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Review

The human amygdala and the emotional evaluation of sensory stimuli

David H. Zald*

Department of Psychology, Vanderbilt University, 301 Wilson Hall, 111 21st Ave. S., Nashville, TN 37240-0009, USA

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Abstract

A wealth of animal data implicates the amygdala in aspects of emotional processing. In recent years, functional neuroimaging and neuropsychological studies have begun to refine our understanding of the functions of the amygdala in humans. This literature offers insights into the types of stimuli that engage the amygdala and the functional consequences that result from this engagement. Specific conclusions and hypotheses include: (1) the amygdala activates during exposure to aversive stimuli from multiple sensory modalities; (2) the amygdala responds to positively valenced stimuli, but these responses are less consistent than those induced by aversive stimuli; (3) amygdala responses are modulated by the arousal level, hedonic strength or current motivational value of stimuli; (4) amygdala responses are subject to rapid habituation; (5) the temporal characteristics of amygdala responses vary across stimulus categories and subject populations; (6) emotionally valenced stimuli need not reach conscious awareness to engage amygdala processing; (7) conscious hedonic appraisals do not require amygdala activation; (8) activation of the amygdala is associated with modulation of motor readiness, autonomic functions, and cognitive processes including attention and memory; (9) amygdala activations do not conform to traditional models of the lateralization of emotion; and (10) the extent and laterality of amygdala activations are related to factors including psychiatric status, gender and personality. The strengths and weakness of these hypotheses and conclusions are discussed with reference to the animal literature.

Theme: Neural basis of behavior

Topic: Motivation and emotion

Keywords: Emotion; Face; fMRI; Laterality; Lesion; PET

Contents

*Tel.: +1-615-343-6076; fax: +1-615-343-8449.
E-mail address: david.zald@vanderbilt.edu (D.H. Zald).

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1. Introduction

Neurobehavioral theorists have frequently argued that the amygdala plays a central role in the emotional processing of sensory stimuli. Electrophysiological, neuropharmacological, and lesion studies in animals, have all provided support for the involvement of the amygdala in both the evaluation and response to emotionally salient stimuli. However, there exists a strong need for human data. The relative distribution of sensory representations clearly differs across species. The primate amygdala receives a far greater input from cortical areas including auditory and visual sensory areas than is observed in other mammals such as rodents and cats [194]. These differences appear to have direct functional consequences for the sensory representations received or processed by the amygdala [121]. For instance, over a third of rodent amygdala cells respond to odorants [62], whereas only a very limited and nuclei-specific group of amygdala cells respond to odorants in humans [122]. Even among primate species, there exist differences in the sensory processing of the amygdala, with humans showing less frequent responses to simple auditory or visual stimuli than is seen in monkeys [212,248,303]. Additionally, some aspects of amygdala processing may be uniquely developed or expressed in humans, due to our well-developed use of language and other cognitive abilities. Finally, only human's can directly report on their subjective reactions to stimuli.

With the advent of positron emission tomography (PET), and more recently functional magnetic resonance imaging (fMRI), an increasing body of literature addresses the role of the amygdala in the processing of emotionally salient stimuli in humans. Simultaneously, neurologists and neuropsychologists have begun to utilize sophisticated paradigms to delineate the specific aspects of emotional processing that are affected by amygdala lesions. Taken together, these two lines of inquiry lay the groundwork for refining our theories of amygdala functioning. This article provides an overview of this emerging literature and outlines several of the unique insights provided by this research.

2. Methodological issues

2.1. Neuroimaging

Several issues regarding difficulties in imaging the amygdala warrant attention before embarking on a review of the neuroimaging literature. A basic problem relates to the amygdala's small volume. When considered within the Talairach coordinate system, the amygdala possesses an average width of around 15 mm, and a slightly longer length [189,284]. Estimates of its total volume range from 1.1 to 3.4 cc in each hemisphere (the volume estimates vary greatly depending upon the system of defining the amygdala's borders and may additionally be influenced by approaches to spatial normalization) [2,38,99,234, 282,297]. Prior to the mid 1990s, a frequently repeated fallacy held that PET lacked the spatial resolution to image the amygdala. This fallacy in part arose because the amygdala never emerged as a major focus in early PET studies. However, the mapping resolution of current PET cameras is more than adequate to detect foci in the amygdala. It is important to distinguish the *mapping* resolution from the full-width at half-maximum (FWHM) resolution of PET imaging. FWHM refers to the distance at which two separate foci may be distinguished. After filtering the raw PET data, current PET studies typically report FWHMs of 8–20 mm. Admittedly, at a FWHM of 20 mm, two separate foci occurring in or near the amygdala would be difficult to resolve, but studies with FWHM $<$10 mm generally provide sufficient spatial resolution to distinguish foci within the amygdala from foci falling in nearby structures. In contrast to FWHM, the

mapping resolution of neuroimaging techniques refers to the ability to localize an individual peak. Modern PET techniques (even with relatively large FWHMs) can map peaks to within 1–2 mm. This has been most clearly demonstrated in the visual cortex, where PET allows retinotopic mapping in the calcerine cortex [101]. Although, additional factors such as errors introduced by warping to Talairach space and intersubject variability lower this mapping resolution in group analyses, the resolution typically remains more than adequate to localize a peak in the amygdala should such a peak occur.

Functional MRI techniques clearly possess the spatial resolution to image foci in the amygdala. However, the level of localization error introduced by draining vein effects, which may mislocalize foci by 5 mm or more at lower field strengths (i.e. 1.5 T), adds a level of uncertainty to findings arising in fMRI studies [160,173]. Both PET and low-field fMRI lack the spatial resolution to examine activations in individual nuclei within the amygdala (although it is sometimes possible to make statements about the general medial–lateral, anterior–posterior, or inferior–superior position of a focus within the amygdala). Functional MRI performed at higher field strengths with high spatial resolution may allow discrimination of different nuclear groups within the amygdala, but to date, no real demonstrations of this sort exist. The animal literature indicates that different amygdaloid nuclei possess distinct connections and functions [14]. Indeed, the amygdaloid region has been argued to represent a heterogeneous conglomeration of nuclear groups, rather than a single functionally or anatomically integrated structure [281]. Nevertheless, the ability to map responses to this region provides an enormous source of information on the functions subserved by the amygdala in humans. This remains true even if the term amygdala is used only to designate an anatomical region as opposed to a functionally integrated circuit.

Another localization problem arises as a result of variability in the exact location of the amygdala across subjects. However, the general location of the amygdala appears fairly consistent (Fig. 1). This consistency is reflected in the similarity of amygdala coordinates in different brain atlases. According to the Talairach atlas [284], the amygdala occupies a region that runs from 17 to 30 mm lateral to the midline, 1 mm anterior to 11 mm posterior to the anterior commissure (AC) and 7–21 mm below the intercommissural (AC–PC) line. By comparison, the Mai atlas [189] indicates that the amygdala occupies an area from 12 to 27 mm lateral to the midline, with an anterior boundary 1 mm in front of the AC, the bulk of the amygdala extending to roughly 13 mm posterior to the AC, and a thin strip extending as far as 18 mm posterior to the AC. In the inferior–superior dimension, Mai et al. indicate that the amygdala extends ventrally to 20 mm below the AC–PC line, and at its posterior extreme extends as high as five mm below the AC–PC line. Studies, utilizing coregistered MRIs generally agree with these coordinates, although some studies suggest that the amygdala may extend several more millimeters ventrally or anteriorly[1]. Given the accuracy of current warping techniques and coregistration procedures, it is usually possible to identify with confidence foci falling near the middle of these ranges. Foci that occur near the boundary of the amygdala and neighboring regions must be interpreted with greater caution, especially when examined without reference to individual MRIs. For the sake of brevity, I will avoid discussing whether foci in individual studies truly fall within the amygdala as opposed to neighboring areas. However, a quick examination of reported stereotactic coordinates indicates that there are numerous instances where confidence in the localization is limited.

In considering the Talairach coordinates for the amygdala, it must be noted that these coordinates apply only to the 'amygdala proper', and not to the 'extended amygdala'. The extended amygdala refers to corridors of cells that extend from the central and medial nuclei of the amygdala through the sublenticular/basal forebrain region to the bed nucleus of the stria terminalis [13,132]. Because of its anatomical and functional relationship to the corticomedial nuclei of the amygdala, it is increasingly common to see foci in this region referred to with reference to the amygdala, despite the foci's location in the basal forebrain as opposed to the medial temporal lobe. However, this may in some cases lead to confusion when clear distinctions are not made between the extended amygdala and amygdala proper. It also must be noted that data regarding variability in the precise location of the extended amygdala corridors is lacking, and the limited spatial resolution of current neuroimaging techniques, makes it difficult to identify whether foci truly fall within the extended amygdala vs. neighboring sublenticular regions.

Additional methodological factors warrant particular attention in fMRI studies of the amygdala. Specifically, the region encompassing the anterior–medial temporal lobe contains high levels of inhomogeneity in magnetic susceptibility due to its proximity to the sphenoid sinus. The field distortions produced by these inhomogeneities are so great as to lead to a large and frequently irrecoverable loss of signal in this region during echo planar imaging [73,98,168]. They also lead to distortions that can lead to signal mislocalization. These problems may be partially alleviated by the selection of appropriate imaging techniques (i.e., use of sequences such as FLASH or reverse

[1]Some variability in coordinates is also produced by the use of the Montreal Neurological Institute template in SPM (Welcome Cognitive Neurology: London, UK), which is among the most popular image analysis packages for functional neuroimaging studies. Although researchers often refer to coordinates based on MNI template as Talairach coordinates, they are not actually identical to Talairach stereotactic coordinates and the coordinates for the amygdala are slightly shifted relative to those produced when warping to true Talairach space.

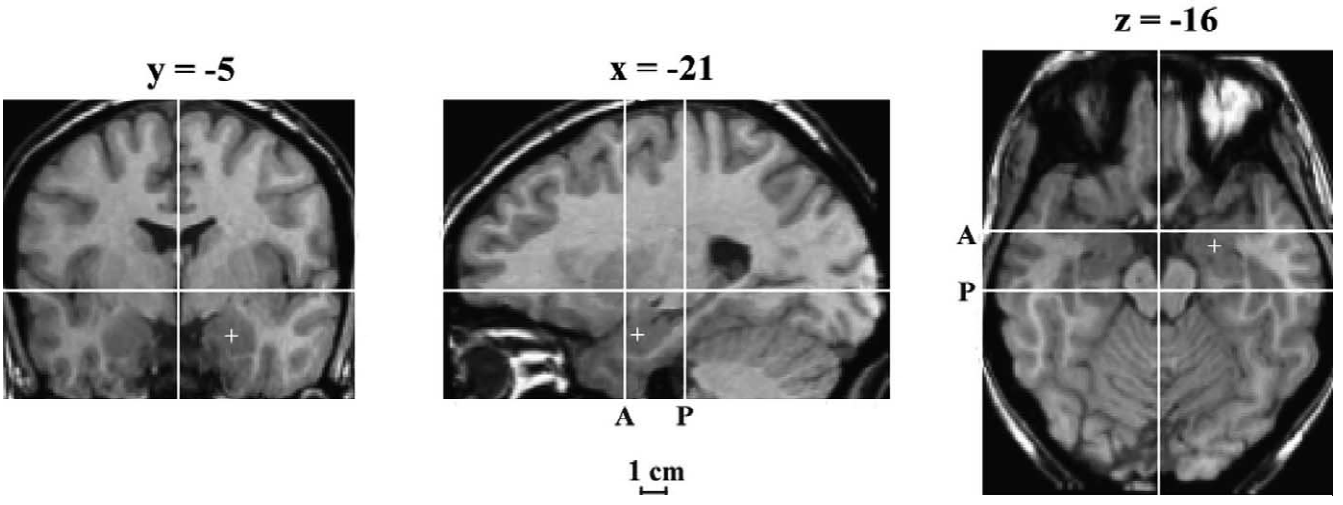

Fig. 1. A structural $T-1$ weighted MRI of a subject with a typically positioned amygdala. The subject's MRI was aligned along the intercommissural plane and linearly warped to Talairach space. Talairach coordinates represent; (x) mm lateral to the midline (left = −), (y) mm anterior–posterior to the anterior commissure (posterior = −), and (z) mm inferior–superior to the anterior commissure–posterior commissure plane (inferior = −). The white horizontal line in the sagittal and coronal slices represents the intercommissural plane ($z = 0$). The lines marked 'A' and 'P' in the transverse and sagittal slices run through the anterior and posterior commissures at $y = 0$ and $y = -23$, respectively. The crosshairs lie near the central point of the left amygdala and indicate the location of the other two displayed slices. Note that at this resolution (which is typical of anatomical MRIs collected as part of functional studies), it is difficult to visualize the borders of the subnuclei or even the border of the amygdala relative to neighboring gray matter regions.

spiral, application of higher-order shimming, application of locally adjusted refocusing gradients, reduction of slice thickness and pixel size, tailored RF pulses, etc . . .) [73,86,112,117,196,278,279,310]. Unfortunately, techniques for addressing inhomogeneity often require implementation of methods that are not standard on most clinical scanners and come at the sacrifice of temporal resolution, field of view, or signal to noise ratios in other areas of the brain. Because of this, most studies use techniques that provide suboptimal measurement of signal from the amygdala. Unfortunately, authors frequently fail to report whether extra precautions were taken in imaging this region. When left unaddressed, the susceptibility artifacts in the amygdaloid region may lead to both false positive and false negative findings, although the bias is towards false negative results due to signal dropout. Despite these problems, fMRI has already begun to dramatically contribute to our understanding of the amygdala and will certainly continue to provide unique insights in the future.

Temporal resolution must also be considered in evaluating the ability of neuroimaging techniques to detect changes in amygdala activity. PET studies of regional cerebral blood flow (rCBF) typically assay activity over a 30–90 s period with the greatest sensitivity occurring during the first half of scanning [237,271]. Such a long duration requires that the amygdala maintain elevated activity over a period of time for an activation to be detected. Thus, PET may fail to detect very brief increases in rCBF. However, in many cases the magnitude and the length of activation is more than enough to allow detection of activations with rCBF PET. Indeed, FDG-PET studies that involve the aggregate glucose metabolism over 30 min or longer have observed foci in the amygdala, suggesting that the amygdala is capable of responding in a relatively sustained manner [42,116]. In many cases, using repeated stimulus presentations, or varying the nature of the stimulus over the scan period, may rectify problems associated with detecting brief activations. However, if there is rapid habituation of amygdala firing, and the habituation generalizes to other stimuli from the same class of stimuli, the temporal resolution will remain a problem. In contrast to PET, fMRI can provide far greater temporal resolution, with scanning times primarily limited by the temporal characteristics of the hemodynamic response. However, because fMRI studies require repeated trials, they are often subject to many of the same habituation issues faced by PET studies.

2.2. Lesion studies

The largest methodological problem in studies of patients with amygdala lesions involves the rarity of observing complete amygdala damage without observing damage to the adjacent cortex. Most studies include patients with only partial damage with significant damage to areas of neighboring temporal cortex. Even selective lesions to the amygdala are likely to effect neighboring temporal lobe structures due to the presence of fibers of passage traversing the region [95,115]. The disruption of fibers of passage and the encroachment of neighboring areas of temporal cortex represents a serious issue. Studies using neurotoxic lesions in animals increasingly demonstrate that a number of functions that were previously thought to be subserved

by the amygdala relate instead to areas of the inferior temporal lobe whose fibers pass through the amygdala [190]. Understanding the effects of amygdala lesions in patients with epilepsy is further complicated by the presence of premorbid pathology related to seizures. Patients with Urbach–Wiethe syndrome provide a unique exception to the above confounds due to the relative selectivity of the calcification of the amygdala [192,211,291], but even in these cases, concern arises regarding the effects of calcification on fibers of passage. Moreover, patients with Urbach–Wiethe are extremely rare, making it difficult to accumulate even small samples of such subjects.

3. Multimodal responses to aversive stimuli

Exposure to aversive stimuli in multiple sensory modalities induces activation of the amygdala. Examples include olfactory [39,316], gustatory [214,312,314], visual [141,176,285,286,308], and auditory [126,197,199,318] modalities. Unpleasant interoceptive sensations such as shortness of breath or hypercapnia also induce amygdala activations [45,96]. Thus, the amygdala's responsiveness to aversive stimuli appears to reflect a common, multimodal feature of amygdala coding (Table 1).

The specific emotion associated with exposure to aversive stimuli is often unclear. Unpleasant stimuli may induce disgust or anxiety. Alternatively, they may induce an undefined negative state associated with disliking, which lacks the features of the more commonly defined emotions. Although animal studies often emphasize the role of the amygdala in fear or anxiety, it is clear that many of the stimuli invoking amygdala responses are not specifically associated with fear or anxiety. For instance, disgust represents the predominant emotional response to unpleasant stimuli in studies in the chemical senses. Many of the studies using emotionally valenced visual stimuli mix threatening (e.g., a pointed gun) and gory (e.g., mutilated bodies) pictures, leaving unclear whether anxiogenic or disgust invoking stimuli specifically contribute to the response. An unpublished study by J. Nagode and J.V. Pardo (personal communication) indicates that the left amygdala activates when subjects view gory pictures alone. This suggests that direct threat is not necessary to induce rCBF increases in the amygdala. Taken together with studies in the chemical senses, it appears that stimuli with disgusting features can induce amygdala activations, and that these stimuli do not have to be perceived as overtly threatening to induce amygdala activity.

Although numerous studies have included threatening stimuli, studies examining exposure only to inherently threatening sensory stimuli (not contaminated by other emotions) in healthy subjects are surprisingly scarce. Previously neutral stimuli that are associated with aversive consequences either through conditioning [21,50,51,76,167,199,205] or explicit instructions [226] can activate the amygdala. However, several findings raise questions about the generalizability of the amygdala's responses to threatening stimuli. First, in conditioning studies, the amygdala often stops differentially responding to the conditioned stimulus (CS+) and may even show BOLD signal decreases in response to the CS+ after the initial acquisition of conditioning is completed [50,51,167]. Thus, at least under certain conditions, the presence of a CS+ alone may not be enough to increase amygdala activity. Second, in subjects with specific phobias, sight of the phobic object does not typically produce measurable increases in amygdala activity [238,301]. Third, in animals the extent to which amygdala lesions impair fear-related responses to threatening stimuli appears to vary depending upon the class of threatening stimuli and the type of response being measured [20,191,219,262,293,296]. Thus, although a wealth of data link amygdala processes to the control of certain responses to threatening stimuli, future research is still needed to define the parameters under which such stimuli invoke amygdala activations.

Given the amygdala's response to stimuli in 4 of the 5 major exteroceptive sensory modalities, as well as its response to unpleasant interoceptive information, it seems natural to ask about the somatosensory modality. The amygdala receives input from the insular somatosensory association area [102,207], which provide a clear route for somatosensory input to reach the amygdala. However, to date no reports have examined amygdala responses to nonpainful, but unpleasant stimuli (e.g., wearing wet socks). Similarly one might predict that painful stimuli would provoke robust activation of the amygdala. A number of lines of evidence from animal studies implicate the amygdala in some aspect of pain processing. The amygdala receives nociceptive information via projections from the spino–parabrachial pain system [34], the trigeminal system [27], the posterior intralaminar thalamic region [309] and the insula [266]. Cells with responses to pain have been observed in the central nucleus of rodents [35,36]. Moreover, painful stimuli are among the most frequently used unconditioned stimuli in fear conditioning paradigms, and conditioning to these stimuli can be blocked by lesions affecting the nociceptive projections to the amygdala [265]. Finally, lesions and pharmacological manipulations of the amygdala often produce analgesic-like effects on behavioral measures of pain in animals [12,130,133,134,148,298]. Yet, most neuroimaging studies of pain have observed no changes in amygdala activity, and in a few cases decreased activity has been reported [87,222,223]. However, two recent fMRI studies reported correlations between pain intensity and amygdala activity [43,254]. Two factors may contribute to this confusing picture. First, data from an event-related study by Bornhovd and colleagues [43] suggest that mildly to moderately painful stimuli may actually cause decreases in

Table 1
Amygdala foci in studies of aversive stimulation

Author	Method	Contrast	Talairach coordinates[a]	Comment
Olfaction				
Zald and Pardo [316,317]	PET	Smelling aversive sulfides –odor detection	26, −1, −14 −26, −1, −18	Coordinates based on high resolution reanalysis
Birbaumer et al. [39]	fMRI	Smelling aversive fermented yeast–no odorant	Bilateral NG	Effect seen in both normals and social phobics
Gustation				
Small et al. [272]	PET	Mismatched smell–taste combination–matched smell–taste combination	−28, −6, −26	Mismatched smell–taste combination experienced as unpleasant and novel
Zald et al. [314]	PET	Tasting aversive saline–water	21, 1, −16	
Zald and Pardo [312]	PET	Tasting aversive quinine –water Tasting aversive quinine –baseline resting	−18, −10, −14 −19, −1, −18	Quinine-HCL experienced as highly unpleasant and novel
O'Doherty et al. [214]	fMRI	Tasting saline–artificial saliva	−24, −5, −21 18, −4, −14	Effect only seen in 2 of 7 subjects on each side
Vision				
Irwin et al. [141]	fMRI	Unpleasant pictures–neutral pictures (passive viewing)	±15, −6, −11 26, −6, −12	
Lane et al. [176]	PET	Unpleasant pictures–neutral pictures (passive viewing)	−26, −6, −16	
Taylor et al. [285]	PET	Unpleasant pictures–neutral pictures (hedonic rating)	−15, −13, −18 −17, −4, −11	
Liberzon et al. [188]	PET	Unpleasant–Neutral (combined over both recognition and hedonic rating trials) Interaction of rating vs. recognition and unpleasant vs. neutral stimuli	Bilateral NG 24, −8, −14	Right amygdala activity correlated with skin conductance response Activity greater during hedonic rating than recognition but tasks
Garavan et al. [108]	fMRI	High and low arousal negatively valenced pictures –neutral pictures	ROI Bilateral	Only high arousal, negatively valenced pictures induced significant activity
Hamann et al. [126]	PET	Negatively valenced pictures–neutral, low-interest pictures	−20, −4, −16 18, −4, −12	Subjects told to experience whatever feelings the stimuli evoked
Schaefer et al. [251]	fMRI	Unpleasant–neutral pictures	Bilateral NG	Greater activity arose in the delay following negative pictures when subjects were instructed to maintain the emotion
Yamasaki et al. [308]	fMRI	Unpleasant vs. neutral pictures (task distractors)	ROI bilateral	
Canli et al. [64]	fMRI	Neutral to unpleasant pictures In male subjects In female subjects	 −25, −8, −16 −25, −8, −14 −21, −4, −13	Foci represent areas correlating with a 4-point rating of emotional intensity

Table 1. Continued

Author	Method	Contrast	Talairach coordinates[a]	Comment
J. Nagode and J.V. Pardo (personal communication)	PET	Gory pictures–neutral pictures	−28, −10, −14	Only used gory pictures from IAPS
Audition				
Mirz et al. [197]	PET	Tinnitus-like environmental sounds–no sounds	28, −11, −14 16, −7, −26	
Morris et al. [199]	fMRI	100 db White-noise burst (UCS during conditioning) –trials in which the UCS was absent	−30, −10, −10	
Zald and Pardo [318]	PET	Aversive sound collage–white noise	28, −11, −14 16, −7, −26	Only subjects who described themselves as reactive to unpleasant sounds studied
Interoceptive				
Brannan et al. [45]	PET	Air hunger induced with hypercapnia-oxygen inhalation	21, −12, −22 −20, −12, −18	
Evans et al. [96]	fMRI	Air hunger induced by restricting tidal volume–normal tidal volume	−20, 2, −14 24, 4, −14	
Pain				
Derbyshire et al. [87]	PET	Thermal pain (warm, just pain, mild and moderate pain)	↓ −28, −8, −16	Negative correlation with pain stimulus intensity
Petrovic et al. [223]	PET	Mechanically induced allodynia in patients with mononeuropathy	↓ 22, −14, −12	Decreased activity relative to no stimulus
Petrovic et al. [222]	PET	Cold pressor test–cool temperature	↓ −16, 0, −22	Decreased activity relative to nonaversive cool stimulus only when subjects knew the stimulus duration would be long
Schneider et al. [254]	fMRI	Vascular pain	12, −11, −17 14, −16, −20	Correlation with perceived pain intensity
Bornhovd et al. [43]	fMRI	Thermal pain (no pain, mild, through high)	24, 0, −24 −27, 0, −27	Correlation with pain intensity, with mild to moderate pain showing decreases relative to no stimulation

[a] Studies utilizing a priori 'regions of interests' are listed with respect to laterality and denoted *ROI*. Studies that did not formally define ROIs, but do not provide Talairach coordinates are denoted *NG* for 'none given'). In some cases the coordinates reflect MNI template coordinates which differ slightly from Talairach coordinates. These are not noted separately because many papers using the SPM software leave unclear whether they are using SPM or MNI template coordinates. See Fig. 1 legend for additional explanation of Talairach coordinates. ↓ indicates a decrease in activity relative to the comparison condition.

amygdala activity, with increases only emerging when stimuli are experienced as highly painful. Second the context of the stimulation may be important. Petrovic and colleagues [222] indicate that the context of the pain stimulation influences amygdala activity, with subjects who know that the pain is going to continue for a longer period showing decreases in amygdala activity. The authors suggest that the decrease reflects a mechanism for coping with the pain. Taken together, such studies make evident that pain does not categorically increase amygdala activity, but instead amygdala activity appears closely tied to the context and level of aversiveness of the stimuli.

The observation that the degree of pain is related to the amount of amygdala activation parallels findings in other sensory modalities. In most of the studies observing amygdala responses in other modalities, the stimuli produced strong ratings of unpleasantness. In contrast, stimuli invoking weaker emotional responses appear much less

effective at consistently or robustly activating the amygdala. In studies of olfaction [233,316,317], and viewing unpleasant pictures [64,66,142], ratings of unpleasantness correlated with the degree of amygdala activation. These findings converge with reports that the extent of increases in amygdala activity correlate with ratings of procaine induced fear [154], ratings of fearful faces [204], unpleasantness and bizarreness of faces with expressional transfiguration [242],[2] and the intensity of conditioned autonomic responses during fear conditioning [105,167]. Taken together, such data suggest that the intensity of affective responses directly relates to the magnitude of the amygdala response. However, this pattern is not universally observed. Specifically, using PET, Taylor et al. [286] failed to observe a graded effect of exposure to mildly aversive vs. highly aversive visual stimuli[3]. Nevertheless, the association between valence magnitude and amygdala activity has occurred in enough studies to warrant consideration when evaluating amygdala responses to different stimuli.

4. Positively valenced stimuli and the importance of arousal and motivation

Multiple studies have reported amygdala activation in response to pleasant or positively-valenced stimuli [31,108,126,162,163,169,177,214,215,319]. However, such increases appear far less consistently than activations induced by negative stimuli. A number of critical factors may contribute to this discrepancy, and their elucidation may provide several key insights into the characteristics that are necessary for stimuli to engage the amygdala (Table 2).

4.1. Arousal

Arousal refers to the extent to which stimuli are calming (low arousal) or activating (high arousal). This dimension is typically presented as lying orthogonal to the valence (pleasantness–unpleasantness) dimension [178]. An interpretational difficulty arises in many neuroimaging experiments because unpleasant and pleasant stimuli often differ in their arousal level. Indeed, many studies utilize negative stimuli that are both highly unpleasant and highly arousing, while utilizing positive stimuli that are neither as strongly pleasant nor as arousing. A few neuroimaging studies have attempted to tease apart the valence and arousal influences on amygdala responses to visual stimuli. A fully consistent picture has yet to emerge from these studies, but they do suggest that arousal level influences responses to emotionally valenced stimuli, with higher amygdala activity associated with greater arousal. This effect has been reported both when pleasant and unpleasant pictures were analyzed together and when just negative stimuli were analyzed [108,174]. However, it remains to be seen whether the effects of arousal can be detected when positive stimuli are treated in isolation.

In considering the effect of arousal, it must be noted that although arousal is conceptualized as orthogonal to valence, within a specific valence dimension, it often correlates with valence intensity. Indeed, in stimuli ranging from neutral to highly unpleasant, there is almost always a strong correlation between arousal ratings and ratings of unpleasantness [180]. For instance, in a recent study using neutral to unpleasant pictures from the International Affective Picture System (IAPS) [181], 79% of the variance in arousal ratings were explained by unpleasantness ratings [64]. The relationship between valence intensity and arousal appears more complex for pleasant stimuli: highly pleasant stimuli can be experienced as arousing or as extremely relaxing and calming. For example, a painting of a landscape might be viewed as highly pleasant and calming, whereas a picture of a beautiful model in a provocative pose might be viewed as equally pleasant but highly arousing. Similarly, the taste of highly pleasant food might be arousing and cause the subject to desire more food, or it might be experienced as relaxing. In contrast, it is hard to imagine examples of highly unpleasant, but calming stimuli. Unfortunately, no studies to date have compared calming and arousing stimuli that were otherwise matched for valence intensity. To the extent that arousal is critical in elucidating amygdala responses, it would be predicted that highly arousing pleasant stimuli would cause significantly more amygdala activation than equally pleasant calming stimuli.

4.2. Sexual arousal

One source of potential confusion in the literature on arousal involves the manner in which sexual arousal fits with other aspects of arousal. Many of the pleasant, high arousal stimuli in the IAPS contain sexually provocative pictures (e.g., women in bathing suits).[4] There exists a large literature implicating the medial amygdala and the medial portions of the extended amygdala in male sexual behavior in rodents [210]. Sexual hallucinations occasion-

[2]Expressional transfiguration refers to the Thatcher illusion in which inversion of the eyes and the mouth in a face produces a marked change in the emotional valence of the facial expression.

[3]This study differs from many of the above-mentioned studies in that it did not report a correlation or covariance analysis, but instead analyzed the effect of condition (mild vs. high). This contrasts with many of the other studies, which looked at the correlation over a wide range of valence intensities, or examined the between activity and individual differences in perceptual or emotional self-report.

[4]The inclusion of these types of pictures also raise complications for gender issues, because men find erotic stimuli more arousing than women [151], which makes it easier to provide high arousal stimuli for men than women.

Table 2
Amygdala signal increases during exposure to pleasant, arousing and appetitive motivating stimuli

Author	Method	Contrast	Talairach coordinates	Comment
Pleasant pictures				
Lane et al. [177]	PET	Viewing happy film–neutral film	−20, −6, −8	Focus appears superior to amygdala proper
Lane et al. [174]	PET	High arousal pleasant and unpleasant pictures–low arousal pleasant and unpleasant pictures	−26, 0, −10	Effect was not seen when high and low arousal neutral pictures were included in the analysis
Garavan et al. [108]	fMRI	High and low arousal pleasant pictures–neutral pictures	ROI Bilateral	Both high and low arousal positive pictures produced effects
Hamann et al. [126]	PET	High arousal pleasant pictures–neutral low-interest pictures	−26, 0, −14	Subjects told to experience whatever feelings the stimuli evoked
Sexual stimuli and pictures of opposite gender				
Beauregard et al. [31]	fMRI	Sexual videos –neutral videos	25, −3, −14	No amygdala response emerged when subjects were instructed to inhibit their reactions
Karama et al. [151]	fMRI	Sexual videos–neutral stimuli		
		in males	−18, −8, −16 14, −9, −18	
		in females	−18, −1, −22 18, −1, −20	
Aharon et al. [11]	fMRI	Men viewing beautiful women's faces–beautiful male faces	−18, 0, −15 −27, −6, −21	Responses also localized to the extended amygdala in this contrast and contrasts with average female faces
Other motivating stimuli				
Zalla et al. [319]	fMRI	Increasing win feedback	−36, −3, −18	Amount of win and lose feedback were parametrically varied across trial blocks
		Increasing lose feedback and decreasing win feedback	24, 0, −15	
Knutson et al. [163]	fMRI	Anticipation of monetary reward–anticipation of nonreward	16, −7, −7	No change was observed in response to actual reward
Knutson et al. [162]	fMRI	Anticipation of monetary reward–nonreward	−14, −2, −9	
O'Doherty [215]	fMRI	Anticipation of tasting glucose–tasting glucose	28, −8, −14	No effect was observed relative to anticipating artificial saliva, but an effect was observed in the left amygdala relative to anticipating saline
LaBar et al. [169]	fMRI	Interaction between viewing food and hunger state	−21, −3, −27	Amygdala only activated when subjects were hungry (effect only observed in 2 of 9 subjects)
Gustation				
O'Doherty [214]	fMRI	Tasting sucrose-artificial saliva	−20, −5, −21 25, −4, −24	Effect only seen in 2 of 7 subjects on the right

Table 2. Continued

Author	Method	Contrast	Talairach coordinates	Comment
Drug craving				
Grant et al. [116]	FDG-PET	Cocaine dependent subjects: Exposure to cocaine related video–neutral video	ROI Laterality not addressed	Metabolism correlated with craving
Childress et al. [69]	PET	Cocaine dependent subjects: Cocaine related video–neutral video	ROI Bilateral	Significant increase and correlation with craving
Kilts et al. [158]	PET	Cocaine imagery–Neutral imagery	20, −9, −9 −18, 0, −18	Activity was not correlated with craving and failed to reach significance in a contrast between cocaine imagery and an anger imagery script
Bonson et al. [42]	FDG-PET	Cocaine abusing or dependent subjects: Cocaine related video and script–neutral video and script	−18, −12, −36	Peak correlated with cocaine craving, (extends ventral to the amygdala)
Due et al. [93]	fMRI	Abstinent cigarette smokers viewing smoking cues vs. neutral cues during target detection	ROI Right posterior	
Schneider et al. [257]	fMRI	Detoxified alcohol dependent subjects: smelling ethanol vs. room air	24, −4, −24	Healthy subjects and subjects who completed cognitive behavioral therapy (CBT) after detoxification did not show this response

ally arise during electrical stimulation of the amygdala in women [110,111][5]. Two recent fMRI studies observed amygdala activation in subjects experiencing sexual arousal while viewing sexually explicit videos [31,151]. Additionally, the amygdala proper and/or the extended amygdala showed increased activity when men simply viewed pictures of beautiful women's faces relative to men's faces or more average female faces [11]. Thus, the material may not need to be sexually explicit for certain gender related information to engage the amygdala.

4.3. Appetitive motivation and drug craving

Another important variable in evaluating emotionally valenced stimuli reflects the motivational value of stimuli. In the present context, motivational value refers to the extent to which the stimuli motivate the person to approach/engage or withdraw from/avoid the stimuli). The appetitive motivational value (wanting) can be dissociated from how much a person likes something [11,37,273]. For instance, a picture of a chocolate cake may always be rated as pleasant, but the extent to which a person wants to eat the cake may vary widely depending upon their current level of hunger, and how many sweet foods they have recently eaten. In other words, the person's internal state may dramatically influence the incentive motivational value of stimuli.[6] LaBar and colleagues [169] provide an example of the importance of motivation in a study in which they observed left amygdala activation during exposure to pictures of food when subjects were hungry, but not when the subjects were full. However, this effect appears highly subject to individual differences. Only a minority of subjects in the LaBar study, and 3 of 10 subjects in a PET study by Morris and Dolan [201], showed enhanced responses to food pictures during hunger, indicating that this is by no means a consistent response.

Another way to study appetitive motivation is to examine anticipation of reward, which may involve either wanting or an expectancy that a reward is about to occur. O'Doherty et al. [215] recently reported a greater activation of the amygdala during anticipation of a pleasant taste (glucose) than during the actual tasting of the glucose. Similarly, Knutson and colleagues [162,163] indicate that anticipation of monetary reward leads to amygdala activa-

[5]This effect is relatively rare, and appears restricted to women.

[6]Some theorists might debate whether motivational value reflects a truly distinct concept from arousal level. However, approach and avoidance tendencies represent two different or bipolar dimensions, whereas arousal is typically treated as a unipolar dimension.

tion. Such findings are consistent with animal single cell recordings that suggest that some amygdala cells code for expected reward outcomes [259]. Anticipatory responses in the amygdala are probably not unique to rewarding conditions. For instance, Breiter et al. [46] observed certain anticipatory responses in the amygdala in a gambling simulation during trials that were likely to lead to a bad outcome. Similarly, responses during fear conditioning and explicitly instructed fear studies may be interpreted as reflecting anticipation of an aversive event.

Drugs of abuse possess extremely high appetitive motivational value in drug dependent subjects during abstinence. In both humans and animals with drug dependence, exposure to drug related cues produce craving for drugs, drug-seeking behavior, and drug-taking behavior [68,97]. Self-administration of drugs of abuse does not depend upon the amygdala. However, lesions of the amygdala abolish the ability of drug related cues to trigger drug seeking behavior [103,149,165,195,300]. Similarly, cocaine dependent subjects show increased amygdala rCBF and metabolism when exposed to cocaine related cues or cocaine related imagery during abstinence [42,69,116,158]. Moreover, the amount of cocaine craving appears to correlate with amygdala activity [42,116]. Increases in amygdala activity have also been reported in studies of abstinent smokers viewing smoking cues [93] and detoxified alcohol dependent subjects smelling ethanol relative to room air [257]. These data make clear that, at least in drug dependent subjects, amygdala activation occurs in response to cues that produce a strong incentive motivational state.

In summary, stimuli that are experienced as arousing or motivating can induce amygdala activity regardless of their valence. The idea that the arousal or motivational value of stimuli is critical to understanding amygdala processing is not novel and has parallels in the animal literature. For instance, in a series of studies with rodents, Cahill and McGaugh [58] observed that learning associated with mildly arousing appetitive and aversive stimuli was largely unaffected by amygdala lesions, whereas learning associated with a more arousing stimulus (footshock) was impaired. They interpreted this as suggesting that the amygdala's influence on learning is especially related to highly arousing stimuli. Thus, the neuroimaging data appears consistent with ideas derived from animal lesions studies.

4.4. Perceptual intensity

Pleasant stimuli may additionally activate the amygdala if they are perceptually intense. Preliminary support for this contention arises from studies in both the olfactory [274] and the gustatory domains (Dana Small, personal communication), in which perceptual intensity or stimulus concentration) was directly related to amygdala activation. This finding is notable in that highly aversive stimuli in several modalities (olfactory, gustatory and auditory) are often perceptually intense (i.e., high concentrations in the smell and taste modality, high volume at certain frequencies within the auditory domain). In contrast, pleasant stimuli are not as consistently presented at such a high perceptual intensity. It is unclear if, or how, the dimension of perceptual intensity would relate to the visual domain (e.g., luminosity, complexity, color saturation, spatial or temporal frequency, contrast), or whether visual–perceptual features distinct from recognizable content can engage the amygdala. Nevertheless, this dimension appears to warrant further exploration in future studies of amygdala processing.

4.5. The amygdala sometimes shows decreased activity in response to highly positive emotional stimuli

Despite evidence of amygdala activation by pleasant stimuli, in at least some instances positively valenced stimuli cause decreases in amygdala activity (Table 3). One of the most striking examples of such a decrease arises from a study by Blood and Zatorre [41]. These authors, observed a decrease in amygdala rCBF when subjects listened to highly pleasant, 'chill' inducing, music. The extent of the decrease correlated with subject ratings of pleasantness and chill intensity. This finding is notable in that the stimuli were experienced as highly pleasant, and were arousing enough to produce chills. Indeed, the subjects showed psychophysiological evidence of increased arousal as demonstrated by increased heart rate, respiration, and electromyogram (EMG). However, these psychophysiological effects were not directly associated with the amygdala response, in that they did not correlate with the extent of the amygdala decrease, and the relationship between chill intensity and amygdala activity remained significant even after controlling for the amount of psychophysiological activation.

Other examples of decreases in amygdala activity include viewing faces of loved ones [29], viewing happy faces [204,299], and euphoria induced by procaine [154]. These signal decreases do not always emerge in subtraction analyses, but often arise in regressions with subject's ratings of stimuli. For instance, in examining left amygdala responses to odorants, no significant changes emerged in subtraction analyses of pleasant odorants, but there was an inverse correlation with ratings of pleasantness, such that subjects who rated the stimuli as most pleasant, also showed the greatest decreases in left amygdala activity (D. H. Zald and J.V. Pardo, unpublished observation). Taken together, these data suggest that exposure to some pleasant stimuli may act to inhibit or deactivate certain amygdala-dependent processes. The range of instances in which this sort of response occurs has yet to be fully defined. However, it is notable that the declines appear most strongly associated with extreme experiences of pleasure. These stand in contrast to many of the incentive motiva-

Table 3
Decreases in amygdala signal during exposure to pleasant stimuli relative to control conditions

Author	Method	Contrast	Talairach coordinates	Comment
Viewing faces				
Morris et al. [204]	PET	Happy faces	ROI, Left	Regression of intensity of happy and fearful expressions shows less activity with increasing happiness intensity
Whalen et al. [299]	fMRI	Masked Happy faces–fixation	ROIs in each hemisphere based on activation in fear–happy contrast	Significance levels only reported for fear–happy contrasts, but inspection of ROIs shows substantial decreases in happy relative to fixation
Bartels and Zeki [29]	fMRI	Individual who the person is romantically in love with –friend	−22, −10, −26 22, −8, −22	Bilateral in women: left side only when collapsed across gender
Audition				
Blood and Zatorre [41]	PET	Highly pleasant 'chill' inducing music–non-chill inducing music	−23, −14, −23 21, −6, −21	rCBF inversely correlated with chill intensity and ratings of pleasantness

tional types of conditions that cause increased amygdala activity. Rather than invoking an incentive motivational state, the conditions leading to decreased amygdala activity tend to reflect extremely rewarding consummation experiences. One noteworthy exception to this pattern derives from a study in which cocaine dependent subjects were injected with cocaine [48]. Subjects varied in their responses with some subjects showing decreased amygdala activity and others showing increased activity. Surprisingly, changes in amygdala activity were inversely correlated with craving, such that subjects showing decreases experienced more craving than those showing increases. It remains unclear how to reconcile this finding with the other studies on drug craving and the other examples of decreased amygdala activity, although the fact that the incentive motivational state was induced by the drug itself, rather than by external cues, may represent a critical factor.

5. Facial expressions

Neuroimaging studies of responses to emotional facial expressions show strong convergence with studies of other sensory stimuli (Table 4). The amygdala shows greater and more consistent activation when humans view negative, especially fearful, facial expressions than when viewing neutral or happy expressions [47,65,114,139,204,221,229, 230,252,253,294,302,307]. These findings converge with data from patients with amygdala lesions who show selective deficits in recognizing negative emotions, especially fear [7–9,18,63,276]. Interestingly, some lesion studies have emphasized the importance of the right anterior medial temporal lobe in the recognition of negative emotional expressions [7,18], whereas the neuroimaging studies have more frequently observed left amygdala activations. Amygdala activations have also emerged when subjects view faces of people who are viewed in negative ways, such as being untrustworthy, bizarre looking or from a negatively viewed ethnic group [225,242,305].

As with the literature on positive visual stimuli, the literature on viewing positive facial expressions appears inconsistent. Some studies provide examples in which happy faces produce signal increases in the amygdala [47,114,155,164,221,307] but many do not, and in some instances happy facial expressions produce signal decreases [204,299]. Moreover, many of the examples of amygdala activations to happy facial expressions involve contrasts between happy faces and nonfacial stimuli (e.g., fixation, or objects) [114,137,155,164]. Such studies do not provide evidence of a preferential response of the amygdala to happy relative to neutral stimuli. Indeed, in one of the studies, the authors performed direct contrasts between face conditions and a nonfacial control condition, and observed greater significance levels with neutral faces than with the positive faces [137]. Elucidating the source of these discrepancies may prove informative. For instance, a recent fMRI only observed significant increases in amygdala activity to happy faces in more extraverted subjects [65]. Thus, trait personality differences across samples might explain the variability in results across studies.

Table 4
Increased amygdala activity during exposure to negative facial expressions, negatively-valenced faces, and positive facial expressions[a]

Author	Method	Contrast	Talairach coordinates	Comment
Negative expressions				
Morris et al. [204]	PET	Fearful–happy	−18, −6, −16	Focus correlated with emotional ratings
Breiter et al. [47]	fMRI	Fearful–neutral	−19, −3, −9 25, −3, −9 −28, −9, −13	
Phillips et al. [230]	fMRI	Fearful–neutral/happy	−26, −14, −13 −26, −6, −7	Foci failed to reach significance with more extreme fearful expressions
Phillips et al. [229]	fMRI	Fearful–neutral/happy	−29, −11, −13	A small focus also emerged in the left amygdala when disgust was subtracted from fearful
		Disgust–neutral/happy	26, −11, −18	
Vuilleumier et al. [294]	fMRI	Fearful–neutral	−26, 0, −20	Effect was similar regardless of whether or not face occurred at a spatially attended location
Canli et al. [65]	fMRI	Fearful–neutral	−23, −6, −18 24, −7, −17	
Williams et al. [302]	fMRI	Fearful–neutral	25, −4, −11 −25, −7, −8	Only left amygdala reached significance when limited to trials showing a galvanic skin response
Pessoa et al. [221]	fMRI	Fearful–neutral	−18, −6, −12 23, −7, −12	Differential response to fearful faces only emerged when subjects attended to the face
		Attended fearful–unattended fearful	−18, −6, −10 20, −5, −9	
		Interaction between valence (fearful and happy) and attention	−20, −9, −19	Fearful greater than happy only when faces were attended to
Baird et al. [26]	fMRI	Fearful–fixation or nonsense visual images	ROI (laterality not addressed)	Subjects were adolescents
Hariri et al. [127]	fMRI	Matching fearful and angry expressions –geometric figures	−24, −10, −22 24, −2, −22	Amygdala activation did not arise when subjects verbally labeled the facial expressions
Thomas et al. [287]	fMRI	Fearful–fixation	30, 0, −19 23, −8, −10	Male adults showed greater amygdala activation during fearful vs. neutral faces, but male children showed reverse pattern.
Kilgore et al. [155]	fMRI	Fearful–fixation	ROI (Left >Right)	Magnitude of focus not reported. Laterality effect not seen when women analyzed separately
Iidaka et al. [139]	fMRI	Gender discrimination of negative expressions –gender discrimination of neutral	−26, −4, −14	

Table 4. Continued

Author	Method	Contrast	Talairach coordinates	Comment
Iidaka et al. [137]	fMRI	Discrimination of negative from neutral expressions–discrimination of size of rectangles	22, −8, −16 −18, −6, −16	Response seen in young adults but not elderly subjects
Kosaka et al. [164]	fMRI	Discrimination of negative from neutral expressions–discrimination of size of rectangles	22, −2, 10	
Gorno-Tempini et al. [114]	fMRI	Disgust–scrambled faces	−24, −8, −20	Effect emerged for both explicit judgments and implicit (gender) judgments
		Explicit disgust–Explicit happy	−28, 0, −20	
Schneider et al. [253]	PET	Sad–happy (subjects told to feel the emotion)	ROI, Left	Significant increase in left amygdala ROI relative to right amygdala ROI
Schneider et al. [252]	fMRI	Sad–neutral (subjects told to feel the emotion)	Left, NG	
Schneider et al. [256]	fMRI	Interaction between condition (sad, happy, neutral) gender and laterality (subjects told to feel the emotion)	ROI	Right amygdala activated during sad condition in men, but not women
Blair et al. [40]	PET	Increasing intensity of sad relative to angry expressions	−20, −10, −18	
Wright et al. [307]	fMRI	Schematic drawings of angry faces–neutral faces	ROI, Left	Angry faces did not produce significant greater activity than happy faces
Whalen et al. [299]	fMRI	Masked fearful faces–masked happy faces	18, −6, −15 −15, 0, −12	
Rauch et al. [239]	fMRI	Masked fearful faces–masked happy faces	−28, −6, −9	Coordinates based on combined sample of PTSD patients and normal controls
Other negatively valenced faces				
Phelps et al. [225]	fMRI	Caucasians viewing black vs. white faces	−18, −5, −11	Focus represents the area that correlated with an implicit measure of racism
Rotshtein et al. [242]	fMRI	Expressional Transfiguration–upright faces	Right>Left, NG	Amygdala activity correlated with ratings of bizarreness and emotional load
Winston et al. [305]	fMRI	Untrustworthy through trustworthy faces (parametric effect of untrustworthiness	18, 0, −24 −16, −4, −20	Effect seen in both implicit and explicit conditions, and when controlling for ratings of facial expression (in the right amygdala)
Positive expressions				
Breiter et al. [47]	fMRI	Happy–neutral	ROI Left anterior	Did not emerge when fear presented before happy. Response showed habituation

Table 4. Continued

Author	Method	Contrast	Talairach coordinates	Comment
Pessoa et al. [221]	fMRI	Happy–neutral	NG	No significant response to happy faces vs. neutral faces when faces were unattended
		Attended happy–unattended happy	−18, −5, −9 21, −5, −9	
Gorno-Tempini et al. [114]	fMRI	Happy–scrambled faces	−24, −8, −20 −24, −8, −16	Effect emerged for both explicit expression and implicit (gender) judgments
Kilgore et al. [155]	fMRI	Happy–fixation Males Females	ROI Right>Left Left>Right	Magnitude of foci not reported in either hemisphere
Wright et al. [307]	fMRI	Schematic drawings of happy–neutral faces	ROI, Left	
Canli et al. [65]	fMRI	Happy–neutral	−22, −9, −20	Focus represents the area in which activation correlated with extraversion ratings. Activation not seen in group subtraction analysis
Kosaka et al. [164]	fMRI	Discrimination of happy and neutral–discrimination of the size of rectangles	−22, −6, −8 20, 0, −16	
Iidaka et al. [138]	fMRI	Discrimination of happy and neutral–discrimination of size of rectangles	18, −2, −18 −14, −4, −20	Effect only seen in young adult subjects and not older adults

[a] Studies are included in the table even if the emotional faces are contrasted with nonfacial stimuli. Contrasts of emotional faces with nonfacial stimuli must be interpreted cautiously, because the activity may be no greater than that produced by neutral faces.

6. Semantic and nonverbal auditory processing

Studies on the processing of emotionally meaningful words parallel those of other emotionally meaningful stimuli (Table 5). Specifically, the amygdala shows a responsiveness to aversive or threatening words relative to neutral words [124,143,280,283]. This indicates that emotionally valenced semantic processing can activate some of the same limbic circuits as stimulation with sensory stimuli. Using a list of what were described as high-arousal positive words (e.g., ecstasy, thrill), Hamann et al. [124] recently reported that positively valenced words are also capable of engaging the amygdala.

From an evolutionary perspective, one might expect that perception of nonverbal emotional vocalizations (fear sounds, prosody, etc . . .) would be more closely tied to the amygdala than verbal aspects of language. However, studies of nonverbal processing have provided inconsistent results. Two patients with bilateral amygdala lesions have been reported who displayed impaired auditory recognition of fear [260,276]. In contrast, other researchers have failed to replicate this finding, even in patients who showed impairment in the visual recognition of fear [5,15]. This discrepancy may relate to the involvement of additional structures in the patients displaying the deficits, although this hypothesis has never been formally tested. Neuroimaging studies of nonverbal aspects of emotional vocalizations indicate that the amygdala is responsive to nonverbal vocalizations, although a fully coherent picture of when the amygdala activates remains lacking. For instance, Sander et al. [247] observed increases, particularly in the right amygdala, during exposure to both laughter and crying. Similarly, Phillips et al. [229] reported increased signal in the right amygdala/hippocampus region in response to fearful vocal expressions relative to mildly happy sounds. In contrast, Morris and colleagues [206] observed fear-specific decreases in the right amygdala relative to happy, sad and neutral sounds. Fear-related sounds may also modulate amygdala responses to stimuli arriving from other sensory modalities. For instance, Dolan et al. [89] indicate that hearing congruent fear sounds enhances amygdala responses to fearful faces compared to when fearful faces are shown with incongruent happy sounds. While such data suggest certain specific effects of

Table 5
Amygdala modulation during emotional linguistic processing and nonverbal expressions

Author	Method	Contrast	Talairach coordinates	Comment
Linguistic				
Crosson et al. [77]	fMRI	Generating emotional words–repeating neutral words	−21, −7, −22 −15, 10, −7	Only measured left hemisphere activity/foci extend into hippocampus and hypothalamus
Isenberg et al. [143]	PET	Threat words–neutral words	24, −8, −18 −32, −6, −18	
Strange et al. [280]	fMRI	Emotional odd balls (negatively valenced words embedded in a string of nonaversive semantically related words)	−27, −9, −12	Responses occurred regardless of depth of processing
Tabert et al. [283]	fMRI	Unpleasant words–neutral words	26, −6, −12	Subjects were selecting words that were the most unpleasant or most neutral respectively
Hamann et al. [124]	fMRI	High arousal negative words–neutral words High arousal positive words–neutral words	−24, −8, −16 −24, −8, −20	
Moll et al. [198]	fMRI	Unpleasant sentences–neutral sentences	−20, −12, −6	
Nonverbal				
Morris et al. [206]	fMRI	Listening to fearful sounds–happy, sad and neutral sounds	↓−18, −4, −22	Focus represents a *decrease* in amygdala activity
Phillips et al. [229]	fMRI	Listening to fearful sounds–mild happy	12, −19, −13	Focus described as amygdala/hippocampus
Sander and Scheich [247]	fMRI	Listening to laughter –silence or aurally presented math problems Listening to crying –silence or aurally presented math problems	ROI Bilateral (greater right) Bilateral (greater right)	Whether laughter or crying produced greater effects varied depending on control condition

vocalizations on amygdala activity, the current literature does not support a broader role for the amygdala in processing prosody in language [7,49,109,140,229].

7. Contrasting the effects of positively and negatively valenced stimuli

In a recent meta-analysis of studies involving emotional inductions, exposure to pleasant or unpleasant pictures or sounds and exposure to emotional facial expressions or prosody, Wager and colleagues [295] reported 38 foci arising in either amygdala in response to negatively valenced stimuli relative to only 5 for positively valenced stimuli. Although the meta-analysis did not include a number of the examples of highly arousing or motivating positively valenced conditions that have been described in the previous sections, the ratio of negative to positive studies is nonetheless striking.

Surprisingly, only a relatively small number of studies have provided specific contrasts of pleasant and unpleasant stimuli. When such contrasts reach statistical significance, they indicate greater activation during exposure to the unpleasant stimuli. This has occurred in the olfactory [317], gustatory [314], and visual [159,217] modalities, and with negatively valenced vs. positively valenced faces [114,204,221,239,253,299]. However, studies frequently find no significant differences between pleasant and un-

pleasant stimuli, and this appears especially evident in studies where care has been taken to balance the pleasant and unpleasant stimuli in terms of both intensity and arousal level [108,174,286].

As touched on above, it is difficult to match strongly pleasant stimuli with strongly unpleasant stimuli in terms of valence intensity, arousal level and motivational value. In particular, highly aversive stimuli are almost always experienced as highly arousing and motivating (rarely do we dislike a stimulus without being motivated to terminate it), whereas highly pleasant stimuli may be associated with varying degrees of arousal level and motivational value (e.g., we may feel that a picture or a piece of music is beautiful, but experience little arousal or motivation to obtain or even continue exposure to the stimulus). These differences are not simply a result of poorly chosen laboratory stimuli, but rather reflect psychological differences in the perception of emotionally valenced stimuli. Specifically, mammals respond with greater intensity to unpleasant stimuli. This phenomenon is referred to in the psychological literature as the *negativity bias*. The negativity bias is a well documented, and robust phenomenon that has been demonstrated to effect behavioral, cognitive, and physiological responses in a wide range of species and situations [53]. Such a bias possesses a strong adaptive benefit since in most situations we may postpone coming in contact with positive stimuli, but we cannot afford to postpone avoiding aversive and potentially harm-inflicting stimuli. More consistent or robust amygdala activations to unpleasant emotional stimuli may simply represent a neurobiological correlate of this bias.

The greater consistency of responses to negatively valenced stimuli converges with clinical studies of humans and animal lesion studies. For instance, intraoperative electrical stimulation of the amygdala and amygdala seizures frequently produce negative emotions or negatively valenced sensory hallucinations, but rarely produce positively valenced emotions or hallucinations [111]. Humans with amygdala lesions have been reported to show specific reductions in negative emotions such as anger, without accompanying descriptions of a loss of specific positive emotions [10,209].[7] A similar bias also appears in the animal conditioning literature. Numerous studies have observed deficits in fear-related responses to aversively conditioned stimuli following amygdala lesions in animals [183]. Although the range of situations and responses under which the deficits occur and the critical processes accounting for the deficits remain active areas of study and debate, the number of studies demonstrating the effect is substantial.[8] The amygdala is also implicated in certain types of reward learning [30,54,107,152,153,220]. Yet, the literature on the amygdala involvement in appetitive or reward learning is substantially smaller than the literature on aversive conditioning. This difference may in part arise as an artifact of research interests and funding, or the greater frequency and ease with which negative stimuli induce arousal and strong motivational states. Alternatively, the contrast in the size of these literatures may reflect an innate negativity bias in amygdala processing. Regardless of the source, the neuroimaging and animal lesion data converge on a similar pattern of results.

8. Habituation, temporal characteristics and novelty

Amygdala responses demonstrate rapid habituation (Table 6). This pattern of decreasing responses during repeated exposure to stimuli has been observed during exposure to unpleasant visual stimuli [188,285], fearful faces [47,227,287,306], novel ingroup faces [129], and complex visual stimuli [100]. This decline may reflect a process through which stimuli are rapidly reevaluated based on the lack of consequences arising from their previous exposure. Habituation may not occur universally, but may reflect a selective process. For instance, Hart et al. [129] observed rapid habituation of responses to faces from the same ethnicity, while showing sustained responses to faces from outside the subjects ethnicity. Such valence-specific habituation effects may critically alter contrasts between stimuli. Taken together, this line of research indicates that the temporal pattern of amygdala responses is more complex and dynamic than is captured by the temporally fixed (stationary) models that characterize most fMRI analyses.

Habituation in the above studies refers to decreased responses over repeated stimulations. A related issue reflects the extent to which responses occur transiently at the start of a stimulus or whether they are sustained throughout a prolonged stimulus exposure. For instance, when examining olfaction, Poellinger et al. [232] observed significant amygdala responses to relatively brief 9-s stimulations, but failed to observe activations during

[7] It is possible that this difference does not reflect a negativity bias as much as an influence on extreme states of arousal. Since extreme states of positive arousal are likely to be both less frequent and less problematic, these may simply not get reported.

[8] While the effects of amygdala lesions have typically been interpreted as reflecting a critical involvement of the amygdala in the acquisition of fear conditioning, several investigators have questioned the generalizability and nature of the amygdala's role. The debate centers on two primary issues. First, examples exist in which basolateral amygdala lesions (a critical site in many fear conditioning studies) have failed to eliminate the expression or reacquisition of certain fear-related responses [60,157,219]. Second, some data indicate that lesions impair unconditioned fear responses [293]. Because the status of unconditioned responses are often not tested following lesions, such response deficits might be inappropriately interpreted as reflecting conditioning deficits rather than response deficits).

Table 6
Studies demonstrating marked temporal features or habituation in amygdala responses

Author	Method	Contrast	Talairach coordinates	Comments
Faces				
Breiter et al. [47]	fMRI	Fearful faces–neutral faces	−19, −3, −9 25, −3, −9 −28, −9, −13	Response at these foci only seen in early blocks
Hart et al. [129]	fMRI	Outgroup faces–ingroup faces	−15, −6, −15 9, −6, −15	The difference only emerged in later stimulus presentations, because subjects habituated more to ingroup faces
Phillips et al. [227]	fMRI	Fearful faces–neutral faces	ROI	Right amygdala showed more rapid decline in response to fearful faces than left amygdala
Thomas et al. [287]	fMRI	Fearful faces (block 1 vs. block 2)	18, −2, −26	
Emotional vision				
Taylor et al. [285]	PET	Unpleasant pictures–neutral pictures (tasks: rating first, recognition second)	−15, −13, −18 −17, −4, −11	Foci emerged first time subjects saw pictures, but not second time, but task is a confound.
Liberzon et al. [188]	PET	Unpleasant pictures–neutral pictures (tasks: rating first, recognition second)	24, −8, −14	Foci emerged first time subjects saw pictures, but not second time, but task is a confound.
Emotional language				
Tabert et al. [283]	fMRI	Unpleasant words–neutral words (tasks: hedonic decision first, recognition second)	26, −6, −12	Foci emerged first time subjects saw pictures, but not second time, but task is a confound.
Conditioning				
Büchel et al. [51]	fMRI	CS+ vs. CS− (time by condition interaction)	−24, 3, −24 27, −3, −24	Early acquisition greater than late acquisition
LaBar et al. [167]	fMRI	CS+ vs. CS− (early acquisition) CS+ vs. CS− (early extinction)	14, −4, −19 17, −4, −11	Effects emerge in early stages rather than later stages
Büchel et al. [50]	fMRI	Trace conditioning CS+ vs. CS− (time by condition interaction)	24, −3, −24 −21, −6, −24	Early acquisition greater than late acquisition
Morris et al. [199]	fMRI	Masked conditioning CS+ vs. CS− (time by condition interaction)	−18, 2, −14	Early acquisition CS+ higher than CS−, late acquisition direction reversed
Olfaction				
Poellinger et al. [232]	fMRI	Increase to a 9-s odorant exposure Decrease to a 120-s odorant exposure	12, −6, −15 −25, −15, −15 −21, −9, −9	Initial phasic increases followed by sustained decreases with prolonged exposure

prolonged stimulations. Temporal issues of this kind have not been widely explored, and there may exist differences in the extent to which different classes of stimuli produce transient versus prolonged firing. One can easily envision how this might affect results in different types of paradigms. For example, PET studies using prolonged stimulations have had difficulty observing robust activations in the amygdala during exposure to pleasant tastes

and flavors [273,312,314]. In contrast, using fMRI, O'Doherty and colleagues [214] observed amygdala activations during brief exposures to sweet tastes. Such a difference could easily result if sweet tastes produce only brief transient responses. Moreover, the greater ability of aversive stimuli to activate the amygdala in PET studies, might result from their ability to cause sustained activity, whereas in fMRI studies this relative advantage may disappear due to the use of brief stimulations, or analytic techniques that emphasize brief time-locked activations.

The tendency for the amygdala to respond during early exposures to stimuli is also reflected in its response patterns during aversive ('fear') conditioning. Specifically, several studies have indicated that the CS+ causes amygdala activation relative to the discriminative stimulus (CS−) early in acquisition, but this response decreases, and may even appear as a deactivation later in the conditioning process [50,51,167,199]. This effect does not appear to occur in all portions of the amygdala [199], nor in all conditioning paradigms [21,76]. While the conditioning parameters that influence whether or not one sees a decreasing response to the CS+ over time remain unclear, the observation of decreases in several studies makes evident that careful attention must be paid to the temporal features of the conditioning process.

The flip side of amygdala habituation lies in the amygdala's responsiveness to novel stimuli. Electrophysiological studies in animals [187,213,261,304,304] have often highlighted the effect of novelty on amygdala processing and amygdala lesions dramatically reduce neophobia [52,94,208,267]. Neuroimaging studies support this contention. For instance, Small et al. [272] observed left amygdala activation during exposure to novel flavors (taste/smell combinations) relative to exposure to the same stimuli with traditional taste/smell combinations. In the visual modality, Hamann et al. [126] observed left amygdala activation during exposure to unusual pictures (e.g., a chrome rhinoceros, scenes from a surrealistic film, etc.) relative to low-interest scenes (e.g., plants, household scenes, etc.). This finding is notable in that the unusual scenes were given an overall neutral rating, and did not produce high levels of arousal, but were nevertheless capable of activating the amygdala. In the face domain, Rotshtein et al. [242] observed amygdala activation during exposure to faces with expressional transfiguration. Interestingly, the amount of activation correlated with ratings of bizarreness.[9] Taken together these studies suggest that unusual, novel stimuli may engage amygdala processing. This may represent a problematic confound in some studies of emotional processing, since unpleasant stimuli are often more novel than pleasant stimuli.

9. Subliminal processing

Since the early writings of Freud, the role of unconscious processing has been of fundamental interest to psychologists and psychiatrists. Renewed interest in unconscious mechanisms has emerged in recent years with the development of empirical methods for assessing unconscious and preattentive processing of negatively valenced and aversively conditioned stimuli [216]. This has been most dramatically demonstrated by studies utilizing masked stimuli that can elicit autonomic responses without subjects' conscious awareness of the stimuli. Consistent with the amygdala's role in the conscious processing of fearful faces, fMRI data demonstrate amygdala activations during masked exposure to fearful facial expressions [239,299]. Similar increases appear during conditioning to masked faces [76,199,205]. Exposure to a candidate pheromone (oestra-1,3,5(10),16-tetraen-3yl acetate), that was not consciously perceived, has also been reported to cause an increase in BOLD signal within the amygdala [275]. These studies indicate that the amygdala can respond to stimuli despite the subject's lack of declarative knowledge of the stimuli's relevance or existence. Such unconscious processing may rely on projections to the amygdala from thalamic sensory relay nuclei [90]. These projections may allow certain crude sensory information to reach the amygdala extremely rapidly, because it bypasses the multiple layers of cortical processing that are required for the more detailed perception and recognition of stimuli. Indeed, studies of rodents indicate that fear conditioning can occur with auditory or visual stimuli in the absence of their respective sensory cortices [23,184,240]. Similarly, De Gelder et al. [85] have reported a patient, G.Y. who can discriminate facial emotion of pictures presented to his blind hemifield at above chance levels despite lesions to his striate cortex that prevent him from having awareness that he has seen a face. When scanned with fMRI, the patient showed amygdala activations in response to unconditioned fearful faces relative to happy faces presented to his blind hemifield, and additional activations during acquisition of aversive conditioning with a visual CS+ presented to the blind hemifield [200]. The rapid, direct thalamic route may help prime or focus attention on potentially emotionally significant stimuli both at the level of the amygdala and in turn at earlier stages of cortical processing [22] (see [216] for a review of the effects of preattentive processing of emotionally significant stimuli on cognitive processes). However, it is unclear how the geniculate could provide information on something as complex as emotion recognition given the rudimentary nature of visual coding in the geniculate. At best, the direct thalamic route may come at a cost due to the crudeness of

[9] On a related topic, Dubois et al. [92] observed greater left amygdala rCBF when subjects performed gender categorization of unknown faces than when they performed similar categorizations of previously seen faces. However, other studies in the memory and face processing literature have generally not supported a specific response in the amygdala to stimuli that are unfamiliar but typical.

its representations. For instance, one can envision this system leading to inappropriate triggering or overgeneralization of responses due to an inability to differentiate similar, but distinct, stimuli.

10. Laterality issues

Most animal studies of amygdala functions have treated the two amygdalae as functionally equivalent. Hence, most lesion studies utilize bilateral amygdala lesions. Similarly electrophysiological studies rarely report which hemisphere the recordings come from. Neuroanatomical studies also do not generally report which hemisphere the connections were measured in. In some cases the assumption of equivalence may be justified. For instance, unilateral amygdala lesions in rodents [170] and medial temporal lobe lesions in humans [166] appear to attenuate, but not block, fear conditioning, with little effect of side of lesion. However, in other instances, there appear to be significant asymmetries between the functions of the right and left amygdala. For instance, in rodents, right amygdala lesions appear to produce substantially more decrements on certain paradigms related to the expression or consolidation of memories for aversive events [70–72].

While many neuroimaging studies observe bilateral responses during emotional studies, unilateral responses at the group subject level are also common. fMRI studies frequently show individual differences in the lateralization of responses, with some subjects demonstrating right amygdala foci while other subjects show left amygdala foci.[10] Such findings suggest that the two amygdalae do not perform entirely equivalent functions. Moreover, some data suggest that there exist structural differences in the size of the two amygdalae, with the right amygdala reaching larger volumes than the left amygdala (particularly in right handed subjects) [282]. Thus, although the right and left amygdala surely show some degree of functional redundancy, it is reasonable to expect quantitative or qualitative differences in the two amygdalae's involvement in different functions.

10.1. Models of emotion lateralization

Neurobehavioral models of emotion frequently emphasize the asymmetric involvement of the cerebral hemispheres in emotional processing. Three basic models have been posited. The oldest of these models holds that the right hemisphere is dominant for emotional processing. This *right hemisphere dominance* model derives largely from the effects of cortical lesions on emotional recognition, and expression [44,131]. An alternative view of the lateralization of emotions posits that the left hemisphere is preferentially involved in positive emotions and approach, whereas the right hemisphere is preferentially involved in negative emotions and withdrawal [83,270]. This *valence-specific* hypothesis derives from the emotional reactions arising from lateralized frontal brain lesions, asymmetries in anterior EEG alpha power during emotional inductions and the relationship between resting anterior EEG alpha power asymmetries and the propensity towards positive or negative emotional reactions [79–82,246,288]. When interpreted broadly as reflecting all aspects of emotion, these two models appear in conflict. However, it is worth noting that the data supporting each model capture different aspects of emotional processing. Specifically, the right hemisphere dominance model derives from studies with emotional perception and expression, whereas the valence-specific model derives from data regarding emotional experience. A *hybrid model* incorporates these differences, and posits that the right hemisphere is dominant for the perception and expression of emotions, but that subjective emotional experience shows a valence-specific pattern of lateralization [79]. It is also important to note that although some investigators have interpreted the valence-specific model as referring to the entire hemisphere, much of the data supporting the hypothesis appear specific to the prefrontal cortex only [80,82] and thus theorists often restrict the valence-specific model to the prefrontal cortex. A failure of amygdala activations to conform to a left-positive/right-negative dichotomy only challenges a hemisphere-wide conceptualization of the valence-specific hypothesis, and does not contradict more restricted models that only focus on the prefrontal cortex.

The pattern of amygdala responses observed in neuroimaging studies does not conform closely to any of the three models outlined above. Responses to sensory stimuli are particularly inconsistent with existing models. In the visual domain, responses to unpleasant pictures are almost always left lateralized or bilateral [66,126,141,176,188,218,285]. Subjective ratings of emotional intensity of pictures have been similarly reported to be either left lateralized or bilateral [64,66]. In the olfactory domain, the right pyriform/amygdala region appears more generally sensitive to odorants [249,250], which is consistent with a right hemisphere dominance for olfactory processing [146,320,321], but responses in the left amygdala appear more specific to aversive odorants [317]. Indeed, correlations with the aversiveness of odorants have only been reported in the left amygdala [233,316,317]. Studies of gustatory/flavor responses have been less clear, with some studies observing right amygdala [314] and others observing left amygdala responses [272,312]. Both amygdalae appear responsive to aversive auditory stimulation [197,318]. Similarly, both amygdalae show responses to aversive interoceptive information [45,96].

Studies of negative linguistic material also show more

[10]Caution must be taken in interpreting lateralized amygdala responses at the individual subject level in fMRI studies because such responses may reflect asymmetric signal to noise deficits due to susceptibility artifacts which may differ across hemispheres [168].

frequent activation of the left than right amygdala (see Table 5). However, this pattern may relate more to the left hemisphere dominance for language, rather than representing the negative aspects of the stimuli. It is notable in this regard that the lateralized response appears to extend to positive stimuli as well as negative stimuli.

Studies of negative emotional facial expressions converge with studies of unpleasant sensory stimuli in that responses to fearful facial expressions typically localize to the left amygdala or occur bilaterally [47,204,221,229, 287,294,299]. Unlike the verbal linguistic findings, this asymmetry cannot be attributed to a more global lateralization of face processing, since most literature points to a greater role for right than left hemisphere structures in face processing [78]. Moreover, lesion studies indicate that right anterior–medial temporal lesions cause significantly greater impairments in recognizing negative facial expressions than similarly placed lesions in the left hemisphere [7,18]. Thus, the lesion data fits well with traditional models of emotional lateralization, while the neuroimaging data fails to support it. Understanding these conflicting lines of data poses a major challenge. Perhaps the lesion literature reflects involvement of other temporal cortical regions that show lateralized functions, whereas the neuroimaging data avoids this confound. Alternatively, the right amygdala may indeed be more essential for successful recognition of facial emotions, but the left amygdala may show equal, or greater, responses in neuroimaging studies due to asymmetric factors that are not essential for successful recognition. This would represent an example of the classic distinction between defining what areas are involved in (or activated during) a task vs. what areas are necessary for the performance of a task. Accepting this distinction does not answer why the left amygdala is as responsive, or more responsive, to negative faces than the right amygdala, but does provide a starting point for understanding the differences in the neuroimaging and lesion literatures.

In their meta-analysis of emotional induction and exposure to pleasant or unpleasant auditory and visual stimuli, Wager et al. counted 26 examples of left amygdala activations during negative or withdrawal conditions, relative to only 12 examples of right amygdala activation. Taken together, these data indicate that, if there is a pattern of lateralization related to negative affect or withdrawal in the amygdala, it involves a greater involvement of the left amygdala in association with negatively valenced stimuli. This conclusion converges with recent EEG data linking left temporal regions with negative affectivity [119,120].

No clear pattern of lateralization emerges for positive stimuli. A review of Table 2, which lists activations in response to positive stimuli, and Table 4, which includes responses to happy faces, reveals about an equal number of left lateralized, and bilateral activations, with slightly fewer, right lateralized activations. This provides, at best, only weak support for a hemisphere-wide valence specific-hypothesis. Such a contention is further weakened by the far greater frequency of left-lateralized responses induced by negatively valenced stimuli. The pattern across both negative and positive stimuli clearly runs counter to the right-hemisphere dominance hypothesis.

10.2. Other hypotheses regarding lateralization

It has previously been suggested that novelty may also influence laterality. This issue was originally raised in the context of taste studies in which more novel unpleasant tastes or flavors activated the left amygdala [272,312], while familiar tasting unpleasant stimuli activated the right amygdala [314]. The contention finds support from the work of Hamann et al. [126] who observed left lateralized activation during exposure to unusual, high interest pictures. However, the hypothesis has not been exposed to rigorous testing. Moreover, expressional transfiguration, which creates novel and bizarre looking faces has been reported to produce greater right than left amygdala activation [242]. Thus, the generalizability of the effect remains questionable.

As previously mentioned, the amygdala appears capable of processing information that is outside of conscious awareness. Based on a conditioning paradigm using masked and unmasked angry faces, Morris et al. [205] hypothesized that the right amygdala is more involved in responding to unconscious emotionally meaningful stimuli, whereas the left amygdala is more involved in the conscious processing of such stimuli. However, other studies of aversive conditioning of masked and unmasked faces [21,76,167,199] and of unconscious processing of unconditioned stimuli [299], do not support this hypothesis. Dolan and Morris [88] have also suggested that laterality differences may reflect innate vs. conditioned fearful stimuli with the left amygdala playing a greater role in response to innately fearful stimuli. The literature on responses to unconditioned stimuli provide some support for this hypothesis, but, the frequency of left amygdala responses during conditioning does not support the contention that the right amygdala plays a preferential role in conditioning [21,50,51,166,167,199].

Phelps and colleagues have recently provided an alternative model of lateralization, in which cognitively learned fear (anticipatory anxiety) depends upon the left amygdala, whereas experientially learned fear depends upon the right amygdala [104,226]. This model derives from the finding that patients with left medial temporal, but not right medial temporal, lesions show enhanced startle in response to a stimulus that they have been told might lead to a shock [104]. In contrast, patients with right medial temporal, but not left medial temporal, lesions show enhanced startle when exposed to unpleasant pictures. This pattern is supported by neuroimaging data showing left, but not right, amygdala involvement in cognitively mediated anticipatory anxiety [226]. This also appears consistent with

the involvement of the left amygdala in processing verbal (semantic) threat stimuli [77,280]. The lateralization across the cognitively mediated and experientially mediated conditions thus may reflect the left hemisphere dominance for verbal stimuli. Alternatively this could reflect differences in top–down (cognitively mediated) vs. bottom up (sensory driven) processing. In considering these hypotheses, it should be noted that although lesion data suggest that the ability of negatively valenced sensory stimuli to modulate startle depends upon the right amygdala [19], the neuroimaging data indicate that these same stimuli frequently cause left amygdala activations. This left amygdala activation is probably not crucial for startle modulation. However, it clearly indicates that visual sensory information can engage both amygdalae.

Finally, differences in the temporal pattern of firing or the rate of habituation may distinguish the two amygdalae. Specifically, the right amygdala demonstrates more rapid habituation to fearful faces than the left amygdala [227,306]. The more sustained response of the left amygdala may help to explain why it more frequently reaches statistical significance than the right amygdala. In other words laterality differences in many studies might reflect differences in the lateralization of sustained vs. transient responses.

11. The functional consequences of amygdala engagement

To a large extent this article has concentrated on the simple question of what types of stimuli or cognitive demands cause changes in activity within the human amygdala, or more specifically, what types of stimuli cause large enough changes in amygdala activity to be detected with current neuroimaging techniques. Additionally, this article has touched upon several functional consequences of human amygdala processing. A few of these potential functions warrant further elaboration.

11.1. Memory enhancement

It has long been known that emotionally arousing information is recalled and recognized better than emotionally neutral material [144]. Both neuroimaging studies and studies of patients with amygdala lesions converge on the importance of the amygdala in enhancing the retention of emotionally-valenced information [3,25,55–57,64,66,67, 123,125,172,192]. Patients with amygdala lesions fail to show the memory enhancing benefit of emotionally arousing stimuli. Moreover, the neuroimaging data indicate a correlation between amygdala activation for emotionally intense material and the later recognition of the material. These data converge with a large animal literature on the ability of the amygdala to modulate memory acquisition [59]. This modulatory process appears relevant to enhancements of both pleasant and unpleasant, emotionally arousing stimuli (Table 7).

11.2. Conditioning

Conditioning provides clear adaptive advantages. A substantial body of work in rodents has focused on the role of the amygdala in the acquisition of fear conditioning [182]. Although some important criticisms of this literature remain unaddressed [61], it is clear that animals with amygdala lesions fail to show the normal expression of a number of 'fear-related' behaviors in response to aversively conditioned stimuli. Studies of humans with selective amygdala lesions [33] or unilateral temporal lobectomies [171] are supportive of the hypothesis that the amygdala is involved in aversive conditioning. Differential amygdala responses to the CS+ relative to the CS− in neuroimaging studies of conditioning, further support this involvement [21,50,51,76,167,199,205]. However, the human literature leaves a host of questions unanswered. For instance, patient studies have not addressed the range of unconditioned stimulus types (e.g., different sensory modalities, arousal level, or valence), conditioning paradigms, (e.g., trace-conditioning, partial-reinforcement schedules), or response types (e.g., avoidance behaviors, subjective emotional experience), that actually require amygdala processing. Given the animal literature, it is likely that not all types of conditioning will depend upon the amygdala. This contention is supported by the amnesic patient Boswell, who was able to develop associations between affective valence and new persons despite the presence of extensive bilateral medial temporal lobe lesions that left him with no declarative knowledge of previous interactions [289]. Unfortunately, data addressing this issue are likely to be acquired quite slowly due the paucity of available subjects with complete, selective bilateral amygdala lesions. Patients with unilateral medial temporal lesions can provide information regarding these issues, but are limited by the possible effects of lesions to other medial temporal lobe structures and the difficulty in interpreting negative findings (since conditioning may be mediated by the intact amygdala in the opposite hemisphere). Although neuroimaging studies provide information regarding if and when the amygdala becomes active during conditioning, no studies have ever addressed whether this observed activity is actually required for conditioning to occur. For instance, one study reported anterior medial temporal lobe activation during preference conditioning [145], but it is possible that this activity was not actually necessary for the conditioning to occur. Thus, this area of research remains ripe for further exploration.

11.3. Attention modulation

We preferentially attend to emotionally meaningful stimuli. Indeed, emotionally meaningful visual or verbal stimuli can break through into our conscious awareness to

Table 7
Correlations of amygdala activity and later recognition of information

Author	Method	Contrast	Talairach coordinates	Comments
Cahill et al. [56]	FDG-PET	Emotional film clips	19, 5, −16	Correlation with delayed recall
Canli et al. [67]	fMRI	Positive and negative visual pictures	−21, −4, −16 15, −7, −10	Activation to negative correlated with recognition of negative and positive
Hamann et al. [125]	PET	Gruesome visual stimuli	−13, −7, −18 17, −7, −18	Correlation with delayed recognition but not recall
		Erotic visual stimuli	−21, −4, −10 19, −9, −10	
Morris and Dolan [201]	PET	Pictures of food (combined over both hungry and sated states).	−14, −4, −20	The same region showed a negative correlation with recognition of nonfood items
Cahill et al. [57]	FDG-PET	Emotional film clips–Neutral film clips		Results based on conjunction analysis of areas showing increased activity and activity correlating with memory enhancement
		In males	22, 4, −24	
		In females	−14, 2, −22	
Canli et al. [66]	fMRI	Visual pictures ranging from neutral to highly unpleasant	−20, −10, −14	BOLD response correlated with unpleasantness and delayed recognition
Canli et al. [64]	fMRI	Visual pictures ranging from neutral to highly unpleasant		Foci represent the area showing correlation with later recognition memory
		In males	16, −8, −17	
		In females	−25, −8, −17	

a far greater degree than emotionally neutral stimuli. For instance, in the attentional blink paradigm, which allows assessment of the degree to which stimuli are perceived under conditions of limited attention, negatively valenced stimuli show a preferential ability to break through into awareness [16]. Patients with left anterior–medial temporal lesions or bilateral amygdala lesions fail to demonstrate the normal attenuation of the attentional blink when exposed to aversive words [16]. The amygdala's ability to modulate the attentional blink may derive from the rapid, but crude, information that it receives from thalamic sensory relay nuclei. Once identified as significant, the amygdala may utilize two separate pathways to modulate attention. First, the central nucleus sends projections to both cholinergic and noradrenergic cells capable of exerting widespread effects on attention [24,150]. Second, the amygdala possesses robust projections to cortical sensory regions [14]. It is notable in this regard that cortical sensory regions show enhanced responses during exposure to emotionally valenced or conditioned sensory stimuli [179,202,203,235, 283]. In neuroimaging studies, this enhancement is correlated with the amount of amygdala activation [202, 203,283]. Moreover, the enhancement of cortical processing can occur even beyond primary sensory regions. For instance, in rodents, low intensity stimulation of the basal amygdala causes marked enhancements of frontal lobe EEG responses to noxious stimuli [91].

The above conclusions are similar to a hypothesis developed by Gloor [110,111] based on the experiential phenomena induced by seizures or electrical stimulation of the human amygdala. Gloor was struck by the wide range and affective tone of perceptual and experiential phenomena arising from such stimulation. Based on these data, he speculated that that the amygdala plays an 'important role in determining which sensory data and which memories at any given time emerge into consciousness' [110]. He further argued that the affective or motivational features represent the core determinants of which stimuli the amygdala allows to emerge into consciousness. Thus there appears to be a strong convergence between ideas arising from the human electrophysiological, neuropsychological, and neuroimaging literatures.

11.4. Startle, hormonal and autonomic modulation

Models of amygdala functioning frequently emphasize the amygdala's projections to brainstem regions controlling motor, and visceromotor responses, and hypothalamic areas controlling hormonal responses [84,183]. These output systems are generally not under the exclusive

control of the amygdala, leaving patients capable of responding to many classes of stimuli in the absence of a functioning amygdala. For instance, humans with bilateral amygdala lesions are still capable of demonstrating galvanic skin conductance responses (GSR) to orienting stimuli, although the degree of the response may be reduced (but not abolished) [32,185,186,290]. Similarly, animals and humans with amygdala lesions still show startle responses, although even nonpotentiated startle can be reduced (but not abolished) by amygdala lesions [19,136]. Nevertheless, lesions may preferentially weaken or impair the ability of certain classes of stimuli or situations to modulate these output regions. For instance, humans with amygdala or broader medial temporal lobe lesions fail to show the normal potentiation of startle during presentation of negative emotional pictures or anxiety provoking instructions [19,104]. Humans with amygdala or medial temporal lesions also show deficits in GSR during fear conditioning paradigms [32,33,166]. They similarly fail to show normal GSR prior to making risky decisions and after receiving rewards or punishments during card selection tasks [32]. Consistent with the relationship between the amygdala and GSR, some neuroimaging studies have observed relationships between amygdala activity and GSR. For instance, Williams et al. [302] classified responses to fearful faces based on whether or not the subjects showed a GSR for the specific trial. Trials generating GSR were associated with left amygdala activation, whereas no significant amygdala activation emerged in trials in which subjects did not show a GSR. Using PET, Liberzon and colleagues observed a correlation between GSR and right amygdala activity in subjects viewing unpleasant pictures [188]. Similarly, Furmark et al. [105] observed a correlation between amygdala rCBF and GSR in a conditioning paradigm. However, it must be noted that the causal direction of the association in these studies is unclear, in that the level of autonomic arousal could be influencing the level of amygdala activity (see [76]). In animal studies, amygdala lesions also impair modulation of other hormonal (e.g., ACTH) and autonomic (e.g., cardiovascular) responses during certain conditions (most frequently negatively arousing conditions) [106,241,292]. Unfortunately, there is a general dearth of studies in humans addressing the specific effects of amygdala lesions on these variables. Nevertheless, the overall picture in animals and humans supports the hypothesis that the amygdala exerts an influence over certain motoric, hormonal and autonomic processes. This influence likely facilitates the organisms readiness to respond to relevant stimuli in the environment.

11.5. The relationship between amygdala engagement and the modulation of cognitive, motoric, and endocrine responses

Neuroimaging studies on the relationship between amygdala activity and subsequent recall of emotionally valenced information indicate that the extent of this memory enhancing effect is directly related to the extent of amygdala activation [56,57,64,66,67,125]. This suggests that differences in the ability of various stimulus classes (aversive vs. pleasant, arousing vs. calming, fearful vs. happy faces) may directly influence the degree to which the amygdala modulates other processes. For instance, the magnitude of amygdala activation to specific stimuli may directly relate to its ability to influence attention, conditioning, motor readiness, and endocrine release and autonomic arousal. Thus, a full understanding of the stimuli that engage the amygdala may prove essential for understanding when we should predict to see amygdala driven modulations of behavior.

12. Task demands: the effects of explicit emotional evaluation on amygdala activity

To what extent do different task demands influence amygdala responses to emotionally salient stimuli? Given the amygdala's frequently hypothesized role in emotional evaluation, it would seem reasonable to suspect that explicitly directing attention to the hedonic features of stimuli (or the subjective emotional responses that they elicit) would produce amygdala activation. However, at present, little data supports this hypothesis outside of the face domain. Studies specifically contrasting hedonic vs. nonhedonic judgments have generally failed to observe significant changes in amygdala activity within the olfactory [243–245,322], auditory [245,247] and visual modalities [175]. Two exceptions to this pattern have been reported. In both cases, greater right amygdala activity arose during hedonic ratings of aversive stimuli (pictures [188,285] and words [283]) than during recognition conditions. However, these studies are difficult to interpret due to order effects and the use of repeated stimuli in the recognition conditions (leading to a potential habituation effect). Indeed, Phan et al. [224] reported that right amygdala activity actually decreased when subjects made hedonic ratings of affectively valenced slides relative to when they simply viewed the slides and said the word 'picture'.

Numerous studies indicate preferential responses to fearful or negatively valenced faces even when subjects are engaged in making other nonemotional judgments about the faces [74,114,221,242,294,305]. Thus it is clear that one need not attend to the emotional valence of faces in order to observe amygdala activation. What seems less clear is the extent to which explicit judgments of facial expression modify the response relative to passively viewing or making other judgments about faces. Some investigators have observed greater activity during explicit than implicit coding [118], while others have observed no effect of explicit vs. implicit processing of facial emotions

[114,242], or even greater activity during implicit relative to explicit conditions [74]. Further complicating the matter is the finding that the specific type of explicit emotional processing appears to influence the result. Hariri et al. [127] exposed subjects to angry and fearful faces and asked subjects to either match faces in terms of affective expression or label the target emotion with a verbal label. The verbal labeling condition produced significantly less amygdala activation than the matching condition. Indeed, no significant activations localized to the amygdala in the verbal labeling condition relative to the baseline control condition. Thus, the effect of explicit processing of emotion on amygdala activity may be task specific.

To what extent do subjects need to attend to faces in order to see preferential responses to fearful faces? The answer to this question may depend upon the attentional demands required of subjects at the time when the faces are presented. Support for this hypothesis derives from a pair of studies in which faces were presented while subjects were engaged in an unrelated task. The first study by Vuilleumier et al. [294] observed preferential activation of the amygdala to fearful faces, regardless of whether the faces were presented at attended or unattended locations. In contrast, Pessoa et al. [221] reported that both the valence specific and the general response to faces is eliminated when subjects were attending to a demanding line orientation task. Although numerous task differences might account for these contrasting effects, one of the simplest explanations lies in the task difficulty (84% correct in the first study vs. 64% in the second study). Thus, facial emotion may produce automatic activations of the amygdala under normal condition, but the effect may be reduced or even eliminated under conditions of high attentional load.

In considering the effects of explicit task and attentional demands on amygdala activity, it must be noted that the amygdala frequently shows decreased rCBF as subjects move from passive to more active visual tasks [268]. The source of this decrease is unclear, although it has been suggested that it relates to a default brain mode, which is suspended during many types of cognitive processing [236,268]. The presence of such decreases leads to interpretational problems for many neuroimaging studies of the amygdala. Specifically, it is possible that some rCBF changes are caused not because one task engaged the amygdala, but because the comparison task led to a greater suppression of default levels of activity.[11] This issue requires close scrutiny in future studies examining the effects of explicit task demands on the amygdala.

A separate issue relates to what subjects are told to do in terms of modulating their subjective emotional experience in response to viewing faces or other emotional stimuli. Studies by Schneider et al. [252,253,256] are notable in the emotional faces literature in that the subjects were instructed to feel the emotion that was shown to them. This might explain the frequency with which these investigators observed activations to sad faces, while other researchers have generally not seen any effect of viewing sad vs. happy or neutral faces. Along a similar vein, Schaeffer et al. asked subjects to passively view or maintain their emotional responses to negative and neutral pictures [251]. The early component of the response did not show a significant difference between the conditions. However, during the delay period following presentation of negative stimuli, 3 of the 5 subjects (the three with the highest levels of dispositional negative affect) showed substantially greater amygdala activity in the maintain condition. If this result is replicated it would suggest that although explicit task demands may have only inconsistent effects on initial responses to emotional stimuli, they may nevertheless have an impact on subsequent activity in certain vulnerable subjects.

13. Restricted influence of the amygdala on conscious emotional evaluation and subjective emotional experience

Humans with amygdala lesions show grossly normal hedonic ratings of affectively valenced pictures [6,104][12]. However, more subtle biases may exist in these subjects. For instance, Adolphs and Tranel [6] observed a positive biasing in two subjects with bilateral amygdala lesions, in which the lesioned subjects rated stimuli as less aversive than would be expected given the ratings of healthy controls. Indeed, the lesioned subjects gave overall positive ratings to unfamiliar pictures of nonsense line drawing and planet-like spheres that the control subjects had rated as negative. Similarly, in a second study utilizing one of the subjects with bilateral amygdala lesions from the just described study, the patient showed an ability to properly rate the valence direction of a range of stimuli, but failed to accurately rate the level of arousal of negative stimuli [4]. This suggests that the amygdala may heighten negative appraisal or impact the intensity of the negative emotional

[11]This may be particularly germane in regards to understanding the Pessoa study described in the above paragraph. Specifically, the failure of fearful faces to engage the amygdala may relate to an active suppression of amygdala processing during this condition. Thus, the preferential activation of the amygdala by fearful faces may not require active attention to the faces, but instead may require that no active processes of suppression are in effect at the time of stimulation.

[12]Amygdala lesioned patients have also been observed to rate emotional scripts with normal ratings, although such studies typically only use one or two stories, preventing more rigorous analysis of these responses [3,55].

evaluation, even though it is not essential for the gross recognition that the stimuli are unpleasant.

Patients with amygdala lesions are also capable of showing what appear to be intact appraisals of their own emotions. Indeed, humans with amygdala lesions do not report grossly different levels of subjective positive or negative affect relative to control subjects [17]. This suggests that the human amygdala is neither necessary to consciously evaluate and report subjective emotional experiences, nor is it necessary for the more general subjective experience of affective states. Numerous neuroimaging studies exist of subjects experiencing both positive and negative emotions without showing evidence of amygdala activation. Moreover, lesions of the amygdala in monkeys leave dispositional measures of anxiety intact [147]. Rather, the influence of the amygdala on subjective experience is likely to arise in more extreme negative emotional states. Amygdala-lesioned monkeys who show no decrements in anxiety-related measures, nevertheless show blunted fear responses to unconditioned threatening stimuli [147]. This converges with anecdotal reports of the effects of amygdala lesions in humans which describe decreases in more extreme emotional states such as anger and fear [10,209,276] but do not report the development of a global athymia following lesions.[13]

14. Group and individual differences in amygdala responsiveness

Emerging evidence indicates that the amygdala's responsiveness to stimuli varies with a number of subject variables. In some cases these may represent confounds that hamper comparison across studies while in other cases they may provide critical insights into individual differences and aspects of psychopathology.

14.1. Gender differences

Studies in rodents demonstrate sexual dimorphism in amygdala subnuclei [277]. Such dimorphism may also exist in humans. A recent volumetric analysis suggests that the amygdala as a whole may be larger in men than women, which would support such a contention [113]. Gender differences have also been observed in the effects of amygdala lesions in non-human primates. Specifically, Kling observed that some females with amygdala lesions become hyper-aggressive, while males of the same species show hypo-aggression [161]. Several, recent neuroimaging studies suggest that gender differences influence the extent and/or laterality of amygdala responses in human subjects. For instance, studies using both FDG-PET [57] and event-related fMRI [64] have reported gender differences in the extent to which activity in each amygdala correlates with enhanced memory for emotional pictures or films (with males demonstrating the correlation in the right amygdala and females showing correlations in the left amygdala). Interestingly, in the event-related study, no sex differences emerged in the lateralization of correlations with perceived emotional intensity of the stimuli, only with the correlation with later memory, suggesting that the lateralization issue is specific to memory modulation. Sex differences in lateralization of amygdala responses have also emerged in studies involving the viewing of emotional facial expressions [155,156,256,287].

Exploration of gender issues based on preexisting reports is difficult because more than half of the studies reporting amygdala activations to date used combined samples of males and females, and only a handful of studies have provided specific analysis of sex differences. Nevertheless, in their recent meta-analysis of emotion induction and pleasant and unpleasant visual and auditory stimulation studies, Wager et al. identified 22 studies with only males and 14 studies with only female subjects [295]. Both genders showed a similar pattern of lateralization of amygdala findings, with a trend toward greater left amygdala foci than right amygdala foci in both genders (12 left vs. 7 right in males, 8 left vs. 4 right in females). Thus, while there is emerging evidence of gender effects on lateralization related to memory for emotional material and aspects of processing facial emotion, the gender effects are likely to be relatively specific to the domains in question, rather than reflecting a more global difference in the lateralizaton of amygdala responses to all emotional stimuli.

14.2. Handedness

Most studies utilize exclusively right-handers or a combination of right-handers and a few left-handers. It should be noted however, that in right-handers the right amygdala is typically larger than the left amygdala, whereas this asymmetry is typically lacking in left-handers [282]. This suggests that the handedness of subjects might influence the symmetry or lateralization of results.

14.3. Psychopathology and individual differences

Having begun to establish the parameters under which the amygdala responds, it becomes possible to start asking questions regarding whether different types of psychopathological conditions are associated with alterations in the amygdala's responsiveness to different stimuli. This may be expressed as exaggerated or attenuated amygdala

[13]Consistent with the restricted effects of amygdala lesions in humans and monkeys on dispositional measures of negative affect, resting rCBF in the amygdala of healthy human subjects does not correlate with long-term ratings of negative affect [193,315]. A small study in depressed subjects suggested a correlation with negative affect and amygdala metabolism [1], but to the extent that this correlation occurs, it is probably specific to the pathology of depression rather than reflecting a more global dispositional trait.

responses, or as differential susceptibility to habituation [28,39,75,135,164,228,231,239,255,258,263,264,269]. Additionally, researchers are beginning to gage the effects of different pharmacological or psychological manipulations on such responses as a means of assessing the functional correlates of psychiatric treatment [264].

Investigators have also begun to explore individual differences in personality factors or genetic variables in relation to the degree of amygdala activation to various stimuli. As touched on earlier, Canli et al. [65] observed that while happy faces failed to activate the amygdala across all subjects, the level of activation in the left amygdala correlated with subjects level of extraversion. Similarly, Hariri et al. [128] observed that allelic variations in the serotonin transporter promoter gene influence the level of amygdala response to fearful faces.

A rather straight forward hypothesis, that has rarely been tested, posits that the degree of amygdala activation in response to negative stimuli may be directly related to dispositional measures of negative affect. Unfortunately, most neuroimaging studies involve too few subjects to have appropriate statistical power to test this hypothesis. Moreover, given the lack of effects of amygdala lesions on dispositional measures of affect in both human [17] and nonhuman primates [147], there exist reasons to be skeptical about this hypothesis. Nevertheless, two small studies have indicated that the amount of amygdala activity during or following negatively valenced pictures correlates with individual differences in long-term negative affect [142,251]. Although conclusions from these studies are limited by the small sample sizes, they are consistent with the hypothesis that long-term, dispositional levels of negative affect may show a relationship to amygdala reactivity.

Defining individual and group differences is likely to prove highly valuable in the future. First, the effects of studying different subject populations may help explain existing inconsistencies in the literature. Second, results from studies of individual and group differences are likely to lead to the development of direct tests regarding neurobehavioral models of personality, temperament, and psychopathology.

15. Conclusions and future directions

As the current review makes evident, our knowledge of the functions of the human amygdala has increased dramatically in recent years. While in many cases findings from these studies converge well with data from animals, this research has also offered insights that were not attainable solely from animal studies. Such data now provide a strong basis for refining how we conceptualize the functions of the amygdala and its role in psychopathology.

Despite the rapid developments in this field, several factors must be closely attended to if the field will continue to move forward. In the neuroimaging area, careful attention to imaging parameters, subject parameters, temporal issues, and the appropriate description of foci is critical. Unless investigators provide direct evidence that they used scanning techniques that yield good signal to noise ratios of the amygdala, it is difficult to know the quality of the data being reported. Given increasing demonstrations of gender and personality effects, these variables need to be attended to when interpreting findings. Direct examination of the temporal features of amygdala responses will also probably prove beneficial, as these features may critically distinguish responses between different classes of stimuli. Finally, more accurate descriptions of the boundary of what is termed the amygdala is required in order to determine the functional domains of the amygdala proper, extended amygdala, and neighboring cortical areas. In particular, clear distinction between the extended amygdala and amygdala proper are required in describing results.

Particular attention needs to be paid to elucidating and quantitatively measuring the functional consequences of amygdala activation. An understanding of these consequences is necessary if we are to interpret the emerging literature on group and individual differences in amygdala responsiveness. This issue is similarly essential for understanding current and future studies on the effects neuropharmacological and cognitive or behavioral manipulations. Essentially, the question boils down to, ‘What are the actual functional consequences of increased or decreased BOLD responsiveness?’ The significance of group or individual differences will only become clear once we can answer that question.

The literature is also likely to benefit from explorations that seek to determine the boundaries of when the amygdala is required for task performance, and the boundaries of when the amygdala becomes activated. Descriptions of the functions of the amygdala have often been subject to grossly generalized statements in both the scientific and lay literatures. Thus, one sees reference to the amygdala as ‘the center for emotional processing,’ despite the substantial aspects of emotional processing that appear largely unaffected by amygdala lesions. By establishing the boundaries of amygdala functions, we will be able to move toward a far more refined understanding of the amygdala’s functional properties.

Finally, future research into the functions of the amygdala in humans could benefit from a greater consideration of the interactions between the amygdala and other brain regions. Descriptions of the circuitry and functions of the amygdala often treat it as a gateway, with a set of sensory inputs and outputs to effector sites. Lost in this model is a consideration of reentrant pathways and interactions between the amygdala and other brain regions. For instance, the orbitofrontal cortex receives and projects to a number of the same brain areas as the amygdala, as well as receiving and projecting to multiple amygdala nuclei

[313]. Yet, little information is available regarding how these areas interact. Functional neuroimaging possess a unique ability to noninvasively measure activity in multiple regions simultaneously, and thus has the potential to provide information on the functional or effective connectivity between the amygdala and other brain regions. While a few studies have explored this potential [139,202,203,311], it has yet to be widely capitalized upon. Functional neuroimaging can also be utilized to look at the effects of lesions of the amygdala on processing in other brain areas (and visa versa [200]). For instance, sensory areas have been observed to show enhanced activation when exposed to emotional pictures relative to neutral pictures [179]. If this enhancement is caused by the amygdala, it seems logical to predict that it will be absent in patients with amygdala lesions. Similarly, if, as has sometimes been suggested, the frontal cortex can inhibit the 'more primitive' amygdala, then frontal lobe patients might be predicted to show enhanced amygdala responses to stimuli that typically engage the amygdala. Neuroimaging studies of patients with specific lesions can thus provide direct tests of the manner in which the amygdala influences, and is influenced, by other brain regions. Future studies aimed at addressing such influences will be essential if we are to gain a complete picture of the human amygdala's role in processing and responding to sensory stimuli.

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