Neuroscience 299 (2015) 45–55

NEUROSCIENCE FOREFRONT REVIEW

AUDITORY CORTEX INVOLVEMENT IN EMOTIONAL LEARNING AND MEMORY

A. GROSSO,[a†] M. CAMBIAGHI,[a†] G. CONCINA,[a] T. SACCO[a] AND B. SACCHETTI[a,b*]

[a] *Rita Levi-Montalcini Department of Neuroscience, University of Turin, Corso Raffaello 30, I-10125 Turin, Italy*

[b] *National Institute of Neuroscience, Italy*

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.

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

Contents

*Correspondence to: B. Sacchetti, Rita Levi-Montalcini Department of Neuroscience, University of Turin, Corso Raffaello 30, I-10125 Turin, Italy.
E-mail address: benedetto.sacchetti@unito.it (B. Sacchetti).
† These authors contributed equally to the work.

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

http://dx.doi.org/10.1016/j.neuroscience.2015.04.068
0306-4522/

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,b; 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; 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, 2007, 2015; Ohl and Scheich, 2005; 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; 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, 2007, 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,b; Rosen et al., 1992; Falls and Davis, 1993; 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.