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Neuroscience 299 (Forefront Review) 2015 : 45-55

DOI: *10.1016/j.neuroscience.2015.04.068*

Auditory cortex involvement in emotional learning and memory

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Abstract

Emotional memories represent the core of human and animal life and drive future choices and behaviors. Early research involving brain lesion studies in animals lead to the idea that the auditory cortex participates in emotional learning by processing the sensory features of auditory stimuli paired with emotional consequences and by transmitting this information to the amygdala. Nevertheless, electrophysiological and imaging studies revealed that, following emotional experiences, the auditory cortex undergoes learning-induced changes that are highly specific, associative and long lasting. These studies suggested that the role played by the auditory cortex goes beyond stimulus elaboration and transmission. Here, we discuss three major perspectives created by these data. In particular, we analyze the possible roles of the auditory cortex in emotional learning, we examine the recruitment of the auditory cortex during early and late memory trace encoding, and finally we consider the functional interplay between the auditory cortex and subcortical nuclei, such as the amygdala, that process affective information. We conclude that, starting from the early phase of memory encoding, the auditory cortex has a more prominent role in emotional learning, through its connections with subcortical nuclei, than is typically acknowledged.

Abbreviations: BOLD, blood oxygen level-dependent; CS, conditioned, stimulus; LTP, long-term potentiation; US, unconditioned stimulus; VTA, ventral tegmental area.

Key words: emotional learning, auditory cortex, amygdala, long-term memory consolidation, fear conditioning

Introduction

During emotional experiences, sensory stimuli such as sounds, odors and colors acquire a positive or negative value through their association with rewards or punishments, respectively, in a process called “emotional learning”. Emotional learning is typically studied in animals, including humans, using classical pavlovian conditioning; in this procedure, a subject is exposed to a conditioned stimulus (CS), such as a tone, light or odor, in association with an unconditioned stimulus (US). Depending on the type of US, there are two main forms of pavlovian conditioning. In appetitive conditioning, the US is a positive reinforcement such as food, drink or addictive drug. In aversive conditioning, the US is an unpleasant deterrent such as a foot shock, loud noise or air puff. In both

appetitive and aversive conditioning, following pairing of the CS with the US, the CS takes on the affective qualities of the US and later, in the absence of the US, it will evoke a conditioned emotional reaction.

The memory of past emotional and sensory events is encoded, at least in part, in the sensory cortex. Early attempts to identify the neural circuitry underlying emotional learning found that lesions in the auditory or visual cortex of rodents did not prevent the formation of auditory or visual memories of fear (LeDoux et al., 1989, Romanski and LeDoux, 1992a, Romanski and LeDoux, 1992b and Falls and Davis, 1993). Moreover, these lesions did not affect the retention of auditory or visual fear memories when they were made shortly after training (Jarrell et al., 1987, Rosen et al., 1992 and Campeau and Davis, 1995). Romanski and LeDoux (1992b) compared the effects of lesions in the thalamo-cortico-amygdala projection and in the thalamo-amygdala projection: destruction of either pathway alone had no effect on auditory fear conditioning, while combined lesions in both sensory pathways disrupted it. These data led to the standard hypothesis, which states that sensory inputs to the amygdala come from both the thalamus and the sensory cortex and that fear conditioning to a simple auditory stimulus ("cued fear conditioning") can be mediated by either of these pathways (LeDoux, 2000). More recently, however, Boatman and Kim found that lesions in the thalamo-amygdala projection caused severe but incomplete deficits in the retention of auditory fear memories, while lesions in the thalamo-cortico-amygdala connectivity abolished it completely; these authors therefore suggested that the thalamo-cortico-amygdala route is the principal pathway for auditory fear learning in intact rat brain (Boatman and Kim, 2006).

Altogether, these lesion studies lead to the idea that the auditory cortex is dispensable for emotional memory formation and retrieval. However, electrophysiological studies have provided evidence for learning-induced plasticity in the auditory cortex that transcends the analysis of physical properties of auditory stimuli and their transmission to the amygdala. Auditory cortical plasticity has been reported in animal models and for both appetitive and aversive conditioning (see Weinberger, 2004, Weinberger, 2007, Weinberger, 2015, Ohl and Scheich, 2005 and Brosch et al., 2011a for extensive reviews). Furthermore, evidence of learning-evoked plasticity in the human auditory cortex has been provided by neuroimaging studies using PET (Molchan et al., 1994 and Morris et al., 1998), functional MRI (Thiel et al., 2002), and magnetoencephalography (Kluge et al., 2011). Plasticity in the auditory cortex was strictly related to learning processes, in both humans and animals. Furthermore, it developed rapidly and became stronger over days without further training, lasting up to 8 weeks in rodents (Weinberger, 2004, Weinberger, 2007 and Weinberger, 2015). These findings are at odds with the previously mentioned lesion studies. As a consequence, despite more than 30 years of research, the roles and conditions of auditory cortex involvement in emotional processing remain largely controversial. In this Forefront Review, we discuss: (i) the roles of the auditory cortex in emotional learning and memory processing, (ii) the dynamics of auditory cortex recruitment during the course of emotional memory formation, consolidation and storage, and (iii)

the functional interplay between the auditory cortex and subcortical nuclei, specifically the amygdala and striatum, during memory encoding and retrieval.

Roles of the auditory cortex in emotional learning and memory processing

Emotional learning involves several processes: the elaboration and subsequent memorization of the sensory features of the CS and US ("perceptual learning"); the linking of different sensory stimuli ("S–S learning"); and the association of the CS to the value of (or the response to) the US. The most commonly employed learning paradigms, such as fear conditioning and appetitive conditioning, engage these processes simultaneously and thus do not allow them to be studied separately. Furthermore, most of the data about the auditory cortex have been obtained using different types of fear conditioning models (i.e., with a simple pure tone or a complex auditory stimulus as the CS), during different phases of memory processing (i.e., acquisition, consolidation, storage or retrieval) and by investigating different cortical regions (e.g., primary cortex or higher order areas). As a consequence, the role of the auditory cortex in emotional learning and memory processes remains a matter of debate.

Auditory cortex in the analysis of auditory CS physical properties

In general terms, sensory cortices process and encode the physical attributes of perceived stimuli. One of the roles of the auditory cortex in emotional learning may therefore be the analysis and subsequent memorization of the physical attributes of auditory stimuli acting as CSs. However, as previously said, irreversible lesions in the entire auditory or visual cortex do not affect learned fear to simple auditory or visual CSs in rodents (Jarrell et al., 1987, LeDoux et al., 1989, Romanski and LeDoux, 1992a, Romanski and LeDoux, 1992b, Rosen et al., 1992, Falls and Davis, 1993 and Campeau and Davis, 1995). Furthermore, lesions in the auditory cortex do not impair the ability to discriminate frequencies, as shown in cats (Butler et al., 1957). As such, these lesion studies demonstrate that the auditory cortex is not essential for simple auditory behaviors in mammals. These findings lead to the idea that the complexity of auditory stimuli is the key condition for the engagement of the auditory cortex in emotional learning (LeDoux, 2000). However, Talwar and Gerstein (2001) showed that the reversible inactivation of the auditory cortex, while rats performed a simple auditory task, induced profound deficits in frequency discrimination. These authors therefore concluded that the auditory cortex is normally required for basic acoustic processing. They also argued that our understanding of the cortex's involvement in simple auditory tasks is confounded by the reorganization of the auditory system, which, in the long-term, compensates for the loss of cortical processing induced by irreversible lesions (Talwar and Gerstein, 2001). Two recent studies in rodents showed that acute reversible inactivation (Letzkus et al., 2011) and optogenetic manipulation (Weible et al., 2014) of the auditory cortex during training prevented auditory fear learning. However, both studies used complex tones, namely frequency-modulated sweeps (Letzkus et al., 2011) and temporally structured sounds (Weible et al., 2014), as the CS.

Thus, it remains unclear if the observed amnesia was due to the acute blockade of the auditory cortex upon learning, preventing compensative neural mechanisms, or, alternatively, to the use of complex auditory stimuli. Therefore, if the auditory cortex is necessary for the analysis and encoding of simple auditory CS remains controversial.

Besides the putative role of the auditory cortex in the analysis of auditory CSs, it may also take part in the changes in sensory perception that occur after fear learning. Aizenberg and Geffen (2013) showed that, depending on the level of learning specificity to the conditioned tone, mice displayed either an increase or a decrease in their abilities to discriminate the frequencies of simple auditory stimuli. This process was dependent on the auditory cortex, as inactivation of this area during memory retrieval canceled the changes in sensory acuity evoked by fear conditioning. Similar results were obtained in humans in an odor-conditioned task (Li et al., 2008). This study showed that emotional learning induces plasticity in the olfactory cortex in order to enhance the perception of sensory cues in support of adaptive behavior. These two studies therefore pointed out that the sensory cortex is involved in the changes in perception of simple sensory stimuli that follow emotional learning.

Altogether, these data indicate that the auditory cortex participates in the analysis and encoding of complex auditory CSs. It also participates in the development of plasticity in the perception of auditory stimuli that follows emotional learning. However, it remains controversial if this area is required for encoding simple CSs.

Auditory cortex and emotional processes

Since at least 1990, numerous studies have suggested that the auditory cortex is also involved in several higher cognitive and emotional processes related to the sensory experience (reviewed in Weinberger, 2004, Weinberger, 2007, Weinberger, 2015, Fritz et al., 2007 and Shamma and Fritz, 2014). Several recent works revealed that motivational-emotional processes are pronounced within the auditory cortex, where they can help to link the CS's physical attributes to the affective charge or to the behavioral responses occurring during emotional experiences. We recently showed that the neuronal activity of the rat auditory cortex increases more following the presentation of a tone previously paired with an emotional experience than after a similar tone never paired with an affective or motivational stimulus (Sacco and Sacchetti, 2010) (Fig. 1). This finding was confirmed by Kwon et al. (2012). Brosch et al. (2011b) reported that, in the monkey auditory cortex, neuronal firing during an auditory task reflected both the expectancy for a reward and the response to the size of the reward actually received. Similarly, Bieszczad and Weinberger (2012) reported that the extinction of emotional responses to behaviorally relevant CS is associated with a decrease in the size of the area of representation of the tone. Remarkably, the amount of area loss correlated with the amount of extinction. The authors concluded that changes in the cortical representation of tones likely predict emotional reinforcements, such as reward or punishment.

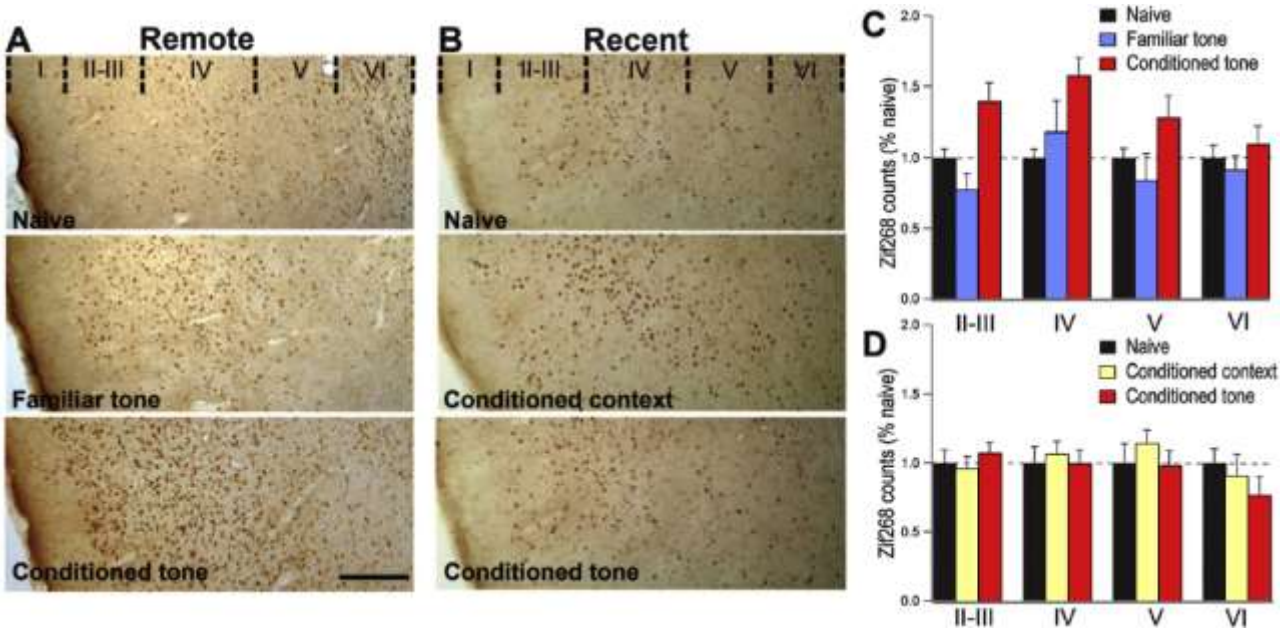

Fig. 1. Recall of remote, but not recent, fearful memories induces neuronal activation in the Te2 area of rats. (A, B) Immunohistochemical staining of Zif628 protein, a marker of neuronal activity, in Te2 cortical layers I–VI after a test of remote (A) or recent (B) memory of fear. Scale bar=150 lm. (C) After the remote memory test, Zif268-positive nuclei counts in layers II–III and IV were significantly higher in fear-conditioned rats than in naive animals or in those that had already heard the tone in the absence of pairing with an emotional stimulus (‘‘familiar’’ group). (D) After the recent memory test, immunohistochemistry revealed no significant difference between the groups in any Te2 cortical layer. All data are normalized to naive values. Adapted from Sacco and Sacchetti (2010).

Two other studies provided further insights into the emotional–motivational processes occurring in the auditory cortex. Some cortical interneurons in the auditory cortex were shown to be responsive not only to auditory CSs but also to painful USs (Letzkus et al., 2011 and Pi et al., 2013) and appetitive USs (Pi et al., 2013), indicating that the activity of cortical neurons is modulated by emotional information. Remarkably, in the latter study, two different punishments (air puff and foot shock) generated similarly strong phasic activations of cortical neurons at short latencies, thereby suggesting that such neurons “signal the aversive quality of the negative feedback” (Pi et al., 2013). In the same study, the water reward tended to generate weaker (but more sustained) increases in firing rate than did aversive stimuli, again supporting the view that the activity of some auditory cortical neurons is driven by the emotional–motivational charge of the CS. A similar suggestion came from studies showing that the emotional content provided by similar auditory stimuli, but paired to an aversive or appetitive US, shaped the plasticity of the auditory cortical receptive field in opposite ways (David et al., 2012 and Yin et al., 2014) (Fig. 2). Altogether, these findings suggest that the activity of the auditory cortex is profoundly influenced by the emotional information that is assigned to sensory stimuli during affective experiences.

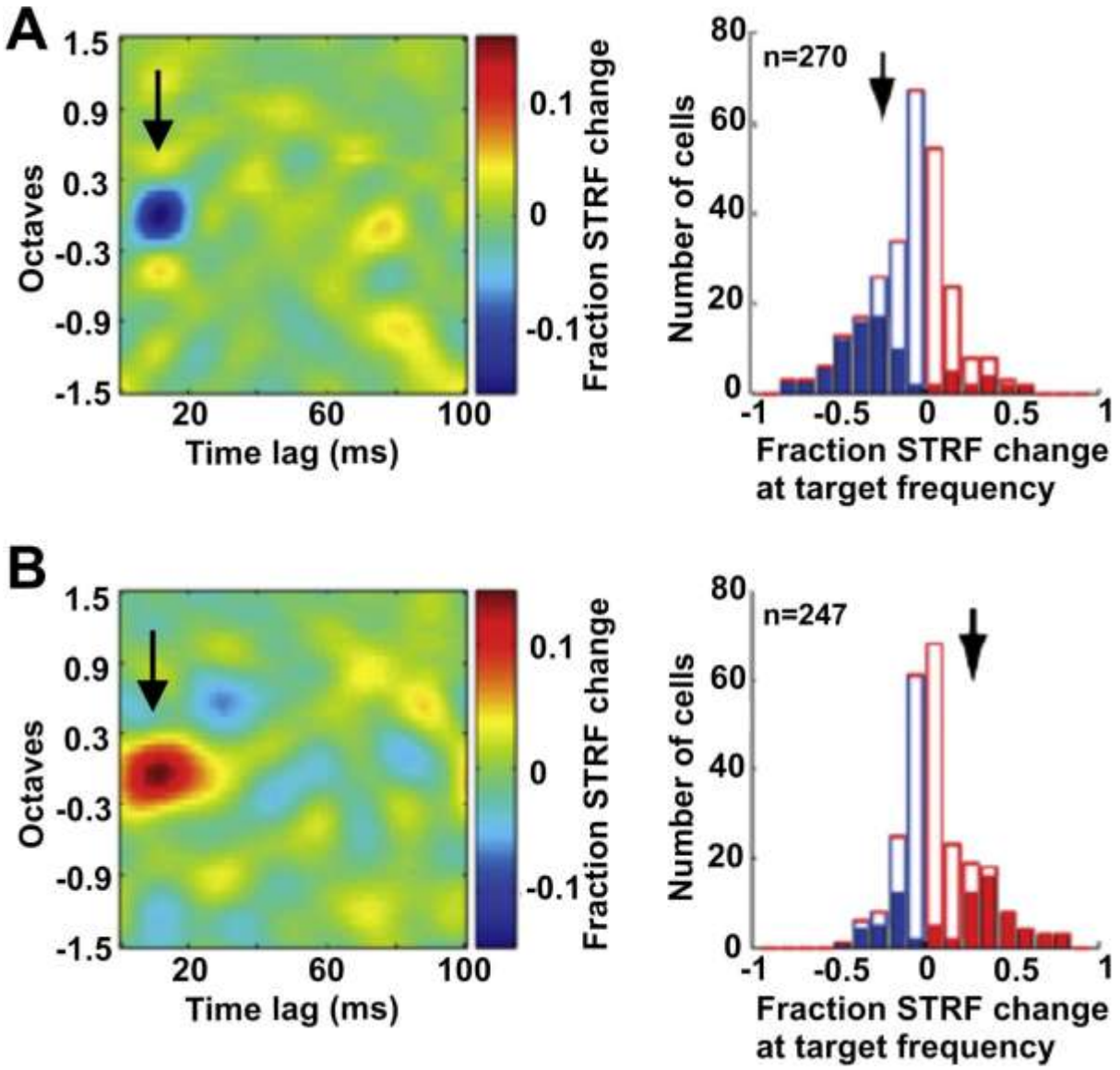

Fig. 2. Positive and negative emotional-motivational processes differently activate the primary auditory cortex to a specific tone. (A, B, left panels) Average neural response measured as spectrotemporal receptive field (STRF), representing neural selectivity as a function of frequency and time after stimulus (time lag, ms). Arrows point to the main response in the appetitive (A) and aversive (B) recall. An appetitive behavioral recall resulted in a consistent decrease in neural responsiveness, as shown by the number of neurons activated to the target frequency with respect to passive listening (A, right panel). In contrast, an aversive recall induced a marked enhancement in neural activity (B, right panel). Adapted from David et al. (2012).

Do primary and higher order auditory cortices play similar or distinct roles in emotional learning and memory processing?

Most of the aforementioned studies did not differentiate between primary and higher order auditory areas despite the fact that, in mammals, these areas have been defined on the basis of anatomical, cytoarchitectonic and electrophysiological criteria (Kolb and Tees, 1990 and Paxinos, 2004) (Fig. 3). In rodents, the auditory cortex is subdivided into a central core and a surrounding belt region. The central core, corresponding to area Te1 of Zilles (1985), is assumed to be the primary auditory

cortex, while the surrounding regions (areas Te2 and Te3 of Zilles) are considered higher order auditory cortices (Zilles, 1985, Kolb and Tees, 1990 and Paxinos, 2004). Te2 receives lighter projections from the acoustic thalamic nuclei than does the primary auditory cortex (Kolb and Tees, 1990, Romanski and LeDoux, 1993 and Paxinos, 2004), but it has heavier connections with the other neocortical areas and with subcortical nuclei, such as the amygdala and the nucleus accumbens (Kolb and Tees, 1990 and Romanski and LeDoux, 1993).

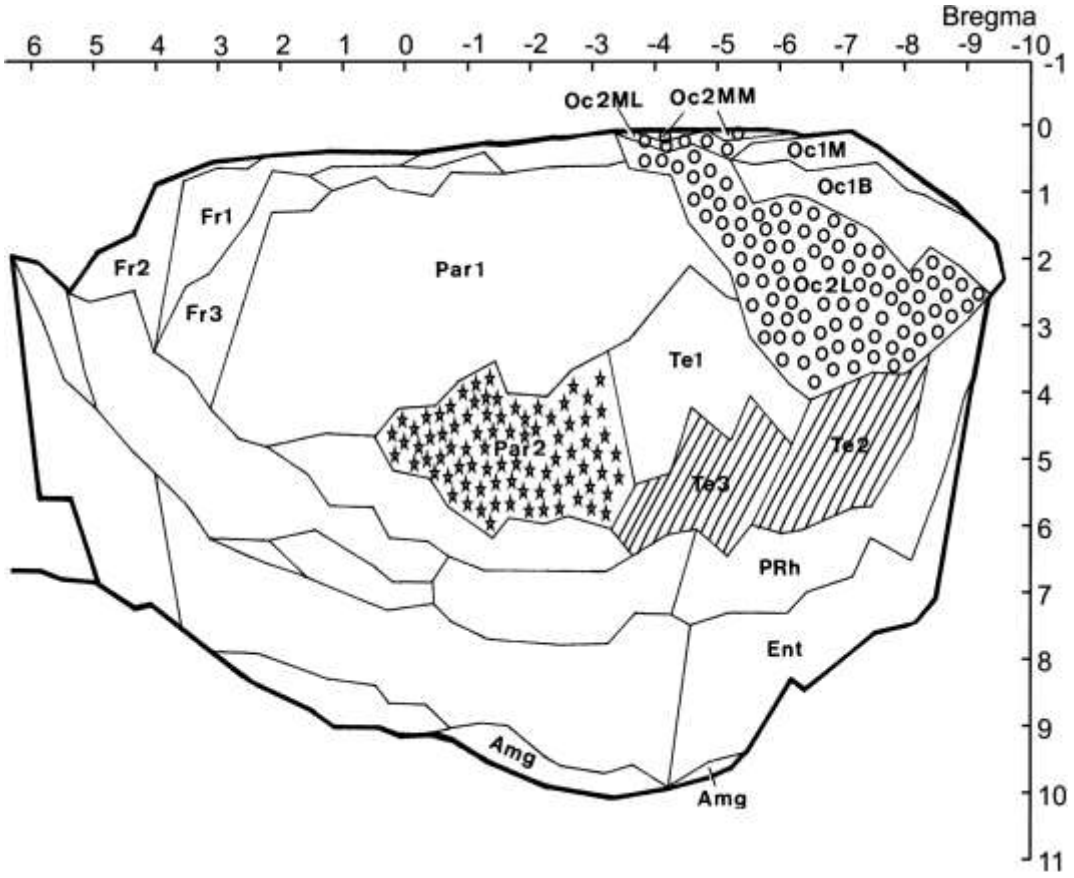

Fig. 3. Primary and higher order sensory cortices in rodents. Lateral view of the cortical mantle showing the primary and higher order auditory, visual and somatosensory cortices. The primary auditory cortex (Te1) is surrounded by two higher order cortices, namely Te2 and Te3. The primary visual cortex (Oc1) is divided into the monocular (Oc1M) and binocular (Oc1B) areas, and surrounded by higher order visual areas in lateral (Oc2L), mediolateral (Oc2ML) and mediomedial (Oc2MM) positions. The somatosensory cortex is divided into primary (Par1) and secondary (Par2) regions, indicated with stars. The upper axis indicates positive and negative distances from the bregma. Plate adapted from Zilles (1985). PRh, perirhinal cortex; Ent, entorhinal cortex; Amg, amygdaloid body; Fr1, Fr2 and Fr3, primary, secondary and tertiary frontal cortices, respectively.

Many studies have shown that the learned emotional–motivational value of sounds shapes the activity of neurons, not only in the primary auditory cortex (Letzkus et al., 2011, Bieszczad and Weinberger, 2012, David et al., 2012, Pi et al., 2013 and Yin et al., 2014) but also in the Te2 (Kraus

and Disterhoft, 1982 and Diamond and Weinberger, 1984) and the Te3 (Quirk et al., 1997). In studies that compared the three auditory cortices following emotional learning, neuronal activity was seen to increase more in Te2 than in the other higher order cortex Te3 or in the primary cortex Te1 (Poremba et al., 1997, Poremba et al., 1998 and Holschneider et al., 2006). Bao et al. (2001) found that the pairing of an auditory stimulus to the electrical stimulation of the ventral tegmental area (VTA) increased the selectivity of the neural responses to that sound, in both Te1 and Te2. However, the authors wrote that "strong, sharply tuned responses to the paired tones also emerge in a second cortical area [Te2], whereas the same stimuli evoke only poor or non-selective responses in this second cortical field in naive animals." In other words, Te2 activity "becomes sharply and almost exclusively tuned to the paired stimulus frequency in VTA-stimulated animals" whereas it was "poorly responsive to tonal stimuli and non-selective for tone frequency in naive animals" (Bao et al., 2001) (Fig. 4). These findings indicate that Te2 activity is strictly related to emotional experiences, whereas the primary auditory cortex also responds to neutral auditory cues. This view is in accordance with the fact that Te2 is not significantly activated by non-associative processes, such as long-term habituation to a sensory stimulus (Gonzalez-Lima and Scheich, 1985 and Gonzalez-Lima et al., 1989). Moreover, we showed that lesions in the secondary sensory cortices did not destroy the long-term ability to recognize the physical features of the sensory stimuli ("recognition memory") (Sacco and Sacchetti, 2010). Accordingly, novel and familiar sounds activate Te2 neurons in a similar manner in the absence of conditioning (Wan et al., 2001 and Sacco and Sacchetti, 2010), while neural activity in this area increases significantly if the sounds had previously acquired a behavioral value (Sacco and Sacchetti, 2010 and Kwon et al., 2012). Overall, these data support the view that higher order sensory cortices, and particularly Te2, are parts of the auditory stream that are most modulated by the emotional–motivational aspects of sensory experiences.

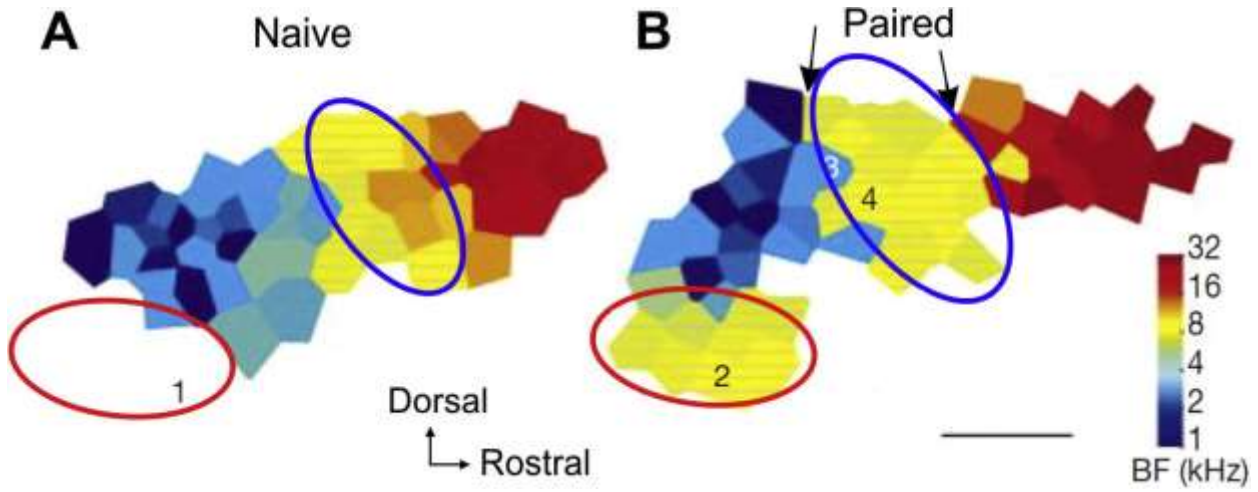

Fig. 4. Reorganization of the primary and secondary auditory cortices in response to microstimulation of the ventral tegmental area (VTA) paired with a tone. The association of a pulsed tone (9 kHz) with VTA stimulation (paired) expanded the tone-responsive auditory cortex associated to that frequency, as shown by a representative cortical tonotopic map from one naive (A) and one paired animal (B); in the latter animal, there are two tone-responsive areas, namely Te1 (*blue circle*) and Te2 (*red circle*). Arrows indicate transitional boundaries surrounding Te1. *BF*, best frequencies. Scale bar = 500 μm. Adapted from Bao et al. (2001).

Similar results have been reported in humans, where the vocal expressions of emotions consistently activate several subregions in the primary and higher order auditory cortices (Belin et al., 2000, Ethofer et al., 2009, Ethofer et al., 2012 and Frühholz and Grandjean, 2013). The activity of some of these subregions is driven specifically by the emotional valence expressed by speech (Frühholz and Grandjean, 2013).

Concerning human fear learning, Kluge et al. (2011) assessed auditory cortical plasticity in subjects exposed to two tones (phase 1), when one of the tones was associated with a shock (phase 2; classical aversive conditioning paradigm), and when the shock was associated with the other tone (contingency reversal; phase 3). Overall, they found distinct cognitive and emotional influences on auditory cortical processes. In particular, they showed that the auditory-evoked field components P1m, N1m and P2m, measured from sensors over the auditory cortex, displayed distinct changes during emotional learning and contingency reversal. P1m, which likely arises in medial aspects of the primary auditory cortex, changed after new learning but not after contingency reversal. Conversely, the P2m component, which has several contributing sources from higher order auditory cortices (Tarkka et al., 1995), rapidly reversed its selectivity when contingencies changed. According to the authors of the study (Kluge et al., 2011), these changes reflect different constraints on the various levels of the auditory cortical hierarchy.

Differences in the activities of the auditory cortices during emotional learning were recently uncovered by Apergis-Schoute et al. (2014). These authors used functional MRI to measure, in healthy persons, the blood oxygen level-dependent (BOLD) signal in the amygdala and in the primary and higher order cortices during the extinction of fear responses to a learned frightening stimulus. They found that the BOLD signal decreased progressively in a threat extinction paradigm in the amygdala and primary auditory cortex (Fig. 5). In contrast, representation of the fear memory in the higher order auditory cortex persisted throughout the extinction sessions, which the authors explained as “a way to keep the possible threat of this stimulus highlighted” (Apergis-Schoute et al., 2014). Similarly, but working in the taste system, Small et al. (2003) reported that the secondary taste areas of the orbitofrontal cortex were responsive to the emotional valence that had been assigned to taste stimuli. Similar results have been obtained in the study of olfaction, where the primary olfactory cortex was found to be driven by the intensity of odorants while the orbitofrontal regions responded to the valence independent of the intensity (Anderson and Sobel, 2003 and Anderson et al., 2003).

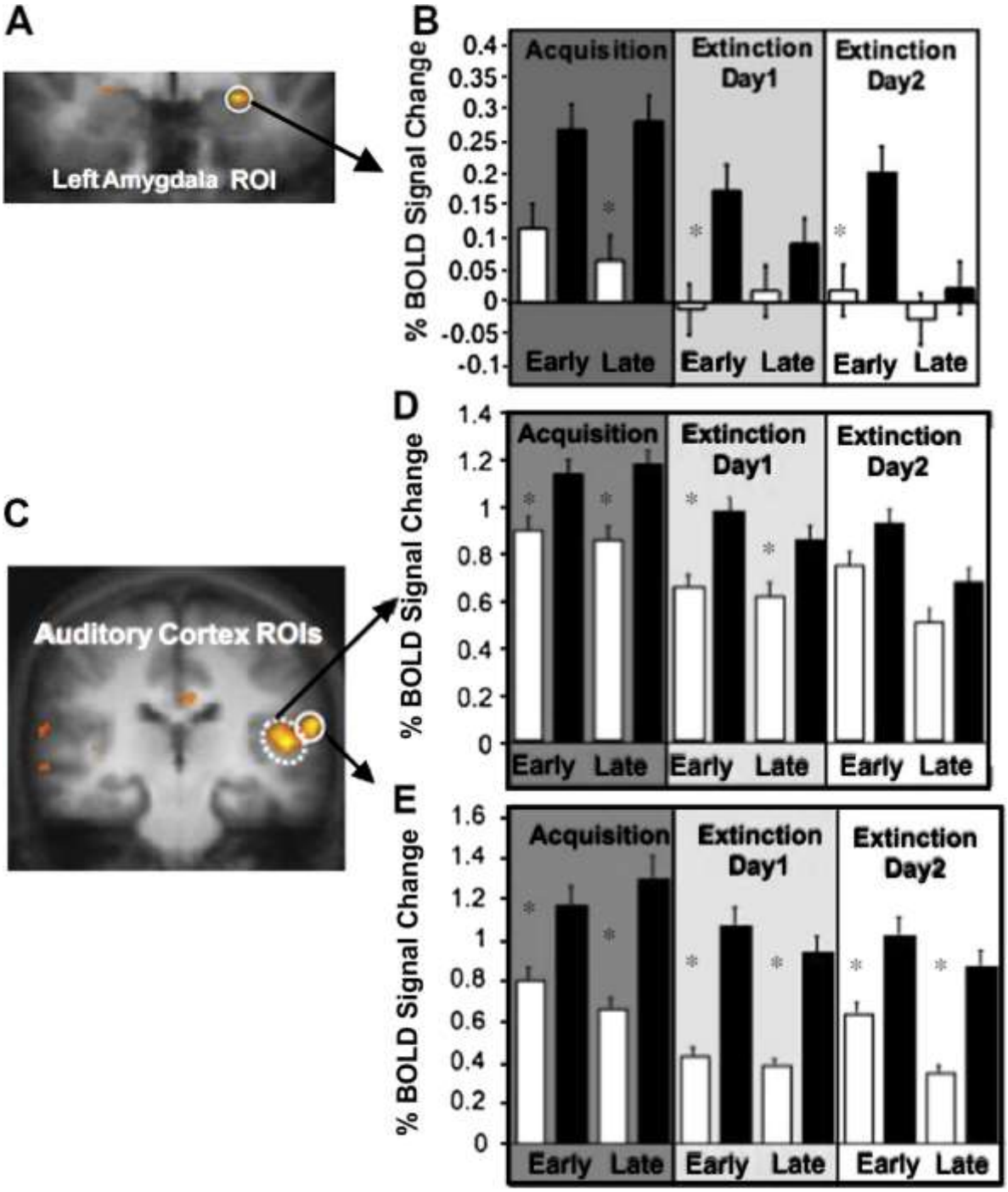

Fig. 5. Different activity patterns in primary and association auditory cortices following threat memory extinction in humans. (A) Functional MR image of amygdala during threat acquisition (activation). (B) Percent change in BOLD signal upon hearing tones that were either unpaired (*white bars*) or paired with a CS (*black bars*), at acquisition and extinction on the same day and one day later. (C) Functional MR image of auditory cortex during acquisition. *Dashed circle*, primary auditory cortex; *solid circle*, higher order auditory cortices. (D, E) Corresponding BOLD signal changes, as in A. Asterisks indicate significant changes between unpaired and paired tones. The activation (i.e., difference between unpaired and paired tones) is greater in the higher order auditory cortex (E) than in the primary auditory cortex (D) on both extinction days. Adapted from Apergis-Schoute et al. (2014).

Collectively, these findings suggest that the higher order sensory cortices are part of sensory areas whose activities are shaped by the emotional charge that the perceived stimuli have acquired. If confirmed by further studies, these data will be the basis of a new conceptual framework about the brain circuitry that stores memory of behaviorally significant stimuli. Higher order sensory cortices appear to be the crucial link between the sites that elaborate perceived stimuli and those that are activated by the emotional reinforcement; they participate in linking sensory stimuli to their affective meaning and in storing this information over time. Such information becomes widely distributed throughout the brain, with each sensory cortex coding the valence of the stimuli specific for that sensory modality.

Auditory cortex and the formation of recent and remote emotional memories

Memories are thought to require a prolonged consolidation process in order to be stabilized and maintained for weeks, months and years (McGaugh, 2000, McGaugh, 2015 and Frankland and Bontempi, 2005). Memory consolidation involves reorganization at the synaptic and system levels. Synaptic consolidation is based on changes in synaptic architecture, whereas consolidation at the system level involves changes in the neural circuits that support memory. The standard theory of system-level memory consolidation, regarding declarative and spatial memories, states that the hippocampus integrates information from a distributed cortical network (Frankland and Bontempi, 2005). As these memories mature, the role of the hippocampus gradually diminishes whereas cortical areas become capable of sustaining permanent memories.

Regarding fear memories related to explicit sensory stimuli, in contrast, it is largely unknown if they involve reorganization at the system level. Two recent studies showed that the circuits that store and retrieve fear memories changed with time (Sacco and Sacchetti, 2010 and Do-Monte et al., 2015), thus supporting the view that also emotional memories undergo system-level reorganization. In particular, we found that, 24 h after training, irreversible or reversible inactivation of the higher order auditory cortex did not affect fear memory retention tested one week later (recent memory) (Sacco and Sacchetti, 2010), in line with previous studies (LeDoux et al., 1989, Romanski and LeDoux, 1992a and Romanski and LeDoux, 1992b). Conversely, we also found that auditory cortical blockade performed 1 month after training impaired subsequent retention of fear memory (remote memory). This finding suggests that the neural network that forms or stores such information undergoes reorganization. Three major hypotheses can explain how such neural system reorganization occurs (Fig. 6).

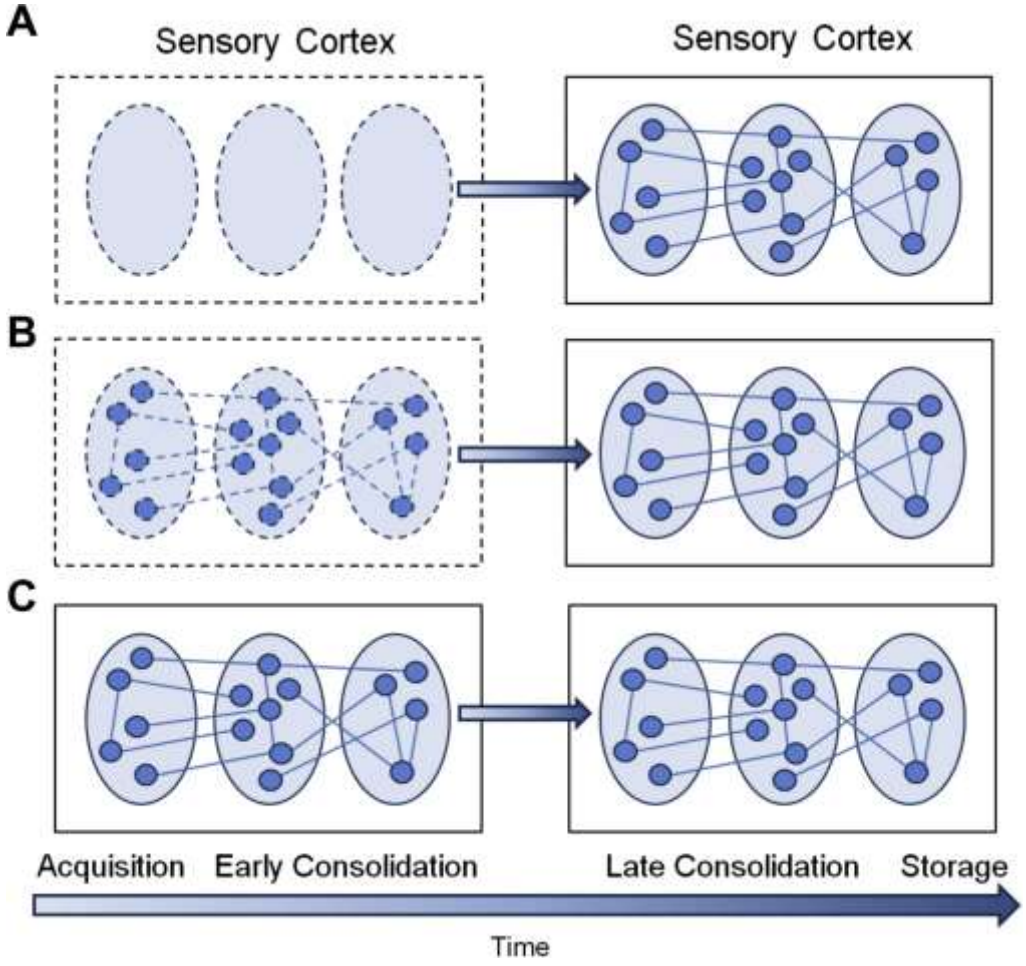

Fig. 6. Three major hypotheses on the role of the sensory cortex in the formation of recent and remote emotional memories. (A) In the first model, the sensory cortex is not involved in the acquisition or early consolidation of emotional memories. Over time, some of the memory information encoded elsewhere is transferred to the sensory regions for late consolidation and permanent storage. (B) In the second model, the sensory cortex is engaged upon memory encoding, in a selective manner, to form stable, long-lasting memories; in this condition, recent emotional memories recruit different brain circuits. (C) In the third hypothesis, the sensory cortices are recruited upon encoding to form both recent and remote emotional memories. However, in the early period, other structures are also processing recently learned information. As a consequence, lesions in the sensory cortex do not cause amnesia of recently acquired emotional memories.

In the first model, the auditory cortex is not involved in the acquisition or early consolidation of memories shortly after training (Fig. 6A). In this framework, early memory formation requires other structures, such as the thalamo-amygdala pathway (LeDoux, 2000 and Weinberger, 2011), the connections between the prefrontal cortex and amygdala (Herry and Johansen, 2014), and the cerebellum (Sacchetti et al., 2002,Sacchetti et al., 2004 and Ruediger et al., 2011). Over days to weeks, as memories mature (late consolidation), some of this information is transferred to the auditory cortex to be stored permanently. This hypothesis is however contrasted by many studies showing that the activity of the auditory cortex is changed shortly after learning (Quirk et al., 1995, Quirk et al., 1997, Weinberger, 2004, Weinberger, 2007, Weinberger, 2011,Chavez et al., 2009, Chavez et al., 2013, Bieszczad and Weinberger, 2012, Gdalyahu et al., 2012 and Weible et

al., 2014). In accordance with the recruitment of the auditory cortex in the early processes of memory formation, in hippocampus-dependent memories cortical structures undergo a "tagging process" upon encoding to ensure memory formation (Lesburguères et al., 2011).

The second hypothesis states that the auditory cortex is engaged upon encoding to selectively form long-term, remote memories (e.g., 30-day-old memories), while it is not required for the formation of short-term memories or more recent long-term memories (e.g., 1-day-old memories) (Fig. 6B). The third possibility is that auditory cortex is involved upon encoding to form both recent and remote memories (Fig. 6C). In this latter case, the absence of amnesia observed shortly after training (Jarrell et al., 1987, Rosen et al., 1992, Romanski and LeDoux, 1992b and Campeau and Davis, 1995; Sacco and Sacchetti, 2010) can be explained by the fact that recent auditory memories are also acquired by other structures; therefore a lesion in the auditory cortex would not be expected to impair recent memory retention. In other words, sensory stimuli that have acquired affective-motivational significance recruit multiple brain sites upon encoding and these different pathways support recent memory retention independently. However, these circuits act as a temporary memory buffer and cannot maintain memory for longer time intervals, since remote memories are compromised by cortical inactivation.

So far, it is not known if the auditory cortex is dedicated to the formation of remote memories (the second hypothesis) or if it also participates in recent memory encoding (the third hypothesis). Evidence in favor of the third hypothesis was provided by studies which revealed that fear conditioning to a *complex* auditory stimulus required the auditory cortex during training to form recent memories (Letzkus et al., 2011 and Weible et al., 2014). On the other hand, about *simple* auditory CSs, we found that the activity of Te2 neurons was the same before and after the recall of recent memories, while it was significantly enhanced after remote memory retrieval (Sacco and Sacchetti, 2010). Kwon et al. (2012) confirmed these observations, and also showed that hearing a tone recalling a recent fear memory resulted in a stronger activity in individual Te2 neurons than did hearing a familiar tone, in the absence of significant changes in the total activity of Te2 neurons. Collectively, these data suggest that the auditory cortex is engaged shortly after training to form both recent and remote emotional memories, although the neural mechanisms that underlie the two processes may be markedly different.

Functional interplay between the auditory cortex and the subcortical structures

Subcortical nuclei, such as the amygdala and striatum, are fundamental for the processing of affective information. These structures are reciprocally connected to the auditory cortex (Kolb and Tees, 1990, Amaral et al., 1992, Romanski and LeDoux, 1993 and Paxinos, 2004); thus these brain areas may interact in the course of emotional memory encoding. Nevertheless, the direction of the information flux between the auditory cortex and these subcortical nuclei may vary during the acquisition and retrieval of emotional memories.

Formation of emotional memories

During memory formation, auditory information is thought to reach the amygdala through cortical and subcortical pathways, where some plasticity processes underlying emotional memory formation occur (LeDoux, 2000). In this framework, information about the conditioned tone is carried by means of cortical axons from the auditory cortex to the amygdala (LeDoux, 2000). On the other hand, because the amygdala also sends axons to the sensory cortices, it may modulate learning-evoked plasticity occurring in the auditory cortex. In fact, the amygdala is also known to modulate memory trace formation in its target regions, including the hippocampus (McGaugh, 2000 and McGaugh, 2015), cerebellum (Zhu et al., 2011) and perirhinal cortex (Paz et al., 2006). Recent studies supported this view by showing that the amygdala is capable of promoting highly specific, associative and enduring changes in the auditory cortex (Chavez et al., 2009 and Chavez et al., 2013). These authors coupled electrical stimulation of the rat amygdala to the presentation of a tone, causing a tuning shift toward the frequency of the paired tone in the primary auditory cortex. Such a tuning shift was highly specific for the frequency of the tone, and it increased over time and lasted several days (Chavez et al., 2009 and Chavez et al., 2013). The authors therefore concluded that the amygdala may strengthen emotional memory trace formation occurring in the auditory cortex. This idea is supported by a recent study that showed that, in humans, unilateral amygdala damage reduced the activation of the auditory cortices in response to emotional voices (Frühholz et al., 2015). Finally, the amygdala has been also reported to modulate the activity of the visual cortex during the processing of visual stimuli paired to emotional information (Vuilleumier et al., 2004 and Pessoa and Adolphs, 2010). Altogether, these data indicate that the amygdala is crucial for emotional learning processes in the auditory cortex and suggest that the dialog between these two sites during the initial phase of memory formation is bidirectional, with some auditory information reaching the amygdala from the auditory cortex and some emotional information coming from the amygdala to the cortex.

A similar dialog may also occur between the auditory cortex and other subcortical nuclei that process emotional information, specifically the VTA and striatum. Bao et al. (2001)found that VTA stimulation caused the release of dopamine, a neurotransmitter known to be involved in reward processes, in the auditory cortex. As a consequence, this cortex undergoes profound changes in the representation of the frequency of the auditory stimulus paired to VTA stimulation. Thus, subcortical nuclei drive auditory cortical activity during emotional experiences. The interplay between the auditory cortex and the striatum has been observed in humans. Activity in the striatal areas, especially the nucleus accumbens, is most associated with the emotional pleasantness of musical stimuli (Salimpoor et al., 2013 and Zatorre and Salimpoor, 2013). Nevertheless, these authors also examined if the nucleus accumbens interacts with other brain regions in persons listening to music that they had never heard before. They found that, as musical sequences gained reward value, the nucleus accumbens displayed enhanced functional connectivity with the primary and higher order auditory cortices. Remarkably, this connectively occurred specifically when

individuals listened to pieces they found most desirable (Salimpoor et al., 2013 and Zatorre and Salimpoor, 2013).

Collectively, these findings indicate that, in humans and animal models, subcortical nuclei (amygdala, VTA and striatum) drive the activity of the auditory cortex so as to enhance the sound representation in this area. As a consequence, the functional connectivity between the auditory cortex and subcortical structures is significantly enhanced.

Retrieval of emotional memories

The directionality of such cortical-subcortical interplay may change during the retrieval of emotional memories. Descending connections from the auditory cortex to the amygdala and striatum may drive subcortical activity during the retrieval of emotional memory. In fact, the amygdala and striatum are the targets of descending axons from the auditory cortex (Kolb and Tees, 1990, Amaral et al., 1992, Romanski and LeDoux, 1993 and Paxinos, 2004;). In fact, changes in the activity of mammalian auditory cortical neurons predicted behavioral performance in several tasks (Villa et al., 1999,Weinberger, 2004, Weinberger, 2007, Weinberger, 2015 and Jaramillo and Zador, 2011). Remarkably, selective stimulation of the auditory cortical neurons that project to the striatum biased mice's behavioral decisions in the direction predicted by the frequency coded by the stimulated neurons, whereas inactivation of the same cells biased decisions in the opposite direction (Znamenskiy and Zador, 2013). This study suggests that the auditory cortex drives subcortical nuclei during emotional memory retrieval so as to determine the appropriate behavioral responses.
A similar information flux during memory recall likely occurs between the auditory cortex and the amygdala. *In vitro* studies showed that descending axons from the auditory cortex to the amygdala display long-term potentiation (LTP) (Humeau et al., 2003 and Fourcaudot et al., 2009). Remarkably, LTP expression was mediated by a persistent increase in the presynaptic probability of neurotransmitter release at cortical afferents (Humeau et al., 2003 and Fourcaudot et al., 2009), that is, synaptic plasticity occurs at the level of cortical descending axon synapses. Interestingly, the major sources of sensory input to the amygdala are not the primary sensory cortices but the higher order cortices, such as Te2 (Kolb and Tees, 1990 and Romanski and LeDoux, 1993) and the higher order visual regions (Amaral et al., 1992), i.e., the areas essential for remote memory storage and retrieval (Sacco and Sacchetti, 2010).

Intriguingly, a similar interplay may also occur between the auditory cortex and the cerebellum. Auditory cortical outputs arrive at the cerebellar vermis by passing through a cortico-pontine-cerebellar pathway (Azizi et al., 1985). The cerebellar vermis then translates emotional learned information into motor responses, as we have shown (Sacchetti et al., 2002, Sacchetti et al., 2004, Sacchetti et al., 2009 and Ruediger et al., 2011).

Conclusions

Our understanding of the neuroanatomy of emotional learning, especially fear learning, has evolved substantially from the early theories developed in the 1980s. Initially, the amygdala was considered a key node, whereas the auditory cortex was considered mostly a CS analyzer that transmitted sensory information to the amygdala, especially for more complex auditory stimuli (reviewed in LeDoux, 2000). Starting in the mid-1980s, Scheich and colleagues (Ohl and Scheich, 2005 and Brosch et al., 2011a) and Weinberger and colleagues (2004, 2007, 2015) discovered learning-evoked changes in the auditory cortex. Since then, an increasing number of studies has emphasized that the auditory cortex, whether primary or higher order, is critically involved in associative and higher cognitive processes.

In particular, it is now known the auditory cortex is involved in all the phases of emotional memory processing, starting from learning up to the remote storage and retrieval of this information. During these phases, the auditory cortex likely interacts with subcortical structures, such as the amygdala and the striatum, that process emotional information. Nevertheless, the directionality of cortical-subcortical dialog may vary depending on the phase of memory processing. During memory acquisition, the auditory cortex reciprocally interacts with the amygdala and the striatum, with auditory information being carried from the cortex to these nuclei and emotional information going from the nuclei to the cortex so as to modulate cortical learning-evoked plasticity. Conversely, during memory retrieval, the auditory cortex may prominently drive amygdala and striatum activity so as to recognize learned emotional stimuli and direct emotional behavior.

Overall, the auditory cortex plays a larger part in the processing of learned emotional stimuli than is traditionally assumed. The auditory cortex likely plays more than one role in emotional memory processing, even though the precise conditions that require the sensory cortices are still poorly understood, because of the different paradigms employed, the diverse cortical subregions analyzed, and the different phases of memory processing investigated. In addition to the traditional view that this area processes and encodes the physical attributes of the conditioned tones, it also takes part in changing auditory acuity in response to emotional experiences. In addition, based on early and recent findings, we raised the intriguing possibility that some auditory cortical regions link sensory stimuli to the emotional valence and participate in the long-term encoding of this association. Descending axons from these auditory areas to the amygdala and striatum may therefore be a crucial pathway for the storage and retrieval of emotional memories.

The identification of the roles played by the sensory cortex in fearful learning and of the functional connectivity between this area and subcortical structures provides new insights into the study and treatment of fear-related disturbances. A dysfunction in these structures or in their fine connectivity with subcortical nuclei may affect a person’s ability to differentiate between neutral and frightening stimuli. Such a dysfunction could lead to generalized fear and anxiety disorders.

Acknowledgements

We are grateful to A. Renna and L. Milano (University of Turin, Turin, Italy) for critical comments on the manuscript and for their continuous support and advice. We also thank V. Matarese for the critical reading and editing of the manuscript. This work was supported by grants from the European Research Council (ERC) under the European Union's Seventh Framework Program (FP7/2007-2013/ERC grant agreement no.281072) and from the Compagnia di San Paolo, Progetto d'Ateneo, Università di Torino2011 (no. 811M33N).

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