The auditory cortex and the emotional valence of sounds

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Abstract

How and where sensory stimuli, such as tones or lights, are linked to valence is an important unresolved question in the field of neuroscience. The auditory cortex is essential to analyse the identity and the behavioural importance of tones paired with emotional events. On the contrary, whether the auditory cortex may also encode information on the emotional-motivational valence of sounds is much more controversial. Here, we reviewed recent studies showing that the activity of cortical neurons reflects information about the content of emotional stimuli paired with tones. Critically, the blockade of these neuronal processes prevents animals from recognising sounds as aversive or pleasant. Based on these findings, we proposed a conceptual model in which the auditory cortex may incorporate ascending information from subcortical nuclei about the valence of sounds in sound representations and may consequently drive the activity of subcortical structures towards emotionally laden tones.

This hypothesis may also have important implications in the characterisation of neural circuits engaged by maladaptive affective disorders, such as phobias.

Keywords

Auditory cortex, amygdala, emotional memory, fear learning, anxiety disorders, valence and salience

Main Text

1. Introduction

In the mammalian brain, the auditory cortex performs a detailed analysis of the physical properties of sounds. The auditory cortex decodes the spectral and temporal information embedded in sounds and forms a neural representation of them. The pioneering studies of M.M. Merzenich, H. Scheich and N.M. Weinberger provided strong evidence that the auditory cortex is also plastic in adulthood and that it can change the neural representation of auditory stimuli in response to experience or injury (for recent reviews see Brosch et al., 2011; de Villers-Sidani and Merzenich, 2011; Weinberger, 2015). These features allow the auditory cortex to incorporate new information about auditory stimuli, which is an essential task in a continuously changing world. Nevertheless, which information is encoded through the plastic changes that occur within the auditory cortex with experience is poorly understood.

Based on its ability to represent the physical properties of sounds, the auditory cortex may encode the **identity of sounds** (i.e., what it sounds like) that has acquired behavioural importance. For instance, if a sound is paired with an aversive event, the auditory cortex performs a detailed analysis of the physical properties of this sound and stores them for a long time. This function enables animals to rapidly recognise behaviourally meaningful tones and discriminate them among others. Many studies have provided important insights into the neural mechanisms engaged in the auditory cortex during this discrimination process (Aizenberg et al., 2013, 2015; Blackwell and Geffen, 2016; Concina et al., 2018; Wigestrand et al., 2016). In addition to this function, changes in the representation of tones in the auditory cortex have been proposed to reflect **behavioural salience**, i.e., the degree of importance that tones have acquired with experience. Among others,

Rutkowski and Weinberger tested this hypothesis by variably motivating rats with auditory cues through different levels of water deprivation (2005). Electrophysiological recordings showed an enlargement in the cortical representation of trained tones and this expansion correlated with the level of the behavioural importance of tones (Rutkowski and Weinberger, 2005).

Within this framework, the **emotional-motivational valence** of sounds**,** i.e., whether sounds are positive or negative, is thought to be processed by subcortical sites, such as the amygdala and nucleus accumbens, and higher order cortices, such as the orbitofrontal cortex. However, some recent studies have shown that the activity of neurons in the auditory cortex is profoundly influenced by emotional/motivational processes and that neurons in the auditory cortex can distinguish between the positive and negative valence of sounds. Critically, the blockade of these processes prevents animals from recognising sounds as aversive or pleasant. Taken together, these data lead to the alternative idea that the auditory cortex may also encode the emotional-motivational valence of sounds. In the present review, we addressed this hypothesis by presenting evidence in favour or against it. We also addressed the possible source of emotional information provided to the auditory cortex. Additionally, we highlighted the importance that this idea may have for the identification of the neural circuits responsible for emotional diseases, such as phobias.

2. The auditory cortex and the emotional-motivational valence of sounds

Since early studies on the plasticity of the auditory cortex that were performed in the 1980s, it has been clear that pairing a tone with an emotional event (pleasant or unpleasant) causes a pronounced rearrangement in the cortical representation of this tonal stimulus. Because these studies employed reinforcement stimuli with only one type of valence (positive or negative), determining whether the observed changes were related to the encoding of auditory stimuli or to the acquired emotional-motivational valence has been difficult. Indeed, the observation that some of the changes occurring in the auditory cortex were similar during aversive or appetitive experiences led some authors to

propose that “changes in tuning curves reflect learning of specific stimulus properties rather than the associative linking of the stimulus to a particular behavior or emotional state” (Aschauer and Rumpel, 2018).

More recently, some studies aimed at investigating the cellular mechanisms involved in the encoding of the association between tones and emotional stimuli uncovered that emotional stimuli by themselves can modify the neuronal activity of the auditory cortex. In 2011, by using two-photon calcium imaging of neurons located in layer 1 of the mouse auditory cortex, Letzkus et al. found strong activation of these cells induced by the delivery of foot shock in the absence of any sound presentation (Letzkus et al., 2011). Similarly, in mice, painful stimuli alone trigger the induction of immediate early genes, namely, zif268 and cfos, in the auditory cortex (Gruene et al., 2016; Peter et al., 2012) and lead to a transient modification in spine turnover (Moczulska et al., 2013). Altogether, these studies showed that neuronal activity of the auditory cortex is influenced by emotional stimuli, thereby suggesting that the auditory cortex may also incorporate information about emotional stimuli. Claims in this direction were previously provided in two landmark studies performed by Quirk, Armony and LeDoux in 1997 and 1998 in rats (Quirk et al., 1997; Armony et al., 1998). These authors found that following the association between a tone and painful unconditioned stimuli, both the amygdala and auditory cortex displayed learning-evoked changes that differed between regions. Unlike learning-evoked changes in the amygdala, learning-evoked changes in the auditory cortex needed more trials to develop and displayed delayed responses that critically peaked at the time of shock occurrence, i.e., “seemed to anticipate the unconditioned stimulus”.

A more compelling investigation of the idea that the activity of the auditory cortex also reflects information about emotional stimuli paired with tones was performed by Brosch and colleagues in the primate auditory cortex. The authors trained monkeys in a performance-dependent reward schedule, so that after an error trial the subject expected to receive a smaller reward for the next correct trial (Brosch et al., 2005). By recording neurons in the auditory cortex, the authors

observed the emergence of tonic firing activity that slowly changed over a range of seconds. Critically, these changes terminated with the delivery of reinforces. Moreover, a larger reward prediction error was associated with an increase in the firing rate while no changes in activity pattern were observed in the case of incorrect trials with zero reward prediction errors (Brosch et al., 2005, 2011a). In a subsequent study, the authors further demonstrated that the neuronal firing in the auditory cortex reflects both the mismatch between the expected and delivered rewards and the size of the reward obtained (Brosch et al., 2011b). Taken together, these studies provided evidence that the auditory cortex encodes information not only about the physical features and the behavioural salience of sounds but also about the occurrence, the type and the content of unconditioned emotional stimuli associated with tones. Nevertheless, none of these studies directly compared the activity of the auditory cortex in the presence of similar tones paired with an appetitive reward or an aversive stimulus. In 2012, David and colleagues performed this analysis for the first time (David et al., 2012). Ferrets were trained to perform two different tasks, each requiring discrimination between reference and target tone sequences. In the approach version of the task, animals received a reward if they started licking during the target tones, while in the avoidance version of the task, they received a mild shock for failing to inhibit licking at the onset of target tones. Thus, depending on the task, the same target tone was associated with a different valence (positive or negative). According to the authors, "one might predict two different outcomes during the two behaviors. If behavioral control of A1 reflects contrast between reference and target sounds, independent of task structure, one would expect to find enhanced responses to targets for both approach and avoidance tasks. If, however, top-down control signals reflect *stimulus valence* or the associated behavior, one would expect effects during the approach task to have an opposite sign to those observed during the avoidance task". Task-dependent changes in neural response properties were measured through the analysis of neural firing by obtaining spectro-temporal receptive fields (STRFs). Overall, STRFs exhibited an opposite pattern of activity, depending on the behavioural meaning of the target tone, showing a decrease (or an increase) in their response depending on the

valence of the same frequency tone (**Fig. 1A, B**). This result underlined a change that did not reflect the mere acquired salience of the target tone but rather the acquired valence or associated response. This idea was fully confirmed in subsequent studies performed by Pi et al. (2013) and by Grosso et al. (2015a, 2017).

Pi and colleagues reported that within the auditory cortex of mice, interneurons that express vasoactive intestinal polypeptide (VIP) displayed different activity in the presence of tones paired with painful stimuli or a water reward (Pi et al., 2013). Painful stimuli caused strong phasic activations of cortical neurons at short latencies, while the water reward tended to generate weaker but more sustained increases in firing rate than did aversive stimuli. Critically, two different punishments (air puff and foot shock) generated similar activations, thereby suggesting that such neurons "signal the aversive quality of the negative feedback" (**Fig. 1C**).

Grosso and colleagues demonstrated in rats that tones paired with appetitive or painful stimuli engaged a large percentage of cells responding to both experiences but also a small fraction of neurons that exclusively respond to one experience (**Fig. 2A-C**) (Grosso et al., 2015a). Changing the intensity (i.e., the salience) but not the valence of these experiences still results in the recruitment of a fraction of neurons that exclusively respond to pleasant or unpleasant tones (**Fig. 2D, E**), thus supporting the idea that these populations process the valence rather than the salience of emotional experiences. Critically, the pharmacogenetic blockade of neurons engaged by aversive stimuli impairs the subsequent ability to recognise aversive tones, while it leaves the ability to recognise pleasant tones intact and *vice versa* (**Fig. 2F)** (Grosso et al., 2015a). The latter findings add the new and important information that within the auditory cortex, some neurons exhibit activity that is not only shaped by the valence of tones but also *necessary* to recognise it. In a subsequent study, the authors also showed zones that are engaged by both pleasant and unpleasant experiences within the auditory cortex, whereas other subregions are activated only by one type of experience (Grosso et al., 2017).

Taken together, these studies support the idea that in addition to performing a detailed analysis of the physical properties of auditory stimuli and encoding the physical attribute of meaningful sounds, the auditory cortex may participate in the encoding of the emotional-motivational valence that is assigned to auditory stimuli during affective experiences.

Notably, some of the aforementioned studies were performed in the primary auditory cortex (Te1), while other works investigated the activity of the higher order auditory cortex (Te2). Therefore, both regions may be involved in the processing of emotional stimuli. However, some recent studies uncovered differences between the Te1 and Te2 cortices. In particular, compared with the activity of the Te1 cortex, the activity of the Te2 cortex mostly appears to be modulated when sounds are paired with emotional events in rats (Bao et al., 2001; Holschneider et al., 2006; Poremba et al., 1997, 1998) and Te2 lesions, not Te1 lesions, impair the retention of remote (28-day-old) auditory fearful memories in rats (Cambiaghi et al., 2016a; Sacco and Sacchetti, 2010). These findings may suggest that certain regions, namely, the higher order auditory field, may be particularly involved and necessary for the encoding of tones imbued with emotional-motivational significance within the auditory cortical stream (see Grosso et al., 2015b for a recent review on this topic).

3. Afferent and efferent connections between the auditory cortex and brain structures involved in emotional events

The idea that the auditory cortex may encode information about the emotional-motivational valence of sounds raises the following related questions: i) how does information about the emotional content reach the auditory cortex; and ii) which interactions occur between the auditory cortex and subcortical centres involved in emotional events, such as the amygdala and nucleus accumbens?

3.1 Neuromodulatory systems and the auditory cortex

In addition to the well-defined ascending auditory stream that carries information about the spectral, temporal and spatial characteristics of sounds, the auditory cortex is the recipient of fibres from *neuromodulatory systems*, i.e., the cholinergic, dopaminergic, noradrenergic and serotoninergic systems, that are widely engaged by emotionally laden events (Atzori et al., 2005; Letzkus et al., 2011; Happel et al., 2014; Roozendaaland and McGaugh, 2011; Schultz, 2016; Stark and Scheich 1997). In addition, many studies demonstrated that these systems can shape and drive also the processing of sounds within the auditory cortex (Bao et al. 2001; Edeline et al., 2011; Huang et al., 2016; Letzkus et al., 2011; Martins and Froemke, 2015). Therefore, these systems might contribute to provide information to the auditory cortex about the emotional content of sounds. However, because they modulate a variety of processes within the auditory cortex, it is hard to disentangle whether these systems provide information about the specific valence, i.e., positive or negative, of sounds or whether they enable auditory stimuli to acquire behavioural salience regardless of their emotional valence. By keeping this in mind, here we briefly report some examples of studies showing whether and how neuromodulatory systems can modulate the processing of emotionally laden tones within the auditory cortex.

The release of acethylcholine from basal forebrain afferents has been reported to mediate the activation of cortical neurons induced by aversive stimuli (Letzkus et al., 2011). Moreover, the administration of the acethylcholine receptor agonist nicotine into the auditory cortex affected auditory fear memories while it left the memory of a similar tone paired to incentive stimuli intact, thus suggesting that nicotine, when acting acutely in the auditory cortex, may interfere with the aversive content acquired by tones during fear learning (Cambiaghi et al., 2015).

Several studies have demonstrated the effects also of dopamine on the auditory cortex (Atzori et al., 2005; Bao et al. 2001; Happel et al., 2014; Stark and Scheich 1997). The auditory cortex receives direct dopaminergic innervations from the ventral tegmental area (VTA). Bao et al. showed that the pairing of VTA stimulation with an auditory stimulus increases the selectivity of neural responses to that sound in rats (Bao et al., 2001). Similar results were subsequently reported

by Brosch in primates (Huang et al., 2016). The release of dopamine from the VTA to several brain centres, such as the nucleus accumbens, globus pallidus and orbitofrontal cortex, represents a key mechanism to link sensory stimuli to their rewarding attributes (Schultz, 2016). Therefore, a similar process might occur in the auditory cortex, thereby linking tonal stimuli to their pleasant consequences. Alternatively, as stated above, enhanced dopamine efflux in the auditory cortex might serve to encode salient tones, regardless of their emotional meaning. Thus, further studies are required to better define this important issue.

The auditory cortex is also the target of ascending noradrenergic inputs arriving from the locus coeruleus. During emotional events, especially those related to frightening experiences, norepinephrine is largely released in many brain areas where it can help to strengthen learning and memory processes (Roozendaaland and McGaugh, 2011). Accordingly, pairing a tone with locus coeruleus stimulation induces a shift in the best frequency in auditory cortical neurons in rats (Edeline et al., 2011, Martins and Froemke, 2015). Finally, serotoninergic inputs arriving from the raphe nuclei modulate the activity of the auditory cortex. For instance, VIP interneurons express both cholinergic receptors and serotonin receptors (Pi et al., 2013), and according to Pi et al., “these neuromodulatory systems or other long-range pathways probably convey information about reinforcement events” (Pi et al., 2013).

Taken together, these studies showed that the neuromodulatory systems are able to modulate the activity of the auditory cortex during emotional events. However, the precise nature of the information carried by these systems to the auditory cortex is far to be defined. Therefore, further studies are required to clarify whether the neuromodulatory systems might provide to the sensory cortex information about the emotional content of sensory stimuli.

3.2 The basolateral amygdala and auditory cortex

The auditory cortex receives many *ascending inputs* from subcortical structures engaged in processing emotional events. Among these structures, the anatomical and functional connections between the basolateral nucleus of the amygdala (BLA) and auditory cortex are the most studied and best characterised. The BLA plays a key role in the processing of innate and learned emotional stimuli (McGaugh, 2004; Roozendaal and McGaugh, 2011). Moreover, the BLA promotes learning and memory processes in its target regions, including the hippocampus (see McGaugh, 2004 for an extensive review), cerebellum (Zhu et al., 2011) and perirhinal cortex (Paz et al., 2006). Anatomically, the BLA is reciprocally connected with the auditory cortex (Yang et al., 2016; McDonald, 1998; Romanski and LeDoux, 1993). On the one hand, BLA sends direct projections to the auditory cortex (Yang et al., 2016). On the other hand, BLA is the target of axons mostly descending from the higher order cortices and a lower percentage of axons directly from the primary auditory cortex (McDonald, 1998, Romanski and LeDoux 1993).

Several studies have demonstrated that the BLA drives plasticity processes in the auditory cortex during emotional events. Chavez et al. showed that BLA stimulation temporally coupled with the delivery of a tone determined a specific and long-lasting tuning shift to the frequency of the tone in rats' auditory cortex (Chavez et al., 2009, 2013). This tuning shift occurred only in the case of temporally coupled stimulation of the BLA and tone presentation. Moreover, this shift began one day after training and was maintained for at least three weeks. Therefore, these studies revealed that the BLA can promote "highly specific, enduring, learning-related modifications of stimulus representation" in the auditory cortex. More recently, Poo and colleagues provided compelling evidence in mice that axons arriving from the BLA to the auditory cortex are critically involved in the long-term retention of auditory fear memories (Yang et al., 2016). The authors showed a progressive increase in bouton and spine formation between the axons of amygdala neurons and cells located in layer 5 of the auditory cortex after fear learning (**Fig. 3A, B**). This process took several days to occur. Importantly, chemo- and optogenetic blockade of this pathway impaired the long-term expression of defensive responses towards tonal stimuli. Interestingly, this

process is highly selective for amygdala projections to the auditory cortex because it does not occur for inputs arriving at the auditory cortex from the auditory medial geniculate nucleus of the thalamus (Yang et al., 2016). Therefore, this pathway may represent a way to encode threatening tones in the auditory cortex for the long term.

The auditory cortex also sends descending axons to the BLA (McDonald, 1998; Romanski and LeDoux 1993). In 2006, Boatman and Kim proposed that the thalamic-cortico-amygdala route is the principal pathway for auditory fear memory (Boatman and Kim, 2006). Many studies have provided compelling evidence that axons arriving from the auditory cortex to the BLA are capable of undergoing profound and long-lasting remodelling and that this plasticity may be involved in emotional memory processes. *In vitro* studies showed that descending axons from the auditory cortex to the amygdala display long-term potentiation (LTP) that occurs at the presynaptic locus, i.e., at the level of cortical terminals (Fourcaudot et al., 2009; Humeau et al., 2003; Sigurosson et al., 2010; Tsvetkov et al., 2002). A similar form of electrically-induced LTP was occluded following emotional learning in rats, consistent with the idea that fear learning leads to an LTP-like phenomenon in axons descending from the auditory cortex to the BLA (Tsvetkov et al., 2002). More recently, the reversible blockade of the auditory cortex (Cambiaghi et al., 2017) or the selective optogenetic inhibition of auditory cortex terminals of the auditory cortex in the lateral and basal amygdala (Manassero et al., 2018) was shown to impair fear memory retention in rats (**Fig. 4 A, B**) and to prevent fear-related activity within the amygdala. Altogether, these findings showed that information conveyed from the auditory cortex to the amygdala is essential for the encoding and expression of emotional memories. Interestingly, in another line of research aimed at investigating the interplay that may occur between the auditory cortex and striatum during the association between tones and pleasant stimuli, descending axons from the auditory cortex to the striatum were found to underlie long-term associative processes, perhaps suggesting a general mechanism for the control of emotional behaviours by the sensory cortex. In more detail, by using a perceptual decision-making paradigm and by optogenetically manipulating the activity of

corticostriatal projection neurons within the auditory cortex of rats, Znamenskiy and Zador (2013) demonstrated that this pathway carries information that drives the animals' behavioural responses. By training rats with a similarly rewarded auditory discrimination task, Xiong and colleagues demonstrated that the aforementioned projections from the auditory cortex to the striatum encoded the association between sounds and the relative behavioural response. Specifically, the strengthening of these synapses reflected the improvement in the behavioural performance over the course of training, signalling the learned association and allowing the "transformation of sounds into actions" (Xiong et al., 2015a).

However, all these studies could not determine whether these cortical-amygdala pathways are essential to convey information only about the identity of auditory stimuli to the amygdala or also convey information about the emotional charge of sounds. Claims supporting the latter possibility were recently reported by Cambiaghi et al (2016b). In the presence of a tone previously paired with aversive stimulation, the authors demonstrated that rats' auditory cortex displayed sustained oscillatory activity consisting of an increase in the low theta (3-7 Hz) frequency. This enhanced activity at low theta frequencies has been repeatedly associated with fear memory encoding in the amygdala (Likhtik et al., 2014; Lesting et al., 2011; Seidenbecher et al., 2003), prefrontal cortex (Herry et al., 2016; Lesting et al., 2011) and hippocampus (Lesting et al., 2011; Seidenbecher et al., 2003). In the auditory cortex, enhanced theta activity was highly synchronised with the activity of BLA, thus suggesting a functional connectivity between these sites (**Fig. 4C**). Critically, this oscillatory activity occurred earlier in the auditory cortex than in the BLA, and a preponderant auditory cortex-to-BLA directionality characterised this dialogue (**Fig. 4D, E**). Moreover, the percentage of time that the auditory cortex led the BLA predicted the animals' ability to recognise auditory stimuli as aversive (**Fig. 4F**). Altogether, these data strongly suggest that descending pathways from the auditory cortex to the BLA may also serve to recognise tones as aversive and consequently lead BLA activity.

The idea that the auditory cortex may lead the activity of subcortical centres to drive behavioural responses to emotionally laden tones was further corroborated by a recent study performed in mice by Xiong et al. (2015b). Their study showed that a corticofugal pathway from the auditory cortex to the inferior colliculus (IC) drives innate, sound-driven defence behaviour. In more detail, the optogenetic inhibition of this pathway impaired sound-induced flight responses, while the optogenetic activation of auditory cortex-to-inferior colliculus neurons or their projection terminals in the IC was sufficient for initiating flight responses.

4. Comparison of two models

The involvement of the auditory cortex in emotional processes related to auditory stimuli may be schematised through two different models. One widely accepted idea is that during the association between sounds and emotional stimuli, the auditory cortex processes the physical features of sounds, thereby encoding the identity of the tone paired to emotional stimuli. Moreover, the auditory cortex may encode the behavioural salience of these tonal stimuli. These processes may require both the activation of neuromodulatory systems and ascending inputs from subcortical nuclei that process emotional stimuli, such as the striatum and amygdala. Additionally, other brain structures, such as the amygdala and nucleus accumbens, process the emotional content of an experience. In these sites, information about sounds conveyed by axons descending from the auditory cortex is imbued with their emotional valence. During the subsequent re-presentation of the tones, the auditory cortex rapidly recognises the meaningful sounds and passes this information to other cortical (e.g. prefrontal cortex) and subcortical centres where their valence is encoded, thereby eliciting behavioural reactions. A recent study also proposed this division of labour between the gustatory cortex and amygdala (Wang et al., 2018).

However, in this review, we presented the idea that the auditory cortex may also encode information on the valence of sounds that may lead to an alternative model. During the association

between a sound and emotional stimuli, the auditory cortex processes the physical features of the sound, while subcortical sites analyse the emotional aspects of the experience. In the meantime, due to the inputs arriving from subcortical nuclei, such as the amygdala, as well as from neuromodulatory systems, information about the emotional-motivational valence is incorporated into the neural representation of sounds in the auditory cortex. Thus, the association between sounds and emotional stimuli may be encoded also at the level of the auditory cortex, in its descending inputs to the amygdala and nucleus accumbens, as well as in its cortico-cortical projections. Subsequently, during the re-presentation of stimuli previously paired with emotional events, the information about the identity of sounds and on their behavioural significance (i.e., pleasant or unpleasant) is retrieved within the auditory cortex and its connections with cortical and subcortical nuclei, which in turn drive the appropriate behavioural reactions.

Remarkably, in the second model, there is still a division of labour between the auditory cortex, which processes auditory stimuli, and subcortical nuclei, which analyse emotional stimuli. However, the convergence of this information occurs at the level of the sensory cortex and subcortical nuclei. The large amount of data showing that an amygdala blockade impairs the acquisition and expression of emotional responses towards tones supports both models, not only the first model as sometimes claimed. In fact, the amygdala blockade during the acquisition trial may also affect the transfer of information about the valence of tones from the amygdala to the auditory cortex, thereby preventing the encoding of the emotional-motivational valence in the cortex. Moreover, the blockade of the amygdala during the representation of threatening tones may impair the expression of defensive behaviours activated by descending axons from the auditory cortex to the amygdala. A similar logic may also be applied to the recent literature showing that the optogenetic activation of amygdala neurons enables associative processes as well as elicits defensive responses towards aversive stimuli (see for instance Johansen et al., 2010; Gore et al., 2015).

The two proposed models are not necessarily incompatible. Emotional stimuli encompass many different features, such as physical attributes, intensity, valence and behavioural consequences, and elicit a multifaceted repertoire of brain processes, ranging from the analysis and encoding of sensory stimuli to sensory-motor transformation, choice behaviour and attentional control. Therefore, it might be that some features of the emotional experience, such as the precise nature and identity of aversive stimuli, are mainly encoded at the level of the amygdala thereby resembling the first model whilst other information related to emotional events, such their valence and/or behavioural consequences, might be encoded also within the auditory cortex, as proposed in the second model.

The functional importance of encoding emotional information about sounds in the auditory cortex may be manifold. First, the process will provide a more complete picture of the history and the functional importance of sounds at an earlier sensory stage. In addition, this process may enable rapid but accurate discrimination across safe, threatening or positive tones.

Because parallel descending pathways originating from the auditory cortex target several structures that regulate autonomic, motor and behavioural processes, such as the amygdala, striatum, inferior colliculus and cerebellum, the encoding of the emotional valence at the level of auditory cortex may enable the simultaneous and concomitant activation of these multiple descending pathways, thereby favouring the expression of a more complete, integrated response towards emotionally laden sensory stimuli. Consequently, sensory cortices enable identical stimuli to trigger different responses depending on past experience.

Furthermore, the parallel storage of this information at both the cortical and subcortical levels would prevent the loss of fundamental survival information. Finally, this conceptual model may also be applied to all sensory modalities, whereby other sensory cortices, such as the visual, olfactory and gustatory cortices, may encode emotional information about perceived stimuli in a modality-specific manner (Sacco and Sacchetti, 2010). Therefore, such information becomes widely distributed throughout the cortex, with each sensory cortex coding the valence of stimuli of a

specific modality. Notably, recent studies have uncovered that also the visual cortex contains neurons whose activity is related to the history of reward paired to visual stimuli and that may predict the behavioural outcome of stimuli (Ramesh et al., 2018). In addition, it has been also shown that the visual cortex and amygdala may interact in a similar way to that reported in the case of the auditory cortex during the retention of visual aversive memories (Thompson et al., 2018). Compared with the amygdala and nucleus accumbens, these widespread cortical areas may allow the encoding of a larger amount of information about emotionally laden stimuli.

5. Conclusions and future directions

In the last two decades, an increasing number of studies have provided evidence that the involvement of sensory cortices, such as the visual and auditory cortices, in the processing of sensory stimuli imbued with emotional-motivational charges is more prominent than originally acknowledged. In addition to the exquisite and highly detailed analysis of the spectral, temporal and spatial information of sensory stimuli, these cortices play further important roles. Among these roles, two different but not mutually exclusive roles may be of particular relevance. Sensory cortices may encode the behavioural importance acquired by sensory stimuli during emotional experiences, i.e., their behavioural salience. In addition to performing this function, sensory cortices might participate in encoding the emotional charge that stimuli acquire during emotional events. Here, we reviewed recent evidence obtained in the auditory cortex that may support the latter idea. We also reviewed anatomical and functional studies showing that the auditory cortex is reciprocally interconnected with subcortical nuclei that process emotional stimuli. Moreover, we underlined recent studies showing that the auditory cortex can lead the activity of these nuclei to recognise emotionally laden stimuli. However, we emphasised that the current literature has not universally accepted this idea. Indeed, it remains poorly understood whether and how the emotional charge of sounds might be encoded at the level of the auditory tonotopic map, one of the most important

mechanisms that the auditory system employs to process and encode information about sounds. Therefore, more comprehensive studies are required to address these ideas.

The hypothesis presented here may also have important consequences for the characterisation of the neural circuitry involved in **affective disorders**. In particular, this hypothesis leads to the intriguing possibility that some **fear-related disorders,** such as specific and generalised phobias, may be related to an alteration in sensory processes and memory plasticity occurring in sensory cortices. Such dysfunction might alter the capacity to differentiate between neutral and frightening stimuli, thus leading to generalised fear and anxiety disorders. In this situation, treatments specifically aimed at decreasing the overall activity of the amygdala may produce the detrimental effect of blocking the expression of fear memories and not impact the memory trace in the auditory cortex.

Another important insight may be related to the identification of the neural mechanisms of **drug craving and relapse**. Drug use and relapse involve learned associations between drug-associated sensory stimuli and drug effects. Responses to drug-associated stimuli persist during prolonged abstinence and may lead to compulsive drug taking and episodes of intense drug craving. In individuals who are trying to remain abstinent, the tendency to relapse is a major but unrealised treatment target for drug addiction. Most studies on this issue have addressed the neural processes activated in the striatum. Within this framework, the hypothesis that sensory cortices participate in the encoding of the emotional-motivational charge of sensory stimuli may suggest that the association between sensory cues and drug effects occurs in part within sensory cortices. Therefore, these cortical sites should be the target of treatments aimed at dampening the association between sensory stimuli and drug-seeking behaviours.

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Figure Legends

Fig 1. Similar tones but paired with opposite emotional stimuli elicit different pattern of activity in the auditory cortex. (A-B) Average neural response measured as spectrotemporal receptive field (STRF), representing neural selectivity as a function of frequency and time after stimulus (time lag, ms) in ferrets' auditory cortex. Arrows point to the mean change in neurons responses in the appetitive **(A)** and aversive **(B)** recall. The presentation of a tone paired to appetitive stimuli caused a decrease in neural responsiveness, as shown by the number of neurons activated to the target frequency with respect to passive listening. In contrast, a tone paired with a painful stimulus caused a marked enhancement in neural activity. Adapted from David et al. (2012). **(C)** Raster plots (top) and PETHs (bottom) aligned to reinforcement (reward, green or punishment, red) recorded in vasoactive intestinal peptide (VIP) neurons of mice auditory cortex. All VIP neurons were strongly recruited by punishment (foot shock: 1–4, marked by asterisks; air puff: 5–10), whereas water reward induced weaker and more sustained activation (9 of 10 cells showed significant firing rate increase for reward). Adapted from from Pi et al., 2013.

Fig 2. Distinct neuronal populations are activated within the auditory cortex by tones paired either with a punishment or a reward. (A) Representative fluorescent photomicrographs showing neuronal nuclei expressing Homer 1a (H1a, green arrowheads) or activity-regulated cytoskeletal-associated protein (Arc, red) mRNA or both (yellow) in fear-fear, appetitive-appetitive (app-app), and appetitive-fear groups. H1a and Arc mRNA were expressed following the presentation of two different tones (conditioned stimuli 1 and 2, CS1 and CS2). **(B)** The percentages of neurons expressing only H1a and only Arc were significantly higher in the appetitive-fear group than in either the fear-fear or appetitive-appetitive group, with a corresponding reduction in doubly labeled cells. **(C)** The reactivation ratio, calculated as the percentage of cells expressing both Arc and H1a

divided by the number of cells expressing H1a, was significantly less in the appetitive-fear group than in control groups. Scale bar, 20 μm**. (D, E)** By increasing the strength of aversive conditioning (app-fear↑↑), the freezing response (D) was higher in this appetitive-fear group than in the previous appetitive-fear experiment (see panel A). However, the percentages of cells expressing only H1a, only Arc or both H1a and Arc (E) were similar between stronger (app-fear↑↑) and weaker (app-fear) fear-conditioned animals. Scale bar, 20 μm. **(F)** Daun02 inactivation method was employed to permanently disrupt cells activated during fear or appetitive memory recall. Targeted inactivation of neurons activated during fear recall resulted in an impairment of the fear memory while leaving appetitive memories unaffected. In a complementary experiment, animals showed amnesia to appetitive memories but not to fear memories when the Daun02 was injected after the reactivation of appetitive memories. Adapted from Grosso et al., 2015.

Fig 3. Synaptic contacts between cortical neurons and axons arising from the basolateral amygdala sustained a prolonged rearrangement following auditory fear learning and are necessary for the long-term retention of fear memories. (A) Colocalization of amygdala axons (GFP, green) and apical dendrites of neurons in the layer 5 of auditory cortex (YFP, red). Scale bar, 100 μm (fixed slice). Time course of the synaptic modifications of amygdalo-cortical connections after fear learning: in vivo two photon imaging of amygdala axons (green) and cortical neurons (red) after fear conditioning (2 hours and 3 days) and the day before (-1 day). Arrows, triangles and diamonds point to stable, newly formed and eliminated putative synaptic pairs, respectively. Scale bars, 2 μm. **(B)** Percentages of newly formed and eliminated amygdalo–cortical synaptic pairs in control and conditioned mice at 2 hours, 1 day, 2 days and 3 days with respect to the day before conditioning (−1 day). Adapted from Yang et al., 2016.

Fig 4. Auditory cortex drives the activity of basolateral amygdala during the long-term expression of fear memories. (A) Scheme of the strategy used to specifically inhibit Te2 projections to BLA (left). The Te2 was injected with rAAV5/CamKIIa-eNpHR3.0-mCherry-WPRE, while optic fibers were implanted in the BLA, where positive terminals were observed. **(B)** Rats injected with eNpHR-mCherry exhibited significantly lower freezing than mCherry controls during long-term fear memory retention. **(C)** Fear memory retrieval at long-term time point (30 days, red line) is accompanied by an increased in the synchrony between the secondary auditory cortex (Te2) and basolateral amygdala (BLA) activity with respect to unconditioned (naïve, grey line) and recently conditioned (24 h, blue line) rats. The Te2-BLA coherence was significantly higher within the low-theta range (3-7Hz, right graph). **(D)** Te2-to-BLA information flow during long-term fear memory retrieval in an example of filtered LFPs illustrating the power cross-correlation lag analysis (2 s). Arrows go from the leading (Te2, red) to the lagging (BLA, blue) area. (**E)** Distribution of maximal cross-correlation lags during remote memory retrieval, showing mean (red line) and median values (blue line). These data showed that Te2 leads BLA activity during long-term memory retention. (**F)** The correlation analysis between the percentages of time Te2 leads BLA during memory recall and the latency to respond (freezing) by the animal shows that higher Te2-leading activity results in faster behavioral responses to the CS. Adapted from Manassero et al., 2017 and Cambiaghi et al., 2016b

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