are treated to control seizures onset rather than handling the cause of the disease. Epilepsy being an evolving disorder (frequency and severity of seizures can change over time), treatments have to be regularly adjusted. Moreover, one-third of epileptic cases are “refractory” or “intractable” to current antiepileptic treatments (Chen et al. 2018; Faraji and Richardson 2018).

Epilepsy is thought to be linked to a failure of the excitatory to inhibitory balance (E/I balance), and PV+ neurons were rapidly assumed to participate in icotogenesis (seizure onset) or epileptogenesis (epilepsy appearance and evolution). Indeed, several studies have shown that PV+ neuron density is reduced in epileptic tissue of animal models, as well as in human patients (Zamcnik et al. 2006; Kuruba et al. 2011; Marx et al. 2013; Nakagawa et al. 2017; Cameron et al. 2019; Alhourni et al. 2020). Interestingly, a recent paper observed an increased mitochondrial fragmentation in rat PV+ neurons following induced status epilepticus. Moreover, they show that reducing mitochondrial fission with chemical inhibitor mitigate PV+ neuron loss (Kim and Kang 2017). However, other teams observed a normal number of PV+ neurons with an altered electrophysiological profile or morphology in different animal models with induced seizures (Sun et al. 2007; Gu et al. 2017; Miri et al. 2018). Following experimental observation in mice, it has also been proposed that the parvalbumin protein itself could be lost, rather than the whole PV+ neuronal population, due to Ca^{2+} overload and excessive recruitment of interneuron (Wittner et al. 2001; Wittner and Maglóczy 2017). Given the diversity of causes and symptoms of epilepsy, as well as animal models, finding a consensus is a struggle. Anyway, these observations suggest an increased vulnerability of PV+ neurons in epilepsy but give little information on the role of PV+ neurons in epileptogenesis.

Many genetic mutations in PV+ neurons have been proposed to play a role in epilepsy and were even detected in patients. Many of those have been reviewed by Jiang, Lachance and Rossignol in 2016 (Jiang et al. 2016). In this paper, authors analyzed alterations of PV+ neurons in terms of migration, maturation, excitability, or connectivity. But, from 2016, the list is still growing
and we will thus focus here on several recent findings. Ankyrin-G participates in the clustering of ion channels in nodes of Ranvier and the AIS. In absence of the PV+ specific ankyrin-G isoform 1b, PV+ neurons have reduced excitability, leading to seizures and behavioral alteration associated with bipolar disorder (Lopez et al. 2017). CNTNAP2, a protein belonging to the pre-synaptic cell-adhesion protein family neurexin, is associated with many neurological disorders, including epilepsy. A team recently showed that FS cortical neurons mutated for CNTNAP2 present altered AP width or intern spike interval when transplanted into wild-type mice cortices (Vogt et al. 2018). Even more recently, it was shown that the absence of NHE1 (the Na+/H+ exchanger expressed in neurons and astrocytes) in mouse hippocampal PV+ neurons decreases the frequency and increases the amplitude of mIPSC, probably due to K+ influx into the cell (Fujiwara-Tsukamoto et al. 2020). Recently, it was shown that the absence of NHE1 (the Na+/H+ exchanger expressed in neurons and astrocytes) in mouse hippocampal PV+ neurons decreases the frequency and increases the amplitude of mIPSC, probably due to K+ influx into the cell (Fujiwara-Tsukamoto et al. 2020). Even more recently, it was shown that the absence of NHE1 (the Na+/H+ exchanger expressed in neurons and astrocytes) in mouse hippocampal PV+ neurons decreases the frequency and increases the amplitude of mIPSC, probably due to K+ influx into the cell (Fujiwara-Tsukamoto et al. 2020). Once high, the extracellular K+ concentration eases the depolarization of the excitatory cell, completely free to fire as inhibitory neurons are not active anymore because recovering from the DB. Furthermore, it has been demonstrated that PV+ neurons are recruited before SOM+ neurons and that these 2 populations could be needed to damp seizures (Parrish et al. 2019).

When excessive excitation stimulates interneurons (Fig. 4), the first-line cells are PV+ neurons targeting the soma of the glutamatergic neurons. PV+ neurons strongly and quickly induce inhibition, leading to a surge of Cl− inside the somatic compartment of the PC, which could sustain ion entry for a while, thanks to K+/Cl− symporter like KCC2. Once PV+ neurons are depressed, the second line is represented by SOM+ neurons, which then prevent massive excitation of glutamatergic neurons. SOM+ neurons provide a long-lasting inhibition, maintaining the non-responsive state of PCs that PV+ neurons have begun to build. If PV+ neurons remain active or reactivate, they could saturate PC in Cl− that may start diffusing, overtaking KCC2 capacity. This would impact the dendritic domain, inducing an increase of extracellular K+ where PC receives excitatory drive. SOM+ neurons will not be sufficient to maintain inhibition, and the PC will begin to frenetically fire. Another possibility could involve extrasynaptic GABA receptor, as recently found in SOM+ neurons (Miri et al. 2018).

Interestingly, a reduction of VIP+/CR+ contacts made on OLMs, BiCs, and BCs was reported in the CA1 in pilocarpin mice model. While all interneurons displayed a reduction of spontaneous IPSC frequency, only IPSC amplitudes recorded in BiCs or BCs were decreased after light-evoked VIP+ neuron stimulation. This particular impact on BCs could explain the specific increased activity of PV+ reported by Hansen and Mir (David and Topolnik 2017). The intensity of these inhibitory currents could trigger a massive accumulation of Cl− inside post-synaptic neurons and an increase of extracellular K+ concentration, probably due to K+/Cl− symporter (Fujiwara-Tsukamoto et al. 2007). Once high, the extracellular K+ concentration eases the depolarization of the excitatory cell, completely free to fire as inhibitory neurons are not active anymore because recovering from the DB. Furthermore, it has been demonstrated that PV+ neurons are recruited before SOM+ neurons and that these 2 populations could be needed to damp seizures (Parrish et al. 2019).

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neurons (Bryson et al. 2020). This could explain why PV+ neurons have been reported as a “double agent” in icterogenesis (Shiri et al. 2016; Wang et al. 2017; Lévesque et al. 2019). It has been reported that overexpression of KCC2 prevents the pro-ictal effect of PV+ neurons when stimulated 2 s after a seizure (Majorel et al. 2018). The increased number of KCC2 channels on PC could prevent the spreading of Cl− and keep the increase of extracellular K+ minimal around dendrites.

Conclusion

The last decades have brought to light the crucial role that interneurons play in neurotransmission. Although a minor population, these inhibitory neurons are key fine tuners that regulate signals of projection neurons and have been closely examined after years of being wrongly omitted. As our knowledge piles up, we unravel the broad diversity of interneurons and gain new insights into their various structural, biochemical, and functional aspects. Parvalbumin-positive (PV+) interneurons were characterized based on their specific fast-spiking profile, but beyond this specific characteristic, we keep collecting evidence that indicates they are probably much more diverse than we think. The variety of their neurite arborization, ion balance, synaptic components, and spatial distribution probably confers them miscellaneous functions that we slowly start to grasp.

Epilepsy physiopathology is one example of this specific functionality of these PV+ neurons and by itself, it is not an exception to this rule of diversity. Indeed, it includes a large phenotypical spectrum and is associated with a number of dysregulated molecular and biochemical mechanisms. Getting back to PV+ neurons, growing evidence from the literature sheds light on their role(s) on neuronal networks as they are particularly wired and equipped for influencing those grids. Moreover, these neurons could be the ideal targets for treatment: only a tiny amount of drug acting on this small cell population would be able to trigger a massive effect. Still, this powerful PV+ neuron machinery could turn out to be both ally and enemy for a correct brain function, and the genuine role of these neurons in icterogenesis is yet unclear. Whether an inadequate firing profile is directly linked to seizure, or whether their firing profile is itself impacted by dysregulated essential cellular processes (e.g., energy, transport, cytoskeletal remodeling, etc.) indirectly causing seizure, are questions that should be further investigated.

Much remains to untangle in order to fathom the way PV+ interneurons play in harmony with neighboring neurons, to identify which player in out of tune in pathological conditions, and to ultimately succeed in conducting this orchestra to play a symphony without a false note.

Notes

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References

Alhourani A, Fish KN, Wozny TA, Sudhakar V, Hamilton RL, Richardson RM. 2020. GABA Bouton subpopulations in the human dentate gyrus are differentially altered in mesial temporal lobe epilepsy. J Neurophysiol. 123(1): 392–403.

Andersson SA, Olson AH, Esguerra JLS, Heimann E, Ladenwall C, Edlund A, Salehi A, Taneera J, Degerman E, Groop L, et al. 2012. Reduced insulin secretion correlates with decreased expression of exocytotic genes in pancreatic islets from patients with type 2 diabetes. Mol Cell Endocrinol. 364(1–2): 36–45.

Aponce Y, Bischofberger J, Jonas P. 2008. Efficient Ca2+-buffering in fast-spiking basket cells of rat hippocampus. J Physiol. 586(8): 2061–2075.

Awasthi A, Ramachandran B, Ahmed S, Benito E, Shinoda Y, Nitzan N, Heukamp A, Rannio S, Martens H, Barth J, et al. 2019. Synaptotagmin-3 drives AMPA receptor endocytosis, depression of synapse strength, and forgetting. Science. 363(6422): 1–14.

Azim E, Jabaoud D, Fame R, Macklis JD. 2009. SOX6 controls dorsal-ventral progenitor parcellation and interneuron diversity during neocortical development. Nat Neurosci. 12(10): 1238–1247.

Bartolini G, Ciceri G, Marín O. 2013. Integration of GABAergic interneurons into cortical cell assemblies: lessons from embryos and adults. Neuron. 79(5): 849–864.

Batista-Brito R, Rossignol E, Hjerling-Leffler J, Denaxa M, Wegner M, Lefebvre V, Pachnis V, Fishell G. 2009. The cell-intrinsic requirement of Sox6 for cortical interneuron development. Neuron. 63(4): 466–481.

Ben-ari Y. 2002. Excitatory actions of GABA during development: the nature of the nurture. Nat Rev Neurosci. 3(September): 728–739.

Bhalla A, Chicks MC, Chapman ER. 2008. Analysis of the synaptotagmin family during reconstituted membrane fusion: uncovering a class of inhibitory isoforms. J Biol Chem. 283(31): 21799–21807.

Blanquie O, Yang J-W, Kilb W, Sharopov S, Sinning A, Luhmann HJ. 2017. Electrical activity controls area-specific expression of neuronal apoptosis in the mouse developing cerebral cortex. Elife. 6:1–21.

Bocker HT, Heinrich T, Liebmann L, Hennings JC, Seemann E, Gerth M, Jakóvczevski I, Preobraschenski J, Kessels MM, Westermann M, et al. 2019. The Na+H+ exchanger Nhe1 modulates network excitability via GABA release. Cereb Cortex. 29(10): 4263–4276.

Bornschein G, Schmidt H. 2019. Synaptotagmin Ca2+ sensors and their spatial coupling to presynaptic Cav channels in central cortical synapses. Front Mol Neurosci. 11(January): 1–15.

Bottoms CA, Schuermann JP, Agah S, Henzl MT, Tanner JJ. 2004. Crystal structure of rat alpha-parvalbumin at 1.05 Å resolution. Protein Sci. 13: 1724–1734.

Bouhours B, Gjonj E, Kochubey O, Schneggenburger R. 2017. Synaptotagmin2 (Syt2) drives fast release redundantly with Syt1 at the output synapses of Parvalbumin-expressing inhibitory neurons. J Neurosci. 37(17): 4604–4617.

Bryson A, Hatch RJ, Zandt BJ, Rossert C, Berkovic SF, Reid CA, Grayden DB, Hill SL, Petrov S. 2020. GABA-mediated tonic inhibition differentially modulates gain in functional subtypes of cortical interneurons. Proc Natl Acad Sci U S A. 117(6): 3192–3202.

Bucurenciu I, Bischofberger J, Jonas P. 2010. A small number of open Ca2+ channels trigger transmitter release at a central GABAergic synapse. Nat Neurosci. 13(1): 19–21.
Bucurenciu I, Kulik A, Schwaller B, Frotscher M, Jonas P. 2008. Nanodomain coupling between Ca2+ channels and Ca2+ sensors promotes fast and efficient transmitter release at a cortical GABAergic synapse. Neuron. 57(4):536–545.

Buhl EH, Halasy K, Peter S. 1994. Diverse sources of hippocampal unitary inhibitory postsynaptic potentials and number of synaptic release sites. Nature. 368(28 april):823–828.

Cameron S, Lopez A, Glabman R, Abrams E, Johnson S, Field C, Gulland FMD, Buckmaster PS. 2019. Proportional loss of parvalbumin-immunoreactive synaptic boutons and granule cells from the hippocampus of sea lions with temporal lobe epilepsy. J Comp Neurol. 527(14):2341–2355.

Camiré O, Lazarevich I, Gilbert T, Topolnik L. 2018. Mechanisms of Supralinear calcium integration in dendrites of hippocampal CA1 fast-spiking cells. Front Synaptic Neurosci. 10(December):1–16.

Camiré O, Topolnik L. 2014. Dendritic calcium nonlinearities switch the direction of synaptic plasticity in fast-spiking interneurons. J Neurosci. 34(11):3864–3877.

Cardis R, Cabungcal JH, Dwir D, Do KQ, Steullet P. 2018. A lack of GluN2A-containing NMDA receptors confers a vulnerability to redox dysregulation: consequences on parvalbumin interneurons, and their perineuronal nets. Neurobiol Dis. 109(7uly 2017):64–75.

Carulli D, Rhodes KE, Fawcett JW. 2007. Upregulation of Aggrecan, link protein 1, and Hyaluronal syntheases during formation of perineuronal nets in the rat cerebellum. J Comp Neurol. 501:83–94.

Chang MC, Park JM, Pelkey KA, Grabenstatter HL, Xu D, Linden D, Sutula TP, Mcbain CJ, Worley PF. 2011. Narp regulates homeostatic scaling of excitatory synapses on Parvalbumin interneurons. Nat Neurosci. 13(9):1090–1097.

Chen Z, Brodie MJ, Liew D, Kwan P. 2018. Treatment outcomes in patients with newly diagnosed epilepsy treated with established and new antiepileptic drugs a 30-year longitudinal study. JAMA Neurol. 75(3):279–286.

Chen J, Jonas P. 2017. Synaptotagmins: That’s why so many. Neuron. 94(4):694–696.

Chen C, Satterfield R, Smy J, Jonas P. 2017. Triple function of Synaptotagmin 7 ensures efficiency of high-frequency transmission at central GABAergic synapses. Cell Rep. 21(8):2082–2089.

Chiavini B, Turi GF, Katona G, Kémlo S, Lódi P, Búrton J, Pachnis V. 2018. Modulation of apoptosis controls inhibitory interneuron number in the cortex. Cell Rep. 22(7):1710–1721.

Doischer D, Aurel Hosp J, Yanagawa Y, Obata K, Jonas P, Vidá I, Bartos M. 2008. Postnatal differentiation of basket cells from slow to fast signaling devices. J Neurosci. 28(48):12956–12968.

Donato F, Chowdhury A, Lahr M, Caroni P. 2015. Early- and late-born Parvalbumin basket cell subpopulations exhibiting distinct regulation and roles in learning. Neuron. 85(4):770–786.

Eggermann E, Bucurenciu I, Goswami SP, Jonas P. 2012. Nanodomain coupling between Ca2+-channels and sensors of exocytosis at fast mammalian synapses. Nat Rev Neurosci. 13(1):7–21.

Eggermann E, Jonas P. 2012. How the “slow” Ca2+ buffer parvalbumin affects transmitter release in nanodomain-coupling regimes. Nat Neurosci. 15(1):20–22.

Faraji AH, Richardson RM. 2018. New antiepileptic drugs have not improved treatment outcomes. Clin Neurosurg. 82(5):1.

Favuzzi E, Marques-Smith A, Maeso P, Jezequel J, Exposito-Alonso D, Balia M, Kroon T, Hinojosa AJ, Maraver EF, et al. 2019. Neurodevelopment: distinct molecular programs regulate synapse specificity in cortical inhibitory circuits. Science. 363(6425):413–417.

Favuzzi E, Marques-Smith A, Deogracias R, Winterfeldt CM, Sánchez-Aguilera A, Mantoan L, Maeso P, Fernandes C, Ewers H, Rico B. 2017. Activity-dependent gating of Parvalbumin interneuron function by the Perineuronal net protein Brevican. Neuron. 95(3):639–655.

Ferguson BR, Gao WJ. 2018. Pv interneurons: critical regulators of E/I balance for prefrontal cortex-dependent behavior and psychiatric disorders. Front Neural Circuits. 12(May):1–13.

Foggetti A, Baccini G, Arnold P, Schifferholz T, Wulff P. 2019. Spiny and non-spiny Parvalbumin-positive hippocampal interneurons show different plastic properties. Cell Rep. 27(13):3725–3732.

Fricker D, Miles R. 2000. EPSP amplification and the precision of spike timing in hippocampal neurons. Neuron. 28(2):559–569.

Frischnecht R, Heine M, Perrais D, Seidenbecher CI, Choquet D, Gundelfinger ED. 2009. Brain extracellular matrix affects AMPA receptor lateral mobility and short-term synaptic plasticity. Nat Neurosci. 12(7):897–904.

Fujisawa-Tsukamoto Y, Isomura Y, Imanishi M, Fukui T, Takada M. 2007. Distinct types of ionic modulation of GABA actions in pyramidal cells and interneurons during electrical induction of hippocampal seizure-like network activity. Eur J Neurosci. 25(9):2713–2725.

Fujisawa-Tsukamoto Y, Isomura Y, Kaneda K, Takada M. 2004. Synaptic interactions between pyramidal cells and interneurone subtypes during seizure-like activity in the rat hippocampus. J Physiol. 557(3):961–979.

Galarreta M, Hestrin S. 1999. A network of fast-spiking cells in the neocortex connected by electrical synapses. Nature. 402(6757):72–75.

Geiger JRP, Lübke J, Roth A, Frotscher M, Jonas P. 1997. Submillisecond AMPA receptor-mediated signaling at a principal neuron-interneuron synapse. Neuron. 18(6):1009–1023.
Geiger JRP, Melcher T, Koh DS, Sakmann B, Seeburg PH, Jonas P, Monyer H. 1995. Relative abundance of subunit mRNAs determines gating and Ca2+-permeability of AMPA receptors in principal neurons and interneurons in rat CNS. Neuron. 15(1):193–204.

Gelman D, Griveau A, Dehorter T, Teissier A, Varela C, Pla R, Pierani A, Marin O. 2011. A wide diversity of cortical GABAergic interneurons derives from the embryonic preoptic area. J Neurosci. 31(46):16570–16580.

Gelman DM, Martini FJ, Nobrega-Pereira S, Pierani A, Kessaris N, Gulyás AI, Mlles R, Hájos N, Freund TF. 1993. Precision and variability in the CA1 area of the rat hippocampus. J Neurosci. 29(23):9380–9389.

Goldberg EM, Jeong HY, Kruglikov I, Tremblay R, Lazarenko RM, Geiger JRP, Melcher T, Lazarenko RM, Koh DS, Sakmann B, Seeburg PH, Jonas P, Monyer H. 2011. A wide diversity of cortical GABAergic interneurons. J Neurosci. 31(46):16570–16580.

Goldberg JH, Yuste R, Tamas G. 2003b. Ca2+-dependent insulin secretion vesicles. Dev Cell. 5(3):347–361.

Goldberg JH, Tamas G, Yuste R. 2003a. Ca2+-dependent insulin secretion vesicles. Dev Cell. 5(3):347–361.

Grasse DW, Karunakaran S, Moxon KA. 2013. Neuronal synchrony and the transition to spontaneous seizures. Exp Neurol. 248:72–84.

Gu F, Parada I, Shen F, Li J, Bacci A, Graber K, Taghavi RM, Scalise K, Schwartzkroin P, Wenzel J, et al. 2017. Structural alterations in fast-spiking GABAergic interneurons in a model of posttraumatic neocortical epileptogenesis. Neurobiol Dis. 108:100–114.

Gulyás AI, Megías M, Emri Z, Freund TF, Gulyás AI, Megías M, Emri Z, Freund TF. 1999. Total number and ratio of excitatory and inhibitory synapses converging onto single interneurons of different types in the CA1 area of the rat hippocampus. J Neurosci. 19(22):10082–10097.

Gulyás AI, Miles R, Hájos N, Freund TF. 1993. Precision and variability in postsynaptic target selection of inhibitory cells in the hippocampal CA3 region. Eur J Neurosci. 5(12):1729–1751.

Halasy K, Buhl EH, Lörinczi ZZZ, Tamas G, Somogyi P, Tamás G, Somogyi P, Tamas G, Somogyi P. 2002. Synaptic target selectivity and input of GABAergic basket and bistratified interneurons in the CA1 area of the rat hippocampus. Hippocampus. 6(3):306–329.

Hansen MG, Ledri LN, Kirik D, Kokaia M, Martina M. 2018. Preserved function of afferent Parvalbumin-positive Perisomatic inhibitory synapses of dentate granule cells in rapidly kindled mice. Front Cell Neurosci. 11(January):1–13.

Hanson E, Armbruster M, Lau LA, Sommer ME, Klaft Z-JJ, Swanger SA, Traynelis SF, Moss SJ, Noubary F, Chadhanchkar J, et al. 2019. Tonic activation of GluN2C/GluN2D-containing NMDA receptors by ambient glutamate facilitates cortical interneuron maturation. J Neurosci. 39(19):3611–3626.

Haucke V, Wenk MR, Chapman ER, Farsad K, De CP. 2000. Dual interaction of synaptotagmin with µ2- and alpha-adaptin facilitates clathrin-coated pit nucleation. EMBO J. 19(22):6011–6019.

Hefft S, Jonas P. 2005. Asynchronous GABA release generates long-lasting inhibition at a hippocampal interneuron–principal neuron synapse. Nat Neurosci. 8(10):1319–1328.

Hendry SHC, Jones EG, Emson PC, Lawson DEM, Heizmann CW, Streit P. 1989. Two classes of cortical GABA neurons defined by differential calcium binding protein immunoreactivities. Exp Brain Res. 76(2):467–472.

Herculano-Houzel S, Mota B, Lent R. 2006. Cellular scaling rules for rodent brains. Proc Natl Acad Sci U S A. 103(32):12138–12143.
Rossignol E, Kruglikov I, van den MAMJM, Rudy B, Fishell G. 2013. Characterization of focal cortical dysplasia with balloon cells by layer-specific markers: evidence for differential vulnerability of interneurons. Epilepsia. 58(4):635–645.

Ogiwara I, Miyamoto H, Morita N, Atapour N, Mazaki E, Inoue I, Takeuchi T, Itohara S, Yanagawa Y, Obata K, et al. 2007. Nav1.1 localizes to axons of Parvalbumin-positive inhibitory interneurons: a circuit basis for epileptic seizures in mice carrying an Scn1a gene mutation. J Neurosci. 27(22):5903–5914.

Okaty BW, Miller MN, Sugino K, Hempel CM, Nelson SB. 2009. Transcriptional and electrophysiological maturation of neocortical fastspiking GABAergic interneurons. J Neurosci. 29(21):7040–7052.

Orlando C, Ster J, Gerber U, Fawcett JW, Raineteau O. 2012. Perisynaptic chondroitin sulfate proteoglycans restrict structural plasticity in an integrin-dependent manner. J Neurosci. 32(50):18009–18017.

Pan-Vazquez A, Weifelmayr W, Gonzalez Sabater V, Neves G, Burrone J. 2020. Activity-dependent plasticity of A xo-axonic synapses at the axon initial segment. Neuro. 106(2):265–276.

Parrish RR, Codadu NK, Mackenzie-Gray Scott C, Trevelyan AJ. 2019. Feedforward inhibition ahead of ictal wavefronts is an ex vivo and in vivo study in Gad67-GFP mice. Exp Neurol. 267:177–193.

Rudy B, Mcbain CJ. 2001. Kv3 channels: voltage-gated K+ channels designed for high-frequency repetitive firing. Trends Neuro. 24(6):307–309.

Saegusa C, Fukuda M, Mikoshiba K. 2002. Synaptotagmin V is targeted to dense-core vesicles that undergo calcium-dependent exocytosis in PC12 cells. J Biol Chem. 277(27):24499–24505.

Sancho I, Bloodgood BL. 2018. Functional distinctions between spine and dendritic synapses made onto Parvalbumin-positive interneurons in mouse cortex. Cell Rep. 24(8):2075–2087.

Schwaller B. 2009. The continuing disappearance of “pure” Ca2+ buffers. Cell Mol Life Sci. 66(2):275–300.

Shirai S, Manseau F, Lévesque M, Williams S, Avoli M. 2016. Activation of specific neuronal networks leads to different seizure onset types. Ann Neurol. 79(3):354–365.

Sik A, Penttonen M, Ylilnana J, Buzsáki G, Buzsáki G. 1995. Hippocampal CA1 interneurons: an in vivo intracellular labeling study. J Neurosci. 15(10):6651–6665.

Soh H, Park S, Ryan K, Springer K, Maheshwari A, Tzingounis AV. 2018. Depletion of KCNQ2/3 potassium channels from PV interneurons leads to homeostatic potentiation of excitatory transmission. Elife. 7:1–14.

Sommerje P, Levelt CN. 2012. Synaptotagmin-2 is a reliable marker for parvalbumin positive inhibitory boutons in the mouse visual cortex. PLoS One. 7(4):e1–12.

Somogyi P, Klausberger T. 2005. Defined types of cortical interneuron structure space and spike timing in the hippocampus. J Physiol. 562(1):9–26.

Southwell DG, Paredes MF, Galvao RP, Jones DL, Froemke RC, Sebe JY, Alfaro-cervello C, Chang Y, Jose M, Rubenstein JL, et al. 2012. Intrinsically determined cell death of developing cortical interneurons. Nature. 491(7422):109–113.

Sun C, Mchedlishvili Z, Bertram EH, Erisir A, Kapur J. 2007. Selective loss of dentate hilar interneurons contributes to reduced synaptic inhibition of granule cells in an electrical stimulation-based animal model of temporal lobe epilepsy. J Comp Neurol. 500(5):876–893.

Sun Q-QQ, Zhang Z, Jiao Y, Zhang C, Szabó G, Erdelyi F. 2009. Differential metabotropic glutamate receptor expression and modulation in two neocortical inhibitory networks. J Neurophysiol. 101(5):2679–2692.

Szabadics J, Varga C, Molnar G, Olah S, Barzo P, Tamas G. 2006. Excitatory effect of GABAergic Axo-Axonic cells in cortical microcircuits. Science. 311:233–235.

Takeda-Uchimura Y, Uchimura K, Sugimura T, Yanagawa Y, Kawasaki T, Komatsu Y, Kadoshita K. 2015. Requirement of keratin sulfate proteoglycan phosphacan with a specific sulfation pattern for critical period plasticity in the visual cortex. Exp Neurol. 274:145–155.

Talos DM, Fishman RE, Park H, Folkert RD, Follett PL, Volpe JJ, Jensen FE. 2006. Developmental regulation of alpha-Amino-3- Hydroxy-5-Methyl-4-Isoxazole-propionic acid receptor subunit expression in forebrain and relationship to regional susceptibility to hypoxic/ischemic injury. I. Rodent cerebral white matter and cortex. J Comp Neurol. 497:42–60.

Tamas G, Buhl EH, Lörincz A, Somogyi P. 2000. Proximally targeted GABAergic synapses and gap junctions synchronize cortical interneurons. Nat Neurosci. 3(4):232–238.
Tanimuchi H, Lu J, Huang ZJ. 2013. The spatial and temporal origin of chandelier cells in mouse neocortex. Science. 339(615): 70–74.

Tasic B, Menon V, Nguyen TN, Kim TK, Jarsky T, Yao Z, Levi B, Gray LT, Sorensen SA, Dolbeare T, et al. 2016. Adult mouse cortical cell taxonomy revealed by single cell transcriptomics. Nat Neurosci. 19(2):335–346.

Tasic B, Yao Z, Graybeck LT, Smith KA, Nguyen TN, Bertagnolli D, Goldy J, Garren E, Economo MN, Viswanathan S, et al. 2018. Shared and distinct transcriptomic cell types across neocortical areas. Nature. 563(7729):72–78.

Ting JT, Kelsoy BG, Sullivan JM. 2006. Synaptotagmin IV does not alter excitatory fast synaptic transmission or fusion pore kinetics in mammalian CNS neurons. J Neurosci. 26(2):372–380.

Tovar KR, Westbrook GL. 2017. Modulating synaptic NMDA receptors: a tutorial. Neuropharmacology. 112:29–33.

Traynelis SF, Wollmuth LP, McBain CJ, Menitti FS, Vance KM, Ogden KK, Hansen KB, Yuan H, Myers SJ, Dingledine R. 2010. Glutamate receptor ion channels: structure, regulation, and function. Pharmacol Rev. 62(3):405–496.

Tremblay R, Lee S, Rudy B. 2016. GABAergic interneurons in the neocortex: from cellular properties to circuits. Neuron. 91(2):260–292.

Tricoire L, Pelkey KA, Erkilia BE, Jeffries BW, Yuan H, McBain CJ. 2011. A blueprint for the spatiotemporal origins of mouse hippocampal interneuron diversity. J Neurosci. 31(30):10948–10970.

Tukker JJ, Lasztoczi B, Katona L, Roberts JDB, Pissadaki EK, Dailezos Y, Marton L, Zhang I, Klausberger T, Somogyi P. 2013. Distinct dendritic Arborization and in vivo firing patterns of Parvalbumin-expressing basket cells in the hippocampal area CA3. J Neurosci. 33(16):6809–6825.

Ueno H, Suemitsu S, Murakami S, Kitamura N, Wani K, Okamoto M, Aoki S, Ishihara T. 2017a. Postnatal development of GABAergic interneurons and perineuronal nets in mouse temporal cortex subregions. Int J Dev Neurosci. 63:27–37.

Ueno H, Suemitsu S, Okamoto M, Matsumoto Y, Ishihara T. 2017b. Parvalbumin neurons and perineuronal nets in the mouse prefrontal cortex. Neuroscience. 343:115–127.

van Bokhoven H, Selten M, Nadif Kasri N. 2018. Inhibitory control of the excitatory/inhibitory balance in psychiatric disorders. F1000Research. 7(0):1–16.

van Hooft JA, Giuffrida R, Blatow M, Monyer H. 2018. Differential expression of group I metabotropic glutamate receptors in functionally distinct hippocampal interneurons. J Neurosci. 20(10):3544–3551.

Verney C, Takahashi T, Bhide PG, Nowakowski RS, Caviness VS. 2000. Independent controls for neocortical neuron production and histogenetic cell death. Dev Neurosci. 22(1–2):125–138.

Vo T, Carulli D, Ehler EM, Kwok JCF, Dick G, Mecollari V, Moloney EB, Neufeld G, de Winter F, Fawcett JW, et al. 2013. The chemorepellent axon guidance protein semaphorin3A is a constituent of perineuronal nets in the adult rodent brain. Mol Cell Neurosci. 56:186–200.

Vogt D, Cho KKA, Shelton SM, Paul A, Huang ZJ, Sohal VS, Rubenstein JLR. 2018. Mouse Cntnap2 and human CNTNAP2 ASD alleles cell autonomously regulate PV + cortical interneurons. Cereb Cortex. 28(September 2017):3868–3879.

von Bartheld CS, Balneey J, Herculano-Houzel S. 2016. The search for true numbers of neurons and glial cells in the human brain: a review of 150 years of cell counting. J Comp Neurol. 524(18):3865–3895.

von Engelhardt J, Bocklisch C, Tönges L, Herb A, Mishina M, Monyer H. 2015. GluN2D-containing NMDA receptorsmediate synaptic currents in hippocampal interneurons and pyramidal cells in juvenile mice. Front Cell Neurosci. 9(March):1–16.

Vreugdenhil M, Jefferys JGRR, Celio MR, Schwanler B. 2006. Parvalbumin-deficiency facilitates repetitive IPCs and gamma oscillations in the hippocampus. J Neuropysiol. 89(3):1414–1422.

Wang C, Grishanin R, Earles C, Chang P, Martin T, Chapman E, Jackson M. 2001. Synaptotagmin modulation of fusion pore kinetics in regulated exocytosis of dense-core vesicles. Science. 294(November):1111–1115.

Wang C, Kang X, Zhou L, Chai Z, Wu Q, Huang R, Xu H, Hu M, Sun X, Sun S, et al. 2018. Synaptotagmin-11 is a critical mediator of parkin-linked neurotoxicity and Parkinson’s disease-like pathology. Nat Commun. 9(1):1–14.

Wang C-T, Lu J-C, Bai J, Chang PY, Martin TFJ, Chapman ER, Jackson MB. 2003. Different domains of synaptotagmin control the choice between kiss-and-run and full fusion. Nature. 424(6951):943–947.

Wang C, Wang Y, Hu M, Chai Z, Wu Q, Huang R, Han W, Zhang CX, Zhou Z. 2016. Synaptotagmin-11 inhibits clathrin-mediated and bulk endocytosis. EMBO Rep. 17(1):47–63.

Wang Y, Xu C, Xu Z, Ji C, Liang J, Wang Y, Chen B, Wu X, Gao F, Wang S, et al. 2017. Erratum: depolarized GABAergic signaling in Subicular microcircuits mediates generalized seizure in temporal lobe epilepsy. Neuron. 95(5):1221.

Wegner F, Hättig W, Bringmann A, Grosche J, Wohlfarth K, Zschatterer W, Brückner G, Hartig W, Bringmann A, Grosche J, et al. 2003. Diffuse perineuronal nets and modified pyramidal cells immunoreactive for glutamate and the GABA receptor α1 subunit form a unique entity in rat cerebral cortex. Exp Neurol. 184(2):705–714.

Wen TH, Binder DK, Ethell IM, Razak KA. 2018. The Perineuronal ‘safety’ net? Perineuronal net abnormalities in neurological disorders. Front Mol Neurosci. 11(August):1–17.

Wichterle H, Turnbull DH, Nery S, Fishell G, Alvarez-Buylla A. 2001. In utero fate mapping reveals distinct migratory pathways and fates of neurons born in the mammalian basal forebrain. Development. 128(19):3759–3771.

Wittner I, Magločzky Z. 2017. Synaptic reorganization of the Perisomatic inhibitory network in hippocampal of temporal lobe epileptic patients. Biomed Res Int. 2017:1–13.

Wittner I, Maglóczky Z, Borhegyi P, Halasz S, Toth L, Erross L, Szabo Z, Freund TF. 2001. Preservation of Perisomatic inhibitory input of granule in juvenile mice. Neuroscience. 108(4):587–600.

Woodruff AR, McGarry LM, Vogels TP, Inan M, Anderson SA, Yuste R. 2011. State-dependent function of neocortical chandelier cells. J Neurosci. 31(49):17872–17886.

Wu S, Esumi S, Watanabe K, Chen J, Nakamura KC, Nakamura K, Kometani K, Minato N, Yanagawa Y, Akashi K, et al. 2011. Tangential migration and proliferation of intermediate progenitors of GABAergic neurons in the mouse telencephalon. Development. 138(12):2499–2509.

Wu X, Hu S, Kang X, Wang C 2020. Synaptotagmins: beyond presynaptic neurotransmitter release. Neurosci. 26(1):9–15.

Xu Q, Xie Q, Qiu Z, Li J, Wang L, Zhang X, Jin X, Sun H, Li Y, Wu X, et al. 2015. Synaptic reorganization in the hippocampus of temporal lobe epileptic patients. Neurosci. 253:368–379.
Yamada J, Jinno S. 2017. Molecular heterogeneity of aggregcan-based perineuronal nets around five subclasses of parvalbumin-expressing neurons in the mouse hippocampus. *J Comp Neurol.* 525(5):1234–1249.

Ye Q, Miao Q-L. 2013. Experience-dependent development of perineuronal nets and chondroitin sulfate proteoglycan receptors in mouse visual cortex. *Matrix Biol.* 32(6):352–363.

Zaitsev AV, Povyshева NV, Lewis DA, Krimer LS. 2007. P/Q-type, but not N-type, calcium channels mediate GABA release from fast-spiking interneurons to pyramidal cells in rat prefrontal cortex. *J Neurophysiol.* 97(5):3567–3573.

Zamecnik J, Krsek P, Druga R, Marusic P, Benes V, Tichy M, Komarek V. 2006. Densities of parvalbumin-immunoreactive neurons in non-malformed hippocampal sclerosis-temporal neocortex and in cortical dysplasias. *Brain Res Bull.* 68(6):474–481.

Zeisel A, Muñoz-Manchado AB, Codeluppi S, Lönnnerberg P, La Manno G, Juréus A, Marques S, Munguba H, He L, Betsholtz C, et al. 2015. Cell types in the mouse cortex and hippocampus revealed by single-cell RNA-seq. *Science.* 347(6226):0–5.

Zhang Z, Bhalla A, Dean C, Chapman ER, Jackson MB. 2009. Synaptotagmin IV: a multifunctional regulator of peptidergic nerve terminals. *Nat Neurosci.* 12(2):163–171.

Ziburkus J, Cressman JR, Barreto E, Schiff SJ. 2006. Interneuron and pyramidal cell interplay during in vitro seizure-like events. *J Neurophysiol.* 95(6):3948–3954.