Neuroscience and Biobehavioral Reviews 132 (2022) 61–75

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review article

Inhibition in the auditory cortex

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ARTICLE INFO

Keywords:
Auditory cortex
Inhibitory interneurons
Sound processing
Contextual modulation

ABSTRACT

The auditory system provides us with extremely rich and precise information about the outside world. Once a sound reaches our ears, the acoustic information it carries travels from the cochlea all the way to the auditory cortex, where its complexity and nuances are integrated. In the auditory cortex, functional circuits are formed by subpopulations of intermingled excitatory and inhibitory cells. In this review, we discuss recent evidence of the specific contributions of inhibitory neurons in sound processing and integration. We first examine intrinsic properties of three main classes of inhibitory interneurons in the auditory cortex. Then, we describe how inhibition shapes the responsiveness of the auditory cortex to sound. Finally, we discuss how inhibitory interneurons contribute to the sensation and perception of sounds. Altogether, this review points out the crucial role of cortical inhibitory interneurons in integrating information about the context, history, or meaning of a sound. It also highlights open questions to be addressed for increasing our understanding of the staggering complexity leading to the subtlest auditory perception.

1. Introduction

Sensory cortices of different modalities in the mammalian brain share certain structural and functional features. They are composed of excitatory and inhibitory neurons arranged into six cortical layers, where they form local microcircuits (Harris and Mrsic-Flogel, 2013) within functional cortical columns (Mountcastle, 1957). For a long time, all sensory cortices were thought to be driven similarly through a canonical circuit (Douglas and Martin, 1991; Douglas et al., 1989), and findings from one sensory area could be inferred to all others. Although this has proven true to some extent (Markram et al., 2004; Tremblay et al., 2016), recent evidence has demonstrated multiple structural and functional differences between sensory cortices. For instance, one specific neuronal subpopulation can display different tuning properties when comparing visual and auditory cortices (Mesik et al., 2015). Another example is that movement increases sensory-evoked information in the visual and somatosensory cortices, whereas it decreases evoked responses in the auditory cortex (Fu et al., 2014; Schneider et al., 2014; Ayaz et al., 2019; Bigelow et al., 2019). Such differences are especially apparent in rodent auditory cortex (AC), which has so far been studied less than the visual or the somatosensory cortices, probably because of its high degree of computation and its anatomical location that makes it more difficult for the experimenter to access.

Auditory signals travel along the auditory pathway, from the cochlea to the AC, through the cochlear nuclei, the superior olivary nucleus and the lateral lemniscus in the brainstem, the inferior colliculus (IC) in the midbrain, and the medial geniculate body (MGB) in the thalamus. The AC is composed of primary auditory fields, which are characterized by their tonotopic organization, and higher-order secondary auditory areas (in cats: Hind, 1953; in monkeys: Merzenich and Brugge, 1973; Bendor and Wang, 2008; in rats: Sally and Kelly, 1988; in ferrets: Bizley et al., 2005; in mice: Guo et al., 2012; for a review, see Hackett, 2011). Recent studies have taken advantage of methodological advances in genetically modified rodent models such as optogenetics and chemogenetics to tag, characterize, and manipulate subpopulations of cortical neurons *in vivo* to examine their role in auditory processing and their relevance for sound perception. This review discusses recent discoveries about the role inhibitory neurons play in the AC, considerably changing our understanding of sound processing and perception. It adds to previous reviews on the auditory cortex, where the focus is more centered on excitatory neurons (Wang, 2016; Kuchibhotla and Bathellier, 2018). The focus is on the primary auditory cortex (A1), which is known to be necessary for complex sound integration (Ceballo et al., 2019; Dalmay et al., 2019).

2. The different interneuron populations of the auditory cortex

Inhibition is essential for cortical processing (Isaacson and Scanziani,

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https://doi.org/10.1016/j.neubiorev.2021.11.021
Received 28 June 2021; Received in revised form 20 October 2021; Accepted 15 November 2021
Available online 22 November 2021

Table 1
Three major subpopulations of inhibitory interneurons are present in the auditory cortex.

	PV+	SST+	5HT3a-R+
Proportion	~40 % [1]	~30 % [1]	~30 % [1]
Secondary marker	/	/	NDNF or VIP [2,3]
Density	L4 > L5/6 > L2/3 [4,5]	L5/6 > L2/3, L4 [6]	L1, L2/3 > >L4, L5/6 [2,3]
Morphology	basket or chandelier cell [7]	martinotti, bipolar, or bitufted cell [7,8]	bipolar, bitufted, double bouquet,or basket cell [9,10]
Firing	fast spiking [10]	low threshold, bursting, adaptive [8]	slow spiking [10]
Axonal spread	narrow [7]	wide [7]	narrow [2,9,10]
Projection targets	soma, proximal dendrites and axon [7]	apical dendrites [8]	apical dendrites [3], interneurons [2,11]
Involved in :			
- frequency tuning	+++ [12,13]	+ [14]	+ [2]
- lateral inhibition	+++ [12,13]		+ [2,9,11]
- network suppression		+++ [14, 15]	
- intensity coding			+++ [10]

Table summarizing the main structural and functional properties of PV+, SST+ and 5HT3a-R+ interneurons within the mouse primary auditory cortex. Number in parentheses correspond to the following references: [1] Rudy et al., 2011; [2] Takesian et al., 2018; [3] Abs et al., 2018; [4] Ouellet and de Villers-Sidani, 2014; [5] Desgent et al., 2005; [6] Reinhard et al., 2019; [7] Reyes and Levy, 2012; [8] Yavorska and Wehr, 2016; [9] Pi et al., 2013; [10] Mesik et al., 2015; [11] Letzkus et al., 2011; [12] Li et al., 2014; [13] Aizenberg et al., 2015; [14] Kato et al., 2017; [15] Lakunina et al., 2020.

2011) and for sensory integration (for reviews, see Petersen, 2007; Harris and Mrsic-Flogel, 2013; Feldmeyer et al., 2013, 2017; Wood et al., 2017). It is provided by several different classes of neurons that produce the neurotransmitter γ-aminobutyric acid (GABA) (Tremblay et al., 2016). All classes of GABAergic interneurons are generated during early embryonic life in the ganglionic eminences and follow a tangential migration to invade the neocortex (for reviews see Wonders and Anderson, 2006; Bandler et al., 2017). Neurons can be classified based on their specific functional properties, morphology, and molecular markers (Markram et al., 2004; Ascoli et al., 2008) or more recently based on the expression of transcription factors (Gouwens et al., 2020; Yuste et al., 2020; Yao et al., 2021). In this review, we chose to classify inhibitory neurons based on their expression of calcium-binding proteins, receptors, and neuropeptides. We will mainly focus on parvalbumin-expressing (PV+), somatostatin-expressing (SST+), and ionotropic serotonin receptor 5HT3a-expressing interneurons (5HT3a-R+) (Table 1). These interneurons have been most intensively studied and represent more than 95 % of cortical inhibitory neurons (Rudy et al., 2011).

2.1. Parvalbumin-expressing interneurons

Parvalbumin is a calcium-binding protein expressed in a subset of inhibitory interneurons. Most inhibitory neurons in the neocortex are PV+ interneurons (Tremblay et al., 2016). They are surrounded by perineuronal nets (PNN), an extracellular matrix which protects and stabilizes their connections (Happel et al., 2014; Fader et al., 2016). The expression of parvalbumin in this neuronal subpopulation is directly related to activity, since their chemogenetic inhibition reduces the expression of PV and PNNs, whereas only a trend of increased expression could be found by their chemogenetic activation (Cisneros-Franco and Villers-Sidani, 2019). Besides the specific role they play in auditory coding, PV+ interneurons have recently been the focus of studies that have provided significant insights into how auditory circuits function. Indeed, when the expression of excitatory opsins is successfully induced in PV+ neurons, their strong photoactivation allows the experimenter to silence or strongly downregulate local brain areas, and therefore to assess the contribution of these areas to sound processing (Hamilton et al., 2013; Seybold et al., 2015; Ceballo et al., 2019; Christensen et al., 2019; O'Sullivan et al., 2019; Weible et al., 2020).

2.1.1. Morphological and intrinsic properties

In the AC, PV interneurons have an ovoid somata (Desgent et al., 2005; Oswald and Reyes, 2011; Rock et al., 2018; Zurita et al., 2018). They can be subdivided into different classes depending on their morphology and targets (Fig. 1). Basket cells are bi- or multipolar, and target the soma and proximal dendrites of excitatory neurons (Levy and Reyes, 2012). Chandelier cells are multipolar or bitufted, and target the initial segment of the axon of excitatory neurons (Levy and Reyes, 2012) (Table 1). Callosal PV+ interneurons, i.e. those that project to the contralateral hemisphere, present a larger and more complex dendritic tree (Zurita et al., 2018).

Most PV+ interneurons are characterized by higher spontaneous and tone-evoked firing rates than excitatory neurons (Li et al., 2015; Mesik et al., 2015; Cohen et al., 2016; Zurita et al., 2018; Liang et al., 2019) and, thus, are also referred to as *fast spiking interneurons*. They present a short action potential (AP), a strong and short afterhyperpolarization, and a low spike rate adaptation (Oswald and Reyes, 2011; Zurita et al., 2018). These properties progressively develop during brain maturation, especially between postnatal days 14 (P14) and 18 (P18) in mice, with a progressive decrease of AP and afterhyperpolarization duration (Oswald and Reyes, 2011). PV+ interneurons have higher resting membrane potential than excitatory neurons but comparable input resistances (Chen et al., 2015; Li et al., 2015). The properties of synaptic transmission between PV+ interneurons and nearby excitatory neurons change between P10 and P29 in mice, leading to a shorter inhibitory postsynaptic potential (IPSP) latency, rise time, peak time, and decay constant (Oswald and Reyes, 2011).

2.1.2. Distribution and density

PV+ interneurons are present in all layers of the primary auditory fields of the AC and are densest in the thalamorecipient layer 4 (L4), followed by L5/6, and then L2/3 (Cruikshank et al., 2001; Ouellet and de Villers-Sidani, 2014; Desgent et al., 2005). A recent study comparing primary auditory fields in mice found more PV+ interneurons in the anterior auditory field (AAF) than in A1 (Reinhard et al., 2019).

The representation of PV+ interneurons in A1 during postnatal development has been studied in different animal models. In rats, the expression of PV increases rapidly after birth, peaks at P20 and decreases very slowly after P120 (Ouellet and de Villers-Sidani, 2014). In ferrets, the number of PV expressing neurons decreases between P1 and P20, and then continuously and slowly increases until adulthood (Gao et al., 2000). These changes in PV expression during postnatal development suggest that this neuronal subtype might play an important role in experience-driven cortical maturation.

In older ages, the density of PV+ interneurons decreases (Brewton et al., 2016). One hypothesis is that the progressive hearing loss observed with age could result from a lack of PV. However, a recent paper has demonstrated that the decrease of PV immunoreactivity in old animals was not correlated with the degree of hearing loss (Rogalla and Hildebrandt, 2020). In addition, it has been shown that this age-related decrease in PV expression can be prevented by auditory-driven behavioral training or by rearing in a specific sound environment (Cheng et al., 2017; Bhumika et al., 2020; Cheng et al., 2020).

2.1.3. Connectivity

Within the AC, PV+ interneurons contact and strongly inhibit nearby excitatory neurons (Letzkus et al., 2011; Kato et al., 2017). They provide

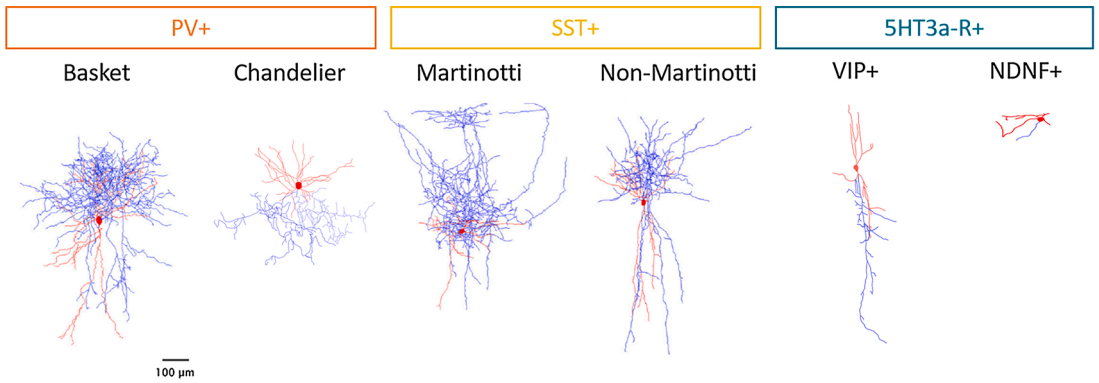

Fig. 1. Morphology of the main inhibitory interneurons in the auditory cortex. PV+ interneurons display local axonal spread. SST+ interneurons have more diffuse axons, especially Martinotti cells that send dense axonal arborization up in the cortical column. VIP+ neurons tend to send their axons down in the column and NDNF+ cell axons stay in L1. Adapted from biocytin-field neurons in Reyes and Levy, 2012 for Basket, Martinotti and Non-Martinotti cells, Woodruff and Yuste, 2008 for Chandelier cells, and AAV-mediated staining in Takesian et al., 2018 for VIP+ and NDNF+ cells by permission from Nature Neuroscience. All illustrations come from the primary auditory cortex except for the Chandelier cell that comes from the neocortex (red: soma and dendrites, blue: axons).

efficient and strong inhibition in a radius of up to 130 µm, which is similar to that of excitatory neurons (Levy and Reyes, 2012) but narrower than that of other interneuron subpopulations, such as SST+ interneurons (300 µm) (Kato et al., 2017). As a consequence, the photoactivation of PV+ interneurons decreases the spontaneous activity of neighboring neurons within the cortical column, but not of neurons in-between columns (Hamilton et al., 2013). Hence, PV+ interneurons play a fundamental role in robustly, albeit predominantly locally, controlling excitatory neurons. It is noteworthy that recent papers propose that PV+ neurons could also inhibit more distant excitatory cells, given that about 40 % of PV+ neurons project to the contralateral AC (Rock et al., 2018; Zurita et al., 2018).

In the AC, PV+ interneurons receive inputs from first-order auditory thalamus (MGBv) predominantly in L4, but also in all other layers (Ji et al., 2016; Rock et al., 2018). MGBv inputs to PV+ interneurons are stronger than inputs to excitatory or other subpopulations of inhibitory neurons (Ji et al., 2016). The latencies of these inputs are equivalent across all neuronal populations (Ji et al., 2016). These MGBv inputs can be locally inhibited by 5HT3a-R+ interneurons (Takesian et al., 2018).

In the cortex, PV+ interneurons are thought to mainly receive inputs

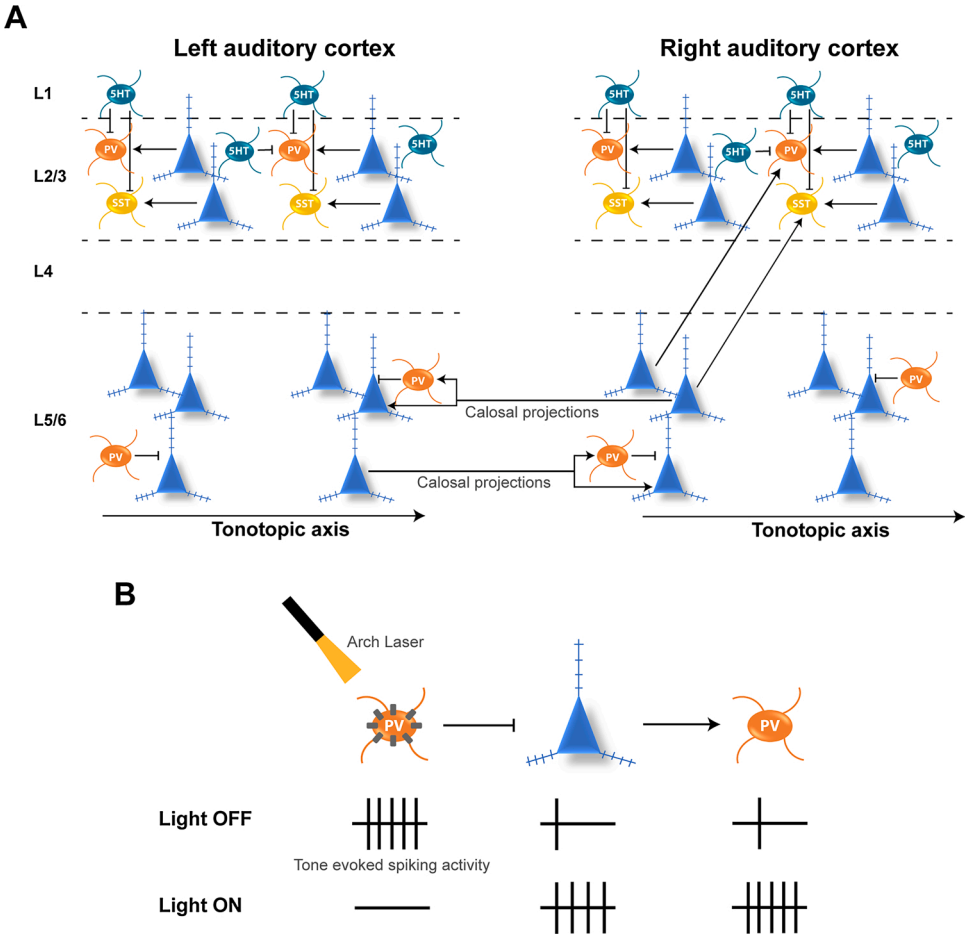

Fig. 2. Particular connectivity patterns observed in the primary auditory cortex. (**A**) Deep-layer excitatory neurons contact PV+ and SST+ interneurons in tonotopic areas of higher best frequency in the right auditory cortex (Oviedo, 2017). PV+ interneurons receive inputs from contralateral auditory cortex (Rock et al., 2018; Zurita et al., 2018). (**B**) PV+-to-excitatory -to-PV+ neurons form a feedforward inhibitory circuit, highlighted by optogenetic silencing of PV+ interneurons (Moore et al., 2018).

from excitatory neurons within the same column and layer (Oviedo, 2017). Functional connectivity mapping by laser scanning photostimulation has revealed, however, an asymmetry in the excitatory inputs received by L3 PV+ interneurons between the left and right hemispheres (Oviedo, 2017). Indeed, PV+ interneurons in the left hemisphere receive mostly local inputs, whereas PV+ interneurons in the right hemisphere also receive excitatory inputs from infragranular neurons not centered on the tonotopic column, with a bias from low to high frequencies (Oviedo, 2017) (Fig. 2A). This asymmetry is consistent with the connectivity of excitatory neurons and SST+ interneurons in the right hemisphere (Levy et al., 2019; Oviedo, 2017). PV+ interneurons also receive inhibitory inputs from L1 neurons, and are thus involved in a disinhibitory circuit of nearby excitatory neurons (Letzkus et al., 2011). In addition, PV+ interneurons receive direct callosal inputs from the contralateral AC and inhibit, in a feedforward circuit, callosal recipient L5 excitatory neurons (Rock and Apicella, 2015; Slater and Isaacson, 2020).

Besides thalamic and cortical inputs from auditory areas, PV+ interneurons receive direct inputs from brain regions outside the auditory pathway. The role of these long-range inputs is the subject of intense research. So far, studies have highlighted direct excitatory inputs from the secondary motor cortex (M2) (Nelson et al., 2013), direct inhibitory inputs from the basal forebrain (Kim et al., 2015), and direct cholinergic inputs from the basal forebrain (Nelson and Mooney, 2016). This list will likely increase in the near future.

Altogether, PV+ interneurons are the most common type of inhibitory cells in the AC. They strongly control the output activity of local excitatory neurons. Their intrinsic properties ease their identification during electrophysiological recordings, which may partially explain the large number of studies exploring the role of PV+ interneurons in sound processing.

2.2. Somatostatin-expressing interneurons

Somatostatin is an inhibitory neuropeptide released from the axons and dendrites of SST+ interneurons; it acts on G-protein coupled receptors (for review see Yavorska and Wehr, 2016). The expression of SST throughout the auditory pathway was first reported in 1979 (Tachibana et al., 1979). More recently, neocortical SST+ interneurons were found to be the second largest subpopulation of cortical inhibitory interneurons, accounting for ~30 % of cortical GABAergic interneurons (Rudy et al., 2011) (Table 1).

2.2.1. Morphological and intrinsic properties

SST+ interneurons form a heterogeneous population composed of Martinotti and non-Martinotti cells (Yavorska and Wehr, 2016) (Fig. 1). Martinotti cells project their axon into L1 where it arborizes (Levy and Reyes, 2012). Their dendrites branch locally or in deeper cortical layers (Levy and Reyes, 2012). Non-Martinotti cells can be bitufted, multipolar, basket, horizontal, or long-range projecting cells (for reviews, see Tremblay et al., 2016; Yavorska and Wehr, 2016).

Like PV+ interneurons, SST+ interneurons are characterized by a higher resting membrane potential than excitatory neurons (Chen et al., 2015), but SST+ interneurons have a higher input resistance than excitatory and PV+ neurons (Chen et al., 2015). They display an intermediate AP duration, which is slightly shorter than that of excitatory neurons but longer than that of PV+ neurons (Chen et al., 2015; Li et al., 2015). SST+ interneurons have a spontaneous activity close to 2 Hz and a tone-evoked firing rate lower than that of PV+ neurons but similar to that of excitatory neurons (Li et al., 2015). When exposed to sounds, SST+ interneurons are characterized by a ramping spiking activity, conferring them slower activation dynamics than PV+ interneurons (Lakunina et al., 2020).

2.2.2. Distribution and density

As previously mentioned, SST+ interneurons form a heterogeneous population of neurons, with Martinotti cells mainly present in L2/3 and L5/6, and non-Martinotti cells mainly in L4 and L5 (Yavorska and Wehr, 2016). In the mouse AC, SST+ interneurons are more numerous in L5/6 than L2/3/4, whereas in the rat AC, they are equally distributed among cortical layers (Ouellet and de Villers-Sidani, 2014; Reinhard et al., 2019). With respect to primary cortical auditory fields, SST+ interneurons are equally distributed between A1 and AAF (Reinhard et al., 2019). Like PV + interneurons, SST+ interneurons can be surrounded by PNN, but mostly in superficial layers (Reinhard et al., 2019). During development in rat A1, SST+ interneurons appear later than PV+ interneurons (at P20), and slowly increase in number with a peak at P120, before decreasing regularly until P800 (Ouellet and de Villers-Sidani, 2014).

2.2.3. Connectivity

In the AC, SST+ interneurons project to the apical dendrites of excitatory neurons and are believed to inhibit them tonically (Table 1) (Phillips and Hasenstaub, 2016). Indeed, SST+ interneuron photoactivation in the AC increases sparseness by decreasing both spontaneous and tone-evoked activity (Blackwell et al., 2020). Martinotti cells project mainly to L1 whereas non-Martinotti cells send axons mainly in L4 and L2/3 (Nigro et al., 2018). SST+ interneurons project widely, and they efficiently inhibit excitatory neurons up to 300 μm along the tonotopic axis (Kato et al., 2017). SST+ interneurons also inhibit PV+ interneurons in a disinhibitory circuit (Pfeffer et al., 2013; Kato et al., 2015, 2017). They present a more diffuse transcolumnar inhibition than PV+ interneurons (Kato et al., 2017), consistent with their wider receptive field (Lakunina et al., 2020). Together, this suggests that PV+ and SST+ inhibitory subpopulations play fundamentally different roles: while PV+ interneurons robustly control excitatory neurons locally, SST+ interneurons modulate an extended excitatory network.

As for input connectivity, SST+ interneurons receive direct excitatory inputs from the first-order thalamus only in L4, but to a lesser extent than PV+ interneurons (Ji et al., 2016). SST+ interneurons also receive cholinergic inputs from the basal forebrain (Nelson and Mooney, 2016). Intracortically, these interneurons receive local excitatory inputs from neighboring neurons (Oviedo, 2017), in general weaker than those received by PV+ interneurons (Oviedo, 2017). As is the case for PV+ and excitatory neurons (Levy et al., 2019; Oviedo, 2017), the functional connectivity of L3 SST+ interneurons shows slight differences between the left and right hemisphere of the AC (Oviedo, 2017). In the left hemisphere, SST+ interneurons receive feedforward excitatory inputs from L4 and local intralaminar inputs from L2/3 (Oviedo, 2017), consistent with observations in other sensory areas (Fino and Yuste, 2011). In the right hemisphere, SST+ interneurons share the same connectivity as in the left hemisphere, but half of them also receive excitatory inputs from L6 (Oviedo, 2017). As seen in excitatory and PV+ neurons, this functional connectivity in SST+ interneurons from L6 to L3 is biased from low to high frequency, and not centered on the columnar axis (Oviedo, 2017) (Fig. 2A). Finally, SST+ interneurons also receive inhibitory inputs from local vasointestinal peptide (VIP+) interneurons, thereby forming a disinhibitory circuit (Askew et al., 2019).

Recent studies have reported that a few SST+ interneurons from the AC project to long-range brain areas. Indeed, a subset of SST+ interneurons located in L5 and L6 of A1 directly inhibits spiny neurons of the dorsal striatum (Rock et al., 2016). Another study describes SST+ interneurons that directly project to the lateral amygdala (LA) and modulate the spiking activity of its principal and cortical-projecting neurons (Bertero et al., 2019). Such a microcircuit could balance the known direct excitatory cortico-LA projection involved in fear behavior. Finally, SST+ interneuron photoinhibition increases spontaneous activity in the IC, suggesting that there is either a direct SST+-mediated inhibition from the AC to the IC, or a modulation of cortical IC-projecting neurons by SST+ interneurons (Blackwell et al., 2020). Since photoinhibition of SST+ interneurons decreases the cortical spontaneous activity but not the evoked activity (Blackwell et al., 2020),

a disinhibitory circuit from the AC to the IC is more likely.

In summary, SST+ interneurons provide tonic inhibition in the AC. They present slower activation dynamics than PV+ interneurons. They also display wider projections, placing them in a perfect position to modulate the inputs received by excitatory neurons.

2.3. 5HT3a-R-expressing interneurons

The third main subpopulation of interneurons present in the AC expresses the serotonin receptor 5HT3a (5HT3a-R+) (Fig. 1). This subpopulation can be further subdivided based on the expression of VIP and neuron-derived neurotrophic factor (NDNF) (Tremblay et al., 2016; Abs et al., 2018; Schuman et al., 2019) (Table 1). Some VIP+ interneurons also express choline acetyl transferase (ChAT) (Ouellet and de Villers-Sidani, 2014) or nicotinic acetylcholine receptors (nAChR) (Takesian et al., 2018), which underlines their putative link to the cholinergic system.

2.3.1. Morphological and intrinsic properties

In the AC, VIP+ interneurons have an ovoid soma and bipolar, bitufted, double bouquet, or basket morphology (Pi et al., 2013; Mesik et al., 2015). NDNF+ interneurons have dendrites and axonal arborization that are mainly constrained to L1 (Schuman et al., 2019). The spiking activity of VIP+ interneurons is lower than that of PV+ but faster than that of excitatory neurons (Mesik et al., 2015). Their spike waveform is large and very similar to that of excitatory neurons (Mesik et al., 2015). The intrinsic properties of the 5HT3a-R+ subpopulation, especially those of NDNF+ interneurons, are less well characterized than those of the other neuronal subgroups, and should therefore be the subject of future studies.

2.3.2. Distribution and density

5HT3a-R+ interneurons represent 30 % of cortical GABAergic cells (Rudy et al., 2011). VIP+ interneurons account for about 40 % of 5HT3a-R+ interneurons and NDNF+ for about 60 % (Schuman et al., 2019). In the AC, NDNF+ interneurons are mainly located in L1, and VIP+ interneurons in L2/3 but are also present in the other layers (Pi et al., 2013; Mesik et al., 2015; Takesian et al., 2018; Abs et al., 2018). Unlike the number of PV+ and SST+ interneurons, that of VIP+ interneurons remains stable across the lifespan of rats (Ouellet and de Villers-Sidani, 2014). Whether NDNF+ interneurons vary in number over time has yet to be addressed.

2.3.3. Connectivity

NDNF+ interneuron axons and dendrites are mainly restricted to L1, where they strongly inhibit the distal dendrites of excitatory neurons (Abs et al., 2018; Schuman et al., 2019). They also inhibit PV+ interneurons in L2/3 (Letzkus et al., 2011) as well as in L4 (Takesian et al., 2018). VIP+ interneurons send axons down the cortical column and contact PV+ interneurons in L2/3 and L4 (Takesian et al., 2018). In L2/3, VIP+ interneurons mediate disinhibitory control over SST+ interneurons, and also, to a smaller extent, over PV+ interneurons (Table 1) (Pi et al., 2013; Askew et al., 2019). Recordings of evoked inhibitory postsynaptic current (IPSC) by VIP+ photoactivation in slice revealed that VIP+ interneurons contact almost 80 % of the neighboring SST+ interneurons but only 27 % of PV+ interneurons and 7 % of excitatory neurons, albeit with a similar inhibitory strength (Pi et al., 2013). In L4, however, VIP+ interneurons from L1 contact more PV+ interneurons than excitatory neurons of the same column, and the IPSCs evoked by their photoactivation are of higher amplitude and narrower in PV+ interneurons than in excitatory neurons (Takesian et al., 2018). As a result of this functional connectivity, the photoactivation of VIP+ interneurons induces two types of effects: (i) a rapid and sustained inhibition of neighboring neurons, including of putative PV+ interneurons, and (ii) a delayed activation of other neurons (Pi et al., 2013). This first inhibition of a subset of neurons followed by an activation of their post-synaptic partners is the hallmark of a disinhibitory circuit, that here acts presumably via SST+ interneurons in L2/3 (Pi et al., 2013; Askew et al., 2019).

VIP+ interneurons receive direct inputs from the thalamus in L1 (Takesian et al., 2018) and in L4, but these inputs are weaker than those received by PV+ interneurons (Ji et al., 2016). NDNF+ interneurons also receive direct, tonotopically organized inputs from the first-order thalamus in L1 (Takesian et al., 2018). This thalamus-to-5HT3a-R + interneuron connection is believed to control thalamic inputs in L4. Indeed, MGBv simultaneously activates both excitatory neurons in L4, activation controlled by local PV+ interneurons, and 5HT3a-R+ interneurons in L1 (Takesian et al., 2018). In turn, those L1 interneurons inhibit PV+ interneurons from L4, thereby disinhibiting L4 excitatory neurons and increasing their response to thalamic inputs through a feedforward disinhibitory circuit (Takesian et al., 2018).

Like PV+ and SST+ interneurons, VIP+ interneurons receive direct cholinergic inputs from the basal forebrain (Nelson and Mooney, 2016). They express nAChR and are thus activated by acetylcholine and nicotine (Takesian et al., 2018; Askew et al., 2019). Nicotine-evoked activation of VIP+ interneurons increases IPSCs in excitatory and SST+ neurons (Askew et al., 2019). This inhibitory influence of VIP+ interneurons on SST+ interneurons is characteristic of a disinhibitory circuit (Askew et al., 2019).

L1 is also one of the main recipient layers of top-down inputs from higher-order brain areas (Abs et al., 2018; Pardi et al., 2020). Moreover, a recent study has shown that during development, bottom-up first-order thalamic inputs to 5HT3a-R neurons in L1 of primary visual cortex are necessary for the establishment and reinforcement of top-down inputs present in adults (Ibrahim et al., 2021). Whether this is also the case in the auditory cortex is not known yet.

Altogether, 5HT3a-R+ interneurons represent an important subpopulation of GABAergic neurons in the AC that is still not fully characterized. These interneurons provide a major source of disinhibition through their connections to SST+ and PV+ interneurons.

2.4. Other subpopulations of inhibitory interneurons

Although PV, SOM and 5HT3a-R allow researchers to identify almost all cortical interneurons, a few additional neurochemical markers can be used to identify other non-overlapping subpopulations of cortical interneurons in the auditory system. Of the remaining cortical interneurons, the most frequent are the calretinin (CR) expressing interneurons (Ouellet and de Villers-Sidani, 2014). They are well represented at young age (<P20 in rats), then decrease and reach a stable expression in adult age (Ouellet and de Villers-Sidani, 2014). Cholecystokinin (CCK)-expressing interneurons and neuropeptide-Y (NPY)-expressing interneurons are present in A1, with a stable expression during the lifespan for CCK, but a regular increase for NPY (Ouellet and de Villers-Sidani, 2014). These groups are understudied in the AC, and their respective roles in auditory processing have not yet been elucidated.

3. The involvement of interneurons in sound processing

In this section, we discuss how inhibitory interneurons control both spontaneous and sound-evoked activity in the AC. We describe how interneurons modulate the signal-to-noise ratio and how they participate in the spectral, intensity, and temporal coding of sound. The results described are mainly derived from neuronal responses to pure tones or wideband noise, as the role that inhibition plays in coding more complex sounds remains largely unexplored (Maor et al., 2016).

3.1. Network processing

Recent advances in genetic tools, such as optogenetics or chemogenetics, have greatly facilitated studying the involvement of neuronal

subpopulations in network processing. These tools make it possible to highlight the control exerted by inhibitory interneurons on both the spontaneous and sound-evoked activity of excitatory cells. For most inhibitory neuron subpopulations, multiple scenarios have been observed when applying photomodulation. This also highlights the complex interpretation of such experiments (Seybold et al., 2015; Blackwell and Geffen, 2017).

PV+ interneurons in the AC modulate information transfer and network activity (Aizenberg et al., 2015; Phillips and Hasenstaub, 2016; Phillips et al., 2017; Cisneros-Franco and Villers-Sidani, 2019; Lakunina et al., 2020; Blackwell et al., 2020). Photoinhibiting PV+ interneurons increases both tone-evoked IPSCs and excitatory postsynaptic currents (EPSCs) in excitatory neurons (Moore et al., 2018), resulting in increased tone-evoked responses of excitatory neurons in all layers (Moore et al., 2018; Cisneros-Franco and Villers-Sidani, 2019; Krause et al., 2019). It also decreases the latency of MGBv-evoked response in L2/3 and L5/6 excitatory neurons (Krause et al., 2019). Surprisingly, PV+ interneuron photoinhibition also increases tone-evoked responses of PV+ interneurons that are outside of the effective optogenetic inhibition (Moore et al., 2018). This highlights the feedforward interconnection between PV+ interneurons where (i) by photoinhibiting a subpopulation of PV+ interneurons, others are more activated by disinhibited excitatory neurons, and (ii) the balance between excitation and inhibition is in favor of excitation if the break (= inhibitory component) is inhibited (Fig. 2B). On the other hand, photoactivating PV+ interneurons decreases both spontaneous and evoked activity in the AC (Hamilton et al., 2013; Seybold et al., 2015; Christensen et al., 2019; Blackwell et al., 2020), which can result in a lower signal-to-noise ratio (Hamilton et al., 2013; Aizenberg et al., 2015; Seybold et al., 2015). Overall, PV+ interneurons may, by modulating sound-evoked information transfer from the thalamus to the cortex, control bottom-up signal and processing (Hamilton et al., 2013).

Photoinhibiting SST+ interneurons increases tone-evoked neuronal responses (Phillips and Hasenstaub, 2016) and network activity (Phillips et al., 2017; Blackwell et al., 2020). Photoactivating SST+ interneurons leads, instead, to a strong inhibition of the AC and decreases both spontaneous and tone-evoked neuronal responses (Seybold et al., 2015).

Contrary to PV+ and SST+ populations, photoinhibiting VIP+ interneurons decreases first-order thalamus-evoked activity in the AC (Takesian et al., 2018). Photoactivating VIP+ interneurons leads to a decreased tonal response of the inhibited PV+ interneurons, which causes an increased tone-evoked response in the subsequently disinhibited excitatory neurons (Pi et al., 2013; Bigelow et al., 2019).

Altogether, these results illustrate different roles, among others, that

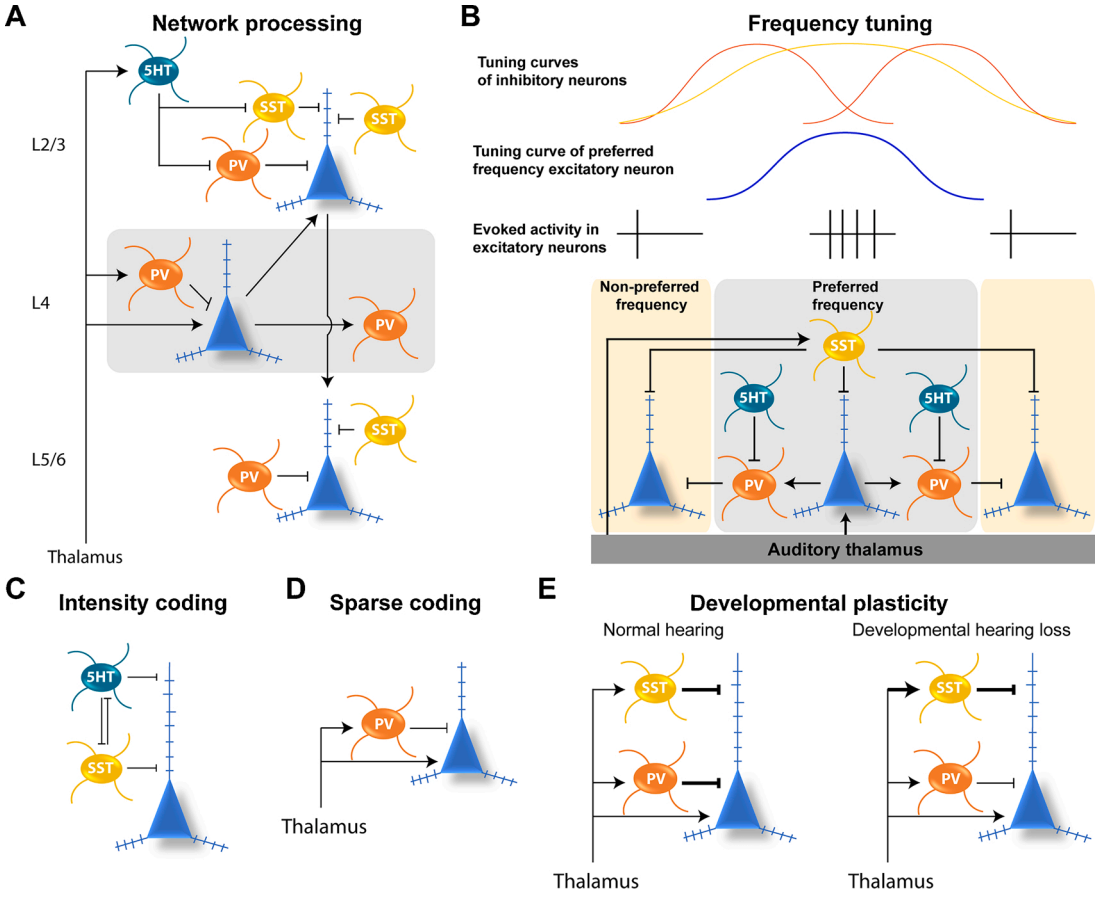

Fig. 3. Neuronal circuits describing the involvment of interneurons in sound processing. (**A**) Thalamic inputs send information to excitatory neurons mainly in layer 4 of the AC. This information is locally modulated by feedforward inhibition through PV+ interneurons. The second level of modulation of the network comes from 5HT3a-R+ interneurons receiving direct thalamic inputs and inhibiting PV+ and SST+ interneurons, creating a disinhibitory control over excitatory neurons. (**B**) The frequency tuning of excitatory neurons in AC is inherited from first-order thalamic inputs and strengthened by cortical inhibition. PV+ interneurons modulate cortical freqency tuning through lateral inhibition and SST+ interneurons through network supression. 5HT3a-R+ interneurons participate in frequency tuning by modulating PV+ interneurons. (**C**) A subset of 5HT3a-R+ neurons are tuned to sound intensity. They therefore may play a role in the modulation of sound intensity in excitatory neurons. They can also modulate excitatory neurons intensity processing through SST+ disinhibition. Another subset of 5HT3a-R+ neurons present a progressive decreased response with sound intensity associated with the progressive increased response of SST+ interneurons. (**D**) PV+ interneurons are involved in sparse coding through feedforward inhibition, thereby decreasing sound-evoked responses. (**E**) PV+ and SST+ inhibition strengthens during brain development. This reinforcement is altered in developmental hearing loss: PV+ inhibition is decreased whereas thalamic activation of SST+ interneurons is increased, reinforcing their inhibitory control on excitatry neurons.

the three main inhibitory subpopulations can play in sound processing. PV+ interneurons can constrain the sound-evoked activation of excitatory neurons in time and strength. They can also modulate sound-evoked responses from the thalamus to the cortex to control bottom-up signal transfer. SST+ interneurons can reduce auditory noise and thus could play a key role in the discriminability of salient signals. VIP+ interneurons are, in part, involved in the modulation of the gain of sound-evoked responses in the AC (Fig. 3A).

3.2. Frequency tuning

The tuning of neurons to specific features is present in most sensory cortices. In the AC, the tuning to sound frequencies allows for the identification of a neuron's preferred or best frequency: the frequency that a neuron responds to most strongly. The topographical progressive change of best frequencies within an auditory region is what underlies tonotopy. Frequency tuning is inherited from the first-order thalamus and refined by cortical inhibition (Wehr and Zador, 2003). Different inhibitory mechanisms have been proposed to explain this tuning process in the cortex. Some studies have shown that excitation and inhibition are balanced and co-tuned in auditory neurons shortly after the onset of a sound (Wehr and Zador, 2003; Dorrn et al., 2010). The authors of these studies have suggested that the small and stable delay between excitation and inhibition creates a time window prone to tone-evoked responses (Wehr and Zador, 2003). They thus suggested that this delay orchestrates the excitability of excitatory neurons, and in consequence, their tuning (Wehr and Zador, 2003). This mechanism is different from the classical view of lateral inhibition that is essential to sensory tuning in other senses (Isaacson and Scanziani, 2011). Lateral inhibition is believed to be produced through the activation of excitatory neurons by first-order thalamic inputs, which in turn activate inhibitory interneurons that then inhibit surrounding excitatory neurons in a feedforward inhibitory circuit (Isaacson and Scanziani, 2011). Lateral inhibition causes neuronal hyperpolarization and increases input resistance for non-preferred frequencies (Li et al., 2013; Kato et al., 2017). As a consequence, excitatory neurons can be activated by some pure tones and suppressed by others (Kato et al., 2017; Gillet et al., 2018; Lakunina et al., 2020). Network suppression has also been suggested to serve as a mechanism for frequency tuning (Kato et al., 2017). In network suppression, a more widely tuned and slower inhibition is combined with a more narrowly tuned and faster excitation (Kato et al., 2017). Hence, the association of network suppression and lateral inhibition in the AC, both governed by local inhibition, produces a sound-evoked response that is spatially limited and specific to the input stimulus (Wehr and Zador, 2003; Isaacson and Scanziani, 2011; Kato et al., 2017).

The main subpopulations of inhibitory interneurons are involved in shaping the frequency tuning of excitatory neurons through diverse mechanisms (Fig. 3B). PV+ interneurons shape frequency tuning in L2/3 excitatory neurons (Li et al., 2014) through fast feedforward inhibition (Wehr and Zador, 2003). Indeed, the photoactivation of PV+ cells narrows the tuning curves of excitatory neurons, whereas their photoinhibition has the opposite effect (Aizenberg et al., 2015) and increases the slower responses to tones of non-preferred frequencies (Kato et al., 2017). PV+ interneurons also receive strong contralateral excitatory inputs that facilitate tuning sharpness via feedforward inhibition (Slater and Isaacson, 2020). Altogether, the activation of PV+ interneurons seems to enhance frequency selectivity (Aizenberg et al., 2015; Christensen et al., 2019). This function is supported by the limited spatial extent of the connectivity of PV+ interneurons, which is restricted to the neurons' isofrequency vicinity within A1 (Yuan et al., 2011).

SST+ interneurons are believed to participate in the frequency tuning of excitatory neurons through network suppression (Kato et al., 2017; Lakunina et al., 2020), where excitatory inputs are suppressed by strong inhibitory inputs elicited by a tone of a non-preferred frequency (Kato et al., 2017; Aponte et al., 2021). Indeed, the photoinhibition of SST+ interneurons has little effect on the fast EPSCs that are evoked by the preferred frequency, but it abolishes the slow IPSCs induced by non-preferred frequencies (Kato et al., 2017). The evidence of the role that SST+ interneurons play in network suppression is supported by their wider connectivity compared to PV+ interneurons (Kato et al., 2017). Moreover, network suppression in excitatory neurons is weak at sound onset (Kato et al., 2017). This is in line with the ramping activation of SST+ interneurons during sound presentation (Lakunina et al., 2020). It is of note that PV+ and SST+ interneurons do not seem subject to network suppression themselves (Lakunina et al., 2020).

Finally, 5HT3a-R+ interneurons also play a role in frequency tuning. Their photoinhibition quickly decreases first-order thalamus-evoked neuronal activation within the same cortical column and leads to a delayed increase in the activation of the surrounding columns (Takesian et al., 2018). Thus, 5HT3a-R+ interneurons (mostly VIP+ interneurons) actively but indirectly participate in lateral inhibition. By inhibiting PV+ interneurons from the same column, 5HT3a-R+ interneurons increase the response in excitatory neurons from neighboring columns through a disinhibitory mechanism (see 2.3.3) (Letzkus et al., 2011; Pi et al., 2013; Takesian et al., 2018). These observations highlight the central role that VIP+ interneurons play in frequency tuning, in part through the modulation of PV+ interneurons.

How inhibitory interneurons themselves are tuned to frequency is still debated (Mesik et al., 2015; Li et al., 2019). Some studies have shown that PV+ interneurons are broadly tuned (Atencio and Schreiner, 2008; Li et al., 2014; Mesik et al., 2015; Li et al., 2015, 2019; Liang et al., 2019), whereas SST+ and VIP+ interneurons exhibit narrower tuning curves that are more similar to the tuning curves of excitatory neurons (Li et al., 2014, 2015; Mesik et al., 2015). But other studies have demonstrate that SST+ interneurons display broadly tuned excitation and are not themselves subject to lateral inhibition (Moore and Wehr, 2013; Kato et al., 2017; Lakunina et al., 2020). The same studies found that PV + interneurons present narrower excitation tuning than SST+ interneurons, a tuning that is more similar to that of excitatory neurons. The fact that SST+ interneurons display higher peak responses to white noise than pure tones at their best frequency is another argument in favor of wider tuning curves (Kato et al., 2017; Lakunina et al., 2020). Whether this is due to a weaker lateral inhibition of these neurons or to inputs from a wider range of frequencies remains to be confirmed.

In sum, the frequency tuning of excitatory neurons in the AC is controlled by inhibition at different levels: PV+ interneurons mediate feedforward inhibition, SST+ interneurons mediate network suppression, and VIP+ interneurons mediate gain modulation (Fig. 3B). How wide the different subpopulations of inhibitory neurons are tuned to frequency has not yet been fully determined.

3.3. Intensity coding

The intensity of a sound is a key feature for its detection and localization (Grothe et al., 2010; van der Heijden et al., 2019). It is one of the two basic criteria for defining the tuning-receptive field of a cell, with the frequency. In the AC, PV+ interneurons start to respond to a sound at a similar intensity as excitatory neurons do (Liang et al., 2019), whereas the intensity threshold for responses in SST+ interneurons is higher (Li et al., 2015). Above threshold, both PV+ and SST+ interneurons display a monotonic increase of their evoked response with sound intensity (Mesik et al., 2015; Kato et al., 2017; Abs et al., 2018). Inversely, NDNF+ neurons present a monotonic decrease of the evoked responses with sound intensity (Abs et al., 2018). Interestingly, a recent study has shown that when blocking SST+ axonal inputs to L1, those same NDNF+ cells present a progressive increase of their response to sound of increasing intensity (Abs et al., 2018). This suggests a direct modulation exerted by SST+ neurons on the tuning of NDNF+ cells to sound intensity. By contrast, half of VIP+ interneurons are selective to sound intensity and respond more to medium sound pressures than to higher ones (Mesik et al., 2015). They also tend to respond to lower intensities than PV+ and excitatory neurons do (Mesik et al., 2015). This suggests

that VIP+ interneurons could play a major role in intensity processing. By directly inhibiting dendrites of excitatory neurons or by indirectly disinhibiting excitatory neurons through an intermediate SST+ interneuron (Askew et al., 2019) (Fig. 3C), VIP+ interneurons could also be central to modulating the responses of excitatory neurons at low intensity.

Overall, evidence suggests that, as VIP+ interneurons are intensity tuned, they may support intensity coding in the AC, whereas SST+ interneurons may control intensity tuning of NDNF+ neurons.

3.4. Sparse coding

Sparse coding is a key feature of sensory processing in the cortex (Crochet et al., 2011; Sakata and Harris, 2009). It corresponds to the fact that, in a dense neuronal population, only a few neurons are activated by the same sensory feature. Although non-responsive neurons might receive sense-triggered inputs, these do not add up to generate APs (Liang et al., 2019). Sparse coding might be due to a change in the excitation-inhibition balance in favor of inhibition, bringing neurons to silence (Liang et al., 2019).

In the AC, sparse coding is present in excitatory neurons but absent in SST+ interneurons (Liang et al., 2019; Liu et al., 2019). Whether or not it is observed in PV + interneurons is still under debate. Liang et al. (2019) showed that as much as 95 % of PV+ interneurons in L2/3 are activated by sound, suggesting that sparse coding is absent in PV+ interneurons. However, Liu et al. (2019) found that most PV+ interneurons are suppressed during tone presentation. These contradictory results could be interpreted as due to different sound protocols, conditions, and recording techniques used in both studies. Independently of the amount of sparseness PV+ neurons show, they do play a central role in the regulation of sparse coding in the AC: photoinhibiting them turns non-responsive L2/3 excitatory neurons into sound-responsive ones (Liang et al., 2019), whereas photoactivating them increases network sparseness (Blackwell et al., 2020) (Fig. 3D). Whether this interaction is direct or mediated by a disynaptic disinhibitory circuit, possibly involving VIP+ interneurons, remains to be elucidated.

Overall, it remains unclear whether all different types of interneurons are subject to sparse coding. However, PV+ interneurons are believed to facilitate sparse coding in the AC. The circuits involved, as well as the role of other inhibitory subpopulations, has not yet been addressed.

4. Developmental plasticity of sound representation

In primary auditory cortices, neurons are tuned to sound frequencies (see 3.2). Neurons sharing the same best frequency are topographically grouped together. They are organized from low to high frequencies in a gradual and directional way (Bizley et al., 2005; Guo et al., 2012). This stereotyped spatial arrangement of tuned neurons forms, at the macroscopic scale, the tonotopic map.

Tonotopy stabilizes during a critical period of brain maturation (P12-P15 in mice), and can be altered by passive exposure to pure tones (de Villers-Sidani et al., 2008; Barkat et al., 2011; Vickers et al., 2018; Kalish et al., 2020; Nakamura et al., 2020). The opening of this critical period is controlled by GABAergic inhibition: increasing GABA accelerates the critical period, while decreasing GABA delays it (Kalish et al., 2020; Nakamura et al., 2020). In particular, PV+ interneurons play an important role in this control (Lee et al., 2017; Kalish et al., 2020). Indeed, the critical period is under control of the homeobox protein Otx2 which regulates the maturation of PV+ interneuron (Lee et al., 2017). Moreover, rearing in a sound environment with a repeated 7 kHz pure tone between P12 and P15 decreases the expression of PV and increases the number of 7 kHz responsive cells (Kalish et al., 2020). This illustrates the tight link between the maturation of PV+ interneurons and plastic tonotopic changes. L1 5HT3a-R+ but not VIP+ interneurons also orchestrate this developmental plasticity through cholinergic inputs (Takesian et al., 2018). During brain maturation, inhibition is therefore essential for the adaptation of the tonotopic map to the animal's auditory environment.

Inhibition does not only play a role in controlling the critical period for tonotopy. Indeed, white noise exposure between P30 and P40 blocks the usual decrease in the density of PV+ interneurons and delays the critical period for frequency modulated sweeps (Bhumika et al., 2020). This indicates that preventing interneuron maturation influences developmental plasticity and sound representation.

During brain maturation, inhibitory synaptic transmission in the AC strengthens (Sanes and Kotak, 2011). Developmental hearing loss, one of the most common sensory diseases in humans (Lieu et al., 2020), alters this strengthening (Kotak et al., 2007; Sanes and Kotak, 2011; Takesian et al., 2010, 2011, 2013; Mowery et al., 2019). In developmental hearing loss, the first-order thalamic inputs received by fast-spiking PV+ interneurons, and the synapses made by these interneurons onto excitatory neurons, are weakened (Takesian et al., 2010, 2013). On the contrary, the thalamic inputs received by low-threshold spiking SST + interneurons are increased (Fig. 3E). Although the synapses made by these neurons onto excitatory neurons remain strong, they also show increased short-term depression (Takesian et al., 2010, 2013). Together, these GABA transmission alterations can lead to long lasting functional and cognitive deficits (Mowery et al., 2019).

Overall, these studies highlight the key role played by different inhibitory subpopulations during brain maturation. They represent a very short overview of the knowledge acquired in the field. Given the importance of developmental plasticity for sound processing and hearing in health and disease, we feel this subject deserves a review by itself, as confirmed by a recent review on some aspects of auditory brain development (Chang and Kanold, 2021).

5. The role of inhibition in contextual sound processing

How we make sense of the sounds we hear is modulated by the context we are in. For instance, hearing a honk can be either scary when walking across a street, annoying in a traffic jam, or joyful if following a wedding ceremony. In this section, we will see how sound perception can be modulated, or even altered, by stimulus history, engagement, movement, attention, or learning. We will discuss the role of inhibition in these modulations.

5.1. Stimulus history

The influence of the history of sound presentation on auditory processing can be observed in the modulation of neuronal responses to sound as well as in behavioral readout. The perception, integration, and representation of a sound can be modulated by another preceding sound. A typical example of the modulation exerted by previous sounds on both neuronal and behavioral responses is the prepulse-inhibition (PPI) startle-response paradigm. In this task, the presentation of a prepulse (a sound different from the background) decreases the startle response evoked by a subsequent, loud sound (Geyer et al., 2002). Inhibitory neurons of the AC play a major modulatory role in this PPI. Indeed, the photoinhibition of SST+ interneurons reduces the startle response when applied after the prepulse, but increases it when applied before the prepulse (Weible et al., 2014, 2020). The photoinhibition of PV+ interneurons has a similar but weaker effect, whereas the photoinhibition of excitatory neurons has the opposite effect: it increases the startle response when applied after the prepulse, but decreases the startle response when applied before it (Weible et al., 2014).

Another example of the influence of stimulus history on sound processing is adaptation to a repeated stimulus. This adaptation is characterized by the reduction of the evoked response in excitatory neurons. The role of PV+ interneurons is minimal in this adaptation, as they exert a stable inhibition of excitatory neurons throughout repeated

stimulation (Natan et al., 2017), which is consistent with their low spike rate adaptation (Oswald and Reyes, 2011; Zurita et al., 2018)(see 2.1.1). Conversely, the inhibitory control exerted by SST+ interneurons over excitatory neurons increases with the number of stimulus repetitions (Natan et al., 2017), which is consistent with the ramping and sustained activity of this neuronal type during the presentation of sound (Lakunina et al., 2020)(see 2.2.1). Interestingly, SST + interneurons modulate mainly excitatory neurons, but do not influence PV + interneurons (Natan et al., 2017). Indeed, the photoinhibition of SST+ interneurons exclusively impairs the adaptation of excitatory neurons (Natan et al., 2017) (Fig. 4A). This highlights the role that this neuronal subtype plays in adaptation to repeated stimuli and in the control of the excitability of excitatory neurons, and, more generally, the sensitivity of SST+ interneurons to stimulus history (Chen et al., 2015). The mechanism driving the progressive regulatory role of SST+ interneurons is not yet well understood. It could be related to a reinforced synaptic drive between SST+ and excitatory neurons with stimulus repetition, to the influence of top-down modulation, or to a disinhibitory circuit between SST+ and PV+ interneurons (Natan et al., 2017).

Adaptation to repeated stimuli is also thought to facilitate the detection of deviant tones and unexpected changes in the environment. This is highlighted by stimulus-specific adaptation (SSA), where a sound is presented frequently (the standard) and another one is presented rarely (the deviant). In such a paradigm, commonly called oddball paradigm, the neuronal response to a sound is larger when it is presented rarely than when it is presented frequently (Nelken, 2014; Carbajal and Malmierca, 2018). Both PV+ and SST+ interneurons exhibit SSA (Chen et al., 2015; Natan et al., 2015). PV + interneurons exhibit two adaptive processes to repeated stimuli: a fast adaptation at the onset of tone that is, however, weaker than that of excitatory and SST+ neurons; and a late adaptation 200−400 ms after tone onset, which is also present in excitatory neurons but absent in SST + interneurons (Chen et al., 2015). The photoinhibition of PV+ interneuron increases the response to both standard and deviant tones in an oddball paradigm, whereas the inactivation of SST+ interneurons only increases the evoked responses of excitatory neurons to the standard but not to the deviant tone (Natan et al., 2015).

Yet another example of the influence of stimulus history is forward suppression or forward masking, where a tone suppresses the neuronal response to another tone of different frequency that appears shortly after it. The difference between forward suppression and SSA is that forward suppression occurs after a shorter latency between sounds (~20 ms) and does not need repeated stimuli (Wehr and Zador, 2005; Phillips et al., 2017). Although forward suppression is already occurring in the thalamus, its cortical expression is not solely due to MGBv inputs: cortical inhibition also plays a major role in this process (Wehr and Zador, 2005). Indeed, the photoinhibition of SST+ interneurons decreases the strength of forward suppression, whereas the photoinhibition of PV+ interneurons increases it, but also decreases the dependence on the sound's frequency (Phillips et al., 2017).

Overall, inhibitory interneurons exert a diverse set of regulatory mechanisms that respond to the history of stimuli. PV+ interneurons

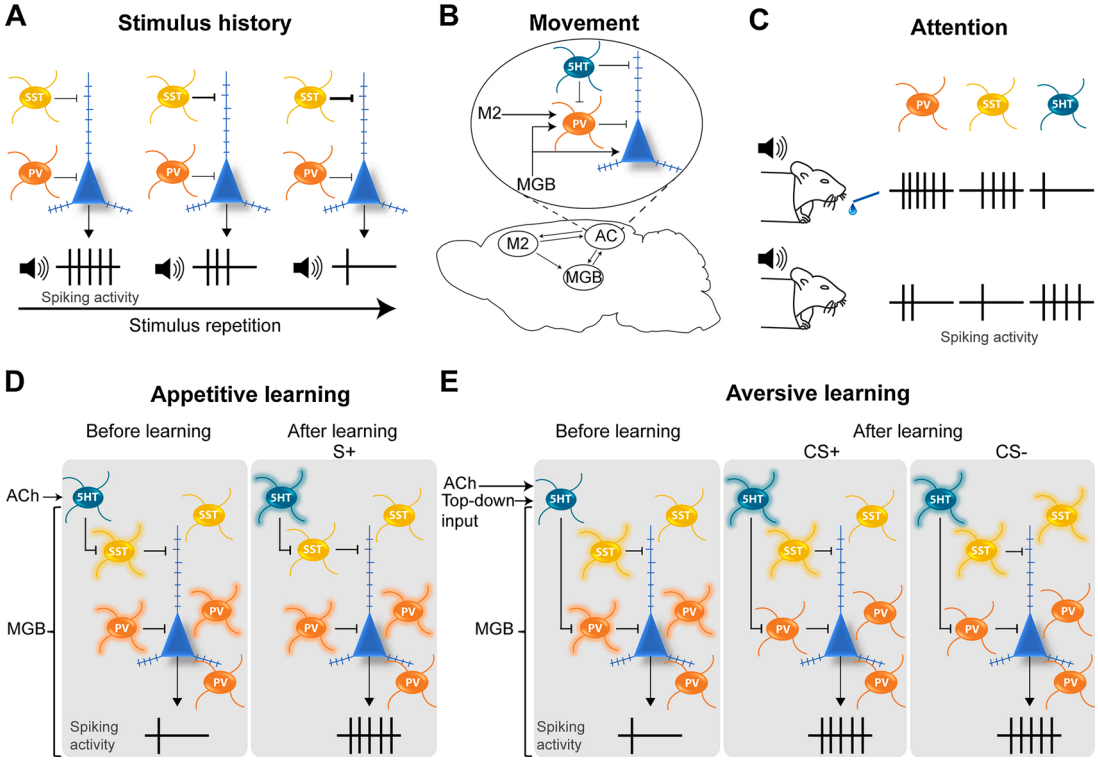

Fig. 4. Role of inhibition in contextual sound processing. (**A**) SST + interneurons increase their response with sound repetition. This leads to a progressive increase of their inhibitory modulation on excitatory neurons, which is suggested to lead to adaptation of evoked-responses. (**B**) Circuit of the modulation exerted by movement on neuronal activity in the AC. During movement, the secondary motor cortex (M2) drives input to PV+ interneurons in the AC which decreases sound evoked activity. (**C**) Comparing sound evoked responses between passive hearing (low attention) and active listening during task engagement (high attention) allows to test for the effect of attention on sound processing. PV + and SST+ interneurons are more active during task engagement with active listening. 5HT3a-R+ interneurons are more active during passive presentation of sounds. (**D**) Appetitive auditory learning has many effects on neuronal response in the AC. It shifts the frequency tuning of excitatory neurons and PV+ interneurons to S+ (rewarded sound). It increases the response of 5HT3a-R+ neurons to S+, which can disinhibit excitatory neurons through SST+ inhibition (shaded dendrites represent active neurons). (**E**) Aversive auditory learning increases the response of excitatory neurons to CS+ (reinforced sound) and CS- (non-reinforced sound). This could be due to the increased activation of 5HT3a-R+ interneurons, leading to the disinhibition of excitatory neurons through PV+ inhibition. SST+ interneurons are also affected by aversive auditory learning. Their response to sounds remain stable, but the number of SST+ neurons responding to CS- increases (shaded dendrites represent active neurons).

exert a stable inhibitory control over excitatory neurons, whereas SST+ interneurons progressively decrease the response of excitatory neurons to temporally repeated stimuli and facilitate the response to deviant tones. SST+ interneurons thus appear to be key players in temporal response adaptations at both short and long timescales. The role played by 5HT3a-R+ interneurons in the adaptation to stimulus history remains poorly understood.

5.2. Movement

Studying the effect of movement on auditory processing has been of great interest in recent years. Movement reduces sound-evoked activity in the AC (Nelson et al., 2013; Zhou et al., 2014; Schneider et al., 2014, 2018; Bigelow et al., 2019), which is opposite to the motor control over primary visual or somatosensory cortices (Fu et al., 2014; Manita et al., 2015). Indeed, locomotion decreases both spontaneous activity and tone-evoked responses of L2/3 excitatory neurons (Zhou et al., 2014; Schneider et al., 2014). Two contradictory effects of movement on inhibition in the AC have been observed. One study found increased spontaneous and sound-evoked activity of L1 inhibitory neurons during movement, which potentially explains the decreased activity observed in L2/3 excitatory neurons (Zhou et al., 2014). The increased inhibitory neuron activity in L1 was also associated with a decrease in the activity of PV+ interneurons in L2/3 (Zhou et al., 2014). By contrast, another study found an increased activation of PV+ interneurons in L2/3 during movement, which would potentially directly decrease the activation of excitatory neurons (Schneider et al., 2014). A good candidate for the brain region responsible for this motor modulation of cortical sound processing is the secondary motor cortex (M2). Indeed, it has been shown that M2 projects directly to excitatory and PV + neurons in the AC (Nelson et al., 2013). The photoactivation of M2-to-AC projecting neurons has been proven sufficient and necessary to drive motor-like modulation in the AC, and to decrease sound evoked activity (Nelson et al., 2013; Schneider et al., 2014). Thus, two mechanisms have been proposed to explain how movement affects auditory processing; both of them relate to inhibition. The effect could be due to the feedforward inhibition from M2 to AC PV+ interneurons (Nelson et al., 2013) or to an increased tonal inhibitory control of L1 inhibitory neurons over L2/3 neurons, coming presumably through motor or neuromodulatory inputs (Zhou et al., 2014). Alternatively, the motor-to-MGB connection could indirectly modulate cortical sound processing, but the specific effects of locomotion on thalamo-cortical connections remains ambiguous. On one hand, a study reported that movement did not affect tone-evoked L4 and MGBv activity (Zhou et al., 2014). On the other hand, another study found decreased evoked responses in cortical excitatory neurons after MGBv stimulation during movement (Schneider et al., 2014), consistent with a cortical locus of motor modulation (Fig. 4B).

In sum, this suggests that PV+ interneurons are involved in inhibiting sound evoked neural responses in the AC during movement. The roles that SST+ and 5HT3a-R+ interneurons play in the movement-related modulation of sound processing remain to be addressed.

5.3. Attention

Sound coding is dependent on brain states, and can be influenced by cognitive conditions such as attention (Schneider et al., 2014; Zhou et al., 2014; Kato et al., 2015; Kuchibhotla et al., 2017; Bigelow et al., 2019; De Franceschi and Barkat, 2020). Historically, gamma band oscillation has been used as a readout of attentional modulation in the AC (Tiitinen et al., 1993). Gamma band oscillation is known to be generated by local cortical PV+ interneurons (Sohal et al., 2009; Cardin et al., 2009; Kim et al., 2015). In the AC, PV+ interneurons receive direct inputs from cholinergic neurons in the basal forebrain (Nelson and Mooney, 2016). Thus, by directly mediating phasic inhibition on cortical PV+ interneurons (Kim et al., 2015), the basal forebrain is involved in attentional states (Poulet and Crochet, 2019).

One way of deciphering the influence that attention has on sound coding is to compare the sound-evoked response during the passive and active presentation. This is a way to compare hearing with listening. In two studies, head-fixed mice were presented tones and had to lick a spout in response to the sound to receive a reward in the active phase. In the passive phase, they were exposed to the same tones, but no reward was delivered (Kuchibhotla et al., 2017; De Franceschi and Barkat, 2020). The comparison of both phases revealed that auditory interneurons are modulated by task engagement and attention (Kuchibhotla et al., 2017; De Franceschi and Barkat, 2020). PV+ and SST+ interneurons fired more during active listening than during passive hearing, unlike VIP+ interneurons, which fired more during the passive presentation of the tone than during active listening (Kuchibhotla et al., 2017) (Fig. 4C). One should keep in mind that in such a task, other factors than attention might play a role, such as movement, arousal or reward. In order to disentangle the contribution of each factor, different approaches have been taken. For example, Kuchibhotla et al. (2017) minimized the contribution of movement by adapting the task design such that the response window began after the sound termination. De Franceschi and Barkat (2020) separated the specific contribution of attention by simultaneously monitoring changes in pupil size. In addition, the behavioral paradigm and task reward structure might dictate the specific types of activity changes observed in the different neuronal subpopulations (David et al., 2012). Aversive tasks might give rise to very different results than the appetitive tasks described above.

These findings suggest a bidirectional control of attentional modulation on auditory processing, with PV+ and SST+ interneurons on one side, and VIP+ interneurons on the other side. Together, these cell types orchestrate attentional modulation. The current findings also highlight the need for more in-depth studies on the specific role of each subpopulation of inhibitory neurons in attention modulation at the auditory circuit level.

5.4. Auditory learning

Auditory learning is the process in which a sound is associated with a new meaning. It can take different forms. In associative learning, a sound is associated with a behavioral outcome, whereas in perceptual learning, the capacity to discriminate sound is refined (Irvine, 2018). Auditory learning can also be either appetitive, when a sound is associated with a reward, or aversive, when a sound is associated with a punishment such as a foot shock. Finally, a task can be either classical, when passive physiological responses to a stimulus are measured (Letzkus et al., 2011; Aizenberg et al., 2015; Abs et al., 2018; Dalmay et al., 2019), or operant, when the subject has to actively choose to respond to the stimulus (Kuchibhotla et al., 2017; Gillet et al., 2018; Ceballo et al., 2019). It is of note that appetitive learning usually involves operant conditioning. Recent findings have highlighted that A1 is necessary for learning to discriminate complex sounds and for retrieving them from memory, but not for memory retrieval in easier tasks, such as discriminating two pure tones spectrally far apart (Gillet et al., 2018; Ceballo et al., 2019; Dalmay et al., 2019; Christensen et al., 2019).

Appetitive auditory learning has many consequences on the activity of inhibitory interneuron. In an appetitive associative auditory-learning task, in which mice had to learn to discriminate between two pure tones, VIP+ interneurons displayed an increased response to the rewarded tone (Pi et al., 2013). In an appetitive perceptual learning task of increasing difficulty in which animals had to discriminate between pure tones spectrally closer to each other, both excitatory and PV+ neurons shifted their frequency tuning toward the rewarded tone (Polley et al., 2006; Maor et al., 2020). PV+ neurons also displayed wider receptive fields (Maor et al., 2020). The effects of appetitive associative learning on PV+ and SST+ interneurons, and of appetitive perceptual learning on 5HT3a-R+ and SST + subpopulations, have not yet been addressed.

Aversive learning has been studied mainly with classical fear conditioning. In such a paradigm, animals learn to discriminate between a

sound that is associated with a foot-shock (the conditioned stimulus, CS+), and another sound that is not (CS-) (Krabbe et al., 2018). The measure of the conditioning is then the amount of freezing during the presentation of the CS+ (Letzkus et al., 2011; Aizenberg et al., 2015; Abs et al., 2018; Dalmay et al., 2019). In a fear conditioning paradigm using pure tones of different frequencies, the photoinhibition of PV+ interneurons increases or generalizes freezing for tones of all frequencies and not only for the CS+ (Aizenberg et al., 2015). This observation is consistent with the role that PV+ interneurons play in frequency tuning (see 3.2). Interestingly, the photoactivation of PV+ interneurons during fear learning significantly decreases fear behavior (Letzkus et al., 2011), whereas the photoactivation of PV+ neurons after fear learning, that is in trained mice, does not modify the learned behavior (Aizenberg et al., 2015). A recent study also showed that the tone-evoked response of SST+ interneurons to the CS- did not increase after learning, whereas the response of NDNF+ interneurons did increase (Abs et al., 2018). Moreover, these NDNF+ interneurons control the influence of higher-order thalamic inputs to the AC that are involved in aversive associative memory (Pardi et al., 2020). These findings suggest that most interneurons play a critical role in classical aversive auditory learning.

In operant fear learning, animals have to actively choose to respond to the CS- but not to the CS+, such as by licking for the CS- to get a reward but not for the CS+ that is associated with a shock (Gillet et al., 2018). During learning in such a task, the number of PV+ interneurons that respond to both the CS- and the CS+ decreases (Gillet et al., 2018). By contrast, the number of SST+ interneurons activated by the CS- increases (Gillet et al., 2018). This could explain the decreased activity in excitatory cells in response to the CS- after fear learning (Gillet et al., 2018) and further supports the view that SST + interneurons play a critical role in modulating auditory fear learning (Fig. 4D).

Another form of experience-driven plastic changes is what happens in mothers after giving birth. It has been shown that the neuronal response to pup calls is increased in mothers in comparison to naïve mice (Marlin et al., 2015; Shepard et al., 2015; Schiavo et al., 2020). These changes could be related to the odors of pups that are believed to decrease PV+ feedforward inhibition (Cohen and Mizrahi, 2015). On the contrary, another study has found an increased inhibitory response to pup calls in mother mice (Galindo-Leon et al., 2009). In fact, the tuning of inhibition to pup calls in naïve mice is poor compared to the tuning in mother mice, whereas excitatory tuning is similar for both (Schiavo et al., 2020). Motherhood even shifts the tuning of PV+ interneurons to higher frequencies (Cohen and Mizrahi, 2015). This suggests that inhibitory interneurons in the AC become tuned to behaviorally relevant sounds through maternal experience. Oxytocin is believed to be involved in this maternal plastic changes (Marlin et al., 2015). Indeed, oxytocin release can balance excitation and inhibition in response to pup calls, presumably through a direct modulation of PV+ and SST+ cortical interneurons, both of which express oxytocin receptors (Marlin et al., 2015).

Being aware of the context is essential for associating one sound with its behavioral relevance during learning. It has been suggested that context regulation is mediated by neuromodulatory inputs in inhibitory neurons, during both behavioral engagement (see 4.3) and auditory learning (Reed et al., 2011; Kuchibhotla et al., 2017; Takesian et al., 2018; Glennon et al., 2019). Cholinergic inputs from the basal forebrain excite, among others, inhibitory interneurons in superficial layers in the AC (Letzkus et al., 2011; Kuchibhotla et al., 2017) through direct activation of nAChRs in both 5HT3a-R+ and VIP+ interneurons (Takesian et al., 2018; Askew et al., 2019). Such activation of VIP+ interneurons inhibits SST + interneurons and indirectly engages excitatory neurons in a disinhibitory circuit (Askew et al., 2019) (Fig. 4E). In the context of fear conditioning, it has been shown that the cholinergic activation of interneurons in superficial layers of the AC can lead to an increased activation of excitatory neurons, either by disinhibiting L2/3 PV+ interneurons, which is essential for the association of shock and sound (Letzkus et al., 2011), or by disinhibiting L2/3 SST+ interneurons (Askew et al., 2019).

Learning-related changes in cortical activity are often transient. In a study pairing a tone with the stimulation of the nucleus basalis in rats, pairing increased the paired-tone representation in AC and increased the speed to learn to discriminate the paired tone from another tone (Reed et al., 2011). But this increased representation renormalized within weeks, despite a stable improved discrimination capacity (Reed et al., 2011). Such transient learning-related changes are simultaneous with the temporary decrease of inhibitory synaptic transmission that occurs during the first days of operant associative learning (Sarro et al., 2015). Such decreased inhibition could be due to noradrenergic inputs (Martins and Froemke, 2015). These findings suggest that a short-term reduction of inhibitory transmission could facilitate auditory learning until good behavioral performance is acquired.

Training in sound discrimination tasks can also have, however, different long-term effects. Indeed, it has been shown that, in addition to altering the spectro-temporal representation of sound, such training reduces the typical decrease of PV+ interneurons during aging, independent of whether the training occurs in old rodents (Villers-Sidani et al., 2010; Cheng et al., 2020) or young rodents (Cheng et al., 2017). In young rodents, the same effect has been observed in the SST + neuronal population (Cheng et al., 2017).

Overall, auditory learning impacts the activity of inhibitory interneurons. Although all subpopulations of GABAergic neurons seem to be involved, either in learning acquisition or retrieval, the plastic changes that take place seem to be very much dependent on the task. Further studies at the circuit level are needed to fully understand the inhibitory mechanisms that improve sensory skills. So far, most of the research on auditory learning has focused on associative learning. However, perceptual learning might be even more relevant because it changes sensory stimulus perception and enhances sensory discrimination (Seitz, 2017). More work will help us better understand the inhibitory neuronal circuits involved in auditory skills and perceptual learning.

6. Perspectives

In this review, we have summarized the important work performed over the past few years to disentangle the specific roles played by inhibition in the auditory system. Sound processing in the AC is tightly controlled by inhibitory interneurons. Since inhibitory neurons are highly diverse, we decided to focus our attention on the three most represented subpopulations: PV+, SST+ and 5HT3a-R+ interneurons. They each display specific intrinsic properties, firing modes, and connectivity. All three subpopulations receive local and thalamic inputs, but they also receive distal inputs from brain areas outside the classical auditory pathway (Fig. 5). These top-down inputs determine the role these neurons play in modulating sound representation in behaviorally relevant conditions.,

As discussed, PV+ interneurons are involved in many sound processing mechanisms. First, they play a major role in the shaping and maturation of sound representation within the AC during development, especially by controlling the opening and closing of critical periods (Barkat et al., 2011; Lee et al., 2017; Kalish et al., 2020; Bhumika et al., 2020; Nakamura et al., 2020). In addition, they constrain the sound-evoked activation of excitatory neurons in time and strength, thereby actively shaping frequency tuning (Li et al., 2014; Aizenberg et al., 2015). They also facilitate sparse coding (Liang et al., 2019; Blackwell et al., 2020). Finally, PV+ neurons are embedded in a wider network of auditory modulation in which inputs from motor areas inhibit sound-evoked neuronal responses during movement (Schneider et al., 2014; Zhou et al., 2014).

The second-most-represented inhibitory subpopulation in the AC are SST+ interneurons. The arguably most striking function of SST + neurons is to progressively modulate the response of excitatory neurons to

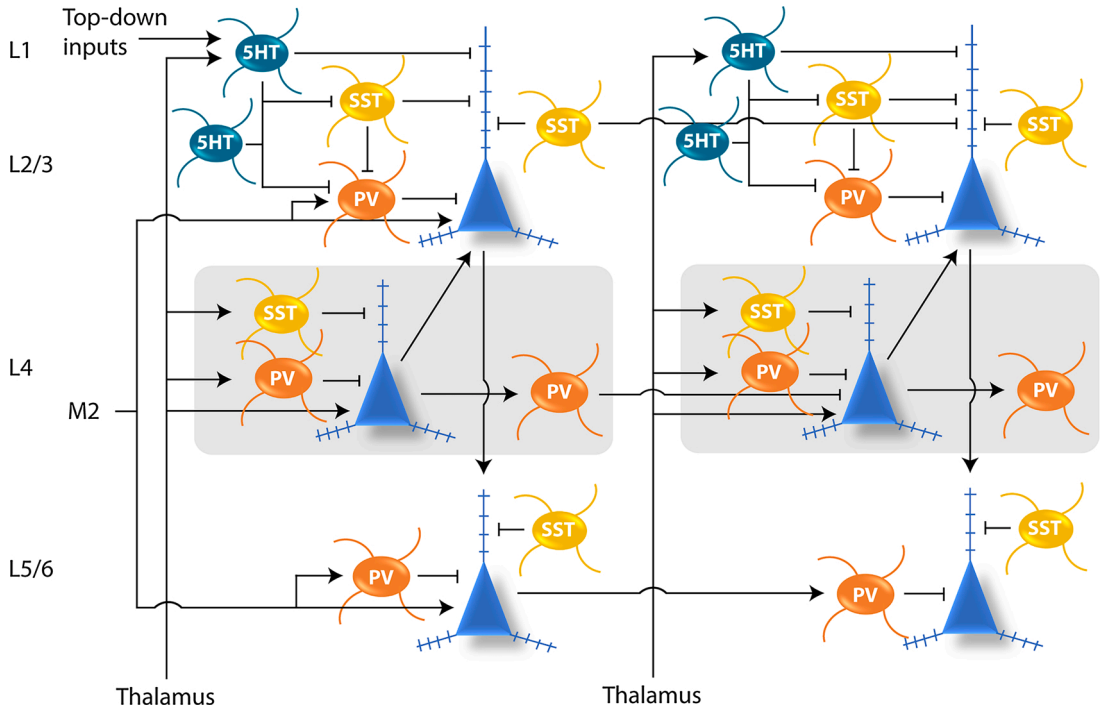

Fig. 5. Global wiring diagram. This diagram represents the overall connectivity of neurons in the AC. The thalamus sends inputs to both excitatory and inhibitory neurons in different cortical layers. This creates an inhibitory feedforward thalamus-to-PV+-to-excitatory neuron circuit, especially in layer 4. PV + interneurons contact excitatory neurons at the soma, proximal dendrites and initial segment of the axon. SST + and 5HT3a-R + interneurons contact excitatory neurons at their apical dendrites. Interneurons form disinhibitory circuits such as 5HT3a-R+-to-SST+, 5HT3a-R+-to-PV + or SST+-to-PV+. Auditory inhibitory neurons receive also inputs from long distance brain areas such as secondary motor cortex (M2) or higher-order brain areas (Top-down inputs).

sounds (Natan et al., 2017). This capacity is directly linked with their own sound response dynamics, that is their ramping activation and low adaptation (Lakunina et al., 2020). These properties allow SST+ interneurons to modulate the auditory network to both repeated stimuli and long-lasting stimulations (Natan et al., 2017). By controlling the effect of stimulus history, SST+ interneurons could serve as a gate to auditory memory formation, but this has to be further investigated. Another interesting role SST+ interneurons play in sound processing is through network suppression (Kato et al., 2017). This mechanism, once again directly linked with their own sound-evoked response dynamics, is crucial for the representation of simple sounds, but also for the integration of more complex and ethologically relevant sounds (Kato et al., 2017; Aponte et al., 2021).

The third subpopulation reviewed here were 5HT3a-R+ interneurons, from which VIP+ and NDNF+ neurons represent important groups. As of now, 5HT3a-R+ neurons have been less studied than PV+ or SST+ neurons, but they definitely deserve more attention. So far, we know that they inhibit both excitatory and inhibitory neurons (Letzkus et al., 2011; Pi et al., 2013; Takesian et al., 2018; Abs et al., 2018; Askew et al., 2019), which enables them to modulate the gain of sound evoked responses (Pi et al., 2013; Takesian et al., 2018). A unique property they display is their non-monotonic tuning to sound intensity. They might therefore play a central role in intensity coding (Mesik et al., 2015). In behavioral studies, VIP+ interneurons have displayed increased responses to rewarded sounds (Pi et al., 2013), and NDNF+ interneurons have been seen to gate top-down information involved in aversive associative learning (Pardi et al., 2020).

The past decade has shown extensive development of our understanding of the inhibitory network in the auditory cortex. However, we have seen throughout this review that many questions remain to be addressed. For example, so far only VIP+ interneurons have been put forward in sound intensity coding because of their non-monotonic increase of evoked response with sound intensity. More extensive research is needed to better understand the role of this neuronal subpopulation on intensity coding in excitatory neurons, and whether it is crucial for perceiving the intensity of a sound.

Then, sparse coding is essential for sensory processing (Petersen and Crochet, 2013), but its mechanism is not yet fully understood in the auditory cortex. The hypothesis that cortical inhibition is involved in sparse coding is undeniable, but it has not been fully addressed yet.

Next, NDNF+ interneurons have been identified quite recently. Their role in cortical inhibition is not fully understood yet. Future studies unraveling in more detail their role in sound processing and context modulation are needed. Similarly, new classes of cortical interneurons may be identified.

Also, the role of inhibition in aversive auditory learning is not fully understood yet, but has been more extensively studied than its appetitive counterpart. Future studies unraveling the role of specific subpopulations of inhibitory neurons in auditory learning are needed.

Finally, most of the basic properties of sounds are already encoded in nuclei of the auditory pathway that precede the AC. One of the most exciting question in auditory neuroscience today is therefore whether the actual role the AC plays in sound processing is to code the sound itself, or to associate it with its behavioral output. This review suggests that, thanks to its inhibitory network, the AC computes and compares all the information received from bottom-up and top-down inputs about the auditory environment, such as context, history and sound value. In the near future, further studies on the role of inhibition in the auditory cortex will greatly increase our understanding of auditory integration and perception.

Funding

This work was supported by a Marie Sklodowska-Curie Individual Fellowship (MSCA-IF EU project 894719 – AudiLearn), and by the Swiss National Science Foundation (ERC Transfer grant CRETP3-166735).

Acknowledgements

We thank Magdalena Solyga and Sebastian Reinartz for helpful comments on the manuscript, and Anthony Mahler and Claudine Neyen for proofreading the article.

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