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Thesis presented by
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To obtain the degree of doctor in Psychology
by the University of Barcelona
PhD programme in Neurosciences, 2004-2006

Supervised by Dr. Carles Escera i Micó

Barcelona, January 2008

Als meus pares.

A la meva àvia.

A tots els meus amics.

ACKNOWLEDGEMENTS

Este trabajo está dedicado a todas aquellas personas que, quizá sin saberlo, me han acompañado en esta etapa y que, sin saberlo también, han hecho que cada uno de mis días sea un poco mejor. Porque entre todos, de una forma u otra, habéis construido esta tesis.

Primero, la realización de parte de este trabajo ha sido posible gracias a la colaboración del Prof. Manfred Herrmann, del Department of Neuropsychology and Behavioral Neurobiology, Universidad de Bremen, Alemania, y su equipo investigador. Big thanks to Sina Trautmann for our uncountable working hours together and so motivating conversations, for sharing with me all good and bad moments, to Sascha Fruehholtz for our great lunch times, Christina Regenbogen for our scientific cocktails, and all the staff in the lab of whom I will always keep good memories, Thorsten Fehr, *Frau* Muntz, Daniela Galashan, Caroline Haak, Sascha Clamer, Stephan Miedl, Dorit Klieman and, of course, Peter Erhard and Melanie Löbe from the Center for Advanced Imaging. A mis amigos en Bremen Isaac Puch Rojo, Johannes Adams, Xavi Prieto, Ivan Romero, Maria Olmedo. Y a todos los que no he mencionado pero ahí estaban.

To Martin Vestergaard, for all the hours shared with me, both in the cold Lammi and in Barcelona. To Hanne and Tuomas, you were also part of my adventure. Gracias al Prof. Sven Ahlenius, por todo lo que me enseñó en vida sin saberlo.

A los amigos de mi antiguo trabajo y con quien todavía tengo contacto, Evelyn, Núria, Álvaro. Ellos me animaron a empezar aquí. A Heidi, Hanne y Cati, por todas esas fantásticas tardes de noruego.

A la Marta, com no. La meva *germana*. Per tot el que m'has aguantat i et queda per aguantar. A Jorn, por haber sido lo que has sido en mi vida, por

haber estado siempre, siempre ahí, y ser en parte responsable de que yo hubiera empezado todo esto. A Ivan, a Javi, a Ángel, a Oscar, por haberme hecho feliz en incontables horas. A ti María Navarro, mi compañera de tantísimas movidas. A Marta Merino, por todas las horas de sobremesa y de hogar. A Jordi Navarra y los compañeros de Básica. A Juan Bakri, por su ayuda en el laboratorio. A Nevil por las más entrañables calçotadas. A Dani González. A Virgi. A la Laia. A la Júlia. Al Dani, el meu super-veí. A Sebastián, por todos esos momentos.

Por supuesto, a tu mama, a ti papa, a tu iaia, sin vuestro apoyo en todos los sentidos nada, nada de esto habría sido posible.

Por penúltimo, gracias de verdad a vosotros, mis compañeros de aventura, con quien he compartido hasta ahora 35.000 horas dentro y fuera del laboratorio, por haberme hecho tan feliz, por todos los momentazos que hemos pasado, buenos y horrorosos, por esas crisis científicas y personales en que creíamos que se acababa el mundo pero luego era mentira. Os cito por orden alfabético porque no podría hacerlo de otra manera: Vanessa Carral, Sílvia Corbera, Mj Corral, Miriam Cortiñas, Manu Garcia, Rafal Nowak, Iria SanMiguel, la nueva hornada, Jordi Costa, Paco Díaz. A mis antiguos compañeros de búnker, Lluís y Josep. Y por supuesto a todos los compañeros de departamento.

Per últim, gràcies Carles, per haver-me donat l'oportunitat de fer això, per haver estat sempre allà, per la constant i incombustible motivació transmesa, per haver-me convençut durant aquest temps que hi ha poques coses impossibles, ni tan sols les més difícils dates límits. Gràcies per la llibertat i la confiança que sempre ens has donat.

A todos los que no os he nombrado pero habéis estado ahí, muchas gracias.

SUMMARY

The present thesis encloses four studies that sought to asses the neural correlates, timing and modulatory effects of a negative emotional context on the processing of task-irrelevant novel sounds within the framework of auditory-visual oddball experimentation. Study I, II and III were conducted using event-related brain potentials (ERP) and Study IV used functional magnetic resonance imaging (fMRI).

In Study I, fourteen healthy volunteers responded to a visual discrimination task, with either neutral or threatening sceneries, while a 64-channel electroencephalogram (EEG) was recorded. In Study II, fourteen healthy female volunteers responded to visual stimuli displaying either threatening or neutral sceneries, using an optimised version of the task, while a 64-channel electroencephalogram (EEG) was recorded. In Study III, fourteen female subjects and fourteen male subjects were recorded using a 64-channel electroencephalogram (EEG) while performing the same visual discrimination task as in Study II. In Study IV, seventeen healthy female volunteers responded to a visual colour discrimination task, with images of emotional facial expressions (angry, fearful or neutral), while neuroimaged in a 3Tesla scanner. In all experimental designs, single auditory stimuli, consisting of a majority of standard tones and infrequent novel environmental sounds, preceded the images and had to be ignored by the subjects.

The main results in all four studies were pointing at comparable conclusions. Novel sounds elicited a distracting effect on subjects' performance, reflected by longer response times compared to those in standard trials. This effect was consistently magnified when preceding and following images were of a negative emotional load as compared to the neutral images. In Study III, women, but not men, showed this effect.

Brain responses recorded with ERPs revealed, in Study I, an enhancement of late novelty-P3 responses to novel sounds in negative context, compared to the neutral one. Furthermore, Study II demonstrated that this modulatory effect can also occur in the early phase of this ERP component. Study III showed that the modulation of the early novelty-P3 was present only in women. Hemodynamic responses, in turn, showed that activation induced by novel sounds in superior temporal gyrus, comprising secondary cortex, planum temporale and primary auditory cortex, was enhanced when subjects responded to faces with a negative emotional expression compared to the neutral ones.

The combination of results in the four studies show that the emotional context enhances excitability of auditory novelty cerebral regions at early stages of processing, making irrelevant sounds become more available in the attentional set under threatening conditions. Still, gender differences may be present in these effects, possibly due to differences in the evaluation of the emotional stimuli.

LIST OF ORIGINAL PUBLICATIONS

Theoretical review:

Domínguez-Borràs, J. & Escera, C. Attentional bias towards threatening emotional face expressions. In: *Emotional face comprehension. Neuropsychological perspectives.* Ed: Michela Balconi. Nova Science Publisher (New York) (*in press*).

Study I:

Domínguez-Borràs, J., Garcia-Garcia, M., Escera, C. Negative emotional context enhances auditory novelty processing. *NeuroReport* (*in press*).

Study II:

Domínguez-Borràs, J., Garcia-Garcia, M., Escera, C. Emotional context enhances auditory novelty processing: behavioural and electrophysiological evidence (*submitted*).

Study III:

García-García, M., Domínguez-Borràs, J., SanMiguel, I., Escera, C. Electrophysiological and behavioral evidence of gender differences in the modulation of distraction by the emotional context (*submitted*).

Study IV:

Domínguez-Borràs, J., Trautmann, S., Erhard, P., Fehr, T., Herrmann, M., Escera, C. Emotional context gates auditory novelty processing in superior temporal gyrus (*submitted*).

This work has been carried out at the Cognitive Neuroscience Research Group (Centre of Excellence established by the Catalan Government - SGR2005-000953) at the Department of Psychiatry and Clinical Psychobiology, Faculty of Psychology (University of Barcelona), and partly at the Department of Neuropsychology and Behavioral Neurobiology, Bremen University, Germany, lead by Prof. Manfred Herrmann, and has been supported by the Spanish Ministry of Education and Science (pre-doctoral fellowship BES-2004-3244 and grants SEJ2006-00496/PSIC and HA2005-0024).

CONTENTS

1. INTRODUCTION

A major constraint on sensory systems is their limited capacity of processing, and the need to detect vital information in a multifarious world. Our brains possess different mechanisms to cope with these limitations and to adjust flexibly to the environment, including mechanisms to guide sensory processing and resolve between competing choices. Such abilities are generally imputed to selective attention and executive functions, which allow the brain to deal with a subset of information in the environment based on its current relevance or salience (Vuilleumier, 2005).

1.1 Effects of processing negative emotional stimuli on perception and attention: behavioural evidence

Emotional processes not only serve to record the value of sensory events, but also to elicit adaptive responses and modify perception (Vuilleumier, 2005). Over the past century, a large body of evidence has shown that emotional stimuli have a status of priority in the sensory systems, eliciting stronger and faster attention capture than non-emotional stimuli (e.g., Hansen & Hansen, 1988; Öhman *et al*., 2001; Carretie *et al*., 2004; Richards & Blanchette, 2004). The importance of emotional salience in attention has an early example in the classic "cocktail party effect" (Cherry, 1953) where an emotionally significant stimulus, such as one's own name, was noticed even when it was heard among a flow of unattended stimuli during a demanding dichotic listening task. Such a mechanism of attentional bias arises from the limited processing capacity of sensory systems, while attending to adaptive and evolutionary advantages: the obvious necessity of rapidly reacting to crucial information for survival.

This effect, in addition, may be especially pronounced with negative or threat-related stimuli (Lang *et al*., 2000). Threatening events are known to engage specific autonomic and somatic reflexes that originally might have promoted survival in dangerous conditions (e.g., heart rate and startle changes, respectively; see Lang *et al*. -2000- for a review).

Behavioural studies have demonstrated that detection of a negative emotional stimulus can be more efficient than detection of a stimulus of neutral or positive emotional content. Hansen & Hansen (1988) showed participants grids of schematic happy faces with a single angry face, and grids of schematic angry faces with a single happy face. Participants were faster at picking the angry face out of a happy grid than vice versa, suggesting that their attention was automatically drawn to the angry faces through a classic ‘pop out’ effect (Treisman & Souther, 1985); that is, as a result of *parallel* processing (Hansen & Hansen, 1988). Similar conclusions were drawn in a search task study where pictures of snakes and spiders were found more quickly than those of flowers or mushrooms (Öhman *et al*., 2001). However, the advantage of threatening stimuli has been recently proposed to be different from an actual ‘pop-out’ effect (Fox *et al*., 2000). The threatening stimulus would be an emergent sensory event that facilitates efficient visual search, but search would still be *serial* as, by increasing the number of distractors in the array, detection of angry faces shows a still present, although reduced, delay in behavioural responses (Fox *et al*., 2000).

Studies involving higher cognitive processes, such as these using the Stroop task, reported that words with a negative emotional content or associated with negative pictures had longer colour naming latencies than words associated to positive or neutral content (Prato & John, 1991; Richards & Blanchette, 2004).

In ‘attentional blink’ experiments, a visual target was usually missed when presented shortly after another target within a continuous stream of stimuli, but such failures were reduced when the second target was emotionally significant (Anderson, 2005).

Finally, negative emotional stimuli serving as cues improved the visual detection threshold of low-contrast stimuli, suggesting a transient capture of spatial attention and enhancement of early processing stages for information at the affectively cued location (Phelps *et al*., 2006).

1.2 Emotional stimuli in research: IAPS pictures and emotional faces

Psychological and physiological investigation has implemented emotion induction in humans by means of a variety of stimuli, such as film clips with emotional content (Ioannides *et al*., 2000), emotion-loaded words (Chung *et al*., 1996), sounds (non-verbal affective stimuli – Meyers & Smith, 1986; Fecteau *et al*., 2007), or even recall of biographical emotional events (Damasio *et al*., 2000). But among them, emotional pictures have been used with special interest, possibly due to the existence of standardized image databases. One example is the so-called International Affective Picture System (IAPS; Lang *et al*., 2005), a set of colour photographs that depicts objects and scenes across a wide range of categories, which was especially developed for investigation on emotional processes. The use of IAPS pictures has been as frequent as more than 100 citations listed in ScienceDirect® in 2006 (Delplanque *et al*., 2007).

Similarly to the IAPS database, pictures of faces displaying emotional expressions have also been extensively used (with an also highly standardized set of pictures, created by Ekman & Friesen, 1976), possibly due to their simple structure and similar feature configuration from one expression to another. Recognition of faces is a phylogenetically old form of social communication and, therefore, facial expressions that reflect basic emotions, particularly fear and anger (Lang *et al*., 2000), seem to especially possess innate salience determined by evolutionary selection (Dolan, 2000). Faces are able to elicit automatic, spontaneous emotional responses (Dolan, 2000).

Although IAPS pictures may be closer to evoke emotion than faces and emotional faces may be less arousing involving predominantly emotion recognition (Britton *et al.*, 2006), both IAPS pictures and faces elicit similar hemodynamic responses, such as in amygdala, hippocampus, ventromedial prefrontal and visual cortices (Britton *et al.,* 2006; Fig. 1). This fact makes results between studies using both sets of stimuli, if not directly, at least indirectly comparable.

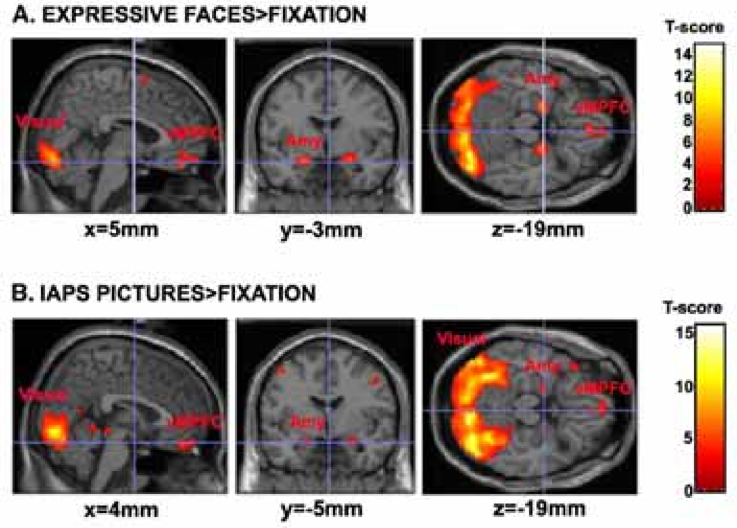

Fig. 1 Common regions of activation to (A) emotional faces and (B) IAPS pictures relative to fixation, comprising visual cortex (visual), ventromedial prefrontal cortex (vMPFC), and amygdala (Amy). Activated voxels are displayed with P <.005 uncorrected, k>5. Reprinted from Britton *et al*., 2006.

1.3 Effects of processing negative emotional stimuli on sensory and attentional brain responses

Similarly to behavioural studies on attentional processes, neuroimaging investigation in this field has shown enhanced responses in different sensory areas towards negative affective information. Face-selective regions such as fusiform cortex (George *et al.*, 1999), or early visual areas in the occipital lobe, have been consistently shown to enhance their activation particularly with negative expressions as compared to neutral faces (Morris *et al.*, 1998; Sugase *et al.*, 1999; Vuilleumier *et al.*, 2001; Pessoa *et al.*, 2002). Likewise, visualising emotional IAPS pictures enhances hemodynamic responses in primary visual areas as compared with the neutral ones (Bermpohl *et al.*, 2006). Even the processing of emotional words has been shown to elicit increased activity in bilateral regions of the visual cortex (Ortigue *et al.*, 2004) and, in a similar way, increased activations in primary auditory cortex (PAC) have been reported when processing negative emotional sounds (Fecteau *et al.*, 2007).

Electrophysiological evidence gives support to the fact that such attentional bias is a very early effect, as seen in modulation by the emotional face expression of the occipito-temporal N170 event-related brain potential (ERP) component (Eimer, 2000). This component peaks at a latency of 150-200 ms post-stimulus onset and shows a high specificity for face structural encoding (Eimer, 2000). Another early component showing a similarly increased amplitude is the P1, a positive-going deflection, maximal over occipital lobe and peaking approximately 130 ms after stimulus onset, both for faces (Pourtois *et al.*, 2005) and emotional pictures (Smith *et al.*, 2003; Carretié *et al.*, 2004). Still earlier effects have been described with negative emotional faces, around 80-90 ms (Eger *et al.*, 2003) or 90 ms (Pourtois *et al.*, 2004) post-stimulus onset. Thus, the rapid detection of emotional salient stimuli seems to be necessary, as mammals need to respond defensively to an ambiguous stimulus before the object is identified as either threatening or innocuous.

Finally, later responses have been also modulated by unpleasant pictures, as, for instance, described in target-P3 modulation, with sources in occipital and posterior parietal areas (Keil *et al*., 2002) or enhancement of novelty and target-P3 with rare negative IAPS pictures in oddball experimentation (Delplanque *et al*., 2006; see the last section of the Introduction for a detailed description of the novelty-P3).

1.4 Effects of processing negative emotional stimuli on perception and attention: the role of the amygdala

Even though the precise mechanisms by which emotion modulates sensory processing are still unclear, results from hemodynamic and electrophysiological brain imaging in humans and animal models have achieved important advances in this issue. The amygdala, a nuclear complex located on the medial temporal lobe, anterior to the hippocampus, is known to play a crucial role in affective processing (LeDoux, 1996, 2000), capable of organizing rapid reactions to danger, even without the participation of the cerebral cortex (LeDoux, 1998).

Amygdala has been reported to respond even when focal attention is directed away from the negative emotional stimuli (Vuilleumier *et al*., 2001; Anderson *et al*., 2003; Williams *et al*., 2005). However, still controversy exists on this aspect, as no differential activation of amygdala was observed when emotional faces where subliminally presented (Pessoa *et al*., 2006) or when the attentional resources where strongly depleted (Pessoa *et al*., 2002). Thus, the question of whether negative emotional stimuli should be considered susceptible to attentional load, similarly to neutral stimuli, remains open (Williams *et al*., 2005).

The amygdaloid complex is known to be extensively and reciprocally interconnected with cortical brain regions (Amaral *et al*., 1992), such as sensory cortices (Young *et al*., 1994), and also with subcortical areas, such as thalamus (see Le Doux, 2000 for a review). This nucleus exerts strong influence on a number of cognitive processes such as emotional learning (LeDoux 1996, 2000), memory (Adolphs *et al*., 2005; Paz *et al*., 2006) and attention (Weinberger, 1995; Anderson & Phelps, 2001). At a sensory level, the amygdaloid complex seems to have a substantial modulatory control over all processing stages in the ventral visual stream, V1 included (Amaral *et al*., 2003, Freese & Amaral, 2005) as well as, for instance, over auditory cortices (LeDoux, 2000). Therefore, it seems likely that this nucleus may play a critical role in the emotional modulation of sensory processing.

Activations of amygdala occur also very early during the processing of negative emotional stimuli (e.g. 200 ms post-stimulus onset in faces, Krolak-Salmon *et al*., 2004). However, intracranial recordings have reported somewhat earlier responses (120-160 ms) to fearful faces in ventral prefrontal cortex (Kawasaki *et al*., 2001). Although the amygdala seems the most plausible source of sensory modulation, there is the possibility that, for instance, prefrontal sources exert even an earlier modulatory effect. This would be in agreement, then, with the early emotional effects mentioned above (e.g., Pourtois *et al*., 2004, 2005).

In sum, the amygdala has a pivotal role on the processing of emotional stimuli, and may be partly responsible for the early modulation of sensory areas by providing top-down signals onto the sensory pathways.

1.5 Gender differences in the processing of negative emotional stimuli

A number of neuroscience studies have demonstrated that men and women process emotional stimuli differently. Kemp *et al*., (2004) described a widespread frontal latency reduction associated to the processing of unpleasant IAPS pictures on a study using steady-state visually evoked potentials. This latency reduction was present in women but not in men. In an ERP study, Orozco & Ehlers (1998) found significantly enhanced amplitudes in frontal regions in response to sad faces as compared to neutral faces both in men and women. However, women, in relation to men, showed larger amplitude on P450, an ERP component related to the “intensity” of response to emotional stimuli, suggesting that women may be more sensitive to emotional stimuli than men (Orozco & Ehlers, 1998). Moreover, fMRI studies exploring the neural correlates of emotional processing using IAPS images, described stronger right amygdala activation in women as compared to men (Wrase *et al*., 2003; Hofer *et al*., 2006). It is remarkable that the amygdala not only differs in men and women functionally, but also in terms of structure and in several aspects of brain development (Goldstein *et al*., 2001). This difference may contribute to the unequal prevalence of emotion-related disorders. Finally, recent neuroimaging studies have reported more widespread activations of emotion-related areas in female subjects in response to emotional stimuli (Canli *et al*., 2002). All these differences may be important, for instance, for determining which emotional stimuli should be chosen when working with male and female subjects in affective neuroscience.

1.6 Emotion vs attention

Emotional enhancement of perception is comparable to what would be expected from classic effects of attention (Phelps, 2006), since attention leads to enhanced activation in early visual areas (e.g., Luck *et al*., 1997;

Mangun *et al.*, 1998). Attentional processes have been systematically linked to the cholinergic system, which projects to widespread cortical regions including early visual areas or cortical areas related to attentional control (Sarter *et al.*, 2004). Cholinergic neurons in the basal forebrain are known to receive inputs from the amygdala (Sarter & Bruno, 2000). Though it would appear logical, however, it seems unlikely that cholinergic projections are responsible for the emotional modulation, since induction of cholinergic enhancement appears to cause insignificant increased responses of amygdala or fusiform cortex when processing emotional faces (Bentley *et al.*, 2003). Moreover, a patient suffering from spatial neglect, presenting damage in the parietal lobe (an area linked to attention and awareness), showed the normal increased response of fusiform cortex for fearful faces presented in the neglected field (Vuilleumier *et al.*, 2002).

Thus, the effect of emotion on perception would be independent from common top-down signals related to fronto-parietal circuitries (Vuilleumier & Pourtois, 2007). Alternatively, emotional processes would often collaborate with the attentional systems (Vuilleumier, 2005; Schupp *et al.*, 2007).

(A detailed discussion of the ideas presented here and supporting evidence, focussed on negative emotional face processing, can be found in Domínguez-Borràs & Escera, *in press*; Annex 1).

1.7 Effects of processing negative emotional stimuli across sensory modalities: emotional context vs attentional competence

As described above, a great deal of investigation has shown the effects of negative emotional processing within a sensory pathway. A major question that remains unsolved is what happens across sensory modalities.

Numerous neuroscience studies have shown that, for instance, stimulation of one sensory modality can modify responses to stimuli in other non-related sensory pathways (Kawashima *et al*., 1995; Shulman *et al*., 1997; Foxe *et al*., 2002; Laurienti *et al*., 2002; Inan *et al*., 2004).

Similarly, processing emotional stimuli may affect responses to non-related events coming from different sensory modalities. A number of psychophysiological studies have demonstrated that peripheral responses elicited by auditory stimuli, such as the startle reflex, are potentiated while visualizing negative emotionally loaded pictures (Stanley & Knight, 2004; Bradley *et al*., 2006). Conversely, it has been repeatedly shown that late auditory responses to the same sounds are attenuated when these negative stimuli are visualised, suggesting that fewer attentional resources might be available for sound processing as a consequence of allocating more attention to these affective stimuli (Schupp *et al*., 1997; Cuthbert *et al*., 1998; Keil *et al*., 2007). Such processing attenuation may be therefore due to a mechanism of *sensory competence* between a neutral and an emotionally salient stimulus presented in different sensory modalities.

However, no investigation to date has examined the effects of processing emotional stimuli on the processing of auditory events while avoiding such sensory competence. This would introduce to the idea of *emotional context.* The term *emotional context* would include all incoming information that forms and characterizes the emotional load of the task in which sounds are processed. One example of this idea can be illustrated in the last sequences of a famous Hollywood thriller, *The Silence of the Lambs*, where Agent Clarice Starling enters into the serial killer's house and fumbles through the darkness. As she emerges from the bathroom with both hands on the gun, in her raw-nerved blackness, every sound occurring in that moment is unnaturally magnified (the humming of the refrigerator, the trickle of water or even her own terrified breathing). To examine this aspect in laboratory conditions, it is necessary to use a task which may be optimal for isolating any contextual effects on auditory processing.

1.8 Top-down vs bottom-up processes: the use of an auditory-visual oddball task

As introduced previously, due to the limited processing capacity of sensory systems only a part of the incoming information gains access to consciousness. For this purpose, the human nervous system maintains two attentional processes under constant equilibrium: active selection, or top-down control, and the *breakthrough of the unattended* (James, 1890), responding to bottom-up signals, which enable the conscious evaluation of potentially important events that are not being top-down selected. This has been consistently illustrated in oddball experimental designs, where the unexpected occurrence of auditory novel events recruits attentional resources from the ongoing task and leads to behavioural disruption, a phenomenon called distraction (Schröger, 1996; Alho *et al.,* 1997; Schröger & Wolff, 1998; Escera *et al.,* 1998, 2000, 2001, 2002, 2003, Escera & Corral, 2007). This effect is accompanied by a well-defined pattern of neuroelectrical activation characterised mainly by the N1-enhancement/MMN ERP component, which indexes a mechanism for stimulus change detection, leading to attention capture (Escera *et al*., 1998, 2000; Alho *et al*., 1998; Escera & Corral, 2003, 2007) and the novelty-P3 potential (Escera *et al.,* 1998, Escera & Corral, 2007), associated with the evaluation of these novel events for subsequent behavioural action (Friedman *et al*., 2001; Ranganath & Rainer, 2003). This neuroelectrical pattern of auditory novelty processing is mainly subserved by activations in supratemporal (Alho *et al*., 1998; Downar *et al*., 2000; Kiehl *et al*., 2001), prefrontal (Downar *et al*., 2001; Bledowski *et al*., 2004) and parietal cortices (Clark *et al*., 2000; Downar *et al*., 2001), and is often followed by a frontally-distributed 'reorienting negativity' (RON), which reflect processes in the context of reorienting attention towards the task after distraction (Schröger & Wolff, 1998).

In this sense, it has been suggested that processing of novel sounds may be modulated if the amount of attentional resources available is modified by the task conditions (Berti & Schröger, 2003; SanMiguel *et al.*, 2008; see Lavie, 2005 for a review), that is, for instance, by increasing working memory load.

The auditory-visual oddball task chosen in the four studies, created in this laboratory, has been demonstrated to be a useful tool for examining such effects of the task conditions, or top-down control, on the mechanisms of auditory novelty processing and distraction or, what would be the same, on bottom-up processes (SanMiguel *et al.*, 2008). The task consists of a sequence of visual stimuli presented shortly on screen, to which subjects have to respond according to the experimental settings. Visual stimuli are always preceded in 300 ms by a single sound. The sounds, which have to be ignored by the subjects, can be a standard, repetitive pure tone, in approximately 80% of the presentations, or rare environmental novel sounds.

This task provides a specific pattern of behavioural and brain responses during task performance, where voluntary attention is required, and, simultaneously, measures with precision behavioural and brain responses related to involuntary attention, that is, attention capture by the task-irrelevant stimuli (e.g., Escera *et al.*, 1998, 2001, 2002, 2003; see reviews in Escera & Corral, 2003, 2007). In the latter case, the behavioural effects would reflect the so-called *distraction* phenomenon and brain responses elicited would denote *auditory novelty processing* mechanisms. Thus, this task allows us to control and quantify the balance which, per se, both voluntary and involuntary attention mechanisms (top-down and bottom-up) are constantly maintaining.

Specifically, it is a simple way to examine how the task conditions exert a modulation on attention-capture by task-irrelevant sounds, that is, the *contextual effect*. The main goal of the four studies was to examine such top-down modulatory effects, seen from a slightly different perspective from traditional experiments on attention: the emotional content of the task, which is supposed, as exposed above, to influence sensory processes similarly and parallelly to common top-down signals (Vuilleumier, 2005).

An important advantage of this task is that it allows examining the effects of the emotional context on involuntary attention while avoiding sensory and attentional competence between the visual emotional stimuli and the auditory events, as visual and auditory events are never presented simultaneously throughout the task. Thus, it is likely that the effects observed on auditory novelty processing in the present studies are due to a contextual effect, more than to pure sensory competence.

In summary, processing negative emotional stimuli exerts a strong influence on perception and potentiates the perceptual effects of attention. This effect occurs at very early stages of information processing in the human brain, enhancing responses on the sensory cortices. The amygdala, together with other areas such as ventromedial prefrontal cortex, may play a key role in such modulation. The idea that this emotional effect may not only occur within but also across sensory modalities raised the question of whether a context of processing visual negative emotional stimuli actually enhances or attenuates auditory novelty processing at a central level in the brain. For that, an auditory-visual oddball task was used to asses the modulatory effects, timing and localization of such interference, by means of four experiments using ERP and fMRI techniques. In addition and, given the evidence that gender differences in emotional processing exist, an examination of these responses was conducted comparing male and female subjects.

2. AIM OF THE STUDIES

The specific objectives of the present studies can be formulated as follows:

2.1 Study I

First, to examine the modulatory effects of a negative emotional context on the processing of novel auditory events, by analysing subjects' behavioural responses. That is to say, to establish whether the emotional load of the current task has an impact on behavioural distraction.

Second, to depict brain responses and timing of this modulatory effect, by examining de subsequent ERP components. That is to say, to establish in which stage within the auditory novelty processing stream this modulation occurs.

2.2 Study II

First, to examine the modulatory effects of a negative emotional context on the processing of novel auditory events, by analysing subjects' behavioural responses in a modified version of the task. As well as in Study I, to establish whether the emotional load of the current task has an impact on behavioural distraction.

Second, to depict brain responses and timing of this modulatory effect, by examining de subsequent ERP components. That is to say, to establish in which stage within the auditory novelty processing stream this modulation occurs.

2.3 Study III

First, to examine the gender differences that may exist on this modulatory effect, by analysing behavioural responses to the same task as the one used in Study II, establishing whether the emotional load of the current task has an impact on behavioural distraction.

Second, to asses the gender differences of the electrophysiological responses underlying this modulation, by examining de subsequent ERP components in women and in men.

2.4 Study IV

First, to examine the modulatory effects of a negative emotional context on the processing of novel auditory events, by analysing subjects' behavioural responses in a similar task as in Studies I, II and III, adapted for fMRI experimentation. As well as in Study I, II and III, to establish whether the emotional load of the current task enhances or diminishes distraction.

Second, to depict the cerebral regions along the auditory novelty processing system which are modulated by the emotional context.

3. METHODS

Subjects

The first, second and third studies were conducted at the Department of Psychiatry and Clinical Psychobiology, Faculty of Psychology of University of Barcelona. A total of 14 healthy volunteers (7 men), 14 healthy female volunteers and 28 healthy volunteers (14 men) were recruited for Study I, II and III respectively. The fourth study was carried out at the Department of Neuropsychology and Behavioral Neurobiology, Bremen University, Germany, from where 17 healthy female volunteers participated.

All participants were evaluated with a clinical interview and none of them reported any neurological or psychiatric illness history, treatment for any personality or anxiety disorder, specific phobias, drug consumption or abnormal audition. All subjects had normal or corrected-to normal vision and gave informed consent to participate in the studies, according to the Declaration of Helsinki.

Stimuli

For the first, second and third studies, pictures selected from the International Affective Picture System database (IAPS; Centre for research in Psychophysiology, University of Florida, Gainesville) were used as emotional stimuli. They included both neutrally and negatively valenced pictures, the latter depicting scenes of extreme violence and disgust. Pictures were presented two by two on screen with a central fixation cross (Fig. 2).

In Study IV, the emotional stimuli consisted of monochromatic faces, depicting neutral and fearful or angry expressions, compiled at the Department of Neuropsychology and Behavioral Neurobiology, Bremen University (Germany). Faces were surrounded by a colour frame and presented one by one on screen (Fig. 3). Faces were considered more suitable for this study, using fMRI, to avoid unwanted variability due to differences in spatial frequency between picture sets (Delplanque *et al.*, 2007).

In all four studies, auditory stimuli consisted of a 700 Hz standard tone and unique environmental novel sounds, delivered through headphones to the subjects at 75 dB SPL in the first three studies and 20dB over sensation level (SL) in Study IV.

Task and conditions

In the four studies, participants performed a modified version of a well-characterized auditory-visual distraction paradigm (Escera *et al.*, 1998, 2000, 2001, 2003). All stimuli were presented with the stimulation program Presentation®. Auditory stimuli preceded images in 300 ms, being these either a standard tone (p=0.8) or a novel sound (p=0.2). For Study I, trial length was of 1500 ms along the experimental session. Alternatively, in Study II and III, trial length ranged from 1500 to 2100 ms (mean 1800 ms ± 300 ms) to avoid unwanted synchronisation of brain activity preceding the sounds. Similarly, in Study IV, trial length ranged from 2600 to 3200 ms (mean 2900 ms ± 300 ms). In the first three studies, pairs of IAPS pictures appeared in the centre of the screen and subjects were instructed to press a button to respond as rapid and accurate as possible whether the two pictures were equal or different, while ignoring the sounds and not gazing away from the fixation cross (Fig. 2). In the fourth study, pictures appeared in the middle of the screen and subjects were instructed to press a response button to respond whether the colour of the frame matched the colour of the face (Fig. 3).

Although the auditory stimuli were identically distributed using an event-related design in the four studies, distribution of the emotional content of the visual stimuli was event-related-wise throughout the experimental sequence only in Study I. For the design of Study II, III and IV a block-wise distribution of the images was chosen, in order to overcome the possible emotional interference from a negative stimulus onto the following neutral stimulus and thus optimise the effects of the emotional context.

In Study IV, previous to each measurement, sound calibration was implemented inside the scanner to adjust hearing threshold and correct balance for each individual subject with the help of a sound amplifier. During the course of this procedure, a shim echo-planar sequence was applied to ensure that subjects would hear the sounds also in the scanning session.

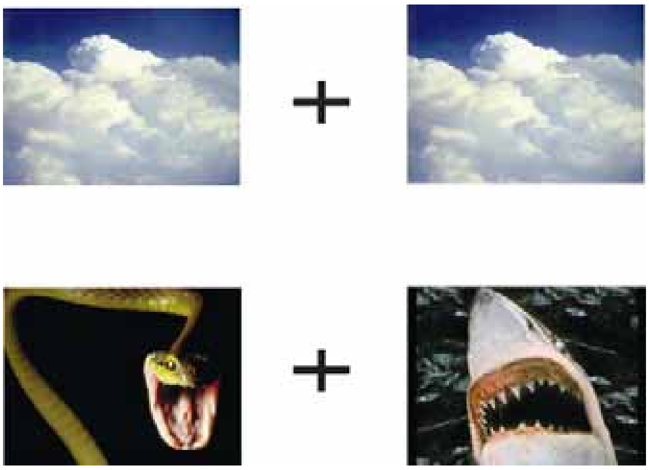

Fig. 2. Sample visual stimuli from the IAPS (Lang *et al*., 2005) used in Study I, II and III. Two equal neutral pictures (top) and two different negative pictures (bottom).

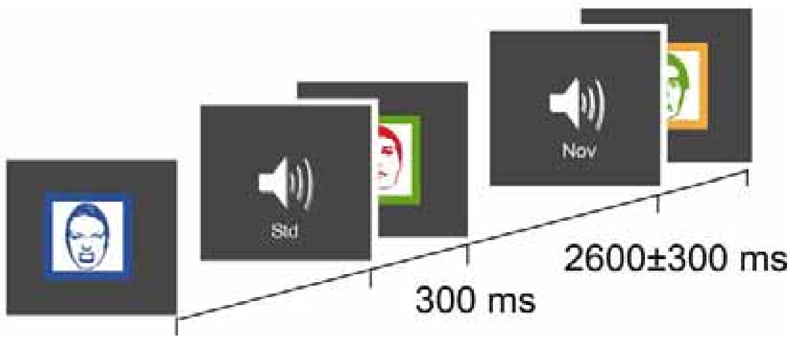

Fig. 3. Sample of the trial structure used in Study IV.

Data acquisition and processing

In Study I, II and III, electroencephalogram (EEG) was recorded during task performance from 64 scalp electrodes following the 10/10 convention in an electrically and acoustically shielded room. The horizontal and vertical electro-oculogram (EOG) were recorded with electrodes placed on the outer cantus of the right eye and above the right eye. The common reference electrode was placed on the tip of the nose, and the ground was located on the chest. ERPs were averaged off-line for standard and novel trials for an epoch of 1200 ms, including a 200 ms pre-auditory stimulus baseline. Only trials where the auditory stimuli were preceded and followed by a picture of the same valence and followed by a correct response were selected for averaging. Standard tone trials following novel sound trials were excluded from analysis. Individual ERPs were digitally band-pass filtered between 0.1 and 30 Hz. EOG artefact compensation was performed via a regression algorithm. Then, trials exceeding amplitude of ±30 μV standard deviation within the continuous data (200 ms window) were manually rejected.

In Study IV, MRI data were acquired on a 3T Siemens Allegra scanner (Erlangen, Germany), using a whole brain local gradient coil. Structural images were acquired with a T1-weighted MPRAGE sequence (160 slices, TR 2.3s, TE 4.38 ms, flip angle 8°, 256x256 matrix, FOV 296x296, inversion time 900 ms, 1mm³ voxels). Functional images were obtained using a gradient echo-planar (EPI) T2* sequence optimized for BOLD (Blood Oxygenation Level Dependency) contrast. The EPI sequence comprised 44 contiguous slices covering the whole brain, taken every 3 mm with no interslice gap and incorporating the following parameters: TE 30 ms, TR 2.5 s, 64x64 matrix, FOV 192x192, flip angle 90°, resolution 3x3 mm^2, interleaved ascending. Functional images were slice time corrected, realigned, normalized spatially to the Montreal Neurological Institute (MNI) template and smoothed with an 8 mm FWHM gaussian kernel using SPM2 (Wellcome Department of Cognitive Neurology, London, England, 2003).

Data analysis

For behavioural, ERP and fMRI analyses, only hit-trials with sounds surrounded (both preceded and followed) by an image of the same valence were taken into account. For behavioural analysis, a correct button press within 100-1200 ms after visual stimulus-onset was regarded as a hit. Hit rate and hit-response times were compared with a two-factor repeated-measure ANOVA and pair-wise *post hoc* comparisons, using the Bonferroni adjustment, were computed.

In the first three studies, N1-enhancement/MMN and novelty-P3 were isolated for both emotional contexts in the difference waves obtained by subtracting the standard-tone trial ERPs from those elicited to the novel-sound trial. The first deflection was measured as the mean amplitude at F3, Fz, F4, C3, Cz and C4. ANOVA for repeated measures of this response was used to analyse contextual effects and scalp distribution. Early and late phases of novelty-P3 were measured as the mean amplitude at F3, Fz, F4, C3, Cz, C4, P3, Pz and P4. ANOVA for repeated measures were also applied to analyse contextual effects and scalp distribution.

In Study II and III, P300 to visual targets was examined in four consecutive latency windows, measured as the mean amplitude at F7, F3, FZ, F4, F8, FT7, FC3, FCZ, FC4, FT8, T7, C3, CZ, C4, T8, TP7, CP3, CPZ, CP4, TP8, P7, P3, PZ, P4, P8. Grand-average ERPs to the standard trials were statistically compared by means of ANOVA with repeated measures to analyse contextual effects and scalp distribution, performed after ERP amplitude normalization.

In Study III, RON was measured in the difference waves as the mean amplitude at F3, Fz, F4, C3, Cz, C4, P3, Pz and P4, and ANOVA for repeated measures was applied to analyse contextual effects and scalp distribution. Additionally, an ANOVA was performed for early stages of the difference wave at Fz (P50 component), to examine contextual effects.

Additionally, all ANOVAs performed in Study IV included an inter-subject variable Gender to analyse differences between men and women.

Greenhouse-Geisser correction of the degrees of freedom was applied for all ANOVAs and post-hoc tests were conducted wherever there were significant interactions between the main factors.

In Study IV, at the first level, 15 event types were modelled: six events referred to trials containing sounds surrounded by equally valenced pictures and followed by a correct response, six comprising misses and errors and three for all trials at the beginning of every valence block or after breaks. Data were high-pass filtered (1/128Hz), corrected for intrinsic autocorrelations, and convolved with a standard HRF and its temporal derivative. Second level analysis was performed on single-subject statistical parametric maps, serving as random effects. A pooled analysis was used to identify activations additively significant for [(STD-Fear)+(STD-Anger)] and [(NOV-Fear)+(NOV-Anger)], which resulted into the new NEG conditions.

Three contrasts of interest were defined, by means of voxel-referred t-tests, to compare BOLD signal for the following conditions: (STD-NEU<NOV-NEU; *novelty processing in neutral context*); (STD-NEG<NOV-NEG; *novelty processing in negative context*); (STD-NEU<STD-NEG; *emotional face processing*). A fourth contrast of interest (*emotional effects on novelty processing*) was examined with a one-factor ANOVA: [(STD-NEU<NOV-NEU)<[[(STD-Fear)+(STD-Anger)]<[(NOV-Fear)+(NOV-Anger)]]]. An additional one-factor ANOVA was performed (the *reverse contrast)*: [(STD-NEU<NOV-NEU)>[[(STD-Fear)+(STD-Anger)]<[(NOV-Fear)+(NOV-Anger)]]].

Activation was considered significant when at least 20 contiguous voxels survived a threshold of p<.001 (except for STD-NEU<STD-NEG; p<.005), uncorrected for multiple comparisons. Stereotactic MNI coordinates were translated into standard Talairach space (Talairach & Tournoux, 1988) following nonlinear transformations.

Due to the considerable interindividual and interhemispheric differences in size and location of PAC in humans (Penhune *et al*., 1996), a three-dimensional probabilistic cytoarchitectonic map was used**.** Primary auditory cortex, microstructurally defined and normalized in space (Eickhoff, *et al*., 2005), was then set as an anatomical ROI for every single subject. Then, the relative extents of activation for those clusters showing the highest probability to be part of the three cytoarchitectonic areas of bilateral PAC (TE1.0, TE1.1, TE1.2) were computed for the contrasts of interest *emotional effects on novelty processing* and the *reverse contrast*.

4. RESULTS AND DISCUSSION

Study I.

Domínguez-Borràs, J., Garcia-Garcia, M., Escera, C. Negative emotional context enhances auditory novelty processing. *NeuroReport* (*in press*).

Subject: NeuroReport: Decision on Negative emotional context enhances auditory noveltyprocessing
From: NeuroReport <nr@lww.co.uk>
Date: Tue, 15 Jan 2008 09:07:06 -0500
To: cescera@ub.edu

15 January 2008

Dear Professor Escera,

Submission no.: NR-D-07-6352
Article title: Negative emotional context enhances auditory novelty processing
Corresponding author: Prof. Carles Escera

Your re-submitted manuscript has been received and checked, and we are happy with the revision that you have carried out. I find the paper now acceptable for publication. I am pleased to let you know that we will therefore publish it in the next issue of NeuroReport to be compiled.

Thank you for sending your interesting work to our Journal and for your patience with the revision.

Kind regards.

Yours sincerely,

Giorgio Gabella, MD DSc
Editor in Chief
NeuroReport

NeuroReport

Negative emotional context enhances auditory novelty processing

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Received 10 January 2008; accepted 15 January 2008

We used an auditory–visual distraction task to investigate the functional relationship between distraction elicited by auditory novel events and a context of negative emotional processing, both at behavioural and electrophysiological (event-related brain potentials) levels in humans. Participants performed a decision task on pictures disclosing sceneries with a task-irrelevant emotional load or neutral, whereas ignoring sounds presented concomitantly. Our data showed that novel sounds yielded stronger behavioural disruption on participants' visual task performance in negative context compared to the neutral one. Accordingly, late novelty P3 responses to novel sounds were enhanced. These results demonstrate that the negative emotional context enhances the activation of neural networks in the auditory novelty system, enhancing auditory novelty processing under potentially threatening conditions. *NeuroReport* 00:000–000 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Keywords: emotion, event-related brain potentials, involuntary attention, novelty P3

Introduction

Adaptive behaviour requires the ability to select salient stimuli from a complex environment. Emotional stimuli, especially negative, are known to have a status of priority in a network of limited sensory systems (see Ref. [1–4]), interfering on the processing of concomitant stimuli. This occurs not only 'within' (see Ref. [2,5]) but also 'across' sensory modalities; for instance, psychophysiological studies have demonstrated that peripheral responses elicited by auditory stimuli, such as the startle reflex, are potentiated while visualizing negative emotionally loaded pictures [6,7]. At the same time, however, it has been repeatedly shown that late auditory responses to these sounds are attenuated, suggesting that fewer attentional resources might be available for sound processing when emotional stimuli are visualized as a consequence of allocating more attention to these affective stimuli [8–10]. Such processing attenuation may be therefore because of a mechanism of sensory competence between stimuli and not strictly to the emotional context in which sounds were processed. To date, no investigation has examined the effects of the emotional context on involuntary attention while avoiding such attentional competence.

In this study, event-related brain potentials (ERPs) were used to assess the effects of manipulating the implicit emotional load in a visual task, by means of images loaded with a negative valence, towards the processing of task-irrelevant novel sounds. The unexpected occurrence of auditory novel events leads to behavioural disruption, a phenomenon called distraction [11–15]. This effect is accompanied by a sequence of neuroelectrical activations characterized by the N1 enhancement/mismatch negativity (MMN) and the novelty P3 cognitive potentials [13,14], followed by a 'reorienting negativity' (RON; [12]). This sequence of involuntary attention events can be modulated when the amount of attentional resources available is modified by the conditions of the task [16,17].

AQ2

To avoid sensory competence between stimuli and ensure a contextual effect, visual and auditory events were never presented simultaneously throughout the task. If the emotional context facilitates the processing of task-irrelevant novel events, these sounds should elicit greater distraction when participants respond to emotionally loaded stimuli as compared to neutral ones. If, on the contrary, emotional processing depletes most of the attentional resources, distraction should decrease. In either case, the electrophysiological pattern of novelty-processing responses should be accordingly modulated.

Methods

participants

Fourteen healthy volunteers (19–30 years old, mean age 23.3 years ±3.9, seven men, three left-handed), recruited at the Faculty of Psychology, participated in this study. Participants were evaluated with a clinical interview and none of them reported any neurological or psychiatric illness history, treatment for any personality or anxiety disorder, specific phobias, drug consumption, or abnormal audition. All participants had normal or corrected to normal vision, and gave informed consent according to the Declaration of Helsinki.

Emotional stimuli

The emotional stimuli were 282 pictures taken from The International Affective Picture System (Centre for research in Psychophysiology, University of Florida, Gainesville [18]). They included 188 neutrally and 94 negatively valenced pictures, the latter depicting scenes of extreme violence and disgust. All pictures were selected among the most highly rated at the American Self Assessment Manikin standards, both for arousal (mean ratings: neutral 3.95 ± 1.2, negative 6.12 ± 0.7; meaning 9 the highest) and emotional valence dimensions (mean ratings: neutral 5.84 ± 1.1, negative 2.5 ± 1; meaning 1 the most negative). Valence and arousal rates differed significantly for neutral and negative pictures [valence: $T_{(280)}=24.26$, $P<0.001$; arousal: $T_{(280)}=16.74$, $P<0.001$]. Pictures were presented two by two on screen, all equally and proportionally paired. Only pictures of the same valence were coupled. Pairs could consist of equal (50%) or different pictures (50%). Pictures had a resolution of 643 × 482 pixels, time on screen 400 ms, distance from screen 150 cm, vertical angle 4°, horizontal angle 12°, this accounting for two pictures presented simultaneously and a fixation point between them, mean luminance: 112.5–113.5 luminance units. Participants were never exposed before to these pictures, with the exception of a 2-min practice session, in which they responded to random neutral pictures.

Auditory stimuli

The auditory stimuli were a 700 Hz, 200 ms standard tone ($P=0.8$), and 100 unique environmental novel sounds ($P=0.2$, 200 ms duration, root mean square-normalized), generated as in Escera *et al.* [13] and rated by a sample of 30 participants, on a 1–5 scale of semantic familiarity [15], chosen between the most highly rated (mean rate: 2.54 ± 0.5). All sounds were delivered binaurally through headphones at an intensity of 75 dB sound pressure level. During the practice block no sounds were presented.

Task and conditions

Participants performed a modified version of the auditory–visual distraction task used in earlier studies [13–15]. Auditory stimuli preceded the visual stimuli in 300 ms, and the latter contained two pictures of either neutral or negative emotional valence. Participants were instructed to respond whether the two pictures were equal or different by pressing the corresponding response button with the middle and index fingers of their dominant hand (response mapping was counterbalanced across participants), and to ignore the sounds. Previous to each recording session, participants performed a practice block with no sounds, in which they were required to reach a minimum of 85% hit rate.

Electroencephalogram recording and averaging

AQ3

Electroencephalogram was recorded (A/D rate 512 Hz, impedances below 15 kΩ) from 64 scalp locations (ANT Software B.V., Enschede, Netherlands) from the 10/10 convention, in an electrically and acoustically shielded room. The horizontal and vertical electrooculogram was recorded with electrodes placed at the outer canthus and below the right eye, respectively. The common reference electrode was placed on the tip of the nose and ground was located on the chest. ERPs were averaged off-line for standard and novel trials for an epoch of 1200 ms, including a 200 ms preauditory stimulus baseline. Only trials where the auditory stimuli were preceded and followed by a picture of the same valence and followed by a correct response were selected for averaging. Standard tone trials following novel sound trials were excluded from analysis. Individual ERPs were digitally band-pass filtered between 0.1 and 30 Hz. Electrooculogram artefact compensation was performed via a regression algorithm. Then, trials exceeding an amplitude of ± 30-μV standard deviation within the continuous data (200 ms window) were manually rejected. On average, a minimum of 77.3% was retained for averaging.

Data analysis

Both for behavioural and ERP analyses, only hit trials with sounds surrounded (both preceded and followed) by a picture of the same valence were taken into account. For behavioural analysis, a correct button press within 100–1200 ms after visual stimulus onset was regarded as a hit. Hit rate and hit response times were compared with a two-factor repeated measure analysis of variance (ANOVA) for the factors Sound (standard vs. novel) and Context (negative vs. neutral) and pairwise post-hoc comparisons, using the Bonferroni adjustment for multiple comparisons, were computed.

For both emotional contexts, N1 enhancement/MMN, novelty P3 and RON were isolated in the difference waves obtained by subtracting the standard-tone trial ERPs from those elicited to the novel sound trial. The first deflection was measured as the mean amplitude at F3, Fz, F4, C3, Cz, and C4 in the 100–140 ms window. ANOVA for repeated measures of this response included the factors Context (neutral vs. negative), Laterality (left vs. centre vs. right), and Electrode. Early and late phases of novelty P3 were measured as the mean amplitude at F3, Fz, F4, C3, Cz, C4, P3, Pz, and P4 in the 210–280 and 280–340 latency windows, respectively. ANOVA for repeated measures included the factors Context (neutral vs. negative) × Phase (early vs. late) × Frontality (F3, Fz, F4 vs. C3, Cz, C4 vs. P3, Pz, P4) × Laterality (F3, C3, P3 vs. Fz, Cz, Pz vs. F4, C4, P4). RON was measured as the mean amplitude at F3, Fz, F4, C3, Cz, C4, P3, Pz, and P4 in the 420–520 ms latency window. ANOVA for repeated measures of this response included the factors Context (neutral vs. negative) × Frontality (F3, Fz, F4 vs. C3, Cz, C4 vs. P3, Pz, P4) × Laterality (F3, C3, P3 vs. Fz, Cz, Pz vs. F4, C4, P4). Additionally, an ANOVA was performed for early stages (70–100 ms latency window) of the difference wave at Fz (P50 component [19]), including the factor Context. Greenhouse–Geisser correction of the degrees of freedom was applied for all ANOVAs. *P*-values following correction were reported.

Results

Behavioural results

Participants had an overall hit rate of about 90%, which decreased significantly in the negative context [$F(1,13)=8.14$, $P=0.014$; Fig. 1a]. Response times in novel trials were longer compared with those of standard trials [$F(1,13)=38.04$, $P<0.001$], indicating that participants were distracted by the unexpected occurrence of the task-irrelevant novel sounds, as they delayed responses (Fig. 1b). These response time differences between standard and novel trials were significantly larger for the negative context compared with the neutral context [F(1,13)=14.04, $P=0.002$]. This enhancement of distraction in negative context was because of response time differences in novel trials ($T_{13}=3.303$, $P=0.006$), as response time was similar in the standard trials ($T_{13}=2.04$, n.s.). No statistical differences were seen between handedness, either for response time or hit rate.

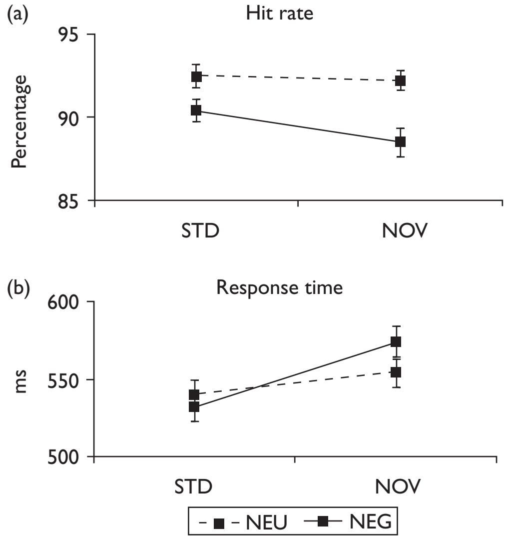

Fig. 1 (a) Mean hit rates for standard and novel trials, both when sounds were preceded and followed by neutral (neutral context condition), and negative (negative context condition) pictures. Bars indicate the standard error of the mean (±SEM). (b) Mean response times for standard and novel trials both in neutral and negative context conditions.

AQ5

Electrophysiology

Brain activity associated to novelty processing and its modulation by emotional context was analyzed in the difference waves resulting from subtracting the ERP in the standard trials from those in the novel ones – as usual (see Ref. [13–15]) – for both contexts separately (Fig. 2). These difference waves were characterized by a well-defined N1 enhancement/MMN, a double-phased, frontocentrally distributed novelty P3, and a frontally distributed RON.

The N1 enhancement/MMN was of similar amplitude for neutral and negative contexts, as the ANOVA yielded no significant effects of these factors or interactions between them. Yet, a modulation trend was observed at P50 stages [Context: F(1,13)=4, $P=0.067$], showing a slightly larger amplitude in negative context. In turn, the novelty P3 had a frontocentral distribution [Frontality: F(2,26)=34.15, $P<0.001$; Laterality: F(2,26)=6.5, $P<0.01$], with its late phase having larger amplitudes at frontal and right sites [Phase × Frontality: F(2,26)=8.13, $P<0.01$; Phase × Laterality: F(2,26)=7.87, $P<0.01$; Phase × Frontality × Laterality: F(4,52)=2.93, $P=0.047$]. Interestingly, a significant Context × Phase × Laterality interaction [F(2,26)=4.85, $P=0.029$] revealed that the late novelty P3 response was larger in negative context, particularly at the central electrodes (Fig. 2). Finally, whereas RON was frontally distributed [Frontality: F(2,26)=7.83, $P=0.009$; Fig. 2], no effects of Context were revealed in the RON ANOVAs.

Discussion

Novel sounds elicited a distraction effect on participants' performance in agreement with earlier studies [13,15]. This

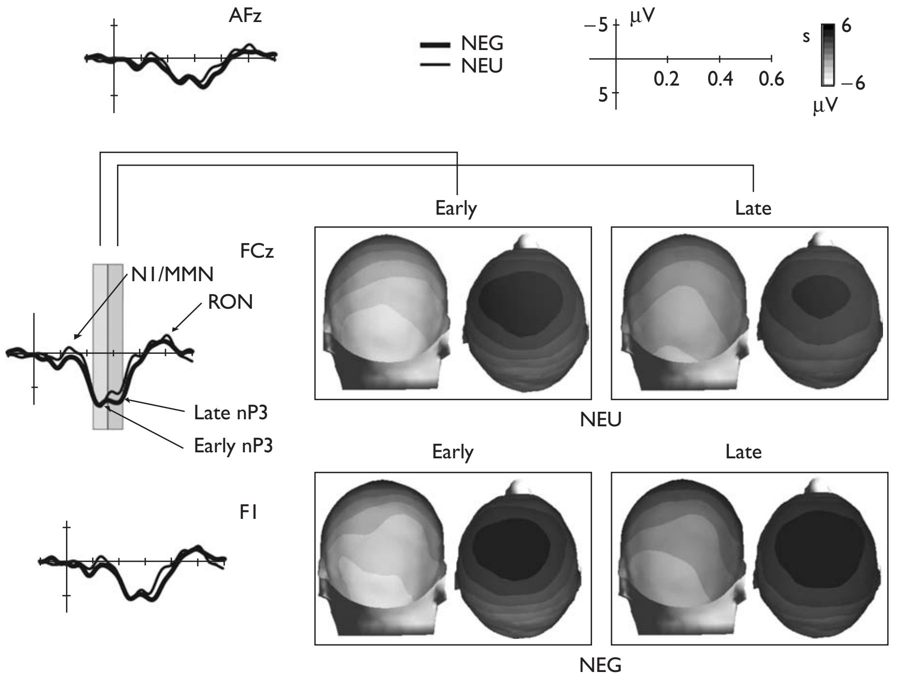

Fig. 2 Difference waves obtained by subtracting the standard sound event-related brain potentials from those elicited to novel sounds (0.1–20 Hz filtered), for neutral (thin line) and negative context (thick line), and scalp-distribution maps of the two phases of the novelty P3 (nP3).

distraction effect was stronger when sounds were preceded and followed by pictures of emotionally negative valence in contrast to the neutral ones, that is, when processed in a negative context. A similar effect has been observed in two related studies using similar tasks, not only with International Affective Picture System pictures as visual stimuli (Domínguez-Borràs J, Garcia-Garcia M, Escera C, submitted), but also with emotional faces (Domínguez-Borràs J, Trautmann SA, Erhard P, Fehr T, Herrmann M, Escera C, submitted).

Early stages of novelty detection, associated to N1 enhancement/MMN [7,20] were apparently insensitive to the emotional context of their occurrence, as no significant differences were obtained between the amplitude of this waveform recorded in the two emotional contexts. This result contrasts, however, with recent studies showing suppression of the sensory gating of P50 [21] under emotional threat. We, however, cannot fully disregard a modulation of early stages of the sensory filter, as the P50 enhancement in novel trials of the present experiment showed, in fact, a tendency towards modulation in the negative emotional context.

The most striking result of this study was that novelty P3, reflecting a mechanism of evaluation of novel stimuli that already captured attention [13,14,22], showed enhanced amplitude on its late phase when novel sounds occurred in the negative context. Other studies showing that novelty P3 amplitude increases linearly as a function of the eliciting stimulus salience [15,23], or that the more salient the sound the larger the behavioural distraction and novelty P3 [13,15,24], support the notion that larger novelty P3 indicates stronger orienting of attention in our negative emotional context. These results are in agreement with a recent study of ours (Domínguez-Borràs J, Garcia-Garcia M, Escera C, submitted), where novelty P3 responses to novel sounds were also enhanced in a negative emotional context.

It is worth noting that the emotional effects on novelty P3 observed in the present experiment differ from other studies using startle reflex measurements [7–10]. In these studies, whereas the blink reflex was enhanced for startle probes while viewing unpleasant pictures [7–9], auditory P3 decreased in amplitude [8–10] even for unexpected simple tones [9], suggesting a greater allocation of attentional resources to the affective visual stimuli in a limited-capacity system, which might deplete the attentional resources from processing the auditory ones. We suggest that the reasons of this disagreement might be the presence or absence of perceptual competence in all studies. In these experiments, sounds appeared while pictures were on screen and stimulus display was of 1.5 or 6 s. In our study, sounds appeared when no image was being displayed. With this and the short duration of the stimuli, we manipulated the emotional load of the task while images and sounds never overlapped and attentional resources were never forced to compete. Yet, any comparison between studies using startle reflex and the one reported here should be taken with caution.

It is possible that an effect of 'negative expectation' could be present in our results, since pictures of neutral and unpleasant valence were presented in a random order. This fact, in accordance with Herwig *et al.* [25], might make participants be constantly prepared for the processing of unpleasant pictures, activating areas related to negative emotional processing when the emotional load of the upcoming stimulus is unknown. Still, if negative expectation was present in our study, it exerted a stronger modulatory effect on the processing of novel sounds when preceding and following pictures were indeed negative, as compared with the neutral ones. On the other hand, the possibility that habituation to the negative stimuli was present throughout the experimental session cannot be disregarded. Brain responses to negative target pictures have, however, been demonstrated to be similar even after 1200 presentations [26]. Finally, the possibility that the findings of the present experiment may arise from any emotional activation, irrespective of the valence, or whether they apply also to positive context, should await to be clarified in future research.

Conclusion

The results of this study show that processing negative emotional information magnifies brain responses involved in involuntary attention towards task-irrelevant novel stimuli. Consequently, the distractor effects naturally elicited by these novel sounds become potentiated. The mechanisms underlying this magnification effects would respond to evolutionary advantages, making possible that unexpected auditory events, irrelevant in neutral environmental conditions, become available for the attentional set in a threatening situation, providing critical information for survival. These findings provide a novel illustration of how emotion mediates involuntary attention and awareness.

Acknowledgements

The authors would like to thank Elisa Pazgón for her advice on the design of the study.

Supported by grants from the Spanish Ministry of Education and Science [Consolider-Ingenio 2010 – CSD2007-00012, SEJ2006-00496/PSIC, AP2006-00731, and BES-2004-3244] and from the Generalitat de Catalunya [SGR2005-00953].

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Study II.

Domínguez-Borràs, J., Garcia-Garcia, M., Escera, C. Emotional context enhances auditory novelty processing: behavioural and electrophysiological evidence (*submitted*).

Emotional context enhances auditory novelty processing: behavioural and electrophysiological evidence

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Abstract

Viewing emotionally negative pictures has been proposed to attenuate brain responses towards sudden auditory events, as more attentional resources are allocated to the affective visual stimuli. However, peripheral reflexes have been shown intensified. These observations have raised the question of whether an emotional context actually facilitates or attenuates processing in the auditory novelty system. Using scalp event-related potentials we measured brain responses induced by novel sounds when participants responded to visual stimuli displaying either threatening or neutral sceneries. We then tested the modulatory effect of the emotional task conditions on auditory responses. Novel sounds yielded a stronger behavioural disruption on subjects' visual task performance when responding to negative pictures compared to when responding to the neutral ones. Accordingly, very early novelty-P3 responses to novel sounds were enhanced in negative context. These results provide strong evidence that the emotional context enhances the activation of neural networks in the auditory novelty system, gating acoustic novelty processing under potentially threatening conditions.

Keywords: attention, emotion, ERP, novelty-P3.

Introduction

The ability to select salient stimuli from a complex environment is crucial for adaptive behaviour. Due to the limited processing capacity of sensory systems, only a part of the incoming information gains access to consciousness. For this purpose, the human nervous system maintains two attentional processes under constant equilibrium: active selection, or top-down control, and the *breakthrough of the unattended* (James, 1890), responding to bottom-up signals, which enable the conscious evaluation of potentially important events that are not being top-down selected. This has been consistently illustrated in oddball experimental designs, where the unexpected occurrence of auditory novel events recruits attentional resources from the ongoing task and leads to behavioural disruption, a phenomenon called distraction (Schröger, 1996; Alho *et al.,* 1997; Schröger & Wolff, 1998; Escera *et al.,* 1998, 2000, 2001, 2003). This effect is accompanied by a well-defined pattern of neuroelectrical activation characterised mainly by the N1-enhancement/MMN and the novelty-P3 cognitive potentials (Escera *et al.,* 1998, 2000; Escera & Corral, 2003).

In this sense, it has been suggested that involuntary attention and its underlying neural substrate may be modulated if the amount of attentional resources available is modified by a competing task (Berti & Schröger, 2003; SanMiguel *et al*., 2007; see Lavie, 2005 for a review), that is, for instance, by increasing working memory load. In a similar vein, this critical role of top-down processes on involuntary attention may be considered in terms of the emotional load of the task. A large body of literature has evidenced that emotional stimuli have a privileged status in the neural processing systems, eliciting stronger and faster attention capture than non-emotional stimuli (e.g., Eastwood *et al,.* 2001; Öhman *et al.,* 2001; Carretié *et al.,* 2004; Richards & Blanchette, 2004) and interfering the processing of concomitant stimuli, not only *within* (e.g. Öhman *et al.,* 2001; Fox, 2002) but also *across* sensory modalities: psychophysiological studies have yielded a potentiation of peripheral responses elicited by auditory stimuli while visualizing emotionally loaded pictures, such as the startle reflex, typical after the sudden burst of a white noise (Stanley & Knight, 2004; Bradley *et al.,* 2006). However, it has been suggested that less attentional resources might be available for sound processing when emotional stimuli are visualized, as a consequence of allocating more attention to these valenced stimuli (Schupp *et al.,* 1997; Cuthbert *et al.,* 1998; Keil *et al.,* 2007). In the present study, we used event-related brain potentials (ERPs) to assess the effects of manipulating the implicit emotional load in a visual task, by means of images loaded with a negative valence, towards the processing of irrelevant novel sounds. If the emotional context facilitates the processing of task-irrelevant novel events, these sounds should elicit greater distraction when subjects respond to emotionally loaded stimuli as compared to the neutral ones. If, on the contrary, emotional processing depletes most of the attentional resources, distraction should decrease. In either case, the electrophysiological pattern of novelty-processing responses should be modulated accordingly at a certain stage.

Materials and Methods

Subjects

Fourteen right handed female volunteers, aged between 18 and 29 yrs (mean 22 yrs, ±4.2) without past neurological or psychiatric history, no reported specific phobias, drug consumption or abnormal audition participated in the present study. All subjects had normal or corrected-to normal vision and presented anxiety levels within the normal range of the Anxiety Trait and State scale (STAI, Spielberger, 1983). All subjects gave written informed consent and the experimental protocol was approved by the Ethical Committee of University of Barcelona, according to The Code of Ethics of the World Medical Association (Declaration of Helsinki).

Stimuli

Emotional stimuli The emotional stimuli were two-hundred and eight pictures taken from The International Affective Picture System (IAPS, Centre for research in Psychophysiology, University of Florida, Gainesville, Lang *et al.,*(2005). They included a total of 188 neutrally and 120 negatively valenced pictures (see the Supplementary Material section), the latter depicting scenes of extreme violence and disgust. Pictures were selected among the most highly rated at the Self-Assessment Manikin (SAM) standards (Lang, 1980) both for arousal (meaning 1 the highest) and emotional valence dimensions (meaning 1 the most positive), and evaluated by the participants after the experimental session. Average rates of neutral pictures were 4 ±0.3 and 5.41 ±0.4 for valence and arousal, respectively, and average rates of negative pictures were 7.89 ±0.2 and 3.14 ±0.6 for valence and arousal, respectively. Valence and arousal rates differed significantly for neutral and negative pictures (valence: $F_{(1,13)}$=239.06, p<0.001; arousal: $F_{(1,13)}$=27.12, p<0.001). Pictures were presented two by two on screen, all equally and proportionally paired. Only pictures of the same valence were coupled. Pairs could consist of equal (50%) or different pictures (50%). All pictures were presented with a resolution of 643x482 pixels, a mean luminance of 112.5 to 113.5 luminance units, duration on screen of 400 ms, a distance from screen of 150 cm, a vertical angle of 9º and a horizontal angle of 25º (this accounting for two pictures presented simultaneously and a white cross as a fixation point between them).

Auditory stimuli The auditory stimuli were a 700 Hz standard tone (STD) and 100 unique environmental complex, novel sounds (NOV; 200 ms duration, 75 dB SPL), generated as described in previous studies (Escera *et al.*, 1998) and rated by a sample of 30 subjects, on a 1-5 likert-scale of semantic familiarity (as reported in previous studies -Escera *et al.*, 2003- about effects of familiarity on novelty processing), chosen between the most highly rated (2.54 mean rate; ±0.5). Sounds were delivered through Sehnheiser® HD202 headphones (Wedemark, Germany).

Task and conditions

Participants performed a modified version of a well-characterized auditory-visual distraction paradigm (Escera *et al.*, 1998, 2000, 2001, 2003). All stimuli were presented with the stimulation program Presentation® by Neurobehavioral Systems Inc. (Albany, CA, USA). Auditory stimuli preceded images in 300 ms, being these either a standard tone (STD condition, p=0.8) or a novel sound (Nov condition, p=0.2). Trial length ranged from 1500 ms to 2100 ms (mean 1800 ms, ± 300 ms). Pictures could be neutral (NEU context condition) or negative (NEG context condition) in emotional valence. Pairs of images appeared in the centre of the screen and subjects were instructed to press a button (left or right with same dominant hand, buttons counterbalanced across subjects) to respond as rapid and accurate as possible whether the two pictures were equal or different, while ignoring the sounds and not gazing away from the fixation cross. A unique sequence was designed, which divided 1000 trials into in 66 blocks of 10, 15 or 20 trials of the same valence. NEU and NEG pictures were never mixed in the same block. All blocks were pseudo-randomized in a probabilistic non-stationary way so that, in the beginning, a higher proportion of neutral blocks was presented, decreasing progressively and turning into a higher proportion of negative pictures at the end. These sequences were counterbalanced across subjects with a Latin square design, so that half of the subjects started with neutral pictures whereas the other half started with negative pictures. Previous to each experimental session, subjects performed a practice block with no sounds, in which they were required to reach a minimum of 85% hit rate.

EEG recording and averaging

Electroencephalographic activity was recorded during task performance from 64 scalp electrodes (ANT Software b.v., Enschede, Netherlands) following the 10/10 convention, in an electrically and acoustically shielded room. The horizontal and vertical electro-oculogram (EOG) was recorded with electrodes placed at the outer canthus and above the right eye, respectively. An electrode placed on the tip of the nose was used as common reference and ground was located on the chest. The electroencephalogram was amplified and digitized at a sampling rate of 512 Hz. Impedances were kept below 15kΩ. ERPs were averaged offline for each auditory stimulus type for an epoch of 1400 ms, including a 200 ms pre-stimulus baseline. Only those auditory stimuli surrounded (both preceded and followed) by a picture of the same valence and followed by a correct response were selected for averaging. Standard tones presented after a novel sound were excluded from analysis. Frequencies above 30 Hz were digitally filtered out from the individual ERPs. EOG artifact compensation was performed via a regression algorithm. Then, trials exceeding amplitude of ±30 μV standard deviation within the continuous data (200 ms window) were manually rejected. On average, 79.3 % of epochs with standard, 81.1% of epochs with novel sounds in neutral context, as well as 82.9 % epochs with standard and 84.7 % epochs with novel sounds in negative context were retained for averaging. On average, 82 trials were included for the NOV condition and of 213 trials for the STD condition.

Data analysis

Both for behavioural and ERP analyses, only hit-trials with sounds surrounded (both preceded and followed) by a picture of the same valence were taken into account. For behavioural analysis, a correct button press within 100-1200 ms after visual stimulus-onset was regarded as a hit. Hit rate and hit-mean response times (RT) were computed across equal and different pairs of pictures and compared by means of a two-factor repeated-measure ANOVA for the factors Sound (STD, NOV) and Context (NEU, NEG) and pair-wise *post hoc* comparisons with non-pooled error terms. In order to examine the effects of the emotional load of the task on attentional processes, P300 to visual targets was examined in four consecutive latency windows (600-700 ms, 700-800 ms, 800-900 ms, 900-1000 ms) measured as the mean amplitude at F7, F3, FZ, F4, F8, FT7, FC3, FCZ, FC4, FT8, T7, C3, CZ, C4, T8, TP7, CP3, CPZ, CP4, TP8, P7, P3, PZ, P4, P8. Grand-average ERPs to STD-NEU and STD-NEG stimulus pairs were statistically compared by means of ANOVA with repeated measures [factors: Context (NEU versus NEG) x Frontality (F7, F3, Fz, F4, F8 versus FT7, FC3, FCz, FC4, FT8 versus T7, C3, Cz, C4, T8 versus TP7, CP3, CPz, CP4, TP8 versus P7, P3, Pz, P4, P8) x Laterality (F7, FT7, T7, TP7, P7 versus F3, FC3, C3, CP3, P3 versus Fz, FCz, Cz, CPz, Pz versus F4, FC4, C4, CP4, P4 versus F8, FT8, T8, TP8, P8)]. Scalp-distribution analyses for P300 were performed after normalizing ERP amplitudes to prevent amplitude differences between different components from washing out the genuine scalp-distribution differences. This normalization was done by dividing the amplitude at each electrode by the sum of the squared amplitudes at all electrodes (McCarthy & Wood, 1985).

Both for the NEU and the NEG context, N1-enhancement/MMN and novelty-P3 were isolated in the difference waves obtained by subtracting the standard-tone trial ERPs from those elicited to the novel-sound trial. The first deflection was measured as the mean amplitude at F3, Fz, F4, C3, Cz and C4 in the 110-160 ms latency window. ANOVA for repeated measures of this response included the factors Context (NEU and NEG), Laterality (Left, Right) and Electrode. Early and late phases of novelty-P3 were measured as the mean amplitude at F3, Fz, F4, C3, Cz, C4, P3, Pz and P4 in the 200-290 and 290-370 ms latency windows, respectively. ANOVA for repeated measures of these two responses included the factors Context (NEU versus NEG) x Phase (early versus late) x Frontality (F3, Fz, F4 versus C3, Cz, C4 versus P3, Pz, P4) x Laterality (F3, C3, P3 versus Fz, Cz, Pz versus F4, C4, P4).

For all statistical analyses, Greenhouse-Geisser adjustments to the degrees of freedom were used when appropriate and *P*-values following this correction were reported. Post-hoc tests were conducted wherever there were significant interactions between the main factors.

Results

Behavioural results

Subjects had an overall hit rate of about 91%, which decreased significantly in NEG condition (Context: $F_{(1,13)}$=12.43, p<0.01; Fig. 1a). Only a trend of main Sound effect ($F_{(1,13)}$=4.2, p=0.06) was found for accuracy. In general, response times (RT) were longer when subjects responded to negative pictures than when responding to the neutral ones (Context: $F_{(1,13)}$= 12.14, p<0.01; Fig. 1b). A two-factor repeated-measurement ANOVA revealed significantly longer RT in trials containing NOV sounds compared to those containing STD sounds (sound: $F_{(1,13)}$=11.61, p<0.01), indicating that subjects were distracted by the unexpected occurrence of a task-irrelevant novel sounds, as they delayed responses (Fig 1b) in agreement with previous studies (Alho *et al.* 1997; Escera *et al.* 1998, 2001, 2003). These RT differences between STD and NOV trials were significantly larger for the NEG context compared to the NEU context (context*sound: $F_{(1,13)}$=6.4, p=0.025), as revealed by post-hoc t-tests (STD-NEU versus NOV-NEU: t=2.13, p=0.053; STD-NEG versus NOV-NEG: t=3.84, p=0.002). No statistical differences were seen between counterbalanced runs or response button, either for RT or hit rate.

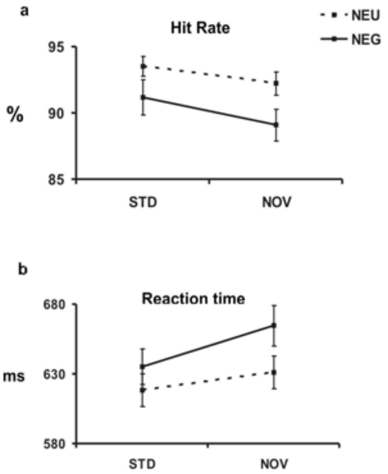

Figure 1. a. Mean hit rates for STD and NOV trials, both when sounds were preceded and followed by neutral (NEU context) and negative (NEG context) pictures. Subjects were less accurate in their responses during processing of negative pictures, compared to the neutral ones. Bars indicate the standard error of the mean (±s.e.m.). **b.** Mean response times for STD and NOV trials both in NEU and NEG context. NOV sounds caused a delay on subjects' responses, being this effect significantly enlarged when preceding and following images were emotionally negative. Bars indicate the s.e.m.

Electrophysiology

Emotional picture processing

Grand-average ERPs to STD-NEU and STD-NEG stimulus pairs revealed a sequence of auditory P1, N1 and P2 and visual target-related P300 deflections (Fig. 2). The statistical scalp-distribution analyses of target-P300 across NEU and NEG conditions yielded a P300 distribution over posterior electrodes, both for NEU and NEG context, in the four consecutive latency windows analysed (Frontality; 600-700 ms: $F_{(4,52)}$=6.99, p<0.02; 700-800 ms: $F_{(4,52)}$=40.46, p<0.001; 800-900 ms: $F_{(4,52)}$=61.05,

$p<0.001$; 900-1000 ms: $F_{(4,52)}=76.32$, $p<0.001$), and over lateral more than central regions (Fig. 2; Laterality; 600-700 ms: $F_{(4,52)}=5.12$, $p<0.05$; 700-800 ms: $F_{(4,52)}=49.85$, $p<0.001$; 800-900 ms: $F_{(4,52)}=66.87$, $p<0.001$; 900-1000 ms: $F_{(4,52)}=77.31$, $p<0.001$; Frontality x Laterality; 700-800 ms: $F_{(16,208)}=41.62$, $p<0.001$; 800-900 ms: $F_{(16,208)}=58.82$, $p<0.001$; 900-1000 ms: $F_{(16,208)}=73.3$, $p<0.001$). P300 amplitude was enhanced in NEG context as compared to NEU context for the 600-700 ms latency window (see Fig. 2; Context: $F_{(1,13)}=11.82$, $p<0.01$), showing in NEG context a more posterior-central distribution, as revealed by the interactions Context x Frontality ($F_{(4,52)}=5.53$, $p<0.05$), Context x Laterality ($F_{(4,52)}=5.79$, $p<0.05$) and Context x Frontality x Laterality ($F_{(16,208)}=6.51$, $p<0.03$). Only a trend of Context interaction effect was found for the 700-800 ms latency window (Context x Frontality: $F_{(4,52)}=3.12$, $p=0.098$) and no effects of Context appeared in further windows.

Auditory novelty processing

Both for NEU and NEG contexts, difference waves between NOV-sound and STD-sound ERPs revealed the neuroelectric activation underlying auditory novelty processing, which was characterized by a well-defined N1-enhancement, possibly composed of overlapping N1 and MMN components (Alho *et al.,* 1998, Escera *et al.,* 1998) and a novelty-P3 deflection (Fig. 3).

The ANOVA on the two phases of the novelty-P3 across both conditions confirmed that both early and late phases were maximal over the fronto-central scalp (Frontality: $F_{(2,26)}=14.14$, $p<0.01$; Laterality: $F_{(2,26)}=28.36$, $p<0.001$), with the late phase having larger amplitude at fontal and right sites (Phase x Frontality: $F_{(2,26)}=8.77$, $p<0.01$; Phase x Laterality: $F_{(2,26)}=5.14$, $p<0.02$; Frontality x Laterality: $F_{(4,52)}=6.74$, $p<0.01$; Phase x Frontality x Laterality: $F_{(4,52)}=6.56$, $p<0.01$).

Novelty-P3 analyses for NEU and NEG context separately revealed a main effect of Frontality in both context conditions (NEU: $F_{(2,26)}=12.15$, $p<0.01$; NEG: $F_{(2,26)}=13.81$, $p<0.01$), Laterality (NEU: $F_{(2,26)}=24.28$, $p<0.001$; NEG: $F_{(2,26)}=25.1$, $p<0.001$), Phase x Frontality (NEU: $F_{(2,26)}=9.31$, $p<0.01$; NEG: $F_{(2,26)}=7.78$, $p<0.01$), Phase x Laterality (NEU: $F_{(2,26)}=3.96$, $p<0.05$; NEG: $F_{(2,26)}=6.41$, $p<0.01$), Frontality x Laterality (NEU: $F_{(4,52)}=5.49$, $p<0.01$; NEG: $F_{(4,52)}=7.34$, $p<0.01$), and Phase x Frontality x Laterality (NEU: $F_{(4,52)}=5.49$, $p<0.01$; NEG: $F_{(4,52)}=6.81$, $p<0.01$). The late novelty-P3 presented similar amplitude from parietal to frontal sites (Frontality: $F_{(2,26)}=2.91$, $p=0.108$), whereas its early phase was more prominent in fronto-central locations ($F_{(2,26)}=34.3$, $p<0.001$). Indeed, the early novelty-P3 inverted polarity at posterior and lateral sites (Fig. 3) whereas the late subcomponent did not.

Gating of auditory novelty processing in emotional context

Early stages of novelty processing did not present effects due to emotion. Accordingly, N1 enhancement was of similar amplitude both for NEU and NEG context, as the ANOVA yielded no significant effects of these factors or interactions between them. However, early novelty-P3 responses showed enhanced amplitude in NEG context (Fig. 3), as indexed by the interaction Context x Phase ($F_{(1,13)}$=9.52, p=0.009). Subsequent separate ANOVAs for NEU and NEG context revealed that no main effect of Phase is present in NEG, due to the enhancement of the early deflection in this condition (NEU: $F_{(1,13)}$=7.62, p=0.016; NEG: $F_{(1,13)}$=1.24, p=0.286). In general, no topographical differences between NEU and NEG were observed for both phases of novelty-P3, suggesting a pure enhancement of the early phase in NEG context.

Discussion

Emotional picture processing

The results of the present study provide an illustration of how emotion mediates involuntary attention and awareness. Subjects were unable to fully ignore emotional information even when it was task-irrelevant, in agreement with a variety of studies (Vuilleumier *et al.,* 2001; Anderson *et al.,* 2003). The amplitude enhancement of visual P300 over centro-parietal sites revealed that participants processed negative pictures more deeply as compared to the neutral ones. In this sense, subjects might have remained engaged in the emotional content of the display at the expense of processing the relevant aspects of the task. This interpretation would be supported by the behavioural results, in which subjects were shown to be slower and less accurate when responding to negative pictures than to the neutral ones. This target-related ERP component is known to represent memory updating mechanisms (Donchin & Coles, 1988) and has been shown sensitive to the intrinsic affective properties of pictures in previous studies (Amrhein *et al.,* 2004; Delplanque *et al.* 2005). Thus, amplitude modulation of visual P300 was a necessary requirement for evaluating any emotional effect on auditory novelty processing.

Gating of auditory novelty processing in emotional context

Brain responses to stimulus salience not only depend on novelty or frequency of occurrence, but also on the behavioural context (Katayama & Polich, 1998) and, particularly, on the emotional relevance of the context. Novel sounds elicited a distraction effect on subjects' performance, as indexed by a prolonged response time both during neutral and negative picture processing. This effect was paralleled by the well-defined N1-enhancement/ MMN and novelty-P3 ERP components observed in the difference waves, both for neutral and negative context conditions separately. The morphology and distribution of this pattern would represent the neuroelectric activation underlying novelty processing, a mechanism concerned with the evaluation of novel stimuli that have already captured attention (Escera *et al.,* 1998, 2000; Friedman *et al.,* 2001) or, in line with a recent interpretation from task-switching experiments (Barceló *et al.,* 2006), an internal updating of goals, a goal-directed response selection elicited by sensory signals, rather than a simple orientation response.

Both behavioural and electrophysiological results in our study are consistent with literature (Alho *et al.,* 1997, 1998; Escera *et al.,* 1998, 2000, 2001, 2003; Yago *et al.,* 2003) and confirm that auditory novel events were processed differently with regard to the repetitive standard sounds (*novelty processing*), recruiting attentional resources from the ongoing task in subjects and causing a delay in the average performance (*distraction*) regardless of the emotional load within the task. Crucially, these novel sounds elicited a stronger distraction effect when preceded and followed by pictures of emotionally negative valence, in contrast to the neutral ones. In other words, when novel sounds were surrounded by emotionally negative pictures and thus processed in a negative context.

N1-enhancement, consistently associated with novelty detection in the auditory cortex (Alho *et al.,* 1998; Escera *et al.,* 1998) was not affected by the emotional load of the task, indicating that the transient and change-detection mechanisms indexed by this deflection may be independent of task conditions. Interestingly, novelty-P3 amplitude appeared enhanced to novel sounds processed during the performance of the task involving negative pictures. Studies showing that novelty-P3 amplitude increases linearly as a function of the eliciting stimulus salience (Yago *et al.,* 2001; Escera *et al.,* 2003), that the more salient the sound the larger the behavioural distraction and novelty-P3 (Escera *et al.,* 1998, 2003; Zink *et al.,* 2006), or that behavioural distraction and novelty-P3 amplitude are modulated in parallel by working memory load (Berti & Schröger, 2003; SanMiguel *et al.*, 2007), support the notion that a larger novelty-P3 denotes stronger orienting of attention to distractors and, in the present study, under a negative emotional context.

Temporality and distribution of emotional gating effects

The emotional load of the task exerted a modulation of the early novelty-P3. The early novelty-P3 subcomponent has been proposed to be associated with the violation of the regularity registered by the automatic novelty detection system (Escera *et al.,* 1998, 2001), whereas late novelty-P3 would reflect the actual orienting of attention towards odd auditory stimuli (Escera *et al.,*1998). Although the aim of the present study was not to examine the sensitivity of early novelty-P3 to task conditions, our data clearly indicate that this phase may be responsive to certain attentional manipulations, contrarily to what was previously proposed (Escera *et al,.* 1998) and to what was reported in recent experiments (Roye *et al.,* 2007; SanMiguel *et al.*, 2007). However, modulation of early novelty-P3 has been observed in another study where, for instance, identifiable novel sounds enhanced novelty-P3 responses compared to the non-familiar novels along a 100 ms window (covering both early and late phases, Escera *et al.*, 2003). In either case, it can be concluded from our results that the emotional context modulates novelty processing in immediately previous stages to the orientation response, about 200 ms after sound occurrence. Early novelty-P3, and not the late phase, showed inverted polarity at posterior and lateral electrodes (Fig. 3), suggesting generators bilaterally located in the vicinity of the temporal and parietal lobes (Scherg & von Cramon, 1986; Alho *et al.,*1998; Escera *et al.,* 1998). A study in which fMRI and ERP results were combined by dipole seeding during auditory oddball sessions (Opitz *et al.,* 1999), revealed novelty processing responses in the middle part of superior temporal gyrus and, furthermore, proposed these areas (together with the anterior part superior temporal gyrus –Alho *et al.,* 1998) to subserve novelty-P3 (Opitz *et al.,* 1999). Temporo-parietal lesions, centered in the superior temporal cortex, have been shown to attenuate P3 to novel sounds (Knight *et al.,* 1989). The modulation of early novelty-P3 obtained in this study may be thus in agreement with recent functional magnetic resonance imaging (fMRI) data, using a related paradigm, (Domínguez-Borràs *et al.,* submitted), where activation induced by novel sounds in bilateral superior temporal gyri was enhanced when participants responded to negative emotional faces in contrast to neutral ones. Moreover and, accordingly to the results in the present experiment, novel sounds yielded a stronger behavioural disruption on subjects' visual task performance when these responded to faces with a negative expression than when responding to neutral faces (Domínguez-Borràs *et al.,* submitted). Emotional faces and IAPS pictures have been reported to elicit similar hemodynamic responses on emotion-sensitive areas, such as amygdala, ventromedial prefrontal and visual cortices (Britton *et al.,* 2006). This fact makes results in both studies comparable.

In conclusion, emotion modulates attentional and perceptual processes not only within a single sensory modality, as has been previously reported (Öhman *et al.,* 2001; Fox, 2002), but also exerts a strong influence on the processing of other sensory signals presented concomitantly through an effect of facilitation. This modulation might be independent from voluntary mechanisms of attentional control but still would respond to common top-down regulation (Vuilleumier, 2005). Our results show a spread emotional modulation over frontal sites during novelty processing stages (Fig. 3). These results could confirm the role of ventral prefrontal areas on emotional processing reported in different studies (Northoff *et al.,* 2000; Kawasaki *et al.,* 2001) giving support to a role of this area on emotional top-down regulation of attention (Armony & Dolan, 2002; Carretié *et al.,* 2005).

In general, the present results are in agreement with some observations reported in previous studies. Yamashita *et al.* (2005) reported that auditory P50 suppression became attenuated while subjects visualized negatively valenced slides. Suppression of P50, known as auditory sensory gating, responds to the pre-attentive ability of the brain to modulate its excitability to an incoming stimulus. It is hypothesized to be a protective mechanism that prevents sensory overload of higher brain functions by filtering out the irrelevant sensory inputs (Braff & Geyer, 1990). Thus, all sounds in their study were presumably better processed under negative emotional conditions, surpassing these protective mechanisms.

However, the emotional effects on auditory-P3 observed in the present experiment differ notably from a number of studies using startle reflex measurements (Schupp *et al.*, 1997; Cuthbert *et al.,* 1998; Bradley *et al.,* 2006; Keil *et al.,* 2007). In these studies, whereas blink reflex was enhanced for startle probes while viewing unpleasant pictures (Schupp *et al.,* 1997; Cuthbert *et al.,* 1998; Bradley *et al.,* 2006 –the latter only for probes presented at late stages after picture onset), auditory-P3 decreased in amplitude (Schupp *et al.,* 1997; Cuthbert *et al.,* 1998; Keil *et al.,* 2007) even for unexpected simple tones (Cuthbert *et al.,* 1998), suggesting a greater allocation of attentional resources to the affective visual stimuli in a limited-capacity system. Although still unclear, we suggest that the reasons of this disagreement might be the presence or absence of perceptual competence in the studies. In their experiments, sounds appeared while the picture was on screen and stimulus display was of 1.5 or 6 s. In our study, sounds appeared when no image was being displayed. Sounds were presented on average 1400 ms after the picture offset and always 300 ms before the onset of the next image. With this and the short duration of the stimuli, we manipulated the emotional load of the task while images and sounds never overlapped and attentional resources were never forced to compete. This trial structure was optimal, on the other hand, to favour novelty processing and behavioural distraction (Escera *et al.,* 1998, 2000). Yet, any comparison between these studies and the one reported here should be taken with caution. In startle experiments, probes were identical across presentations, whereas we used 100 different novel sounds. Although both startle probes and novel sounds appeared unexpectedly in all studies and, thus, can be treated as novel auditory events, the structure of the audio-visual oddball paradigm used here differs notably from that used by startle reflex measurements.

In summary, the results of the present study show that processing emotionally salient information influences mechanisms of involuntary attention at very early stages of the orientation response, being this modulation an enhancement. As a consequence, the distractor effects normally elicited by novel sounds undergo potentiation. Such mechanism would make possible that unexpected auditory events, irrelevant in neutral environmental conditions *per se*, became more available to the attentional set in a threatening context, providing thus, if necessary, crucial information for survival.

Acknowledgements

This work was supported by grants from the Spanish Ministry of Education and Science [SEJ2006-00496/PSIC, BES-2004-3244 and AP2006-00731] and from the Generalitat de Catalunya [SGR2005-00953].

Abbreviations

ERP, event-related brain potential; STD, standard sound; NOV, novel sound; NEU, neutral context; NEG, negative context.

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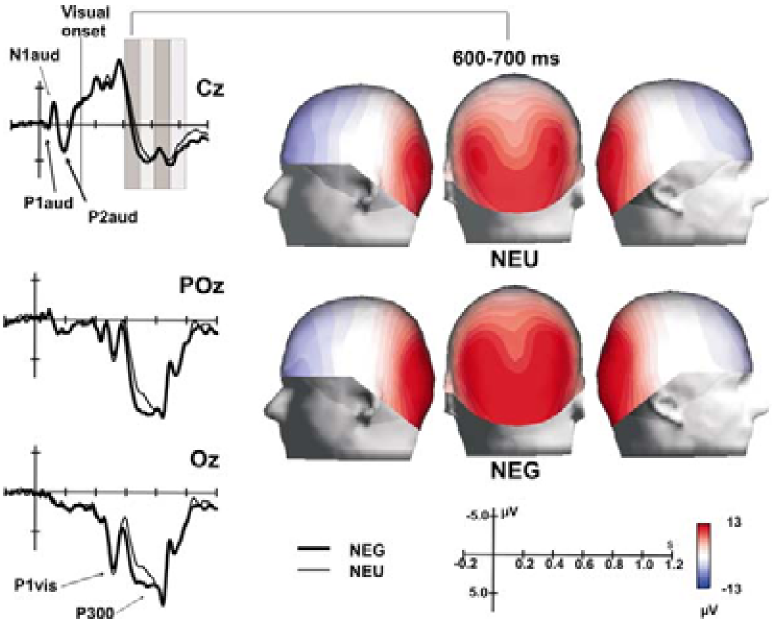

Figure 2. ERPs for STD trials only: neutral (NEU, thin line) versus negative context (NEG, thick line) and scalp-distribution maps. An early P300 enhancement shows that emotionally negative pictures were more deeply processed as compared to neutral pictures.

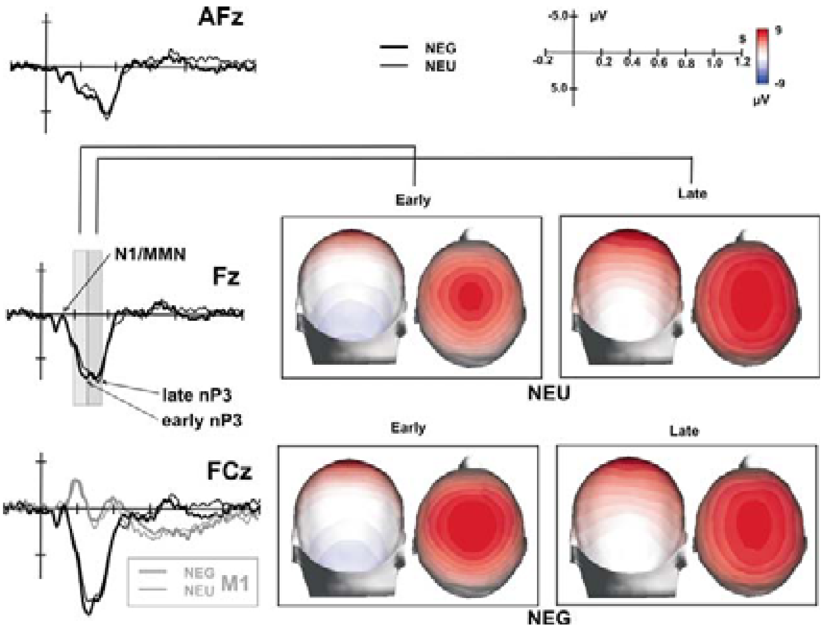

Figure 3. Difference waves obtained by subtracting the standard (STD) sound ERPs from those elicited to novel (NOV) sounds both for neutral (NEU, thin line) and negative context (NEG, thick line) and scalp-distribution maps. Early novelty-P3 responses to novel sounds were enhanced in NEG context. The early novelty-P3 inverted polarity at posterior and lateral sites, for instance as shown at the left mastoid electrode (M1), whereas the late subcomponent did not.

Supplementary material

IAPS identification numbers. Emotional pictures: 1050, 1051, 1052, 1120, 1200, 1270, 1300, 1301, 1930, 1931, 2710, 2750, 2800, 3000, 3010, 3015, 3022, 3030, 3051, 3053, 3061, 3062, 3063, 3071, 3080, 3100, 3102, 3110, 3120, 3130, 3140, 3150, 3160, 3168, 3170, 3230, 3250, 3261, 3266, 3400, 3550, 6250, 6260, 8230, 9040, 9265, 9405, 9490, 9570, 1019, 1111, 1201, 1274, 1275, 2141, 2352_2, 2691, 2730, 2900, 3060, 3064, 3301, 3500, 3530, 3550_1, 6212, 6213, 6312, 6313, 6350, 6360, 6540, 6550, 6560, 6821, 6831, 6838, 6940, 9050, 9250, 9252, 9253, 9400, 9402, 9410, 9420, 9421, 9433, 9520, 9910, 9920, 9921, 1022, 1101, 1113, 1121, 1240, 1280, 1321, 3190, 3181, 2753, 2900, 2900_2, 3350, 3180, 9592, 6190, 6200, 6250, 6210, 6243, 6510, 6830, 6836, 9611, 9911, 9490. Neutral pictures: 1450, 1560, 1590, 1600, 1620, 1640, 1660, 1670, 1740, 1810, 2190, 2200, 2206, 2210, 2214, 2215, 2221, 2372, 2383, 2410, 2440, 2480, 2487, 2495, 2500, 2570, 2600, 2749, 2751, 2752, 2840, 2880, 8300, 5395, 5410, 5460, 5470, 5480, 5500, 5660, 5700, 5740, 5870, 5875, 5890, 5900, 6150, 7000, 7002, 7004, 7006, 7009, 9830, 7010, 7020, 7025, 7030, 7034, 7035, 7040, 7050, 7060, 7080, 7090, 7095, 7096, 7100, 7110, 7130, 7140, 7150, 7170, 7175, 7184, 7185, 7190, 7211, 7233, 7235, 7490, 7491, 7705, 7820, 7950, 8021, 8041, 8090, 8130, 8160, 8200, 8250, 8260, 8280, 8340, 8465, 8510, 9210, 1601, 1604, 1721, 1812,1850, 1900, 1910, 1942, 4100, 2515, 2560, 2580, 2791, 2850, 4233, 4605, 5000, 5001, 5020, 5200, 5201, 5390, 5500, 5510, 5520, 5530, 5532, 5533, 5534, 5535, 5621, 5623, 5760, 4617, 5780, 5830, 5849, 5891, 5910, 5450, 5994, 5600, 5831, 7031, 2209, 7186, 7187, 7200, 7205, 7217, 7224, 7234, 7220, 7283, 7280, 7281, 7284, 7285, 7286, 7320, 7350, 7390, 7402, 7410, 7481, 7495, 7496, 7501, 7510, 7560, 7590, 7595, 7620, 7640, 7700, 7710, 8030, 8033, 8116, 8117, 8162, 8185, 8220, 8311, 8420, 8500, 7284, 7289, 9390, 9417, 9700.

Study III.

Garcia-Garcia, M., Domínguez-Borràs, J., SanMiguel, I., Escera, C. Electrophysiological and behavioral evidence of gender differences in the modulation of distraction by the emotional context (*submitted*).

Electrophysiological and behavioral evidence of gender differences in the modulation of distraction by the emotional context

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Abstract

Negative emotion interacts with the processing of other stimuli, even when irrelevant, also across sensory modalities. Gender differences in brain activity while processing emotional stimuli have been demonstrated by neuroimaging and electrophysiological data. In the present study, we aim at elucidating the gender differences in the modulation of unexpected auditory stimulus processing by an emotional context elicited by aversive images. Fourteen men and fourteen women performed a well-established auditory-visual distraction paradigm in which distraction was elicited by novel stimuli within a neutral or negative emotional context induced by images from IAPS. Response time increased after unexpected novel sounds as a behavioral effect of distraction, and this increase was larger for women, but not for men, within the negative emotional context. Novelty-P3 was also modulated by the emotional context for women but not for men. These results reveal a stronger novelty processing in women than in men during a threatening situation.

Keywords: Event-related potentials, Novelty-P3, RON, Emotional context, Involuntary attention

Introduction

The occurrence of an unexpected novel or deviant auditory stimulus during task performance induces behavioral distraction, as shown by delayed response time obtained in a range of experiments using both auditory-auditory (Schröger & Wolff, 1998; Berti & Schröger ,2001; Roeber, Berti & Schröger, 2003) and auditory-visual (Alho et al., 1997; Escera et al., 1998, 2000, 2001, 2002, 2003; Yago et al., 2001a, 2001b, 2003) “distraction paradigms” (see reviews in Escera et al., 2000; Escera & Corral, 2003, 2007). These paradigms derived from a modification of the so-called “oddball” paradigm, in which a high probability standard stimulus is replaced randomly by a rare or “odd” stimulus. Concomitant recordings of event-related potentials (ERP) show a prominent response, the so-called novelty-P3 or P3a, which is associated with the evaluation of these novel events for subsequent behavioral action (Friedman et al., 2001; Ranganath & Rainer, 2003). P3a is an ERP component of the “P300 family”, which discloses the early and frontocentral P3a elicited by unexpected stimuli from the later centro-parietal P3b elicited to task-relevant target stimuli (see Polich, 2007). The P3a or novelty-P3 component has been described to have two subcomponents, the early and the late ones, clearly disclosed on the basis of their respective latency, scalp distribution and psychological concomitants (Escera et al., 1998, 2000; Polo et al., 2003; Yago et al., 2003). Preceding this positivity a negative response combining an enhancement of the auditory N1 component, and the *mismatch negativity* (MMN) is observed. This negativity indexes a mechanism for stimulus change detection, leading to attention capture (Escera et al., 1998; Alho et al., 1998). The auditory N1 component is elicited by the onset of any abruptly commencing sound (Näätänen & Picton, 1989). MMN is an ERP component elicited by any discriminable change in the otherwise repetitive auditory stimulation (Näätänen, 1989; Näätänen et al., 2007). After the novelty-P3, another negative deflection may be observed: the 'reorienting negativity' (RON), reflecting processes in the context of reorienting attention towards task-relevant aspects of stimulation following distraction (Schröger & Wolff, 1998). These typical waves index three main stages of exogenous attentional control (Escera et al., 2000; Escera & Corral, 2003).

In the mechanisms controlling for attention, a recent body of evidence suggests a constant interaction between exogenous attentional control and endogenous cognitive control (Pashler et al., 2001). In an ERP study, an auditory distraction paradigm was applied while manipulating the working memory load to show that in a condition with working memory load, distraction decreases (Berti & Schröger, 2003), as reflected by the attenuation of novelty-P3 amplitude while attentional resources are consumed by a competing task (SanMiguel et al, 2008). In a similar way, negative emotion may play a role in this top-down modulation of involuntary attention. Indeed, processing of negative emotion interacts with processing of other stimuli either facilitating or competing with them, not only within (Mogg & Bradley, 1999; Anderson, 2005) but also across sensory modalities. For instance, stimuli with an affective load have been shown to elicit stronger and faster attention capture than non-emotional stimuli (Hansen & Hansen, 1988; Öhman et al., 2001). Emotional stimuli capture attention at a very early stage of information processing in the human brain (around 100-200 ms after stimulus onset, Smith et al., 2003; Carretié et al., 2004; Krolak-Salmon et al., 2004; or even earlier, 50-100 ms after stimulus onset, Sugase et al., 1999) even when the emotional stimuli appear out of the attentional set, that is, automatically (Vuilleumier et al., 2001; Schupp et al., 2003; Carretié et al., 2005; Williams et al., 2004) or almost automatically (modulated by attention but never abolished, Pessoa et al., 2002). A visually induced negative emotion interacts with the processing of concomitant auditory inputs, as indexed by startle reflex potentiation by the picture arousal (Amrhein et al., 2004; Stanley & Knight, 2004), and P3 attenuation by the valence of the image (Schupp et al., 1997; Cuthbert et al., 1998). A recent fMRI study has reported that areas involved in novelty processing (bilateral superior temporal gyri) are significantly more activated in a negative emotional context, as compared with a neutral one (Domínguez-Borràs, Trautmann, Erhard, Fehr, Herrmann & Escera, *submitted*), demonstrating a modulation of orienting of attention towards salient stimuli by emotional context, analogous to top-down mechanisms of attentional control. On a similar ERP study, the electrophysiological results revealed an enhancement of novelty-P3 when novel sounds were processed during the performance of a task involving emotionally negative pictures (Domínguez-Borràs, Garcia-Garcia & Escera, *In Press*).

Previous studies have demonstrated that men and women process emotional stimuli differently. Kemp, Silberstein, Arstrong & Nathan (2004) found widespread frontal latency reduction associated to the processing of unpleasant pictures from the International Affective Picture System (IAPS; Lang et al., 1998) on a steady-state visually evoked potentials study, in women but not in men. In an ERP study, Orozco & Ehlers (1998) found significantly enhanced amplitudes in frontal regions in response to sad faces as compared to neutral faces both in men and women, but larger amplitude for women in comparison to men on P450, an ERP component related to the “intensity” of response to emotional stimuli, suggesting that women may be more “sensitive” to emotional stimuli than men. Moreover, fMRI studies exploring the neural correlates of emotional processing using images from the IAPS (Lang et al.,1998), described stronger right amygdala activation in women as compared to men (Wrase et al., 2003; Hofer et al., 2006). This subcortical structure located in the anterior medial temporal lobe, the amygdala, has a crucial role in the processing of emotions (LeDoux, 2000). It is remarkable that the amygdala not only differs in men and women functionally, but also in terms of structure and in several aspects of brain development (Goldstein et al., 2001). This difference may contribute to the unequal prevalence of emotion-related disorders. Recent neuroimaging studies have elucidated some gender differences in the activation of the amygdala and its connected network in responses to emotional stimuli, where females have been found to activate more regions (Canli et al., 2002).

Unexpected novel stimuli in an emotionally negative situation, such as a threatening or fear environment, acquire a vital importance as they may be potentially harmful, so a stronger processing becomes crucial and has an obvious adaptive value. In the present study we aim at elucidating by means of ERPs the gender differences in the modulatory effect of an aversive emotional context on the brain response to task-irrelevant novel sounds. As previous studies have demonstrated a more intensive response of women to affective stimuli, we hypothesize that women will show a larger modulatory effect on auditory novelty processing by a negative emotional context in comparison to male participants.

Materials and Methods

Participants

Fourteen female subjects (right handed, mean age 22 ± 4.2 years, range 18-29 years) and fourteen male subjects (one left-handed, mean age 23 ± 3.5 years, range 18-29 years) participated in the present study. All subjects reported a history with no neurological or psychiatric illness, phobias, drug consumption, or abnormal audition, and they gave informed consent according to the Declaration of Helsinki and to procedures set by the local ethical committees. All subjects had normal or corrected-to-normal vision and were within the normal range of anxiety levels (assessed with the Anxiety Trait and State scale STAI; Spielberger, 1983). Male and female subjects did not differ significantly either in anxiety-state or -trait scores.

Stimuli and Task

The emotional visual stimuli were 308 pictures, with either neutral or negative valence, selected from the International Affective Picture System (IAPS)[1] (Lang, Bradley & Cuthbert, 2005). We included a total of 188 neutral pictures and 120 negative pictures picked among the most neutral and negative pictures of IAPS rated at the Self-Assessment Manikin (SAM) (Lang, 1980). These dimensions were also evaluated by the participants after the experiment using a different scale (1-to-9 scale in which 1 indicated the most positive and arousing and 9 the most negative and less arousing for valence and arousal, respectively) in order to ensure that they evoked the affective reaction reported by Lang (1980). Average rates were of 4.1±0.8 and 5.5±0.9 for neutral images' valence and arousal respectively, and 7.7±0.5 and 3.1±1.1 for negative images' valence and arousal, respectively. Rates both in valence and arousal were significantly different for neutral and negative pictures (Valence: $F_{(1,26)}=269.92$, $p<0.001$; Arousal: $F_{(1,26)}=54.39$, $p<0.001$). For the present experiment, each visual stimulus was composed by two pictures of 643x482 pixels of the same emotional valence and a fixation point (a white cross in the center of the screen), appearing simultaneously with a duration on the screen of 400 ms, subtending a vertical angle of 9º and a horizontal angle of 25º, at 150 cm distance from subject's eyes. A unique sequence was deigned in which a total of 1000 trials were divided in 66 blocks of 10, 15 or 20 trials of the same valence. All blocks were pseudorandomized in one unique sequence, which could either begin with a higher proportion of neutral pictures ending with a higher proportion of negative pictures, or begin with a higher proportion of negative pictures ending with a higher proportion of neutral pictures. However, the emotional content of the images was task irrelevant, as the participants were neither informed about the emotional content of the images, nor instructed to pat any attention to their affective content. These two different stimuli distributions were counterbalanced across subjects with a Latin square design. Within the sequence, 50% picture pairs were composed by two identical pictures and 50% by two different pictures.

Auditory stimuli were a 700 Hz standard tone and 100 unique environmental complex novel sounds, generated as in Escera et al. (1998), chosen amongst the most highly rated by a sample of 30 subjects on a scale of familiarity (Escera et al., 2003). Along the sequence the probability of occurrence of the standard tone was 0.8, and novel sounds occurred with a probability of 0.2, so that every novel sound was delivered only once within each emotional condition. The duration of all auditory stimuli was 200 ms, delivered binaurally through Sehnheiser® HD202 headphones. All stimuli were presented with the stimulation program Presentation® (Neurobehavioral Systems Inc.).

Participants performed a modified version of a well-characterized auditory-visual distraction paradigm (Escera et al., 1998, 2000, 2001, 2003). Auditory stimuli preceded in 300 ms the visual stimulus onset. Subjects sat on a comfortable chair and were instructed to press a response button as fast and accurate as possible to respond whether the two pictures, which appear simultaneously, were equal or different, while ignoring the sounds. Along the sequence, 50% of picture pairs were composed by two identical pictures, and 50% were composed by two different pictures. The response buttons (left or right with the same hand) were counterbalanced across participants. Trial duration varied randomly from 1500 ms to 2100 ms (mean length 1800 ± 300 ms). A ten trials practice block was delivered without auditory stimuli before the performance of the task.

EEG Data Acquisition

Electroencephalographic activity was recorded (ANT Software b.v. Netherlands) during task performance from 64 scalp electrodes following the 10/10 convention in an electrically and acoustically shielded room. The horizontal and vertical electro-oculogram (EOG) were recorded with electrodes placed on the outer cantus of the right eye and above the right eye. The common reference electrode was placed on the tip of the nose, and the ground was located on the chest. The electroencephalogram (EEG) was amplified and digitized at a sampling rate of 512 Hz. Impedances were kept below 15 kΩ during the whole experimental recording session, which lasted about 35 minutes, including short rest periods.

Data processing

ERPs were averaged offline for novel and standard trials separately, for an epoch of 1400 ms including a pre-stimulus baseline of 200 ms. Only those auditory stimuli surrounded by visual stimuli of the same emotional valence were selected for averaging. The first five trials of each block and the first ten trials of the sequence, as well as standard trials following a novel trial were excluded from analysis. Frequencies above 30 Hz were digitally filtered out from the individual ERPs. EOG artifact compensation was performed via a regression algorithm, in which trials exceeding a standard deviation of ± 30 μV within the continuous data (200 ms window) were manually rejected. On average, 82.6% of epochs with standard, 82.9% of epoch with novels sounds in neutral context, as well as 84.7% epochs with standard and 86.6% epochs with novel sounds in negative context were retained for averaging. On average, a minimum of 152 trials were included in each condition.

Data analysis

For behavioral analysis, a correct button press within 100-1200 ms after visual stimulus onset was regarded as a hit, and the mean response time (RT) was computed for hit trials only. Hit rate and RT were compared by means of three-factor repeated-measure ANOVA including the factors Sound (standard, novel), Context (neutral and negative), separately for sounds surrounded (preceded and followed) by neutral pictures and those surrounded by negative pictures, and the inter-subject variable Gender (men and women), and pair-wise *post hoc* comparisons were also performed, when necessary.

In order to examine the effects of the emotional load of the task on attentional processes, P300 to visual targets was measured as the mean amplitude at F7, F3, Fz, F4, F8, FT7, FC3, FCz, FC4, FT8, T7, C3, CZ, C4, T8 TP7, CP3, CPz, CP4, TP8, P7, P3, Pz, P4, P8 in four consecutive latency windows, these including 300-400 ms, 400-500 ms, 500-600 ms, 600-700 ms after visual stimuli onset (that is 600-700 ms, 700-800 ms, 800-900 ms and 900-1000 ms after auditory stimuli onset). Scalp-distribution analyses for P300 were performed after normalizing ERP amplitudes to prevent amplitude differences between different components from washing out the genuine scalp-distribution differences. This normalization was done by dividing the amplitude at each electrode by the sum of the squared amplitudes at all electrodes (McCarthy & Wood 1985). ANOVA for repeated measures was performed including the factor Context (negative, neutral), Frontality (five levels), Laterality (five levels) and the inter-subject variable Gender (men and women).

N1-enhancement/MMN, novelty-P3 and the reorienting negativity (RON) were isolated in the difference waves obtained by subtracting the standard-tone trial ERPs from those elicited to novel-sound trials. N1-enhancement/MMN and the early and late phases of novelty-P3 were measured as the mean amplitude at F3, Fz, F4, C3, Cz and C4 in the 110-155, 200-290 and 290-370 ms latency windows after auditory stimuli onset, respectively. RON was analyzed as the mean amplitude at F5, F3, Fz, F4, F6, C5, C3, Cz, C4, C6, P5, P3, Pz, P4 and P6 in the 440-510 ms. latency window after auditory stimuli onset. ANOVA for repeated measures of all ERP responses of interest were performed including the factor Context (negative, neutral), Frontality (two levels for novelty-P3 and N1-enhancement/MMN, and three levels for RON), Laterality (three levels for novelty-P3 and N1-enhancement/MMN, and five levels for RON), inter- subject variable Gender (men and women), and only for novelty-P3 Phase (early, late) as described in Escera et al. (1998, 2001). Greenhouse-Geisser correction of the degrees of freedom was applied. The *P*-values following correction were reported.

Results

Behavioral results

Participants had an overall hit rate of about 91%, which decreased significantly in the emotionally negative condition (Context: $F_{(1,27)}$=8.95, p=0.006), as well as on trials including a novel sound (Sound: $F_{(1,27)}$=5.10, p=0.032; see Fig.1). A two-factor repeated-measures ANOVA revealed that response time was significantly delayed after novel sounds (Sound: $F_{(1,27)}$=41.36, p<0.001), indicating that subjects were distracted by the unexpected occurrence of task-irrelevant novel sounds, in agreement with previous studies (Alho et al., 1997; Escera et al., 1998, 2001, 2003). Response time was significantly longer in the negative condition as well (Context: $F_{(1,27)}$=15.12, p=0.001). Even though there was no significant interaction between these two factors, a tendency for longer delay of response after novel sounds was apparent in negative context as compared to neutral context (Sound X Context: $F_{(1,27)}$=2.99, p=0.095). Further analysis separately for male and female subjects indicated that this marginal effect could be due to women**'s** performance, where the distraction effect on response time was significantly larger in emotionally negative context (Sound X Context: $F_{(1,14)}$=7.85, p=0.014), while in men no significant interaction between context and sound was found. No statistical differences were seen between counterbalanced runs, or response buttons, either for RT or hit rate.

Electrophysiological results

Difference waves obtained by subtracting the ERPs elicited to standard trials from those elicited to novel ones revealed the neuroelectric activation underlying novelty processing, which was characterized by a well-defined N1-enhancement/MMN, a novelty-P3, and a reorienting negativity (RON; Fig.2A).

No significant difference of mean amplitudes was found on ANOVA performed over the negative electrophysiological response combining an enhancement of auditory N1 and MMN.

The ANOVA on novelty-P3 revealed a main effect of Phase ($F_{(1,26)}$=6.83, p=0.015), Frontality ($F_{(1,26)}$=12.82, p=0.001) and Laterality ($F_{(4,108)}$=61.53, p<0.001), and the interactions Phase X Laterality ($F_{(2,52)}$=3.67, p=0.034), Laterality X Frontality ($F_{(2,52)}$=16.73; p<0.001) and Laterality X Frontality X Phase ($F_{(2,52)}$=23.36, p<0.001), supporting the common frontal distribution of this potential, and revealing larger amplitudes on the right hemisphere, particularly of its late phase, and larger amplitudes of the early phase at central sites. This pattern of results is in agreement with that obtained in previous studies (Escera et al. 1998, 2001) The amplitude of the early phase of novelty-P3 was larger for the negative context (Context X Phase: $F_{(1,26)}$=5.17, p=0.031). The general ANOVA on novelty-P3 also yielded some effects of the intersubject variable Gender. A multiple interaction of location, emotional context and gender (Group X Frontality X Phase X Context: $F_{(1,26)}$=5.25, p=0.030) was found. Further analysis separately for groups revealed significantly larger amplitudes of the early phase of novelty-P3 in women (Context X Phase: $F_{(1,13)}$=9.85, p=0.008), which were not found in men (Fig. 2B). The general ANOVA revealed an interaction of Laterality, Phase and Group ($F_{(2,52)}$=3.47, p=0.040). The early phase of novelty-P3 was shown to be significantly larger for women than for men (Laterality X Group: $F_{(2,52)}$=3.85, p=0.029; Group: $F_{(1,26)}$=4.27, p=0.048; Fig. 3B), as revealed by subsequent analyses separately for phases.

As for the RON component, a general three-factor ANOVA revealed a significant interaction disclosing larger amplitudes for the negative context (Fig.4) (Context: $F_{(1.26)}$=5.30, p=0.030). A main effect of Frontality ($F_{(2,52)}$=11.56, p=0.001) and Laterality ($F_{(2,52)}$=4.49, p=0.024) were shown as well. A marginal effect was found for Gender (Group: $F_{(1,26)}$=3.61, p=0.069) revealing an attenuated RON for women as compared to men .

Grand-average ERPs to standard trials for both conditions (see the Methods section) revealed a sequence of auditory P1, N1 and P2 and visual target-related P300 deflections (Fig. 5). The statistical scalp-distribution analyses of target-P300 across neutral and negative conditions (ANOVA for normalized amplitudes with three factors: Context, Laterality and Frontality) yielded a P300 distribution over posterior electrodes in the four consecutive latency windows (Frontality: $F_{(4,104)}$=211.59, p<0.001; $F_{(4,104)}$=261.15, p<0.001; $F_{(4,104)}$=72.75, p<0.001; $F_{(4,104)}$=153.01, p<0.001;) and over lateral more than central sites (Laterality: $F_{(4,104)}$=35.02, p<0.001; $F_{(4,104)}$=22.12, p<0.001; $F_{(4,104)}$=10.30, p<0.001; $F_{(4,104)}$=4.54, p=0.011). P300 amplitude was enhanced in negative context as compared to neutral for the 600-700 ms latency window (Context: $F_{(1,26)}$=48.44, p<0.001), particularly on posterior-central locations, as revealed by the interaction Context X Laterality ($F_{(4,104)}$=3.27, p=0.046), and for the 900-1000 ms latency window ($F_{(1,26)}$=4.63, p=0.041). P300 amplitude was larger for women as compared to men for the

700-800 ms latency window (Group: $F_{(1,26)}$=8.38, p=0.008), particularly on the right hemisphere (Group X Laterality: $F_{(4,104)}$=3.76, p=0.025). A tendency was found in the same direction for the 600-700 ms latency window (Group: $F_{(1,26)}$=3.94, p=0.058).

Discussion

The results of the present study revealed that the increase of response time elicited by the unexpected novel sound as a behavioral effect of distraction was larger within the negative emotional context, but only for women and not for men. Electrophysiological data supported this behavioral dissociation effect with the modulation of the novelty-P3 component by the emotional context in women, but not in men.

The occurrence of unexpected auditory novel stimuli resulted in larger response times and in decreased hit rate, showing the behavioral effects of distraction, and were paralleled in the electrophysiological recordings by an N1-enhancement/MMN, followed by a biphasic novelty-P3 and RON responses. As expected, response times were also delayed by aversive images, and the increase of response time elicited by novel stimuli was significantly larger for emotionally negative condition in women. This suggests a stronger modulation of distraction by the emotional context in women than in men. This however contrasts with the lack of modulation of the amplitudes of the N1-enhancement /MMN by emotional context. No gender differences were found on enhanced N1/MMN either.

The visual target-related P300 is known to represent updating mechanisms of task-relevant information (Donchin & Coles, 1988) and has been shown to be influenced by the emotional characteristics of pictures (Amrhein et al*.,* 2004). This visual component showed an amplitude enhancement on emotionally negative trials demonstrating that negative images were more deeply evaluated than neutral ones, and that participants were unable to ignore the affective content of the picture, even when task-irrelevant, which is in agreement with previous studies (Vuilleumier *et al*., 2001; Anderson *et al*., 2003). Processing of negative pictures had a response time cost, as compare to the processing of neutral ones, and induced an impaired task performance. That might be explained by a higher attentional capture by the emotional content of the pictures. Gender differences in the amplitude of this visual target-related potential have been previously reported (Polich & Geisler, 1990; Deldin et al., 1994), showing larger visual P300 amplitude in women than in men.

Subjects experienced a stronger orienting of attention towards the novel auditory stimulus while viewing negative images, as indicated by the increased amplitude of novelty-P3 in negative context. Previous studies elucidated the notion that larger novelty-P3 indicates stronger orienting of attention (Yago et al., 2001a; Escera et al., 1998, 2003), and thus an enhanced processing of the novel stimulus, as this potential is seen to reflect the evaluative aspect of the orienting response (Cycowicz & Friedman, 1998; Friedman et al., 2001). Novel sounds caused a delay on participants' response, which was marginally longer on sounds preceded and followed by aversive pictures. Emotional load modulated the mechanisms of involuntary attention and, thus, distraction. These results are in accordance with fMRI data showing that auditory novel events elicit greater activation in areas involved in novelty processing during a visually evoked emotionally negative situation (Domínguez-Borràs et al., *submitted*). The stronger processing of the unexpected novel stimuli in a threatening or fear situation has an evident adaptive value, as in such condition the novel auditory stimuli may be potentially harmful. The present study, thus, demonstrates that negative emotion plays a role in the mechanisms of modulation of stimulus-driven attention in the same way that working memory load does (Berti & Schröger, 2003; SanMiguel et al., 2008). Nevertheless, some psychophysiological studies have concluded that less attentional resources may be available for evaluating sounds during processing of visually (Schupp et al., 1997; Cuthbert et al., 1998; Keil et al., 2007) or auditory (Keil et al., 2007) induced negative emotion. The task utilized on these studies created a direct competence for the attentional resources between emotional stimuli and sounds, since they appeared simultaneously, so that attentional resources were captured by the emotional stimuli. In the present study, however, emotional visual stimuli appeared 100 ms after auditory stimulus offset, that is, when auditory stimulus had already finished. Thus, the modulation was due to the emotional context where the sounds occurred, rather than by competence for the attentional resources. This may explain the opposite findings between the present study and the startle reflex experiments, and contribute to the understanding of the mechanisms involved in the emotional modulation of attentional processes.

It is worth noting that our female subjects showed a larger amplitude enhancement of novelty-P3 than male subjects in an emotionally negative condition, and that behavioral distraction was significantly larger for sounds within affectively negative blocks. These results support the notion that negative emotion has a stronger effect on women than on men (Canli et al., 2002; Kemp, Silberstein, Arstrong & Nathan, 2004; Orozco & Ehlers, 1998), and indicate that novelty processing during a threatening situation undergoes stronger facilitation in women than in men. Women's processing of unexpected stimuli in an emotionally negative situation, where they may be potentially harmful, is stronger than in a neutral environment, while in men this enhancement of novelty processing does not occur. This is a accordance with the notion of a lower threshold for vigilance of danger signal detection in females, suggested by neuroimaging data showing an enhancement of female amygdala response during perception of facial fear stimuli, while men showed an attenuation

(Williams et al., 2005). Larger amplitudes of the early phase of novelty-P3 were also found in the present study for women as compared to men, independently of the emotional content. This suggests a deeper processing of novel stimuli, or a greater allocation of attentional resources on incoming unexpected novel stimuli in women than in men.

In previous studies, the late phase of novelty-P3, and not the early one, was shown susceptible to modulation (Escera et al., 2003; Polo et al., 2003; SanMiguel et al., 2008), but surprisingly, the early phase of the novelty-P3 was the one which appeared to be modulated in the present study. This modulation of the early phase of the novelty-P3, instead of its late phase might reflect the fact that emotional processing occurs at a very early stage of information processing (Smith et al., 2003; Carretie et al., 2004; Krolak-Salmon et al., 2004; Sugase et al., 1999). Prefrontal responses to affective aspects of visual stimulation have been recorded around 100 ms after stimulus onset (Kawasaki et al., 2001). The amygdala may facilitate this short response latency as it processes aversive information very rapidly, and receives early visual inputs (LeDoux, 2000), and interacts with many areas related to attention (Bentley et al., 2003). Thus, the amygdala may elicit a rapid activation of these areas in order to facilitate the reaction to potentially dangerous events. The functional and structural gender differences described on this structure (Goldstein et al., 2001; Canli et al., 2002) may help to understand the differences found on the emotionally induced modulation on mechanisms of involuntary attention.

The results obtained in the present experiment also showed modulation by emotional context on the later RON component related to the reorienting of attention towards task-relevant aspects of the stimulation (Schröger & Wolff, 1998; Escera et al., 2000, 2001). In the emotionally negative context the amplitude of this negative component was larger in both men and women. RON has been found to reflect at least two different processes of attention reallocation: one related to the process of refocusing attention onto task-relevant information at a working memory level which is task-specific, and one distractor-specific referring to a more general reorientation after distraction (Escera et al., 2001; Munka & Berti, 2006). We may thus argue that this modulation of RON amplitude may be due to a higher attention capture by novel sounds on the negative context, as reflected on the enhancement of novelty-P3 amplitude, and to a higher need of cognitive resources for reorienting attention towards the current task.

A marginal effect of gender was also found on the RON component. Women showed a parietal positive deflection in response to novel sounds instead of RON. This late positivity could correspond to $P3_2$ described by Friedmann (1993) as reflecting the encoding into working memory of the irrelevant auditory stimuli, or a P3b that is thought to reflect working memory update

(Donchin & Coles, 1988). This effect of working memory update found in women and not in men might be in accordance to the greater allocation of attentional resources on irrelevant auditory stimuli showed by the larger novelty-P3 amplitude for women as compared to men. It may be also due to differences in the image processing. The visual target-related P300 potential showed smaller amplitude in men than in women, supporting findings reported previously (Polich & Geisler, 1990; Deldin et al., 1994). As RON occurs about 150-200 ms after visual stimuli onset in our study, gender differences in visual ERPs may be affecting the electrophysiological results at parietal sites on this latency window.

In conclusion, the results of the present study may help to understand gender differences of brain responses to emotion and novelty, as well as the interaction of processing of emotion and orienting of attention towards unexpected stimuli for both men and women, demonstrating that evaluation of incoming stimuli under an emotionally aversive situation is stronger in females. This may reflect more developed mechanisms of preventing potential harm in women than in men as an effect of females' greater importance on infant survival due to pregnancy and maternal care.

This work was supported by grants from the Spanish Ministry of Education and Science [SEJ2006-00496/PSIC; AP2006-00731; BES-2004-3244; Consolider-Ingenio 2010 CSD2007-00012] and from the Generalitat de Catalunya [SGR2005-00953; 2005FI 00467].

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Footnote 1:

IAPS identification numbers. Emotional pictures: 1050, 1051, 1052, 1120, 1200, 1270, 1300, 1301, 1930, 1931, 2710, 2750, 2800, 3000, 3010, 3015, 3022, 3030, 3051, 3053, 3061, 3062, 3063, 3071, 3080, 3100, 3102, 3110, 3120, 3130, 3140, 3150, 3160, 3168, 3170, 3230, 3250, 3261, 3266, 3400, 3550, 6250, 6260, 8230, 9040, 9265, 9405, 9490, 9570, 1019, 1111, 1201, 1274, 1275, 2141, 2352_2, 2691, 2730, 2900, 3060, 3064, 3301, 3500, 3530, 3550_1, 6212, 6213, 6312, 6313, 6350, 6360, 6540, 6550, 6560, 6821, 6831, 6838, 6940, 9050, 9250, 9252, 9253, 9400, 9402, 9410, 9420, 9421, 9433, 9520, 9910, 9920, 9921, 1022, 1101, 1113, 1121, 1240, 1280, 1321, 3190, 3181, 2753, 2900, 2900_2, 3350, 3180, 9592, 6190, 6200, 6250, 6210, 6243, 6510, 6830, 6836, 9611, 9911, 9490. Neutral pictures: 1450, 1560, 1590, 1600, 1620, 1640, 1660, 1670, 1740, 1810, 2190, 2200, 2206, 2210, 2214, 2215, 2221, 2372, 2383, 2410, 2440, 2480, 2487, 2495, 2500, 2570, 2600, 2749, 2751, 2752, 2840, 2880, 8300, 5395, 5410, 5460, 5470, 5480, 5500, 5660, 5700, 5740, 5870, 5875, 5890, 5900, 6150, 7000, 7002, 7004, 7006, 7009, 9830, 7010, 7020, 7025, 7030, 7034, 7035, 7040, 7050, 7060, 7080, 7090, 7095, 7096, 7100, 7110, 7130, 7140, 7150, 7170, 7175, 7184, 7185, 7190, 7211, 7233, 7235, 7490, 7491, 7705, 7820, 7950, 8021, 8041, 8090, 8130, 8160, 8200, 8250, 8260, 8280, 8340, 8465, 8510, 9210, 1601, 1604, 1721, 1812,1850, 1900, 1910, 1942, 4100, 2515, 2560, 2580, 2791, 2850, 4233, 4605, 5000, 5001, 5020, 5200, 5201, 5390, 5500, 5510, 5520, 5530, 5532, 5533, 5534, 5535, 5621, 5623, 5760, 4617, 5780, 5830, 5849, 5891, 5910, 5450, 5994, 5600, 5831, 7031, 2209, 7186, 7187, 7200, 7205, 7217, 7224, 7234, 7220, 7283, 7280, 7281, 7284, 7285, 7286, 7320, 7350, 7390, 7402, 7410, 7481, 7495, 7496, 7501, 7510, 7560, 7590, 7595, 7620, 7640, 7700, 7710, 8030, 8033, 8116, 8117, 8162, 8185, 8220, 8311, 8420, 8500, 7284, 7289, 9390, 9417, 9700.

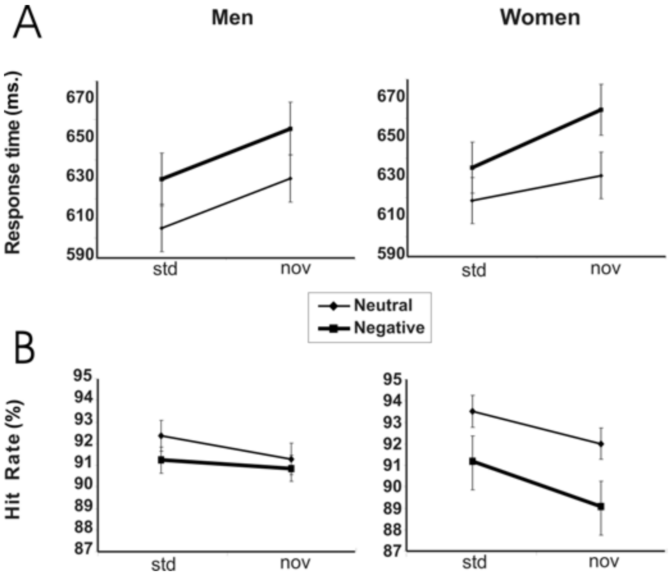

Figure 1. Visual task performance for women and men in standard and novel trials and for the two emotional conditions. Response times (A) increased and hit rate (B) decreased for both men and women after novel auditory stimuli and for negative emotional context. Only in women the distraction effect elicited by novel sounds increased in the negative emotional context condition.

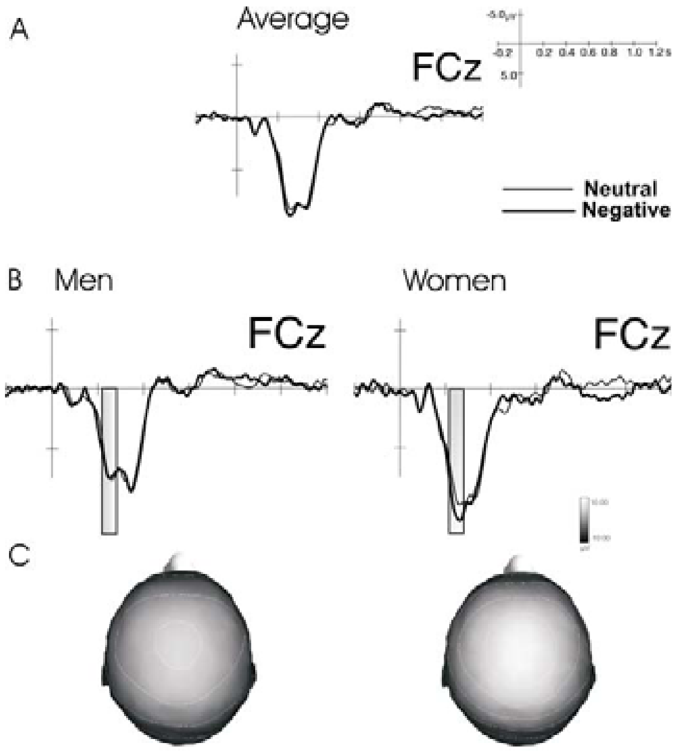

Figure 2. (A) Distraction potential (novel – standard difference waveforms) for all participants at FCz for neutral and negative emotional conditions. Amplitude of the early phase of novelty-P3 was enhanced in the negative context condition. (B) Distraction potentials on FCz for men and women separately, for both neutral and negative conditions. Enhancement of the early phase of novelty-P3 in negative context was greater for women. (C) Scalp distribution maps of early novelty-P3 (200-290 ms.) in the negative context condition for women and men separately.

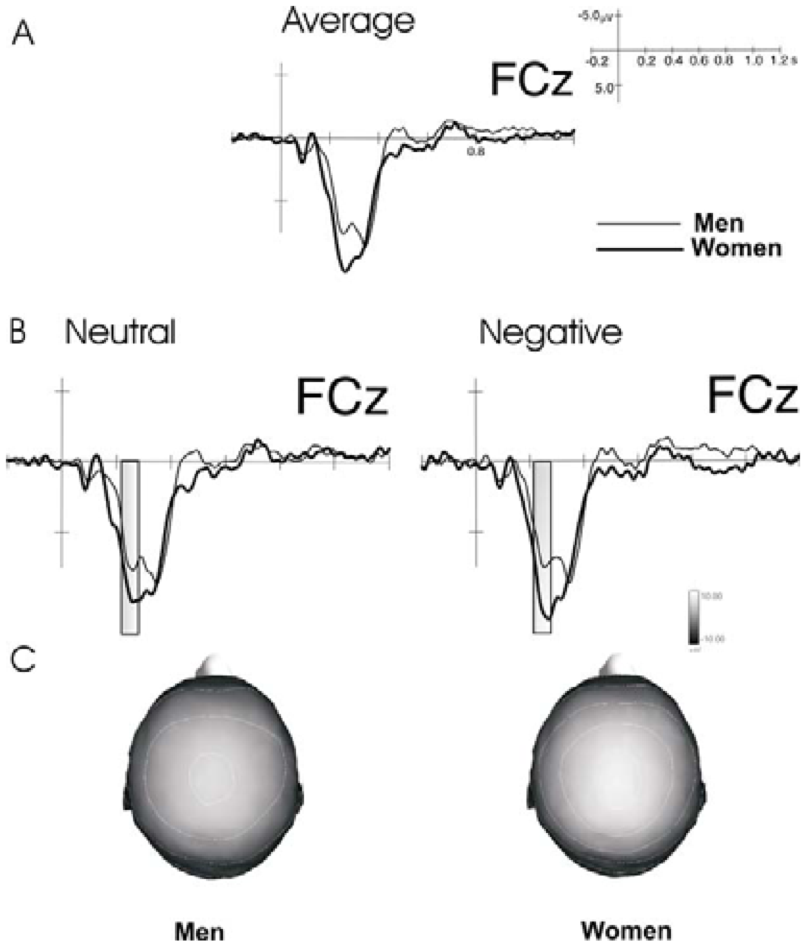

Figure 3. (A) Distraction potential (novel – standard difference waveforms) for both conditions at FCz for men and women. Amplitude of the early phase of novelty-P3 was larger for women. (B) Distraction potentials on FCz for neutral and negative conditions separately, for both men and women. Larger amplitudes of early-P3 for women in both conditions were found, but the difference was greater for the negative condition. (C) Scalp distribution maps of early novelty-P3 (200-290 ms.) in the neutral context condition for women and men separately.

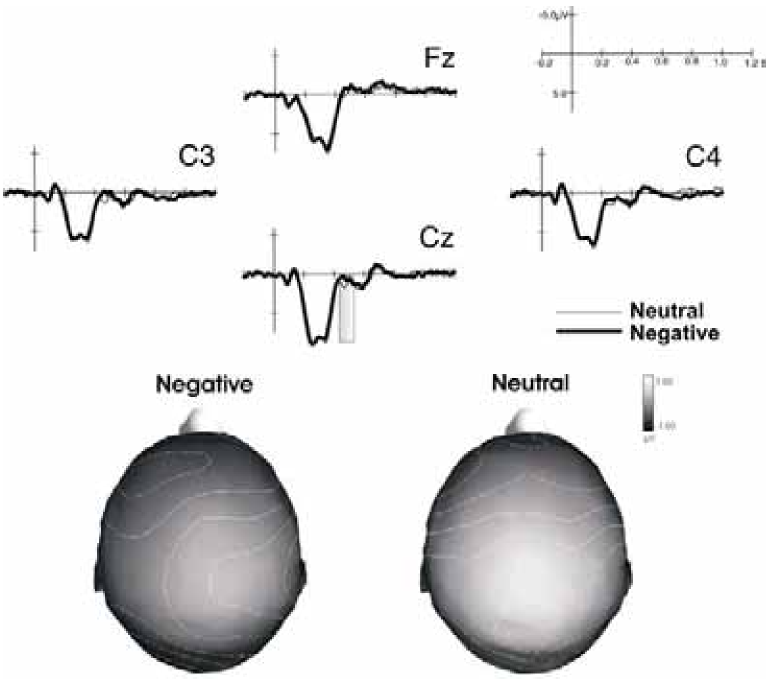

Figure 4. (A) Distraction potential (novel – standard difference waveforms) for all participants at four frontocentral electrodes for neutral and negative emotional conditions, showing a positive deflection on neutral condition, instead of the component RON. (B) Scalp distribution maps of RON (440-510 ms.) for all participants separately for neutral and negative context conditions. The map shows a centro-parietally distributed positive potential for neutral condition.

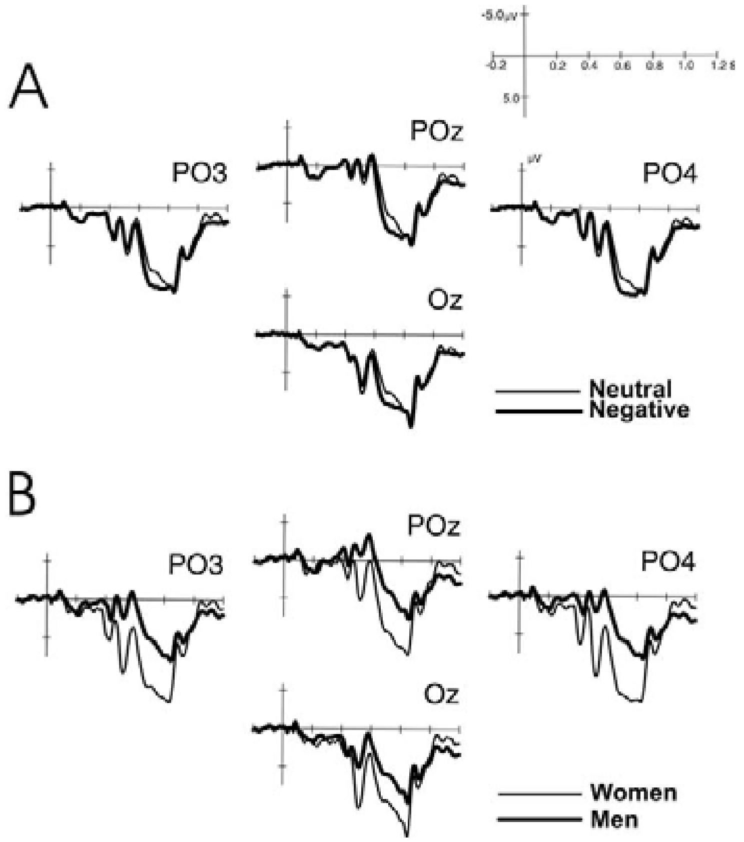

Figure 5. (A) Grand average waveforms for all subjects in standard trials for neutral and negative condition at four parietal electrodes. Notice that the affective content of pictures, although task-irrelevant, was processed, as reflected by the amplitude enhancement of P300 for the negative images. (B) Average waveforms for neutral context and in standard trials separately for men and women at four parietal electrodes. Notice that women showed larger P300 amplitude than men for processing emotionally neutral images.

Study IV.

Domínguez-Borràs, J., Trautmann, S., Erhard, P., Fehr, T., Herrmann, M., Escera, C. Emotional context gates auditory novelty processing in superior temporal gyrus (*submitted*).

Emotional context gates auditory novelty processing in superior temporal gyrus

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Abstract

Visualizing emotionally loaded pictures intensifies peripheral reflexes towards sudden auditory stimuli, suggesting that the emotional context may potentiate responses elicited by novel events in the acoustic environment. However, psychophysiological results have reported that attentional resources available to sounds become depleted, as attention allocation to emotional pictures increases. These findings have raised the challenging question of whether an emotional context actually enhances or attenuates auditory novelty processing at a central level in the brain. To solve this issue we used functional magnetic resonance imaging to first identify brain activations induced by novel sounds when participants made a color decision on visual stimuli containing both negative and neutral facial expressions. We then measured modulation of these auditory responses by the emotional load of the task. Contrary to what was assumed, activation induced by novel sounds in superior temporal gyrus (STG) was enhanced when subjects responded to faces with a negative emotional expression compared to neutral ones. Accordingly, novel sounds yielded stronger behavioral disruption on subject's performance in the negative context. These results demonstrate that the emotional context enhances excitability of auditory and possibly multimodal novelty cerebral regions, gating acoustic novelty processing in a potentially harming environment.

Keywords: amygdala, attention, emotion, fMRI, novelty processing, superior temporal gyrus.

Introduction

The human nervous system has evolved for efficiently detecting salient information in a multisensory environment, a necessary ability for adaptive behavior. Particularly, a large body of evidence has shown that emotional stimuli have a status of priority in the neural processing systems, eliciting stronger and faster attention capture than non-emotional stimuli (e.g. Eastwood and others 2001; Öhman and others 2001; Carretié and others 2004; Richards and Blanchette 2004). Such a mechanism of attentional bias arises from the limited processing capacity of sensory systems, while attending to adaptive and evolutionary advantages. In this sense, emotion interferes the processing of concomitant stimuli, not only *within* (Öhman and others 2001; Fox 2002), but also *across* sensory modalities: a number of psychophysiological studies have yielded potentiation of the effects elicited by auditory stimuli in emotional context. Peripheral responses such as eye-blinks after the sudden burst of an acoustic stimulus (known as startle reflex), have been shown intensified while visualizing emotionally loaded pictures (Stanley and Knight 2004; Bradley and others 2006). However, psychophysiological measures have suggested that, at the same time, less attentional resources might be available for sound processing as a consequence of allocating more attention to these motivationally pertinent stimuli (Schupp and others 1997; Cuthbert and others 1998; Keil and others 2007). This controversy led us to inquire about the neural mechanisms of sound processing and detection of acoustic changes in emotional environment and whether an affective context can either enhance or attenuate novelty processing in the auditory modality. Unraveling this effect would provide a better understanding of how emotion mediates involuntary attention and awareness.

In the present study, functional magnetic resonance imaging (fMRI) was used to assess the effects of manipulating the implicit negative emotional load in a visual task, by means of fearful and angry faces, on the processing of task-irrelevant odd auditory stimuli. The occurrence of unexpected novel sounds has been typically shown to elicit a specific pattern of neuronal activations localized in supratemporal (Alho and others 1998; Downar and others 2000; Kiehl and others 2001), prefrontal (Downar and others 2001; Bledowski and others 2004) and parietal cortices (Clark and others 2000; Downar and others 2001), subserving the neural mechanisms of *auditory novelty processing* (Ranganath and Rainer 2003). This pattern of neuronal activations is usually accompanied by behavioral disruption of the ongoing task, a phenomenon called *distraction* (Escera and others 1998, 2000, 2001). If the emotional context facilitates the processing of task-irrelevant novel sounds, these novel sounds should elicit greater distraction when subjects respond to emotionally loaded stimuli as compared to neutral ones. Moreover, areas related to auditory novelty processing should become more activated. If, on the contrary, emotional processing depletes most of the attentional resources, distraction should decrease and areas related to auditory novelty processing should become rather inhibited. To test this hypothesis, we presented our participants with task-irrelevant novel sounds while they judged whether the color of a monochromatic face, with task-irrelevant neutral or negative facial expression, matched the color of the surrounding frame (Fig.1a).

Materials and Methods

Subjects. Seventeen healthy right-handed female volunteers, aged between 19 and 30 yrs (mean 22 yrs, ±3.35), without past neurological or psychiatric history and reported normal hearing participated in the present study, which was approved by the Center of Advanced Imaging direction board and the Ethical Committee of University of Barcelona. All subjects gave informed consent according to procedures set by the local ethics committee and completed the color-blindness Ishihara test (Kanehara Shuppen Company, Ltd., Tokyo, Japan,1974) to ensure normal color vision.

Stimuli

Emotional valent stimuli. The emotional valent stimuli consisted of 120 monochromatic pictures including neutrally (60) and negatively valenced facial expressions (30 fearful, 30 angry), and 6 positive for an additional ending block. They were compiled at the Department of Neuropsychology and Behavioral Neurobiology, Bremen University, Bremen, Germany (unpublished thesis by Veronika Weitzel) and evaluated by a sample of 73 subjects (age 19-40 yrs, mean 25.16, ±5.1). Faces with the highest correctly categorized hit rate were selected (displaying neutral -mean 79.6%, ±8.9; angry -mean 97.2%, ±2.2, or fearful expressions -mean 93.3%, ±3.4). Pictures disclosed 50% male and 50% female faces (resolution 500x500 pixels, duration on screen 400 ms), back-projected onto a mirror mounted on the MRI head coil. Visual angles varied with the distance from screen (35 to 40 cm depending on subjects' head size) and were of 17º to 15º horizontal angle and 18º to 16º vertical angle, respectively.

All faces were surrounded by frames. Colors of both faces and frames were presented in green, blue, red or orange in equal proportions, all equally and proportionally balanced. Frames and faces could be of same (50%) or different color (50%) across trials. Every neutral face appeared a total of 6 times. From these neutral faces, the 7 most rated (8 for the no-match condition) appeared 8 times instead. All negative faces (angry and fearful) appeared a total of 6 times. From these negative faces, the 7 most rated (or 8 for match condition) appeared 8 times instead.

Auditory stimuli. The auditory stimuli were presented at 20dB sensation level (SL) and consisted of a 700 Hz standard tone (STD) and 100 unique environmental complex, novel sounds (NOV; 200 ms duration), equalized for root-mean-square (See the Supplementary Material section) energy to keep the energy contour of all auditory stimuli constant over time, generated as described in previous studies (Escera and others 1998), similar in spectrotemporal features (See the Supplementary Material section) and rated by a sample of 30 subjects, on a 1-5 likert-scale of semantic familiarity (as previously reported -Escera and others 2003, about effects of familiarity on novelty processing), chosen between the most highly rated (2.54 mean rate; ±0.5). Along the session, all novel sounds appeared once except for the 50 most familiar, which appeared twice, all of them in random order.

Task and conditions.
Participants performed a modified version of a well-characterized auditory-visual distraction paradigm (Escera and others 1998, 2000, 2001, 2003). Auditory stimuli preceded images in 300 ms, being these either a standard tone (STD condition; p=0.8) or a novel sound (NOV condition; p=0.2). Faces could be neutral (NEU context condition) and negative (NEG context condition). Pictures appeared in the middle of the screen and subjects were instructed to press a response button (left or right hand, counterbalanced across subjects) to respond whether the color of the frame matched the color of the face (Fig. 1a), while ignoring the sounds. Trial length ranged from 2600 to 3200 ms (mean 2900 ms ± 300 ms). A unique sequence was designed, which divided 750 trials into 50 blocks of 15, 10 or 20 trials. NEU and NEG faces were never mixed in the same block. In this manner, scanning time per condition was of a minimum of 26 s (10 trials, 26000 ms). All blocks were pseudo-randomized in a probabilistic non-stationary way so that, in the beginning, a higher proportion of neutral blocks was presented, decreasing progressively and turning into a higher proportion of negative pictures at the end. These sequences were counterbalanced across subjects.

Procedure. Previous to each measurement, subjects performed an only-standard-sound practice block of the task outside the scanner. Sound calibration was implemented inside the scanner to adjust hearing threshold and correct balance for each individual subject with the help of a sound amplifier. During the course of this procedure, a shim echo-planar sequence was applied to ensure that subjects would hear the sounds also in the scanning session.

FMRI scanning. MRI data were acquired on a 3T Siemens Allegra scanner (Erlangen, Germany), using a whole brain local gradient coil. Structural images were acquired with a T1-weighted MPRAGE sequence (160 slices, TR 2.3s, TE 4.38 ms, flip angle 8°, 256x256 matrix, FOV 296x296, inversion time 900 ms, 1mm^3 voxels). Functional images were obtained using a gradient echo-planar (EPI) T2* sequence optimized for BOLD (Blood Oxygenation Level Dependency) contrast. The EPI sequence comprised 44 contiguous slices covering the whole brain, taken every 3 mm with no interslice gap and incorporating the following parameters: TE 30 ms, TR 2.5 s, 64x64 matrix, FOV 192x192, flip angle 90°, resolution 3x3 mm^2, interleaved ascending. Functional images were slice time corrected, realigned, normalized spatially to the Montreal Neurological Institute (MNI) template and smoothed with an 8 mm FWHM gaussian kernel using SPM2 (Wellcome Department of Cognitive Neurology, London, England, 2003).

Data analysis. Behavioral performance was analyzed by calculating accuracy (hit rate) and response times for every condition, and post-hoc comparisons were performed using the Bonferroni adjustment for multiple comparisons. Only those trials in which sounds were surrounded (both preceded and followed) by both NEU or NEG faces and containing correct responses were analyzed, both for behavioral and fMRI data. At the first level, 15 event types were modeled: six events referred to trials containing sounds surrounded by equally valenced pictures and followed by a correct response, six comprising misses and errors and three for all trials at the beginning of every valence block or after breaks. Data were high-pass filtered (1/128Hz), corrected for intrinsic autocorrelations, and convolved with a standard HRF and its temporal derivative. Second level analysis was performed on single-subject statistical parametric maps, serving as random effects. A pooled analysis was used to identify activations additively significant for [(STD-Fear)+(STD-Anger)] and [(NOV-Fear)+(NOV-Anger)], which resulted into the new NEG conditions. Three contrasts of interest were defined, by means of voxel-referred t-tests, to compare BOLD signal for the following conditions: (STD-NEU<NOV-NEU; *novelty processing in neutral context*); (STD-NEG<NOV-NEG; *novelty processing in negative context*); (STD-NEU<STD-NEG; *emotional face processing*). A fourth contrast of interest (*emotional effects on novelty processing*) was examined with a one-factor ANOVA: [(STD-NEU<NOV-NEU)<[[(STD-Fear)+(STD-Anger)]<[(NOV-Fear)+(NOV-Anger)]]]. An additional one-factor ANOVA was performed (the *reverse contrast)*: [(STD-NEU<NOV-NEU)>[[(STD-Fear)+(STD-Anger)]<[(NOV-Fear)+(NOV-Anger)]]].

Activation was considered significant when at least 20 contiguous voxels survived a threshold of p<.001 (except for STD-NEU<STD-NEG; p<.005), uncorrected for multiple comparisons. Stereotactic MNI coordinates were translated into standard Talairach space (Talairach and Tournoux 1988) following nonlinear transformations.

Localization of BOLD response in primary auditory cortex (PAC). Primary auditory cortex is known to be particularly involved in initial detection of changes in the acoustic environment (Ullanovsky and others 2003; Schönwieser and others 2007). Finding emotional modulation in this region would help us to constrain the timing of this effect in the novelty processing stream. One important issue that concerned us was the difficulty for localizing specific activations of PAC in functional imaging data. Cytoarchitectonic studies demonstrate considerable interindividual and interhemispheric differences in size and location of PAC, as well as duplications of Heschl's Gyrus (Penhune and others 1996). The MNI template is known to be roughly based on the Talairach space and it does not totally match the Talairach brain size or shape (Brett et al, 2002). Therefore, Talairach labels for the cytoarchitectonic allocation of functional activations is problematic because it does not provide information about the inter-individual variability of the cytoarchitectonic areas (Eickhoff and others 2005). Thus, the risk for Type II errors (false negatives) in respect to PAC for the first and second level analyses was present. To overcome this limitation, we used a three-dimensional probabilistic cytoarchitectonic map based on an observer-independent quantification of cell volume densities and areal borders of PAC on ten human post-mortem brains (Morosan and others 2001; Rademacher and others 2001). Primary auditory cortex, microstructurally defined and normalized in space (Eickhoff and others 2005), was then set as an anatomical ROI for every single subject. Then, the relative extents of activation for those clusters showing the highest probability to be part of the three cytoarchitectonic areas of bilateral PAC (TE1.0, TE1.1, TE1.2) was computed for the contrasts of interest *emotional effects on novelty processing* and the *reverse contrast*.

Results

Behavioral Data. Subjects had an overall hit rate of about 95% (STD in NEU: $\bar{X}$=95.9, σ=2.84; NOV in NEU: $\bar{X}$ =96.5, σ =2.46; STD in NEG: $\bar{X}$ =97.1, σ =1.98; NOV in NEG: $\bar{X}$ =96.0, σ =4.19). There were no statistical differences in accuracy between sound effects for NEU and NEG conditions, although a significant decrease of accuracy was found for NOV sounds in Fear condition (context*sound: $F_{(1,16)}$=7.19; p=.016). A two-factor repeated-measurement ANOVA revealed significantly longer response times in trials containing NOV sounds compared to those containing STD sounds (STD in NEU: $\bar{X}$ =536, σ =78.6; NOV in NEU: $\bar{X}$ =570, σ =75.6; STD in NEG: $\bar{X}$ =537, σ =76.0; NOV in NEG: $\bar{X}$ =581, σ =79.6; sound: $F_{(1,16)}$=35.93; p=.001), indicating that subjects were distracted from task performance by the task-irrelevant occurrence of novel sounds as they delayed responses, in agreement with many previous studies (Alho and others 1997; Escera and others 1998, 2001, 2003) (Fig. 1b). These response time differences between STD and NOV trials were significantly larger for the NEG context compared to the NEU context (context*sound: $F_{(1,16)}$=5.3; p=.035). Two-tailed dependent t-tests showed difference between NOV trials in NEG and NEU context (NOV in NEU vs. NOV in NEG: T_{16}=2.6; p=.019), while response time in STD trials was similar for both NEG and NEU context (T_{16}=.06; p=.95).

Imaging data

Emotional face processing. Hemodynamic responses for the STD sounds showed a differential activation pattern during processing of angry and fearful expressions compared to the neutral ones in bilateral fusiform gyrus and right inferior temporal gyrus (Fig. 2, Table 1), areas known to be involved in face processing (both fusiform gyrus -George and others 1999- and inferior temporal gyrus -Rolls 1992). Fusiform cortex has been found to be modulated by emotional faces in a variety of studies (Sugase and others 1999; Vuilleumier and others 2001).

Additionally, early visual processing areas (bilateral middle occipital gyrus) as well as right precentral gyrus (premotor cortex) were widely activated. Visual cortices, such as V2, are known to exhibit an increased response to faces with fearful expressions compared to neutral ones (Morris and others 1998). Passive viewing of emotional faces has also previously elicited enhanced activations in the right ventral premotor area (Leslie and others 2004), suggesting a right hemisphere mirroring system that may subserve the neural substrate for empathy. Interestingly, in our results, BOLD response of limbic lobe areas such as right parahippocampal gyrus and right amygdala was observed. This limbic right lateralization is consistent with evidence attributing affective comprehension to the right hemisphere, as seen in patients with right amygdala damage which were unable to interprete facial expressions (Anderson and others 2000), or patients with left hemisphere damage which presented difficulties comprehending words but could report the meaning of their emotional prosody (Barrett and others 1997). A large body of evidence indicates that amygdala is critically involved in processing aversive information (Adolphs and Tranel 2004), capable of organizing rapid reactions to danger, even without the participation of the cerebral cortex (LeDoux 1998).

Differential brain activations in fearful and angry faces compared to neutral expressions were a necessary prerequisite for evaluating any further emotional effect on novelty processing and distraction.

Auditory novelty processing. Before examining emotional modulation of novelty processing we tested the effects of novelty processing in every single context. Novelty processing engaged a cerebral network expressed in prefrontal (bilateral inferior frontal gyrus) parietal (bilateral precuneus) and temporal cortices (bilateral STG and middle temporal gyrus) both for the NEU and the NEG context (Fig. 3, Table 2).

Despite the lack of consensus upon the neural substrates for novelty processing, some common results can be observed across oddball studies. Investigation using novelty oddball paradigms, both with auditory and visual novel events, has yielded novelty responses in inferior parietal (Clark and others 2000), precuneus (Downar and others 2001), superior temporal sulcus and gyrus (Alho and others 1998; Clark and others 2000; Downar and others 2000; Kiehl and others 2001), and prefrontal areas (IFG -Bledowski and others 2004; Downar and others 2001-dorsolateral -Bledowski and others 2004). In general, the network observed in our results may subserve those mechanisms responsible for identification and evaluation of salient sensory stimuli in a complex environment, underlying a *novelty evaluation system* which refers to a mechanism concerned with the evaluation of novel stimuli that already captured attention (Näätänen 1992; Friedman and others 2001; Ranganath and Rainer 2003).

The combination of hemodynamic and behavioral results in our study led us to confirm that auditory novels were processed differently with regard to the repetitive standard sounds (*novelty processing*), recruiting attentional resources from the ongoing task in subjects and causing a delay in the average performance (*distraction*) regardless of the emotional load within the task.

Gating of novelty processing in negative emotional context. As can be observed in Fig. 4 and Table 3, bilateral STG, including bilateral secondary auditory cortex (cytoarchitectonic area Te2 -BA42- and BA21), and bilateral planum temporale (cytoarchitectonic area Te3, BA22), showed a stronger response when subjects processed auditory NOV events in a NEG emotional context as compared with the NEU one. Subsequent analysis of the relative extents of activation, based on probabilistic maps, showed that 2.9% of the activated voxels were allocated into right Te1.0 and, from these, 3.4 % showed significantly increased activations. A smaller proportion of activated voxels was allocated into Te1.2 (0.2%), from which 0.5 % was more activated. On the left hemisphere, 13.4% of the activated voxels were allocated into Te1.0, showing significant activations on 15% of them, and 6.1% were included in Te1.1, with a 7.9% significantly activated. It can be therefore concluded that, based on probabilistic maps, part of the voxels which showed more activation when processing auditory novelty in NEG context, compared to NEU, were likely allocated into PAC.

Activations obtained with the *reverse contrast* were expressed in bilateral fusiform gyrus, bilateral inferior temporal gyrus and bilateral middle occipital gyri (Table 4). Analysis of the relative extents of activation, based on probabilistic maps, showed no activations in any of the three PAC subregions.

Discussion

Processing of stimulus salience depends not only on novelty or frequency of occurrence, but also on the behavioral context (Katayama and Polich 1998) and, in a special manner, on the emotional relevance of the context. In the present study, we have shown that subjects were unable to fully ignore emotional information even when it was task-irrelevant (Vuilleumier and others 2001). Emotional faces were processed differently compared to the neutral ones by activating amygdala (LeDoux 2000; Vuilleumier and others 2001; Adolphs and Tranel 2004) and, importantly, by modulating face-selective regions such as fusiform gyrus (George and others 1999; Sugase and others 1999; Vuilleumier and others 2001), or early visual areas in the occipital lobe (Morris and others 1998). The possibility that differences in emotional face processing could be caused by differences in basic visual features is still present, although, in other studies, any effects related to emotional face processing disappeared when faces were inverted (and, therefore, the holistic face perception was reduced –Fox and others 2000).

Novel auditory events activated a network of frontal (inferior frontal gyrus), temporal (superior temporal gyrus) and parietal (precuneus) components, all areas known to be crucially involved in novelty processing (Downar and others 2000, 2001; Bledowski and others 2004.). Furthermore, these sounds, which already caused a delay on subjects' responses regardless of the context, elicited a stronger distraction effect when preceding and subsequent faces displayed a fearful or angry expression in contrast to neutral faces. In other words, when novel sounds were surrounded by negative faces and thus processed in a negative context. In this vein, bilateral superior temporal gyri, comprising bilateral planum temporale, bilateral secondary auditory cortex and a portion of PAC showed a stronger response when subjects processed auditory novel events in a negative emotional context as compared with the neutral one.

STG has been consistently linked to novelty processing (Alho and others 1998; Opitz and others 1999a; Opitz and others 1999b) and has been argued to subserve the novelty-P3 event-related brain potential (ERP; Opitz and others 1999b). This neurelectric pattern of activation responds to a positive-going deflection that peaks around 300 ms and reflects orienting response towards novel auditory events (Escera and others 1998, 2000). Temporo-parietal lesions, centered in the superior temporal cortex, have been shown to attenuate P3 to novel sounds (Knight and others 1989). Specifically, PAC and planum temporale have been related to the initial detection and detailed analysis of changes in the acoustic environment, respectively (Ullanovsky and others 2003; Schönwieser and others 2007).

Our results did not reveal any

modulatory effect on novelty processing caused by emotion within or in the vicinity of other areas also known to be involved in novelty processing (activations that we indeed observed in every single context separately), such as IFG (Downar and others 2000). According to the novelty encoding hypothesis (Tulving and others 1996), temporal regions would provide the input for frontal encoding networks and, thus, STG would be involved in novelty detection whereas accessing and retrieving semantic concepts related to novel sounds would additionally engage prefrontal cortex (Opitz and others 1999b). Neuropsychological data (Knight 1984) suggest that prefrontal cortex might not be a primary P3 generator. All these arguments and the partial activation of PAC led us to suggest that an emotional context modulates novelty processing in the very primary stage of *detection*.

However, it is still unclear whether these modulated areas correspond to a unimodal network related to auditory novelty processing or to a multimodal circuitry common in multisensory novelty processes. Superior temporal cortices have been claimed to be specific for the auditory sensory modality in novelty and target detection (Downar and others 2000; Kiehl and others 2001). Indeed, the coordinates of STG related to unimodal auditory processing reported before (Downar and others 2000; Talairach [x,y,z] 53/-21/5; -51/-37/10; -53/-15/3) are close to areas identified in the present study and, similarly to our activations, were bilaterally distributed.

On the other hand, some of these regions located in STG could also correspond to the areas described previously as temporoparietal junction (Downar and others 2000, 2001,2002). This brain region has been proposed to play a general role in identifying salient stimuli in the sensory environment across multiple modalities (Downar and others 2000, 2002). A lesion study concerning spatial neglect (Karnath and others 2001), a disorder typically associated with lesions in the posterior parietal lobe, suggested STG to be the neural substrate for spatial awareness in humans. The coordinates corresponding to BA22 and BA42 reported in this study are located closely to ours. However, all these results pointed to a right hemisphere lateralization, postulating a phylogenetic transition of this function from the bilateral distribution seen in the monkey brain (Karnath and others 2001). Given these evidences, the data in our study support the idea that both unimodal and multimodal novelty processing areas may be modulated by the emotional context.

It is important to note that it may be difficult to dissociate between activations related to novelty specifically from those related to spectrotemporal processing, as the novel sounds differed widely from the standard ones in this regard. Moreover, it has been demonstrated that lateral belt areas of rhesus monkey auditory cortex are more responsive to complex sounds than to pure tones (Rauschecker et al 1995). However, novel sounds also differed in their probability of occurrence, and may therefore be considered as *contextually* novel (see Ranganath & Rainer, 2003). According to magnetoencephalography (MEG) data, auditory cortex activation related to this type of novel sounds, actually to a similar set as the one used here, was located halfway between the MEG source of N1 and that of the mismatch field, reflecting novelty detection (Alho et al., 1998). Moreover, the fact that the novel sounds presented in neutral context where statistically similar to those presented in negative context, both in loudness (RMS level) and spectrotemporal features (Cepstral Coefficients), would still demonstrate that a negative emotional context modulates processing of novel sounds in auditory cortical areas.

On the other hand, when performing the one-way ANOVA for emotional effects on novelty processing in the reverse order to test which areas were more activated during novelty processing in neutral context than in the negative one (the *reverse contrast*), we observed activations located in fusiform, inferior temporal and middle occipital gyri (George and others 1999; Rolls 1992). Previous studies using similar auditory-visual paradigms have suggested that the involuntary switching of attention to changes in the acoustic environment can interfere early processing of the successive visual stimuli (Alho and others 1997). Therefore, this finding suggests that a context of emotional faces not only modulated novelty processing areas but at the same time made novel sounds especially attenuate the processing of subsequent visual target stimuli. This effect was consistent with the behavioral data.

In conclusion, emotion processing not only modulates perception when presented within a certain sensory pathway, as has been previously proposed (Öhman and others 2001; Fox 2002), but might also exert a strong influence on the processing of other sensory signals presented concomitantly through an effect of facilitation. This modulation would be independent from voluntary mechanisms of attentional control but still would respond to common top-down regulation (Vuilleumier 2005). The amygdala should indirectly play a critical role in this attentional modulation. It is known to receive sensory inputs from all modalities and to send projections towards different cortical and subcortical areas (Holland and Gallagher 1999). Animal studies focused on fear conditioning to a simple auditory conditioned stimulus postulate that both auditory thalamus and auditory cortex send inputs to the lateral nucleus of amygdala (Romanski and LeDoux 1993). Furthermore, they point to the importance of the direct thalamo-amygdala pathway in this learning process (Morris and others 1999). The direct or indirect connections between auditory pathways and amygdala might be directly involved in the STG enhancement we observed. However, in relation to the design of our study we cannot sufficiently demonstrate an involvement of the amygdala or thalamus in this modulation process. Still, the neural origins of subcortical top-down signals need further investigation.

The results of the present experiment differ from previous electrophysiological studies using P3 and startle reflex measurements (Schupp and others 1997; Cuthbert and others 1998; Bradley and others 2006; Keil and others 2007). In these studies, the amplitude of P3 to the startle probes appeared smaller when blinks were potentiated by the processing of unpleasant pictures (Schupp and others 1997; Cuthbert and others 1998; Bradley and others 2006; Keil and others 2007) even to unexpected simple tones (Cuthbert and others 1998), suggesting a greater allocation of attentional resources to the affective visual stimuli in a limited-capacity system (Keil and others 2007). These effects seem contrary to the modulatory effects we observed in STG. The reasons of this disagreement are still unclear but, still, any comparison between these studies and the experiment here reported should be taken with extreme caution. In startle experiments, probes were identical across presentations, whereas we used 100 different novel sounds. Although both startle probes and novel sounds appeared unexpectedly in all studies and, thus, can be treated as novel auditory events, the structure of the audio-visual oddball paradigm used here differs notably from that used by startle reflex measurements. For instance, in these experiments, sounds appeared while the picture was on screen and stimulus duration was of 1.5 or 6 s. In our study, sounds appeared when no image was being displayed. With this and the short duration of the stimuli, we manipulated the emotional load of the task while images and sounds never overlapped and attentional resources were never forced to compete. This trial structure was optimal, on the other hand, to favor novelty processing and behavioral distraction (Escera and others 1998, 2000).

It is important to emphasize that the emotional effects observed in the present study were elicited by faces displaying an expression of fear and anger. It would be therefore rash to generalize suggesting that the same effects could also be elicited by a task loaded with any other emotional valence.

In either case and, taken together, the results obtained in the present study led us to propose that processing negative emotionally salient information would alter cortical excitability in STG and thus would define this temporal region as a context-dependent area in the auditory novelty system. When mediated by emotion, specific unimodal and multimodal regions of the STG would gate processing of novel auditory events in novelty-related areas. These events, irrelevant in neutral environmental conditions, could potentially convey crucial information in a context of affective relevance and, through the mechanisms described in this study, would warranty greater chances of survival.

Acknowledgements

This work was supported by grants SEJ2006-00496/PSIC and HA2005-0024 from the Spanish Ministry of Education and Science and SGR2005-00953 from the Generalitat de Catalunya. Address correspondence to Carles Escera, Cognitive Neuroscience Research Group, Department of Psychiatry and Clinical Psychobiology, University of Barcelona, P. Vall d'Hebron 171, 08035 – Barcelona, Catalonia-Spain. Email: cescera@ub.edu.

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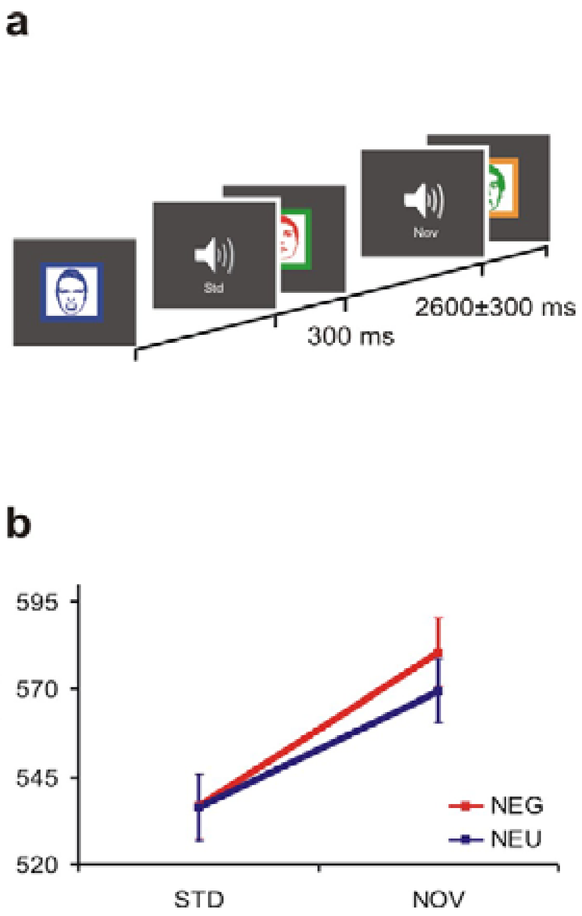

Fig. 1. Trial structure and behavioral data. **a.** Sample visual and auditory stimuli. **b**. Mean response times for STD and NOV trials, both when sounds were preceded and followed by neutral faces (NEU context) and when sounds were preceded and followed by negative faces (NEG context). NOV sounds caused a delay on subjects' responses, being this effect significantly enlarged when preceded and followed by fearful or angry faces. Bars indicate the standard error of the mean (±s.e.m.).

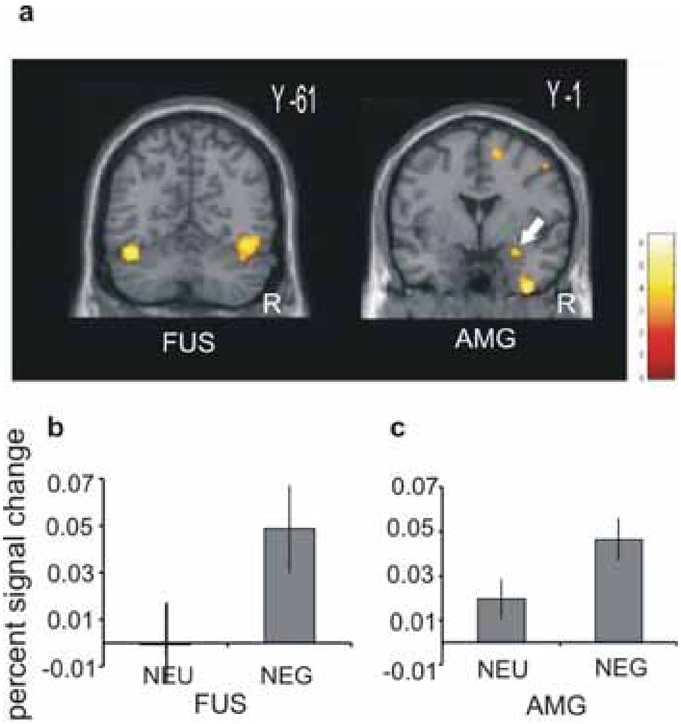

Fig. 2. Emotional face processing. **a.** Bilateral fusiform gyrus (FUS, left corner) and right amygdala activations (AMG, right corner, white arrow) for negative versus neutral faces. The plane coordinates of each slice are indicated in the upper right-hand corner. Bright colors in coronal slides represent significance levels of contrasts, as indicated by the scale bar. **b.** Average activity (±s.e.m.) across conditions for a left fusiform cluster (mean *x y z*, -42 -57 -16, 1222 voxels at p<.005). **c.** Average activity (±s.e.m.) across conditions for the right amygdala cluster (mean *x y z*, 28 -1 -17, 83 voxels at p<.005).

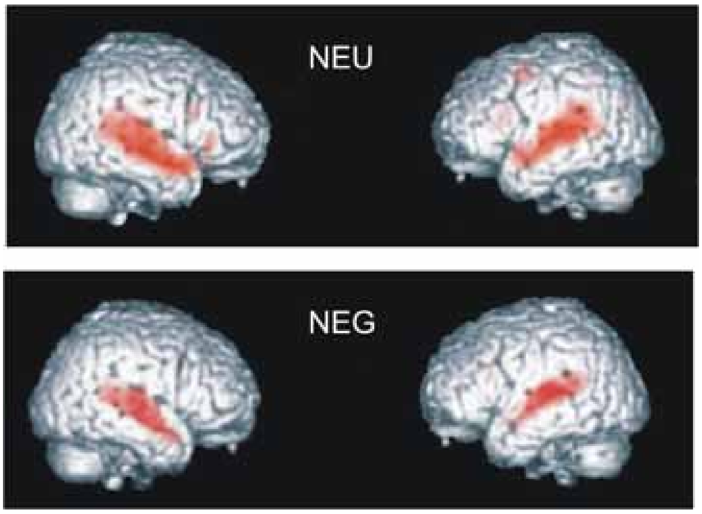

Fig. 3. Novelty processing (NOV>STD)**.** BOLD activations for NOV versus STD trials (*novelty processing*) in NEU context (top) and NEG context (bottom). In both contexts, main activations were located in bilateral STG, bilateral inferior frontal gyrus and bilateral precuneus.

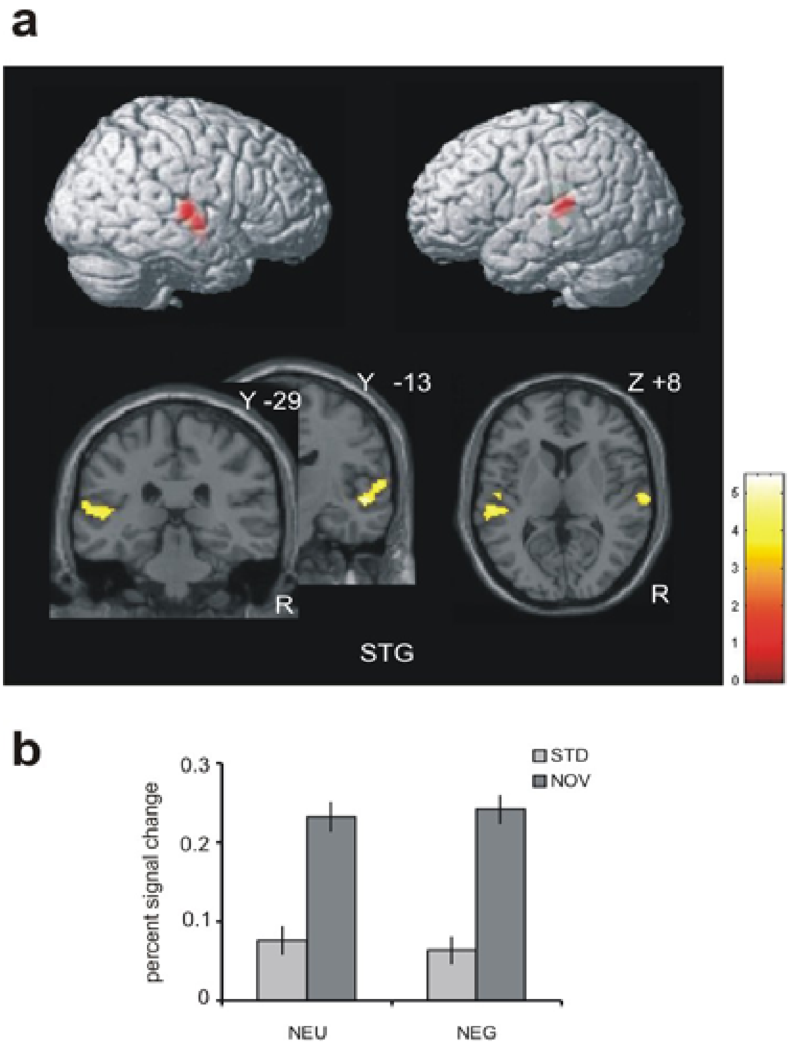

Fig. 4. Emotional effects on novelty processing (NOV>STD in neutral context) < (NOV>STD in negative context). **a.** Bilateral STG activations for novelty processing in NEU context < novelty processing in NEG context. The plane coordinate of the slice is indicated in the upper right-hand corner. Bright colors in axial and coronal slides represent significance levels of contrasts, as indicated by the scale bar. **b.** Average activity (±s.e.m.) across conditions for the right STG cluster (mean *x y z*, 59, -10, -1, 295 voxels at p<.001, k=20.

Table 1. Emotional face processing (STD in NEU context < STD in NEG context): regions activated.

Brain region	**Brodmann area**	**z value**	**Size (voxels)**	**Coordinates**		
				x	**y**	**z**
R fusiform gyrus	37	4.14	278	46	-41	-11
R fusiform gyrus / inferior temporal gyrus	37	4.14		46	-41	-11
R fusiform gyrus	37	3.55		46	-48	-18
R fusiform gyrus	37	3.76	336	42	-61	-10
L fusiform gyrus	37	4.44	1222	-42	-57	-16
L fusiform gyrus	19	4.36		-44	-74	-11
L fusiform gyrus	20	3.47	24	-44	-15	-24
R inferior temporal gyrus / uncus	20	4.12	237	34	-8	-35
R inferior temporal gyrus	20	4.08		38	-2	-39
L inferior temporal gyrus / uncus	20	3.26	40	-32	-8	-35
R superior frontal gyrus/ medial frontal gyrus	6	3.90	62	12	7	55
L cuneus/ middle occipital gyrus	18	3.74	337	-10	-100	14
L middle occipital gyrus	19	3.59		-34	-89	10
L middle occipital gyrus	18	3.58		-28	-87	4
R middle occipital gyrus	18/ 19	3.69	440	34	-85	10
R middle occipital gyrus	19	3.06		51	-74	-5
L lingual gyrus	17	3.46	32	-14	-94	-9
R STG	38	3.45	37	42	7	-17
R STG	38	2.80		48	15	-18
R medial frontal gyrus	11	3.33	65	6	42	-16
L rectal gyrus	11	2.97		-2	36	-22
R precentral gyrus	6	3.12	25	50	0	46
R precentral gyrus	4	2.70		53	-7	46
L insula	13	3.11	35	-36	20	12
R amygdala	-	3.09	83	28	-1	-17

Brain region	**Brodmann area**	**z value**	**Size (voxels)**	**Coordinates**		
				x	**y**	**z**
R parahippocampal gyrus-hippocampus	-	2.95		28	-9	-20

All coordinates reported in Talairach space. Activations shown are based on a voxelwise p<.005, uncorrected, k=20.

Table 2. Novelty processing (STD < NOV): regions activated.

Brain region	**Brodmann area**	**z value**	**Size (voxels)**	**Coordinates**		
				x	**y**	**z**
STD < NOV (NEU context)						
R STG	22	5.96	4513	50	-14	-8
L STG	41	5.67	3962	-50	-29	9
L STG/ transverse temporal gyrus	41	5.56		-57	-23	9
R middle temporal gyrus	21	5.59	4513	55	-20	-4
L middle temporal gyrus	21	3.43	21	-59	-54	3
R inferior frontal gyrus	9 / 46	4.39	146	46	17	21
R inferior frontal gyrus	47	3.87	88	51	29	-1
L inferior frontal gyrus	44 / 45	3.64	72	-44	18	12
L inferior frontal gyrus	13	3.61		-38	22	8
R middle frontal gyrus	46	4.39	146	46	17	21
R medial frontal gyrus	9	3.41	23	4	40	27
R lingual gyrus	18	3.66		22	-56	6
R paracentral lobule	5	4.14	264	6	-42	50
L paracentral lobule	5 / 7	3.18		-10	-46	58
L posterior cingulate	30 / 31	3.67	85	-18	-63	14
R cuneus	17	3.66	24	6	-77	9
R precuneus	7	4.14	264	6	-42	50
R precuneus	31	3.59	63	18	-67	20
L precuneus	7	3.82	264	-2	-46	45
L precuneus	7	3.18		-10	-46	58
L precuneus	31	4.35	85	-10	-67	20
STD < NOV (NEG context)						
R STG / transverse temporal gyrus	42	5.45	3339	67	-17	10

Brain region	**Brodmann area**	**z value**	**Size (voxels)**	**Coordinates**		
				x	**y**	**z**
L STG	22	5.02	3021	-51	-13	8
R inferior frontal gyrus	45	4.73	80	36	27	4
L inferior frontal gyrus	9	3.79	87	-48	19	21
L middle frontal gyrus	46	3.79		-48	19	21
L insula	13	4.17	85	-38	19	1
R precuneus	7	3.86	36	10	-46	45
L precuneus	7	4.49	88	-8	-48	45

All coordinates reported in Talairach space. Activations shown are based on a voxelwise p<.001, uncorrected, k=20.

Table 3. *Emotional effects on novelty processing* (novelty processing in NEU < novelty processing in NEG).

Brain region	**Brodmann area**	**z value**	**Size (voxels)**	**Coordinates**		
				x	**y**	**z**
Novelty processing (NEU<NEG)						
R STG	21/22	3.87	295	59	-10	-1
L STG	22/42	3.72	215	-65	-32	13
L STG	22	3.62		-51	-13	8

All coordinates reported in Talairach space. Activations shown are based on a voxelwise p<.001, uncorrected, k=20.

Table 4. Emotional effect on novelty processing: *reverse contrast* (novelty processing in NEU > novelty processing in NEG).

Brain region	**Brodmann area**	**z value**	**Size (voxels)**	**Coordinates** x	y	z
Novelty processing (NEU>NEG)						
R fusiform gyrus	19	3.51	43	50	-67	-13
R fusiform gyrus	37	3.83		53	-53	-14
L fusiform gyrus	19 / 37	3.73	122	-53	-65	-12
L fusiform gyrus	19	3.71	90	-22	-69	-12
L inferior temporal gyrus	20	3.90	46	-57	-26	-19
R middle temporal gyrus	39	3.57	72	50	-73	13
R inferior temporal gyrus / middle occipital gyrus	19	3.51		57	-66	-2
R inferior temporal gyrus	20	3.83	43	53	-53	-14
R middle occipital gyrus	19	3.95	72	53	-68	7
L middle occipital gyrus	18 / 19	3.61	29	-48	-78	-8
L superior frontal gyrus	22	3.46	22	-10	-4	68
L middle frontal gyrus	10	3.66	58	-38	58	-5
L middle frontal gyrus	11	3.65		-38	52	-13
L postcentral gyrus	2	3.72	21	-57	-22	32
L precentral gyrus	6	4.74	77	-55	1	20
L parahippocampal gyrus	19 / 37	4.05	25	-28	-45	-6
L lingual gyrus	18	3.71	90	-22	-69	-12
L caudate	-	3.63	23	-14	20	8
R superior parietal lobule	7	3.47	32	28	-55	60

All coordinates reported in Talairach space. Activations shown are based on a voxelwise p<.001, uncorrected, k=20.

Supplementary Material

Control of loudness and spectrotemporal features. Novel sounds presented in the two emotional contexts were equivalent in loudness (max RMS power: NEU: -12.22, NEG: -13.27, $F_{(1,58)}$=.629; p=.431; average RMS power: NEU: -14.39, NEG: -15.39, $F_{(1,58)}$=.168; p=.684; total RMS power: NEU:-14.35, NEG: -15.30, $F_{(1,58)}$=.283; p=.597) and spectrotemporal features. To analyze the similarity of spectrotemporal features of sounds, twelve different Cepstral Coefficients were computed using Praat (http://www.fon.hum.uva.nl/praat/) for every novel sound, both for NEU and NEG context separately, and subsequent ANOVA showed that none of these coefficients differed for the sounds used in each of the emotional contexts:

Cepstral coefficient	**ANOVA**	
	F value	**P value**
Cepstrum1	$F_{(1,58)}$=.101	p=.751
Cepstrum2	$F_{(1,58)}$= .289	p=.593
Cepstrum3	$F_{(1,58)}$= .350	p=.556
Cepstrum4	$F_{(1,58)}$= .051	p= .822
Cepstrum5	$F_{(1,58)}$= .000	p= .991
Cepstrum6	$F_{(1,58)}$= .346	p= .559
Cepstrum7	$F_{(1,58)}$= .251	p= .618
Cepstrum8	$F_{(1,58)}$= .369	p= .546
Cepstrum9	$F_{(1,58)}$= .059	p= .809
Cepstrum10	$F_{(1,58)}$= .790	p= .378
Cepstrum11	$F_{(1,58)}$= .299	p= .587
Cepstrum12	$F_{(1,58)}$= .213	p= .646

Cepstral coefficients: NEU

1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
24,40	42,22	40,26	-24,30	5,75	-6,13	-40,61	-37,28	-18,74	-23,39	-7,49	-4,75
-151,38	-54,89	105,39	76,05	49,60	-1,60	11,06	31,94	28,10	6,59	33,64	26,11
-1,51	75,13	102,72	-10,70	10,61	40,51	-1,50	-4,16	10,44	4,50	5,86	1,04

273,43	-14,52	11,47	46,26	-2,59	3,61	3,55	3,40	-12,96	-8,26	-11,55	-14,63
-25,97	-43,33	-6,94	-17,86	-20,58	-15,34	-3,17	2,24	-2,49	-0,96	4,79	10,23
-71,46	-53,83	54,35	17,24	-28,50	21,36	46,72	-15,40	-1,61	20,00	17,68	-41,11
22,93	87,20	65,37	35,63	-21,68	-7,02	-5,83	-15,59	-16,84	8,90	8,29	2,69
7,63	-49,33	66,31	48,87	8,57	-13,06	23,38	1,63	-21,83	-13,65	4,75	-1,89
43,71	133,79	143,59	34,15	8,85	20,39	1,20	-7,87	8,62	-4,86	-4,02	-2,74
12,36	76,37	104,13	9,66	-7,54	-16,99	-18,95	-0,53	-9,78	5,14	-5,29	-12,57
146,40	-34,20	61,92	-16,74	9,07	-14,94	1,70	-16,92	18,25	8,13	1,26	6,43
28,74	83,55	75,65	16,97	3,00	-10,94	-15,78	-36,02	-35,54	-24,84	-12,61	-0,54
198,20	-117,02	-18,05	-2,61	11,06	1,97	-22,47	14,30	13,46	-0,87	-1,66	-13,56
8,13	-74,74	38,60	15,10	38,49	-24,10	13,14	-9,73	-27,70	-11,13	17,13	22,63
127,40	-150,01	166,82	5,33	-16,99	40,00	-30,79	26,84	0,35	-2,38	11,79	-6,92
-174,93	26,52	110,63	56,98	9,19	-4,73	-3,45	26,90	11,46	-29,90	-13,94	15,13
221,78	55,14	48,95	7,51	0,59	8,98	17,89	13,94	13,90	8,05	9,17	5,73
-49,27	7,05	8,50	-19,29	7,89	-11,05	-7,43	6,23	22,77	0,41	22,55	4,82
162,94	-250,12	279,39	-41,28	26,64	12,00	-26,17	65,61	-29,68	1,49	-25,43	12,40
131,91	-51,25	58,53	39,17	-8,95	29,67	5,73	-0,19	30,31	-8,37	-3,22	21,02
-128,58	-61,19	108,21	48,85	42,23	5,01	13,20	41,51	31,82	4,33	31,46	34,30
255,06	-101,61	188,04	-56,91	102,11	20,59	64,15	20,04	3,10	26,40	-1,22	-11,05
448,56	-125,07	40,75	18,47	28,43	-33,72	13,50	-17,18	4,44	-2,50	-5,42	-9,12
423,48	-110,13	83,01	33,62	38,43	-1,45	25,04	-17,57	15,09	3,56	-0,92	5,18
470,25	-13,60	51,41	-20,10	16,32	-55,96	17,01	-26,83	0,93	-10,45	-11,50	5,25
445,33	-42,53	86,83	-0,80	34,04	0,73	21,30	-2,26	27,51	-1,59	10,21	18,32
306,12	-108,55	173,72	-61,46	51,38	0,04	26,19	-20,46	-11,64	9,40	5,32	5,06
145,87	-67,70	175,75	-73,50	111,38	-16,11	79,75	-27,43	52,66	-5,94	40,99	-3,52
332,73	99,46	112,32	-31,51	19,70	-64,37	-24,07	-63,46	-52,05	-46,55	-34,85	-29,34
384,63	-117,30	109,69	-36,97	67,30	10,33	16,06	-25,50	6,87	-9,08	2,95	1,04
291,11	32,23	131,10	50,65	125,77	0,85	70,37	22,20	23,77	-18,73	-4,20	19,46
380,55	-10,47	142,14	24,78	65,74	-6,83	51,53	34,13	38,79	19,69	13,64	14,76
312,76	-188,47	87,13	-84,11	1,93	-15,37	9,54	-34,90	-9,36	-11,65	-9,76	-9,81

370,84	-100,83	162,01	-32,62	50,54	4,42	37,83	0,65	25,56	5,94	5,77	9,35
354,68	-200,09	100,02	-89,72	47,69	13,92	53,35	26,12	11,83	3,31	3,13	-14,46
212,59	-164,81	115,13	-105,75	50,50	-66,07	29,44	-36,85	41,35	12,03	19,49	-16,29
282,64	-279,49	96,95	-64,35	24,74	-4,06	4,28	-15,56	3,28	-8,12	-23,29	-3,12
355,49	-165,71	138,80	-36,71	43,61	-57,98	39,46	-31,14	20,56	-12,10	-6,91	-6,32
233,77	-149,85	236,29	-81,67	91,34	-44,13	24,02	-7,68	-54,63	-49,66	5,89	-22,74
376,31	-123,82	109,45	-20,67	31,84	-47,46	40,83	-17,56	13,68	-10,91	-22,26	-28,88
255,88	-129,24	-2,58	-110,01	19,81	-58,91	83,21	36,65	80,47	33,08	17,93	-55,65
407,89	-141,67	27,66	-33,35	39,89	-36,41	22,17	-53,92	-1,60	-27,18	-13,14	-5,34
357,23	-217,20	98,54	-34,96	46,97	-0,87	18,69	12,63	-1,88	-17,24	-3,45	-15,12
263,90	-148,53	114,85	-104,87	49,73	-18,41	-40,73	7,91	24,35	-2,12	-8,35	-2,59
425,93	-13,45	43,48	-17,98	19,35	-32,87	34,69	-9,91	8,75	14,14	-4,56	-21,60
303,32	15,35	90,81	-1,82	64,45	-33,88	24,18	-28,09	-5,10	-14,70	-20,66	-13,21
361,35	-116,28	70,83	-76,90	58,03	-48,22	13,44	-43,19	10,34	-29,03	-0,85	-6,43
433,47	-98,86	-78,34	-104,73	-11,03	-88,26	-6,90	-18,00	13,67	-23,40	-39,11	-34,11
434,33	-185,73	-25,29	-53,49	-9,95	20,77	12,85	-27,46	20,97	1,10	-21,98	-11,39
484,48	-66,50	-48,40	-62,36	-7,99	-75,01	10,56	-20,52	-15,22	-23,16	-27,15	-22,58
252,77	-164,46	161,33	-50,73	57,99	-59,02	34,65	-35,87	23,48	-33,37	5,12	-17,35
214,41	-160,32	201,78	-71,39	46,63	-28,04	6,16	-29,51	11,03	-15,09	-7,82	2,85
291,12	-195,32	115,25	-94,28	0,50	-63,04	-4,42	-48,16	-1,87	-8,84	-11,34	-19,33
216,03	-268,41	106,80	-100,95	22,64	-56,79	13,76	-12,53	13,15	-10,01	-14,07	-23,13
139,15	-167,24	164,37	-114,67	89,72	-67,76	58,84	-38,50	31,94	-9,97	10,01	7,28
202,71	-205,44	99,56	-140,40	23,05	-51,58	39,21	1,98	19,13	4,68	29,15	18,31
295,06	-193,53	127,71	-65,67	6,48	-59,44	2,97	-27,25	-10,87	7,14	-4,65	-3,59
328,69	-178,19	3,71	-40,19	-22,54	-53,17	7,14	-2,26	4,60	7,07	26,34	0,89
441,28	-14,98	52,90	-56,50	37,06	-59,57	49,53	2,21	-23,08	-26,40	-9,02	-6,04
430,05	20,50	38,53	-28,84	-4,60	-48,85	-4,60	-37,99	-20,14	-20,53	-19,20	-4,10
251,06	-238,67	103,26	-33,31	13,99	-3,97	29,29	-32,26	36,09	9,67	7,62	2,50
323,38	-174,76	8,72	10,78	80,24	-31,22	8,15	-5,46	42,90	-13,35	-19,16	-18,18
394,33	-140,98	133,17	-48,48	47,51	15,86	32,95	7,59	-4,10	-10,96	-4,12	4,48

275,66	-154,91	153,24	-61,93	57,74	4,50	42,30	-26,76	8,61	-1,90	-12,81	-5,45

Cepstral coefficients: NEG

1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
-47,60	-33,45	1,82	9,33	20,20	-22,01	-34,72	17,65	41,01	-18,22	-0,28	8,20
-151,38	-54,89	105,39	76,05	49,60	-1,60	11,06	31,94	28,10	6,59	33,64	26,11
-71,46	-53,83	54,35	17,24	-28,50	21,36	46,72	-15,40	-1,61	20,00	17,68	-41,11
7,63	-49,33	66,31	48,87	8,57	-13,06	23,38	1,63	-21,83	-13,65	4,75	-1,89
58,55	-53,19	67,88	23,70	13,11	18,49	-1,06	-7,35	33,29	-17,27	-8,92	13,99
43,71	133,79	143,59	34,15	8,85	20,39	1,20	-7,87	8,62	-4,86	-4,02	-2,74
311,44	30,55	-13,25	8,86	-34,78	-21,02	-16,20	-1,55	-0,35	-5,66	-6,71	2,03
43,75	-45,59	15,55	5,26	1,19	-11,88	-5,58	-11,93	-28,10	-17,04	-18,59	-11,40
168,50	50,64	123,58	34,72	-6,82	0,74	-6,28	-4,05	-12,57	12,88	6,17	-6,96
28,74	83,55	75,65	16,97	3,00	-10,94	-15,78	-36,02	-35,54	-24,84	-12,61	-0,54
41,74	-44,17	-47,56	2,94	-6,80	14,23	-12,39	-20,09	14,60	-9,75	18,57	-5,00
-174,93	26,52	110,63	56,98	9,19	-4,73	-3,45	26,90	11,46	-29,90	-13,94	15,13
-152,66	76,10	78,91	14,56	21,46	3,67	21,36	22,78	-12,55	14,05	15,26	21,05
30,79	-52,99	38,48	-19,66	45,42	-30,66	-7,79	35,53	25,89	-23,22	-11,50	-7,30
-152,03	85,81	74,09	9,62	28,23	-2,64	7,06	17,70	-16,55	19,15	6,94	16,16
-49,27	7,05	8,50	-19,29	7,89	-11,05	-7,43	6,23	22,77	0,41	22,55	4,82
162,94	-250,12	279,39	-41,28	26,64	12,00	-26,17	65,61	-29,68	1,49	-25,43	12,40
44,65	-234,98	46,65	-44,39	39,35	59,70	-46,59	94,15	16,20	-22,54	-7,01	-38,67
167,14	54,61	43,14	-13,27	-46,89	16,74	-11,50	50,60	27,21	23,07	0,56	-9,62
-48,77	-33,52	19,05	6,82	-14,50	-16,07	38,83	-25,06	-25,77	0,94	-4,25	-38,30
387,02	-136,72	97,01	7,64	48,86	20,45	25,98	-6,70	30,86	-6,86	-9,29	17,42
423,48	-110,13	83,01	33,62	38,43	-1,45	25,04	-17,57	15,09	3,56	-0,92	5,18
266,86	-278,01	77,59	-66,59	53,90	11,38	24,51	-9,24	-21,05	-2,80	-19,92	16,07
356,56	-102,53	152,09	4,07	5,68	20,79	14,86	-6,08	44,42	-2,85	9,46	23,40
432,34	111,40	83,72	-55,66	-16,47	-70,82	-16,35	-19,28	2,59	2,43	0,47	-11,99

332,73	99,46	112,32	-31,51	19,70	-64,37	-24,07	-63,46	-52,05	-46,55	-34,85	-29,34
208,14	-129,32	145,39	-59,57	52,69	-29,64	72,71	-42,00	-44,85	18,12	53,55	-39,50
306,21	-189,98	155,41	-25,44	80,09	-20,12	32,54	4,56	13,37	49,49	5,25	-15,66
291,11	32,23	131,10	50,65	125,77	0,85	70,37	22,20	23,77	-18,73	-4,20	19,46
379,02	-157,25	134,55	-13,43	47,18	19,68	11,11	-2,88	2,73	1,64	-10,13	-19,21
312,76	-188,47	87,13	-84,11	1,93	-15,37	9,54	-34,90	-9,36	-11,65	-9,76	-9,81
419,04	-208,60	65,19	-51,21	-2,63	-27,04	8,44	-24,18	-2,99	-26,41	-24,04	-7,05
365,69	-217,03	120,29	-53,53	-17,67	-33,43	6,31	-36,24	14,22	-15,70	-30,94	4,50
372,57	-152,45	74,47	-11,78	49,01	-6,69	-3,93	-41,92	9,22	5,34	-20,69	-13,65
282,64	-279,49	96,95	-64,35	24,74	-4,06	4,28	-15,56	3,28	-8,12	-23,29	-3,12
212,59	-164,81	115,13	-105,75	50,50	-66,07	29,44	-36,85	41,35	12,03	19,49	-16,29
355,49	-165,71	138,80	-36,71	43,61	-57,98	39,46	-31,14	20,56	-12,10	-6,91	-6,32
233,77	-149,85	236,29	-81,67	91,34	-44,13	24,02	-7,68	-54,63	-49,66	5,89	-22,74
407,89	-141,67	27,66	-33,35	39,89	-36,41	22,17	-53,92	-1,60	-27,18	-13,14	-5,34
357,23	-217,20	98,54	-34,96	46,97	-0,87	18,69	12,63	-1,88	-17,24	-3,45	-15,12
379,04	-179,42	90,28	-57,16	49,65	-54,69	7,50	-34,76	9,73	-7,82	-33,40	-7,73
425,93	-13,45	43,48	-17,98	19,35	-32,87	34,69	-9,91	8,75	14,14	-4,56	-21,60
303,32	15,35	90,81	-1,82	64,45	-33,88	24,18	-28,09	-5,10	-14,70	-20,66	-13,21
312,57	-272,73	116,49	-130,09	-57,95	-72,68	2,96	-33,30	-47,75	-13,23	4,04	-3,18
358,55	-46,88	-3,32	-169,31	14,21	-56,35	31,62	-43,91	27,85	-7,74	15,54	1,31
444,97	-83,95	-94,31	-121,64	15,61	-67,99	-7,23	-23,83	15,31	1,22	4,68	6,31
438,66	25,92	20,31	-94,13	23,64	-41,45	50,45	-1,89	8,09	-24,55	-18,07	-34,10
130,17	-144,03	165,18	-123,89	109,28	-78,33	64,26	-51,01	43,63	-35,82	8,82	-13,02
73,19	-207,60	65,54	-139,72	51,85	-110,94	40,11	-62,21	36,89	-40,82	12,57	-28,59
268,85	-167,87	106,73	-68,23	60,64	-56,92	3,10	-36,19	26,71	-16,33	11,76	-1,95
216,03	-268,41	106,80	-100,95	22,64	-56,79	13,76	-12,53	13,15	-10,01	-14,07	-23,13
385,44	-161,21	45,26	-57,26	-5,00	-41,86	-2,23	-28,00	-15,18	-18,99	-16,19	-4,47
403,26	-85,86	87,23	-10,79	58,87	-63,29	35,18	-44,35	6,01	-22,16	3,20	-0,34
328,69	-178,19	3,71	-40,19	-22,54	-53,17	7,14	-2,26	4,60	7,07	26,34	0,89
192,43	-116,72	76,11	-71,21	93,01	-46,98	65,20	-41,48	30,49	-31,98	14,32	-13,30

341,53	2,68	121,70	21,75	63,65	-42,55	33,13	-26,13	14,74	-8,17	-4,33	0,76
323,38	-174,76	8,72	10,78	80,24	-31,22	8,15	-5,46	42,90	-13,35	-19,16	-18,18
394,33	-140,98	133,17	-48,48	47,51	15,86	32,95	7,59	-4,10	-10,96	-4,12	4,48
233,19	-151,99	159,56	-70,14	37,22	-15,60	17,79	-1,17	17,42	8,48	7,26	17,12

5. GENERAL DISCUSSION

Processing of stimulus salience depends not only on novelty or frequency of occurrence, but also on the behavioral context (Katayama & Polich 1998) and, in a special manner, on the emotional relevance of the context. The results of the present studies showed, first, that subjects were unable to fully ignore emotional information even when it was task-irrelevant, in agreement with a variety of studies (Vuilleumier *et al*., 2001; Anderson *et al.,* 2003). The amplitude enhancement of visual P300 over centro-parietal sites when processing negative IAPS pictures in the second and third studies revealed that participants processed negative images more deeply as compared to the neutral ones. This target-related ERP component is known to represent memory updating mechanisms (Donchin & Coles, 1988) and has been shown sensitive to the intrinsic affective properties of pictures in previous studies (Amrhein *et al.,* 2004; Delplanque *et al.,* 2005). In this sense, subjects might have remained engaged in the emotional content of the display at the expense of processing the relevant aspects of the task. This interpretation would be supported by the behavioural results, in which subjects were shown to be slower and less accurate when responding to negative pictures than to the neutral ones.

Emotional faces, in turn, were processed differently compared to the neutral ones, as shown here, by activating amygdala (LeDoux, 2000; Vuilleumier, *et al*., 2001; Adolphs & Tranel, 2004) and, importantly, by modulating face-selective regions such as fusiform gyrus (George *et al*., 1999; Sugase *et al*., 1999; Vuilleumier *et al*., 2001) as well as early visual areas in the occipital lobe (Morris *et al*.,1998).

Novel sounds elicited a distraction effect on subjects' performance in all four studies, as indexed by a prolonged response time when these preceded the target. This effect was observed across all context conditions, that is, regardless of the emotional load of the task. Thus, the behavioural impairment consistently observed with novel stimuli is in agreement with many previous studies (Alho, *et al*., 1997; Escera *et al*., 1998, 2001, 2003).

As described in the three ERP studies, this distraction effect was paralleled by the well-defined N1-enhancement/MMN components and novelty-P3 deflection observed in the difference waves, both for neutral and negative context conditions separately. The morphology and distribution of this pattern would represent the neuroelectric activation underlying novelty processing, a mechanism concerned with the evaluation of novel stimuli that have already captured attention (Escera *et al.,* 1998, 2000; Friedman *et al.,* 2001).

Moreover, our fMRI data showed that novel auditory events activated a network of frontal (inferior frontal gyrus), temporal (superior temporal gyrus) and parietal (precuneus) components in the fourth study, all areas known to be crucially involved in novelty processing (Downar *et al*., 2000, 2001; Bledowski *et al*., 2004).

In sum, behavioural, electrophysiological and hemodynamic responses observed in the four studies are consistent with literature (Alho *et al.,* 1997, 1998; Escera *et al.,* 1998, 2000, 2001, 2003; Yago *et al.,* 2003) and confirm that auditory novel events were processed differently with regard to the repetitive standard sounds (*novelty processing*), recruiting attentional resources from the ongoing task in subjects and causing a delay in the average performance (*distraction*) regardless of the emotional load within the task.

The core aim of the present studies was to determine whether the negative emotional context had an impact on novelty processing and behavioural distraction. In the first, second and fourth studies, novel sounds elicited a stronger distraction effect when preceding and subsequent images were of a negative emotional content as compared to neutral. In other words, when novel sounds were surrounded by negative emotional stimuli and thus processed in a negative context.

This modulatory effect on distraction was supported by an amplitude enhancement of the novelty-P3 to novel sounds in the first and second studies. Studies showing that novelty-P3 amplitude increases linearly as a function of the eliciting stimulus salience (Yago *et al.,* 2001; Escera *et al.,* 2003), that the more salient the sound the larger the behavioural distraction and novelty-P3 (Escera *et al.,* 1998, 2003; Zink *et al.,* 2006), or that behavioural distraction and novelty-P3 amplitude are modulated in parallel by working memory load (Berti & Schröger, 2003; SanMiguel *et al.*, 2008), support the notion that a larger novelty-P3 denotes stronger orienting of attention to distractors and, in the case of the present experiments, under a negative emotional context.

A fundamental difference between the results in the first and the second studies is that, whereas in the first study novelty-P3 modulation occurred in its late phase, the second study yielded this modulation in its early phase. The early novelty-P3 subcomponent has been proposed to be associated with the violation of the regularity registered by the automatic novelty detection system (Escera *et al.,* 1998, 2001), whereas late novelty-P3 would reflect the actual orienting of attention towards odd auditory stimuli (Escera *et al.,*1998). Although the aim of the present studies was not to examine the sensitivity of early novelty-P3 to task conditions, the data reported here clearly indicate that this phase may be responsive to certain attentional manipulations, contrarily to what was previously proposed (Escera *et al,.* 1998) and to what was reported in recent experiments (Roye *et al.,* 2007; SanMiguel *et al.*, 2008). However, modulation of early novelty-P3 has been observed in another study where, for instance, identifiable novel sounds enhanced novelty-P3 responses compared to the non-familiar novels along a 100 ms window (covering both early and late phases, Escera *et al.*, 2003).

The reasons of such modulatory differences could be due to the task settings. In the first study, neutral and negative pictures appeared on an event-related basis whereas in the second study the emotional content of the pictures was distributed in blocks. Indeed, overall response times were longer in the second than in the first study (Experiment: $F_{(1,13)}$= 7.25, p=0.018). Moreover, negative pictures in the second study exerted a stronger delaying effect on subjects' responses than in the first study (Experiment x Context: $F_{(1,13)}$= 6.97, p=0.02). In addition, trial duration in the first study remained always fixed, whereas in the second study intertrial asynchrony was variable.

In either case, it can be concluded from the results of the first two studies that the emotional context may modulate novelty processing even in immediately previous stages to the orientation response, about 200 ms after sound occurrence.

Another of the main goals of the present studies was to depict the cerebral regions along the auditory novelty processing system where the emotional modulation takes place. In this sense, bilateral STG, comprising bilateral planum temporale, bilateral secondary auditory cortex and PAC, showed a stronger response when subjects processed auditory novel events in a negative emotional context as compared with the neutral one. Superior temporal gyrus has been consistently related to novelty processing (Alho *et al.*,1998; Opitz *et al.*, 1999a; Opitz *et al.*, 1999b) and has been argued to subserve the novelty-P3 ERP (Opitz *et al.*, 1999b). Specifically, PAC and planum temporale have been related to the initial detection and detailed analysis of changes in the acoustic environment, respectively (Ullanovsky *et al.*, 2003; Schönwieser *et al.*, 2007).

Consistently with this, in the second study, early novelty-P3 and not the late phase showed inverted polarity at posterior and lateral electrodes, suggesting generators bilaterally located in the vicinity of the temporal and parietal lobes (Scherg & von Cramon, 1986; Alho *et al.,*1998; Escera *et al.,* 1998). The modulation of early novelty-P3 obtained in the second study may be thus in agreement with the hemodynamic responses observed in the fourth study, giving support to the proposal that an emotional context may modulate novelty processing in its early stage.

Importantly, early stages of novelty detection, associated to N1-enhancement/MMN (Alho *et al*., 1998; Escera *et al*., 1998) were apparently insensitive to the emotional context of their occurrence in the three ERP studies, as no significant differences were obtained between the amplitude of this waveform recorded in the two emotional contexts. This result contrasts, however, with recent studies showing suppression of the sensory gating of P50 (Yamashita *et al*., 2004) when subjects processed threatening pictures.

An important issue that concerns all four studies is that the results observed differ notably from a number of studies using startle reflex measurements (Schupp *et al*., 1997; Cuthbert *et al.,* 1998; Bradley *et al.,* 2006; Keil *et al.,* 2007). In these studies, whereas blink reflex was enhanced for startle probes while viewing unpleasant pictures (Schupp *et al.,* 1997; Cuthbert *et al.,* 1998; Bradley *et al.,* 2006 –the latter only for probes presented at late stages after picture onset), auditory-P3 decreased in amplitude (Schupp *et al.,* 1997; Cuthbert *et al.,* 1998; Keil *et al.,* 2007) even for unexpected simple tones (Cuthbert *et al.,* 1998), suggesting a greater allocation of attentional resources to the affective visual stimuli in a limited-capacity system. Although still unclear, the reasons of this disagreement might be the presence or absence of perceptual competence in the studies. In their experiments, sounds appeared while the picture was on screen and stimulus display was of 1.5 or 6 s. In the present studies, sounds appeared when no image was being displayed. With this and the short duration of the stimuli, we manipulated the emotional load of the task while images and sounds never overlapped and attentional resources were never forced to compete, as described in the Introduction section. Yet, any comparison between startle reflex studies and the ones reported here should be taken with caution.

Finally, the results in the second study suggest that this effect may be present in women but not in men. However, the subject sample in the first study included also male volunteers, and no significant gender differences were seen in these data. Moreover, recent neuroimaging data suggested that women may have lower thresholds for vigilance to danger signal detection, as females showed higher amygdala responses during perception of facial fear stimuli than men. In fact, men showed an attenuation of such responses with the course of time, whereas women showed a sustained activation (Williams *et al*., 2005). This idea raises the suggestion that modulation of auditory novelty processing by the emotional context may indeed be present both in women and in men. It might be possible that, if the emotional stimuli used in the second study were sufficiently arousing for men, the same modulatory effect would have been observed in the male sample. Future experiments should test this hypothesis.

Unsolved questions and future challenges

The results in the second study show a spread emotional modulation over frontal sites during novelty processing stages. These results could confirm the role of ventral prefrontal areas on emotional processing reported in different studies (Northoff *et al.,* 2000; Kawasaki *et al.,* 2001) giving support to a role of this area on emotional top-down regulation of attention (Armony & Dolan, 2002; Carretié *et al.,* 2005). However, the precise mechanisms of these modulatory effects still remain unknown. Future research should unravel the sequence of neural activations that may send the regulatory signals to the novelty system, and whether amygdala or other prefrontal areas related to emotional processing are actually involved in this modulation.

Moreover, the possibility that the findings of the present experiments may arise from any emotional activation, and for instance, would be observed also in a pleasant context should be clarified in future research.

The results presented here demonstrate that processing visual emotional stimuli exerts an influence on the processing of auditory events. Future investigation should assess whether this effect would also occur between other sensory modalities, that is to say, whether this is a real crossmodal effect.

Threat and arousal are usually highly correlated (see Vuilleumier, 2005 for a review). Future investigation should examine whether the effect observed in the four studies correlates with the arousal ratings of the emotional pictures.

With the design of the fourth study, it may be difficult to dissociate between activations related specifically to novelty processing from those related to spectrotemporal processing, as the novel sounds differed widely from the standard ones in this regard (see the Discussion section of Study IV). Future experiments should be able to segregate novelty and spectrotemporal processing.

6. Conclusions

The conclusions of the present thesis can be formulated as follows:

In all studies, novel sounds elicited a distracting effect on subjects' performance, reflected by longer response times compared to those in standard trials. This effect was consistently magnified when preceding and following images were of a negative emotional load as compared to the neutral images. Thus, processing negative emotional pictures or faces enhances the distractor effect of task-irrelevant novel auditory stimuli presented concomitantly, as compared to the neutral ones. It can be concluded, then, that a negative emotional context potentiates the behavioural impact of novel sounds on the ongoing task.

In two different studies, late and early novelty-P3 responses to novel sounds were enhanced in negative context, respectively, compared to the neutral one. Therefore, processing negative emotional pictures enhances novelty-P3 responses to novel sounds in its late phase, as compared to when processing neutral pictures. However, this modulation may also occur in its early phase. Thus, a negative emotional context may modulate brain responses in the novelty system in immediately previous stages to the orientation response.

Nevertheless, in one of the studies, only women showed enhanced distraction and novelty-P3 responses by the emotional context. Therefore, gender differences may be present in these modulatory effects.

Finally, hemodynamic responses showed that activation induced by novel sounds in superior temporal gyrus, comprising secondary cortex, planum temporale and primary auditory cortex, was enhanced when subjects responded to faces with a negative emotional expression compared to the neutral ones. Therefore, a context of negative emotional processing enhances hemodynamic responses to novel sounds in auditory novelty cerebral regions, relative to the neutral one.

In summary, the results described in the present thesis indicate that the emotional context enhances excitability of auditory novelty cerebral regions at early stages of the orientation response, making irrelevant sounds become more available in the attentional set under threatening conditions. These findings provide a novel illustration of how emotion mediates involuntary attention and awareness.

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ANNEX 1

Original publication of

Domínguez-Borràs, J. & Escera, C. Attentional bias towards threatening emotional face expressions. In: *Emotional face comprehension. Neuropsychological perspectives.* Ed: Michela Balconi. Nova Science Publisher (New York) (*in press*).

UNIVERSITÀ CATTOLICA DEL SACRO CUORE
20123 - MILANO - LARGO A. GEMELLI, 1

Milan, May, 30, 2007

Professor Carles Escera

I state that the chapter entitled "Attentional bias towards threatening emotional face expressions", authored by Judith Domínguez-Borràs & Carles Escera, is in press for Nova Science Publishers, New Your, and that it will be inserted into the volume: **Emotional face comprehension. Neuropsychological perspectives** edited by Michela Balconi.

The present letter for the private use of the co-authors Judith Domínguez-Borràs & Carles Escera

Signed by Michela Balconi

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Attentional bias towards threatening emotional face expressions

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ABSTRACT

Emotional faces have a special innate salience in the human attentional set. Recent brain imaging investigation shows that, attending to evolutionary advantages, processing of faces is modulated by the emotional load of their expressions (e.g., fear or anger). For instance, face-selective regions of the brain such as fusiform cortex, or early visual areas in the occipital lobe, have been found to enhance their activation particularly with fearful expressions. This attention bias towards emotion occurs at very early stages of information processing in the human brain, reported even 80-90 ms after stimulus onset. Emotional modulation can also occur under conditions of unconscious perception. Emotion retrieval of faces has been evidenced even when they appear out of the attentional set, although attention might still play a key role. The amygdala, a subcortical structure in the anterior medial temporal lobe, known to serve an important function in affective processing, may be the main responsible for this modulation by sending feedback projections onto the visual cortices. This neural system, although different from attention, operates similarly and possibly in addition to mechanisms of attentional control. Moreover, processing of threatening facial expressions may also modulate perception across sensory modalities, as areas related to acoustic novelty processing have been shown modulated while visualizing fearful and angry faces.

INTRODUCTION

Over the past century, a large body of evidence has shown that emotional stimuli have a privileged position in the environment, eliciting stronger and faster attention capture than non-emotional stimuli (e.g., [1-4]). The importance of emotional salience in attention has an early example in the classic "cocktail party effect" [5] where an emotionally significant stimulus, such as one's own name, was noticed even when it was heard among a flow of unattended stimuli during a demanding dichotic listening task. Such a mechanism of attentional bias arises from the limited processing capacity of sensory systems, while attending to adaptive and evolutionary advantages: the obvious necessity of rapidly reacting to potential threats in the environment. Psychological and physiological research has implemented emotion induction in humans by means of a variety of stimulation conditions, such as emotional pictures (e.g., [6] or IAPS database, [7]), film clips with emotional content [8], emotion-loaded words [9], sounds (non-verbal affective stimuli – [10, 11]), or even recall of biographical emotional events [12]. But, among them, emotional faces have been especially useful due to their simple structure and similar feature configuration from one expression to another. Recognition of faces is a phylogenetically old form of social communication and, therefore, facial expressions that reflect basic emotions, particularly fear and anger [13], seem to especially possess innate salience determined by evolutionary selection [14], able to elicit automatic, spontaneous emotional responses [14]. In fact, newborn babies already react to human faces and their expressions [15]. Emotional expression in faces, in addition, can be easily recognized from the simple eyebrow and mouth line drawings [16].

Attentional bias towards threatening emotional expressions: a real ‘pop-out’ effect?

Behavioral studies have demonstrated that detection of an emotional face, especially with a threatening expression, can be more efficient than detection of a face with a neutral or positive expression. Hansen & Hansen [1] showed participants grids of schematic happy faces with a single angry face, and grids of schematic angry faces with a single happy face. Participants were faster at picking the angry face out of a happy grid than vice versa, suggesting that their attention was automatically drawn to the angry faces through a classic ‘pop out’ effect, that is, as a result of *parallel* processing. Furthermore, Öhman [2] observed that angry faces, symbolizing threat, elicited more attention capture than other negative faces (such as sadness). However, recent investigation suggests that the salience of emotionally threatening faces would not be of such a preattentive nature [17]. Specifically, detection of threatening faces would not be due to a parallel search but would still require serial and linear examination just as neutral stimuli. In typical visual search tasks, if detection times do not increase substantially with increasing the number of distractors in the display, the target is said to ‘pop-out’ of the array and search is considered to be automatic [18]. In this sense, the advantage of threatening faces would be clearly different from an actual ‘pop-out’ effect. The threatening facial expression would be an emergent feature that facilitates efficient visual search, but search would still be *serial* as, by increasing the number of distractors, detection of angry faces showed a reduced, but still present, delay in behavioral responses. These authors also demonstrated that the emotional effect was not due to differences in visual *features* but to the holistic *expression* since, when faces were inverted or presented with a single isolated feature (a line resembling the curve of the mouth), the effects of emotional facilitation disappeared. Similar results were obtained by Eastwood and colleagues [19].

Attentional bias towards threatening emotional expressions: an independent process?

Throughout the last two decades, researchers have managed to disentangle and identify face-selective areas in the brain. For instance, studies using functional magnetic resonance imaging (fMRI) have consistently reported fusiform face area (FFA) to be exclusively dedicated to face processing [20]. Interestingly, recent investigation combining single-unit recordings and fMRI on macaque monkeys has yielded for the first time a discrete area in superior temporal sulcus consisting entirely of face-selective cells, dedicated to face structural encoding and identification [21]. The specific functionality of these areas has been compared to the widely studied area MT/V5, specialized for processing visual motion [21].

But still a major question that remains uncertain is whether recognition of expression in faces is completely independent from identity or, on the contrary, both identity and expression systems interact. The traditional cognitive model by Bruce & Young [22] postulated that facial expression and facial identity are processed through two separate routes after visual structural encoding. Therefore, expression could be processed regardless of identity, and identity regardless of expression [23]. In relation to this, recent neurological models [24], giving support to former data in monkeys [25], postulated the existence of two distinct pathways, one encoding changeable facial properties (expression, lipspeech and eye gaze) which involves inferior occipital gyri and superior temporal sulcus, and another encoding rather invariant facial properties (identity) which involves inferior occipital gyri and lateral fusiform gyrus [24]. However, the independence of these two systems has been recently challenged, as, for instance, most cases of prosopagnosia, a visual agnosia restricted to identity recognition in faces, show impairment in expression recognition as well (see [26] and [27] for a review), and only few cases reported intact facial expression recognition [28].

Recent work using image-based analysis techniques, such as Principal Component Analysis (PCA), a statistical procedure which identifies correlations between sets of pixels across the entire set of facial images, suggests that the independence of expression and identity coding is partial, or statistical, rather than absolute: for every face presentation, the distinct visual cues would acquire different probabilities for conveying either expression or identity, or both [29]. Thus, a partial overlap of both types of information could be expected [29]. Taken together and, contrary to what was previously assumed, the separation for expression and identity may be relative and the corresponding underlying systems would often interact. Nevertheless, recognition of expression in faces is still highly localized within the brain, as some cerebral regions appear to be disproportionately involved in different emotional categories. This has been demonstrated in a number of lesion studies, as damage in the amygdala impairs recognition of fear in faces [30, 31], damage of ventral striatum impairs recognition of angry expressions [32], or insula impairs recognition of disgust in faces [33]. It is noteworthy to point out, however, that the functional implications of amygdala lesions have not been clearly delimited to the moment. For instance, a recent study by Adolphs and colleagues [31] suggested that impairment in fear recognition may grow out of an inability to normally use information from the eye region of faces when judging emotions, possibly because patients lack the amount of spontaneous fixations on the eyes during free viewing of faces. Consistently with this idea, patient SM, in their study, recovered recognition of fear entirely after she was instructed to look at the eyes [31].

Threatening emotional expressions modulate brain face-selective areas: involvement of the amygdala

Face-selective regions in brain such as fusiform cortex [34], or early visual areas in the occipital lobe, have been consistently shown to enhance their activation particularly with fearful expressions as compared to neutral faces [35-38].

Even though the precise mechanisms by which emotion modulates face processing are still unclear, results from haemodynamic and electrophysiological brain imaging in humans and animal models have achieved important advances in this issue. The amygdala, a nuclear complex located on the medial temporal lobe, anterior to the hippocampus, is known to play a crucial role in affective processing [39, 40], capable of organizing rapid reactions to danger, even without the participation of the cerebral cortex [41]. It has been suggested that not only expression but also identity of faces may be processed with the common involvement of the amygdala [42].

The amygdaloid complex is known to have extensive connections to numerous brain areas such as sensory cortices [43], and seems to exert strong influence on a number of cognitive processes such as emotional learning [39, 40, 44], memory [45, 46] and, importantly, attention [47, 48] (see [49] for a review).

Brain imaging studies reported an enhanced activation of cortical regions when novel emotional stimuli were presented [50], an effect that actually correlated with amygdala responses [35]. A recent fMRI study by Vuilleumier and colleagues [51] examined patients with lesions in the amygdala, the hippocampus or both, presenting to them faces with fearful and neutral expressions. Healthy subjects and patients with hippocampal damage showed the expected enhanced activation of fusiform and occipital cortex [35-38]. However, such increased cortical activation was absent for patients with amygdala damage [51].

In fact, amygdala seems to have a substantial modulatory control over all stages of sensory processing in the ventral visual stream, V1 included (Fig. 1; [52, 53]). The amygdaloid complex is reciprocally interconnected with widespread regions of the neocortex [54], receiving projections from all sensory modalities. Among all systems, the visual modality provides the major sensory input, specially from rostral areas of the temporal lobe [55]. In turn, amygdala sends projections to the visual cortex, these being even more extensive than the visual inputs to amygdala [53]. These feedback projections are not diffuse but appear rostrocaudally organized such that caudal portions in the basal nucleus of the amygdala project to caudal visual areas, and rostral portions project to rostral levels of visual cortex [52].

However, emotional enhancement of perception is comparable to what would be expected from classic effects of attention [49], since attention leads to enhanced activation in early visual areas [56-58]. Attentional processes have been systematically linked to the cholinergic system, which projects to widespread cortical regions including early visual areas or cortical areas related to attentional control [59]. Cholinergic neurons in the basal forebrain are known to receive inputs from the amygdala [60]. Though it would appear logical, however, it seems unlikely that cholinergic projections are responsible for the emotional modulation, since induction of cholinergic enhancement appears to cause insignificant increased responses of amygdala or fusiform cortex [61]. Moreover, a patient suffering from spatial neglect, presenting damage in the parietal lobe (an area linked to spatial awareness), showed the normal increased response of fusiform cortex for fearful faces presented in the neglected field [62]. Both studies provide evidence that the direct projections from the amygdala lead to this enhanced response of sensory areas, which would be different from (but often collaborating with) common top-down signals related to fronto-parietal circuitries [27]. When a fearful (or angry, e.g., [63]) face is first perceived, very rudimentary visual signals would reach superior colliculus through magnocellular visual pathways: this would correspond to the residual visual route called *blindsight*. Superior colliculus is connected to the pulvinar nucleus of the thalamus and pulvinar seems to send projections to different cortical areas and the amygdala (see [64]). Amygdala in turn would modulate visual cortical areas through the projections mentioned above [65]. An alternative hypothesis would point to a rapid response of the amygdala during the first feedforward sweep through the visual system, when visual awareness is not yielded yet [66].

Amygdala would send the corresponding feedback signals before cortical processing is complete [65].

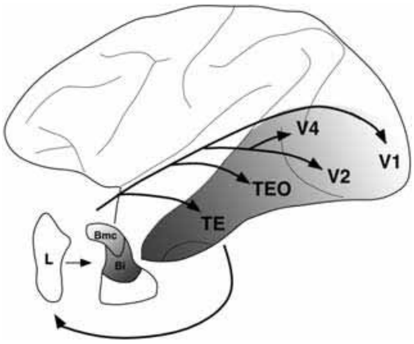

Fig. 1. Projections between the amygdala (L, Bi, Bmc) and ventral visual cortical areas (V1, V2, V4, TEO, TE) in the primate brain. The basal nucleus of the amygdala sends projections to all areas from the ventral visual stream, V1 included, whereas only TE projects to the lateral nucleus of the amygdala. Reprinted from reference [53].

Is amygdala modulation an automatic response?

To date, there is still conflicting evidence on whether the amygdala responds consistently to threatening facial expressions even under conditions of inattention or, on the contrary, top-down mechanisms can modulate the activation of this nucleus. A number of imaging studies reported sustained amygdala activity to fearful faces when focal attention was directed towards a distractor (and thus, away from the fearful faces, [37, 67]). Similarly, recent investigation even reported an increased response of the amygdala when fearful faces were not attended as compared to the attention condition [68]. The latter results would seem rather conclusive because their task configuration tried to overcome all possibly uncontrolled effects in previous designs [37, 67]. The authors concluded that amygdala would give preference to potentially threatening information under conditions of inattention [68]. However, in a very recent study by [69], no differential activation of amygdala was observed when faces were flashed for only 33 ms (and therefore subjects were not aware of their presence). These results were consistent with previous findings showing that amygdala activity decreased substantially when subjects attended peripheral line segments instead of the emotional faces presented at a fixation point [38]. Still this controversy needs further investigation and, moreover, the question of whether face stimuli should be considered susceptible to attentional load, similarly to nonbiological stimuli such as letters or words, remains open [70, 68].

Attentional bias towards threatening emotional expressions: a very early effect

The rapid detection of emotional salient stimuli seems to be necessary: mammals need to respond defensively to an ambiguous stimulus *before* the object is identified as either threatening or innocuous. Congruently, emotional bias for faces occurs at very early stages of information processing. It was formerly speculated that emotional facilitation occurred after the early perceptual encoding and categorization of face stimuli (about 51 ms later [36, 71]). Therefore, the initial structural encoding would provide appropriate descriptive information for subsequent expression and recognition analysis, giving support to the early model described by Bruce & Young [22]. These operations of structural encoding are reflected in the occipito-temporal N170 event-related brain potential (ERP) component (or M170 in MEG [72]), peaking at a latency of 150-200 ms post-stimulus onset and showing a high specificity for faces [73]. This component has been considered independent both of expression [74, 75] and identity [76, 72]. However, recent studies have repeatedly reported N170 modulation by, for instance, fearful emotional expressions [77, 78] (in the latter case [78], intensity of emotion in fearful, angry and disgust faces was the modulatory factor and not the type of emotion); [79] and even earlier effects, such as visual evoked potentials (VEP) around 80-90 ms [80], 80-160 ms post-onset [81], around 90 ms [82] or an increased amplitude of P1 [83], a positive-going deflection, maximal over occipital lobe and peaking approximately 130 ms after stimulus onset. It is noteworthy to point out that there are no evidences in literature showing activity related to a threatening expression in amygdala before 90 ms, but by that moment V1 appears to be already differentially activated [71, 82]. In fact a study by Krolak-Salmon and colleagues [71] reported emotion effects in amygdala only 200 ms after stimulus onset.

Alternatively, intracranial recordings reported earlier responses (120-160 ms) to fearful faces in ventral prefrontal cortex [84]. Although the role of amygdala in processing faces with threatening expressions (fear and anger) seems very plausible to be responsible for feedback projections onto early visual areas, as we have reviewed in this chapter, there is the possibility that, for instance, prefrontal sources exert even an earlier modulatory effect, as observed in scalp recordings (e.g., [79, 82, 83]; see [27] for a review). Nonetheless, further investigation of amygdala response timing may provide a better understanding of how emotion mediates such attentional bias, and would possibly help to build up a model integrating early effects such as V1 modulation with feedback projections from the amygdaloid complex.

Negative faces can also influence perception *across* sensory modalities

As we have revised in this chapter, threatening emotional expressions seem to influence visual processing of faces. In this respect, it would be likely that emotion in faces also affect the processing of stimuli presented through a different sensory pathway, that is, across sensory modalities. Studies using nonfacial stimuli reported that visualizing emotionally loaded pictures intensifies peripheral reflexes towards sudden auditory stimuli, indicating that the emotional context potentiates responses elicited by novel events in the acoustic environment [85-88]. In a recent study of ours using fMRI [89] we instructed our participants to make a color decision on visual stimuli that contained task-irrelevant fearful, angry and neutral faces, while at the same time ignoring task-irrelevant sounds. In this type of experimental design, the occurrence of unexpected novel sounds has been typically shown to elicit a specific pattern of neuronal activations localized in supratemporal [90-92], prefrontal [93, 94] and parietal cortices [95], subserving the neural mechanisms of *auditory novelty processing* [96]. This pattern of neuronal activations is usually accompanied by behavioral disruption of the ongoing task, a phenomenon called *distraction* [97-99]. Using a typical auditory-visual oddball paradigm, which already evidenced effects of distraction and acoustic novelty processing in previous studies [97, 99, 100, 101], we observed that activation induced by novel sounds in superior temporal gyrus (STG) was enhanced when participants responded to emotional in contrast to neutral faces, and, accordingly, novel sounds yielded a stronger behavioral disruption on subjects' visual task performance. These results suggest that novel sounds, irrelevant in neutral environmental conditions, could potentially convey crucial information in a context of affective significance, becoming thus more relevant and warranting greater chances of survival.

CONCLUSION

Emotion enhances perception and potentiates the perceptual effects of attention. We have discussed how, attending to evolutionary advantages, processing of faces is modulated by the emotional load of their expressions (e.g., fear or anger). This rapid detection of faces with threatening expressions, although not *parallel*, as would be considered for a true 'pop-out' effect, is nevertheless highly efficient. On the other hand, despite the fact that expression and identity recognition in faces appear to operate through different pathways in the brain, both systems may often interact and their independence would be relative. Face-selective regions of the brain, such as fusiform cortex or early visual areas in the occipital lobe, have been found to enhance their activation particularly with fearful expressions. The amygdala, a nuclear complex located on the medial temporal lobe, known to have a crucial role in affective processing, may be the main responsible for this modulation through direct projections to the ventral visual pathways. This specific neural system might act, at least in part, independently of other mechanisms associated with more voluntary components of attentional control. We have seen how amygdala responses to fearful faces may depend not only on the physical characteristics of the emotional stimulus but also on visual awareness. Nevertheless, some controversy exists over the automaticity of amygdala activation in emotional face processing. We have reviewed evidence demonstrating that this attention bias towards threatening expressions occurs at very early stages of information processing in the human brain, as emotional effects have already been registered 80-90 ms after the onset of emotional faces. Although no studies have reported earlier activations of amygdala before 200 ms, there is the possibility that other sources such as prefrontal cortex exert an earlier modulatory effect. Given these evidence, further investigation would be necessary to build up a model which integrates early modulation of visual cortices with possible feedback projections from the amygdaloid complex. Finally, we have reported recent data suggesting that emotional faces also influence processing across sensory modalities, for instance enhancing activation of areas related to acoustic novelty processing.

ACKNOWLEDGEMENT

Supported by grants SEJ2006-00496/PSIC and HA2005-0024 from the Spanish Ministry of Education and Science and SGR2005-00953 from the Generalitat de Catalunya.

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ANNEX 2

Summary (Catalan version)

INTRODUCCIÓ

Els processos emocionals serveixen no només per avaluar successos sensorials, però també per iniciar respostes adaptatives i modificar la percepció (Vuilleumier, 2005). Durant aquest últim segle, abundant literatura ha mostrat que els estímuls emocionals tenen un estatus prioritari en els sistemes sensorials, capturant l'atenció més ràpidament i eficaç que els estímuls no-emocionals (e.g., Hansen & Hansen, 1988; Öhman *i cols*., 2001; Carretie *i cols*., 2004; Richards & Blanchette, 2004).

Aquest biaix atencional té origen en la capacitat limitada dels sistemes sensorials, alhora que respon a avantatges evolutius i adaptatius: la necessitat de reaccionar amb rapidesa a aquella informació crucial per la supervivència. Aquest efecte, a més, és especialment pronunciat amb estímuls negatius o amenaçants (Lang *i cols*., 2000).

Experiments utilitzant neuroimatge han mostrat repetidament un augment de la resposta cerebral en diferents àrees sensorials davant d'estímuls emocionalment negatius. Per exemple, l'àrea fusiforme, altament selectiva pel processament de cares, o àrees visuals primerenques al lòbul occipital, augmenten la seva resposta durant el processament de cares amb expressions negatives en relació amb les neutres (Morris *i cols*., 1998; Sugase *i cols*., 1999; Vuilleumier *i cols*., 2001; Pessoa *i cols*., 2002). De forma similar, visualitzar fotografies d'escenes emocionalment negatives augmenta la resposta en àrees visuals primerenques en relació amb les neutres (Bermpohl *i cols*., 2006). De la mateixa manera, el córtex auditiu primari mostra un augment d'activació mentre processa sons amenaçants (Fecteau *i cols*., 2007).

Aquest efecte modulatori ocorre en estadis molt primerencs del processament d'informació, com s'ha demostrat en estudis on fins i tot 80-90 ms després de la ocurrència de l'estímul negatiu s'observen diferències en la resposta electrofisiològica del cervell (Eger *i cols.*, 2003; Pourtois *i cols.*, 2004).

Tot i que els substrats neurals d'aquesta modulació emocional no es coneixen amb precisió, es creu que l'amígdala podria exercir un paper crític en la regulació de les respostes a les àrees sensorials primerenques del cervell (Amaral *i cols.*, 1992; Amaral *i cols.*, 2003, Freese i Amaral, 2005; Vuilleumier, 2005). Aquest nucli es troba extensament i recíprocament conectat amb àrees corticals, com ara les sensorials (Amaral *i cols.*, 1992; Young *i cols.*, 1994). Es creu que l'amígdala podria enviar senyals 'de dalt a baix' a les vies sensorials (Vuilleumier, 2005).

En aquest sentit, evidències electrofisiològiques i estudis de neuroimatge han demostrat repetidament que els homes i les dones processen la informació emocional de forma diferent (Orozco i Ehlers 1998). Per exemple, s'han descrit activacions de l'amígdala més pronunciades en dones que en homes durant el processament d'imatges emocionalment negatives, o s'ha vist que certes respostes cerebrals tardanes són més intenses en dones que en homes vers estímuls negatius (Kemp *i cols.*; 2004).

En conclusió, hi ha nombroses evidències que suggereixen que l'emoció negativa interfereix amb el processament d'estímuls dins una mateixa via sensorial. Tanmateix, una de les qüestions que encara roman incerta és l'efecte que aquests tenen entre modalitats sensorials diferents. En aquest sentit, per exemple, s'ha demostrat que processar imatges emocionalment negatives pot amplificar l'efecte d'altres processaments sensorials, com posa de manifest la potenciació del reflexe de parpalleig (Stanley i Knight, 2004; Bradley *i cols.*, 2006) o la supressió del mecanisme cerebral de filtre sensorial (Yamashita *i cols.*, 2004). No obstant, s'ha mostrat repetidament que les respostes auditives tardanes a aquests sons queden atenuades en les mateixes condicions (Schupp *i cols.*, 1997; Cuthbert *i cols.*, 1998; Keil *i* *cols*., 2007). Aquesta atenuació podria estar relacionada amb un mecanisme de *competència sensorial* entre un estímul neutre i un d'emocional presentats desde diferents modalitats sensorials, més que estrictament l'efecte del *context* en que els sons es van processar. Actualment no existeix cap estudi que examini els efectes del context en l'atenció involuntària, alhora que eviti aquesta possible *competència sensorial*. Per aquest fet, la utilització d'una tasca de distracció *oddball* auditivo-visual, creada en aquest laboratori, (Escera *i cols.,* 1998) permetria aïllar-ne aquest aspecte.

Durant el transcurs d'aquesta tasca, els subjectes responen a uns estímuls visuals, mentre ignoren els sons que els precedeixen. Aquests sons poden ser, bé un to pur repetitiu, en la majoria dels casos, o un so novedós ambiental, altament infreqüent. En aquest cas, l'ocurrència inesperada de sons novedosos produeix sovint una interferència en la conducta, fenòmen conegut com a distracció. Aquest efecte es veu acompanyat d'un patró específic d'activació neuroelèctrica caracteritzat pels potenciales evocats (PEs) N1/MMN i P3a (Escera *i cols.,* 1998, 2000, 2001, 2002; Escera i Corral, 2003, 2007), presumiblement amb origen en mecanismes neuronals del córtex supratemporal (Alho *i cols*., 1998; Downar *i cols*., 2000; Kiehl *i cols*., 2001, parietal (Clark *i cols*., 2000; Downar *i cols*., 2001) i prefrontal (Downar *i cols*., 2001; Bledowski *i cols*., 2004). Aquesta tasca permet avaluar com les condicions de la tasca, o el que és el mateix, del context, exerceixen un impacte sobre el processament dels estímuls auditius novedosos a nivell cerebral i conductual.

OBJECTIUS

La present tesi pretén investigar la relació funcional entre el processament de sons novedosos irrellevants per la tasca, així com el seu efecte distractor, i un context de processament emocional, tant a nivell conductual com electrofisiològic i hemodinàmic en humans. A aquest efecte, es dugueren a terme quatre estudis per descriure els correlats neurals, temporalitat i efectes modulatoris del conext emocional negatiu en el processament de novetat auditiva, dins el marc de l'experimentació *oddball* auditiva-visual. S'utilitzaren dues tècniques diferents: potencials evocats (PE) a l'Estudi I, II i III, i resonància magnètica funcional (RMf) a l'Estudi IV.

A l'Estudi I, s'utilitzà una tasca de discriminació visual, amb imatges d'escenes bé neutres o bé amenaçants, mentre s'enregistrà l'electroencefalograma (EEG) de 64 canals en els subjectes. S'examinà la temporalitat i perfil dels efectes modulatoris del processament de les imatges negatives, respecte les imatges neutres, sobre el processament dels sons distractors, tan a nivell conductual com electrofisiològic.

A l'Estudi II, s'utilitzà una variant de la tasca de discriminació visual utilitzada en l'Estudi I, amb imatges d'escenes bé neutres o bé amenaçants, mentre s'enregistrà l'electroencefalograma (EEG) de 64 canals en els subjectes. S'examinà la temporalitat i perfil dels efectes modulatoris del processament de les imatges negatives, respecte les imatges neutres, sobre el processament dels sons distractors, tan a nivell conductual com electrofisiològic.

A l'Estudi III s'utilitzà igualment una de les tasques de discriminació visual, amb imatges d'escenes bé neutres o bé amenaçants, mentre s'enregistrà l'electroencefalograma (EEG), aquest cop en una mostra més gran d'homes i de dones. S'examinaren les diferències de gènere d'aquests efectes modulatoris, tant a nivell conductual com electrofisiològic.

Finalment, a l'Estudi IV, s'utilitzà una tasca de discriminació visual, amb imatges de cares bé neutres o bé amb expressió amenaçant, durant l'adquisició de la resposta hemodinàmica cerebral en una sessió de RMf. S'examinaren les àrees cerebrals relatives al processament de novetat auditiva que es veuen modulades pel context emocional, així com l'impacte que aquest té sobre l'efecte distractor a nivell conductual.

MÈTODES

Subjectes

El primer, el segon i el tercer estudi es van dur a terme a la Facultat de Picologia de la Universitat de Barcelona. Un total de 14 voluntaris sans (7 homes), 14 dones sanes i 28 voluntaris (14 homes) hi van participar, respectivament. El quart estudi va ser dut a terme al Department of Neuropsychology and Behavioral Neurobiology, Universitat de Bremen, Alemanya, d'on 17 voluntaries hi van participar.

Tots els subjectes van ser avaluat amb entrevistes clíniques i cap d'ells va reportar antecedents personals o familiars neurològics o piquiàtrics, tractament per transtorns de personalitat o transtorns d'ansietat, fòbies específiques, consum de drogues o audició anormal. Tots els subjectes gaudien de visió normal o corregida i van donar consentiment per escrit del procediment experimental, d'acord amb la Declaració de Helsinki.

Estímuls

Pel primer, segon i tercer estudis, es va utilitzar com a estímuls emocionals una selecció de fotografies seleccionades de la base de dades International Affective Picture System (IAPS; Centre for research in Psychophysiology, Universitat de Florida, Gainesville). Les fotografies representaven escenes neutres o emocionalment negatives, incloent les negatives escenes d’extrema violència i fàstic. Les fotografies van ser presentades de dues en dues a la pantalla amb una creu de fixació de la mirada al centre de la pantalla.

A l’Estudi IV, els estímuls emocionals van consistir en cares monocromàtiques, representant expressions neutres i d’amenaça o de por, recopilades al Department of Neuropsychology and Behavioral Neurobiology, Universitat de Bremen (Alemanya). Les cares tenien un marc de color al voltant i van ser presentades d’una en una a la pantalla. Les cares van ser considerades més apropiades per experimentació amb RMf, donat que es volia evitar variabilitat en la freqüència espacial no desitjada entre els diferents sets d’imatges (Delplanque *i cols*., 2007).

En els quatre estudis, els estímuls auditius van consistir en tons de 700 Hz repetitius o estàndard i sons novedosos ambientals únics, presentats als subjectes mitjançant auriculars a 75 dB SPL en els primers tres estudis i a 20 dB sobre el nivell sensitiu (SL) a l’Estudi IV.

Tasca i condicions

En els quatre estudis, els participants van realitzar una versió modificada d’un paradigma auditiu-visual de distracció (Escera *i cols*., 1998, 2000, 2001, 2003). Tots els estímuls van ser presentats amb el programa Presentation®. Els estímuls auditius van precedir les imatges en 300 ms, I podien ser un to repetitiu o estàndard (p=0.8) o un so novedós ambiental (p=0.2). Per l’Estudi I, la duració dels trials va ser de 1500 ms de forma constant, però en els Estudis II, III i IV, la duració era variable per evitar sincronitzacions d’activitat cerebral no-desitjada. En els primers tres estudis, es van presentar parells d’imatges de l’ IAPS al centre de la pantalla i els subjectes havien de respondre amb un botó, si les imatges eren iguals o diferents. Alhora, els subjectes havien d’ignorar els sons. En el quart estudi, les cares apareixien en pantalla i els subjectes havien de respondre si el color de la cara era igual o diferent del color del marc que les envoltava.

Recollida de dades i anàlisi

Als Estudis I, II i III, es va enregistrar l'electroencefalograma (EEG) de 64 elèctrodes pericranials, durant la realització de la tasca, seguint el sistema 10/10 en una cambra aïllada acústica i elèctricament. L' electrooculograma (EOG) vertical i horitzontal va ser recollit amb elèctrodes col.locats al cantus extern de l'ull dret. L'elèctrode de referència es va col.locar a la punta del nas. Els PEs van ser aïllats mitjançant la tècnica del promig, en èpoques de 1200 ms I una línia base de 200 ms anterior a l'estímul. Els PEs van ser filtrats amb un filtre passa-banda de 0.1 a 30 Hz. Els artefactes oculars van ser corregits amb un algoritme de regressió. Aquells assaigs que excedien una desviació estàndard de ±30 μV van ser exclosos de l'anàlisi.

Es van aïllar els components N1/MMN i P3 de novetat, pels tres primers estudis. Pel segon i tercer estudi, es va examinar P300 adicionalment. Pel tercer estudi, tambñe es va aïllar el component RON. En tots els casos, es va examinar l'efecte de context sobre l'amplitud i distribució dels components mitjançant una ANOVA.

A l'Estudi IV, les imatges de RMf van ser adquirides mitjançant un escàner Siemens Allegra de 3T. Les imatges estructurals van ser adquirides mitjançant una seqüència MPRAGE ponderada en T1, seguint els següents paràmetres (160 talls, TR 2.3s, TE 4.38 ms, flip angle 8°, 256x256 matrix, FOV 296x296, inversion time 900 ms, 1mm^3 voxels).

Les imatges funcionals van ser obtingudes amb una seqüència EPI, T2*, optimitzada pel contrast de la resposta hemodinàmica BOLD (Blood Oxygenation Level Dependency). La seqüència EPI va ser aplicada seguint els següents paràmetres (44 talls contigus cobrint la totalitat del cervell, cada 3 mm, sense gap entre talls, incorporant els següents paràmetres: TE 30 ms, TR 2.5 s, 64x64 matrix, FOV 192x192, flip angle 90°, resolució 3x3 mm^2, interleaved ascending. Les imatges funcionals van ser realiniades, normalitzades en l'espai al template del Montreal Neurological Institute

(MNI) i suavitzades (8 mm FWHM gaussian kernel) mitjançant el programa SPM2 (Wellcome Department of Cognitive Neurology, London, England, 2003).

Es van realitzar els contrastos, mitjançant t-tests, d'aquells assaigs amb sons estàndard i sons novedosos per les dues condicions de context. Posteriorment, es van comparar els contrastos de processament de novetat en context neutre i processament de novetat en context negatiu mitjançant una ANOVA. Es van realitzar contrastos adicionals dels assaigs amb sons estàndard en context neutre i negatiu mitjançant t-tests. L'activació va ser considerada significativa quan almenys 20 voxels contigus van sobrepassar el valor de $p<.001$ per tots els contrastos excepte pel contrast on només es van analitzar assaigs estàndard.

Per tots els anàlisis i en tots els estudis, es van tenir en compte només aquells assaigs precedits i seguits d'una imatge de la mateixa valència emocional. Per l'anàlisi conductual, es van comparar els temps de resposta dels assaigs amb resposta correcta amb una ANOVA, per tal d'examinar-ne els efectes del context.

RESULTATS

Estudi I

Els sons novedosos van produïr un efecte distractor en el rendiment dels subjectes, reflexat en temps de resposta més grans. Aquest efecte va ser magnificat quan els subjectes processaven imatges emocionalment negatives, en comparació amb les neutres. La fase tardana de la ona P3 relativa a la novetat, va mostrar una amplitud augmentada quan els subjectes processaven imatges emocionalment negatives.

Estudi II

Els sons novedosos van produïr un efecte distractor en el rendiment dels subjectes, reflexat en temps de resposta més grans. Aquest efecte va ser magnificat quan els subjectes processaven imatges emocionalment negatives, en comparació amb les neutres. La fase primerenca de la ona P3 relativa a la novetat, va mostrar un augment d'amplitud quan els subjectes processaven imatges emocionalment negatives, en comparació amb les neutres.

Estudi III

Els sons novedosos van produïr un efecte distractor en el rendiment dels subjectes, reflexat en temps de resposta més grans. Aquest efecte va ser magnificat en dones quan els subjectes processaven imatges emocionalment negatives, en comparació amb les neutres. Els homes no van presentar aquest patró modulatori. La fase primerenca de la ona P3 relativa a la novetat, va mostrar un augment d'amplitud quan els subjectes processaven imatges emocionalment negatives, en comparació amb les neutres. Aquest efecte va ser present només en dones.

Estudi IV

Els sons novedosos van produïr un efecte distractor en el rendiment dels subjectes, reflexat en temps de resposta més grans. Aquest efecte va ser magnificat en dones quan els subjectes processaven cares emocionalment negatives, en comparació amb les neutres. La resposta hemodinàmica produïda pels sons novedosos en el gir temporal superior, incloent cortex auditiu secundari, planum temporale i cortex auditiu primari, va mostrar un augment quan els subjectes processaven cares emocionalment negatives, en comparació amb les neutres.

DICUSSIÓ GENERAL

El processament de la saliència d'un estímul depèn no només de la seva freqüència d'aparició, sinó també del context conductual en què aquest ocorre (Katayama i Polich, 1998) i, especialment, del context emocional en què es processa. Els resultats dels presents estudis mostraren, principalment, que els subjectes no van poder ignorar la informació emocional dels estímuls, tot i que era irrellevant per la tasca (Vuilleumier *i cols*., 2001).

En els quatre estudis, els sons novedosos van produïr un efecte distractor en el rendiment dels subjectes, reflexat en temps de resposta més grans. Aquest efecte va ser magnificat quan els subjectes processaven imatges emocionalment negatives, en comparació amb les neutres.

Tal com es va observar en els tres estudis amb PEs, aquest efecte distractor va veure's acompanyat d'un patró de resposta caracteritzat pels components N1/MMN i P3 de novetat, tant en el context negatiu com en el neutre. La morfologia i distribució d'aquest patró representa l'activació neuroelèctrica de processament de novetat auditiva, un mecanisme que té a veure amb l'avaluació del estímuls novedosos que han capturat l'atenció (Escera *i cols.,* 1998, 2000; Friedman *i cols.,* 2001)

A més, els resultats de RMf van mostrar que els sons novedosos van activar una xarxa d'activacions en àrees frontals (gir frontal inferior), temporals (gir temporal superior) i parietals (precuneus), àrees àmpliament relacionades amb el processament de novetat auditiva (Downar *i cols*., 2000, 2001; Bledowski *i cols*., 2004).

En concordància amb els resultats conductuals, el component P3 de novetat van mostrar un augment d'amplitud en context emocional negatiu, comparat amb el neutre. En el primer estudi, aquesta modulació va ocórrer en la fase tardana d'aquest component, mentre que en el segon, va ser la primerenca la que va mostrar l'efecte. Aquestes diferències poden ser degudes al disseny de la tasca i, en qualsevol cas, demostren que el context emocional pot modular processament auditiu de novetat ja en estadis immediatament anteriors a la resposta d'orientació.

La resposta hemodinàmica, a més, va mostrar un augment en àrees relacionades amb el processament auditiu de novetat en context negatiu, en relació amb el neutre. Aquestes àrees, localitzades en el gir temporal superior, inclogueren el cortex auditiu secundari, planum temporale i cortex auditiu primari. Aquests resultats poden ser comparats amb els del segon estudi, on la fase primerenca de la P3 va ser modulada (Alho *i cols.,*1998; Escera *i cols.,* 1998).

Aquests resultats modulatoris, no obstant, van ser observats només en dones en un dels estudis. Experiments recents amb neuroimatge mostren que el llindar de les dones per la detecció de senyals de perill és més baixa que en homes (Williams *i cols*., 2005). Aquesta idea suggereix que les diferències de gènere observades aquí poden estar relacionades amb diferent avaluació de les imatges en homes i dones.

CONCLUSIONS

Les conclusions de la present tesi poden ser formulades com s'exposa a continuació:

En tots els estudis, els sons novedosos van provocar un efecte distractor sobre el rendiment dels subjectes, tal com va quedar reflexat en els temps de resposta més llargs, en comparació amb els assaigs estàndard. Aquest efecte va ser repetidament augmentat quan les imatges precedents i següents eren emocionalment negatives, en relació amb les neutres. Per tant, el processament d'imatges o de cares negatives augmenta l'efecte distractor d'estímuls auditius irrellevants per a la tasca que es presenten concomitantment, en relació a les neutres. En conseqüència, el context emocional negatiu potencia l'impacte conductual dels sons novedosos sobre la tasca en curs.

En dos estudis diferents, les fases tardana i primerenca de la P3 de novetat van ser augmentades en context negatiu, respectivament, en comparació amb un context neutre. Per tant, el processament d'imatges negatives provoca un augment de l'amplitud del potencial evocat P3 relatiu al processament de novetat auditiva, en resposta als sons novedosos distractors en la seva fase tardana, en comparació amb les cares neutres. Tanmateix, questa modulació també pot ocórrer en la fase primerenca de la P3. Així, un context emocionalment negatiu modula les respostes cerebrals en el sistema de processament de novetat en estadis immediatament anteriors a la resposta d'orientació d'atenció.

En un dels estudis, només dones van mostrar un augment de distracció i modulació de P3 en context emocional. Es contempla, per tant, la possibilitat de l'existència de diferències de gènere en aquests patrons modulatoris.

Finalment, la resposta hemodinàmica produïda pel processament de sons novedosos va mostrar un augment al gir temporal superior, incloent cortex auditiu secundari, planum temporale i cortex auditiu primari, quan els subjectes processaven cares amb expressions negatives, en relació amb les neutres. Es conclou, per tant, que el context de processament emocionalment negatiu augmenta la resposta hemodinàmica als sons novedosos en àrees cerebrals relatives al processament auditiu de novetat.

En conclusió, els resultats descrits en aquesta tesi indiquen que el context emocional augmenta l'activació de regions cerebrals relacionades amb el processament de novetat auditiva en estadis primerencs de la resposta d'orientació, fent que sons irrellevants en condicions neutres estiguin més disponibles en el set atencional en condicions d'amenaça. Aquests resultats aporten una il.lustració novedosa de com l'emoció exerceix un mecanisme mediador entre atenció voluntària i involuntària.

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