



## Review article

## Neural processing of negative emotional stimuli and the influence of age, sex and task-related characteristics



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## ABSTRACT

Negative emotional stimuli are particularly salient events that receive privileged access to neurocognitive resources. At the neural level, the processing of negative stimuli relies on a set of sensory, limbic, and prefrontal areas. However, controversies exist on how demographic and task-related characteristics modulate this brain pattern. Here, we used activation likelihood estimation (ALE) meta-analysis and replicator dynamics to investigate the processing of negative visual stimuli in healthy adults. Our findings endorse the central role of the amygdala. This result might reflect how this structure modulates perceptual and attentional mechanisms in response to emotional stimuli. Additionally, we characterize how the neural processing of negative visual stimuli is influenced by the demographic factors of age and sex as well as by task-related characteristics like stimulus type, emotion category, and task instruction, with the amygdala showing comparable engagement across different sexes, stimulus types, and task instructions. Our findings practically inform experimentation in the affective neurosciences but also suggest brain circuits for neurobiological investigations of affective symptomatology.

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## 1. Introduction

Successful adjustment to the environment, and therefore well-being, requires the capacity to adequately cope with negative events and situations (Lazarus, 1993). As we are heavily relying on our visual sense, we all deal with negative visual stimuli in our daily lives. They may consist of an angry face staring at us, an alarming headline in a newspaper, or a spider climbing up our boot. All these stimuli are salient events able to urgently mobilize a set of resources that allow rapid detection as well as fine-motor and locomotor control. Over millennia, natural selection processes have evolved mechanisms of detecting and responding to stimuli and situations that are potentially harmful (Darwin, 1872/1965). Possibly as a result of these evolutionary pressures, the neurobehavioral processing of emotional events, such as aversive stimuli, is prioritized over neutral stimuli. For instance, studies suggest that emotional events elicit faster attention (Vuilleumier, 2005) and greater memory consolidation (Phelps, 2006) when compared to neutral stimuli. A core question here concerns the identification of brain circuits that facilitate the processing of emotionally relevant stimuli. Several theoretical models on emotion and cognition have attempted to address this issue. Given their special relevance for visual information processing, here we refer to the *multiple attention gain control* model, the *multiple-waves* model, the *biased attention via norepinephrine* theory, and the *glutamate amplifies noradrenergic effects* model.

The multiple attention gain control model (MAGIC; Pourtois et al., 2013) proposes that emotional stimuli can modulate perception by amplification mechanisms that are independent of other attentional processes. This model emphasizes the pivotal role of the amygdala and interconnected areas (e.g., orbitofrontal cortex and cholinergic areas such as the basal nuclei of the forebrain) in evaluating the emotional charge of stimuli and in increasing their perceptual processing in early sensory pathways.

Some authors, however, have argued against the possibility that affective signals engage *independent* brain mechanisms. According to the multiple-waves model, the processing of affective visual information is associated with *general* perceptual and attentional mechanisms and occurs in multiple brain sites in parallel—including the amygdala, orbitofrontal cortex, anterior insula, and anterior cingulate cortex (Pessoa and Adolphs, 2010). The simultaneous engagement of these areas is able to generate multiple routes (multiple waves) for increased awareness and attention towards emotionally relevant stimuli (Pessoa and Adolphs, 2010).

While the two aforementioned models focus on emotional perception and attention, other theoretical frameworks have also integrated findings on emotional memory. In this vein, the biased attention via norepinephrine model (BANE) emphasizes the important role of norepinephrine in augmenting attention and memory processes in response to arousal (Markovic et al., 2014). This model proposes that norepinephrine signals – released from the locus coeruleus – interact with activity in affective centers of the brain, such as the amygdala and orbitofrontal cortex. These areas, in turn, facilitate activity in the visual cortices as a function of the affective significance of the stimuli, leading to augmented perceptual and attentional mechanisms. The amygdala can also modulate hippocampal activity, thus promoting memory encoding (Markovic et al., 2014).

Finally, another theoretical perspective that tackles the effect of arousal on perception and memory is the *arousal-biased competition* theory (ABC; Mather and Sutherland, 2011). This framework is built on the premise that arousal is associated with amplified perception and memory of prioritized stimuli, while suppressing the attention towards irrelevant stimuli. Within this general framework, the glutamate amplifies noradrenergic effects model (GANE; Mather et al., 2015) provides a neurobiological explanation of the effects of arousal on perception and memory. Similar to the BANE model, the GANE model proposes that arousing events are able to enhance norepinephrine levels in the brain, released from the locus coeruleus. When the locus coeruleus is phasically active (e.g., in response to emotional stimuli), glutamate interacts with norepinephrine to create *hot spots*, which in turn lead to (i) further increases in norepinephrine levels, and to (ii) enhancements in saliency signals, selective attention, and memory consolidation. These processes are coordinated by brain areas that have dense innervations with the locus coeruleus (e.g., amygdala or pulvinar nucleus of the thalamus) as well as by prefrontal areas such as the orbitofrontal cortex and anterior cingulate cortex, where noradrenergic influences on cognitive processes have been observed (Mather et al., 2015).

Although considerable evidence for the aforementioned models comes from studies on negative emotional processing, their postulates are not specific to the perception of aversive or unpleasant stimulus properties. Rather, they refer to an *arousing* property of the stimuli that is also present in positive or rewarding events. In fact, the neural representation of negative and positive information seems to largely overlap (at least at the macroscopic level), for instance in areas like the amygdala, anterior insula, and striatum (Hayes et al., 2014; Lindquist et al., 2015).

In the present study, we systematically assess the visual processing of negative emotional stimuli in healthy adults. In addition to extracting a general pattern of processing negative emotional stimuli, we put a particular focus on how this neural pattern is modulated by participant-related characteristics (i.e., the demographic factors of age and sex) and task-related characteristics (i.e., stimulus type, emotion category, and task instruction).

On the one hand, we aim to inform experimental practice in the affective neurosciences in that our meta-analytic results may influence sample selection and task design or facilitate the formulation of hypotheses.

On the other hand, understanding how negative emotional stimuli are detected and processed in the brain is a clinically relevant process, as both flattened and exaggerated responses to negative stimuli or situations are strongly related to affective symptomatology (Bylsma et al., 2008; Goldin and Manber, 2009; Tréneau, 2006). A deeper comprehension of the neural correlates of negative events in healthy participants and how they are modulated in particular by participant-related characteristics may thus provide a foundation for localizing brain regions and networks compromised in affective disorders.

### 1.1. Aging processes in the neural response to negative events

Despite being exposed to more adverse life events (e.g., death of friends, cognitive declines, or shrinkage of social networks), adults' emotional well-being can be maintained or even improved as they age (Charles and Carstensen, 2010; Mather, 2012). This phenomenon is known as the *emotional paradox of aging* (Mather, 2012). Age-related preservation of subjective well-being has been associated with behavioral biases in the processing of negative and positive emotional information: Relative to younger adults, older adults show reduced processing of negative information together with preferences for positive information (Carstensen, 1999; Mather and Carstensen, 2003; Reed et al., 2014). For example, older adults remember positive faces better than negative faces (Mather and Carstensen, 2003), exhibit a reduced complexity of storyline while recalling negative autobiographic memories (Comblain et al., 2005), and show more attentional preference for happy faces together with less visual fixation on angry faces (Isaacowitz et al., 2006).

In line with the behavioral findings of reduced processing of negative information, neuroimaging studies have observed that older adults show generally diminished activity in the amygdala in response to negative stimuli (Fischer et al., 2010; Leclerc and Kensinger, 2008; Mather et al., 2004; St. Jacques et al., 2010; but see: Wright et al., 2006) together with enhanced recruitment of pre-frontal areas (Brassen et al., 2012; Fischer et al., 2010). Two major theories have been put forward to explain such functional changes in older ages: the *socio-emotional selectivity theory* (Carstensen, 1999) and the *aging brain model* (Cacioppo et al., 2011).

The socio-emotional selectivity theory posits that when remaining life time is perceived as limited, individuals prioritize positive emotional experiences over other goals (Carstensen, 2006; Charles and Carstensen, 2010). Within this theory, healthy aging is associated with a shift in the allocation of cognitive resources, which results in an enhanced activity in cognitive control centers (e.g., the prefrontal cortex) together with a decreased recruitment of salience-related centers (e.g., the amygdala) in response to negative stimuli (Mather and Carstensen, 2005; Nashiro et al., 2012).

The aging brain model, in turn, is based on the observation that patients with damage to the amygdala tend to exhibit diminished arousal ratings *selectively* for negative stimuli along with preserved arousal ratings for positive stimuli (Berntson et al., 2007). This model stresses the fact that age-related neural processes affect the functionality of the amygdala. As a result of these changes, the aging

brain model predicts that, compared to younger participants, older adults will exhibit diminished amygdala activity in response to negative events, which will relate to diminished arousal perception of these stimuli (Cacioppo et al., 2011).

Overall, there is a need to integrate neuroimaging findings in younger and older participants in order to obtain comprehensive information on the possible effect of healthy aging during the processing of negative events. Since results on this topic are likely to be influenced by local historic and geographic characteristics (Steptoe et al., 2014), our meta-analytic approach might be able to identify general trends in healthy aging.

### 1.2. Sex differences in the processing of negative information

In addition to age-related changes, sex might also have an impact on the neural processing of negative information. At least in Western societies, where a Judeo-Christian cultural heritage is predominant, a persistent stereotype attributes diminished emotional responsiveness to men compared to women. The accuracy of this stereotype, however, remains controversial. Behavioral studies seem to point to the direction that women tend to display emotions more frequently than men (Kring and Gordon, 1998). For instance, across different cultures, women tend to report more frequent crying behavior than men (Fischer et al., 2004). However, the experienced intensity of emotions might not actually differ between men and women (Kring and Gordon, 1998). In turn, it might be strongly affected by the existence of social normative pressures and expectations that encourage lower emotional reactivity in men (Grossman and Wood, 1993). Support for this assumption comes from a study by Fischer et al. (2004) who observed that men in Western countries rated feelings of guilt, shame, and sadness as less intense than men in non-Western societies. Together, these findings indicate that although men and women might differ in the frequency of emotional expressions, the actual intensity of experienced emotions might be equivalent across sexes, and might be better explained by the personal identification with gender-related sociocultural roles.

In neurobehavioral research, some studies have examined the possibility of sex differences in emotion processing from the perspective of the *sexual lateralization hypothesis*. One of its most popular formulations proposes that mens' brains would be organized more asymmetrically than womens' brains (e.g., McGlone 1980; Hiscock et al., 2001). Similarly, other authors have advocated the possibility of sex-related lateralization differences, proposing that women tend to activate left-hemispheric regions more while men more strongly engage right-hemispheric regions (Cahill et al., 2004; Canli et al., 2002; Cahill, 2006).

In the field of affective neuroscience, several neuroimaging studies have investigated the possibility of sex-related hemispheric differences, especially in the amygdala. However, whether this region exhibits distinct hemispheric activation, specifically differing between women and men, is still a matter of debate. While different studies have observed sex-related laterality differences in the amygdala during the presentation of negative stimuli (Domes et al., 2010; Hofer et al., 2007; Kempton et al., 2009), at least one study observed no such differences (Hofer et al., 2006). Another study reported that, compared to females, males exhibit stronger activity in the right amygdala during the presentation of anger-related faces along with enhanced activity in the left amygdala during the processing of fear-related faces (Weisenbach et al., 2014). Finally, Caseras et al. (2007) did not observe laterality differences in the amygdala, but reported increased activity in women relative to men in several left-lateralized prefrontal and temporal regions, including the lateral prefrontal cortex and superior temporal gyrus. In an attempt to integrate the divergent results, two meta-analyses have been conducted so far. Wager et al. (2003)

examined sex differences in response to emotional stimuli in density distribution of activation foci through the brain. One of the results related to the sublenticular area of the amygdala, for which the authors observed that, in the left hemisphere, peak density was higher in women than in men, while the opposite was true for the right hemisphere. In a more recent meta-analysis, Stevens and Hamann (2012) reported an extensive pattern of sex differences in response to negative stimuli, including a more reliable brain activity in women relative to men in the left hippocampus/amygdala in response to negative emotional stimuli. Both meta-analyses nicely identified consistencies across studies on sex-related differences. However, they included a considerably high proportion of studies with low sample sizes (<10 subjects) and mixed results from PET and fMRI studies. At the moment of commencing the present meta-analysis, the availability of a multitude of new studies made it feasible to investigate sex differences, applying stricter exclusion criteria and selecting a more homogeneous set of experiments.

### **1.3. Differences in the brain correlates of negative events associated with task-related characteristics**

From a more practical perspective, several aspects of the experimental task might introduce variability in the pattern of brain activity obtained when investigating the processing of negative events. Here, we refer to stimuli-related characteristics and to the effect of the task instructions.

#### **1.3.1. Stimulus types: images, faces, or words**

Studies on the neural processing of negative visual events have mostly presented images, faces, or written words. These three stimulus types have proven to be powerful emotional transmitters (Lang et al., 2008; Lench et al., 2011) and their processing involves distributed cortical and subcortical brain areas (Vuilleumier and Pourtois, 2007; Citron, 2012).

It is still unclear, however, if emotional pictures, faces, and words trigger distinct or overlapping neural patterns. Theoretical works have proposed a differentiation between a semantic system responsible for the perception of pictorial stimuli and a lexicon involved in the processing of linguistic cues (Glaser, 1992). Neuroscientific findings support this idea and suggest that the brain response to images, faces, and words might involve spatially and functionally distinct processes. For example, electrophysiological studies have suggested that while there is a clear facilitation for emotional information at early stages of picture processing, this perceptual advantage might not generalize to verbal information (Hinojosa et al., 2009). Additionally, fMRI studies have observed laterality effects in the neural response to faces and words: For example, Kensinger and Schacter (2006) observed a preferential recruitment of the right amygdala for pictorial stimuli, while Harris et al. (2016) found word-selective regions in the left and face-selective regions in the right fusiform gyrus.

As an alternative to the differentiation between pictorial and verbal information, other authors have proposed semantic knowledge as a unitary system that can be accessed independently of stimulus modality (i.e., pictures or words; Caramazza, 1996). In this model, the presentation of emotional images, faces, and words would trigger a similar neural signature. In support of this possibility, it has been argued that actual neural differences between types of stimuli might be exacerbated in most experimental tasks (Citron, 2012). Images and faces tend to contain more complex perceptual features than word stimuli, which might increase the observed differences between stimuli, in which words elicit weaker effects than images or faces (Citron, 2012). In this vein, Schlochtermeyer et al. (2013) reported comparable neural activity in the lingual gyrus and anterior cingulate cortex during the processing of emotional pictures and words with equivalent perceptual features. How-

ever, contrary to previous studies (e.g., Costafreda et al., 2008), no increased activity for images was observed.

Finally, it has to be noted that differences in the capacity to elicit arousal may also explain some of the distinctions between images, faces, and words: Words might be less capable of yielding emotional reactions when compared with pictures and facial expressions, partly due to a lower arousal level of symbolic stimuli (Hinojosa et al., 2009; but see Bayer and Schacht, 2014). Accordingly, linguistic stimuli (e.g., written words) have been consistently associated with a lower probability of amygdala recruitment (Costafreda et al., 2008). With respect to pictorial stimuli, it has been proposed that contextual (e.g., body and scene) information play a crucial role in the interpretation of facial affect (Aviezer et al., 2012), which, in turn, might suggest an advantage of complex emotional images to elicit arousal in comparison with de-contextualized emotional faces (Keil, 2006). Unfortunately, neuroimaging studies selectively contrasting the presentation of images and faces are scarce. Both stimuli show comparable BOLD activity in the amygdala and in visual areas (Britton et al., 2006; Sabatinelli et al., 2011). Relative to emotional faces, negative images seem to induce greater activity in the occipital cortex (Britton et al., 2006). Conversely, relative to images, negative faces have been associated with an increased activity in the insula, anterior cingulate cortex, and superior temporal gyrus (Britton et al., 2006).

#### **1.3.2. Emotion categories: anger, disgust, fear, and sadness**

Categorical conceptualizations of emotions postulate that affective experience can be classified into a limited number of emotional categories (e.g., Panksepp, 2005). In affective neuroscience, one of the most influential categorical models of emotion was articulated by Paul Ekman, who proposed the existence of six basic and universal emotion categories: anger, disgust, happiness, fear, sadness, and surprise (Ekman et al., 1983; Ekman, 1992). A main assumption of this theory is that basic emotional phenomena can be distinctively defined in terms of physiological signals and antecedent events (Ekman, 1992). Therefore, according to Ekman's theory, different emotion categories should be associated with distinct neural signatures.

Early neuroimaging studies attempted to localize the brain structures that were fundamental for each discrete basic emotion. It was proposed that the amygdala was crucial for fear detection and fear conditioning (LeDoux et al., 1990), while the orbitofrontal cortex was linked with anger-related stimuli (Murphy et al., 2003). However, modern conceptualizations of emotion have challenged the view that emotional categories might be consistently represented in specific brain areas (e.g., Barrett, 2006; Lindquist et al., 2012). In a seminal meta-analysis, Lindquist et al. (2012) reported that areas like the amygdala, the lateral orbitofrontal cortex, and occipital areas were consistently involved across different types of basic emotions (e.g. happiness, fear, or anger). These findings led the authors to discourage the use of locationist approaches to emotion. Instead, following a constructionist approach, they proposed that emotions arise as a result of more basic psychological operations that are not specific to individual emotions. Lindquist et al. (2012) thus provided robust evidence to discard the possibility that individual brain regions are dedicated to single emotions.

Several recent studies have associated emotions with complex patterns of coordinated brain activity (Kragel and LaBar, 2015; Saarimaki et al., 2016; Wager et al., 2015). By departing from locationist approaches towards connectivity-based perspectives of brain function, these studies have shown that emotion categories can be associated with separable patterns of neural activity across broadly distributed cortical and subcortical structures. As an example, Wager et al. (2015) observed that anger-related stimuli and fear-related stimuli were associated with a consistent recruitment of areas ascribed to the cortical dorsal attentional network. The

authors interpreted this association as reflecting neural processes supporting orientation towards external stimuli. On the other hand, disgust was characterized by coactivations in basal ganglia and somatomotor areas, which was proposed to support orientation towards internal perceptions (Wager et al., 2015). The search for neural correlates of emotion categories therefore requires a network- or connectivity perspective.

### 1.3.3. Task instruction: explicit emotional processing, implicit emotional tasks, and passive viewing conditions

In addition to the aforementioned stimuli-related characteristics, the type of instructions in the experimental task can also be assumed to modulate the engagement of neural resources. Affective research usually distinguishes explicit and implicit emotional processes (e.g., Cohen et al., 2015). While explicit emotional processing requires participants to focus on the emotional content of the stimuli (e.g., by labelling the stimuli as “negative” or “neutral”), implicit emotional tasks instruct participants to process a non-emotional aspect of the stimulus (e.g., by identifying the gender of the face or determining if the image was taken indoors or outdoors). Affective features of stimuli are thereby automatically or implicitly evaluated.

Differences between implicit and explicit emotional processing are generally interpreted in accordance with dual-process theories (e.g., Critchley et al., 2000; Hariri et al., 2000), which propose two different pathways of information processing: An automatic, intuitive, experiential, and heuristic pathway in addition to a controlled, conscious, analytic, and systematic one (e.g., Evans, 2008). In implicit emotional conditions, the affective dimension of the stimuli is then processed in a more “automatic” or “bottom-up” manner, while explicit emotional instructions would be related to a more “conscious” and “top-down” processing of affective stimulus features (e.g., Critchley et al., 2000; Scheuerecker et al., 2007). In this vein, neuroimaging studies have shown that, relative to implicit emotional processing, explicit emotional tasks produce greater activity in the middle temporal gyrus (Critchley et al., 2000; Scheuerecker et al., 2007), prefrontal areas (Hariri et al., 2000; Scheuerecker et al., 2007), and fusiform cortex (Habel et al., 2007; Hariri et al., 2000). It is still a matter of debate, however, which type of instruction might yield stronger recruitment of the amygdala. While some studies report greater amygdala activity with the contrast implicit > explicit processing (Critchley et al., 2000; Hariri et al., 2000), other papers have observed opposite effects (Fusar-Poli et al., 2009; Habel et al., 2007).

A third type of instruction widely utilized in emotion research is passive viewing, which does not require participants to perform any type of task. Unfortunately, so far only few studies have compared activity during passive viewing conditions with explicit or implicit emotional instructions. Preliminary results suggest that, relative to explicit emotional tasks, passive viewing might be associated with lower amygdala recruitment (Scheuerecker et al., 2007).

In summary, in addition to participant-related characteristics, different task-related characteristics modulate neural responses to negative stimuli. Therefore, we complemented our general analyses by examining specific neural patterns associated with stimulus type (words, images, or faces), emotion category (anger, disgust, fear, and sadness), and instruction type (explicit or implicit emotion processing and passive viewing).

### 1.4. Methodological overview of meta-analyses

In order to integrate the literature on the processing of negative visual stimuli, we employed a meta-analytical approach. Meta-analyses are essential techniques to determine the convergence of results across independent studies. Activation likelihood esti-

mation (ALE) is a coordinate-based meta-analysis technique that considers spatial coordinates and numbers of participants from neuroimaging studies to model the voxel-wise convergence of results in a whole-brain approach (Turkeltaub et al., 2012).

Adopting a more network-based approach, replicator dynamics can be used to examine functional connectivity between distinct brain regions (Lohmann et al., 2013). Implementing the principle of natural selection, replicator dynamics results in a functional network known as *dominant network*, which is formed by those brain regions that show strong correlations (or co-activations) with all other regions in the network. Importantly, replicator dynamics can be implemented in conjunction with ALE meta-analysis as a mean to assess functional brain connectivity on a meta-analytical level (Neumann et al., 2005).

### 1.5. Aims and hypotheses

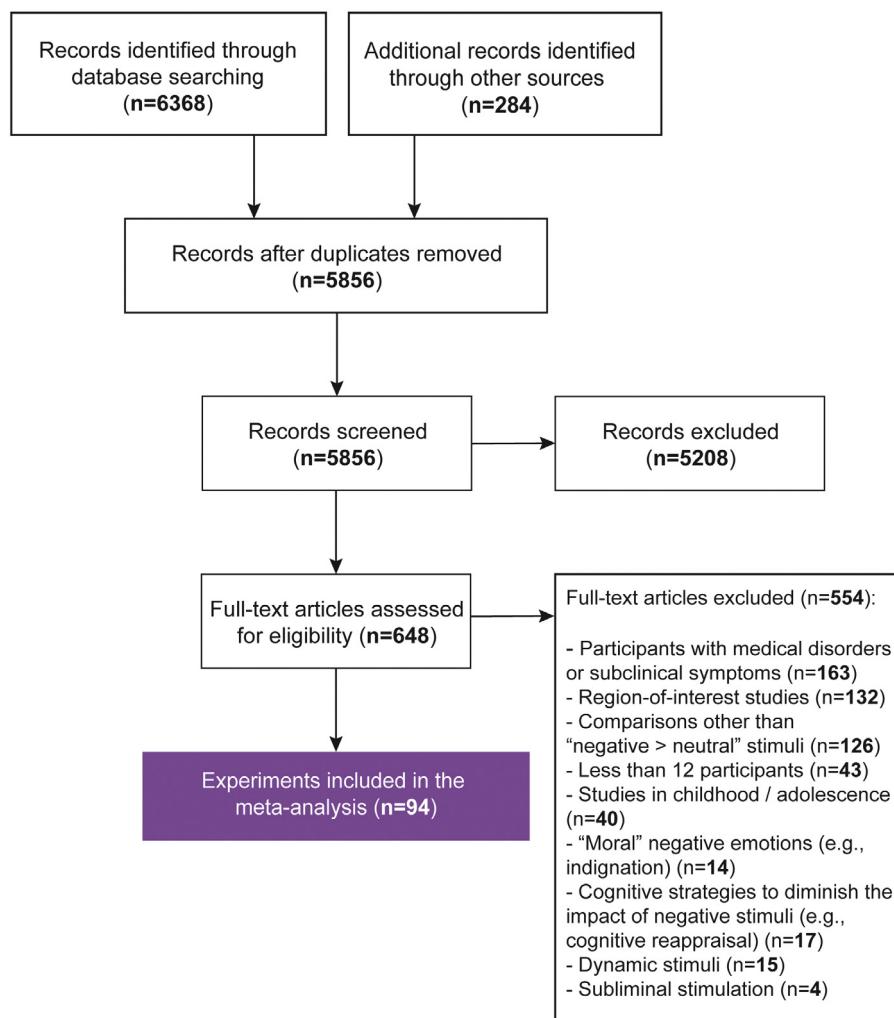
Previous meta-analyses on neuroimaging data have examined the neural correlates of emotional facial expressions (Fusar-Poli et al., 2009), facial emotions and emotive scenes (Sabatinelli et al., 2011), discrete emotional categories (Lindquist et al., 2012), appetitive and aversive stimuli in humans and in animal research (Hayes et al., 2014), positive and negative affective stimuli (Lindquist et al., 2015), and cognitive emotion regulation techniques (Kohn et al., 2013). The need for an objective compilation of different studies on negative visual stimuli leaves scope for the present study. Thus, with the present study we pursue three aims: (i) identify a set of brain regions associated with the perception of negative visual stimuli; (ii) assess the effects of age and sex on the neural processing of these negative visual stimuli; and (iii) disentangle the brain areas that are associated with different stimulus- and task-related characteristics (namely stimulus type, emotional category, and specific task instructions).

Consistent with previous results, we expected to find robust activity in the sensory cortices as well as in multimodal integration centers such as the amygdala, inferior frontal gyrus, and orbitofrontal cortex. We anticipated that differences in age, sex, and stimulus- or task-related characteristics would induce variations in the pattern of brain activity obtained—particularly in the amygdala. More specifically, regarding age, we expected to find a diminished amygdala engagement in older relative to younger participants. With regard to sex, we expected laterality differences, with women more reliably exhibiting activity of the left amygdala, and men more reliably showing engagement of the right amygdala. Finally, considering that previous work has suggested a diminished probability of amygdala activation for words, we also expected to find a less reliable engagement of this structure during the presentation of emotional words.

## 2. Methods

### 2.1. Study selection

We searched for fMRI studies that investigated the processing of negative images, faces and words using PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>). More specifically, we focused on the contrast “negative emotional stimuli > neutral emotional stimuli”. Search terms included combinations of the following: (i) neuroimaging terms: *MRI*, *fMRI*, *brain*, *magnetic resonance*; (ii) stimuli-related terms: *negative*, *unpleasant*, *emotion*, *affect*, *image*, *face*, *word*. Additional articles were collected by manual searches of the bibliographies of the articles retrieved. Inclusion and exclusion criteria are presented in Table 1. Data search and selection was performed by two researchers independently (IGG and JK). Fig. 1 presents an overview of the data selection process.

**Fig. 1.** Flow chart of the data selection process.**Table 1**  
Inclusion and exclusion criteria utilized for the current meta-analysis.

Inclusion criteria	Exclusion criteria
(a) Peer-reviewed original research in English language journals.	(a) Studies in childhood or adolescence (<17 years old).
(b) Healthy adult population.	(b) Participants with medical disorders or subclinical symptoms.
(c) Studying whole-brain fMRI response to negative images, faces or words.	(c) Studies that do not contain a neutral condition
(d) Reporting results in Talairach or MNI space.	(d) Studies including neutral stimuli that are substantially different from the nature of the negative stimuli (e.g., studies contrasting negative faces versus pictures of radios).
(e) Studies reporting the contrast "negative stimuli > neutral stimuli".	(e) Moral negative emotions (e.g., indignation, guilt, or embarrassment).
	(f) Utilization of cognitive strategies that might diminish the impact of the negative stimuli (e.g., studies on emotion regulation).
	(g) Region-of-interest studies.
	(h) n < 12 participants.
	(i) Subliminal stimulation.
	(j) Dynamic stimuli.

## 2.2. Activation likelihood estimation

We examined general effects of negative visual stimulus processing as well as its modulation by task- and participants-related characteristics.

### 2.2.1. General processing of negative visual stimuli

In a first step, we conducted an activation likelihood estimation (ALE) meta-analysis to identify brain regions associated with the processing of negative visual compared with neutral stimuli. ALE meta-analysis was performed using GingerALE v.2.3.3. (<http://www.brainmap.org>). ALE meta-analysis is a method for conducting meta-analyses of neuroimaging data, which focuses on identifying common regions of activation across studies (for a full methodological introduction to ALE see, e.g. [Eickhoff et al., 2012](#); [Turkeltaub et al., 2012](#)). It identifies sets of jointly activated brain regions that are related to the investigated phenomena. In ALE, spatial coordinates are modeled as 3-dimensional Gaussian probability distributions. These probabilities are then combined within and across experiments to produce a whole-brain map of ALE values for each voxel. This empirical ALE map is compared to a null hypothesis map representing the noise distribution. In our analysis, the latter was generated by combining the results of 500 permutations of randomly selected foci, which proved a sufficient number to converge on stable results (i.e., increases in the number of permutations to 1000 and 5000 yielded identical results). Of note, ALE takes

into account the number of subjects in each experiment, such that experiments including a higher number of participants are given a stronger weight in the meta-analysis (Eickhoff et al., 2009). We utilized a non-additive ALE method in order to limit the effect of multiple nearby foci within an experiment (Turkeltaub et al., 2012). For this first overall analysis, results were thresholded at  $p < 0.05$  family-wise error-(FWE)-corrected.

With the resulting pattern, we performed two further analyses: First, we applied replicator dynamics (explained in detail in Section 2.3) in order to determine which brain areas presented the highest number of functional connections with the other areas in the set. Second, we utilized *reverse inference* in order to test for the conceptual validity of our results (Yarkoni et al., 2011). For this, we applied to the obtained ALE map the *decode* function of the Neurosynth database (<http://neurosynth.org>; Yarkoni et al., 2011; as made available via the Neurovault web platform at <http://neurovault.org>; Gorgolewski et al., 2014). The Neurosynth database (version 0.3.0; consulted: 17-08-2015; status: 413429 activations reported in 11406 studies) contains automatically generated meta-analytic maps (activation patterns) for several thousands of psychological concepts, extracted through text-mining techniques (Yarkoni et al., 2011). The *decode* function permits the calculation of voxel-wise Pearson correlations between a given unthresholded functional map (in our case, ALE meta-analysis unthresholded results) and each of the concept-based meta-analysis maps available in the Neurosynth database. This way, the most frequent psychological features associated with a given neural pattern can be identified (Yarkoni et al., 2011).

## 2.2.2. Examination of age-, sex-, and task-related characteristics

We performed comparisons across sub-groups of experiments in order to describe brain patterns associated with different demographic characteristics (i.e., age and sex), and task-related characteristics (i.e., types of stimuli, emotion categories, and task instructions).

Within the ALE framework, conjunction and subtraction analyses facilitate the assessment of commonalities and differences, respectively, between phenomena that were previously investigated in independent imaging studies; such as the use of different task modalities or subject cohorts (Eickhoff et al., 2012). In ALE meta-analysis, conjunctions are assessed by a minimum statistic of images containing the respective significant results (Nichols et al., 2005).

The recommended procedure for performing conjunction and subtraction analyses requires the construction of ALE maps separately for sub-groups of experiments. Here, we decided to follow a conservative strategy in order to avoid false positives due to the relatively small sample sizes in some analyses but, at the same time, to account for the multiple analyses performed in the subtraction analyses. Thus, we constructed individual ALE maps that were initially thresholded at  $p < 0.001$  (uncorrected), and subsequently FWE-corrected at the cluster-level at  $p < 0.05$ . Comparisons across experiments were then performed in a pairwise fashion based on these thresholded ALE maps. Note that for subtraction analyses, a cluster-level inference is not available in Ginger ALE. To account for this, we set the statistical threshold at a conservative  $p < 0.001$  (uncorrected) and added a minimum cluster size criterion of  $100 \text{ mm}^3$  contiguous supra-threshold voxels (Eickhoff et al., 2012). This threshold was chosen as it corresponds to the minimal size determined by the cluster-level inference in most of the individual sub-meta-analyses.

Two further methodological aspects should be considered when interpreting the results of subtraction analyses:

First, Ginger ALE does not facilitate the comparison across more than two conditions. In some cases, we wanted to contrast the effect of three categories (i.e., in the case of stimulus modality: images,

faces and words). To do so, we separated the analyses into multiple pairwise comparisons (i.e., images versus faces, images versus words, faces versus words). We thereby modified the statistical threshold to account for the number of pairwise comparisons using Bonferroni's correction (e.g., having three pairwise comparisons at  $p < 0.001$ ; the final alpha-level was  $0.001/3 = 0.0003$ ).

Second, the current version of Ginger ALE does not implement the possibility of including additional nuisance covariates in the analysis. Age, sex, and task-related characteristics (e.g., the use of a given negative emotion such as anger instead of the utilization of general negative facial stimuli) might impact the results obtained (e.g., Costafreda et al., 2008). In order to correct for the potential effect of demographic and methodological characteristics on the sub-analyses, we matched subgroups of experiments according to their demographic characteristics on a one-to-one basis, and we ensured equivalency across methodological features (see supplementary material Table S1 for a description of all the studies included in the meta-analysis and Table S2 for a list of the experiments matched with the pairing procedure). In other words, we only included in the sub-analyses those pairs of experiments with similar demographic and task-related characteristics. Differences in the average age of the participants across the paired experiments ranged between 0 and 17.98 years, while difference in proportion of females across the experiments ranged between 0 and 30%.

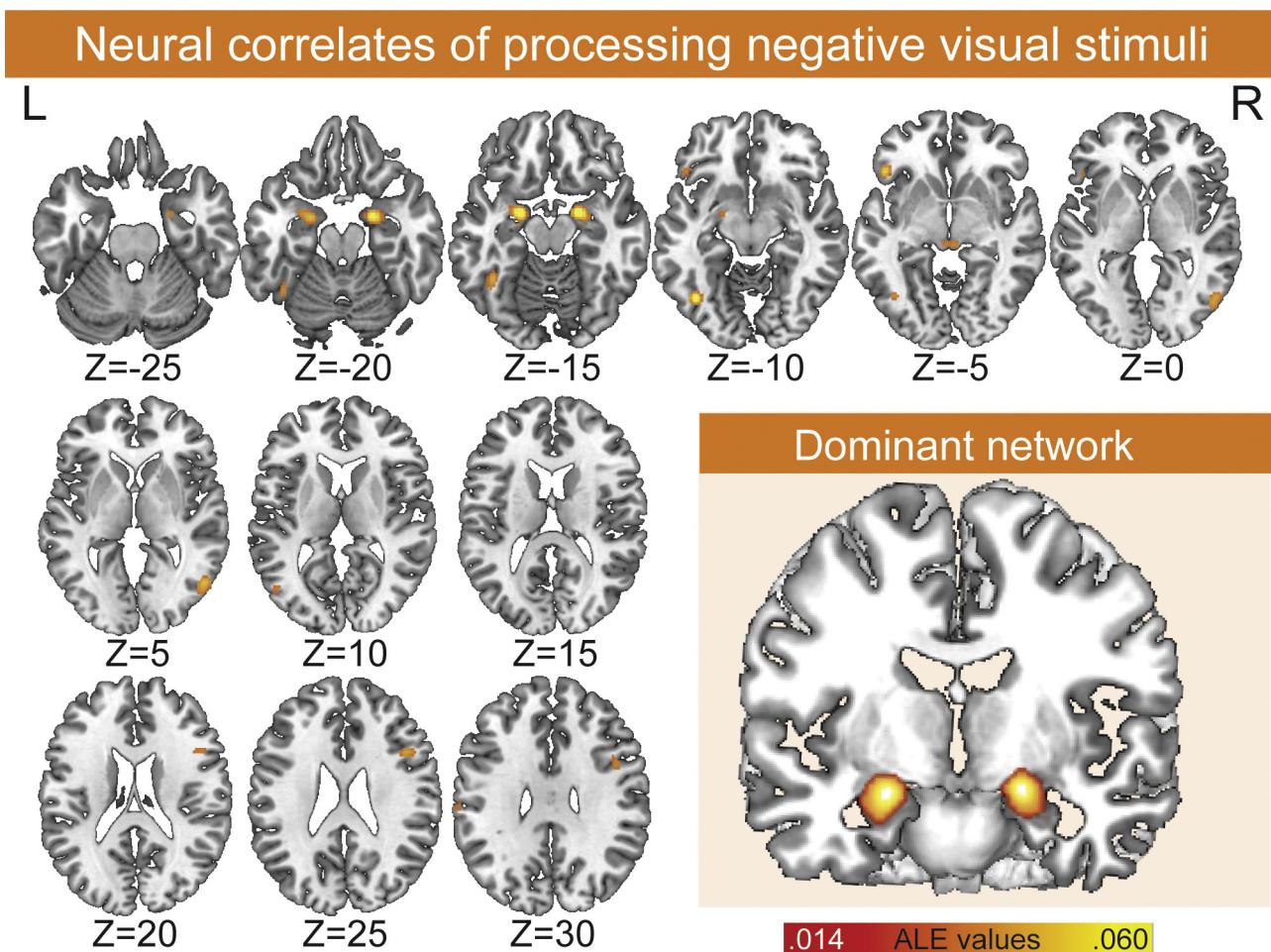
Unfortunately, with this approach, we had to exclude a number of available but unmatched experiments. In the supplement, we specify which studies were included or excluded in each of the sub-analyses. The supplementary material also contains the ALE results obtained for all the experiments that originally fell into each of the sub-group of studies, that is, without matching the experiments on a one-to-one basis (Tables S3–S7).

Concerning demographic characteristics, the majority of studies recruited populations with a broad age range consisting of both female and male participants. However, a sub-set of studies reported coordinates in more homogeneous samples in terms of age and several studies reported results for females or for males only or separately for sexes. Focusing on these studies, we performed age- and sex-specific ALE meta-analyses.

We similarly tested the effect of task-related characteristics, that is, stimulus type (images, faces, and words), emotion category (e.g., disgust-, or fear-related), and task instruction (passive viewing, implicit emotional tasks, and explicit emotional tasks). For each task-related characteristic, we selected pairs of experiments that were equivalent in demographic characteristics and other task-related features.

## 2.3. Replicator dynamics

Replicator dynamics can be used to analyze functional network structures. It identifies scale-free networks of brain activity, in which all elements interact with each other (Lohmann et al., 2013). Here, we applied replicator dynamics to characterize on a meta-analytic level the patterns of functional brain connectivity obtained during the processing of negative events (Neumann et al., 2005). Specifically, after performing ALE meta-analysis, we constructed a coactivation matrix that recorded the number of co-occurrences across the included experiments for each pair of brain regions in the thresholded ALE map. This matrix was then subjected to a replicator process: In an iterative fashion and conceptually based on the principles of natural selection, this process determines a sub-network of brain regions with the property that every region included in the network co-occurs more often than others with every other network member. This way, a *dominant network* consisting of those brain regions that are likely to be most relevant for the investigated phenomenon is identified. Note that the resulting regions can be interpreted as functional hubs, comparable to brain regions that



**Fig. 2.** Brain regions consistently activated by the contrast negative visual stimuli > neutral control stimuli as obtained using ALE meta-analysis ( $p < 0.05$  FWE-corrected). The inset represents the dominant network obtained by replicator dynamics. This network, consisting of bilateral amygdala, is formed by the regions that showed the highest functional connectivity with the other regions in the set. The color scale represents the magnitude of the ALE values, i.e., the consistency across studies.

result, for example, from centrality measures applied to individual fMRI measurements (Lohmann et al., 2013). Methodological details of replicator dynamics and its application in functional imaging meta-analyses are provided by Neumann et al. (2005).

### 3. Results

The literature search retrieved 94 fMRI experiments focusing on the contrast “negative visual stimuli > neutral stimuli” (Fig. 1). These studies were published between November 2000 and June 2015 and included 2226 participants (age 17–84, mean age 30 years; 55% women). Table S1 presents the characteristics of the studies included.

#### 3.1. Effect of all negative visual stimuli

First, we identified brain regions that were reliably associated with the processing of negative visual information. To do so, we jointly analyzed all 94 experiments on the neural responses to images, faces, and written words. Utilizing ALE meta-analysis we observed that the processing of negative visual stimuli produced consistent activation in visual cortices (bilateral fusiform cortex and left lateral occipital cortex), left supramarginal gyrus, brain-stem, bilateral amygdala, left lateral orbitofrontal cortex, and right inferior frontal gyrus. Applying replicator dynamics, we observed that the left and right amygdala presented the highest number of

functional connections with the other regions obtained, thus forming the dominant network (Fig. 2; Table 2).

Finally, by applying reverse inference (Poldrack, 2006), we found that the unthresholded map obtained with ALE meta-analysis presented the highest correlations with the following terms: *faces* ( $r = 0.449$ ); *stimuli* ( $r = 0.438$ ); *neutral* ( $r = 0.434$ ); *face* ( $r = 0.429$ ); *pictures* ( $r = 0.427$ ); *facial* ( $r = 0.423$ ); *emotional* ( $r = 0.415$ ); *amygdala* ( $r = 0.409$ ); *fearful* ( $r = 0.399$ ) and *expressions* ( $r = 0.397$ ).

#### 3.2. Effects of participant-related characteristics

##### 3.2.1. Age effects

We included 8 studies in younger adults (17–31 years old) and 8 studies in older adults (59–84 years old). Groups of experiments were matched by sex distribution (differences in the percentage of females across studies:  $t = -0.047$ ;  $p = 0.963$ ). Studies were also equivalent in task-related characteristics (proportion of studies on images, faces, or words:  $X^2 = 0.343$ ;  $p = 0.843$ ; proportion of studies containing a specific negative emotion such as anger, or disgust:  $X^2 = 1.33$ ;  $p = 0.513$ ; proportion of studies using attentional tasks, explicit emotional processing, passive viewing tasks or other instructions:  $X^2 = 1.200$ ;  $p = 0.753$ ).

In younger participants, negative stimuli elicited activation in the medial frontal pole, right inferior frontal gyrus, left amygdala, left lateral occipital cortex, and right temporal occipital fusiform cortex. In older participants, activation was found in the right inferior temporal gyrus, left inferior frontal gyrus, and right superior

**Table 2**

Neural activation in response to negative stimuli &gt; neutral stimuli.

Size (mm <sup>3</sup> )	MNI coordinates			ALE values	Replicator dynamics	Anatomical Location
	X	Y	Z			
1328	20	-4	-16	0.0656	0.5000*	Right amygdala
1208	-22	-4	-16	0.0648	0.5000*	Left amygdala
952	52	-66	2	0.0493	6.510e-26	Left lateral orbitofrontal cortex
736	44	16	24	0.0450	6.404e-36	Right inferior frontal gyrus
584	-40	-66	-10	0.0493	7.0636e-36	Left occipital fusiform cortex
560	-40	-50	-16	0.0457	4.9722e-12	Left temporal occipital fusiform cortex
552	-48	26	-6	0.0521	2.7407e-48	Left lateral orbitofrontal cortex
240	4	-28	-6	0.0415	1.2328e-96	Brainstem
200	-48	-70	8	0.0423	0	Left lateral occipital cortex
120	-64	-24	32	0.0391	0	Left supramarginal gyrus

Abbreviations: ALE, activation likelihood estimation; MNI, Montreal Neurological Institute.

Notes: 94 contributing experiments; sample size = 2234 foci = 1009.

p &lt; 0.05 FWE-corrected.

Replicator dynamics: 96 iterations.

**Table 3**

Age influences on the neural processing of negative visual information.

Size (mm <sup>3</sup> )	MNI coordinates			ALE value	Anatomical Location		
	X	Y	Z				
Younger adults (17–31 years)							
Eight contributing experiments; sample size = 150; foci = 96.							
784	8	60	26	0.0141	Medial frontal pole		
688	52	34	6	0.0141	Right inferior frontal gyrus		
656	48	18	22	0.0161	Right inferior frontal gyrus		
432	-20	-4	-12	0.0161	Left amygdala		
424	-40	-68	-12	0.0146	Left lateral occipital cortex		
424	44	-52	-12	0.0137	Right temporal occipital fusiform		
Older adults (59–84 years)							
Eight contributing experiments; sample size = 134; foci = 57.							
Statistical threshold: initial p < 0.001 uncorrected and additional cluster-level FWE correction for multiple comparisons at p < 0.05.							
504	48	-44	-20	0.0138	Right inferior temporal gyrus		
424	-40	20	22	0.0126	Left inferior frontal gyrus		
264	20	-52	44	0.0095	Right superior parietal lobule		
Conjunction analysis (younger and older adults)							
No results							
Subtraction analysis (younger and older adults)							
ALE meta-analysis: p < 0.001 uncorrected; minimum cluster size = 100 mm <sup>3</sup>							
No results							
ALE, activation likelihood estimation; MNI, Montreal Neurological Institute.							

parietal lobule. The conjunction and subtraction analyses did not reveal significant results (Table 3; Fig. 3).

### 3.2.2. Sex differences

Regarding sex differences, we included 7 studies in women and 7 studies in men, matched by age of the participants (group differences in mean age across studies:  $t = -0.436$ ;  $p = 0.671$ ). Groups of experiments were equivalent in task-related characteristics (proportion of studies on images, faces, or words:  $\chi^2 = 0$ ;  $p = 1$ ; proportion of studies containing a specific negative emotion such as anger or disgust:  $\chi^2 = 1.95$ ;  $p = 0.744$ ; proportion of studies using attentional tasks, explicit emotional processing, passive viewing tasks or other instructions:  $\chi^2 = 1.200$ ;  $p = 0.753$ ).

In women, negative stimuli yielded activation in the bilateral amygdala, lateral occipital cortex, left frontal operculum, and left temporal occipital fusiform cortex. For men, we found consistent activity in the right amygdala, anterior medial prefrontal cortex, right temporal pole, and left thalamus. The conjunction analysis showed that a cluster in the right amygdala was consistently involved in the processing of negative stimuli across sexes. The subtraction analysis did not show any cluster repre-

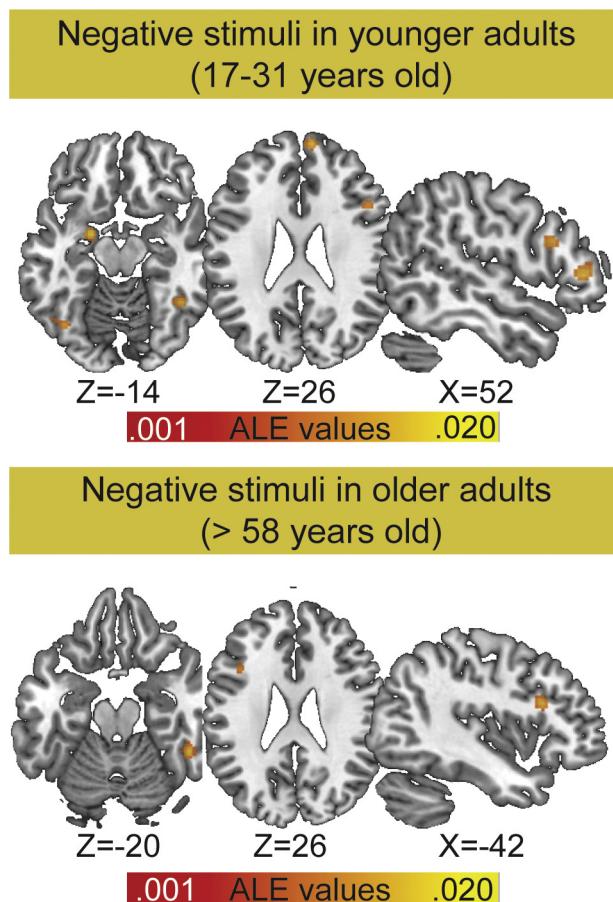
senting statistically significant differences between sexes (Table 4; Fig. 4).

### 3.3. Effects of task-related characteristics

#### 3.3.1. Stimulus type (images, faces, or words)

The examination of stimulus type (images, faces, or words) included 12 experiments on negative images, 12 experiments on negative faces, and 12 studies on negative words. Experiments were matched for age and gender distribution (group differences in mean age:  $F = 0.010$ ;  $p = 0.990$ ; group differences in the percentage of females:  $F = 0.071$ ;  $p = 0.932$ ). Additionally, experiments were equivalent in the proportion of emotion categories utilized ( $\chi^2 = 9.804$ ;  $p = 0.275$ ) and in the task instructions that were used ( $\chi^2 = 3.667$ ;  $p = 0.722$ ).

Negative images were associated with consistent activity in the right inferior frontal gyrus, right lateral occipital cortex, right amygdala, medial frontal pole, and juxtapositional cortex (supplementary motor area). Negative faces were associated with activity in the right amygdala, left lateral occipital and temporal occipital fusiform cortex, left lateral orbitofrontal cortex, right lateral



**Fig. 3.** Neural processing of negative visual stimuli for younger adults (17–31 years) and older adults (59–84 years). Individual maps were thresholded at  $p < 0.001$  (uncorrected) with subsequent cluster-level FWE-correction at  $p < 0.05$ . The color scale represents the magnitude of the ALE values, i.e., the consistency across studies.

occipital cortex, left occipital pole and left putamen. Finally, negative words triggered consistent activity in the precuneus, right precentral gyrus, and anterior cingulate cortex. Conjunction analyses showed that both negative images and negative faces produced similar activity in the right amygdala. Our analyses did not detect overlapping brain activity between images and words, or between faces and words. Subtraction analyses revealed that, relative to words, both negative images and negative faces were more likely to yield activation in the right lateral occipital cortex. Additionally, relative to negative words, negative images were associated with a more reliable activity in the right amygdala. We did not find differences between images and faces. (Table 5; Figs. 5 and 6).

### 3.3.2. Discrete emotion categories (disgust and fear)

Fourteen experiments in disgust were matched by age and sex distribution with fourteen experiments in fear (differences in the mean age across studies:  $t = -0.218$ ;  $p = 0.829$ ; differences in the mean percentage of females across studies:  $t = 0.243$ ;  $p = 0.810$ ). Experiments were identical in the proportion of studies using images, faces, or words ( $X^2 = 0$ ;  $p = 1$ ) and comparable in task instructions ( $X^2 = 0.867$ ;  $p = 0.833$ ). The low number of studies available using sadness-related stimuli and the absence of experiments using anger-related images or words impeded the inclusion of these categories into the analyses.

Disgust-related stimuli elicited consistent activity in the left lateral orbitofrontal cortex, occipital pole, left inferior temporal gyrus, left supramarginal gyrus, superior frontal gyrus, and left inferior frontal gyrus. Fear-related stimuli were associated with activity in

the lateral occipital cortex, lateral frontal pole, left amygdala, and brainstem. No significant results emerged in the conjunction and subtraction analyses (Table 6; Fig. 7).

### 3.3.3. Type of task instruction (passive viewing tasks, implicit emotional tasks, and explicit emotional tasks)

We compared 15 experiments with an implicit emotional task (e.g., determination of the gender of a given face), 15 studies that required the participants to explicitly process emotions, and 15 experiments with passive viewing instructions. Groups of experiments were matched for age and gender distribution (differences in the mean age across studies:  $F = 0.031$ ;  $p = 0.972$ ; differences in the percentage of females across studies:  $F = 0.009$ ;  $p = 0.991$ ). Experiments were equivalent in the use of images, faces, and words ( $X^2 = 0.209$ ;  $p = 0.994$ ), as well as in the utilization of different negative emotional categories, such as anger or fear ( $X^2 = 4.361$ ;  $p = 0.823$ ).

Implicit emotional processing tasks were associated with activity in the amygdala, left temporal occipital fusiform, right cerebellum, right inferior frontal gyrus, left lateral orbitofrontal cortex, left precentral gyrus, right lateral occipital cortex, and lingual gyrus. Explicit emotional tasks elicited brain activity in the left postcentral gyrus, paracingulate gyrus, right amygdala, right precentral gyrus, and left superior parietal lobule. Finally, passive viewing tasks involved activation in the lateral occipital cortex, right temporal occipital fusiform, left amygdala, right parahippocampal gyrus, medial frontal pole, right inferior temporal gyrus, and medial superior frontal gyrus.

The conjunction analyses showed overlapping activity between implicit emotional tasks and passive viewing conditions in the amygdala and left temporal occipital fusiform cortex. We did not find overlapping clusters between explicit and implicit emotional tasks or between explicit emotional and passive viewing tasks. In the subtraction analysis, explicit emotional tasks, relative to passive viewing tasks, were more likely to be associated with activity in the paracingulate cortex. The other pairwise comparisons did not yield results (Table 7, Figs. 8 and 9).

### 3.4. Additional analysis: contrasting “negative $\geq$ positive” stimuli

In the present paper, we have mainly focused on the contrast between negative and neutral stimulation. This comparison, however, does not allow discerning whether the results represent general emotional processing or whether they are specific for negative stimulation. While future studies should address this issue in depth, here we have included an analysis of studies reporting the contrast “negative  $\geq$  positive” stimuli. For this additional analysis, ten studies were included (Table S8). The mean age across studies was 29.52 (age range between 18 and 72 years old) and the average percentage of female participants was 59%. With regards to task-related characteristics, 2 studies were conducted with images, 6 studies used faces, and 2 studies presented words. While 4 studies were conducted on general negative/positive emotions, 6 studies focused on specific emotions (e.g., happy, fearful, or sad). Finally, 3 studies employed implicit emotional tasks, 2 studies gave explicit emotional instructions, 3 studies utilized passive viewing instructions, and 2 studies gave another type of instruction (e.g., “imagine that you are in the situation described by the following words”) (Table 8; Fig. 10).

Relative to positive stimuli, negative stimuli elicited activity in the brainstem, right temporal pole, and left inferior temporal gyrus.

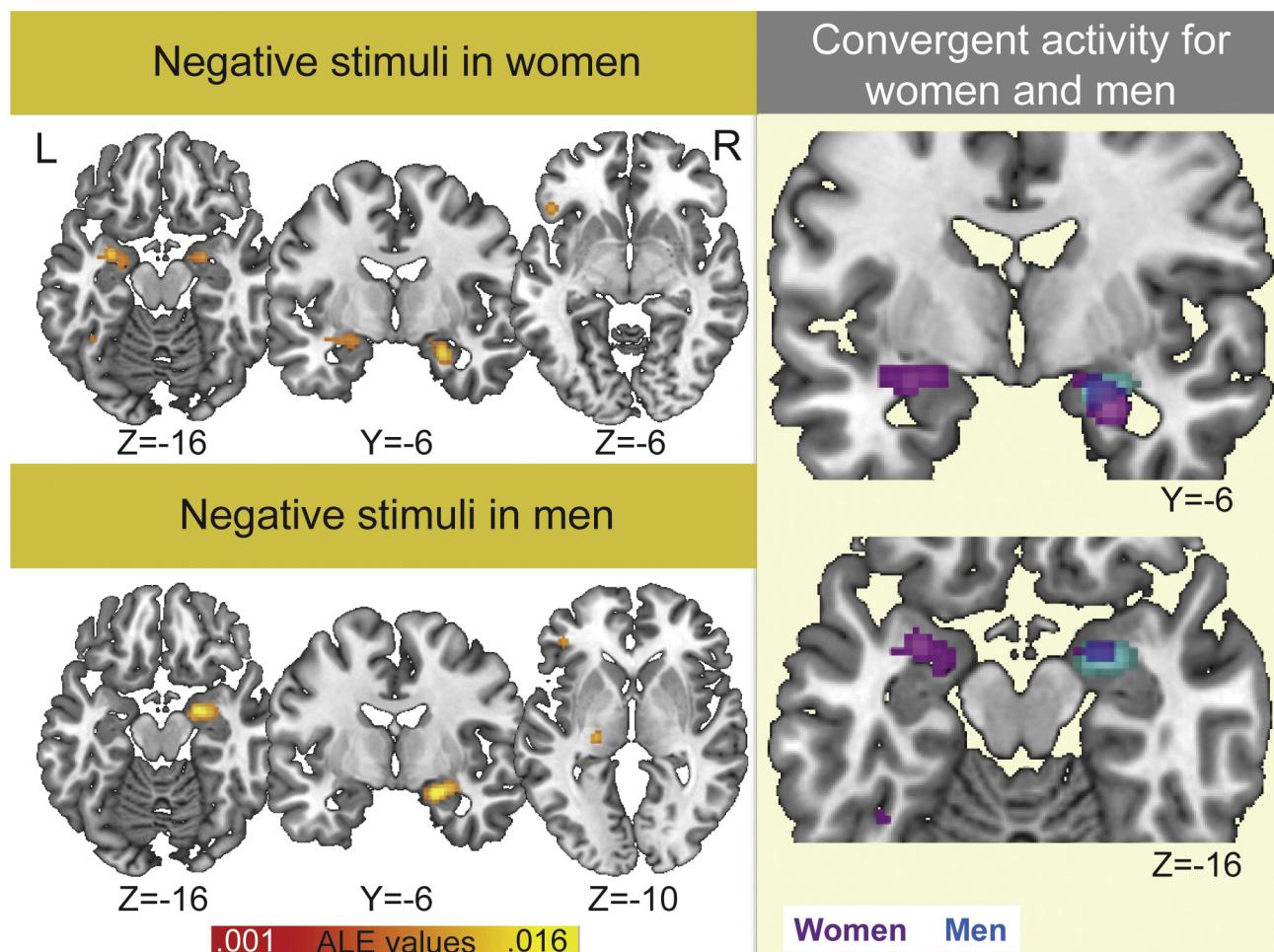
## 4. Discussion

The present study sought to integrate the existing literature on functional brain patterns associated with the processing of nega-

**Table 4**

Sex differences in the neural processing of negative visual information.

Size (mm <sup>3</sup> )	MNI coordinates			ALE value	Anatomical Location		
	X	Y	Z				
<b>Women</b>							
Seven contributing experiments; sample size = 150; foci = 79.							
Statistical threshold: initial p < 0.001 uncorrected and additional cluster-level FWE correction for multiple comparisons at p < 0.05.							
848	24	-4	-22	0.0165	Right amygdala		
776	-30	-2	-16	0.0133	Left amygdala		
392	-44	-78	-12	0.0134	Left lateral occipital cortex		
320	-46	24	-4	0.0120	Left frontal operculum		
168	-40	-50	-18	0.0095	Left temporal occipital fusiform		
152	54	-72	2	0.0096	Right lateral occipital cortex		
<b>Men</b>							
Seven contributing experiments; sample size = 148; foci = 126.							
Statistical threshold: initial p < 0.001 uncorrected and additional cluster-level FWE correction for multiple comparisons at p < 0.05.							
1064	22	-6	-18	0.0165	Right amygdala		
424	-4	64	26	0.0145	Medial frontal pole		
304	46	10	-24	0.0111	Right temporal pole		
264	-22	-22	0	0.0121	Left thalamus		
264	-42	38	2	0.0125	Left lateral frontal pole		
Conjunction analysis (women and men)							
344	22	-4	-18	0.0142	Right amygdala		
Subtraction analyses (women and men)							
ALE meta-analysis: p < 0.001 uncorrected; minimum cluster size = 100 mm <sup>3</sup>							
No results							
ALE, activation likelihood estimation; MNI, Montreal Neurological Institute							

**Fig. 4.** Neural processing of negative visual events for women and men. Individual maps were thresholded at p < 0.001 (uncorrected) with subsequent cluster-level FWE-correction at p < 0.05.

**Table 5**

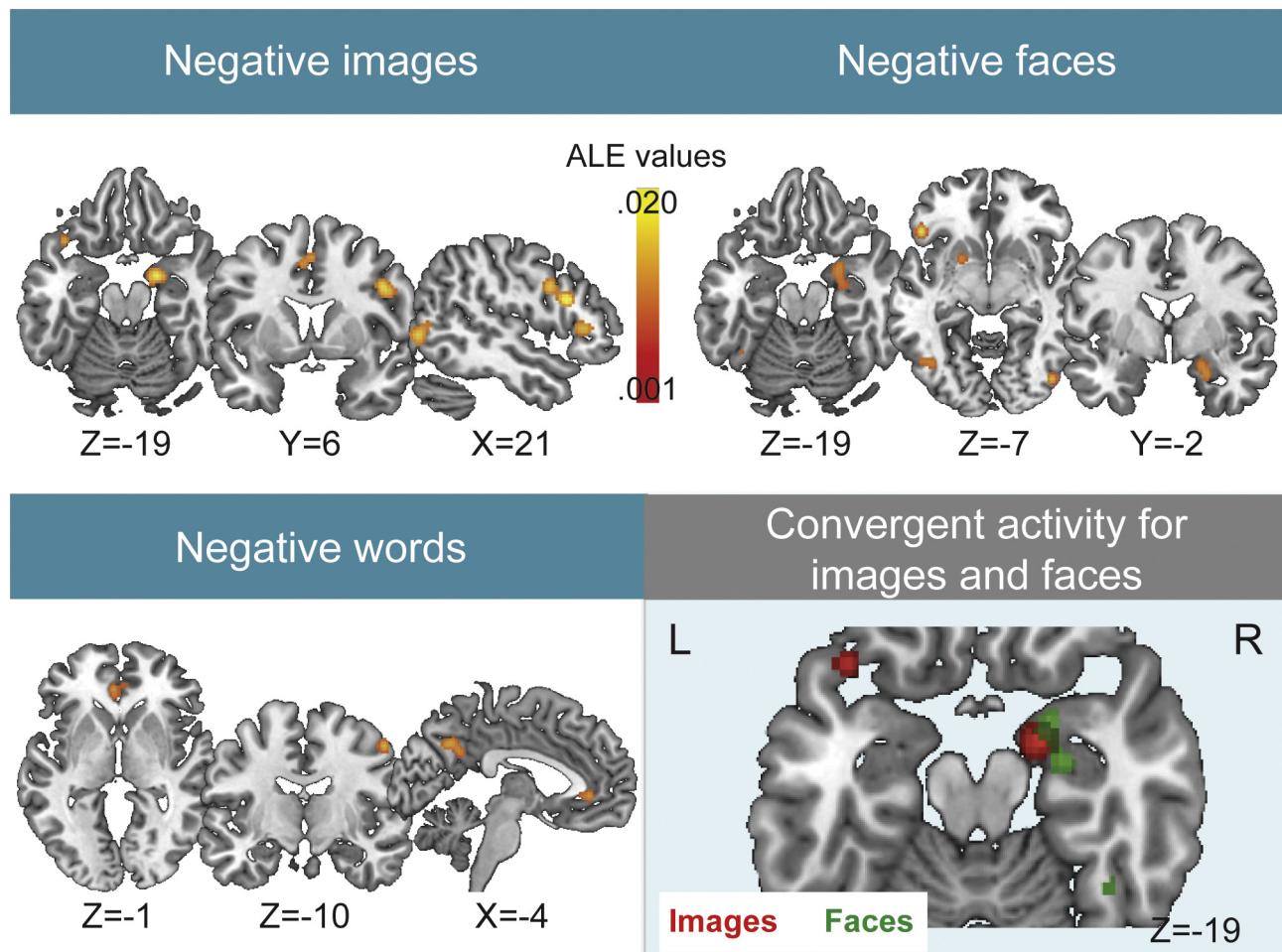
Neural activity associated with different types of negative visual stimuli.

Size (mm <sup>3</sup> )	MNI coordinates			ALE value	Anatomical Location		
	X	Y	Z				
<b>Negative images</b>							
Twelve contributing experiments; sample size = 317; foci = 166. Statistical threshold: initial p < 0.001 uncorrected and additional cluster-level FWE correction for multiple comparisons at p < 0.05.							
1800	50	18	22	0.0213	Right inferior frontal gyrus		
1296	50	-72	2	0.0163	Right lateral occipital cortex		
1216	20	-4	-18	0.0196	Right amygdala		
1072	50	30	4	0.0175	Right inferior frontal gyrus		
864	-4	66	26	0.0150	Medial frontal pole		
440	0	6	50	0.0128	Bilateral juxtapositional cortex		
376	-40	20	-18	0.0164	Left lateral orbitofrontal cortex		
<b>Negative faces</b>							
Twelve contributing experiments; sample size = 229; foci = 112. Statistical threshold: initial p < 0.001 uncorrected and additional cluster-level FWE correction for multiple comparisons at p < 0.05.							
1160	22	0	-20	0.0120	Right amygdala		
784	-40	-66	-10	0.0139	Left lateral occipital fusiform cortex		
688	-48	26	-8	0.0172	Left lateral orbitofrontal cortex		
576	44	-78	-8	0.0147	Right lateral occipital cortex		
352	-40	-54	-24	0.0154	Left temporal occipital fusiform cortex		
352	-26	-92	4	0.0132	Left occipital pole		
320	42	-48	-14	0.0118	Right temporal occipital fusiform cortex		
272	-20	6	-8	0.0115	Left putamen		
<b>Negative words</b>							
Twelve contributing experiments; sample size = 234; foci = 105. Statistical threshold: initial p < 0.001 uncorrected and additional cluster-level FWE correction for multiple comparisons at p < 0.05.							
1128	-4	-60	36	0.0133	Bilateral precuneus		
480	52	-10	50	0.0142	Right precentral gyrus		
464	-4	38	-2	0.0128	Bilateral anterior cingulate cortex		
<b>Conjunction analyses</b>							
Negative images and negative faces							
496	22	-2	-20	0.0120	Right amygdala		
Negative images and negative words							
No results							
Negative faces and negative words							
No results							
<b>Subtraction analyses</b>							
Statistical threshold for each pairwise comparison: p < 0.00033 uncorrected (3 pairwise comparisons at p < 0.001). Minimum cluster size = 100 mm <sup>3</sup>							
Negative images versus negative words:							
Negative images > Negative words							
1296	51	-71	2	3.090	Right lateral occipital cortex		
640	18	-3	-19	3.090	Right amygdala		
Negative faces versus negative words:							
Negative faces > negative words							
360	45	-78	-8	3.090	Right lateral occipital cortex		
Negative images versus negative faces:							
No results							
ALE, activation likelihood estimation; MNI, Montreal Neurological Institute							

tive visual stimuli in healthy adults. We identified a set of brain regions associated with sensory, attentional, and emotional mechanisms that robustly respond to negative visual stimuli. Amongst these regions, the bilateral amygdala exhibited the highest functional connectivity. This result suggests that this structure plays a central role in the processing of negative visual information. Additionally, we describe the correlates of processing negative visual information independently for different sub-categories of studies – across different age ranges, sexes, and task-related characteristics (stimulus types, emotion categories, and task instructions). Together, our results delineate a set of brain regions and functional circuits that may serve as neurobiological underpinnings of the processing of negative information. Our findings thus practically inform experimentation in the affective neurosciences and suggest candidate regions for examining the neural correlates of affective symptomatology.

#### 4.1. Brain correlates of processing negative affective visual stimuli

We identified a set of brain regions consistently associated with the processing of negative relative to neutral visual stimuli. These regions encompass visual cortices, left supramarginal gyrus, brainstem (including the superior colliculi, according to the Duvernoy's atlas of the human brain stem: Naidich et al., 2009), bilateral amygdala, left lateral orbitofrontal cortex, and right inferior frontal gyrus. The pattern obtained was associated with content-relevant psychological terms like "emotional", "fearful", and "expressions", as shown by the reverse inference analysis using Neurosynth. Additionally, we identified left and right amygdala as the brain regions with the highest co-activity (i.e., functional connectivity). The amygdala has been considered a convergence zone for highly processed sensory information (Pessoa and Adolphs, 2010). The amygdala receives inputs from the sensory cortices (Phelps, 2006), with its basolateral complex presenting reciprocal connec-



**Fig. 5.** Neural processing of negative images, faces, and words. Individual maps were thresholded at  $p < 0.001$  (uncorrected) with subsequent cluster-level FWE-correction at  $p < 0.05$ . The color scale represents the magnitude of the ALE values, i.e., the consistency across studies.

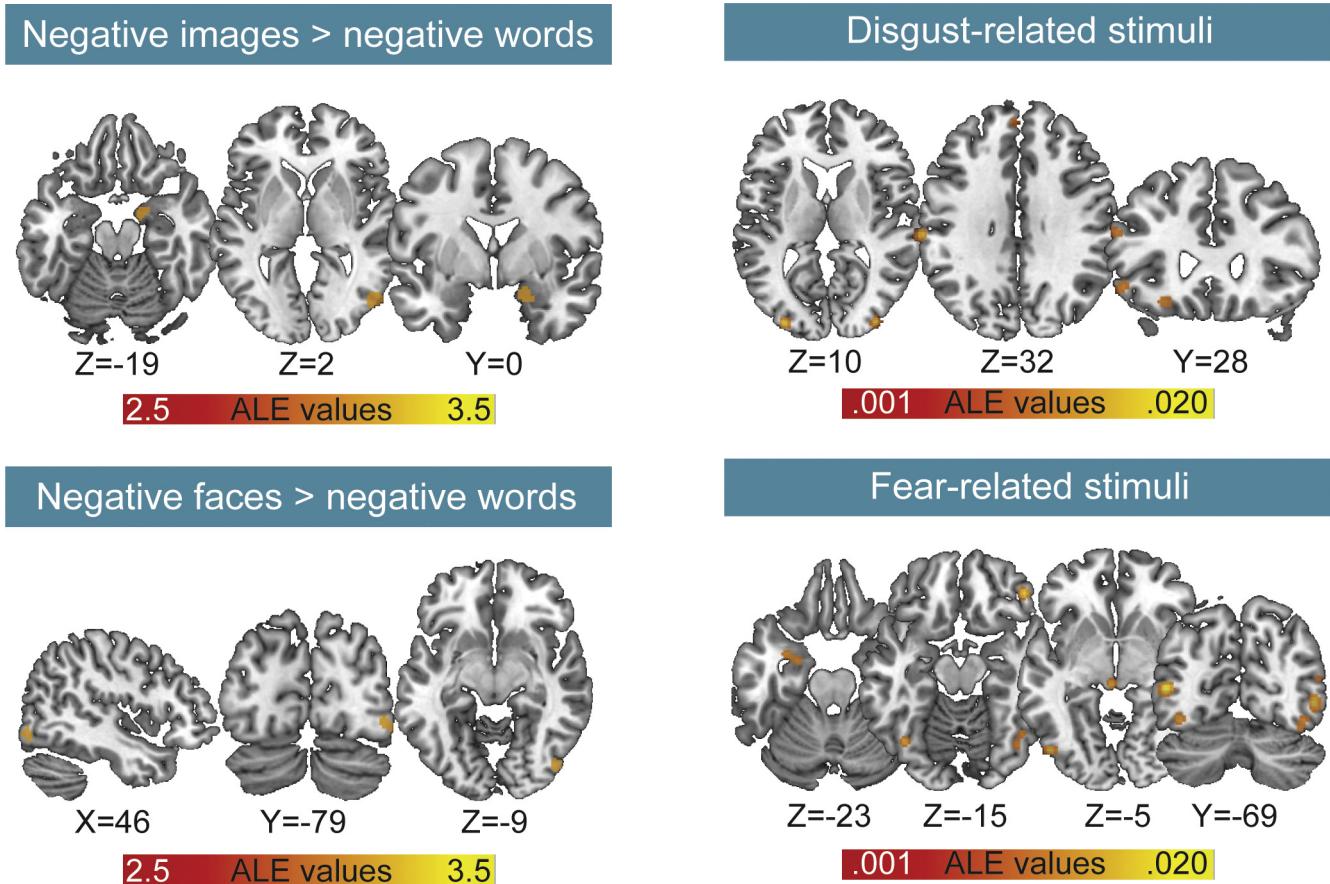
tions with sensory association areas (Janak and Tye, 2015). Animal studies have described direct colliculus-thalamo-amygdala connections, which would allow the organisms to react rapidly in response to danger (Phelps and LeDoux, 2005). However, the presence of these direct connections in humans is so far inconclusive (cf. ; Pessoa and Adolphs, 2010; Tamietto and de Gelder, 2010). Functional neuroimaging studies have also shown the existence of strong functional coupling between the amygdala and the inferior frontal gyrus (Bzdok et al., 2013), as well as extensive structural connections between the amygdala and the orbitofrontal cortex (Haber and Knutson, 2010).

Thus, according to the multiple-waves model, the role of the amygdala in the processing of visual emotional stimuli might stem from its distributed connectivity across cortical and subcortical brain areas (Pessoa and Adolphs, 2010). Researchers have emphasized the participation of amygdala circuits in several aspects of emotional processing. Different theoretical models on the effects of salience on attentional processing – e.g., the MAGiC model (Pourtois et al., 2013) or the BANE model (Markovic et al., 2014) – highlight the role of the amygdala in facilitating attentional and perceptual mechanisms in response to salient events (see also Vuilleumier 2005). The amygdala has also been associated with the acquisition and storage of fear conditioning (Phelps and LeDoux 2005). In fact, both the BANE (Markovic et al., 2014) and the GANE model (Mather et al., 2015) propose an important role of norepinephrine signaling in the amygdala in the enhancement of memory consolidation in response to salient events. Our findings endorse the

central function of the amygdaloid complex in the processing of negative visual stimuli. The pivotal role played by this structure and by its functional connections may reflect its contribution to a number of perceptual, attentional, cognitive, and emotional mechanisms associated with the processing of negative visual stimuli.

In agreement with the aim of the study – to examine which brain areas are responsive to negative affective stimuli – we selected the relation “negative stimuli  $\geq$  neutral stimuli” as contrast of interest. This contrast has two important advantages. First, it should be suitable to reflect brain activity driven by the emotional load of the stimuli. Second, it provides an adequate control of stimuli-related characteristics that could act as confounding variables. However, an important caveat of this contrast is the impossibility to disentangle which regions might be more reliably associated with negative rather than with pleasant or positive stimulation. To address this last point, we additionally included an examination of the differences between negative and positive stimuli. We observed that, relative to positive stimuli, negative stimuli reliably engaged the brainstem, right temporal pole, and left inferior temporal gyrus.

Previous meta-analyses have revolved around the comparison between positive and negative stimuli (Lindquist et al., 2015) or appetitive and aversive events (Hayes et al., 2014). These studies have highlighted the existence of a number of brain regions – including the amygdala, anterior insula/inferior frontal gyrus – that signal the detection of both pleasant and unpleasant events. Furthermore, the meta-analysis by Lindquist et al. (2015) found little evidence for areas showing clear preferences for positive or



**Fig. 6.** Results of the subtraction analyses across different types of negative visual stimuli (images, faces, and words). Results were thresholded at  $p < 0.001$  (uncorrected) with an additional criterion of minimum cluster size  $>100 \text{ mm}^3$ . The color scale represents the magnitude of the ALE values, i.e., the consistency across studies.

negative information, with only one region in the rostral anterior cingulate cortex/medial prefrontal cortex exhibiting greater engagement during positive versus negative stimuli. Together with these findings, our results call for caution in the interpretation of the pattern obtained for negative relative than neutral stimuli, since it is possible that several of the brain areas that we report signal general emotional processes rather than being preferentially ascribed to the processing of negative events.

#### 4.2. The effect of age on the neural processing of negative events

Normal aging processes induce changes in the structure and the functionality of widespread regions in the brain. Frontal, striatal, and temporal structures might be particularly vulnerable to suffer structural brain changes with age (Fjell et al., 2013; Smith et al., 2007). Additionally, neuroimaging studies have reported age-related connectivity changes in large-scale functional networks, such as the default mode network or the dorsal attention network (e.g., Tomasi and Volkow, 2012).

Aging, therefore, might be associated with modifications in the neural processing of negative events. As such, in the present study, we included an examination of studies conducted on younger and older adults separately. In contrast to our hypothesis, we did not find statistical differences between younger and older participants in the processing of negative emotional stimuli. Additionally, none of the brain areas obtained in younger participants overlapped with the pattern obtained for older adults. The inferior frontal gyrus, on the other hand, was activated in both age groups, with younger

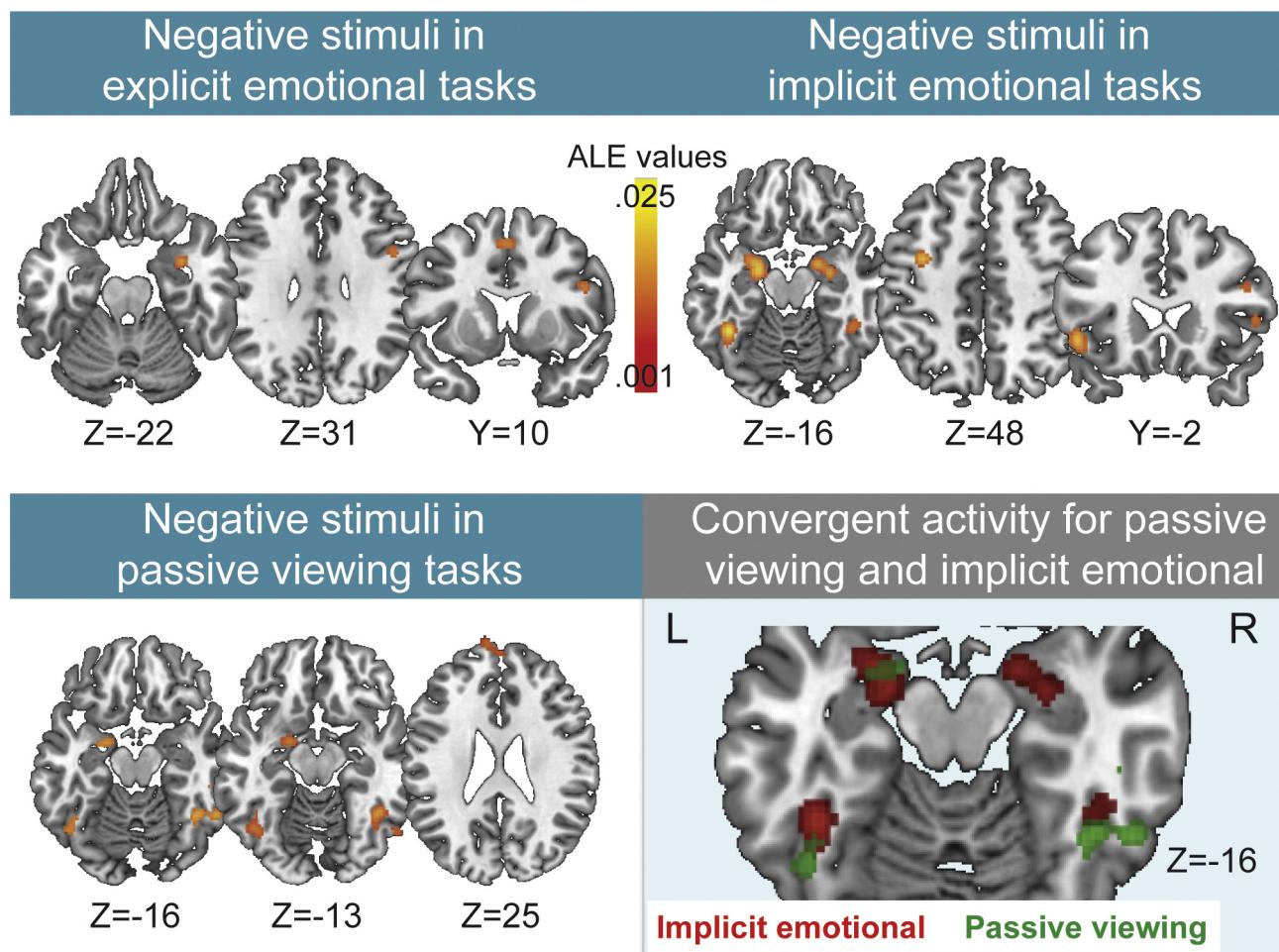
**Fig. 7.** Neural processing of disgust-related stimuli and fear-related stimuli. Individual maps were thresholded at  $p < 0.001$  (uncorrected) with subsequent cluster-level FWE-correction at  $p < 0.05$ . The color scale represents the magnitude of the ALE values, i.e., the consistency across studies.

participants presenting robust activity in its right side, and with older adults exhibiting an engagement of the left side.

Aging theories have proposed the existence of functional changes in response to negative emotional stimuli. According to the socio-emotional selective theory, aging is associated with decreased activity in the amygdala and increased activity in cognitive control areas in response to negative stimuli, reflecting a differential allocation of cognitive resources between younger and older participants (e.g., Mather and Carstensen, 2005). According to the aging brain model, age is related to a decrease in general amygdala function in older participants (Cacioppo et al., 2011). The lack of differences between groups in our meta-analysis does not support either of these theories. However, it may well be that subtle functional differences can be captured in future studies or meta-analysis with higher sample sizes.

Another consideration is whether the contrast between negative and positive stimuli might prove more sensitive for detecting age-related differences. The socio-emotional selectivity theory highlights that healthy older adults exhibit preferences for positive information together with diminished processing of negative information (Carstensen, 2006). In fact, compared with younger participants, older adults seem to exhibit diminished activation in areas comprising the amygdala, fusiform gyrus, and cerebellum during negative relative to positive stimuli (Leclerc and Kensinger, 2011).

Delineating which areas are responsible for the processing of negative information in healthy aging can provide relevant *a priori* information for the evaluation of patients with late-life anxiety or depressive symptoms. Neuroimaging studies on elderly partic-

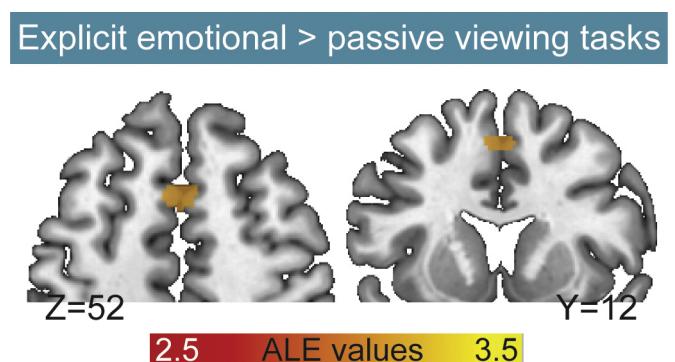


**Fig. 8.** Neural processing of explicit emotional tasks, implicit emotional tasks, and passive viewing stimuli. Individual maps were thresholded at  $p < 0.001$  (uncorrected) with subsequent cluster-level FWE-correction at  $p < 0.05$ . The color scale represents the magnitude of the ALE values, i.e., the consistency across studies.

ipants with affective symptomatology are scarce. However, they point to the direction that, in these participants, the ability to adequately engage the prefrontal cortex in response to negative events might be compromised. As such, relative to healthy senior participants, patients with late-life affective disorders present lower activity in the anterior cingulate cortex (Brassen et al., 2012; Brassen et al., 2008), left inferior frontal gyrus, and right superior frontal gyrus (Price et al., 2011). In particular, alterations in the inferior frontal gyrus in patients with late-life anxiety disorders have been suggested to reflect deficits in top-down regulation of negative affect (Price et al., 2011). Our findings confirm that, in healthy older adults, the left inferior frontal gyrus is reliably recruited during the processing of negative relative to neutral emotional stimuli. It could be speculated that the engagement of this area might be associated with adequate attentional processes towards affective stimuli in healthy aging (Leclerc and Kensinger, 2008). As such, together with previous studies on late-life affective symptomatology, our findings highlight this area as an important candidate region for further studies in the affective neuroscience in aging.

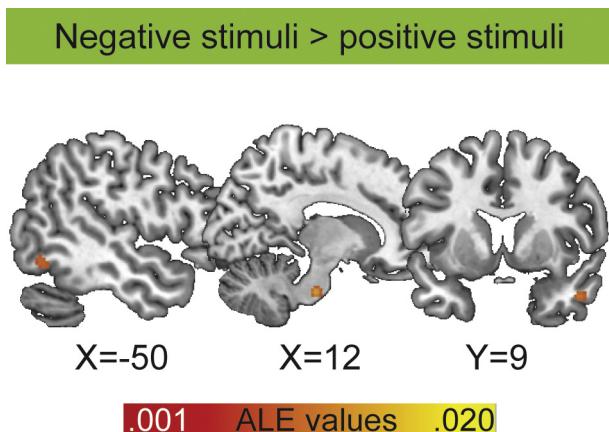
#### 4.3. Sex-related effects on the neural processing of negative events

Neuroimaging studies have suggested the existence of sex-related differences in the brain. For instance, studies on structural connectivity have reported an effect of sex on white matter integrity, especially in the corpus callosum, with men exhibiting a



**Fig. 9.** Results of the subtraction analyses across different types of task instructions (implicit emotional tasks, and passive viewing stimuli). Results were thresholded at  $p < 0.001$  (uncorrected) with an additional criterion of minimum cluster size  $>100 \text{ mm}^3$ . The color scale represents the magnitude of the ALE values, i.e., the consistency across studies.

higher overall fractional anisotropy than women (Gong et al., 2011). In the present study, we obtained the patterns of brain activity for negative stimuli separately for sexes, and performed conjunction and subtraction analyses. Our findings suggest that the results obtained in women and in men present robust similarities. Specifically, we found that an extended cluster in the right amygdala was consistently involved in the processing of negative stimuli in



**Fig. 10.** Brain regions consistently activated by the additional contrast "negative visual stimuli > positive stimuli" as obtained using ALE meta-analysis. ALE maps were thresholded at  $p < 0.001$  (uncorrected) with subsequent cluster-level FWE-correction at  $p < 0.05$ . The color scale represents the magnitude of the ALE values, i.e., the consistency across studies.

both sexes. No area presented statistically significant differences between men and women.

Previous studies have observed the existence of sex-related functional lateralization in the amygdala (e.g., Cahill et al., 2004; Domes et al., 2010). The lack of sex-related differences in our results, however, does not support the sexual hemispheric lateralization hypothesis. Alternatively, our findings are in consonance with behavioral studies suggesting that, although women are commonly conceived of as being more emotionally reactive, the experienced intensity of emotions does not differ between sexes (Fischer et al., 2004; Kring and Gordon, 1998).

A meta-analysis from Stevens and Hamann (2012) showed extended functional differences between men and women during the processing of negative stimuli. The authors reported that women compared to men exhibited greater activation in the left amygdala, left hippocampus, and bilateral hypothalamus. Conversely, men exhibited greater activation than women in areas including the right precentral gyrus, bilateral inferior frontal gyrus, and bilateral insula (Stevens and Hamann, 2012). In contrast with these findings, we did not detect sex-related differences. Clear divergences in exclusion criteria (e.g., inclusion of experiments matched by age, exclusion of experiments in PET, exclusion of studies with an  $n < 12$ , and focus on visual stimuli) may account for the differences between the results presented here and the results of the previous meta-analysis. It should be acknowledged, moreover, that due to our strict inclusion criteria, the number of studies included in the sub-analysis was low. This fact might have weakened the statistical power of the sex comparison. Finally, our matching procedure for the analysis on sex differences resulted in the inclusion of studies on participants ranging from young to middle-aged adulthood (mean age for women: 29.0; mean age for men: 27.7). Therefore, we cannot exclude the possibility of sex-related differences in older adults.

In the context of sex differences, hormonal status is an additional significant factor to consider in studies including women at reproductive ages. Indeed, sex hormones interact with several neurotransmitter systems, including serotonin, dopamine, GABA, and glutamate (Barth et al., 2015). Some studies have suggested that hormonal levels may modulate the neural responses to emotional stimuli. For instance, the administration of progesterone – a steroid hormone that presents high concentrations during the luteal phase of the menstrual cycle – seems to yield increases in amygdala reactivity to emotional stimuli (van Wingen et al., 2008). In a similar setting, the amygdala and the hippocampus showed

greater responses to emotional images during the mid-luteal phase relative to the early follicular phase (Andreano and Cahill, 2010). The use of oral contraceptives, moreover, has been associated with lower amygdala activity in response to emotional images (Petersen and Cahill, 2014). While this line of investigation needs further testing, these findings highlight the need to account for hormonal status in future studies on sex differences.

#### 4.4. The effect of task-related characteristics on the processing of negative events

Several task-related characteristics might modify the neural response to negative information. Here, we have addressed three potential sources of variation: stimulus types, emotion categories, and task instructions. By conjunction and subtraction analyses across and between the different characteristics, we aimed to discern (a) brain areas that are consistently activated across different task-related characteristics, and (b) brain areas that are associated with specific sub-mechanisms of emotional processing.

Concerning the types of stimuli, we observed a complex pattern of similarities and differences between images, faces, and words. Negative images and negative faces exhibited a robust cluster of overlapping activity in the right amygdala. However, no clusters overlapped between pictorial (images or faces) and lexical (words) stimuli.

The similarities observed between images and faces agree with studies reporting comparable activity between these two stimulus types (Britton et al., 2006; Sabatinelli et al., 2011). This congruent brain activity might be due to the partially overlapping content between images and faces, since IAPS pictures (Lang et al., 2008), which are utilized in the vast majority of experiments with negative images, also contain facial stimuli.

We observed that pictorial stimuli were associated with a higher probability of engagement of the right lateral occipital cortex. Moreover, relative to images, the use of words was related to a lower probability of recruitment of the right amygdala. Studies have proposed that the processing of linguistic stimuli yields a reduction in amygdala activity when compared with pictorial stimuli (Costafreda et al., 2008). In fact, pictorial stimuli are generally considered to be more salient than words, and might also elicit greater emotional reactions (e.g., Hinojosa et al., 2009). Additionally, the observed differences agree with studies proposing the existence of hemispheric specializations in the amygdala during the processing of pictorial versus lexical information, with the right amygdala showing more probabilities of engagement for pictures than for words (e.g., Kensinger and Schacter, 2006). Despite these differences, it should be taken into account that, as argued by some authors (e.g., Citron, 2012; Schlochtermeier et al., 2013), pictorial stimuli might be visually more complex than words, which in turn, might exacerbate the actual neural differences between verbal and non-verbal stimuli.

In addition to the nature of the stimuli, the emotional category employed in the experiments might modify the neural pattern obtained across studies. In the last decade, several authors have challenged *locationist* theories of emotion, or the notion that emotional categories are innately wired in the brain in specific brain areas (e.g., Barrett, 2006). Instead, emotional categories might be associated with distinct functional brain activity and co-activation across distributed cortical and subcortical structures (e.g., Wager et al., 2015). In the present study, we presented the patterns of brain activity that were associated with disgust- and fear-related stimuli. The subtraction analyses did not yield statistical differences between these two emotional stimuli. However, the lack of differences could be related to the small sample size. Although the patterns obtained for fear and disgust did not directly overlap, several visual areas emerged during the processing of both emotional

**Table 6**

Brain correlates of negative visual stimuli according to emotion categories.

Size (mm <sup>3</sup> )	MNI coordinates			ALE value	Anatomical localization		
	X	Y	Z				
Disgust-related stimuli							
Fourteen contributing experiments; sample size = 350; foci = 67.							
Statistical threshold: initial p < 0.001 uncorrected and additional cluster-level FWE correction for multiple comparisons at p < 0.05.							
536	-28	32	-16	0.01146	Left lateral orbitofrontal cortex		
480	36	-90	8	0.01688	Right lateral occipital pole		
456	-32	-90	10	0.01459	Left occipital pole		
400	-42	-50	-12	0.01036	Left inferior temporal gyrus		
385	-66	-26	34	0.01436	Left supramarginal gyrus		
344	-2	12	56	0.01288	Medial superior frontal gyrus		
208	-54	28	22	0.01052	Left inferior frontal gyrus		
208	-2	52	34	0.01014	Bilateral superior frontal gyrus		
Fear/threat-related stimuli							
Fourteen contributing experiments; sample size = 377; foci = 106.							
Statistical threshold: initial p < 0.001 uncorrected and additional cluster-level FWE correction for multiple comparisons at p < 0.05.							
1856	48		-2	0.0165	Right lateral occipital cortex		
1200	-48		8	0.0178	Left lateral occipital cortex		
584	56		8	0.0153	Left lateral frontal pole		
504	-24		-22	0.0115	Left amygdala		
448	-40		-10	0.0159	Left lateral occipital cortex		
368	46		-14	0.0159	Right lateral frontal pole		
344	50		14	0.0141	Right lateral occipital cortex		
304	-2		-6	0.0130	Brainstem		
Conjunction analysis (disgust- and fear/threat-related stimuli)							
No results							
Subtraction analyses (disgust- and fear/threat-related stimuli)							
ALE meta-analysis: p < 0.001 uncorrected; minimum cluster size = 100 mm <sup>3</sup>							
No results							
ALE, activation likelihood estimation; MNI, Montreal Neurological Institute							

categories. This finding can be taken as supporting the importance of the visual cortex in the evaluation of different negative emotional categories. In addition, disgust-related stimuli included activity in the lateral orbitofrontal cortex and inferior frontal gyrus, whereas the pattern obtained for fear-related stimuli included the engagement of the amygdala.

The detection of disgusting and threatening elements is fundamental for survival, and threatening and disgusting stimuli are traditionally considered to be highly salient and arousing. In this setting, the engagement of visual-frontal networks might reflect greater allocation of perceptual and attentional resources to the external environment (Vuilleumier, 2015; Pourtois et al., 2013; Phelps, 2006). The inferior frontal gyrus, engaged during the presentation of disgust-related stimuli, has extensive functional connections with areas forming the frontoparietal network (Goulas et al., 2012) – a circuit involved in working memory and attentional processes (Rubia et al., 2006). In the context of fear detection, moreover, the amygdala has been widely discussed in association with threat conditioning learning (Phelps, 2006) and with a boost in perceptual processes (Phelps, 2006; Vuilleumier, 2015). As such, the patterns of activity obtained for disgust and fear might reflect the engagement of adaptive mechanisms for a heightened perception and processing of emotionally salient cues.

Finally, we examined the effects of different task instructions: implicit emotional tasks, explicit emotional processing, and passive viewing instructions.

The application of dual processing interpretations to the study of emotional processing highlights the importance of the contrast between implicit and explicit affective processing (e.g., Critchley et al., 2000). Implicit processes would involve automatic and unconscious processes mainly supported by limbic circuitry, while explicit processing would involve conscious and controlled processes that engage areas traditionally assigned to cognitive control, such as the anterior cingulate cortex (Evans, 2008). In our study,

however, the contrast between implicit and explicit emotional processing did not yield significant differences. The lack of results might be explained by the heterogeneity of the tasks included in each of these two categories. Although implicit emotional tasks are supposed to automatically engage emotional processes, instead of cognitive control processes, the difficulty of the implicit task might obscure the results. For example, gender-labelling tasks might be difficult to perform when presented with faces with androgynous features. Similarly, indicating whether an image was taken indoors or outdoors might also prove complicated when the image contains ambiguous elements.

Relative to passive processing, explicit emotional instructions yielded more reliable activation in the paracingulate cortex. The paracingulate cortex has been widely involved in processes associated with theory of mind, that is, with ascribing (also non-affective) mental states to others (e.g., Gallagher and Frith, 2003). Our finding may thus also reflect non-emotional or cognitive demands required by explicit emotional processing tasks. However, this hypothesis should be further explored using specifically designed experiments.

With regard to similarities across types of tasks, we observed that implicit emotional tasks and passive viewing tasks shared reliable activation in the bilateral amygdala and left fusiform cortex. The pattern of activity obtained for explicit emotional tasks did not overlap with the other two task instructions. However, explicit emotional tasks also showed reliable activity in the right amygdaloid nucleus. Together, these findings corroborate the importance of the amygdala and the fusiform cortex in the processing of negative information and suggest that their role might be generalizable across different task demands.

#### 4.5. Methodological limitations

This study has several limitations that should be considered when interpreting the results. First, since this is a coordinate-based

**Table 7**

Brain correlates of negative visual stimuli according to task instructions.

Size (mm <sup>3</sup> )	MNI coordinates			ALE value	Anatomical localization		
	X	Y	Z				
Implicit emotional processing: negative stimuli > neutral stimuli							
Fifteen contributing experiments; sample size = 313; foci = 192.							
Statistical threshold: initial p < 0.001 uncorrected and additional cluster-level FWE correction for multiple comparisons at p < 0.05.							
2840	-20	-8	-14	0.0227	Left amygdala		
2072	-42	-48	-18	0.0231	Left temporal occipital fusiform		
1418	20	-4	-16	0.0171	Right amygdala		
1352	38	-52	-24	0.0153	Right cerebellum/lateral temporal occipital cortex		
1112	52	26	6	0.0181	Right inferior frontal gyrus		
824	44	16	24	0.0204	Right inferior frontal gyrus		
736	-48	24	-6	0.0190	Left lateral orbitofrontal cortex		
680	-34	-4	48	0.0192	Left precentral gyrus		
640	50	-70	10	0.0158	Right lateral occipital cortex		
368	2	-84	0	0.0139	Bilateral lingual gyrus		
Explicit emotional processing: negative stimuli > neutral stimuli							
Fifteen contributing experiments; sample size = 348; foci = 200.							
Statistical threshold: initial p < 0.001 uncorrected and additional cluster-level FWE correction for multiple comparisons at p < 0.05.							
952	-62	-24	32	0.0205	Left postcentral gyrus		
528	0	10	52	0.0143	Bilateral paracingulate gyrus		
520	34	0	-24	0.0184	Right amygdala		
496	48	8	26	0.0164	Right precentral gyrus		
464	26	-56	58	0.0178	Left superior parietal lobule		
Passive viewing: negative stimuli > neutral stimuli							
Fifteen contributing experiments; sample size = 320; foci = 117.							
Statistical threshold: initial p < 0.001 uncorrected and additional cluster-level FWE correction for multiple comparisons at p < 0.05.							
1576	56	-68	-10	0.0172	Right lateral occipital cortex		
1224	-40	-66	-10	0.0192	Left lateral occipital cortex		
1184	42	-54	-14	0.0162	Right temporal occipital fusiform cortex		
936	-52	-72	6	0.0191	Left lateral occipital cortex		
784	-20	-4	-14	0.0140	Left amygdala		
744	22	0	-30	0.0140	Right parahippocampal gyrus		
664	-10	68	26	0.0144	Medial frontal pole		
464	48	-40	-22	0.0138	Right inferior temporal gyrus		
304	4	56	40	0.0134	Medial superior frontal gyrus		
Conjunction analyses							
Implicit emotional processing and passive viewing task							
408	-20	-4	-14	0.0140	Left amygdala		
128	-42	-58	-16	0.0101	Left temporal occipital fusiform cortex		
64	22	-2	-24	0.0108	Right amygdala		
Implicit and explicit emotional processing							
No results							
Explicit emotional processing and passive viewing tasks							
No results							
Subtraction analyses							
Statistical threshold for each pairwise comparison: p < 0.00033 uncorrected (3 pairwise comparisons at p < 0.001). Minimum cluster size = 100 mm <sup>3</sup>							
Explicit emotional processing > passive viewing							
492	0	11	52	3.090	Paracingulate cortex		
Implicit and explicit emotional processing							
No results							
Implicit emotional processing and passive viewing tasks							
No results							
ALE, activation likelihood estimation; MNI, Montreal Neurological Institute							

**Table 8**

Brain correlates of the contrast: "negative stimuli &gt; positive stimuli".

Size (mm <sup>3</sup> )	MNI coordinates			ALE value	Anatomical localization		
	X	Y	Z				
Ten contributing experiments; sample size = 206; foci = 70.							
Statistical threshold: initial p < 0.001 uncorrected and additional cluster-level FWE correction for multiple comparisons at p < 0.05.							
400	12	-22	-36	0.01344	Brainstem		
272	48	10	-30	0.01089	Right temporal pole		
200	-50	-62	-12	0.00957	Left inferior temporal gyrus		
ALE, activation likelihood estimation; MNI, Montreal Neurological Institute							

meta-analysis, we are not comparing the amplitude of brain activity in response to negative stimuli, but the spatial consistency of reported peaks of activity between different groups of studies. This consistency is not influenced by the intensity of the neural activation but by the number of studies that have reported activation in these areas.

Second, the number of experiments available does not enable the investigation of interactions between variables in the processing of negative visual stimuli. Of note, previous studies suggest that the effect of age, sex, and task-related characteristics might interact with each other in a complex manner. Age, for instance, might modulate sex differences in negative emotional processing. A study on memory performance reported that younger and older women showed equal accuracy for negative and neutral pictures. In the case of men, conversely, younger males exhibited better accuracy for negative pictures relative to neutral pictures, whereas for older men this difference presented a non-significant trend (Gavazzeni et al., 2012). Age-related differences might also be dependent on the instructions associated with the task. In this setting, it has been suggested that older adults prioritize positive over negative information in those cases in which participants are instructed to simply view emotional stimuli rather than explicitly process them (Reed and Carstensen, 2012). On the other hand, for those experiments requiring greater cognitive control, such as divided attention, the advantage of positive over negative information seems to disappear (Knight et al., 2007; Reed and Carstensen, 2012). Finally, and also with regards to age effects, it is possible that different emotional categories may yield divergent results. Accordingly, relative to younger adults, older participants seem to report lower levels of anger (Charles and Carstensen, 2008) but heightened sadness reactivity (Seider et al., 2011).

Last but not least, the validity of the meta-analysis is intrinsically dependent on the quality of the studies included. In addition, publication biases might restrict the availability of (new) studies (Behrens et al., 2013) and negative findings. We hope that in the near future initiatives to promote the publication of negative results and internet-based data sharing platforms (e.g., Poldrack and Gorgolewski, 2014) might mitigate this limitation.

## 5. Conclusions

In the present study, we have addressed the issue of how the human brain processes negative events or environmental stimuli that should be avoided. We observed that the bilateral amygdala presented the highest functional connectivity with other regions involved in emotional processing. Based on that, we propose that the amygdaloid complex constitutes a core component of functional brain networks associated with the neural processing of negative visual information. The central role played by this structure might reflect its contribution to a number of perceptual, attentional, and emotional mechanisms associated with the processing of negative stimuli (Phelps and LeDoux, 2005). We described the correlates obtained for the participant-related characteristics of age and sex as well as for the task-related characteristics of stimulus type, emotion category, and task instruction. Our findings may thereby practically inform empirical experimentation in the affective neurosciences and provide a basis for the neurobiological investigation of affective symptoms.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.neubiorev.2016.04.020>.

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