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Threat and anxiety affect visual contrast perception

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Abstract

Threat cues activate the visual cortex and are detected faster than neutral cues as evidenced by functional brain imaging during viewing of visual threat and neutral stimuli. The functional visual processes underlying these phenomena have not been determined. Pattern visual evoked potentials were elicited in a baseline and a verbal threat condition with two stimulus contrasts in subjects with high and low trait anxiety. Threat reduced the latency of the early P100 wave in the low but not the high anxious group. The reduction was greater with increasing stimulus contrasts. The dependence of the P100 latency on trait anxiety is reminiscent of the Yerkes-Dodson inverted U-shape curve, which relates anxiety to behavioural responses. These results show that threat affects perceptual processes and suggest that data based on the effects of threat in visual search studies should be reappraised to include acceleration of contrast perception.

Key words

contrast perception; healthy volunteers; P100 latency; threat; trait anxiety; visual evoked potentials

Introduction

Visual search studies have repeatedly shown that pictorial stimuli with threatening content are detected more efficiently than those with emotionally neutral or positive content. For instance, angry facial expressions are detected faster and more efficiently than happy faces (Fox, *et al*., 2000; Eastwood, *et al*., 2001), and visual search studies have shown that spiders and snakes in a field are detected more easily than flowers or mushrooms (Ohman, *et al*., 2001). Functional imaging studies have established that viewing of such threatening pictures induces accentuated activations in occipital and inferior temporal cortical regions (Bradley, *et al*., 2003; Sabatinelli, *et al*., 2005; Junghofer, *et al*., 2005, 2006;), and event-related potential (ERP) studies show late (Mini, *et al*., 1996; Palomba, *et al*., 1997; Cuthbert, *et al*., 1998; Ito, *et al*., 1998) and early (Junghofer, *et al*., 2001; Keil, *et al*., 2001) ERP effects generated in the same visual regions (Keil, *et al*., 2002, 2003).

The functional visual processes underlying these observations have not been determined yet. There is some indirect evidence that threat may enhance contrast perception because the visual detection threshold for low-contrast stimuli improves following threat cues (Phelps, *et al*., 2006). Recently, single-cell electrophysiology studies have shown evidence for modulation of neuronal activity in the primary visual cortex by feedback influences related to attention and memory functions (Vidyasagar, 1998; Vidyasagar and Pigarev, 2007). Moreover, visual evoked potentials (VEPs) have been found to be affected by poor alertness (Harter and Salmon, 1972; Kulikowski and Leisman, 1973). However, there is no direct electrophysiological evidence linking threat with such a specific and basic feature detection mechanism as contrast perception.

Sensitivity to contrast is a basic subcomponent of spatial visual perception, which may be at the root of bottom-up feature processing in the visual search tasks and the affective picture viewing paradigms described above. The ability to detect relative changes in luminance, that is, achromatic contrast, is an early perceptual function, which reflects the spatiotemporal properties of the neurons in the retinocortical

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pathways (Hicks, *et al*., 1983; Derrington and Lennie, 1984; Kaplan and Shapley, 1986; Plainis and Murray, 2005) but is also limited by the neuronal substrate of primary visual cortex (Movshon, *et al*., 1978; Bauer, *et al*., 1999). Contrast processing has been evaluated psychophysically (Kulikowski, 1975; Kulikowski, 1976; Pokorny and Smith, 1997; Murray and Plainis, 2003) and physiologically (Murray and Kulikowski, 1983; Murray, *et al*., 1987; Mihaylova, *et al*., 1999), using the P100 wave of VEPs as a measure of the integrity of precortical and early (within 100 ms) visual processing.

The present research questions were first whether acute threat alters P100 latency of pattern VEPs in healthy subjects and second whether and how subjects' trait anxiety modulate this effect because the impact of threat evaluation may differ depending on trait anxiety (Holmes, *et al*., 2007). For this reason, we studied the effects of verbal threat on the early P100 peak of grating onset VEPs, elicited by passive viewing of nonemotional contrast stimuli of two different intensities, in healthy subjects characterised for their trait anxiety.

Materials and methods

Subjects

This study was approved by the Ethics Committee of the University of Crete, and all participants gave their written informed consent. Participants were recruited from our laboratory list of 136 university student volunteers, characterised for their trait anxiety, according to the State-Trait Anxiety Inventory − Trait questionnaire (STAI-T), a widely accepted measure of trait anxiety (Spielberger, 1983). In all, 12 subjects were preselected based on their STAI-T score falling below, and another 12 were preselected based on their STAI-T score falling above the group's median (STAI-T = 35.5). All 24 subjects were contacted by phone and entered the study based on the following additional criteria: no history/presence of major medical or neurological disorders, no history/presence of ophthalmological conditions, no personal or family (up to second degree) of major psychiatric disorders, no history of head trauma, no use of prescribed or recreational drugs, free of ocular or corneal disease, normal binocular and colour vision and optically corrected (if needed) for the viewing distance with spectacles. Participants were tested between 9:00 a.m. and 2:00 p.m. in two sessions.

Clinical examination

All participants underwent a brief physical, ophthalmological and psychiatric assessment using the Mini-International Neuropsychiatric Interview (Sheehan, *et al*., 1998) by an experienced clinician (PB). Subjects were all medication-free, and they all completed urine toxicology screening amphetamine, cannabis, opiates, methamphetamine, benzodiazepines, barbiturates and cocaine.

Tests and apparatus

Recordings took place in a dark, sound-attenuated room. VEPs were recorded using silver-silver chloride electrodes. An active electrode was positioned 10% of the inion-to-nasion distance and referenced to an electrode placed at Fpz with a ground electrode placed on the forehead. Trigger synchronisation was achieved using CED 1401 'micro' (Cambridge Electronic Design, Cambridge, UK). The waveforms were amplified using the CED 1902 (Cambridge Electronic Design). Amplifier bandwidth was set at 0.5–30 Hz (together with a 50 Hz notch filter), and signals were sampled at a rate of 1024 Hz with an analysis time of 0.970 s. Gain was 10.000. Data acquisition and averaging was controlled using the Signal software (vs. 2.15, Cambridge Electronic Design). Each VEP trace was the average of 128 epochs of 1 s duration each. This is twice the minimum number of sweeps per average (64) suggested by the International Society of Clinical Electrophysiology of Vision (ISCEV) (Odom, *et al*., 2004). Computerised artifact rejection was performed before signal averaging, according to standard ISCEV guidelines (Brigell, *et al*., 2003), to discard epochs in which deviations in eye position, blinks, or amplifier blocking occurred.

VEPs were elicited using onset/offset vertically oriented gratings at a rate of 2 Hz with square wave modulation, having a spatial frequency of 4 c/deg. The stimulus was shown on a Sony GDM F-520 CRT monitor by means of a VSG 2/5 stimulus generator card. The stimulus subtended a circular field of seven degrees with a constant mean luminance of 30 cd/m^2 and was surrounded by a neutral background (chromatic coordinates $x = 0.310$, $y = 0.316$) of the same luminance. Subjects viewed the stimulus monocularly from a distance of 150 cm, with their dominant eye open and natural pupils. They were corrected for distance and they were instructed to maintain steady fixation during the recordings, on a centrally placed cross, to minimise eye movements.

For electrical stimulation, a constant current square pulse (1.5 mA, 50 ms) was delivered to the skin overlying the median nerve of the left wrist through disposable silver surface electrodes using a Grass stimulator (SD 9). State anxiety and alertness were self-rated on Visual Analogue Scales (VAS). For each subject, the raw values (mm) for each VAS item were weighted by multiplication with their respective factor loading, and the weighted values for each item were then allocated to 'alertness' and 'anxiety' factors, based on a principal component analysis (Bond and Lader, 1974). Each factor's average weighted value was entered in the statistical analysis.

Procedures

The experiment comprised two sessions (Figure 1), of which the second (experimental) session consisted of part 1 (baseline) and part 2 (threat of shock).

Session 1 Subjects had been previously informed that they would participate in two sessions where their VEPs would be

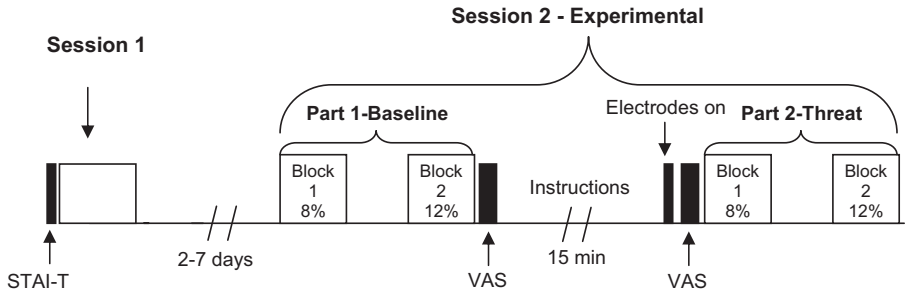

Figure 1 Time course of the experiment. STAI-T, Speilberger's Trait Anxiety Inventory; VAS, Visual Analogue Scales.

elicited using gratings of various contrasts on a computer screen. Scalp electrodes were then applied, and the VEPs were elicited using a wide range of decreasing stimulus contrasts from 100 to 2% (100, 40, 30, 20, 15, 12, 10, 8, 6, 4 and 2%). Based on the resulting group mean P100 latency curves, two different stimulus contrasts from the low range (8 and 12%) were chosen as the optimal experimental stimuli. These low range stimuli were chosen for two reasons a) they are of a sufficient level to generate reliable VEP responses with 128 repeats (see 'experimental session' below) and most importantly b) they obviate a floor effect which, theoretically, could occur with higher contrast stimuli. For instance, it is conceivable that a putative threat-induced latency reduction could be curtailed by the already short P100 latency seen with higher contrast stimuli (floor effect).

Session 2 (experimental session) The experimental session comprised two parts, almost 15 min apart. In the first part (Baseline), VEPs were elicited using 8 and 12% stimulus contrasts in two separate and counterbalanced blocks of 128 stimulus (duration of 1 s) repetitions each. The average of the 128 waveforms per block was taken as the VEP trace of that block. Subsequently, subjects rated their subjective anxiety and alertness using the VAS, and then they were given detailed instructions (see below) for part 2. Subjects were reminded that they did not have to participate any further; however, all subjects agreed to participate and signed new consent forms for part 2 of the session. Subsequently, the skin on the subjects' left wrists was prepared, the instructions were reviewed (see below), and the electrodes were applied and remained fixed throughout the rest of the session. Subjects then rated again their subjective anxiety and alertness in the VAS.

Part 2 was then started with VEPs recorded in two identical blocks, associated with the 8 and 12% stimulus contrast with the same within-subject order as in the baseline blocks of part 1. The blocks in part 2 were associated with shock anticipation (Threat condition) because the subjects were instructed to anticipate a total of 1–3 electric shocks, delivered to their left wrists during the duration of the block (128 s). The subjects did not know the exact number and timing of the electric shock(s). The shocks were described as painful stimuli inducing a short-lived localised unpleasant sensation on the wrist. Only one non-painful (Bitsios, *et al*., 1996) mild shock (1.5 mA, 50 ms) was delivered at the end of the last block associated with the Threat condition. The duration of a block was 128 s with an inter-block interval of 120 s. Therefore, the experimental session lasted approximately 30 min (15 min of recording the two baseline and the two threat blocks in part 2 and approximately 15 min interval between part 1 and part 2).

Data reduction and analysis

VEP waveforms were stored on a PC and were further analysed using an accompanying software package (Signal software, vs. 2.15, Cambridge Electronic Design). For improving the clarity and presentation of VEPs, a lowpass digital filter with a 20 Hz cutoff was applied. Scoring of P100 amplitude requires manual definition of the lowest negative peak prior to P100 peak, and amplitude is scored as the difference between these two points. However, the VEP waveform prior to the P100 peak may be rather unstable due to various attentional and other confounds that affect VEP amplitude but not latency (Fahle and Bach, 2006). This may render amplitude a rather unreliable measure, and for this reason, the measure of primary interest in this study was P100 latency. This is scored automatically off-line by the analysis software as the time taken from stimulus onset to the peak of the VEP response. The latency of the P100 peak was calculated on the average waveform of the 128 epochs per block and entered the statistical analysis as the responses of that block. Separate mixed model analyses of variance (ANOVAs) with group (low and high trait anxiety) as the between-subject factor and stimulus contrast (8 and 12%) and condition (Threat and Baseline), as the within-subject factors were used to analyse the P100 latency data. A dimensional approach was also used whereby the relationship between trait anxiety and VEP latency in the entire group was explored with Pearson correlation coefficients. ANOVAs with group as between- and occasion (before and after the application of electrodes) as the within-subject factor were used to analyse the VAS 'anxiety' and 'alertness' data.

Table 1 Demographic characteristics for the two trait anxiety groups (mean ± SD)

	Low trait	High trait	F (or x^2)	P
Sample size	8	9		
Male: female ratio[a]	5:3	6:3	<1	>0.9
Age (years)	26.9 (2.8)	26.2 (1.9)	<1	>0.6
Education (years)	19.3 (0.9)	18.7 (1.8)	1	>0.3
Smokers/nonsmokers[a]	3:6	4:5	<1	>0.6
Cigarettes/day	9 (1.7)	11 (6.6)	<1	>0.6
Baseline VAS anxiety, mm	24.2 (13.3)	25.1 (18.6)	<1	>0.9
Baseline VAS alertness, mm	55.4 (4.8)	46.2 (14.9)	3.1	>0.09
STAI-T score	29.9 (3.9)	41.4 (3.2)	45.5	<0.001

STAI-T, State Trait Anxiety Inventory – Trait questionnaire; VAS, Visual Analogue Scales.
[a]Chi square comparison.
For the F ratios, df = 1,15.

Results

In all, 17 subjects were included in the analysis out of the 24 who participated in the study. Three participants from the high trait anxiety group were excluded due to poor VEP waveforms, whereas from the low trait anxiety group, two subjects were blinking excessively during recording and two dropped out after the first session. Table 1 shows the profile of the two groups. Although the two groups differed significantly in trait anxiety, there were no group differences in demographic variables or in state (VAS) anxiety and alertness at baseline.

Figure 2 shows the group means of subjective state anxiety and alertness obtained with the VAS. State anxiety increased after the application of electrodes, and this effect was greater for the high trait anxiety group. There was a significant occasion main effect [$F(1,15) = 6.6$; $P < 0.021$] and a significant group by occasion interaction [$F(1,15) = 6.5$; $P < 0.023$], but the group main effect was not significant ($P > 0.3$). Alertness was lower in the high trait anxiety group although this effect fell short of statistical significance [$F(1,15) = 3.2$; $P = 0.09$]. The occasion main effect and the group by occasion interaction were not significant (Fs < 1). Trait anxiety correlated with VAS (state) anxiety ($r = 0.84$, $P < 0.001$).

An overall $2 \times 2 \times 2$ (group × stimulus × condition) ANOVA of the P100 latency data showed a significant stimulus main effect [$F(1,15) = 63.3$; $P < 0.001$] and a significant group by condition interaction [$F(1,15) = 10.2$; $P < 0.006$]. The significant group by condition interaction was followed

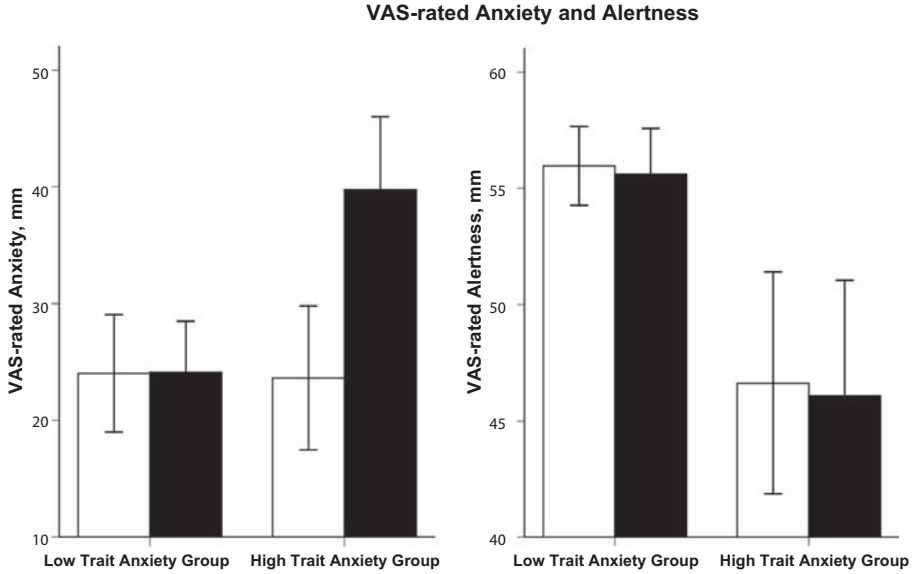

Figure 2 Subjective anxiety and alertness obtained with VAS, before (open columns) and after (closed columns) instructions and connection with shock electrodes. Columns represent group means and bars standard error of the mean.

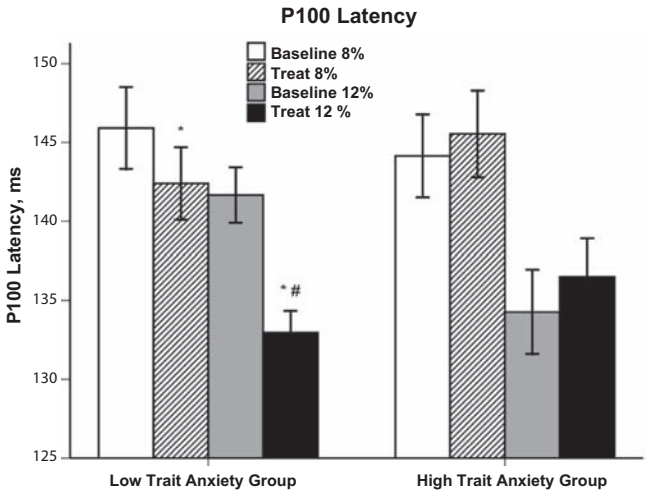

Figure 3 Latency of P100 VEPs obtained at 8 and 12% stimulus contrasts for the Baseline (open columns) and Threat (closed columns) conditions in the low and high trait anxiety groups. Columns represent group means and bars standard error of the mean. *Significantly shorter from its own Baseline; #significantly shorter from 8% Threat.

up with separate 2×2 (stimulus $\times$ condition) ANOVAs for each trait anxiety group. Figure 3 (left) shows for the low trait anxiety group that compared with baseline, P100 latency was smaller in the threat condition for both stimuli but more so for the higher 12% contrast stimulus. There were significant main effects of stimulus [$F(1,7) = 14.5$; $P < 0.007$] and condition [$F(1,7) = 11.1$; $P < 0.01$] and a significant stimulus by condition interaction [$F(1,7) = 5.4$; $P < 0.05$]. Identical ANOVA for the high trait anxiety group showed only a significant stimulus main effect [$F(1,8) = 75.0$; $P < 0.001$; $\eta^2 = 0.9$] (all other Fs < 1). In this group, P100 latency was higher in the threat condition for both stimuli (Figure 3 – right), but this effect was not significant.

Table 2 shows the correlation matrix between trait anxiety and VEP latency in the entire group. Figure 4 shows that the greater the trait anxiety, the smaller the magnitude of latency reduction (P100 latency at Baseline − P100 latency at Threat) for both stimulus contrasts.

Discussion

Several important findings emerged from this study. First, we found that compared with the baseline condition, threat reduced the P100 latency, but surprisingly, this was true only for the low trait anxiety group as evidenced by the group by condition interaction and shown in Figure 3. This finding offers neurophysiological confirmation to the study of Phelps, *et al*. (2006) who found improvement in visual detection threshold for low-contrast stimuli following threat cues. Secondly, we found that in the low trait anxiety group, the more intense the contrast stimulus the greater was the latency reduction by threat, as evidenced by the significant stimulus by condition interaction in this group of subjects. This is consistent with a multiplicative gain control mechanism, which may be mediated by greater allocation of attention to the more intense contrast stimuli. This finding confirms the sensory gain mechanism, also referred to as motivated attention (Lang, *et al*., 1997), which has been hypothesized to amplify sensory processing according to the importance of the stimulus for the organism. Such a light stimulus dependence of the effect of threat has been previously described when the pupillary light reflex was used to examine fear responses to threat of shock (Hourdaki, *et al*., 2005). Our results strengthen the idea of an interaction between threat and attention at the early stages of visual processing (Junghofer, *et al*., 2001; Keil, *et al*., 2001), the latter being susceptible to modulation by stimulus size (De Cesarei and Codispoti, 2006).

Whatever the nature of the P100 latency reduction mechanism, its efficiency must depend on trait anxiety because these results did not extend to the high trait anxiety group (Figure 3). In agreement with this, the dimensional analyses showed that low trait anxiety was associated with greater latency reductions and high trait anxiety was associated with small or no reductions or even increases in P100 latency by threat (Figure 4). That the most anxious subjects suffered a deterioration of their contrast perceptual processes is in line with the study of Wik, *et al*. (1996) who observed anxiety related decreases in regional cerebral blood flow (rCBF) within primary visual cortical regions amongst phobic individuals. Our results point towards the presence of a biologically meaningful adaptive mechanism, by which accelerated contrast processing brought about by an arousing or anxiety provoking cue in natural settings would allow faster visual detection of potential threats

Table 2 Correlation matrix between P100 latency and trait anxiety in 17 subjects

	Baseline 8%	Baseline 12%	T 8%	T 12%	Δ 8%	Δ 12%
STAI-T	0.032	−0.348	0.348	0.497*	−0.65**	−0.75***

T, Threat condition; Δ, Difference Baseline-Threat
*$P < 0.05$.
**$P < 0.01$.
***$P < 0.001$.
Values represent Pearson's correlation coefficients

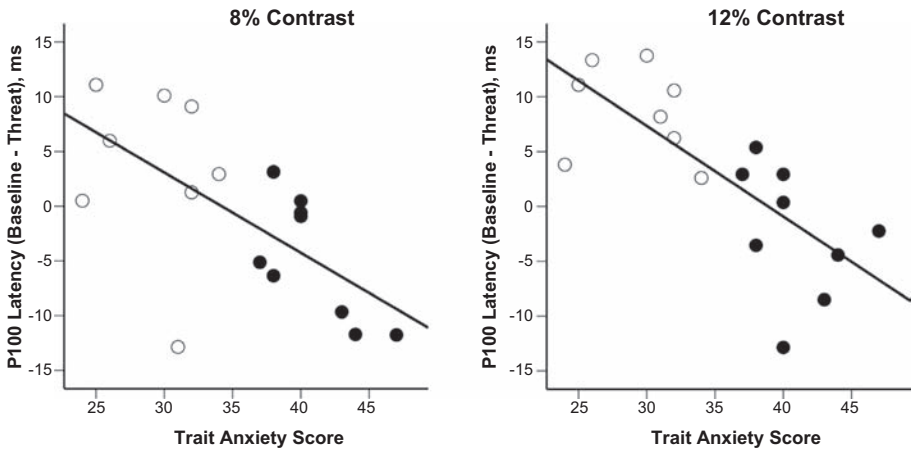

Figure 4 Plots of the difference between Baseline and Threat P100 latency as a function of the Trait Anxiety Score at 8 and 12% contrast levels. High trait anxiety score refers to more anxious subjects, and the negative values of the vertical axis show an increase in latency under Threat condition. Open circles, subjects with low trait anxiety scores; closed circles, subjects with high trait anxiety scores.

and thus a more efficient response. Our results strikingly suggest that this adaptive mechanism does not operate efficiently in high anxious subjects. This deterioration of the P100 latency reduction mechanism with increasing trait anxiety is surprisingly reminiscent of the Yerkes-Dobson inverted U-shape curve, which relates arousal and anxiety to motor/behavioural performance responses; low arousal/anxiety is beneficial whereas high arousal/anxiety is detrimental for such responses (Yerkes and Dodson, 1908). Here, we show for the first time that this is also true of sensory processes; the results clearly show that low anxiety is beneficial whereas high anxiety is detrimental for the P100 latency reduction mechanism. High trait anxiety is associated with enhanced processing of threat information (Weinstein, 1995), greater reactivity to threat (Najström and Jansson, 2007) with difficulty in 'switching off' (Barrett and Armony, 2008). In agreement with this, the high trait anxiety subjects developed greater levels of state (VAS) anxiety in response to the imminent shock, which may have tipped them over the right side of the putative inverted Yerkes-Dodson U-shaped curve with deleterious consequences for visual contrast perception. The amygdala is the critical area from which fear responses are propagated to the rest of the brain (Davis, 1992) including the primary visual cortex (Amaral, *et al*., 1992), and it is activated in threat of shock studies (Phelps, *et al*., 2001). The prefrontal cortex (PFC) provides attentional control of threat-related stimuli (Kim and Hamann, 2007), but its activity as well as control over the amygdala is reduced in highly anxious subjects (Bishop, *et al*., 2004; Hermann, *et al*., 2007, Hare, *et al*., 2008). It is therefore possible that the failure of subjects with high trait anxiety to reduce P100 latency may be the result of excess ratio of amygdala to PFC activation during threat, leading to suboptimal control of fear responses by the PFC and deterioration rather than improvement of contrast perception. However, we cannot confirm this hypothesis based on the present data because the reported VEPs are not specifically localised in deep structures such as the amygdala.

The stimulus dependence of this mechanism in the low trait anxiety subjects is important in several ways; firstly, it suggests that even emotionally neutral environmental visual stimuli acquire motivational relevance during threat merely by virtue of their physical characteristics, for example, intensity. Lang has suggested that protective/defensive responses to potentially adverse stimuli are primed when matched by an aversive ongoing emotional state (Lang, *et al*., 1990). Our results extend Lang's theory to emotionally neutral visual stimuli depending on their contrast level. In a real life-threatening environment, more intense stimuli (e.g., higher contrast stimuli) might convey greater risk and thus deserve priority processing. Moreover, in the constant streamline of visual information processing in a threatening environment, fast detection of the more obviously salient environmental stimuli allows for greater attentional allocation to processing of stimuli with lower salience, for example, lower contrast from the surroundings, such as in predators using camouflage. Therefore, our findings suggest that under conditions of natural threat, high anxious subjects have a biological disadvantage because they may not be as able to detect the source of threat. However, in the absence of any behavioural data in our study, it is not possible to conclude that the observed effects of threat and trait anxiety on contrast perception have any behavioural significance, that is, affect behavioural fear responses (e.g., delayed reaction times). In light of the present findings, it would be interesting for future studies to simultaneously examine contrast VEPs and reaction times during threat in subjects with high and low trait anxiety.

Previous functional imaging studies report increases in rCBF within occipital cortical regions (Bradley, *et al*., 2003; Sabatinelli, *et al*., 2005; Junghofer, *et al*., 2005, 2006), and a study using steady-state flash VEPs during verbal threat

showed increases in localised excitatory processes within the extrastriate occipital cortex (Gray, *et al*., 2003). To our knowledge, this is the first study to determine that acceleration of contrast perception is at least one visual function that underlies such observations. Visual perception is the first stage of stimulus processing along a series of downstream cognitive functions from memory and reasoning to physiological and behavioural responsivity to stimuli and contexts. All these processes may be affected as a result of the influence of anxiety on visual perceptual functions. Contrast perception is a basic visual function, directly related to visual reaction times (Plainis and Murray, 2000) and essential for demanding judgments. The seemingly pervasive influence of threat on contrast perception observed here may underpin the pattern of findings in visual search and visual attention tasks, which entail the detection of biologically threatening stimuli (e.g., snake) in a cluttered background of neutral stimuli such as flowers and mushrooms (Ohman, *et al*., 2001; Tipples, *et al*., 2002; Lipp, *et al*., 2004). Perhaps data based on the effects of threat on visual search studies should be reappraised to include an effect of threat on speed of contrast perception by the cortex.

In this study, VEPs were elicited by pattern onset gratings, which are considered to give a much more accurate measure of contrast processing in area V1 (Campbell and Kulikowski, 1972; Murray and Kulikowski, 1983; Mihaylova, *et al*., 1999). The latency of the P100 pattern VEP peak is a graded response; it is about 100–120 ms for stimuli of 100% contrast, progressively increasing with decreasing contrast (Campbell and Kulikowski, 1972; Murray and Kulikowski, 1983; Odom, *et al*., 2004). In the current study, P100 latency conformed to this principal in both the baseline and threat conditions, as evidenced by the significant stimulus main effect. Figure 3 shows that in the baseline condition, P100 latency reached the values expected, that is, ~130–145 ms, for the relatively low contrast levels (8 and 12%).

The experimental design ensured that anticipation of shock rather than its actual delivery was the relevant independent variable, because although the shock was delivered at the end of the last threat block, the subjects expected it to occur at any time during the duration of either threat block. All recordings in the threat condition, therefore, took place before any shock delivery, thus circumventing problems of between-subject variability in sensitivity to shock and inflation of their electrophysiological responses from shock sensitisation. We did not include 'safe' comparison blocks intermixed with the 'threat' blocks, as in previous verbal threat studies (Grillon, *et al*., 1993; Bitsios, *et al*., 1998, 1999), and we used the baseline blocks as the control instead. Physiological reactivity in intermixed 'safe' blocks can be affected because of the highly anxiogenic context of the experiment (Baas, *et al*., 2002), thus reducing the sensitivity of safe-threat block comparisons and potentially resulting in type II errors.

In summary, we demonstrated that anxious anticipation, caused by threat of shock, accelerates the cortical processing of visual pattern stimuli in low but not high anxious subjects, in a stimulus intensity-dependent manner. These results allow us to trace the effects of anxiety from the behavioural response systems back to the basic perceptual processes and suggest that trait anxiety modifies this response according to an inverted-U relationship. This deleterious effect of anxiety needs to be explored further in patient populations, with the view to establish its anterograde effect on the clinical picture and (more importantly) whether it is affected by treatment and how.

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