doi:10.1093/brain/awp255 Brain 2010: 133; 248–261 | 248

BRAIN
A JOURNAL OF NEUROLOGY

Integration of gaze direction and facial expression in patients with unilateral amygdala damage

Chiara Cristinzio,[1,2] Karim N'Diaye,[1,2] Margitta Seeck,[3] Patrik Vuilleumier[2,4] and David Sander[1,4]

1 Laboratory for the Study of Emotion Elicitation and Expression (E3 Lab), Department of Psychology, FPSE, University of Geneva, Geneva, Switzerland
2 Laboratory for Neurology and Imaging of Cognition, Department of Neurology and Department Neuroscience, Medical School, University of Geneva, Geneva, Switzerland
3 Epilepsy Unit, Department of Neurology, Geneva University Hospital, Geneva, Switzerland
4 Swiss Centre for Affective Sciences, University of Geneva, Geneva, Switzerland

Correspondence to: Chiara Cristinzio,
Hôpitaux Universitaires de Genève,
24, rue Micheli-du-Crest,
1211 Geneva 14,
Switzerland
E-mail: chiara.cristinzio@unige.ch

Affective and social processes play a major role in everyday life, but appropriate methods to assess disturbances in these processes after brain lesions are still lacking. Past studies have shown that amygdala damage can impair recognition of facial expressions, particularly fear, as well as processing of gaze direction; but the mechanisms responsible for these deficits remain debated. Recent accounts of human amygdala function suggest that it is a critical structure involved in self-relevance appraisal. According to such accounts, responses to a given facial expression may vary depending on concomitant gaze direction and perceived social meaning. Here we investigated facial emotion recognition and its interaction with gaze in patients with unilateral amygdala damage ($n = 19$), compared to healthy controls ($n = 10$), using computer-generated dynamic face stimuli expressing variable intensities of fear, anger or joy, with different gaze directions (direct versus averted). If emotion perception is influenced by the self-relevance of expression based on gaze direction, a fearful face with averted gaze should be more relevant than the same expression with direct gaze because it signals danger near the observer; whereas anger with direct gaze should be more relevant than with averted gaze because it directly threatens the observer. Our results confirm a critical role for the amygdala in self-relevance appraisal, showing an interaction between gaze and emotion in healthy controls, a trend for such interaction in left-damaged patients but not in right-damaged patients. Impaired expression recognition was generally more severe for fear, but with a greater deficit for right versus left damage. These findings do not only provide new insights on human amygdala function, but may also help design novel neuropsychological tests sensitive to amygdala dysfunction in various patient populations.

Keywords: amygdala; gaze; facial expression; emotion recognition; temporal epilepsy

Abbreviations: fMRI = Functional magnetic resonance imaging; LTL = left temporal lobectomy; RTL = right temporal lobectomy; TLE = temporal lobe epilepsy

Introduction

Temporal lobe epilepsy (TLE) is the most frequent type of focal epilepsy and the epileptogenic focus often involves structures within the mesial temporal lobe, including the hippocampus and amygdala. This form of epilepsy is associated with mesial temporal sclerosis and presents a strong risk of drug resistance, such that the most common and effective therapy is neurosurgery, involving

Received November 25, 2008. Revised and Accepted August 21, 2009. Advance Access publication October 14, 2009

temporal lobectomy with the removal of a variable extent of amygdala and hippocampus. Behavioural changes in these patients, after surgery, may include social and emotional deficits, but the latter still remain poorly defined and investigated. Furthermore, these patients offer a unique opportunity to understand the function of the amygdala in humans better, as well as the potential hemispheric asymmetry of amygdala function. Such understanding may, in turn, help to design new neuropsychological tests to investigate medial temporal lobe functions because these functions remain difficult to examine in clinical practice, and neuropsychological testing in these patients rarely examines emotional or social domains but tend to focus on hippocampus-dependent memory instead.

In the present study, we built on recent empirical evidence and theoretical accounts (Sander *et al*., 2003, 2007) suggesting that the human amygdala might mediate major emotional, motivational and social functions related to the appraisal of self-relevance (Scherer *et al*., 2001; Sander *et al*., 2005). Specifically, we hypothesized that (i) emotion recognition might normally depend on the self-relevance perceived by an observer; and (ii) the amygdala might play a key role in such encoding of self-relevance. To test these hypotheses, we manipulated the self-relevance of emotionally expressive faces (displaying fear, anger or happiness) by changing their gaze direction (directed towards or away from the viewer), and then compared the effect of such manipulation on emotion recognition in patients with unilateral amygdala damage and healthy controls. We predicted that amygdala lesion might specifically impair recognition of emotion expression when self-relevant, rather than across all expression conditions. Thus, we could not only verify a direct involvement of the amygdala in relevance appraisal, but also design a new test of emotion processing in patients.

A crucial involvement of the human amygdala in social and affective processing is now well established by neuropsychological and neuroimaging research. In particular, a major role of the amygdala in emotional recognition (especially for facial expression of fear) has been reported for many years, but its exact contribution remains controversial (Calder *et al*., 2001; Adolphs, 2002; Cristinzio *et al*., 2007). Early evidence for emotion recognition deficits after amygdala lesion was provided by patients with bilateral damage of either congenital or acquired origin. Following a first classical single-case study reporting a patient who had bilateral amygdala destruction due to Urbach–Wiethe disease and selective impairment in recognizing fear in facial expressions (Adolphs *et al*., 1994), several other studies have described fear recognition deficits after bilateral amygdala lesion (Adolphs *et al*., 1994, 1999; Young *et al*., 1996; Sprengelmeyer *et al*., 1999; Anderson and Phelps, 2000; Schmolck and Squire, 2001). However, fear was not always the only impaired emotion category since some patients also showed deficits for anger, sadness or disgust (Scott *et al*., 1997; Broks *et al*., 1998; Rapcsak *et al*., 2000). Moreover, Hamann and colleagues (1996; Hamann and Adolphs, 1999) reported normal emotion recognition after bilateral amygdala damage in two patients.

More variable deficits have been reported in patients with unilateral amygdala damage. Early studies reported that a small group of patients with unilateral temporal lobectomy showed normal recognition for all types of facial expression (Adolphs *et al*., 1995). In contrast, subsequent studies with larger samples reported significant deficits for several emotion categories but with some differences according to the side of the lesion: deficits were either more severe, or found only in right lobectomy patients (Anderson *et al*., 2000; Adolphs *et al*., 2001; Meletti *et al*., 2003; Benuzzi *et al*., 2004; McClelland *et al*., 2006).

Functional magnetic resonance imaging (fMRI) in healthy participants has also consistently demonstrated an involvement of the amygdala in emotion processing (Pessoa, 2008). Since the study by Morris *et al*. (1996), many others have reported amygdala activation in response to fearful faces (e.g. Whalen *et al*., 1998; Vuilleumier *et al*., 2001). However, amygdala may also be activated by other facial attributes, such as attractiveness (Winston *et al*., 2007) or trust (Said *et al*., 2009) as well as by expressions of sadness (Blair *et al*., 1999), anger (Wright *et al*., 2002; Yang *et al*., 2002) and disgust (Anderson *et al*., 2003*a*). Critically, the amygdala is also activated during the processing of neutral (Wright and Liu, 2006) or even positive expressions such as happy faces (Breiter *et al*., 1996; Canli *et al*., 2002; Pessoa *et al*., 2002), challenging the special status of fear with respect to amygdala activity (Fitzgerald *et al*., 2006).

To account for these data, various interpretations of amygdala function have been proposed as alternatives to the view that the amygdala's domain of processing is restricted to the processing of fear-relevant stimuli (e.g. the 'fear module'; Ohman and Mineka, 2001). Several authors (Anderson *et al*., 2003*b*; Hamann, 2003) suggested that amygdala activity might code for arousal rather than valence (e.g. negative or positive value). However, arousal effects on amygdala response may interact with valence for both facial (Adolphs *et al*., 1999) and non-facial stimuli (Winston *et al*., 2005; Berntson *et al*., 2007), arguing against a strict independence of arousal versus valence processing in the amygdala. Moreover, some findings of amygdala activation to low-arousal information, such as sad events (Levesque *et al*., 2003; Posse *et al*., 2003), do not support the view that the amygdala is tuned to highly arousing stimuli only (see Ewbank *et al*., 2009*a*).

In this context, an 'appraisal' theory of emotions may offer new insights to resolve these apparent discrepancies (Sander *et al*., 2005). A key aspect of appraisal theory is that the processing of emotional stimuli depends on their perceived self-relevance. As the amygdala might act as a relevance detector (Sander *et al*., 2003, 2005, 2007), it could activate to emotional as well as neutral faces, depending on the context, because such stimuli potentially provide highly relevant social information for human individuals.

With respect to the processing of facial expressions, a series of recent behavioural studies have indirectly supported this view in reporting that the perception of facial expressions can be modulated by eye-gaze direction, which provides important signals for social interactions and understanding intentions of others (Adams and Kleck, 2003, 2005; Sander *et al*., 2007). Furthermore, the effect of gaze on facial expression recognition might depend on the type of expression, with a particular pattern of interaction observed for the perception of anger and fear that is thought to reflect an appraisal of the source of threat associated with these emotions. Sander *et al*. (2007) confirmed this

prediction in a behavioural study with dynamic face stimuli that could shift their gaze while they simultaneously expressed anger, fear or happiness. In this experiment, recognition of happy faces was not influenced by gaze direction, but recognition of anger and fear showed an interaction pattern as a function of gaze (direct versus averted). Angry faces were perceived as expressing more anger with direct than averted gaze, whereas fearful faces were perceived as expressing more fear with averted than direct gaze—a pattern consistent with the higher self-relevance of an angry face looking towards the viewer, and that of a fearful face looking to an unknown event close to the viewer. In the case of anger, this pattern is predicted because the aversive dimension of an angry expression should increase when the observer is the object of anger (and hence gazed at). In the case of fear, the potential threat signalled by a fearful face should increase when the face is looking at something away from the observer because the object of fear is also a potential danger for the observer (e.g. a predator or an enemy approaching the observer), whereas this is not the case if the gaze is directed at the observer. Indeed, in the latter condition, the observer themselves would be the object of fear (hence there is no potential danger for him/her). It is important to note that these predictions concern relative differences in self-relevance, and even fearful faces with a direct gaze could have some degree of self-relevance for the observer (e.g. representing a strong distress cue). It is, however, expected that the latter situation should be less self-relevant than a cue of a nearby danger in terms of its significance for goals, needs and values of the individual (Sander *et al*., 2007).

Critically, recent fMRI studies have also provided evidence for an interaction of gaze direction and emotion expression influencing amygdala responses to faces (Adams *et al*., 2003; Sato *et al*., 2004*b*; Hadjikhani *et al*., 2008; N'Diaye *et al*., in press), but the exact pattern of effects still remains controversial. A first study by Adams *et al*. (2003) reported that angry faces with averted gaze and fearful faces with straight gaze elicited stronger amygdala responses, relative to angry faces with direct gaze and fearful faces with averted gaze, respectively. This fMRI result was interpreted as evidence for a specific role of the amygdala in appraising ambiguous situations. In contrast, another fMRI study (Sato *et al*., 2004) found that amygdala activation was stronger when angry faces were presented peripherally and orientated towards, rather than away from, the observer. Hadjikhani *et al*. (2008) also used front-views of emotional faces that were edited to manipulate gaze direction but, unlike Adams *et al*. (2003), they found stronger amygdala activation to fearful faces with averted than with direct gaze. Similar results have been obtained by our group in a recent fMRI study using well-controlled, computer-generated faces with dynamic expressions and gaze-shifts (N'Diaye *et al*., in press). Therefore, current data from neuroimaging studies do not allow a definite conclusion on the role of the amygdala for the integration of gaze and expression in emotion perception. Furthermore, in all imaging studies, the amygdala was activated together with many other brain regions, making it difficult to unequivocally assert an essential contribution of the amygdala to this process. The primary goal of the present study was therefore to test for such effects after unilateral amygdala damage, since these patients provide a unique opportunity to observe any causal role of the left and/or right amygdala.

Therefore, the current study investigated how gaze direction and face expression interact during emotion perception as a function of the perceived self-relevance of expressions, using a similar design as the behavioural study of Sander *et al*. (2007) but with the new dynamic stimuli developed for our recent imaging work (N'Diaye *et al*., in press). To the best of our knowledge, the possible interaction of gaze and emotion perception has never been investigated in patients with amygdala lesions. Here we examined such effects for the first time in patients with either right temporal lobectomy (RTL) or left temporal lobectomy (LTL), as well as in healthy participants. Firstly, based on appraisal theories of emotion (Sander *et al*., 2005), we predicted that gaze direction should modulate the self-relevance of expressions in faces, and hence the perceived emotion in healthy participants (i.e. leading to specific recognition enhancement for fear with averted gaze and anger with direct gaze). Secondly, according to our hypothesis of a critical role for the amygdala in processing self-relevance (Sander *et al*., 2003), we predicted that such integration of gaze and expression should be reduced or abolished in patients.

Experiment 1

Method

Participants

We tested 11 patients with a left unilateral temporal lobectomy, 8 patients with a right unilateral temporal lobectomy and compared their results with those of 10 healthy volunteers (8 male) who participated as control subjects in this study (mean age 27.9 ± 3.2). None of the control subjects had any history of a learning disability or neurological injury. All patients and healthy participants gave informed consent in agreement with the local ethical committee regulation. All participants were right-handed and had normal or corrected-to-normal visual acuity. Patients were selected from the clinical database of the Epilepsy Neurophysiology Unit in the Neurology Department of the University Hospital in Geneva. All patients underwent a standard neuropsychological assessment before and after neurosurgery, using an extensive battery of clinical tests routinely used for this purpose in our unit (e.g. Pegna *et al*., 1998). No patients showed severe cognitive impairment following surgery. One patient (BU) manifested a mild aphasic deficit that recovered well after rehabilitation, whereas three patients (GU, HP and LH) showed mild difficulties in word finding, and two other patients (IN and SY) had mild memory deficit but only in demanding long-term retention tasks. Our criteria for selection were: (i) unilateral temporal lobectomy for the treatments of drug-resistant epilepsy; (ii) time since surgery $\leqslant 11$ years; (iii) no psychiatric disorders pre- or post-surgery; (iv) willingness to participate; and (v) success of surgery with a complete disappearance or important remission of epileptic attacks.

A sample of 78 individuals, operated on since 1995, was contacted, out of which 25 individuals volunteered to participate in the study. Among them, one was excluded because of severe depressive syndrome, three because of an extension of the epileptogenic lesion beyond the mesial temporal structures (amygdala–hippocampus), and two due to severe cognitive deficits (mental retardation attested by poor performance on intelligence scale). Thus, our final cohort

consisted of 19 patients, including eight patients with RTL (mean age 34.6 ± 12.5) and 11 patients with LTL (mean age 33.6 ± 15.6) (Table 1). Information regarding the precise location and volume of the surgical resection was obtained from postoperative MRI in 14 patients (6 from the right lobectomy group, 8 from the left group). Anatomical location and overlap of the lesions were reconstructed using MRICro software (Brett *et al*., 2001) and standard procedures (Mort *et al*., 2003; Grandjean *et al*., 2008). Results from such reconstruction are shown for each group in Fig. 1. There was no significant difference in resection volume between the left and right patient groups (Student *t*-test; $P = 0.19$).

Stimuli

We used a new stimulus set taken from our previous fMRI study in healthy participants (N'Diaye *et al*., in press), consisting of computer-generated animated faces displaying dynamic expressions and eye movements. We created these stimuli using the Facial Action Coding System (FACS)-Gen software, currently developed in our centre (Roesch *et al*., 2006) as an extension of the FaceGen software (FaceGen Modeller 2.0, by Singular Inversion Inc. http://www.FaceGen.com). The FaceGen software has been used in several previous studies investigating the neural substrates of face processing (e.g. Schulte-Rüther *et al*., 2007; Oosterhof and Todorov, 2008; Todorov *et al*., 2008). The FACSGen extension used here exploits the 3D face rendering processor of FaceGen but is designed to manipulate the expressions of 3D faces with a strict control of the time-course of animation, based on the Facial Action Coding System that was developed by Paul Ekman to describe facial motor behaviour (Ekman, 1978). This software and the general methodology of producing the stimuli have been validated in previous studies, including ratings made by

Table 1 Clinical details of patients

Patients	Sex	Age	Date of surgery	Side of lesion	Volume of lesion	Seizure onset (age)
GU	M	57	08.07.2005	R	38	5
MI	M	27	16.07.2004	R	48	5
MA	M	46	19.10.2001	R	64.4	8
SA	M	27	08.12.2006	R	44.4	21
IN	M	39	02.11.2001	R	41.2	0.58
GE	M	33	09.02.1999	R		2
MT	M	40	15.12.1998	R		8
LO	M	31	10.06.2004	R	47.4	13
LH	F	58	11.11.2005	L	26.4	6
GX	F	33	28.11.2005	L	47.4	12
CL	F	19	27.05.2005	L	37	4
WA	F	21	18.01.2007	L	40.2	8
HP	M	41	06.10.2000	L	43.7	25
SY	M	59	09.02.2001	L	52.5	0.5
BU	M	20	14.07.2000	L	32.1	7
MN	M	36	12.07.1996	L		1
NY	F	19	26.05.2000	L	45.3	0.75
PT	M	42	19.03.1999	L		4
PL	F	52	05.03.1999	L		11

Side and volume of post-surgery lesion, plus onset of epilepsy are given for each patient. L = left temporal lobectomy; R = right temporal lobectomy. For patients GE, MT, MN, PT and PL, information about the exact volume of the lesion was not available.

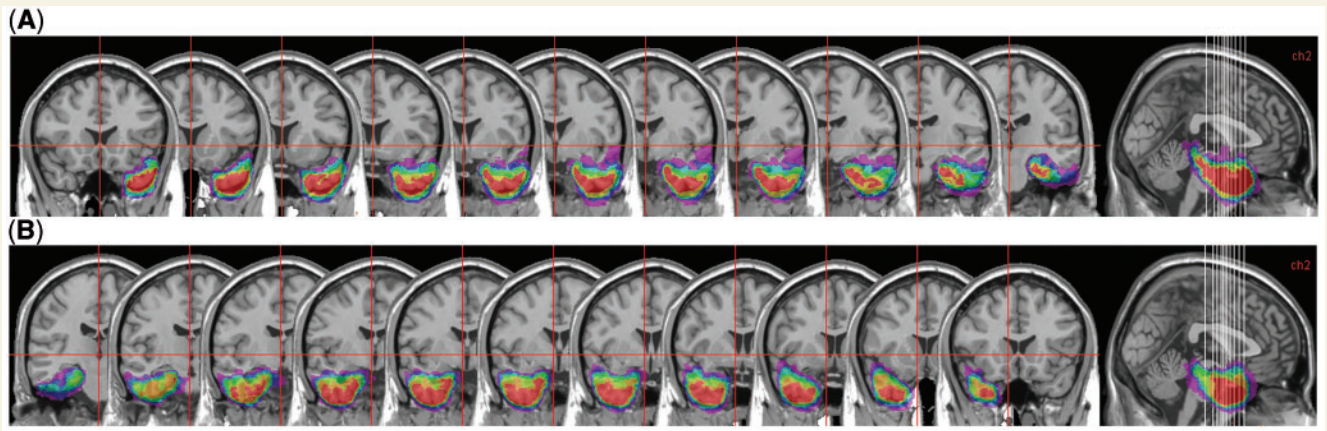

Figure 1 Anatomical reconstruction of the patients' brain lesions. (**A**) Areas of overlap across patients with right lobectomy and (**B**) left lobectomy. Resections were symmetrical in both groups. Note that only the mesial region and anterior pole was damaged, while more superior lateral cortical regions were intact (including anterior and posterior portions of the superior temporal sulcus).

FACS coders (Roesch *et al*., in revision). This tool provides a library of routines that control the morphology as well as the expression of realistic face avatars, which can be modified in a parametric manner, enabling us to produce intermediate faces that are not based on morphing but generated from the anatomical configuration of individual facial action units (Roesch *et al*., in revision). In addition, realistic gaze deviations were created by angular rotation of the eyes relatively to the axis of the head, via a computation of the displacement of the iris texture on a spherical surface that modelled the eyeball. Here, we used gaze deviations to either side (left/right) to generate the different gaze conditions. Low-intensity expressions were obtained by using only the half of the displacement of the meshes modelling the full expressions; the speed of the animation was kept constant.

For the present study, we selected four identities (two males and two females) with three expressions (fear, anger and happiness), each with either low (50%) or high (100%) intensity, and with eye-gaze manipulated between either a straight or averted direction, leading to 48 different stimuli. Each trial consisted of a short movie starting with a neutral face whose gaze was initially directed either straight or averted (rightward or leftward on 50% of trials each). The face remained static for 1200 ms. After this delay, it showed a rapid (100 ms) eye shift, either from a straight to deviated position (averted gaze condition) or from a deviated to straight position (direct gaze condition), respectively (+15 or –15° of deviation). Following this gaze shift, after another brief 100 ms delay, the face displayed an emotional expression of fear, anger or happiness with either a high (full) or low (partial) intensity. The rise-time of low-intensity expressions was always 200 ms long, stopping at the half of maximum movement (50% = partial expression), whereas the rise-time of high-intensity expressions was 400 ms (100% = full expression). This was followed by a constant expression (high or low intensity) during another 400 or 200 ms, respectively (Fig. 2). Hence, the total duration of face presentation in the two conditions of high and low intensity expressions were actually matched with respect to the global duration (2 s) of the face display (i.e. the dynamic unfolding of low-intensity expressions was followed by a 400 ms static display with a 50% expression; whereas high-intensity expressions were followed by a static display with 100% expression for 200 ms after the rise-time).

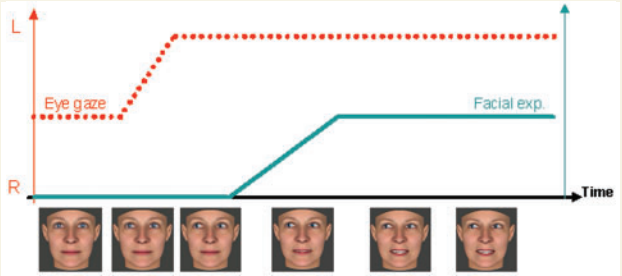

Figure 2 Dynamic pattern of eye movement and facial expression on each trial. For all stimuli used in this experiment, a neutral face gazing either toward or away from the subject was first presented as a baseline. After a 1 s delay, a 100 ms long gaze shift was initiated. After another 100 ms delay, facial expression was unfolded up to 100% or 50% intensity over a period of 400 or 200 ms, respectively, and maintained for another 200 or 400 ms, respectively. Traces represent the time course of the two experimental factors (gaze and expression): in dotted red, eye gaze starts from a central position (in this example) and shifts to the left of the viewer; in solid blue, after the initially neutral expression, an emotional expression starts 100 ms after the end of the eye shift and unfolds during 200 ms to display mild anger (in this example) for 400 ms. The whole movie lasted 2 s for all trials.

Procedure

Patients and healthy controls were tested using the same experimental setting. The 48 stimuli were distributed into four blocks of 12 trials with a pseudorandom order, different for each participant. A short break was introduced between the blocks to avoid fatigue. On each trial, subjects saw the short movie of 2 s, showing a single face displaying a specific emotion and gaze shift, presented centrally on a computer screen. Following the movie, a response window presented a series of seven rating scales (horizontal bars representing a continuous range between 0 and 100). Participants had to rate the general intensity of the expressed emotion on a first 'intensity scale', and then used six other 'category scales' to indicate the extent to which the six different emotion types could be perceived in the face (similar procedure as in Sander *et al*., 2007). To give their response on a given scale, participants were instructed to move the cursor using the mouse and click at the point they chose from 0 to 100. The emotion labels used for the 'category scales' were the French terms for fear, anger, disgust, happiness, surprise and sadness. The order of emotion category scales on the screen was kept constant for a given participant, but randomized across participants (except for intensity which was always the first). Thus, although only one scale corresponded to the 'correct' emotion that was actually presented (i.e. fear rating scale for fearful faces, anger ratings scale for angry faces and happy rating scale for happy faces), the five other scales concerning 'incorrect' emotions could be used by subjects to rate the subjective impression of blends between the target emotion and other emotions. Similar rating scales were used in previous studies to measure recognition of emotion (Adolphs *et al*., 1994; Siebert *et al*., 2003), but using discrete point-scales (from 0 to 5), whereas our participants were requested to make continuous emotion judgements. This type of responding has the advantage of allowing a finer and qualitative measure of responses, including any systematic confusion and blunting of discrimination, not only error rate (Sander *et al*., 2007).

The main dependent variable was the rating given by participants (from 0 to 100) on each scale. To characterize the response of the participants better, we computed two different indices of recognition as previously used by Shaw *et al*. (2007): congruence and discrimination. Congruence was defined as the mean rating given to the 'correct' emotion, and discrimination was the difference between the rating for the 'correct' emotion (congruence) and the mean of ratings given to the other five 'incorrect' emotions.

Statistical tests were conducted using Statistica software (version 6.1; StatSoft Inc., Maisons-Alfort, France). *P*-values below 0.05 were considered significant.

Results

While the main focus of this experiment was to test the prediction that an interaction between emotion (fear versus anger) and gaze direction (direct versus averted) would be observed in healthy controls but not in amygdala patients, we measured both the recognition of expressions and more general intensity ratings for these two emotions of interest, as well as for the happy condition.

Recognition of emotional expressions

To assess the general profile of emotion judgements across the different expressions and across participants, we first analysed the emotion ratings made on the six emotion category scales, regardless of the intensity of expression and direction of gaze. A repeated-measure analysis of variance (ANOVA) was conducted with two within-subject factors: emotion expression (three levels: anger, fear and happiness) and emotion rating (six levels: anger, fear, sadness, happiness, disgust and surprise), plus one between-subject factor: participant group (three levels: control, RTL and LTL). This analysis revealed significant main effects of emotion expression [$F(2, 52) = 19.3$, $P < 0.05$] and of emotion rating [$F(5, 130) = 17.3$, $P < 0.05$]. There was also a two-way interaction between rating and emotional expression [$F(10, 260) = 103.9$, $P < 0.001$] indicating that the three types of emotions were perceived as consistently different from each other, and that different emotion ratings were made for the different facial expressions. Finally, there was a significant three-way interaction between rating, emotional expression and group [$F(20, 260) = 2.9$, $P < 0.05$], which indicated that the rating profile made by the patients across emotion categories was significantly different from the ratings made by controls (Fig. 3). Furthermore, the ratings of fear for the fearful face condition were lower in patients than controls [$F(1, 27) = 7.6$, $P < 0.05$].

Therefore, next we investigated whether the difference between groups primarily concerned the ratings for the 'correct' emotion, or whether the groups also differed more generally in their ratings of 'incorrect' emotions. For each of the three expressions and each of the groups, we calculated two recognition indices, the 'congruence' index (the mean rating given to the 'correct' emotional scale) and the 'discrimination' index (the difference between congruent responses and the mean of ratings given to the other five 'incorrect' emotions). We then systematically compared the two patient groups (right and left) with each other and with the controls, using unpaired *t*-test contrasts for each face expression type.

For the congruence index, both patient groups were found to be significantly worse than control participants at rating the correct emotion category for fear and anger (i.e. lower congruence), but not for happiness. In addition, for the discrimination rate, the left patient group was significantly impaired for angry and fearful expressions as compared to the control subjects, whereas the right patient group was significantly impaired for fearful faces and the difference was marginally significant for angry and happy faces (Table 2). No differences were found between the left and right patient groups, both for the congruence and discrimination measures. Overall, these results confirm a deficit in the recognition of facial expressions of fear and anger in patients with amygdala damage, irrespective of the operated side, but with a trend for a broader deficit extending to happiness in patients with right lesions.

Interaction of emotion recognition and gaze direction

The main new question addressed in our study concerned the interaction of expression and eye gaze during emotion recognition in amygdala patients. We first analysed emotion recognition accuracy using a three-way ANOVA on congruence values (i.e. ratings on the expected 'correct' emotion for each stimulus), including emotion type (anger, fear versus happiness), expression intensity (50% versus 100%) and gaze direction (direct versus averted) as within-subject factors, plus group (control, LTL, versus RTL) as between-subject factor. The results showed significant effects of group [$F(2, 26) = 4.05$, $P < 0.05$], emotion

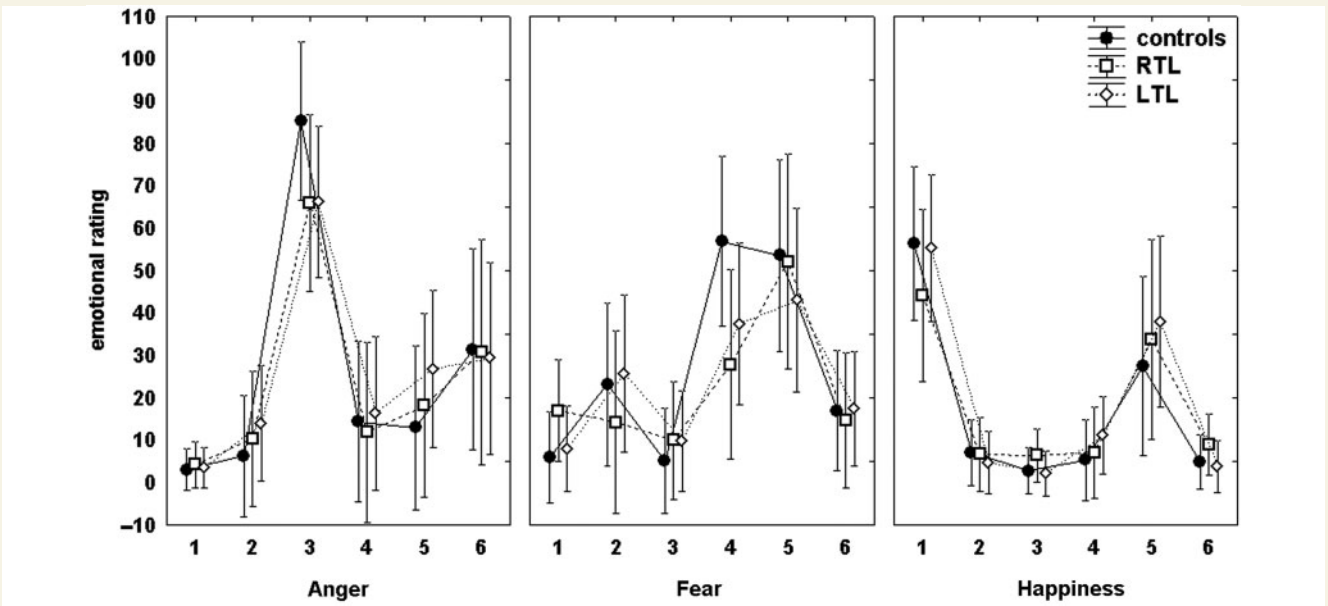

Figure 3 Emotion ratings for the three facial expressions. The average value of ratings made on the six emotion category scales is shown for the control subjects, LTL and RTL patients. The scale correspondence is 1 = happiness; 2 = sadness; 3 = anger; 4 = fear; 5 = surprise; and 6 = disgust. Error bars represent standard deviations around the mean between subjects.

Table 2 Performance indices for emotion ratings

Index	Emotion	Right, M (D.S) ($n=8$)	Left, M (SD) ($n=11$)	Controls, M (SD) ($n=10$)	Group comparison	*t* (*P*)
Congruence	Anger	65.98 (23.54)	66.16 (24.95)	85.25 (8.62)	R versus L	−0.01 (0.98)
					R versus controls	−2.40 (0.02)*
					L versus controls	2.29 (0.03)*
	Fear	27.85 (23.79)	37.44 (22.27)	56.94 (19.50)	R versus L	−0.90 (0.38)
					R versus controls	−2.85 (0.01)*
					L versus controls	2.12 (0.04)*
	Happiness	44.14 (19.88)	55.40 (22.82)	56.50 (15.63)	R versus L	−1.11 (0.27)
					R versus controls	−1.47 (0.15)
					L versus controls	0.12 (0.89)
Discrimination	Anger	50.87 (31.33)	48.18 (23.57)	71.63 (18.06)	R versus L	0.21 (0.83)
					R versus controls	−1.7 (0.09)
					L versus controls	2.53 (0.01)*
	Fear	6.25 (20.38)	16.64 (20.41)	36.00 (16.67)	R versus L	−1.09 (0.28)
					R versus controls	−3.41 (0.003)*
					L versus controls	2.36 (0.02)*
	Happiness	31.55 (17.84)	43.44 (21.85)	46.98 (13.55)	R versus L	−1.26 (0.22)
					R versus controls	−2.08 (0.05)
					L versus controls	0.44 (0.66)

Congruence is the mean rating given to the 'correct' emotion; discrimination is the difference between the rating for the 'correct' emotion (i.e. congruence) and the mean of ratings given to the five other 'incorrect' emotions. Average value and SDs are given for each expression and each group. Asterisks designate significant differences between groups (unpaired *t*-test).

[$F(2, 52) = 26.1$, $P < 0.01$] and intensity [$F(1, 26) = 111.5$, $P < 0.01$] but, as expected, no significant main effect of gaze [$F(1, 26) = 0.8$, $P > 0.3$]. Emotion recognition was better in control participants than in the two patient groups across all stimulus conditions and better for happiness than for other expressions, in all participants (Fig. 3).

The triple interaction between emotion, gaze and group failed to reach significance in the full ANOVA above [$F(4, 52) = 1.2$, $P > 0.3$]. However, our key predictions specifically concerned the influence of gaze direction on the recognition of fear and anger, and the possible consequences of amygdala damage on this specific gaze × expression interaction. Because recognition accuracy showed significant main effects of group and also because previous studies in normal participants showed no significant effects of gaze for happy expression (Sander *et al*. 2007; N'Diaye *et al*., in press), we then focused on planned comparisons for these two emotions of interest. Three new ANOVAs were performed on the congruence values, for each group separately, using emotion type (anger versus fear), expression intensity (50 and 100%) and gaze direction (direct versus averted) as within-subject factors in each group.

For controls, as observed in the full analysis, we found significant effects of emotion [$F(1, 9) = 24.4$, $P < 0.05$] and intensity [$F(1, 9) = 15.5$, $P < 0.05$], as well as the predicted interaction between emotion and gaze [$F(1, 9) = 7.9$, $P < 0.05$], confirming that the 'correct' emotion ratings on target expressions reliably varied as a function of the concomitant gaze direction, thus replicating previous results in normal participants (Sander *et al*., 2007). There was no interaction between emotion and intensity [$F(1, 9) = 0.08$, $P > 0.7$] or between gaze and intensity [$F(1, 9) = 2.5$, $P > 0.1$].

In patients with LTL, main effects of emotion [$F(1, 10) = 10.2$, $P < 0.05$] and intensity [$F(1, 10) = 18.1$, $P < 0.05$] were also significant, accompanied with a reliable interaction of emotion × intensity [$F(1, 10) = 16.7$, $P < 0.05$]. The critical emotion × gaze interaction followed the same direction as in controls, but just failed to reach significance [$F(1, 10) = 4.49$, $P = 0.06$]. There was no significant interaction between gaze and intensity [$F(1, 10) = 0.86$, $P > 0.3$].

On the other hand, patients with right lobectomy showed only main effects of emotion [$F(1, 7) = 22.7$, $P < 0.05$] and intensity [$F(1, 7) = 27.7$, $P < 0.05$], but the interaction between gaze and emotion was not significant [$F(1, 7) = 0.02$, $P > 0.8$]. Likewise, neither the interaction between emotion and intensity [$F(1, 7) = 3.17$, $P > 0.1$] nor that between gaze and intensity [$F(1, 7) = 0.02$, $P > 0.8$] were significant in this group.

The triple interaction emotion × gaze × intensity was not significant in any of the three groups ($P > 0.3$). Taken together, these results indicate that, unlike controls (and to a lesser degree left lobectomy patients), right lobectomy patients did not differently recognize fear versus anger as a function of averted versus direct gaze direction, respectively (Fig. 4). Thus, these findings are consistent with our prediction that, in controls, the perception of self-relevance induced by gaze direction should enhance perceived anger in angry faces when their gaze is direct rather than averted but conversely enhance perceived fear in fearful faces when gaze is averted rather than direct (see also Sander *et al*., 2007; N'Diaye *et al*., in press). Critically, as predicted, this interaction was not observed after right amygdala damage; however, this interaction was reduced but still present in LTL patients.

In order to clarify the different response patterns to fear and anger for right lobectomy patients, as compared with controls and

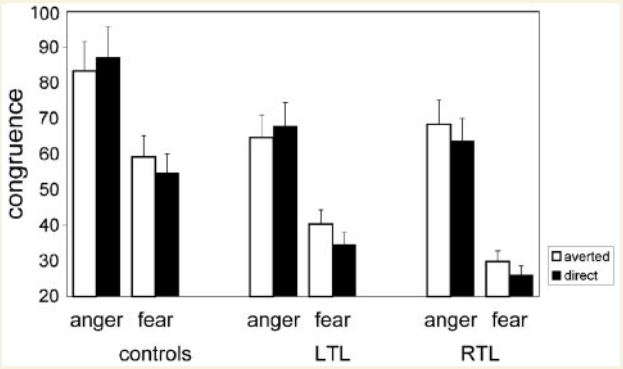

Figure 4 Recognition of anger and fear as a function of gaze direction. Ratings on the congruent emotion category scales (from 0 to 100) are illustrated for each emotion expression and each gaze condition in the three groups of participants. Error bars represent standard deviations around the mean between subjects. Relative to averted gaze, direct gaze generally increased perception of anger but reduced perception of fear (and vice versa), but only in controls and left lobectomy patients, not in right lobectomy patients.

left lobectomy patients, we further analysed the effects of gaze direction for each of these two emotions separately. Additional ANOVAs were performed on congruence values, one for each emotion type, using gaze direction (direct versus averted) and expression intensity (50 and 100%) as within-subject factors and group (control, LTL and RTL) as a between-subject factor.

When exploring responses to angry faces, we found a significant main effect of intensity [$F(1, 26) = 51.3$, $P < 0.01$] and an interaction between intensity and gaze [$F(1, 26) = 4.4$, $P < 0.05$]. Most importantly, we observed an interaction between gaze and group [$F(1, 26) = 4.3$, $P < 0.05$]. This reflected a difference in the influence of gaze on emotion ratings for the right lobectomy patients relative to controls [gaze × group interaction: $F(1, 26) = 4.3$, $P < 0.05$], whereas there was no such difference for left lobectomy patients relative to controls [gaze × group interaction: $F(1, 26) = 0.02$]. Finally, we also observed a marginally significant gaze × group interaction [$F(1, 26) = 3.8$, $P = 0.05$] when directly comparing the two patient groups (LTL versus RTL), suggesting that the effect of gaze on the ratings of anger was more disrupted by right than left amygdala damage.

When exploring responses to fearful faces, we found main effects of group [$F(2, 26) = 4.2$, $P < 0.05$], intensity [$F(1, 26) = 7.5$, $P < 0.05$] and gaze [$F(1, 26) = 4.2$, $P = 0.05$], but no interaction between gaze and group was observed [controls versus RTL: $F(1, 26) = 0.01$, $P > 0.9$; controls versus LTL: $F(1, 26) = 0.04$, $P > 0.8$; RTL versus LTL: $F(1, 26) = 0.09$, $P > 0.7$].

Although happy expressions were used as a control condition, for completeness, we also tested for any effect of gaze on the recognition of happiness. Some studies have reported that perception of happiness might be enhanced with direct, as compared to averted, gaze (Adams and Kleck, 2005; but see Sander *et al.*, 2007 for different results). We therefore repeated a 2 (gaze) × 2 (intensity) × 3 (group) ANOVA on congruence ratings for happy expressions. This showed a main effect of intensity only [$F(1, 26) = 120.9$, $P < 0.01$], but no main effects and no interactions were found with the factors gaze [$F(1, 26) = 0.3$, $P > 0.5$] and group [$F(2, 26) = 1.0$, $P > 0.3$].

Finally, we also confirmed the mirror effect of gaze direction on fear and anger, by measuring the directionality of gaze effects (i.e. relative increases or decreases in emotion ratings) using a sign test across the different face conditions and the different groups. First, we computed the difference between stimuli with direct and averted gaze for ratings on the fear and anger category scales (i.e. positive differences when ratings of a given emotion category were higher with direct gaze; negative differences when ratings were higher with averted gaze). We then compared this measure of gaze-effects for anger versus fearful expressions using a sign test across participants from each group, which revealed that the difference was significant in controls ($P = 0.021$); nearly significant in left lobectomy patients ($P = 0.065$); but non-significant in right lobectomy patients ($P = 0.99$). These results confirm an opposite influence of gaze direction (averted or directed) on the recognition of anger and fear, which were present in normal participants, weaker but still present in LTL patients and totally absent in RTL patients. In contrast, no systematic difference was found for happy expressions (relative to either anger or fear) in any of the three groups.

Taken together, these data converge to show that, in both controls and left lobectomy patients, expression and gaze interacted in the recognition of emotion in faces, with anger being rated higher with direct as compared to averted gaze, but fear being rated higher with averted as compared to direct gaze. No such interaction of gaze and expression was observed in right lobectomy patients. Furthermore, the predicted loss in this interaction for these patients was mainly driven by the abnormal effect of direct gaze on recognition of anger, suggesting that gaze direction and self-relevance might be more important for the appraisal of angry than fearful expression. Most importantly, these data demonstrate that an interaction of gaze and expression during emotion recognition is dependent on the integrity of the (right) amygdala.

Perception of expression intensity

In addition to the emotion scales, participants rated the face expressions on a more general 'emotion intensity scale' (irrespective of emotion category). For completeness, we also analysed these ratings by a repeated-measure ANOVA with emotion (anger, fear and happy), intensity (50 and 100%) plus gaze direction (direct versus averted) as within-subject factors and group (control versus LTL versus RTL) as a between-subject factor. We found main effects of intensity [$F(1, 26) = 110.6$, $P < 0.01$] and emotion [$F(2, 52) = 58.8$, $P < 0.01$], and interactions between intensity and emotion [$F(2, 52] = 6.8$, $P < 0.01$] as well as intensity and group [$F(2, 26) = 6.7$, $P < 0.01$] and emotion and group [$F(2, 52) = 7.2$, $P < 0.01$]. Importantly, there was no main effect of group and no main effect or interaction involving gaze direction.

Planned comparisons revealed that full (100%) expressions were perceived as more intense than partial (50%) expressions in all groups [controls: $F(1, 26) = 81.1$, $P < 0.01$; LTL: $F(1, 26) = 17$, $P < 0.01$; RTL: $F(1, 26) = 26.1$, $P < 0.01$], demonstrating not only the validity of our intensity manipulation but also preserved

processing of expression intensity in the patients. However, comparisons between groups showed that this intensity effect was stronger in controls than in both the LTL [$F(1, 26) = 13.3$, $P < 0.01$] and RTL patients [$F(1, 26) = 4.8$, $P < 0.05$], explaining the significant interaction between intensity and group. In contrast, the interaction between intensity and patient subgroup (LTL versus RTL) was not significant [$F(1, 26) = 1.4$, $P > 0.2$].

The effect of intensity was evident in all three emotions [anger: $F(1, 26) = 75.9$, $P < 0.01$; fear: $F(1, 26) = 56.2$, $P < 0.01$; happiness: $F(1, 26) = 109.3$, $P < 0.01$] but lower for fearful than for happy [$F(1, 26) = 10.3$, $P < 0.01$] or angry faces [$F(1, 26) = 11.5$, $P < 0.05$], explaining the significant interaction between intensity and emotion. Finally, the emotion × group interaction was due to the fact that LTL patients showed a different pattern across the three emotion categories relative to other groups. Whereas both controls and RTL patients generally rated intensity lower for happy faces than for fearful faces [controls: $F(1, 26) = 21.4$, $P < 0.01$; RTL: $F(1, 26) = 13.5$, $P < 0.01$] and angry faces [controls: $F(1, 26) = 57.1$, $P < 0.01$; RTL: $F(1, 26) = 31.1$, $P < 0.01$], this difference failed to reach significance in LTL [$F(1, 26) = 0.5$, $P > 0.4$ and $F(1, 26) = 3.18$, $P = 0.08$, respectively].

Thus, overall, the lack of any significant effect of gaze direction on general intensity ratings further establishes the specificity of its influence on emotion recognition.

Experiment 2

Although the results above suggest a loss of eye-gaze influences on emotion recognition in right lobectomy patients, it is, in principle, possible that our results may reflect a deficit in processing eye-gaze in the first place rather than impaired integration of gaze with expression information. We therefore performed a control experiment to assess eye-gaze perception in the same participants.

Recent evidence from both imaging and neuropsychology studies has suggested an important role for the amygdala in processing the eye region of faces (e.g. Whalen *et al*., 2004; Adolphs *et al*., 2005; Spezio *et al*., 2007) and previous findings indicate that gaze direction perception can be disrupted in patients with temporal lobe damage (Campbell *et al*., 1990; Young *et al*., 1995). In particular, Young *et al*. (1995) reported that a patient with bilateral damage to the amygdala (and neighbouring regions) was impaired in discriminating gaze direction. Such a deficit might in itself explain a loss of interaction between emotion expression and gaze direction in our right lobectomy patients. Our control experiment therefore aimed at checking whether our patients showed any deficit in processing eye-gaze cues *per se*. We therefore presented our participants with an additional gaze discrimination task using neutral faces with variations in gaze direction (see Campbell *et al*., 1990; Young *et al*., 1995).

Methods

Participants

Participants consisted of the same groups of patients and healthy controls as in Experiment 1. All participants were presented with this gaze discrimination after the emotion recognition task.

Stimuli

Similar stimuli were used as those in Experiment 1 but with different identities and always with neutral expressions. We selected four identities (two males and two females) from the same computer-generated face dataset (FaceGen), which were shown in a full-front static condition with different directions of gaze. Seven gaze directions were used: full frontal (0°) or deviated by 5°, 10° and 20° (left or right, on half of the trials each), resulting in a total of 32 items.

Procedure

The testing procedure was derived from the experimental design used by Campbell *et al*. (1990) and Young *et al*. (1995). Neutral faces were presented one at a time during 2 s on a computer screen. After each stimulus, three response labels appeared on the screen: 'left', 'central' and 'right' to indicate the eye-gaze direction. The 'central' label was shown at the centre of the screen, whereas the 'left' and 'right' labels were presented on the left and right sides, respectively. Each participant was requested to indicate if the face looked at him/her, or away from him/her, by choosing the label corresponding to the gaze direction of the previously seen face.

Results

We computed the per cent of items that were perceived as looking straight and measured how this was modulated by the actual gaze direction and whether this modulation differed between the three groups of participants. We focused only on those conditions where the gaze was deviated by 5 and 10°, because in the condition with 20° of deviation all participants correctly perceived the gaze as deviated. We conducted an ANOVA with one within-subject factor, gaze deviation (three levels: direct, deviation of 5 and 10°), plus one between-subject factor, participant group (three levels: control, RTL and LTL). This analysis did not show any effect of group ($P = 0.4$), but there was a significant effect of gaze deviation [$F(2, 4) = 197.3$, $P < 0.001$]. Both controls and patients were practically flawless in judging the gaze direction across all conditions except for the smallest (5°) deviation (Fig. 5). Thus, when the gaze was deviated by 5°,

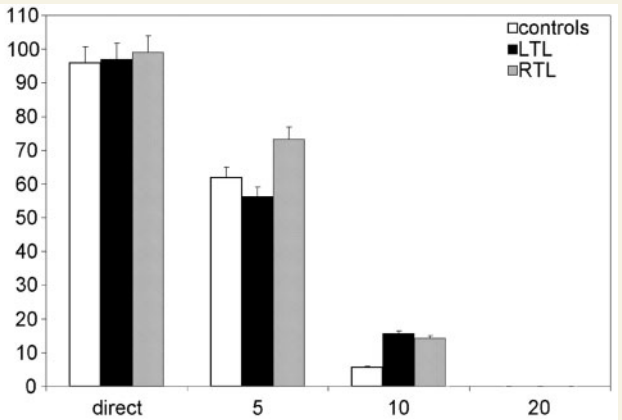

Figure 5 Gaze direction discrimination task. The per cent of 'direct gaze' judgements made for each of the four conditions of eye direction and each of the three participant groups. Error bars represent standard deviations around the mean between subjects.

more than 50% of the faces were judged as looking straight rather than averted, whereas for the other degrees of deviation, less than 10% were judged as straight ($P < 0.05$ for all paired comparisons between conditions). Most critically, there was no significant difference between the three groups in any of the conditions ($P > 0.3$).

Discussion

To the best of our knowledge, the current study demonstrates, for the first time, that unilateral right amygdala damage disrupts the interaction of gaze and expression during emotion perception and thus provides new support to recent proposals that the human amygdala might be critically important for encoding the self-relevance of emotional events. Although it has frequently been reported that bilateral damage to the amygdala can impair emotion recognition, particularly for fearful face expressions (Adolphs *et al*., 1994), the consequence of unilateral amygdala lesion and the contribution of amygdala activity to other emotion categories has remained unresolved. Furthermore, a number of studies in healthy subjects suggested that emotion perceived from faces may be modulated by gaze direction (Adams and Kleck, 2003, 2005; Graham and LaBar, 2007; Sander *et al*., 2007) and that such interaction between gaze and expression may activate the amygdala during fMRI (Adams *et al*., 2003; Sato *et al*., 2004*a*; N'Diaye *et al*., in press), but these findings are also controversial due to discrepant findings (see Bindemann *et al*., 2008; Graham and LaBar, 2007). Here we report new data showing that, in healthy controls, the gaze direction of seen faces (eyes oriented towards or away from the viewer) could modulate the perception of fearful and angry expression, even though facial expression *per se* was visually similar. In contrast, patients with RTL did not show this interaction, while patients with LTL showed a relatively preserved (or slightly reduced) interaction. This deficit in right lobectomy patients was most evident for the effect of direct gaze on the perception of angry expression, suggesting a stronger role of gaze for the appraisal of anger. In addition, both right and left lobectomy patients were also more generally impaired in recognizing expressions of fear and anger, while perception of happiness was generally preserved (except for a marginally significant difference in the discrimination index for happiness between controls and right lobectomy patients). Furthermore, there was no significant effect of gaze direction for happy faces in either group. Altogether, these data provide new insights into the integration of expression and gaze signals in the amygdala and its proposed role for coding the self-relevance of threatening events.

To investigate the modulation of emotion perception by gaze direction, we designed a novel paradigm with well controlled, computer-animated movies of faces displaying different emotional expressions (fear, anger or happiness) in combination with gaze-shifts directed either towards or away from the observer. Replicating earlier behavioural results with a different set of dynamic stimuli (Sander *et al*., 2007), our healthy participants rated angry faces as expressing more anger when these faces were seen with direct gaze than with an averted gaze. Conversely, fearful faces were perceived as expressing more fear when these faces were seen with an averted than with a direct gaze. This result is in agreement with the notion that the perception of emotion is influenced by the self-relevance assigned to a stimulus (Sander *et al*., 2003, 2007) and accords with previous claims that gaze cues can provide crucial information to infer intentions from a seen face and thus influence the subjective significance of their expressions (Adams *et al*., 2003). Thus, our results converge with previous findings (Adams and Kleck, 2003, 2005; Sander *et al*., 2007) that emotional facial perception is not determined by facial features alone but can be modulated by eye-gaze cues, and further underscores the role of self-relevance in the appraisal of facial expressions.

As recently shown by Bindemann *et al*. (2008), the interaction effects between gaze and expression may vary with particular stimuli and task conditions. Some discrepancies between previous studies might result from differences in face stimuli. In particular, Adams *et al*. (2003, 2005) and Bindemann *et al*. (2008) used different sets of static faces and obtained conflicting results; while the present results and those obtained by Sander (2007) were obtained with different stimulus material but using dynamic facial expressions in both cases (N'Diaye *et al*., in press), which may favour the integration of facial features in an integrated percept, given the dynamic nature of facial displays in natural conditions. Our findings therefore also underscore the increasing needs to employ ecologically valid stimuli to study emotional and social processing. Moreover, when using dynamic stimuli to test the interactions between gaze and expression, it may also be important to consider the precise temporal dynamics of the gaze versus expression. For example, Graham and LaBar (2007) found that this interaction effect is sensitive to the relative speed of processing of gaze and emotion. When emotion could be processed faster than (i.e. prior to) gaze, these authors found a general advantage for direct versus averted gaze; but an interaction emerged only when emotion processing was delayed. Bindemann *et al*. (2008) also interpreted their results concerning interaction effects between gaze and expression as indicating that gaze processing plays an earlier role than expression processing in face perception. Their results indicated faster processing of direct gaze angry faces, while gaze did not reliably affect the processing of fear (possibly reflecting a greater relevance of gaze cues in anger than fear). In our experiment, the gaze shift always preceded the unfolding of the expression, which may therefore correspond to optimal conditions for interactivity to appear. Further research is needed to determine whether a different temporal dynamic may induce a distinct recruitment of the amygdala and appraisal processes.

It should also be noted that the fear expressions used in our experiment were difficult to differentiate from surprise (as commonly found in other studies, see Rapcsak *et al*., 2000), perhaps allowing recognition to be most effectively modulated by gaze direction. Thus, it is possible that gaze may serve as a cue to determine the emotion (Adams *et al*., 2005), consistent with the fact that gaze may affect emotion perception in some studies using more ambiguous expressions or particular stimuli, but not in other studies (Graham and LaBar, 2007; Bindemann *et al*., 2008).

Accordingly, a recent fMRI experiment using the same stimuli as this study (N'Diaye *et al*., in press) demonstrated that the crucial interaction between gaze (direct versus averted) and expression (fear versus anger) in the amygdala was particularly strong for faces that had mildly intense expression. In the current study, however, although fearful expressions were more ambiguous and more difficult to recognize, an impaired modulation of gaze on emotion recognition arose predominantly for angry faces, not for fearful faces, indicating that this abnormal pattern was not simply related to reduced recognition rates.

Importantly, both theoretical predictions and empirical evidence has suggested that the amygdala might play a key role in the appraisal of self-relevance, which is thought to mediate the interactions between gaze and expression during emotional perception (Sander *et al*., 2003). In support of this view, recent neuroimaging studies reported a pattern of activation in the amygdala that was consistent with previous behavioural results showing an influence of gaze direction on the recognition of facial expressions (Sato *et al*., 2004*b*; Hadjikhani *et al*., 2008; N'Diaye *et al*., in press). However, other imaging studies have provided divergent findings (e.g. Adams, 2003). In addition, these imaging results brought only indirect evidence for a critical (i.e. causal) involvement of amygdala activity in mediating such effects. Here we directly tested for the impact of amygdala lesions and our results suggest, for the first time, that the integrity of the right amygdala is necessary for the emotional appraisal of self-relevance in emotional expressions. Indeed, contrary to left lobectomy patients and control participants, right lobectomy patients did not show the critical pattern of gaze influences on the perception of angry and fearful faces.

This asymmetry in performance between the two patient groups might reflect a presumed 'dominance' of the right hemisphere for processing emotional and social stimuli (see Borod and Madigan, 2000) as well as self-related information (Van Lancker, 1991). It should also be mentioned that all our right-damaged patients were male and it has been suggested that the right amygdala might be more strongly recruited during emotional processing in the male brain (e.g. Canli *et al*., 2002). A few other studies have already found that lesions in the right amygdala generally lead to more severe deficits in emotion recognition than lesions in the left amygdala (Anderson *et al*., 2000; Adolphs *et al*., 2001; Benuzzi *et al*., 2004; McClelland *et al*., 2006). In addition, fMRI studies on gaze direction processing have reported asymmetrical activation with stronger response in the right superior temporal sulcus (Campbell *et al*., 1990; Pelphrey *et al*., 2004; Calder *et al*., 2007; Engell and Haxby, 2007). As gaze processing in the amygdala may partly depend on inputs from the superior temporal sulcus (Calder and Nummenmaa, 2007), a right-sided dominance of the superior temporal sulcus might in turn explain a greater sensitivity of right than left amygdala to gaze cues. Alternatively, it is also possible that the surgical temporal resection may cause some damage to connections between amygdala and the superior temporal sulcus, and thus impair the integration of information relative to expression and gaze. Note, however, that the volume of right and left temporal lobe damage was similar in our two patients groups.

Furthermore, as showed by our control experiment, the selective effect of right amygdala lesion on the integration of gaze and expression could not be explained by a more general deficit in processing gaze direction, which could have resulted in greater losses in gaze influences for these patients. Indeed, it has been reported not only that bilateral amygdala lesions may impair the perception of eye-gaze position (Young *et al*., 1995), but also that gaze processing may increase amygdala activity in healthy subjects (Wicker *et al*., 1998; Kawashima *et al*., 1999; George *et al*., 2001). However, to rule out the possibility that impaired gaze processing might lead to impaired perception of self-relevance, we ran a control experiment that specifically tested for the ability to discriminate small changes in eye-gaze direction in our patients. This experiment clearly demonstrated that performance of both right and left lobectomy patients was similar to that of healthy controls. All three groups could accurately distinguish direct from averted gaze and all showed equal difficulty with smaller (5°) gaze deviations, suggesting that the task was sensitive enough to measure discrimination performance even in healthy subjects. Therefore, the lack of significant interaction between gaze and expression in right lobectomy patients cannot be attributed to some deficits in upstream processes of gaze direction perception. Although this lack of deficit appears to contrast with the case study of Young *et al*. (1995), their patient had bilateral damage to the temporal lobes with substantial lesions beyond the amygdala. Clinical details described large damage to subcortical regions in the right hemisphere including ''a discrete lesion in the pallidal region at the level of the anterior commissure, extending more dorsally within the striatum at a level rostral to the anterior commissure, with possible damage to adjacent parts of the internal capsule and caudate nucleus'' (Young *et al*., 1995). This difference between bilateral and unilateral lesions might suggest that an intact amygdala in either hemisphere is sufficient to process gaze direction, while integrity of the right amygdala is necessary to integrate information from gaze and facial expression. Alternatively, deficits in gaze direction discrimination might be due to lesions located deeper in the temporal lobe, disconnecting the amygdala from regions in the superior temporal sulcus or other temporal cortical areas that are known to be important for gaze processing (Campbell *et al*., 1990; Calder *et al*., 2007; Engell and Haxby, 2007).

Conversely, the pathological lack of interaction between gaze and expression in right lobectomy patients was essentially due to the absence of gaze effects on the recognition of anger (which differed from both controls and left lobectomy patients), while the effect of averted gaze on fear perception was consistent across all groups (Fig. 4). This might suggest that the role of gaze is more important in the perception of threat signalled by angry faces than fearful faces, perhaps reflecting a greater impact of right amygdala damage on the appraisal of self-relevance of angry faces as a function of gaze direction, which actually accords with the fact that angry faces gazing at the observer should represent the most self-relevant condition relative to angry faces gazing away or to fearful faces. Accordingly, in healthy participants, the effect of gaze on expression processing is generally less reliable for fear than that found for anger (Graham and LaBar, 2007; Bindemann *et al*., 2008), a difference of particular interest given that abnormal lack of gaze effects in our right lobectomy patients arose specifically for angry, rather

than fearful, expressions. Thus, in addition to a general right-hemisphere dominance in emotion and gaze processing, the differences between our two patient groups might also indicate a right amygdala bias in processing the type of threat signalled by anger (e.g. due to its particular social or self-relevance significance).

The existence of any lateralization in amygdala function is still debated in terms of domains and levels of processing (Baas *et al*., 2004; Sergerie *et al*., 2008), but some hemispheric distinction has been proposed on the basis of results in patients with left and right temporal damage (Funayama *et al*., 2001; Phelps *et al*., 2001), suggesting a right amygdala bias for processing perceptual threat cues that elicit arousal and startle-like responses (while the left amygdala would be more involved in fear responses associated with cognitive or linguistic representations; see also Berntson *et al*., 2007). In addition, a right-amygdala lateralization in processing the self-relevance of angry faces is consistent with a recent neuroimaging study showing that higher anxiety levels produce an increased response of the right (but not left) amygdala to angry facial expressions (versus fearful or neutral) specifically when these are task-relevant (Ewbank *et al*., 2009*b*). Altogether, these data point to the possibility that the appraisal of self-relevance (e.g. for angry faces and/or as a function of gaze direction) might be predominantly dependent on integrity of the right amygdala.

In addition, our study also found that unilateral lesions to either side could produce deficits in processing facial expressions of anger and fear, irrespective of gaze direction. As compared with controls, both left and right lobectomy patients perceived less anger in angry faces and less fear but more surprise in fearful faces. However, patient ratings did not consistently differ from those of controls for happy faces. These results agree with previous studies (Anderson *et al*., 2000; Adolphs *et al*., 2001; Fowler *et al*., 2006; McClelland *et al*., 2006) showing impairments in facial expression recognition following unilateral amygdala lesion, as well as those showing more severe impairments for negative or threat-related expressions than for positive expressions (Adolphs *et al*., 2001; Benuzzi *et al*., 2004; Shaw *et al*., 2004; McClelland *et al*., 2006).

In conclusion, our results extend previous findings showing that, in healthy participants, gaze direction can modulate the perception of emotional face expression according to a specific pattern predicted by the appraisal of self-relevance (Sander *et al*., 2003, 2005). Furthermore, we demonstrate for the first time that the amygdala may play a key role in such effects, by showing that patients with right lobectomy do not exhibit such a modulation of emotion perception by gaze and that this deficit cannot be explained by deficits in gaze direction discrimination or emotion intensity perception. These results strongly support a causal role for the amygdala (and possibly adjacent structures within the medial temporal lobe) in processing the self-relevance of emotional and social stimuli. In addition, this research confirms that even unilateral amygdala lesion may lead to deficits in emotion recognition, which underscores the need to properly assess emotional processing properly before and after medial temporal lobe surgery using appropriate tests.

Acknowledgements

We thank two anonymous reviewers for their helpful comments and suggestions.

Funding

Swiss National Science Foundation (FNRS grant No 105314-118267 to D.S. and P.V., partial); Swiss National Centre of Competence in Research (NCCR) in the Affective Sciences (grant No 51NF40-104897).

References

Adams RB Jr, Gordon HL, Baird AA, Ambady N, Kleck RE. Effects of gaze on amygdala sensitivity to anger and fear faces. Science 2003; 300: 1536.

Adams RB Jr, Kleck RE. Perceived gaze direction and the processing of facial displays of emotion. Psychol Sci 2003; 14: 644–7.

Adams RB Jr, Kleck RE. Effects of direct and averted gaze on the perception of facially communicated emotion. Emotion 2005; 5: 3–11.

Adolphs R. Recognizing emotion from facial expressions: psychological and neurological mechanisms. Behav Cogn Neurosci Rev 2002; 1: 21–62.

Adolphs R, Gosselin F, Buchanan TW, Tranel D, Schyns P, Damasio AR. A mechanism for impaired fear recognition after amygdala damage. Nature 2005; 433: 68–72.

Adolphs R, Tranel D, Damasio H. Emotion recognition from faces and prosody following temporal lobectomy. Neuropsychology 2001; 15: 396–404.

Adolphs R, Tranel D, Damasio H, Damasio A. Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. Nature 1994; 372: 669–72.

Adolphs R, Tranel D, Damasio H, Damasio AR. Fear and the human amygdala. J Neurosci 1995; 15: 5879–91.

Adolphs R, Tranel D, Hamann S, Young AW, Calder AJ, Phelps EA, et al. Recognition of facial emotion in nine individuals with bilateral amygdala damage. Neuropsychologia 1999; 37: 1111–7.

Anderson AK, Christoff K, Panitz D, De Rosa E, Gabrieli JDE. Neural correlates of the automatic processing of threat facial signals. J Neurosci 2003a; 23: 5627–33.

Anderson AK, Christoff K, Stappen I, Panitz D, Ghahremani DG, Glover G, et al. Dissociated neural representations of intensity and valence in human olfaction. Nat Neurosci 2003b; 6: 196–202.

Anderson AK, Phelps EA. Expression without recognition: contributions of the human amygdala to emotional communication. Psychol Sci 2000; 11: 106–11.

Anderson AK, Spencer DD, Fulbright RK, Phelps EA. Contribution of the anteromedial temporal lobes to the evaluation of facial emotion. Neuropsychology 2000; 14: 526–36.

Baas D, Aleman A, Kahn RS. Lateralization of amygdala activation: a systematic review of functional neuroimaging studies. Brain Res Brain Res Rev 2004; 45: 96–103.

Benuzzi F, Meletti S, Zamboni G, Calandra-Buonaura G, Serafini M, Lui F, et al. Impaired fear processing in right mesial temporal sclerosis: a fMRI study. Brain Res Bull 2004; 63: 269–81.

Berntson GG, Bechara A, Damasio H, Tranel D, Cacioppo JT. Amygdala contribution to selective dimensions of emotion. Soc Cogn Affect Neurosci 2007; 2: 123–9.

Bindemann M, Burton MA, Langton SRH. How do eye gaze and facial expression interact? Vis Cogn 2008; 16: 708–33.

Blair RJR, Morris JS, Frith CD, Perrett DI, Dolan RJ. Dissociable neural responses to facial expressions of sadness and anger. Brain 1999; 122: 883–93.

Breiter HC, Etcoff NL, Whalen PJ, Kennedy WA, Rauch SL, Buckner RL, et al. Response and habituation of the human amygdala during visual processing of facial expression. Neuron 1996; 17: 875–87.

Brett M, Leff AP, Rorden C, Ashburner J. Spatial normalization of brain images with focal lesions using cost function masking. NeuroImage 2001; 14: 486–500.

Broks P, Young AW, Maratos EJ, Coffey PJ, Calder AJ, Isaac CL, et al. Face processing impairments after encephalitis: amygdala damage and recognition of fear. Neuropsychologia 1998; 36: 59–70.

Calder AJ, Beaver JD, Winston JS, Dolan RJ, Jenkins R, Eger E, et al. Separate coding of different gaze directions in the superior temporal sulcus and inferior parietal lobule. Curr Biol 2007; 17: 20–5.

Calder AJ, Lawrence AD, Young AW. Neuropsychology of fear and loathing. Nat Rev Neurosci 2001; 2: 352–63.

Calder AJ, Nummenmaa L. Face cells: separate processing of expression and gaze in the amygdala. Curr Biol 2007; 17: R371–2.

Campbell R, Heywood CA, Cowey A, Regard M, Landis T. Sensitivity to eye gaze in prosopagnosic patients and monkeys with superior temporal sulcus ablation. Neuropsychologia 1990; 28: 1123–42.

Canli T, Sivers H, Whitfield SL, Gotlib IH, Gabrieli JDE. Amygdala response to happy faces as a function of extraversion. Science 2002; 296: 2191.

Cristinzio C, Sander D, Vuilleumier P. Recognition of emotional face expressions and amygdala pathology. Epileptologie 2007; 24: 130–8.

Ekman P, Friesen WV. Facial action coding system: a technique for the measurement of facial movement. Palo Alto, CA: Consulting Psychologists Press; 1978.

Engell AD, Haxby JV. Facial expression and gaze-direction in human superior temporal sulcus. Neuropsychologia 2007; 45: 3234–41.

Ewbank MP, Barnard PJ, Croucher CJ, Ramponi C, Calder AJ. The amygdala response to images with impact. Soc Cogn Affect Neurosci 2009a; 4: 127–33.

Ewbank MP, Lawrence AD, Passamonti L, Keane J, Peers PV, Calder AJ. Anxiety predicts a differential neural response to attended and unattended facial signals of anger and fear. Neuroimage 2009b; 44: 1144–51.

Fitzgerald DA, Angstadt M, Jelsone LM, Nathan PJ, Phan KL. Beyond threat: amygdala reactivity across multiple expressions of facial affect. NeuroImage 2006; 30: 1441–8.

Fowler HL, Baker GA, Tipples J, Hare DJ, Keller S, Chadwick DW, et al. Recognition of emotion with temporal lobe epilepsy and asymmetrical amygdala damage. Epilepsy Behav 2006; 9: 164–72.

George N, Driver J, Dolan RJ. Seen gaze-direction modulates fusiform activity and its coupling with other brain areas during face processing. Neuroimage 2001; 13: 1102–12.

Graham R, LaBar KS. Garner interference reveals dependencies between emotional expression and gaze in face perception. Emotion 2007; 7: 296–313.

Grandjean D, Sander D, Lucas N, Scherer KR, Vuilleumier P. Effects of emotional prosody on auditory extinction for voices in patients with spatial neglect. Neuropsychologia 2008; 46: 487–96.

Hamann S. Nosing in on the emotional brain. Nat Neurosci 2003; 6: 106–8.

Hamann SB, Adolphs R. Normal recognition of emotional similarity between facial expressions following bilateral amygdala damage. Neuropsychologia 1999; 37: 1135–41.

Hamann SB, Stefanacci L, Squire LR, Adolphs R, Tranel D, Damasio H, et al. Recognizing facial emotion. Nature 1996; 379: 497.

Kawashima R, Sugiura M, Kato T, Nakamura A, Hatano K, Ito K, et al. The human amygdala plays an important role in gaze monitoring: A PET study. Brain 1999; 122: 779–83.

Levesque J, Eugene F, Joanette Y, Paquette V, Mensour B, Beaudoin G, et al. Neural circuitry underlying voluntary suppression of sadness. Biol Psychiatry 2003; 53: 502–10.

McClelland S III, Garcia RE, Peraza DM, Shih TT, Hirsch LJ, Hirsch J, et al. Facial emotion recognition after curative nondominant temporal lobectomy in patients with mesial temporal sclerosis. Epilepsia 2006; 47: 1337–42.

Meletti S, Benuzzi F, Rubboli G, Cantalupo G, Stanzani Maserati M, Nichelli P, et al. Impaired facial emotion recognition in early-onset right mesial temporal lobe epilepsy. Neurology 2003; 60: 426–31.

Mort DJ, Malhotra P, Mannan SK, Rorden C, Pambakian A, Kennard C, et al. The anatomy of visual neglect. Brain 2003; 126: 1986–97.

N'Diaye K, Sander D, Vuilleumier P. Self-relevance processing in the human amygdala: gaze direction, facial expression, and emotion intensity. Emotion. 2009; (in press).

Ohman A, Mineka S. Fears, phobias, and preparedness: toward an evolved module of fear and fear learning. Psychol Rev 2001; 108: 483–522.

Oosterhof NN, Todorov A. The functional basis of face evaluation. Proc Natl Acad Sci USA 2008; 105: 11087–92.

Pelphrey KA, Viola RJ, McCarthy G. When strangers pass. Psychol Sci 2004; 15: 598–603.

Pessoa L. On the relationship between emotion and cognition. Nat Rev Neurosci 2008; 9: 148–58.

Pessoa L, McKenna M, Gutierrez E, Ungerleider LG. Neural processing of emotional faces requires attention. Proc Natl Acad Sci USA 2002; 99: 11458–63.

Posse S, Fitzgerald D, Gao K, Habel U, Rosenberg D, Moore GJ, et al. Real-time fMRI of temporolimbic regions detects amygdala activation during single-trial self-induced sadness. Neuroimage 2003; 18: 760–8.

Rapcsak SZ, Galper SR, Comer JF, Reminger SL, Nielsen L, Kaszniak AW, et al. Fear recognition deficits after focal brain damage: a cautionary note. Neurology 2000; 54: 575–81.

Roesch EB, Reveret L, Grandjean D, Sander D. FACSGen: generating synthetic, static and dynamic, FACS-based facial expressions of emotion. Alpine Brain Imaging Meeting. Switzerland: Champery; 2006.

Said CP, Baron SG, Todorov A. Nonlinear amygdala response to face trustworthiness: contributions of high and low spatial frequency information. J Cogn Neurosci 2009; 21: 519–28.

Sander D, Grafman J, Zalla T. The human amygdala: an evolved system for relevance detection. Rev Neurosci 2003; 14: 303–16.

Sander D, Grandjean D, Kaiser S, Wehrle T, Scherer KR. Interaction effects of perceived gaze direction and dynamic facial expression: Evidence for appraisal theories of emotion. Eur J Cogn Psychol 2007; 19: 470–80.

Sander D, Grandjean D, Scherer KR. A systems approach to appraisal mechanisms in emotion. Neural Netw 2005; 18: 317–52.

Sato W, Kochiyama T, Yoshikawa S, Naito E, Matsumura M. Enhanced neural activity in response to dynamic facial expressions of emotion: an fMRI study. Cogn Brain Res 2004a; 20: 81–91.

Sato W, Yoshikawa S, Kochiyama T, Matsumura M. The amygdala processes the emotional significance of facial expressions: an fMRI investigation using the interaction between expression and face direction. NeuroImage 2004b; 22: 1006–13.

Scherer KR, Schorr A, Johnstone T. Appraisal processes in emotion: theory, methods, research. New York: Oxford University Press; 2001.

Schmolck H, Squire LR. Impaired perception of facial emotions following bilateral damage to the anterior temporal lobe. Neuropsychology 2001; 15: 30–8.

Schulte-Rüther M, Markowitsch HJ, Fink GR, Piefke M. Mirror neuron and theory of mind mechanisms involved in face-to-face interactions: a functional magnetic resonance imaging approach to empathy. J Cogn Neurosci 2007; 19: 1354–72.

Scott SK, Young AW, Calder AJ, Hellawell DJ, Aggleton JP, Johnson M. Impaired auditory recognition of fear and anger following bilateral amygdala lesions. Nature 1997; 385: 254–7.

Sergerie K, Chochol C, Armony JL. The role of the amygdala in emotional processing: a quantitative meta-analysis of functional neuroimaging studies. Neurosci Biobehav Rev 2008; 32: 811–30.

Shaw P, Lawrence EJ, Radbourne C, Bramham J, Polkey CE, David AS. The impact of early and late damage to the human amygdala on 'theory of mind' reasoning. Brain 2004; 127: 1535–48.

Siebert M, Markowitsch HJ, Bartel P. Amygdala, affect and cognition: evidence from 10 patients with Urbach–Wiethe disease. Brain 2003; 126: 2627–37.

Spezio ML, Adolphs R, Hurley RSE, Piven J. Analysis of face gaze in autism using "Bubbles". Neuropsychologia 2007; 45: 144–151.

Sprengelmeyer R, Young AW, Schroeder U, Grossenbacher PG, Federlein J, Buttner T, et al. Knowing no fear. Proc Biol Sci 1999; 266: 2451–6.

Todorov A, Baron SG, Oosterhof NN. Evaluating face trustworthiness: a model based approach. Soc Cogn Affect Neurosci 2008; 3: 119–27.

Van Lancker D. Personal relevance and the human right hemisphere. Brain Cogn 1991; 17: 64–92.

Vuilleumier P, Armony JL, Driver J, Dolan RJ. Effects of attention and emotion on face processing in the human brain: an event-related fMRI study. Neuron 2001; 30: 829–41.

Whalen PJ, Kagan J, Cook RG, Davis FC, Kim H, Polis S, et al. Human amygdala responsivity to masked fearful eye whites. Science 2004; 306: 2061.

Whalen PJ, Rauch SL, Etcoff NL, McInerney SC, Lee MB, Jenike MA. Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. J Neurosci 1998; 18: 411–8.

Wicker B, Michel F, Henaff M-A, Decety J. Brain regions Involved in the perception of gaze: A PET Study. NeuroImage 1998; 8: 221–7.

Winston JS, Gottfried JA, Kilner JM, Dolan RJ. Integrated neural representations of odor intensity and affective valence in human amygdala. J Neurosci 2005; 25: 8903–7.

Winston JS, O'Doherty J, Kilner JM, Perrett DI, Dolan RJ. Brain systems for assessing facial attractiveness. Neuropsychologia 2007; 45: 195–206.

Wright CI, Martis B, Shin LM, Fischer H, Rauch SL. Enhanced amygdala responses to emotional versus neutral schematic facial expressions. Neuroreport 2002; 13: 785–90.

Wright P, Liu Y. Neutral faces activate the amygdala during identity matching. Neuroimage 2006; 29: 628–36.

Yang TT, Menon V, Eliez S, Blasey C, White CD, Reid AJ, et al. Amygdalar activation associated with positive and negative facial expressions. Neuroreport 2002; 13: 1737–41.

Young AW, Aggleton JP, Hellawell DJ, Johnson M, Broks P, Hanley JR. Face processing impairments after amygdalotomy. Brain 1995; 118 (Pt 1): 15–24.

Young AW, Hellawell DJ, Van de Wal C, Johnson M. Facial expression processing after amygdalotomy. Neuropsychologia 1996; 34: 31–9.