

# Electrophysiological Responses in the Human Amygdala Discriminate Emotion Categories of Complex Visual Stimuli

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The human amygdala has been shown to participate in processing emotionally salient stimuli related to threat, danger, and aversion, data that have come primarily from functional imaging and lesion studies. Recording intracranial field potentials from five amygdalae in four patients with chronically implanted depth electrodes, we analyzed responses in the gamma frequency range, a region of the power spectrum thought to reflect especially the contribution of neuronal activity to cognitive processes. Significant changes in the power amplitude of responses were obtained selectively to visual images judged to look aversive but not to those judged to look pleasant or neutral. Several possible confounds were addressed: all four patients had been carefully selected so that the amygdalae from which recordings were obtained were distal to epileptogenic foci, making it likely that we recorded from healthy tissue,

and the observed responses could not be attributed to luminance or color differences between the stimuli. A further analysis of differences in power between the high and low gamma bands revealed an additional structure that discriminated those stimuli related to bodily injury from those related to disgust. Despite the increased power amplitude in the gamma range, there was no stimulus-locked phase coherence. The observed responses in the gamma frequency range may reflect the role of the amygdala in binding perceptual representations of the stimuli with memory, emotional response, and modulation of ongoing cognition, on the basis of the emotional significance of the stimuli.

*Key words: amygdala; human; intracranial recording; local field potential; gamma oscillation; emotion*

A large number of studies in animals have implicated the amygdala in the processing of emotionally salient stimuli (Weiskrantz, 1956; LeDoux, 1996; Rolls, 1999). In humans, functional imaging and lesion studies have suggested a role for the amygdala in processing auditory (Phillips et al., 1998), gustatory (Zald et al., 1998; O'Doherty et al., 2001), and olfactory stimuli (Zald and Pardo, 1997; Royet et al., 2000) that signal or induce unpleasant emotions. In the visual modality, the amygdala is activated by emotionally salient stimuli, especially those related to threat, danger, or aversion (Irwin et al., 1996; Lane et al., 1997; Liberzon et al., 2000), including facial expressions of fear (Breiter et al., 1996; Morris et al., 1996; Whalen et al., 1998, 2001), whose recognition is impaired after bilateral amygdala damage (Adolphs et al., 1994; Calder et al., 1996).

Both functional imaging and lesion studies of the amygdala suffer from imprecise temporal and spatial localization, a limitation that can be overcome with intracranially recorded field potentials. Of special interest is brain electrical activity in the gamma frequency range (20–80 Hz), which has been reported in regions including the visual cortex (Gray et al., 1989; Eckhorn, 1994), somatosensory cortex (Bouyer et al., 1987; Jones and Barth, 1997), motor cortex (Murthy and Fetz, 1992), olfactory bulb (Freeman, 1972; Eeckman and Freeman, 1990), auditory cortex (MacDonald et al., 1996, 1998), hippocampus (Buzsaki,

1986; Traub et al., 1996), and entorhinal cortex (Chrobak and Buzsaki, 1998) and has been linked to several specific aspects of neural function (Sannita, 2000). Gamma oscillations play a role in selective attention, associative learning, ambiguous perception, visuomotor integration, and emotional evaluation (Tiitinen et al., 1993; Roelfsema et al., 1997; Miltner et al., 1999; Müller et al., 1999; Rodriguez et al., 1999). The possible contribution of gamma oscillations to emotional processing has been investigated in studies using scalp EEG (Müller et al., 1999, 2000; Taylor et al., 2000; Keil et al., 2001). Müller et al. (2000) found gamma band responses to aversive and pleasant emotional pictures, and Keil et al. (2001) reported early and late gamma components in response to emotional pictures. Integrating and binding among the disparate features of complex perceptual representations thus appear to be key roles of gamma synchronizations and oscillations, roles that may extend to the association of the visual properties of stimuli with their emotional significance.

To provide further detail to the role of the amygdala in processing emotional visual stimuli, we recorded field potentials from the amygdalae of four patients while we showed them complex images that varied in terms of their emotional meaning. We selected patients in whom we could record from amygdalae that were not associated with seizure foci, and we controlled for possible differences in luminance and color between emotional stimuli. Our analyses of gamma range power spectra separated amplitude and phase information and examined these components of the neuronal response as a function of the emotion category of the stimuli.

## MATERIALS AND METHODS

### *Subjects and electrode implantation*

Four patients with pharmacologically refractory epilepsy (two male and two female) participated in this research. All four patients had complex

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**Table 1. Demographic and neuropsychological information**

Patient	Age	Sex	Language dominance	VIQ	PIQ	Visual-perception	Depression	Language function	Executive function
66	30	Female	Left	125	110	50	None	Normal	Normal
70	39	Male	Right	92	95	50	None	Normal	Normal
74	46	Male	Left	110	120	43	None	Normal	Normal
77	30	Female	Left	97	108	49	None	Normal	Normal

Language dominance was determined by intracarotid sodium amytal injection (Wada test). Verbal and performance IQ (VIQ and PIQ) were evaluated from the Wechsler Adult Intelligence Scale (WAIS)-III or WAIS-R. Visual perception was assessed with the Benton Facial Recognition test (raw scores are given; all were in the normal range). Depression was assessed from interview and with the Beck Depression Inventory. Language function was evaluated from the clinical interview, and executive function was assessed with the Trailmaking test.

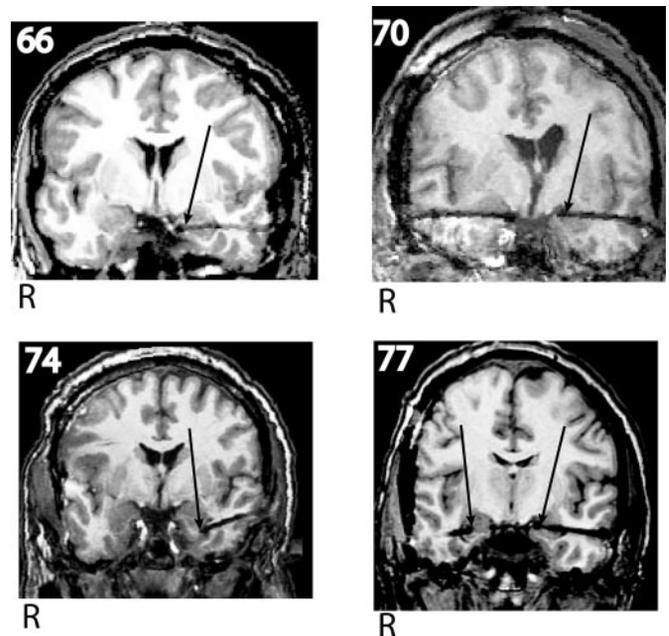
partial seizures whose foci could not be adequately localized by noninvasive methods such as scalp EEG. To aid localization, depth electrodes were surgically implanted in the medial temporal lobe, under a clinical protocol. Electrodes stayed in place chronically for 2–3 weeks, during which time the patients elected to participate in our research studies. Implantation sites were chosen solely on the basis of clinical criteria.

All patients had normal or corrected-to-normal vision and had no history of head trauma or encephalitis. Preoperative structural magnetic resonance imaging (MRI) did not reveal any structural abnormalities in the amygdalas of any of the patients. Neuropsychological assessment of the patients before surgery confirmed normal cognitive functioning (Table 1). Patient 66 had seizures that were eventually localized to the left posterior temporal lobe, distal from the amygdala. Patient 70 had seizures originating from the lateral surface of left or right posterior temporal lobe, or both, that again showed no involvement of the amygdala in the origin of the seizure. Patient 74 had seizures arising from right temporal lobe, and no evidence was found of abnormal electrical activity within the left amygdala from which we recorded. Patient 77 had seizures arising from a cystic mass in the posterior part of the right inferior temporal gyrus with no involvement of the amygdala. Thus it is probable that our recordings were made from normally functioning amygdalas in the four patients, because their seizure foci were located in extra-amygdalar structures, and no structural abnormalities were evident within the amygdalas recorded on MR scans.

We implanted clinical–research hybrid depth electrodes consisting of a tecoflex-polyurethane shaft (1.25 mm outer diameter) with eight high-impedance research contacts (50- $\mu$ m-diameter platinum-iridium wires cut flush with the shaft surface) and two low-impedance contacts used only for clinical monitoring (Howard et al., 1996; Kawasaki et al., 2001). Electrodes were implanted under general anesthesia using a Cosman–Roberts–Wells stereotactic system (Radionics, Burlington, MA) and guided by anatomical information available from preoperative MRI. Localization of the electrodes was subsequently confirmed with MRI that was performed immediately after implantation and that permitted detailed three-dimensional reconstruction of recording sites (Fig. 1) (Damasio and Frank, 1992; Frank et al., 1997). Recordings were bipolar, obtained from research contacts separated by  $\sim$ 200  $\mu$ m. Intercontact impedance ranged from 90 to 200 k $\Omega$  at 1 kHz. A single recording channel thus corresponds to one pair of research contacts providing a bipolar recording. The research protocol was approved by the Human Subjects Committee of the University of Iowa, and written informed consent was obtained from all participants.

#### Visual stimuli and presentation

Emotional visual stimuli were selected from the International Affective Picture Series (IAPS; Lang and Cuthbert, 1993), which provided normative ratings of valence (ratings of the pleasantness as high valence or unpleasantness as low valence) and arousal on a scale from 1 to 10 and which has been widely used for the study of emotion (Kubota et al., 2000; Northoff et al., 2000). For the majority of stimuli, ratings of valence and arousal were not independent but instead showed the pattern depicted in Figure 2; there were relatively few stimuli that had high arousal but neutral valence and few that had low arousal but strong emotional valence (either high or low). Because of these covariances, arousal and valence ratings for the stimuli could not be manipulated entirely independently (Lang et al., 1993; Russell and Carroll, 1999). We chose to divide the stimuli into three broad categories on the basis of their valence ratings: aversive (valence  $<$ 4 and arousal  $>$ 4), pleasant (valence  $>$ 6 and arousal  $>$  3 and  $<$ 6.5) and neutral (valence  $>$ 4 and  $<$ 6 and arousal



**Figure 1.** Anatomical localization of hybrid depth electrodes and recording site for each subject. Structural MR images (1.5 T, 1.5 mm thickness) were obtained immediately after implantation of the electrodes. Note that electrodes appear thicker than they are because of a paramagnetic signal artifact. Arrows indicate the recording site within the amygdala. Following radiological convention, the right side of the brain (R) is shown on the left.

$<$ 3.5). We used 100 images in all, 34 classified as aversive, 32 as pleasant, and 34 as neutral (Fig. 2). Examples included pictures of burn victims and mutilated faces (aversive), pictures of puppies and happy family scenes (pleasant), and pictures of books and furniture (neutral). Two classes of pleasant stimuli, erotic images and pictures of food, were not included in the study because of the variable ratings given by subjects. Further details regarding the aversive stimuli are provided in Table 2.

Between 4 and 14 d after electrode implantation, dependent on the patient's recovery from surgery, subjects were shown 30 randomly selected stimuli from each of the three emotion categories (for a total of 90 stimuli, presented in random order). A second experiment was performed on a separate day with one of the patients (patient 77) but had to be aborted because of fatigue, resulting in a total of only 68 stimuli in this second experiment (21 aversive, 24 pleasant, and 23 neutral).

Whereas the stimuli were selected randomly from the entire set of 100 for three of the patients, patient 66 was shown the same 30 stimuli three times (three repetitions of 10 each of neutral, pleasant, and aversive), thus permitting us to explore the possible effects of repeated presentations of the same stimulus on the responses recorded.

The experiments were postponed if the patient had a seizure within 12 hr before the planned recording session. Stimuli were shown as color digital images on a 14-inch liquid crystal display (LCD) monitor located 1 m in front of the subjects in a darkened, quiet room. Stimulus duration was 1 sec, with a randomly variable interstimulus interval that ranged from 5.0 to 8.0 sec (to minimize any possible anticipatory responses).

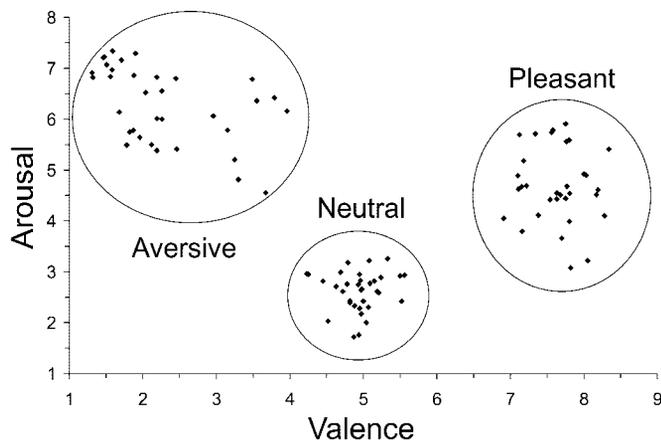


Figure 2. Arousal and valence ratings of stimuli. Mean normative ratings are shown for 100 color images chosen from IAPS and were used to classify the stimuli into three emotion categories (circled regions).

Stimulus presentation was controlled by PsyScope software (Macwhinney et al., 1997; Yee and Vaughan, 1999) on an Apple Macintosh computer. Patients sat comfortably in their beds and were instructed to maintain their gaze on the LCD monitor, to avoid head movement, and to passively watch the stimuli. The wakefulness and gaze of the subject were continuously watched by one of the investigators. All patients appeared alert and attentive for the duration of the experiments analyzed here.

### Local field potential recordings

Continuous bipolar differential recordings were amplified (5000 $\times$ ), bandpass-filtered (1 Hz–6 kHz, Neurodata Amplifier; Grass Telefactor Inc.), and recorded on a multichannel analog tape recorder (StorePlus VL; Rascal Instruments Inc.) together with a trigger signal indicating stimulus onset. Recorded signals were filtered off-line (1–300 Hz, eighth-pole Bessel filter, model 3384; Krohn-Hite Inc.), digitized using a DataWave Experimenter's Workbench (at 20 kHz; DataWave Technologies), and stored for further analysis.

### Signal processing

We recorded local field potentials from a total of 35 bipolar channels (24 in the left amygdala and 11 in the right amygdala) to yield recordings from an initial 2974 trials. To reduce the amount of computation and minimize phase distortion, the raw signal was decimated using a digital finite impulse response filter with a 50-point Hamming window to yield a final sampling rate of 1 kHz. The decimated field potential signals were divided into trial sweeps that encompassed a 1 sec prestimulus period followed by a 1 sec poststimulus period. To reject trials that might be contaminated with noise, we calculated means and SD (from a logarithmic transform of the power amplitudes that normalized their distributions) and rejected any trials whose amplitude exceeded 5 SD above the mean. In addition, every trial was visually inspected to detect and reject trials containing movement artifacts or electrical interference. The overall rejection rate was 10.1% (299 trials were rejected of the initial 2974 trials); there was no association between rejection rate and emotional category of the stimuli ( $\chi^2 = 3.26$ ;  $p = 0.196$ ).

To obtain the time–frequency characteristics of the local field potential, trial signals were digitally convolved with a complex Morlet wavelet (a function that has the shape of a modulated Gaussian in the time domain and a simple Gaussian in the frequency domain and whose Fourier transform has no negative component). This wavelet analysis has been very successful in the analysis of biomedical time series data, because it minimizes the time–frequency spread and reduces the interference between positive and negative frequency components (Sinkkonen et al., 1995; Tallon-Baudry et al., 1995; Carmona et al., 1998; Mallat, 1998; Teolis, 1998; Csibra et al., 2000). The complex Morlet wavelet,  $w(t, f_0)$  is specified as:

$$w(t, f_0) = (\sigma^2\pi)^{-1/4} \exp(-t^2/2\sigma^2) \cdot \exp(2\pi j f_0 t),$$

where  $j$  is the imaginary unit value,  $f_0$  is the center frequency, and  $\sigma$  specifies the width of the wavelet. A feature of the Morlet wavelet is that

it captures an invariant amount of energy regardless of the center frequency. In our analysis, we set the constraint ratio as  $2\pi f_0 \sigma = 7.0$ , and center frequencies ranged from 20 to 60 Hz in 2 Hz intervals. As an example, the wavelet width (2 SD of the envelope in the time domain) at a center frequency of 40 Hz was 55.7 msec.

The power envelope of the signal,  $E(t, f_0)$ , can now be calculated from the squared absolute value of the convolved data:

$$E(t, f_0) = |w(t, f_0) * \text{sig}(t)|^2,$$

where  $\text{sig}(t)$  is the field potential signal,  $w(t, f_0)$  is the wavelet, and  $*$  denotes the convolution operator. To quantify the event-related change in the power envelope that might occur on presentation of a stimulus, we first calculated the median power envelope values from reference periods,  $\text{Ref}(f_0)$ , sampled from 500 msec before the onset of stimuli. We chose to calculate medians rather than means to describe the central tendency, because the distribution of power envelopes was non-normal and positively skewed. The values of event-related band power change (ERBP) at time  $t$  with respect to the reference period is given by the following equation (Gasser et al., 1982; Fernández et al., 1995; Wei et al., 1998):

$$\text{ERBP}(t, f_0) = 10 \cdot \log[E(t, f_0)/\text{Ref}(f_0)] \text{ (dB)}.$$

This equation resulted in ERBPs that were normally distributed, as confirmed with Kolmogorov–Smirnov tests. We calculated ERBP values for all trials.

To evaluate the degree of phase locking from the filtered traces, we calculated phase-locking values (PLVs; Tallon-Baudry et al., 1996; Rosenblum et al., 1998; Tass et al., 1998; Lachaux et al., 1999; Le Van Quyen et al., 2001) defined by the following equation:

$$\text{PLV}(t, f_0) = 1/N \cdot \left| \sum_{\text{trial}} \exp[j \cdot \theta(t, f_0)] \right|,$$

where  $N$  is the number of trials, and  $\theta$  is the instantaneous phase of a trial at a certain time  $t$ . The function  $\theta(t, f_0)$  can be calculated by separating the imaginary and real components of the complex wavelet-transformed data as follows:

$$\theta(t, f_0) = \arctan[\text{imag}[w(t, f_0) * \text{sig}(t)] / \text{real}[w(t, f_0) * \text{sig}(t)]].$$

The PLV thus obtained maps the phase onto a unit circle in the complex plane and represents phase stability over multiple trials. A value of  $\text{PLV} = 1$  represents complete phase locking (the signals from all the different trials are exactly in phase), and a value of  $\text{PLV} = 0$  represents a uniformly distributed phase (the signals from the different trials have a random phase relationship). We calculated PLV only for the range 20–50 Hz to avoid possible contamination and spurious phase locking by 60 Hz noise.

### Statistical analysis

The time–frequency plane was divided into 12 blocks, namely, two frequency bands (lower gamma, center frequencies of 20–34 Hz; and higher gamma, center frequencies of 36–60 Hz) and six time windows (1, prestimulus, –100 msec to stimulus onset; 2, poststimulus, 50–150 msec; 3, 150–250 msec; 4, 250–350 msec; 5, 350–450 msec; and 6, 450–550 msec.). Mean values of the ERBP data in these 12 time–frequency windows were calculated for each trial and used for statistical analysis. Before conducting parametric statistical tests, the normality of the cumulative distributions of these values were assessed with Kolmogorov–Smirnov goodness-of-fit tests. We first chose recording channels that showed a significant ERBP change across these six time epochs by separately calculating, for each of the three emotion categories, one-way repeated measures ANOVAs with the six time windows as a within-subjects factor and the single-trial ERBP values in that channel as the dependent measure (data were collapsed across all frequencies in this analysis). In this analysis, we considered  $p < 0.017$  (0.05/3) as statistically significant to control for multiple comparisons across the three emotion categories. Channels that showed a significant main effect of the time window in at least one emotion category were included in the analyses presented below. Single-trial ERBP values in the selected channels were averaged for each channel and entered into subsequent statistical analyses. Mean ERBP values were assessed by  $6 \times 2 \times 3$  three-way repeated measures ANOVA with factors of time window, frequency range, and stimulus categories. *Post hoc* multiple comparisons used Tukey's honestly significant difference (HSD) test; Huynh–Feldt corrected degrees of freedom were used to correct for inhomogeneity of variance and covari-

**Table 2. Recording channels showing significant responses**

Patient	Session	Channel	Side	Stimulus category					
				Aversive		Pleasant		Neutral	
				<i>p</i>	<i>n</i>	<i>p</i>	<i>n</i>	<i>p</i>	<i>n</i>
66	1	5	Left	<0.001*	29	0.245	25	0.42	24
66	1	7	Left	0.012*	28	0.27	27	0.001*	27
66	1	8	Left	0.016*	29	0.078	26	<0.001*	26
70	1	7	Left	0.012*	29	0.68	28	0.99	28
74	1	1	Left	0.015*	27	0.25	30	0.67	29
74	1	2	Left	0.004*	26	0.78	26	0.34	28
77	1	1	Right	0.016*	25	0.058	17	0.442	28
77	2	1	Right	0.015*	16	0.32	17	0.008*	22
77	2	5	Left	0.010*	17	0.63	17	0.36	20
77	2	6	Left	0.007*	16	0.35	17	0.014*	21
77	2	7	Left	0.007*	16	0.625	17	0.117	21
77	2	8	Left	0.015*	16	0.435	16	<0.001*	18

ERBP responses were initially evaluated with repeated-measures ANOVAs (see Materials and Methods). Channel numbers, side of recording (left or right amygdala), *p* values, and numbers of trials (*n*) are shown for the three emotion categories.

\**p* < 0.017 was considered significant.

ances in the repeated measures (Huynh and Feldt, 1980; Bagciella et al., 2000). Original degrees of freedoms and Huynh–Feldt  $\epsilon$  values are reported.

To assess the statistical significance of the PLV, we used resampling statistics. To correct for slight biases attributable to the unequal number of trials among different emotion categories, data in each channel were first randomly resampled 200 times (without replacement within each resample) using a sample size that was equal to the minimum number of trials originally present in any of the three emotion categories. A histogram of the cumulative resampling distribution was then obtained from the bias-corrected PLV data by resampling 5000 prestimulus time epochs of 500 msec duration. One-tailed *p* values of the poststimulus PLV were then calculated directly from this resampling distribution (Efron, 1979; Manly, 1997). Other statistical analyses were two-tailed, and  $\alpha$  values were set to 0.05 unless otherwise specified. Signal processing and statistical analyses were done using MATLAB (Mathworks Inc.) and SPSS.

#### Additional analyses

**Luminance and color of stimuli.** We analyzed the mean luminance, and the luminance in each of three color channels (red, green, and blue) for our stimuli using the histogram function in Adobe Photoshop.

**Sorting of stimuli.** For an investigation of possible subcategories of stimuli revealed through our field potential analysis, we asked 10 naïve, normal subjects to sort printed photographs of the stimuli into two piles. As described in more detail in Results, we chose 10 stimuli within each emotion category whose ERBP responses showed the most positive difference between the high and low gamma ranges and those 10 stimuli that showed the most negative difference between high and low gamma ERBP (compare with Table 2 for aversive stimuli). Subjects were instructed to sort the stimuli in two piles of any size using whatever strategy they deemed most salient. The significance of the overlaps of the sorted piles with the categories shown by the ERBP analysis was assessed using the binomial distribution.

## RESULTS

### Neuroanatomical location of recording sites

Recording site locations were verified to be in the amygdala with postimplantation MRI scans; however, they were not all within the same region of the amygdala, an issue we comment on further in Discussion. As Figure 1 shows, we recorded from medial (patients 66, 70, and 77), lateral (patients 74 and 77), anterior (patient 70), and posterior (patient 77) regions within the amygdala. Four recording sites were on the left, and one was on the right. Although our sampling of different anatomical sites within the amygdala is too sparse at this time to permit a formal

investigation of the responses seen in different amygdala nuclei, it is hoped that our future accrual of data or combination of data from different laboratories may shed light on the possible differences in responses obtained from different amygdala nuclei.

### Significant ERBP responses

On the basis of our initial statistical analysis (see Materials and Methods), 12 of 35 total channels (34.3%) showed statistically significant ERBP changes over time in at least one emotion category. Ten of these channels were located in the left amygdala, and two were in the right amygdala. All 12 channels showed significant responses to aversive stimuli, five also for neutral stimuli, and none for pleasant stimuli (Table 3). The total number of trials for these 12 channels was 274 for aversive stimuli, 263 for pleasant stimuli, and 292 for neutral stimuli (for a grand total of 829 trials). There was no statistically significant relationship between numbers of rejected trials and stimulus categories ( $\chi^2 = 4.54$ ; *p* = 0.103).

### Analysis of power envelope (ERBP)

In analyzing the ERBP, a previous ANOVA demonstrated that there was no effect of the side of the recording channel (left or right amygdala), and we therefore pooled ERBP data from all the 12 channels shown in Table 3 in subsequent analyses. An examination of the response to each of the three emotion categories as a function of time and frequency (averaged across all 12 channels) showed a strong response to aversive stimuli with a complex pattern in frequency and time (Fig. 3). As can be seen from an examination of Figure 3, the gamma response appeared at ~130 msec after stimulus onset and lasted ~80–180 msec. To assess the statistical significance of these responses, we performed a three-way (time  $\times$  frequency band  $\times$  emotion category) repeated measures ANOVA on the responses averaged within all 12 channels. There was a strong main effect of Time ( $F_{(5,165)} = 15.6$ ; no correction; *p* < 0.001). *Post hoc* Bonferroni-corrected *t* tests indicated that overall responses were significantly different from before stimulus in the poststimulus 150–250 msec (*p* < 0.001), 250–350 msec (*p* < 0.001), 350–450 msec (*p* < 0.001), and 450–550 msec (*p* < 0.001) time windows, with maximal response in the 150–250 msec window. The two-way time  $\times$  frequency

**Table 3. IAPS numbers, mean ERBP values (dB) in the high- and the low-gamma range, and brief description of aversive stimuli**

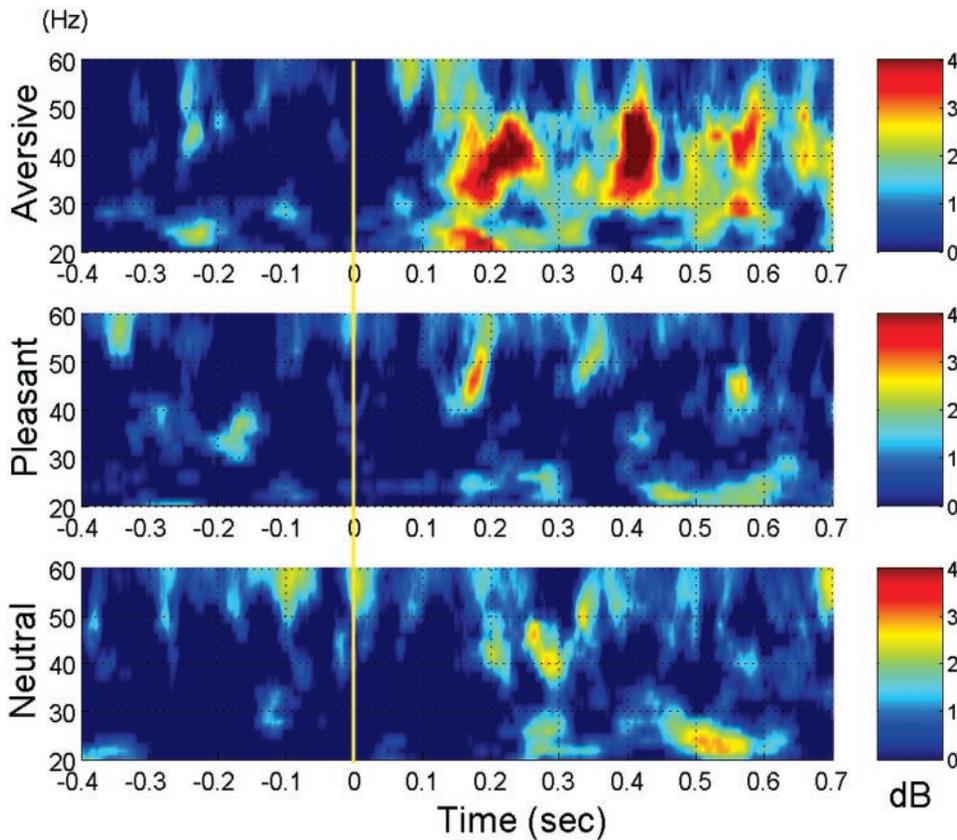
IAPS number	High gamma	Low gamma	<i>n</i>	Description
1201	−3.51	2.99	2	Big spider on shoulder
1275	−0.6	0.77	5	Roaches
2730	−0.26	−0.41	4	Boy and cow
1930	0.23	−2.97	4	Shark
9571	1.8	−0.18	4	Dead cat
9520	2.18	−1.54	8	Kids in pollution
3170	2.26	3.56	13	Cancer tumor
9570	2.44	3.78	3	Rotting dog
3261	2.63	−1.34	4	Mutilation
9921	2.73	7.05	5	Fire
3071	2.98	−2.21	7	Slashed throat
9560	3.15	0.39	8	Duck in oil
9440	3.33	2.68	11	Skulls
3530	3.36	3.78	18	Gun in mouth
6350	3.36	2.45	9	Man with knife
1070	3.71	2.67	9	Snake
3000	3.77	0.11	9	Mutilation
3062	3.87	−0.3	3	Mutilation
9630	3.95	7.54	7	Bomb
3150	4.02	3.86	8	Cut finger
3080	4.11	−1.4	18	Mangled face
1111	4.27	−0.01	4	Snakes
2800	4.33	−0.69	9	Crying boy
9300	4.36	10.23	9	Dirty toilet
6540	4.42	3.52	9	Man with knife
3130	4.58	5.56	14	Body
3053	5.51	0.42	13	Burn victim
1300	5.86	3.6	10	Attacking pit bull
3010	6.13	3.11	9	Mutilation
3120	7.59	−0.81	9	Dead mutilated body
9140	7.77	9.56	8	Dead cow
9410	8.21	7.13	8	Soldier and dead child
6212	8.76	3.04	4	Soldier and child
9042	9.3	0.82	9	Stick through lip

Note the numbers (*n*) of stimuli shown correspond to the final numbers used after trial rejections, accounting for the variance. The stimuli are sorted by their high-gamma values; shaded stimuli show those used in our analyses of subcategories (compare with Results).

interaction was significant ( $F_{(5,165)} = 2.50$ ;  $\epsilon = 0.78$ ;  $p < 0.05$ ). This was attributable to the fact that responses in the high gamma range were greater than in the low gamma range, especially at 150–450 msec after stimulus onset (compare with Fig. 3). The time  $\times$  category interaction was also significant ( $F_{(10,165)} = 5.45$ ; no correction;  $p < 0.001$ ), because the responses to aversive stimuli were much greater than to pleasant or neutral stimuli only in the poststimulus time windows. The two-way frequency  $\times$  category interaction was not significant ( $F_{(2,33)} = 2.18$ ; no correction;  $p = 0.13$ ). The three-way time  $\times$  frequency  $\times$  category interaction was also significant ( $F_{(5,165)} = 5.04$ ;  $\epsilon = 0.78$ ;  $p < 0.001$ ), a consequence of a greater response in the low gamma range for aversive stimuli rather than pleasant or neutral stimuli especially in the window 150–250 msec after stimulus onset and in the high gamma range especially in the windows 150–250 and 350–450 msec after stimulus onset.

These results were confirmed by additional orthogonal one-way ANOVAs with a between-subject factor of emotion category (three levels) performed separately on the ERBP data obtained from each channel (averaged within the high or low gamma range across frequencies) for each of the five poststimulus time win-

dows. For these ANOVAs, we set our  $\alpha$  level at 0.005 to correct for inflation of type I errors attributable to multiple comparisons. These ANOVAs (Table 4) showed that in the low gamma range, responses differed significantly among emotion categories during the time windows of 50–150 and 150–250 msec after stimulus onset ( $F_{(2,35)} = 10.78$ ,  $p < 0.001$ ;  $F_{(2,35)} = 15.75$ ,  $p < 0.001$ , respectively). *Post hoc* Tukey's HSD tests revealed that these amygdala responses to aversive stimuli were significantly different from neutral or pleasant stimuli, but responses to neutral and pleasant stimuli did not differ (50–150 msec window,  $p < 0.05$  and 0.01 for aversive versus pleasant and aversive versus neutral, respectively; 150–250 msec window,  $p < 0.01$  and 0.03). In the high gamma range, ERBP responses differed significantly among emotion categories during time windows of 150–250 and 350–450 msec after stimulus onset ( $F_{(2,35)} = 14.57$ ,  $p < 0.001$ ;  $F_{(2,35)} = 38.89$ ,  $p < 0.001$ , respectively). As for responses in the low gamma range, significant responses in the high gamma range were also driven primarily by aversive stimuli (150–250 msec window,  $p < 0.01$  and 0.01; 350–450 msec window,  $p < 0.01$  and 0.01; Tukey's HSD with the same emotion category contrasts as above) (Figs. 3, 4).



**Figure 3.** Time–frequency plots of ERBP values for each stimulus category. Time is shown on the x-axis (seconds), and frequency (20–60 Hz) is shown on the y-axis. Stimulus onset is indicated by the yellow vertical bar at 0 sec. Color encodes ERBP values in decibels. ERBP values were calculated for individual trials and subsequently averaged across 12 channels in which significant responses were seen relative to a 500 msec prestimulus reference period.

### Effect of repeated presentations

Because stimuli were presented three times to patient 66, we were in a position to examine whether there was any habituation of ERBP values with repeated presentations of the same stimulus. We calculated single-trial ERBP values in time windows of 150–250 and 350–450 msec in the higher gamma range and 50–150 and 150–250 msec in the lower gamma range and averaged over the two time windows within each frequency range for each stimulus (Table 5). These data were then used in one-way repeated measures ANOVAs with a factor of presentation order. There was no statistically significant mean ERBP change attributable to repeated presentation of the same stimuli (aversive: higher gamma,  $F_{(2,50)} = 0.602$ ,  $p = 0.552$ ; lower gamma,  $F_{(2,50)} = 0.326$ ,  $p = 0.723$ ; pleasant: higher gamma,  $F_{(2,38)} = 2.193$ ,  $p = 0.126$ ; lower gamma,  $F_{(2,38)} = 1.118$ ,  $p = 0.337$ ; neutral: higher gamma,  $F_{(2,36)} = 0.752$ ,  $p = 0.479$ ; lower gamma,  $F_{(2,36)} = 0.779$ ,  $p = 0.467$ ; no correction of degrees of freedom was required for these analyses).

### Effect of stimulus valence, arousal, luminance, and color composition

In addition to the above analyses of the effect of the stimulus emotion category, we examined the possible effects of stimulus valence and arousal as continuous measures on the ERBP responses in those time windows in which we had previously found significant responses as described above. Simple linear bivariate correlation analyses were performed for all trials in selected channels. Total ERBP values were calculated in time windows 3 and 5 (150–250 and 350–450 msec after stimulus onset) for responses in the higher gamma range and time windows 2 and 3 (50–150 and 150–250 msec after stimulus onset) for responses in the lower gamma range. There was a weak but significant corre-

lation between these ERBP values in both gamma ranges and valence ratings of the stimuli (Spearman's  $\rho$ :  $-0.30$ ;  $p < 0.001$  for higher gamma;  $r = -0.16$ ;  $p < 0.001$  for lower gamma;  $n = 829$ ) and between these ERBP values and arousal ratings ( $r = 0.25$ ,  $p < 0.001$  for higher gamma;  $r = 0.130$ ,  $p < 0.001$  for lower gamma;  $n = 829$ ). The findings are thus consistent with the ones we reported above; highly arousing and negatively valenced stimuli (i.e., aversive stimuli) drive ERBP responses within the amygdala.

To control for possible effects of the physical properties of the images independently of their emotional meaning, we also performed such correlational analyses for stimulus luminance and color composition (red, green, and blue). There was no statistically significant correlation between ERBP values and global luminance level or individual luminance levels for each of the different color channels in the stimuli in both frequency ranges (global luminance,  $r = -0.011$ ,  $p = 0.740$  for higher gamma;  $r = -0.010$ ,  $p = 0.770$  for lower gamma; red,  $r = 0.028$ ,  $p = 0.425$ ;  $r = 0.017$ ,  $p = 0.620$ ; green,  $r = -0.033$ ,  $p = 0.347$ ;  $r = -0.032$ ,  $p = 0.355$ ; blue,  $r = -0.018$ ,  $p = 0.605$ ;  $r = -0.020$ ,  $p = 0.557$ , respectively;  $n = 829$  for all coefficients). Thus, the effects reported above can be attributed to the emotional meaning of the stimuli and not to their incidental visual properties.

### Analysis of gamma phase (PLV)

We examined the phase stability of responses in the gamma frequency band using PLV values (see Materials and Methods). Bias-corrected PLVs were calculated for each channel and  $p$  values of these PLVs obtained from resampling statistics were averaged across channels and were plotted in color on the time–frequency plane (Fig. 5). We set  $\alpha$  to 0.001 in these statistical analyses to avoid the possible inclusion of very brief occurrences of spurious phase locking. This analysis showed a complete ab-

**Table 4. ERBP responses in five poststimulus time epochs**

Band	Time epoch		Aversive	Pleasant	Neutral
Low gamma	50–150	Mean	2.04	−0.34	−0.69
		SEM	0.6	0.39	0.33
		<i>p</i>		<0.001*	
	150–250	Mean	3.41	0.95	0.28
		SEM	0.51	0.36	0.44
		<i>p</i>		<0.001*	
	250–350	Mean	2.12	0.08	1.53
		SEM	0.28	0.52	0.44
		<i>p</i>		0.107	
	350–450	Mean	1.94	0.45	1.1
		SEM	0.3	0.43	0.28
		<i>p</i>		0.096	
	450–550	Mean	2.14	0.77	2.29
		SEM	0.51	0.43	0.74
		<i>p</i>		0.134	
High gamma	50–150	Mean	0.61	0.11	−0.27
		SEM	0.38	0.29	0.73
		<i>p</i>		0.244	
	150–250	Mean	4.52	0.7	1.16
		SEM	0.73	0.37	0.48
		<i>p</i>		<0.001*	
	250–350	Mean	2.62	0.64	1.9
		SEM	0.51	0.45	0.59
		<i>p</i>		0.035	
	350–450	Mean	4.51	0.03	0.16
		SEM	0.58	0.31	0.27
		<i>p</i>		<0.001*	
	450–550	Mean	2.42	0.43	0.69
		SEM	0.42	0.51	0.37
		<i>p</i>		0.006	

Mean ERBP values and SEM are shown (in decibels). *p* values were from one-way ANOVAs with a between-subject factor of emotional category (df, 2,35). In all time epochs showing significant differences among emotion categories, pairwise Tukey's HSD tests showed that there were significant differences only in contrasts with aversive stimuli. \**p* < 0.005 was considered significant.

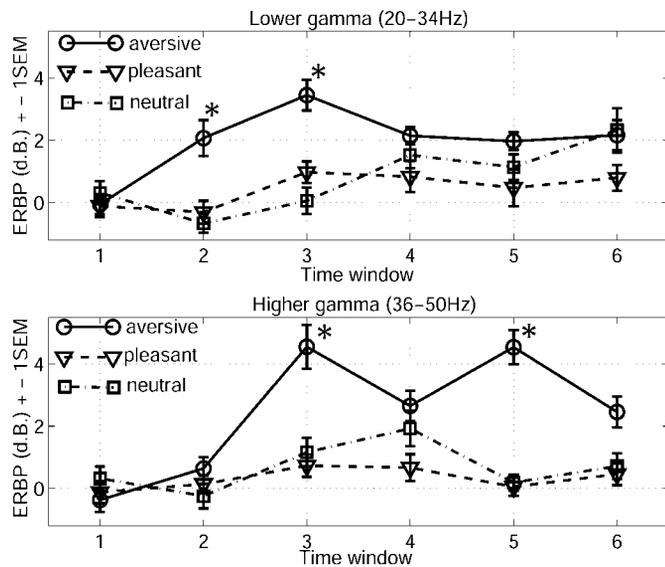
sence of any significant phase-locking state induced by the stimuli. Thus, field potential responses within the amygdala were not phase-locked to the onset of the stimuli (so-called “evoked” responses) but likely resulted from a temporally dispersed evaluation of their emotional meaning to give so-called “induced” responses (Galambos, 1992).

#### Additional emotion categories revealed by analyses of ERBP responses

Given our finding of ERBP responses relatively selective to aversive stimuli, we wondered whether all aversive stimuli contributed equally to this effect or whether additional analyses might reveal emotion subcategories in addition to those that we had predefined. We restricted this exploratory analysis to the aversive stimuli and to mean ERBP values of individual trials within those time windows in which we had previously found significant category responses (150–250 and 350–450 msec in the higher gamma frequency range and 50–150 and 150–250 msec in the lower gamma frequency range). ERBP values were examined for each of the different aversive stimulus images we used (see Table 2 for stimulus identifiers and a brief description of each stimulus). We divided the mean ERBP values of individual pictures within an emotion category into two further groups: the 10 with the highest mean response (HR) and the 10 with the lowest mean response (LR).

For responses in the higher gamma range, we found that images related to human injury occurred frequently in the HR group (8 of 10 stimuli), whereas images related to repulsion and disgust occurred frequently in the LR group (8 of 10 stimuli). Although these findings should be considered preliminary in view of the small numbers of stimuli, this pattern was nonetheless statistically significant when using an exact statistic (Fisher's exact test; *p* = 0.012; *n* = 20). There were no significant differences in luminance levels or in color composition between the HR and LR groups as shown by Mann–Whitney *U* tests (luminance, *U* = 44.0, *p* = 0.650; red, *U* = 47.0, *p* = 0.821; green, *U* = 41.0, *p* = 0.496; blue, *U* = 38.0, *p* = 0.272), nor was there any correlation between ERBP values and luminance level or color composition for the 10 images in either group (Spearman's  $\rho$ : luminance, *r* = −0.023, *p* = 0.925; red, *r* = 0.132, *p* = 0.578; green, *r* = −0.041, *p* = 0.865; blue, *r* = −0.102, *p* = 0.670; *n* = 20). Identical analyses were also performed within the lower gamma range, but we found no significant pattern here.

To investigate the psychological validity of these possible stimulus subcategories reflected in neuronal activity patterns, we asked 10 naïve, normal subjects to sort randomized collections of our stimulus images into binary sets of piles (for details, see Materials and Methods). No instructions were given to the subjects, other than that they should sort the stimuli into the two



**Figure 4.** Time course of averaged ERBP values in six time windows (1, –100 to 0 msec; 2, 50–150 msec; 3, 150–250 msec; 4, 250–350 msec; 5, 350–450 msec; and 6, 450–550 msec) for three emotion categories and two gamma frequency ranges (higher and lower gamma). \*Statistically significant differences between emotion categories that were assessed by ANOVA with  $\alpha = 0.005$ . Error bars represent 1 SEM ( $n = 12$ ).

categories that, in their opinion, most clearly separated stimuli using whatever strategy seemed most salient to them. Subjects indeed sorted the stimuli into piles that bore similarity to the categories revealed by our analysis of the field potential data. Four of the 10 subjects created binary categories that overlapped significantly with those shown from the field potential data ( $p < 0.05$ ; all other  $p < 0.2$ , as calculated from the binomial distribution of their sorting). When subsequently asked what sorting strategy they had used, subjects provided a wide range of responses. No similarity was observed between the field potential categories and subject sortings in the case of pleasant and neutral stimuli (all  $p > 0.25$ , binomial probability).

## DISCUSSION

Our data support three conclusions: (1) gamma power envelope responses discriminate between stimuli in different emotion categories, with significant responses only to aversive stimuli; moreover, this response selectivity could not be attributed to differences in luminance or color between stimuli; (2) responses did not show significant phase locking [i.e., they were induced but not evoked (Galambos, 1992)]; and (3) a preliminary further analysis suggested that, within the aversive category, there were two potential subcategories that might be differentiated by neurons within the amygdala; moreover these categories were psychologically discriminated by naïve human subjects when asked to sort stimuli into piles, suggesting that they correspond to psychologically real categories. Possibly, one type of response was related to images depicting human injury, whereas another type of response was related to disgust. Taken together, the findings support the role of the amygdala in evaluating the emotional meanings of visual stimuli and corroborate its relative specialization for processing stimuli related to threat, danger, and aversion.

The possible contribution of our patients' epilepsy to abnormal electrical activity in the amygdala is an important concern. We addressed this issue in three ways. First, we recorded only during a stable interictal period (the experiments were postponed until

at least 12 hr after the occurrence of a seizure, and we ensured that no postictal symptoms were present). Second, detailed examination of the patients' preimplantation MR scans did not reveal any structural abnormality in the amygdala from which we obtained recordings. Third, we selected our patients to include only those who showed normal cognitive function on several neuropsychological tests and in whom the epileptogenic foci were distal to the amygdala (see Materials and Methods). It is also worth noting that any potentially abnormal electrical activity in extra-amygdala tissue would be unlikely to influence our recordings, because we obtained bipolar differential recordings that measured only local field potentials adjacent to the recording contacts.

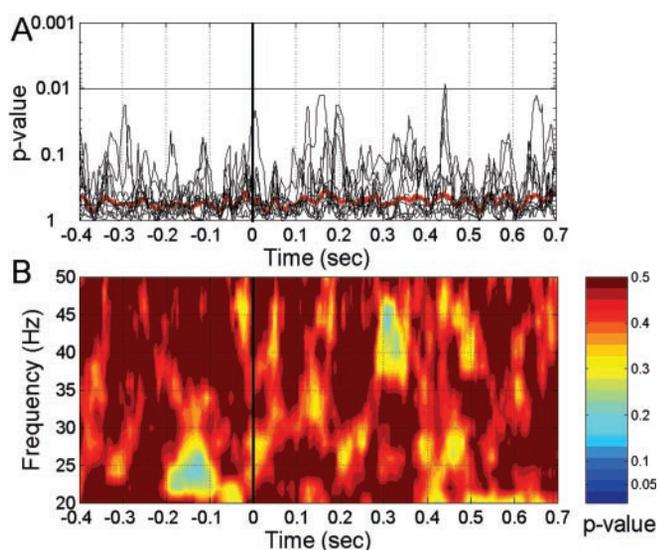
The local field potential (LFP) reflects current flow in the extracellular space resulting from synchronous dendritic and somatic activity within a relatively confined space proximal to the recording site (Bandettini and Ungerleider, 2001; Bressler and Kelso, 2001). We used the LFP to provide the first analysis of gamma band responses recorded in the human amygdala. Our analysis separated phase and amplitude components of the LFP, thus permitting independent examinations of these components. Oscillations recorded in summed neuronal activity can be classified as spontaneous, induced (not time-locked to the stimulus onset), or evoked (time-locked to the stimulus and generally evoked with a short latency ~80–100 msec after stimulus onset; Galambos, 1992). In our study, the PLV within the amygdala showed gamma band responses that appeared to be only of the induced type; that is, there was no phase locking evident, despite increased power density. However, it is important to point out that this negative finding is limited by our use of a large variety of different stimuli, and it remains possible that stimulus-induced phase locking would appear if the same stimulus were presented for a large number of repetitions. For instance, different stimuli may induce responses with slightly different temporal lags, and averaging over such responses would then wash out any stimulus-locked response pattern. We did examine this possibility further in the one patient in whom we were able to obtain triplicate recordings (patient 66); but here also, we found no evidence of stimulus-induced phase locking.

Investigations of phase-locking components (Jokeit and Makeig, 1994; Tallon-Baudry et al., 1996, 1997; Karakas and Basar, 1998) suggest that early (0–150 msec after stimulus onset) phase locking can occur irrespective of the type of stimulus, task demands, or perceptual situation, thus presumably reflecting early sensory processing driven solely by the stimulus features. However, at later times, responses can show an increased power density in the gamma frequency range without any phase locking; such induced gamma oscillations reflect temporally dispersed activity and appear to depend critically on task demands, attention, and the nature of the conscious percept. It is thus likely that such increased gamma power reflects cognitive processing (Karakas et al., 2001). Given that we found no evidence of stimulus-locked responses, the increased gamma power observed in the present study in response to aversive stimuli may represent one mechanism whereby neurons within the amygdala serve to bind perceptual visual representations of the configuration of stimulus features (via projections from temporal visual cortices) with the emotional and social knowledge relating to those stimuli. That is, the responses we observed do not just reflect visual drive from the stimulus but likely reflect the central computations that underlie the association of the visual stimulus with its emotional meaning. Consistent with this interpretation, it is notable that several of our recordings were from the medial aspect of the amygdala and

**Table 5. ERBP data for the analysis of repeated stimulus presentations**

Category	Frequency band	First presentation			Second presentation			Third presentation		
		Mean	SEM	<i>n</i>	Mean	SEM	<i>n</i>	Mean	SEM	<i>n</i>
Aversive	Low gamma	2.56	1.12	30	1.54	0.78	30	2.77	1.28	26
	High gamma	4.85	0.81	30	6.28	0.92	30	4.66	1.19	26
Pleasant	Low gamma	−0.71	1.03	30	0.75	0.98	28	−0.49	1.25	20
	High gamma	1.28	0.85	30	0.56	0.84	28	−1.14	0.85	20
Neutral	Low gamma	−1.14	1.18	30	−1.67	1.01	28	−0.19	1.57	19
	High gamma	0.79	0.71	30	−0.76	0.79	28	−0.36	0.92	19

ERBP values (mean  $\pm$  SEM, in decibels) averaged within the time windows 3 and 5 (150–250 and 350 msec after stimulus onset) for high gamma band and time windows 2 and 3 (50–150 and 150–250 msec after stimulus onset) for low gamma band are shown together with numbers of pictures (*n*) for each emotion category and frequency band. Data were from three channels in patient 66. Note that the numbers of pictures vary somewhat among the three presentations because of trial rejections. There was no significant effect of stimulus presentation order.



**Figure 5.** Phase analysis of responses in the gamma band. *A*, PLVs of 12 individual channels (*thin black lines*) and their mean PLV (*thick red line*) in response to aversive stimuli. The center frequency of the wavelet used in the analysis is 40 Hz. *B*, PLV for aversive stimuli, averaged across 12 channels, plotted in the time–frequency plane. Color represents the *p* value of PLV. *p* values were calculated from the resampling distribution of the 500 msec prestimulus period. No significant phase locking was observed.

are thus unlikely, on anatomical grounds, to reflect simply visual input from temporal association cortices.

Our findings are in line with recent functional imaging studies of the human amygdala, which have shown that amygdala activation reflects the integration of perceptual information with emotional associations for the stimuli (Büchel et al., 1998; LaBar et al., 1998; Phelps et al., 2001), and that such activation occurs even under passive viewing conditions (Breiter et al., 1996), as we used in the present study. There are some important outstanding issues regarding the role of the amygdala in processing emotional information. First, is there hemispheric asymmetry? Most functional imaging studies using emotional faces as stimuli have reported left amygdala activation, and Morris et al. (1998) showed differential activation of the right and left amygdala for subliminally and supraliminally presented stimuli, respectively. Although our small sample of recording sites precludes such analyses, it is interesting to note that we also obtained robust responses from the left amygdala, consistent with the above findings.

A second issue of interest concerns processing by the amygdala

of positively valenced emotional information. Although most functional imaging and lesion studies in humans have focused on the participation of the amygdala in processing aversive stimuli, several recent reports have found responses also to highly arousing, positively valenced stimuli, for instance, sexually explicit movies or pictures (Hamann et al., 1999; Beauregard et al., 2001; Garavan et al., 2001; Aalto et al., 2002; Hamann et al., 2002). One possible explanation for our failure to find amygdala responses to positive stimuli may thus be that our pleasant stimuli did not contain sexually or otherwise sufficiently arousing exemplars.

The category selectivity of the responses we observed deserves further comment. The amygdala appears to contain neurons that respond selectively to a variety of complex visual stimuli (Fried et al., 1997; Kreiman et al., 2000) and appears to be able to do so in large part by virtue of the motivational value with which such stimuli have been associated (Nishijo et al., 1988). Functional imaging studies in humans present a somewhat bewildering array of amygdala responses to visual stimuli: to lexical threat (Isenberg et al., 1999), facial expressions of fear (Breiter et al., 1996; Morris et al., 1996; Whalen et al., 1998, 2001), faces of another race (Hart et al., 2000; Phelps et al., 2000), faces judged to look untrustworthy (Winston et al., 2002), aversive visual stimuli (Irwin et al., 1996; Lane et al., 1997; Liberzon et al., 2000), and in some studies any salient visual stimulus (Phillips et al., 1998). How can these findings be reconciled? We propose the following sketch. First, different nuclei within the amygdala, and possibly even different pools of neurons within a nucleus, may process somewhat different aspects of a stimulus. Second, the presence in our study, in the same field potentials, of responses to subcategories of aversive stimuli suggests that neurons within the amygdala are able to signal information about multiple aspects of the emotional meaning of a stimulus. Third, despite this complexity, all responses we found (as well as those in the majority of other studies) point to a relatively specialized role in processing stimuli of negative valence and high arousal. Given these results, the amygdala might be thought of as a conglomerate of interlocked functional modules that process different aspects of information about the potential threat, danger, aversion, or repulsion signaled by a stimulus (and perhaps extend even to processing highly arousing, positively valenced stimuli). It seems likely that the functions of different amygdala neurons in this respect are probably not rigid but rather are dynamically reorganizable depending on cognitive demand. Future studies that present stimuli under a variety of task demands and that examine responses from single neurons, some of which are currently under way in our laboratory, could investigate these issues in more detail.

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