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Startle reflex and emotion modulation impairment after a right amygdala lesion

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Summary

In the present study, startle responses during resting states as well as during the presentation of a set of emotive slides were recorded from a 32-year-old male patient with a rare localized lesion of the right amygdala. The startle reflex is a response modulated by affective states: it has been reliably used in the literature to measure the aversiveness of emotive stimuli. The animal literature has shown that the circuit of this reflex is directly influenced by amygdala projections. The startle responses of the patient were compared with those of eight age-matched normal subjects. The patient's startle amplitudes showed an overall impaired response and an inhibited reflex contralateral to the lesion. In addition, he failed to show the typical startle potentiation induced by an aversive emotive background. The data confirm, in the human, previous results from the literature in other species on amygdala involvement in startle and emotional responses. Furthemore, the observation of the importance of the right amygdala in the modulation of emotion is consistent with the hypothesis of right hemisphere specialization for aversive emotions. The results are discussed in the context of the literature on human amygdala lesions.

Keywords: emotion; startle reflex; amygdala; right hemisphere

Abbreviations: IAPS = International Affective Picture System; RPC: nucleus reticularis pontis caudalis; SAM = self-assessment manikin

Introduction

In animal as well as in human research the most effective index used to measure the aversiveness of an emotional state is the startle reflex, an immediate and progressive flexor movement of the muscles involving the entire body. A variety of intense stimuli with instantaneous rise time (e.g. light flashes, noise bursts, electric shocks) elicit a startle response. From an evolutionary point of view the startle reflex constitutes an integral part of avoidance responses. In rats, movements of the cage are often used as an indicator of the startle response, whereas in humans the first and most reliable component of the startle pattern is the eye-blink response (Anthony, 1985). The amplitude of the usual eye-blink induced by a loud noise is typically augmented or 'potentiated' by unpleasant emotional states.

In humans, research on emotions has shown startle potentiation in a variety of aversive conditions, such as during shock-expectancy as compared with a safe, neutral condition (Grillon and Davis, 1995), during fear imagery in comparison with neutral and pleasant imagery (Vrana, 1995), expecting unpleasant stimuli versus neutral ones (Haerich, 1994), or when viewing emotive slides (Bradley *et al.*, 1993).

In the animal startle response, the main neuronal circuit receives facilitatory projections from the amygdala at the level of the nucleus reticularis pontis caudalis (RPC; Hitchcock and Davis, 1991; Rosen *et al.*, 1991). Lesions of the amygdala suppress the startle reflex itself as well as the typical potentiation of startle induced by an aversive stimulus.

Previous reports on the effects of amygdala lesions in humans have confirmed that the expression and modulation of emotional responses are primarily affected (*see* Aggleton, 1992). Notwithstanding the difficulties of acquiring human subjects with specific lesions at the level of both amygdalae,

in recent years there were several relevant investigations focused on specific memory-affective performances (Markowitsch *et al.*, 1994), face processing (Jacobson, 1986; Young *et al.*, 1995), recognition of facial expression of emotions (Adolphs *et al.*, 1994; Young *et al.*, 1995) and acquisition of conditioned autonomic responses (Bechara *et al.*, 1995) in patients with localized lesions.

The specific role played by the amygdala in general processing of aversive stimuli, as seen in rats (*see* Le Doux, 1995), has not yet been studied in humans. It is hypothesized that in humans startle potentiation is also mediated by the amygdala. However, this has not been tested, due to the rarity of selective lesions of the amygdala.

Human studies using monaural acoustic startle responses indicate that the right hemisphere shows the strongest relationship with affect (Bradley *et al.*, 1991). However, the laterality of the reflex and the importance of the right amygdala in emotion processing has been demonstrated in rats (Coleman-Mesches and McGaugh, 1995) but only hypothesized in humans. Therefore, the right amygdala is expected to be critical for the startle modulation.

Thus, the present case study was aimed at studying the amygdala–startle relationship in humans by investigating to what extent a unilateral lesion of the amygdala exerts effects on the amplitude, laterality and emotional modulation of the startle response.

Material and methods

Patient

Patient S.G. is a 32-year-old right-handed male. He has no family history of neurological disorders. He had an eighth grade education and works as a cook in a restaurant. In February 1992, he was admitted to the General Hospital of Jesolo (Venezia) following a convulsive seizure. Before this hospital admission the patient had never experienced any neurological symptoms. After a preliminary neurological assessment NMR (nuclear magnetic resonance) scans were taken at the Regional Hospital of Treviso.

Neurological examination

The audiometric examination showed a normal (type A) tympanogram. The stapedial reflex was absent in the right ear (with both ipsi- and contralateral stimulation), whereas it was normal in the left ear (90 dB ipsilateral and 95 dB contralateral threshold).

The MRI images (long TR/long TE, T_2-weighted) showed a small area of hyperintensity in the right temporal lobe, including most of the amygdala, somewhat rostrally extended towards temporal lobe structures and underlying white matter (Fig. 1). In particular, the amygdala lesion involved the whole central nucleus, the lateral nucleus and a large (rostral) part of the basal nucleus and accessory basal nucleus. Most of the medial nucleus of the amygdala (in particular the caudal portion), the whole cortical nucleus and the periamygdaloid area were spared.

At the caudal level, the whole entorhinal cortex and, at rostral level, most of piriform cortex were unharmed. The inner capsule and the anterior commissure were intact too.

Also most of the anterior hippocampus was spared. Very small parts of the anterior portion of the cortex of the hippocampal uncus and of the tail of the nucleus caudatum were probably involved in the lesion.

The visible lesion was probably caused by a benign tumour of the amygdala. This diagnosis is supported by the fact that, three years after the seizure episode, the patient was healthy without taking any specific medication.

Neuropsychological testing

The patient was well oriented with respect to time (date, month, year and season) and in space (place, town, region and state). His spontaneous use of language was fluent, and he did not present any semantic or phonemic paraphasia, verbal perseveration or anomia. He copied the Van Sommers' picture correctly (Van Sommers, 1989). As shown in Table 1, most of the standard neuropsychological tests showed no deficit or impairment. Only a few tests detected lower performances.

Short memory tests showed a moderate impairment [digit span = 4; verbal span = 4 (z = –0.8) and visual span = 6 (Corsi span z = 0.88)] (De Renzi and Nichelli, 1975).

On the Rivermead Test (Italian version: Della Sala, 1990) the patient obtained a screening score of seven. This lies below the cut-off score of nine. The specific items which were affected were prospective memory, recognition of unknown faces and recall of new personal names. The patient had a slight impairment in the recognition of unknown faces (total score 33/50, z = –1.3) but not words (total score 38/50, z = –0.74) (Italian version of Warrington, 1984).

He had no deficits of visuo-spatial intelligence (Raven test: 33/36 corresponding to an IQ of 124) or of verbal intelligence (13 total score errors, corresponding to a verbal IQ of 85; a TIB test, the Italian version of NART, Nelson and O'Connel, 1978). His WAIS score was normal in both verbal and performance scales.

The patient had a lower performance on selective attention (attention matrices total score 45/60, z = –1.2; Spinnler and Tognoni, 1987), while he showed normal orienting of spatial attention (mean reaction time was 261 ms; validity effect normal) as assessed by the Posner task (Posner, 1980).

Control group

The patient's startle responses were compared with those of eight male subjects matched for age (mean age 31.25 years; SD 2.19) who were recruited by an advertisement and paid for their participation. Control subjects were selected according to the following criteria: they had to be right-handed, have no history of traumatic head accidents,

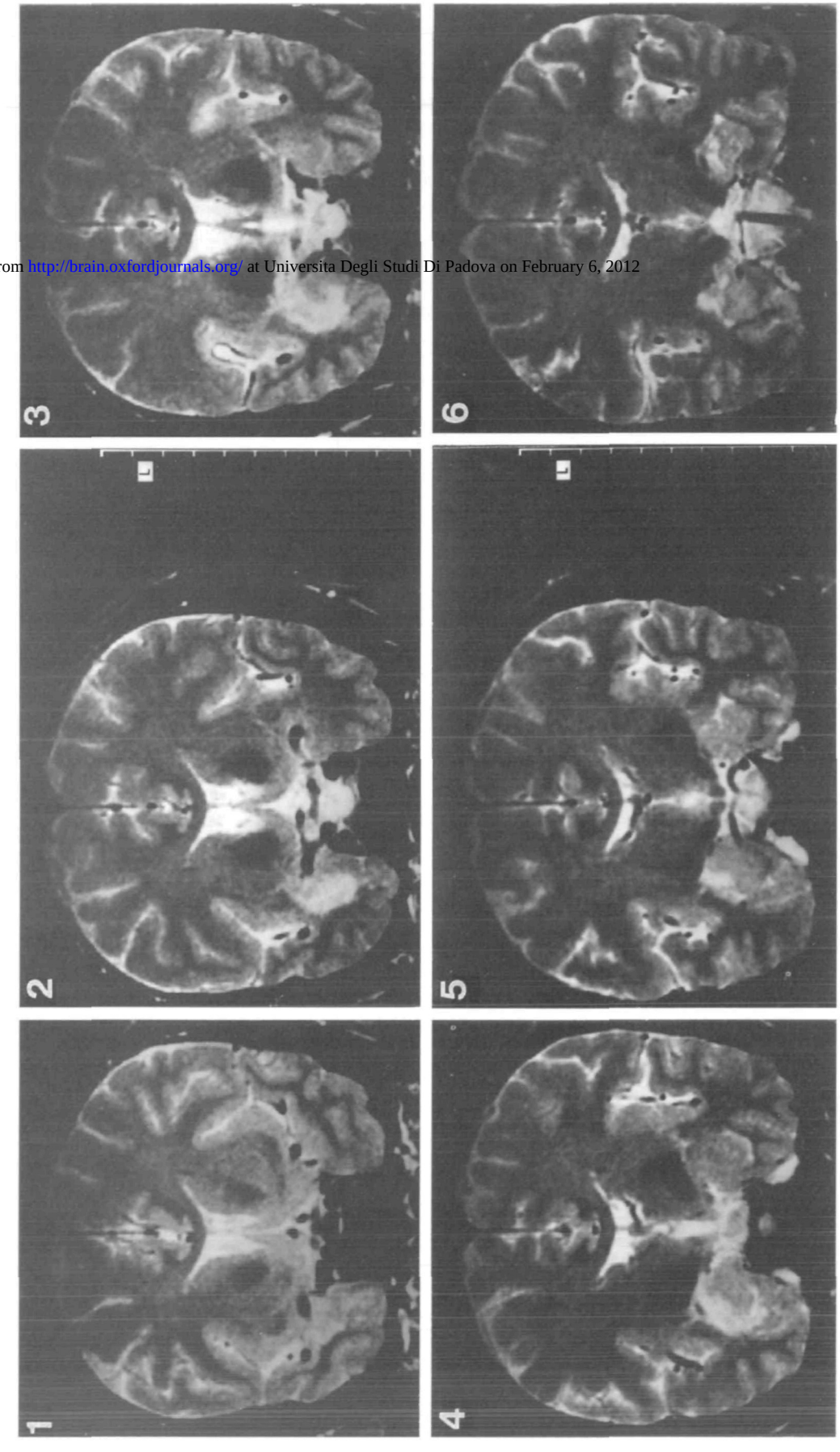

Fig. 1 Coronal MRI sections depicting S.G.'s lesion of the right amygdala. The six sections are numbered in a rostral to caudal direction: each section spans 4 mm thickness. On the lower left side (right hemisphere) of sections (2), (3) and (4), the clear hyperintensity area corresponding to the lesioned amygdala is visible. The lesion spans ~14 mm (three or four sections) along the caudal to rostral direction, and spares the hippocampus (section 6).

Table 1 *Neuropsychological assessment: summary table*

Test	Result
Orientation in time	No deficit
Orientation in space	No deficit
Spontaneous language	No deficit
Comprehension of words	6/6
Comprehension of complex orders	8/8
Token test (De Renzi and Vignolo, 1962)	35/36; $z = 1.07$
Naming	64/64
Short term memory	
Digit span	4
Verbal span	4
Visuo-spatial span	6
Long term memory:	
Buske–Fuld	$z = -0.01$
Incidental memory	$z = 0.09$
Short story	$z = -0.43$
Pair associated	$z = -0.32$
Recognition memory (Warrington)	
Words	$z = -0.74$
Faces	$z = -1.3$
Rivermead test, total score	7
Dyslexia	
Words	10/10
Non-words	10/10
Agrafia	No deficit
Acalculia	No deficit
Apraxia	No deficit
Colour recognition 8/8	
Recognizing unusual views/objects	30/30
WAIS	IQV = 82; IQP = 98
Visuo-spatial capacity	Raven IQ = 124
Verbal capacity (TIB)	Verbal IQ = 85
Selective attention	$z = -1.2$
Orienting of spatial attention	No deficit
Reaction times	In range for age

neurological disorders or encephalitis (such as meningitis and herpes) and no history of infection of the middle or inner ear. The control subjects were submitted to the same startle procedure as the patient.

Normal subjects as well as the patient gave their informed consent to participate in this study of emotions using a non-invasive index, the startle reflex.

Experimental schedule and procedure

Apparatus and stimuli

The acoustic startle stimulus consisted of a 100 dB SPL (sound pressure level) white noise burst of 50 ms duration with an instantaneous rise time (calibrated by a Bruel and Kijer professional phonometer and a dual trace Beckman Industrial Circuitmate 9020 oscilloscope). The noise stimuli were administered to the subjects by closed headphones (Monacor, MC-802). Synchronization of the stimulus administration and the acquisition of the physiological data was obtained by a dedicated computer (Telema) supported by a PC IGS.

In addition to 25 baseline startle stimuli a block of 50 test stimuli was administered during the viewing of 50 slides with emotive content. The slides were selected from the International Affective Picture System (IAPS; Center for the Study of Emotion and Attention, 1995), which had been standardized along two dimensions: arousal and affect potential (unhappy to happy). Slides were split into two groups: aversive slides with potential ratings of <4, and neutral slides with ratings in the range of 4.5–5.5. The slide content within each group was heterogeneous. Among the aversive pictures were frightening stimuli such as a gun or tank aimed at the subject, a large fierce dog, the head of an aggressive snake, and disgusting pictures representing blood, mutilations or surgery, or complex situations, such as war scenes and hospital environments. The specific selection of aversive stimuli was aimed at checking the general role of the amygdala in processing unpleasant emotions, rather than specific emotions such as fear. The neutral slides included household objects, working environments and everyday city scenes. The slides were projected onto a screen at a distance of 1.7 m by means of a Kodak Carousel S-AV 2010 projector. The picture of 86×56 cm was equivalent to a vision angle of 34°. Each slide was projected for 6 s, during which the white noise burst of the startle stimulus was presented (randomly between 2 and 6 s after slide onset). The interslide interval varied randomly between 5 and 21 s.

Physiological recordings

The eye-blink component of the startle response was measured by recording the EMG from the orbicularis oculi muscle beneath the left and right eyelids. Ag/AgCl electrodes with a 7 mm diameter were used. Particular care was used in order to place electrodes in the equivalent position for both eyes (position error <1 mm). Electrodes impedance was kept <10 KΩ (with a 10 MΩ amplifier input impedance, the startle amplitude error due to electrode impedance imbalance is $<0.1\%$). The raw EMG signal was fed into a D150/D160 amplifier system (Digitimer Ltd) with a gain of 60000 and filters set at 53 Hz and 300 Hz. The contour following integrator was unfiltered, so that the signal was only rectified when being fed to an analogue to digital converter (NB-MIO-16, National Instruments) where it was sampled at 1000 Hz. Data acquisition began 100 ms before stimulus onset and lasted for 500 ms. Data acquisition and analysis was performed using a Macintosh II system supported by LabVIEW 3 software. Acquisition, analysis and reduction programs were implemented according to Angrilli (1995).

Procedure

Three blocks of stimuli were administered. For the first block of 25 stimuli the subject was told that the test was aimed at checking his ability to relax under conditions of external noise; he was instructed to ignore the noise and to remain quiet and relaxed (first instruction).

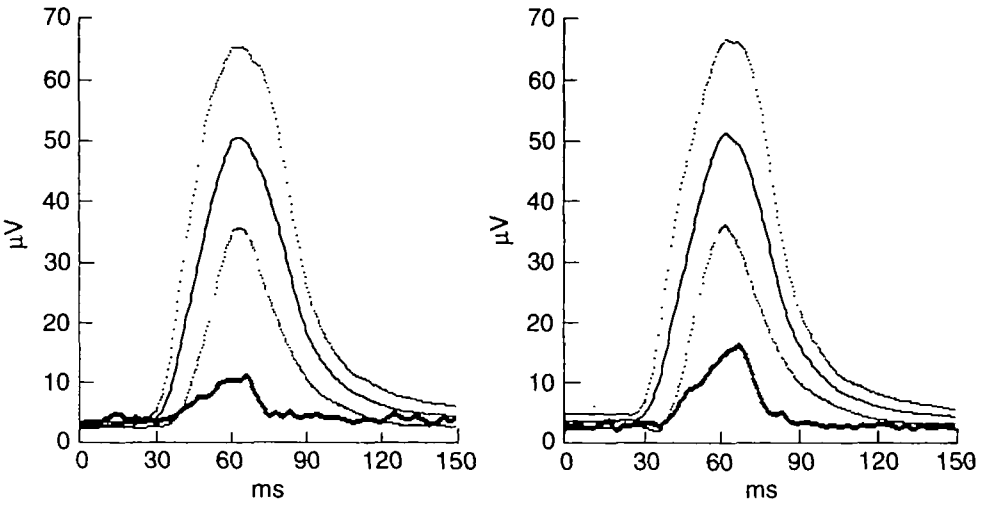

Fig. 2 Averaged startle responses (25 trials) from patient S.G. (thick line, small amplitude response) and from the control group (thin continuous line). Dotted lines represent the standard deviation of the control responses. The response of the left eye is shown on the left and that of the right eye on the right. The time window was restricted to 150 ms of recording; the startle stimulus was delivered at 0 ms.

The second and third blocks of 25 stimuli were each administered during the viewing of 50 emotive slides (25 neutral and 25 aversive) which were presented in random order. The subject was told to pay attention to the slides in order to answer questions about them at the end of the session (second instruction).

After the slide presentation the patient was instructed to write down the content of the slides he could remember. Next he watched a subset of 12 slides taken from the preceeding set and rated the slides on dimensions of affect and arousal according to the SAM procedure (a self assessment manikin procedure, using nine-level scales represented by a stylized human figure ranging from happy to unhappy for affective potential, and from activated to calm for arousal; *see* Hodes *et al.*, 1985).

Data analysis

The unfiltered EMG signal was used to avoid artifacts and to obtain a more clear-cut startle response, especially with respect to the peak amplitude. Three blocks of data were averaged: the first consisted of data from the 25 baseline trials (with eyes open), the second and third consisted of data from the 25 trials with neutral slides and the 25 trials with aversive slides, respectively. Next, the averaged data were displayed graphically, and peak latency and amplitude were calculated. In addition, a 20 ms time-window centred on the peak was used to calculate a mean (smoothed peak) value for each trial. This analysis of relevant windows was preferred to classical peak analysis because of the larger stability of this measure compared with the raw peak data. To reduce noise, data were digitally filtered with a 80 Hz fourth order Butterworth low-pass filter. The mean response amplitude of the EMG signals calculated within the time-window of every trial was subtracted from 100 ms pretrial baseline. Statistical analyses, *t* tests for repeated measures as well as ANOVAs, were all computed using time-windowed startle data. Most *t* tests were computed as one-tailed since the expected direction of the results had been set *a priori* according to published results. Only right/left eye startle differences were checked by two-tailed tests since no *a priori* hypothesis was available for laterality of the reflex.

Results

Startle response in the first block

Figure 2 shows the patient's and control group's averaged responses recorded during the first block of startle stimuli.

Patient's left eye showed a mean startle amplitude of 5.70 μV (SD = 3.94), whereas the control group had a mean startle amplitude of 45.47 μV (SD = 16.67). The patient's startle was significantly lower than that of the controls (>2×SD below the controls' mean). The patient's right eye showed an amplitude of 11.68 μV (SD = 6.21), also in this case significantly lower than the 45.02 μV (SD = 16.67) amplitude of the control group. Statistical comparison of left and right eyes of the patient showed a larger startle on the right eye (paired $t_{24} = 5.29$, $P < 0.00002$, two-tailed). The control group did not show any left–right difference ($t_7 = 0.15$).

Within the block of baseline startle responses, the patient displayed a normal habituation response. Startle was significantly lower in the second half of the block for both eyes: the left eye showed a first half-block startle amplitude of 7.09 μV (SD = 4.51) versus a second half-block amplitude of 4.03 μV (SD = 2.72) ($t_{11} = 2.03$, $P < 0.034$, one-tailed), and the right eye showed a first half-block startle

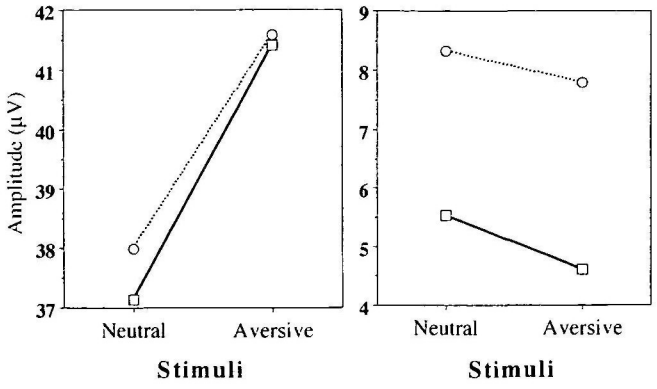

Fig. 3 The effect of aversive background stimulation on mean startle responses recorded from left (squares) and right (circles) eye (orbicularis oculi) in the control group (*left*) and the patient (*right*). Startle stimuli were delivered during the projection of a set of neutral and aversive slides. Values were computed as smoothed means (20 ms time-window means centred on the peak of the response).

of 13.08 μV (SD = 5.42) versus a second half-block amplitude of 9.07 μV (SD = 5.10) (t_{11} = 1.83, $P < 0.047$, one-tailed).

Startle response in the second and third blocks

In the second and third blocks of trials the startle stimulus was presented against a background of potentially emotive stimuli (aversive and neutral slides; *see* Fig. 3). An ANOVA analysis confirmed that the startle response amplitude of the patient for the left (mean ±SD = 5.06±3.15 μV) and right eye (8.06±4.14 μV) showed a significant difference [$F(1,24)$ = 39.04, $P < 0.0001$] (*see* Fig. 3, right-hand side). The peak latencies were 64 ms (left) and 66 ms (right), respectively. The control group (Fig. 3, left-hand side) showed no differences ($F(1,7)$ = 0.031) between left (39.78±17.30 μV, peak latency = 64 ms) and right startle responses (39.28±15.62 μV, peak latency = 63 ms). Even in these blocks, there was a significantly lower startle for both the patient's eyes, in comparison with those of the control group (>2×SD below the control mean).

A potentiation of the startle response by the aversive stimuli could not be observed in the patient for either eye [$F(1,24)$ = 0.693; Fig. 3, right-hand side]. Indeed, a non significant decrease in the startle response was evident in the presence of aversive background stimuli (6.196±3.34 μV) compared with neutral stimuli (6.92±4.48 μV). In contrast, in the normal subjects the averaged startle responses during viewing of the aversive slides (41.50±15.45 μV) showed a clear potentiation [$F(1,7)$ = 8.79, $P < 0.02$] compared with those evoked during the viewing of neutral slides (37.56±16.73 μV).

The data from the patient did not show any significant interaction between startle laterality and emotional condition [$F(1,24)$ = 0.139] and neither did the data from the control group [$F(1,7)$ = 0.237]. Thus, there was no difference in startle potentiation, between left and right eyes, in patient S.G. or in the control group.

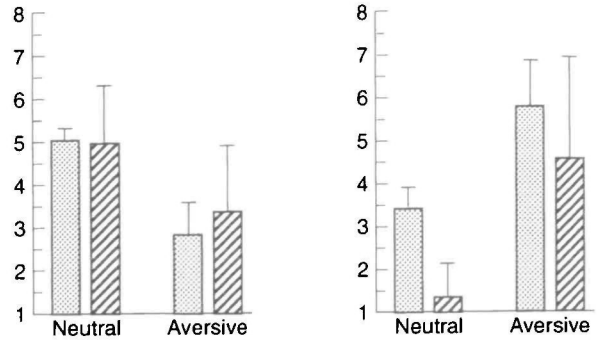

Fig. 4 Patient's self-assessment ratings (SAM) of aversive and neutral slides on the affect (*left*) and arousal (*right*) dimensions, compared with the mean ratings of normal subjects (IAPS). Stippled columns = control group data; black columns = patient data.

Subjective rating data

Figure 4 shows the patient's subjective assessment of affect and arousal (mean SAM ratings) of the patient compared with published mean standardized ratings of the IAPS (drawn from a larger sample of normal subjects).

The patient's subjective ratings of affect were within the normal range of the healthy subjects. In particular, his rating of affect for the aversive slides (Fig. 4, left-hand side) was significantly lower (i.e. subjectively more unpleasant) than for the neutral slides (t_5 = 2.08, $P < 0.05$, one-tailed) and he rated the neutral slides as significantly less arousing than the aversive slides (t_5 = 4.33, $P < 0.001$, one-tailed; Fig. 4, right-hand side), as did the normal subjects.

However, both slide groups (neutral and aversive) elicited lower arousal in the patient compared with the controls. Considering all the subjectively rated slides together, statistical analysis showed an overall decrease of self-reported arousal in the patient compared with the normal subjects (paired t_{11} = 2.87, $P < 0.01$, two-tailed).

Discussion

Neuropsychological assessment

The neuropsychological assessment of the patient was fairly normal. It is known, from the few cases reported, that patients with amygdala lesions tend to have near normal neuropsychological characteristics. The deficits observed are usually moderate and quite selective. These include various memory selective impairments and deficits in facial (emotional) recognition.

The moderate impairments in short-term memory, observed here in our patient, may be associated with right amygdala lesions. Andersen (1978) found a clear impairment (digit span) in seven out nine cases with right amygdalotomy. Even

if less obvious, a span slightly below the normal was also observed in the left amygdalotomy patients (Andersen, 1978).

The poor performance of S.G. on the Rivermead test (prospective memory, recognition of unknown faces, remembering a new personal name), paralleled by the score in the Warrington (faces) sub-test (low, but not reaching significance, $z = -1.3$, $P < 0.1$) , seems to be characteristic of amygdala lesions in both primates (Nakamura *et al.*, 1992) and humans (Jacobson, 1986; Aggleton, 1993; Young *et al.*, 1995).

Arousal was significantly lower in S.G. than in the normal subjects. This corresponds well with the observation that the amygdala projects to the nucleus basalis which provides widespread cholinergic modulation of cortical arousal. For this reason a possible impairment of selective attention could be expected (*see* LeDoux, 1995). In fact, the test on selective attention showed a decreased performance, although this result did not reach significance ($z = -1.2$, $P < 0.11$). This effect was quite selective since orienting of spatial attention, as assessed using the Posner test, was not affected.

Thus, the neuropsychological screening of the patient is in agreement with most of the literature on amygdala.

Startle reflex

The latency of the startle response in our patient was in line with the normal latency ranges reported in the literature (*see* Chokroverty *et al.*, 1992). However, the startle amplitude showed an overall reduction in comparison with matched healthy control subjects.

This result is consistent with the reductions of the startle reflex in rats with localized lesions of the central nucleus of amygdala (Hitchcock and Davis, 1986, 1991). Hitchcock and Davis (1991) interpreted the well-known influence of amygdala damage on both unconditioned and conditioned startle responses as being mediated by the same connections: the caudal ventral amygdalofugal pathway connecting central nucleus of amygdala to the RPC. At this level the amygdala would exert a facilitatory effect on the startle circuit.

From a more general view, Aggleton (1993), in reviewing the literature on amygdala, hypothesized that the inhibition of unconditioned responses associated with amygdala lesions may be related to a wide cortical–subcortical disconnection rather than an association deficit. This interpretation is suggested by the extent of the connections between the amygdala and all other cortical and subcortical areas. Markowitsch *et al.* (1994) found a generalized decrease of glucose metabolism in the brain of two patients affected by a bilateral lesion of amygdala. In particular, the cingulum and the thalamus showed the largest reduction in metabolism (bilaterally) and these two limbic structures are connected to the amygdala by means of the dorsal and ventral amygdalofugal pathways.

The observation of S.G.'s overall inhibited startle, paralleled by the overall reduced arousal, is in agreement with the literature even though S.G. displayed only a unilateral right lesion.

One possible interpretation for the large effect observed with this right lesion could be that the right hemisphere, including amygdala with all its projections to the cortices, has a stronger influence than the left in processes such as aversive emotional activation. Several studies point to the involvement of the right hemisphere in processing of unpleasant stimuli (Dimond *et al.*, 1976; Reuter-Lorenz and Davidson, 1981; Sackeim *et al.*, 1982; Davidson *et al.*, 1990).

The startle stimulus *per se* is moderately aversive, and therefore right amygdala activation could be important for the normal unconditioned emotional response. Thus, it seems that the amygdala could influence overall cortical–subcortical activation, and that the startle inhibition observed in our patient could reflect such an activation deficit.

Affective ratings

Our patient rated the aversive slides as more unpleasant and more arousing than the neutral slides, compared with healthy controls. Similar results, close to those in normal subjects, were observed in other studies aimed at checking arousal and emotional responses in patients with amygdala lesions by means of skin conductance measures (Tranel and Damasio, 1989; Tranel and Hyman, 1990). In these studies, skin conductance was significantly higher in responses to emotive stimuli, compared with those to neutral stimuli. The comparison of the results concerning the self-reported arousal of S.G. with skin conductance responses of other case studies is justified by the high correlation found between skin conductance changes and self-reported arousal in literature using IAPS slides [$r = 0.71$ in Grenwald *et al.* (1989); $r = 0.81$ in Lang *et al.* (1993)].

While the arousal differences between neutral and aversive slides were normal in S.G., the overall reduced arousal already discussed is in contrast the results of two previous studies (Tranel and Damasio, 1989; Tranel and Hyman, 1990) where the skin conductance level was found in range with normal subjects. It is worth noting that only skin conductance changes from a baseline (i.e. within-subject comparison) are highly correlated with self-reported arousal. The absolute skin conductance level is not correlated with arousal or sympathetic nervous system activity (Dawson *et al.*, 1990). This level depends on passive electrical conductivity characteristics of the skin (e.g. skin hydration, thickness of the corneum), which are independent from arousal. Therefore, the comparison between skin conductance levels of patients and normal controls cannot provide information regarding the absolute arousal levels of the subjects tested. For this reason, the arousal assessed in this study by SAM, like the brain metabolism measured by PET (Markowitsch *et al.*, 1994), may allow detection of an overall decrease of activation that could not be detected in the studies using skin conductance measures.

The dissociation between S.G.'s subjective affect ratings,

his discriminating aversive and neutral stimuli, and the suppressed startle potentiation further support Aggleton's (1993) interpretation that lesions of the amygdala are associated with considerable cortical–limbic dissociation. The SAM affect scale probably represents a means of evaluation which is more under the control of cortical structures than of the subcortical system, and reflects the unaffected association capability and performances already observed to be largely intact in the neuropsychological screening of the patient.

Startle laterality

The data also indicate a general reduction of the startle reflex amplitude contralateral to the lesion of the right amygdala. This reduced startle response was present under all conditions (at rest as well as during the emotive test condition). The absence of the right stapedial reflex cannot be responsible for the observed startle response differences, since the stapedial reflex is a protective reflex (*see* Northern *et al.*, 1985) with a long latency and it is normally bilateral (even if the local afferent reflex from one ear is missing, the intact reflex of the other ear projects bilaterally to both stapedii muscles, as reported in this patient). Its absence would thus have augmented the bilateral impact of the startle stimulus.

The anatomical literature in rats points to an ipsilateral pathway from the amygdala to the RPC (Hitchcock and Davis, 1991; Rosen *et al.*, 1991). Cells in the RPC send their axons through the medial longitudinal fasciculus. Since afferent fibres of the startle pathway synapse, at least partially, contralaterally with the RPC cells, and the medial longitudinal fasciculus bifurcates at all levels of the spinal cord, it is not clear whether startle is blocked primarily ipsilaterally or contralaterally to a lesion of the amygdala. Therefore, one tentative interpretation of the contralateral effect on the startle amplitude found in this study might be a predominantly contralateral outflow from subcortical structures which organize the reflex at the level of, or caudal to, the RPC.

However, the startle reflex circuit in humans is still largely unknown (Grillon and Davis, 1995), and therefore any attempt to localize the circuit responsible for this effect is speculative; there may be substantial differences in anatomy between humans and lower mammals.

Startle potentiation

Startle potentiation induced by an aversive emotional background, as seen in the matched normal subjects, was missing in this patient. The control group responses were in accordance with other studies, including larger healthy samples using the same set of visual stimuli (Bradley *et al.*, 1993) and with data comparing startle during neutral and aversive conditions in general (Haerich, 1994; Grillon and Davis, 1995; Vrana, 1995). The lack of startle potentiation cannot be explained by a ceiling effect in this patient, since previous studies have found startle potentiation in subjects with low baseline startles. Indeed, in our control group the subject with the lowest baseline startle responses exhibited a clear (one of the largest) modulation of the startle response with changes in emotional background (17.95 μV mean value for neutral versus 24.49 μV for aversive slides). More importantly, our patient did show internal control of the startle: a significant habituation was observed in both eyes during the startle base recording. Therefore modulation of the startle *per se* was not impaired, and the lacking of startle potentiation cannot be explained by a ceiling effect because that would preclude all startle modulation.

Probably the patient's lack of startle potentiation is related to the overall decreased arousal. This interpretation is supported by other studies, in which the level of arousal is critical in eliciting a heart rate (Sokolov, 1963) or a startle (Cuthbert *et al.*, 1996) defense response to aversive stimuli. If arousal does not reach the threshold above the which the defense response is elicited, the aversive conditions cannot be discriminated from neutral ones at physiological or at the behavioural level. Thus, reaching an appropriate level of arousal might be important for the potentiation of the startle protective reflex and to start the motor and physiological response leading to the active avoidance of potentially dangerous situations.

The total suppression of startle potentiation appears to be completely uncompensated for by the left amygdala in C.G., and this leads us to hypothesize that activity of left and right structures are not equivalent.

The observation of larger regional blood flow in both temporopolar cortices (Reiman *et al.*, 1989), in addition to orbito-frontal and dorsolateral prefrontal cortices (Hugdahl *et al.*, 1995), induced by anticipatory anxiety, suggests that the structures tightly connected to amygdala (Aggleton, 1993) are involved in the processing of aversive states. More important, in both blood flow studies, the bilateral temporal activation observed during the aversive anticipation task, showed a larger activation of the right hemisphere compared with the left. In patient S.G., the amygdala lesion abolished startle potentiation in both eyes, indicating the ability of the right side to affect the overall bilateral aversive induced activation.

Larger right hemisphere activation has been observed in aversive conditions in several studies (Sackeim *et al.*, 1982; Davidson *et al.*, 1990) and startle potentiation has been interpreted as being preferentially mediated by the right hemisphere (Bradley *et al.*, 1991). In addition, in rat studies a specific contribution of right amygdala to the expression of aversively motivated memory was observed (Coleman-Mesches and McGaugh, 1995).

These published results support the observation, in the present case study, of the relevance of right amygdala to startle potentiation, suggesting an important role for the right hemisphere and amygdala in the processing of aversive emotions.

Conclusions

These results suggest that the amygdala primarily, but not exclusively, mediates contralateral startle. The overall reduced

startle amplitude was associated with lower arousal: thus the presence of decreased cortical and subcortical activity may be involved in the impairment of unconditioned responses to aversive stimuli.

In addition, in agreement with most literature on hemispheric specialization of emotions, the lack of a typical startle potentiation induced by aversive stimuli in both eyes points out the relevance of the right amygdala in aversive emotion modulation. The observed dissociation between the intact capability to discriminate aversive and neutral stimuli, assessed by arousal and affect ratings, and the lack of startle potentiation, supports the hypothesis that large cortical-subcortical dissociation can be induced by amygdala lesions (Aggleton, 1993) and are probably mediated by the overall reduced arousal. Such a dissociation appears to be related primarily to emotion processing.

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