



Enhanced neural reactivity and selective attention to threat in anxiety

Sharon Eldar*, Roni Yankelevitch, Dominique Lamy, Yair Bar-Haim

The Adler Center for Research in Child Developmental and Psychopathology, Department of Psychology, Tel Aviv University, Tel Aviv 69978, Israel

ARTICLE INFO

Article history:

Received 16 December 2009
Accepted 16 July 2010
Available online 23 July 2010

Keywords:

Attention bias
Anxiety
Dot-probe
ERP
Threat processing

ABSTRACT

Attentional bias towards threat is implicated in the etiology and maintenance of anxiety disorders. We examined the neural correlates of threat bias in anxious and nonanxious participants to shed light on the neural chronometry of this cognitive bias. In this study, event-related potentials (ERPs) were recorded while anxious ($n = 23$) and nonanxious ($n = 23$) young adults performed a probe-discrimination task measuring attentional bias towards threat (angry) and positive (happy) face stimuli. Results showed an attention bias towards threat among anxious participants, but not among nonanxious participants. No bias to positive faces was found. ERP data revealed enhanced C1 amplitude (~80 ms following threat onset) in anxious relative to nonanxious participants when cue displays contained threat faces. Additionally, P2 amplitude to the faces display was higher in the anxious relative to the nonanxious group regardless of emotion condition (angry/happy/neutral). None of the ERP analyses associated with target processing were significant. In conclusion, our data suggest that a core feature of threat processing in anxiety lies in functional perturbations of a brain circuitry that reacts rapidly and vigorously to threat. It is this over-activation that may set the stage for the attention bias towards threat observed in anxious individuals.

© 2010 Elsevier B.V. All rights reserved.

1. Introduction

The attentional system of anxious individuals is biased in favor of threat-related stimuli (Bar-Haim et al., 2007; Mogg and Bradley, 1998; Williams et al., 1996). This processing bias has been implicated in the etiology and maintenance of anxiety disorders (Beck and Clark, 1997; Eysenck, 1992; Mathews and Mackintosh, 2000). Furthermore, recent studies have used computerized attention training tasks to modify threat-attention patterns in clinically anxious participants and demonstrated significant reduction in anxiety symptoms and even full clinical remission in considerable percentage of patients (Amir et al., 2009; Schmidt et al., 2009; Bar-Haim, 2010; Hakamata, in press).

One of the most widely used tasks to study and modify attention biases in anxiety is the dot-probe task (Bradley et al., 1997; MacLeod et al., 1986). In this task, two stimuli, one threat-related and one neutral, are shown briefly on each trial, and their offset is followed by a small target in the location just occupied by one of them. Participants are required to respond as fast as possible to the target. Based on the attention literature (Navon and Margalit, 1983; Posner et al., 1980), response latencies to the target provide a “snap-shot” of a participant’s attention bias, with faster responses to targets at the

attended relative to the unattended location. Faster reaction times (RTs) to targets appearing at the location of threat relative to neutral stimuli are indicative of an attentional bias towards threat and possibly also difficulty to disengage attention from the threatening stimuli (Fox et al., 2001). The opposite pattern indicates avoidance of threat.

Given the practical and theoretical importance of these behavioral findings for the understanding of the etiology of anxiety disorders and for the potential development of novel treatments (Pine et al., 2009), endeavors to delineate the neural substrates of the threat bias have started to emerge (Armony and Dolan, 2001; Pourtois et al., 2006). More specifically, fMRI studies show that anxious patients relative to nonanxious controls demonstrate enhanced activation in the amygdala and ventro-lateral prefrontal cortex (vlPFC) while performing on the dot-probe task (Monk et al., 2006, 2008). It has been suggested that these anxiety-related activation patterns reflect greater sensitivity and hypervigilance to threats as well as perturbations in frontal emotion regulation in anxious participants. Connectivity analyses further suggest that activations in the amygdala and in the PFC of anxious patients are negatively correlated during dot-probe performance, such that increased PFC activation is associated with reduced response of the amygdala (Monk et al., 2008). And, trait-anxiety was found to be positively correlated with activation in the PFC (Telzer et al., 2008). These data are in accord with models implicating the PFC in the down regulation of amygdala reactivity (LeDoux, 1995, 1996).

* Corresponding author. Tel.: +972 3 6405465; fax: +972 3 6409547.
E-mail addresses: nitzansh@post.tau.ac.il (S. Eldar), yanroni@gmail.com (R. Yankelevitch), domi@post.tau.ac.il (D. Lamy), yair1@post.tau.ac.il (Y. Bar-Haim).

fMRI studies provide important insights on the brain structures associated with threat-related attentional biases in anxious individuals during performance on the dot-probe task. However, performance on this task entails two distinct stages: processing of the emotion cues, and processing of and responding to the targets that follow them. To gain better understanding of the underlying neural correlates of these cognitive processes and their timing, researchers have taken advantage of the superior temporal resolution provided by event-related potential (ERP) techniques. Of particular interest were ERP components known to be modulated by emotion stimuli and spatial attention.

ERP dot-probe studies with healthy adults have shown threat-related modulation in the C1 component time locked to the faces display (Pourtois et al., 2004) and in the P1 component time locked to target onset (Pourtois et al., 2004; Santesso et al., 2008). The C1 component (50–100 ms post-stimulus) was more intense for displays containing threat faces relative to displays containing non-threatening faces (Pourtois et al., 2004). The C1 is the first ERP component triggered by the appearance of a stimulus in the visual field, and is thought to be pre-attentive and independent of spatial attention (Clark et al., 1995; Clark and Hillyard, 1996; Foxe and Simpson, 2002; Fu et al., 2005; Hillyard and Anillo-Vento, 1998; Stolarova et al., 2006). It has been suggested that modulation of the C1 by the emotional valence of the cue display on the dot-probe task could be the consequence of an interaction between the primary visual cortex and subcortical limbic structures responsible for the detection of threats (Pourtois et al., 2004; Stolarova et al., 2006). The P1 component (peaking ~130 ms post-stimulus onset) was found to be enhanced for targets replacing threatening faces compared to happy or neutral faces (Pourtois et al., 2004; Santesso et al., 2008). Augmentation of the P1 component was also found among high trait anxious individuals when performing on different cue-target attention tasks (Li et al., 2005, 2007). These findings were attributed to greater attention allocation to the threatening relative to non-threatening stimuli, and are in line with basic ERP spatial attention research showing P1 modulation by early visuospatial orienting (Clark and Hillyard, 1996; Hillyard and Anillo-Vento, 1998; Mangun, 1995; Mangun and Buck, 1998; Luck et al., 2000).

To our knowledge, only three ERP studies used the dot-probe task to test the chronometry of threat bias in anxious relative to nonanxious control participants (Fox et al., 2008; Mueller et al., 2009; Helfinstein et al., 2008). Fox et al. (2008) used a go/no-go dot-probe task and found that angry face cues elicited an enhanced N2pc component in anxious but not in nonanxious individuals. Mueller et al. (2009) also used a go/no-go variant of the dot-probe task and found that compared to controls, patients with social anxiety disorder showed enhanced P1 amplitudes to angry–neutral versus happy–neutral face pairs. However, unlike the findings in nonselected populations, these authors also found decreased P1 amplitudes to probes replacing emotional (angry and happy) versus neutral faces. Finally, Helfinstein et al. (2008) used the dot-probe task with a prime word before each trial, and showed enhanced P1 and N1 components to the faces display among anxious relative to nonanxious participants. However, all the trials in this particular study contained pairs of angry–neutral faces, thus it was impossible to specifically tie this result to the threatening emotion. These studies used modified versions of the dot-probe task, thus leaving unspecified the neural chronometry associated with performance on the classic dot-probe task, which makes the association of these findings with previous behavioral and imaging fMRI data more difficult.

Here, we examine the chronometry of attention bias to threat and to positive stimuli in anxious relative to nonanxious individuals. ERPs were collected while participants performed a classic dot-probe task. Displays consisting of angry–neutral, happy–neutral, and neutral–neutral face pairs were followed by

a target probe. We expected to replicate the established finding of attentional bias towards threat in anxious participants. That is, faster RTs to targets replacing angry faces than to targets replacing neutral faces in anxious individuals but not in nonanxious controls (Bar-Haim et al., 2007; Mogg and Bradley, 1999). Following Pourtois et al. (2004) and Santesso et al. (2008) who used the dot-probe task with nonselected samples, we also expected that this behavioral pattern will be mirrored by enhanced C1 negativity in anxious relative to nonanxious participants during the faces display when containing threat faces but not when containing happy faces or only neutral faces. This finding would indicate enhanced pre-attentive threat processing in anxious participants. Finally, previous studies were equivocal in their data on P1 amplitude time locked to target onset with Mueller et al. (2009) reporting reduced P1 amplitude for targets appearing at the location of emotional (angry and happy faces) relative to the neutral face in anxious individuals and other studies (Pourtois et al., 2004; Santesso et al., 2008) report enhanced P1 for threatening stimuli in nonselected populations, our analyses remain exploratory in nature. All in all, we expected to complement the extant ERP (Pourtois et al., 2004; Santesso et al., 2008; Li et al., 2005, 2007; Fox et al., 2008; Mueller et al., 2009; Helfinstein et al., 2008) and fMRI findings (Monk et al., 2006, 2008; Telzer et al., 2008) illuminating further the association between anxiety, attention, and brain activation using the classic dot-probe task.

2. Methods

2.1. Participants

Participants were selected from a pool of 190 undergraduate students based on their scores on the trait scale of the State-Trait Anxiety Inventory (STAI-T) (Spielberger et al., 1983). The anxious group consisted of 23 students (17 females, $M_{age} = 22.54$ years, $SD = 1.17$) with the highest trait-anxiety scores. The nonanxious group comprises 23 students (13 females, $M_{age} = 22.52$ years, $SD = 1.23$) with the lowest scores on this scale. The groups differed on trait-anxiety (anxious: $M = 55.52$, $SD = 8.62$; nonanxious: $M = 26.61$, $SD = 1.97$) and state anxiety (anxious: $M = 50.96$, $SD = 7.51$; nonanxious: $M = 27.04$, $SD = 5.17$), $t(44) = 15.67$ and 12.56 , respectively, $ps < 0.0001$. STAI-T mean score of the anxious group exceeded the normal functioning range and was similar to those found among clinically anxious patients (Fisher and Durham, 1999; Yong-Ku et al., 2009).

2.2. The dot-probe task

2.2.1. Stimuli

The fixation display was a gray plus sign (2 cm × 2 cm) presented in the center of the screen. The face stimuli were achromatic photographs (55 mm × 80 mm) of 12 different actors taken from the NimStim stimulus set (Tottenham et al., 2009), each of which displayed three possible expressions of emotion: angry, happy, and neutral (all open mouth). The original NimStim stimuli are chromatic. Adobe Photoshop software was used to convert the stimuli to grayscale and equate their luminance and contrast values. Each faces display was made up of two photographs of the same actor, presented at equal distances at the left and right sides of the screen (center-to-center distance of 16.5 cm) and in the upper visual field. There were three types of face pairs: angry–neutral, happy–neutral, and neutral–neutral (36 different pairs in total). The target display consisted of two dots (5 mm center-to-center). Each dot subtended 2 mm in diameter. The dot pair was oriented either horizontally (..) or vertically (:;) and appeared at the location of the center of either the left or the right photograph of each face pair.

2.2.2. Dot-probe procedure

Each trial in the dot-probe task began with a 500 ms fixation display followed by the faces display for 500 ms, which was immediately replaced by the target display for 200 ms. Following target display the screen went blank for an inter-trial interval (ITI) of 1300 ms after which a new trial began. Participants had to determine the orientation of the dots by pressing one of two pre-specified buttons.

2.2.3. Design

The three types of face pairs (angry–neutral, happy–neutral, and neutral–neutral) made up the three conditions of emotion and were pre-

sented in separate blocks.¹ Order of block presentation was counterbalanced across participants. Within the angry–neutral and happy–neutral blocks, the emotional face (angry or happy) was equally likely to be on the left or on the right side of the screen, the target was equally likely to appear at the location of the emotional or the neutral face, and dots orientation was equally likely to be horizontal or vertical. These variables were fully counterbalanced within each block. In the neutral–neutral block, target location and target orientation were counterbalanced.

2.2.4. Derivation of threat bias scores

For the angry–neutral and happy–neutral conditions, attention bias scores were calculated by subtracting the mean RT for targets appearing at the emotion face location (angry or happy) from the mean RT for targets appearing at the neutral face location. Positive bias values reflect an attention bias towards the emotional face, while negative values reflect avoidance of angry/happy faces (Bradley et al., 1998).

2.3. Electrophysiological recording

2.3.1. EEG recording and artifact scoring

Continuous EEG was recorded from 25 scalp sites (F11, F12, Fp1, Fp2, F7, F3, Fz, F4, F8, T11, T3, C3, Cz, C4, T4, T12, T5, P3, Pz, P4, T6, O1, O2, T9, T10). Electrodes were placed according to the international 10/20 system (Jasper, 1958). All EEG channels were collected with reference to the chin. Vertical and horizontal EOG were recorded from above and below the left eye, and at the right and left outer canthi, respectively. Impedances were kept below 5 k Ω . Sampling rate was 256 Hz, and bio-amplifier band pass filters were set to 0.1–100 Hz. Processing and analysis of the EEG signal was carried out offline. EEG data exceeding $\pm 100 \mu\text{V}$ were automatically removed from further analysis. Eye blinks detected in the EOG signal were regressed out of the EEG using standard procedures described in the literature (see Lins et al., 1993; Miller and Tomarken, 2001). Briefly, propagation factors were calculated to scale the EOG signal for blink correction. First, a three-point algorithm was applied with the vertical EOG channel to quantify the rate of change of the slope with which portions of the data containing blink exemplars were identified. Second, all channels in the EEG record were low-pass filtered at 7 Hz to prepare a data base for computing propagation factors. Third, using the filtered data file of blink epochs, the vertical EOG signal was regressed on each unique EEG site to estimate propagation factors (beta weights) that characterized the linear relation between the vertical EOG site and the blink artifact at each EEG site. Next, the actual blink correction was applied to the entire original unfiltered data. The correction was implemented by using the propagation factors as coefficients in linear transformations to residualize the EEG from the blink-contaminated signal by computing EEG– β EOG for each EEG sample.

Trials containing horizontal eye movements were eliminated from analysis, as well as trials with incorrect responses. Prior to data analyses all ERP waveforms were low-pass filtered at 30 Hz. Mean ERP amplitudes to the faces and the target displays were measured relative to a 100 ms pre-stimulus baseline within preset latency windows. Time windows for analyses were selected based on previous reports in the literature and inspection of the grand mean ERPs. Once selected, the latency windows were the same for all participants and conditions.

2.3.2. ERP components evoked by the faces displays

Our focus was on a priori hypothesis related to the C1 component time locked to faces display onset (60–105 ms). The C1 component is known to have an occipital–parietal distribution (Pourtois et al., 2004; Clark et al., 1995; Andersson et al., 2004). Following inspection of the grand mean ERPs, we decided to quantify the C1 component as the average mean amplitude over the O1 and O2 electrode sites.² For completeness, we additionally analyzed the mean amplitudes over occipital electrode sites (O1 and O2) of other components known to be modulated by attention: P1 (105–145 ms) (see Santesso et al., 2008; Miller and Tomarken, 2001), N1 (148–203 ms) (see Foxe and Simpson, 2002) and P2 (195–250 ms) (see Johannes et al., 1995; Krolak-Salmon et al., 2001).

2.3.3. ERP components evoked by the target displays

Attention allocation is known to modulate the P1 component over occipital electrode sites (e.g., Mangun, 1995). Thus, the P1 component (85–130 ms) time locked to target onset was analyzed over occipital electrodes (O1, O2).

2.4. General procedure

Participants were seated in a comfortable chair 100 cm from the computer screen. Because the C1 component shows retinotopic polarity inversion in scalp

recording, and its amplitude and polarity is sensitive to the position of the stimulus in the visual field (i.e., peripheral upper visual field positions elicit negative polarity whereas the reverse polarity is recorded for peripheral lower visual field positions) (Clark et al., 1995; Clark and Hillyard, 1996; Kelly et al., 2008; Di-Russo et al., 2003; Martinez et al., 1999), the display screen was individually aligned for each participant verifying that the face stimuli are displayed in the upper visual field. Thus, by setting the horizontal meridian of the screen 3° above the eye-line of each participant we ensured that the task stimuli appeared in a fixed position within the upper visual field. This specific alignment was pilot tested in other studies in our laboratory to ascertain that it reliably produces a negative deflection in the ERP around 70 ms after stimuli onset – corresponding to a genuine retinotopic C1 component.

Following this preparation, participants received 32 practice trials, followed by 6 experimental blocks, two for each emotion condition (angry–neutral, happy–neutral, neutral–neutral), 96 trials per block, with a total of 576 trials. Presentation of the emotion condition blocks was counterbalanced across participants within each anxiety group. Short breaks were allowed at the end of each block. EEG was recorded throughout the experiment.

2.5. Data analyses

2.5.1. Behavioral reaction times

Trials with reaction times that exceeded two standard deviations above or below each participant's mean reaction time (calculated separately for each experimental condition) were rejected. Trials with incorrect responses and responses faster than 200 ms were also discarded. All in all, 5% of all trials were excluded from the analyses.

To examine group differences in attention bias scores for each emotion condition, a 2×2 ANOVA was performed with Emotion (angry–neutral, happy–neutral) as a within-subject factor and Anxiety (anxious, nonanxious) as a between-subjects factor. One-sample *t*-tests against zero were used to determine the significance of within-group biases.

We also examined whether the valence of the emotional faces in each block affected accuracy and RT as a function of anxiety. Thus, two separate 3×2 ANOVAs were conducted on accuracy and RTs with Emotion (angry–neutral, happy–neutral, neutral–neutral) as a within-subject factor and Anxiety (anxious, nonanxious) as a between-subjects factor.

2.5.2. ERP analysis

2.5.2.1. Analyses of ERPs evoked by the faces displays. For each ERP component (C1, P1, N1, P2) the mean amplitude over occipital electrodes (O1 and O2) was subjected to a 3×2 ANOVA with Emotion (angry–neutral, happy–neutral, neutral–neutral) as a within-subject factor and Anxiety (anxious, nonanxious) as a between-subjects factor.

2.5.2.2. Analyses of the ERP evoked by the target displays. An ANOVA was performed on mean amplitude of occipital P1 (average of O1 and O2) with Emotion (angry–neutral, happy–neutral), Target Location (emotion face, neutral face), and Emotion Face Location (left, right) as within-subject factors, and Anxiety (anxious, nonanxious) as a between-subjects factor.

3. Results

3.1. Reaction time data

Mean RTs, bias scores, and standard deviations by emotion, target location, and anxiety group are presented in Table 1. The 2×2 ANOVA applied to the bias scores revealed a main effect of Emotion, $F(1,44) = 6.05$, $p < 0.05$, *Cohen's d* = 0.74, with a larger attention bias towards the emotional face in the angry–neutral condition ($M = 7.52$, $SD = 13.36$) than in the happy–neutral condition ($M = -0.03$; $SD = 9.67$). Follow-up comparisons showed that the bias was significant in the angry–neutral condition, $F(1,44) = 7.23$, $p < 0.05$, *Cohen's d* = 0.81, but not in the happy–neutral condition, $F(1,44) = 0.00$, $p = 0.98$, *Cohen's d* = 0.00. As can be seen in Fig. 1, although the Emotion condition effect did not interact with Anxiety group, one-sample *t*-tests show that the attention bias towards angry faces was significantly greater than zero in the anxious group, $t(22) = 2.87$, $p < 0.01$, *Cohen's d* = 1.22, but not in the nonanxious group, $t(22) = 1.03$, $p = 0.31$, *Cohen's d* = 0.44. In addition, no significant bias towards happy faces was observed for either group, $t(22) = 0.87$ and -0.75 , $ps > 0.30$, *Cohen's d* = 0.37 and 0.32, for the anxious and nonanxious groups, respectively. To summarize, anxious participants showed an attention bias towards threat, whereas nonanxious participants did not. Neither group exhibited an attention bias to happy faces.

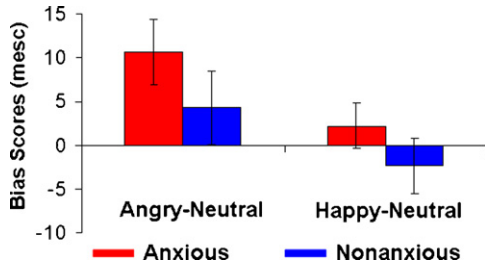
¹ Block design was used rather than randomly interspersing the cue stimuli, because pilot data consistently showed that the “emotional tone” of the experiment had a robust influence on anxiety-related differences in ERP patterns as well as on response times.

² The C1 component has been typically described as having a midline distribution. However, due to technical constraints our montage does not include the Oz electrode. Therefore we averaged the activity over the O1 and O2 electrodes which provide a good representation of ERPs in the occipital region of the scalp.

Table 1

Mean reaction times, bias scores, and standard deviations in milliseconds for each anxiety group by each emotion condition.

	Angry-neutral			Happy-neutral			Neutral-neutral
	Target at angry	Target at neutral	Bias score	Target at happy	Target at neutral	Bias score	
Anxious	572 (74)	583 (82)	11 (18)	576 (75)	578 (78)	2 (12)	570 (73)
Nonanxious	608 (96)	612 (92)	4 (20)	607 (80)	605 (78)	-2 (15)	607 (84)

**Fig. 1.** Bias scores and standard-error bars for anxious (red) and nonanxious (blue) groups for angry-neutral and happy-neutral blocks of trials. (For interpretation of the reference to color in this figure legend, the reader is referred to the web version of the article.)

The 3×2 ANOVA applied to the accuracy scores revealed that these ranged from 88% to 98% across emotion conditions with no significant differences between anxiety groups, $p=0.18$. A main effect of Emotion emerged, $F(2,88)=15.53$, $p<0.001$, *Cohen's d*=0.84. Accuracy was highest for the neutral-neutral condition ($M=97.76$, $SD=2.50$), followed by the happy-neutral condition ($M=96.13$, $SD=5.56$), and the angry-neutral condition ($M=93.95$, $SD=3.59$). Follow-up contrasts revealed that all between-condition differences were significant at $p<0.05$. The 3×2 ANOVA applied to the mean RTs did not reveal significant effects, all $ps>0.15$.

3.2. Electrophysiological data

3.2.1. Analyses of ERPs evoked by the faces displays

Fig. 2 presents ERP waveforms for each emotion condition by anxiety group. Our primary analysis revealed an Emotion by Anxiety interaction effect for C1 amplitude, $F(2,43)=3.15$, $p=0.0529$, *Cohen's d*=0.52. Follow-up between-groups contrasts for each Emotion condition revealed that anxious participants had a more pronounced (more negative) C1 amplitude ($M=-0.82$, $SD=1.22$) than their nonanxious counterparts ($M=-0.16$, $SD=0.89$) in response to the angry-neutral face pairs, $t(44)=2.10$, $p<0.05$, *Cohen's d*=0.63. The anxious and nonanxious groups did not differ in C1 amplitude in response to the happy-neutral face pairs (anxious: $M=-0.68$, $SD=1.30$; nonanxious: $M=-0.36$, $SD=1.20$), $t(44)=0.86$, $p=0.39$, *Cohen's d*=0.26, and for the neutral-neutral

condition (anxious: $M=-0.65$, $SD=1.18$; nonanxious: $M=-0.69$, $SD=1.18$), $t(44)=1.02$, $p=0.91$, *Cohen's d*=0.31. Thus, C1 amplitude in the anxious participants was more pronounced than C1 amplitude in the nonanxious participants only when processing threatening face stimuli.

Analyses of additional ERP components revealed a significantly higher P2 amplitude in the anxious group ($M=2.28$, $SD=2.01$) relative to the nonanxious group ($M=1.00$, $SD=2.01$), $F(1,44)=4.69$, $p<0.05$, *Cohen's d*=1.41, regardless of the emotion condition. No other main or interaction effects emerged from this analysis. Finally, no significant effects were found for the P1 and N1 components.

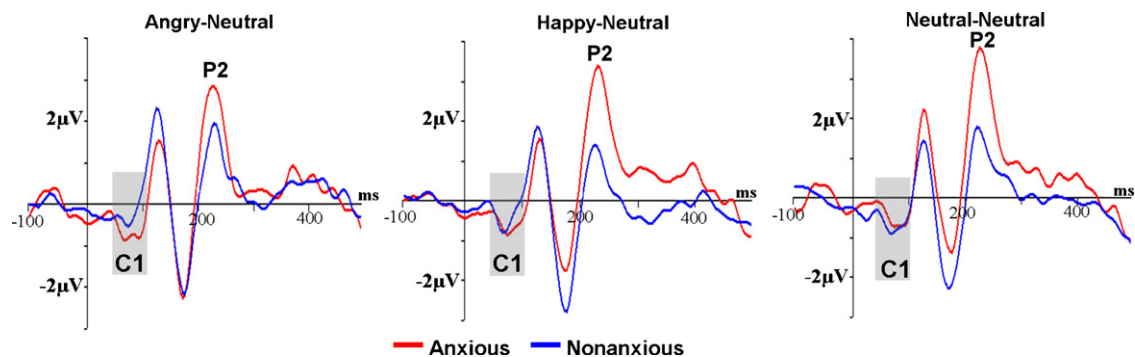
3.2.2. Analyses of the ERPs evoked by the target displays

No significant effects were found for the P1 component time locked to target onset.

4. Discussion

The present study assessed differences between highly anxious and nonanxious participants in the chronometry of neural activation during performance on a classic attention-emotion interaction task – the dot-probe. In accord with the extant literature on attention biases in anxiety (Bar-Haim et al., 2007; Mogg et al., 2004), we detected a small but significantly different from zero effect, of selective threat-related attention in anxious but not in nonanxious participants. Although these results should be interpreted with caution because the interaction between emotion condition and anxiety was not significant, the overall pattern of results suggests that the attention of anxious individuals is indeed specifically biased in favor of threat stimuli. No anxiety-related differences in attention bias were found for positive (happy faces) stimuli. Interestingly, accuracy data revealed that all participants, regardless of anxiety level were more vulnerable to errors when processing threat.

Electrophysiological data revealed that anxious participants had more pronounced C1 negativity than the nonanxious participants exclusively in the threat condition (i.e., angry-neutral trials). C1 modulation by threat stimuli has been observed in previous ERP studies of nonselected populations (Pourtois et al., 2004; Stolarova et al., 2006), and has been associated with rapid reentrant fear cir-

**Fig. 2.** Grand-averaged ERPs over occipital electrode sites for the anxious (red) and nonanxious (blue) participants during the faces display. ERP waveforms are averaged over the O1 and O2 electrodes, separately for each emotion condition (angry-neutral/happy-neutral/neutral-neutral). (For interpretation of the reference to color in this figure legend, the reader is referred to the web version of the article.)

cuitry projections from the amygdala and other limbic regions, thought to enhance processing of threat stimuli in the primary visual cortex (Pourtois et al., 2004; Clark and Hillyard, 1996). Our finding of enhanced C1 amplitude to threat stimuli in anxious participants (peaking earlier than 100 ms post-threat stimulus onset), is also in accord with Monk et al.'s (2008) subliminal dot-probe data indicating greater amygdala activation in GAD patients. Both Monk et al. (2008) findings and the present study implicate perturbations in early, pre-attentive, threat processing as a neurofunctional individual difference in anxiety.

The anxiety-related differences found here suggest a rapid and more intense response to threat among anxious relative to nonanxious individuals, occurring in the primary visual cortex. Such difference in response to threat, in a time frame and a neural marker that are typically considered pre-attentive, might set the stage for the emergence of the well documented anxiety-related attention bias towards threat in spatial attention tasks. However, due to the blocked design of the current experiment, one may argue that the observed C1 amplitude enhancement in anxious participants represents an intense activity in their visual cortex in response to the general “emotional tone” of the threat blocks rather than a differential pre-attentive discrimination processing of threat. This concern is somewhat alleviated by the fact that Group by Face emotion interaction effects did not emerge in ERP components, such as the P1, N1 and EPN, that have been established as being specifically sensitive to emotion-related processing of face stimuli (e.g., Batty and Taylor, 2003; Dennis et al., 2009; Eger et al., 2003; Junghöfer et al., 2001; Pourtois et al., 2005; Schupp et al., 2003, 2004; Streit et al., 2003). Thus, if only the “emotional tone” of the blocks had an influence on the recorded brain activity then the Group by Emotion interaction found for the C1 should have also emerge in these more obvious ERP components.

Taken together, fMRI findings (Monk et al., 2006, 2008; Telzer et al., 2008) and the present ERP results provide a richer and more coherent view of the neural underpinnings of threat processing in anxiety and its functional chronometry. These findings are also consistent with the theoretical framework arising from animal research (LeDoux, 1995, 1996), suggesting that short and rapid neural pathways to the visual thalamus are responsible for fast and crude processing of visual threats, and that this system responds more vigorously in anxious than in nonanxious individuals. Finally, C1 modulation by emotion in the dot-probe task has been shown by Pourtois et al. (2004) in a nonselected sample of participants. The present data further characterize this modulation by showing that it is more intense in highly anxious individuals than in nonanxious individuals.

Our secondary analyses revealed enhanced occipital P2 amplitude in response to the faces displays in anxious relative to nonanxious individuals across all emotion conditions (i.e., not specific to threat). Using a different spatial attention task Bar-Haim et al. (2005) found enhanced P2 amplitude in anxious relative to nonanxious participants for angry faces than fearful, happy, and sad faces. This finding implicates modulation of P2 amplitude as an indicator of attentional recourses commitment to the processing of facial expressions of emotion. Additional research is needed to elucidate the exact nature of the attention–emotion interaction reflected by this P2 modulation.

The present study failed to find threat-related ERP differences in the P1 component locked to the target processing phase of the dot-probe task. Previous studies were not equivocal in their findings on such modulation. As augmentation of the P1 component was found in nonselected samples (Pourtois et al., 2004; Santesso et al., 2008) and among anxious individuals performing on other attention tasks (Li et al., 2005, 2007), a reduction in this component was shown in anxious individuals performing on the dot-probe task (Mueller et al., 2009). Hence, although the behavioral results in the

present study indicate that anxious individuals were selectively biased towards threat, this was not mirrored by selective modulation of the P1 component to the target display. This null result might be due to differences between the tasks used in previous studies and the classic dot-probe used here. The dot-probe task used here taps into the orienting and disengagement components of attention but does not allow separate inferences on each of these components. In contrast, Li et al. (2007) used a Stroop task tapping into attention filtering and interference, and Li et al. (2005) used a Posner task (Posner et al., 1980) tapping more narrowly into attention orienting and attention disengagement/shifting. In a similar vein, Pourtois et al. (2004), Santesso et al. (2008), and Mueller et al. (2009) superimposed a go/no-go task on the dot-probe task, thus ERPs locked to target onset were averaged from the no-go trials only (i.e., trials that did not involve a motor response). One may therefore speculate that the requirement of a motor response in our task may have increased noise and thereby precluded the detection of emotion-based differences in the attention-related components of the target-locked ERPs. The current study does not provide a definitive answer regarding threat and anxiety-related modulations in the P1 component, leaving this issue open for future research.

A noteworthy limitation of our study is that although the anxious group in the present study was comprised of extremely anxious participants with STAI scores in the range of clinical anxiety (Fisher and Durham, 1999; Yong-Ku et al., 2009), we did not apply a full psychiatric evaluation. Thus, it will be important to replicate our findings with participants that are formally diagnosed with anxiety disorders. In addition, although our results rhyme closely with Monk et al. (2008) finding of fast and pre-attentive processing of threat in anxious individuals during performance on the dot-probe task, it would be useful to investigate threat-related modulation of the ERP using subliminal exposures in order to allow for a direct comparison with this study.

In conclusion, the present study demonstrates that anxiety-related differences in threat processing emerge very early, at pre-attentive levels of stimulus analysis. The extant data suggest that a core feature of threat-related biases in anxiety lies in functional perturbations of a brain circuitry that reacts rapidly to threat. It is this over-activation that could trigger the typical hypervigilance towards threat and threat-related attention biases observed in anxious individuals. Such converging evidence from various imaging methods has considerably advanced our knowledge on the neuronal activity underlying threat processing in anxious individuals. Importantly, this knowledge can inform the design and focus of attention-oriented therapeutic interventions (Bar-Haim, 2010; Hakamata, in press; Pine et al., 2009; Eldar and Bar-Haim, 2010; Koster et al., 2009) by pointing to the specific cognitive functions showing anxiety-related perturbations.

Acknowledgments

This study was supported by the Israeli Science Foundation (Grant # 964/08) and Helen and Woolf Marmot.

References

- Amir, N., Beard, C., Burns, M., Bomyea, J., 2009. Attention modification program in individuals with generalized anxiety disorder. *Journal of Abnormal Psychology* 118, 28–33.
- Andersson, F., Etard, O., Denise, P., Petit, L., 2004. Early visual evoked potentials are modulated by eye position in humans induced by whole body rotations. *BMC Neuroscience* 5, 35.
- Armony, J.L., Dolan, R.J., 2001. Modulation of spatial attention by fear-conditioned stimuli: an event-related fMRI study. *Neuropsychologia* 40, 817–826.
- Bar-Haim, Y., 2010. Attention bias modification (ABM): a novel treatment for anxiety disorders. *Journal of Child Psychology and Psychiatry* 51, 859–870.
- Bar-Haim, Y., Lamy, D., Glickman, S., 2005. Attentional bias in anxiety: a behavioral and ERP study. *Brain and Cognition* 59, 11–22.

- Bar-Haim, Y., Lamy, D., Pergamin, L., Bakermans-Kranenburg, M.J., van Ijzendoorn, M.H., 2007. Threat-related attentional bias in anxious and nonanxious individuals: a meta-analytic study. *Psychological Bulletin* 133, 1–24.
- Batty, M., Taylor, M.J., 2003. Early processing of the six basic facial emotional expressions. *Cognitive Brain Research* 17, 613–620.
- Beck, A.T., Clark, D.A., 1997. An information processing model of anxiety: automatic and strategic processes. *Behaviour Research and Therapy* 35, 49–58.
- Bradley, B.P., Mogg, K., Millar, N., Bonham-Carter, C., Fergusson, E., Jenkins, J., Parr, M., 1997. Attentional biases for emotional faces. *Cognition and Emotion* 11, 25–42.
- Bradley, B.P., Mogg, K., Falla, S.J., Hamilton, L.R., 1998. Attention training for threatening facial expressions in anxiety: manipulation of stimulus duration. *Cognition and Emotion* 12, 737–753.
- Clark, V.P., Hillyard, S.A., 1996. Spatial selective attention affects early extrastriate but not striate components of the visual evoked potential. *Journal of Cognitive Neuroscience* 8, 387–402.
- Clark, V.P., Fan, S., Hillyard, S.A., 1995. Identification of early visually evoked potential generators by retinotopic and topographic analyses. *Human Brain Mapping* 2, 170–187.
- Dennis, T.A., Malone, M.M., Chen, C.C., 2009. Emotional face processing and emotion regulation in children: an ERP study. *Developmental Neuropsychology* 34, 85–102.
- Di-Russo, F., Martinez, A., Hillyard, S.A., 2003. Source analysis of event-related cortical activity during visuo-spatial attention. *Cerebral Cortex* 13, 486–499.
- Eger, E., Jedynak, A., Iwaki, T., Skrandies, W., 2003. Rapid extraction of emotional expression: evidence from evoked potential fields during brief presentation of face stimuli. *Neuropsychologia* 41, 808–817.
- Eldar, S., Bar-Haim, Y., 2010. Neural plasticity in response to attention training in anxiety. *Psychological Medicine* 40, 667–677.
- Eysenck, M.W., 1992. *Anxiety: The Cognitive Perspective*. Psychology Press, Hove, England.
- Fisher, P.L., Durham, C.D., 1999. Recovery rates in generalized anxiety disorder following psychological therapy: an analysis of clinically significant change in the STAI-T across outcome studies since 1990. *Psychological Medicine* 29, 1425–1434.
- Fox, E., Russo, R., Bowles, R., Dutton, K., 2001. Do threatening stimuli draw or hold visual attention in subclinical anxiety? *Journal of Experimental Psychology: General* 130, 681–700.
- Fox, E., Derakshan, N., Shoker, L., 2008. Trait anxiety modulates the electrophysiological indices of rapid spatial orienting towards angry faces. *Neuroreport* 19, 259–263.
- Foxe, J.J., Simpson, G.V., 2002. Flow of activation from V1 to frontal cortex in humans: a framework to defining “early” visual processing. *Experimental Brain Research* 142, 139–150.
- Fu, S., Greenwood, P.M., Parasuraman, R., 2005. Brain mechanisms of involuntary visuospatial attention: an event-related potential study. *Human Brain Mapping* 25, 378–390.
- Hakamata, Y., Lissek, S., Bar-Haim, Y., Britton, J., Fox, N.A., Leibenluft, E., Ernst, M., Pine, D.S., in press. Attention bias modification treatment (ABMT): a meta-analysis towards the establishment of a novel anxiety disorder treatment. *Biological Psychiatry*, doi:10.1016/j.biopsych.2010.07.021.
- Helfinstein, S.M., White, L.K., Bar-Haim, Y., Fox, N.A., 2008. Affective primes suppress attention bias to threat in socially anxious individuals. *Behaviour Research and Therapy* 46, 799–810.
- Hillyard, S.A., Anillo-Vento, L., 1998. Event-related brain potentials in the study of visual selective attention. *Proceedings of the National Academy of Sciences of the United States of America* 95, 781–787.
- Jasper, H.H., 1958. The ten–twenty electrode system of the International Federation. *Electroencephalography & Clinical Neurophysiology* 10, 371–375.
- Johannes, S., Münte, T.F., Heinze, H.J., Mangun, G.R., 1995. Luminance and spatial attention effects on early visual processing. *Cognitive Brain Research* 2, 189–205.
- Jungthöfer, M., Bradley, M.M., Elbert, T.R., Lang, P.J., 2001. Fleeting images: a new look at early emotion discrimination. *Psychophysiology* 38, 175–178.
- Kelly, S.P., Gomez-Ramirez, M., Foxe, J.J., 2008. Spatial attention modulates initial afferent activity in human primary visual cortex. *Cerebral Cortex* 18, 2629–2636.
- Koster, E.H.W., Fox, E., MacLeod, C., 2009. Introduction to the special section on cognitive bias modification in emotional disorders. *Journal of Abnormal Psychology* 118, 1–4.
- Krolak-Salmon, P., Fischer, C., Vighetto, A., Manguiere, F., 2001. Processing of facial emotional expression: spatio-temporal data as assessed by scalp event-related potentials. *European Journal of Neuroscience* 13, 987–994.
- LeDoux, J.E., 1995. Emotion: clues from the brain. *Annual Review of Psychology* 46, 209–235.
- LeDoux, J.E., 1996. *The Emotional Brain*. Simon & Schuster, New York.
- Li, X., Li, X., Luo, Y.J., 2005. Anxiety and attentional bias for threat: an event-related potential study. *Neuroreport* 16, 1501–1505.
- Li, W., Zinbarg, R.E., Paller, K.A., 2007. Trait anxiety modulates supraliminal and subliminal threat: brain potential evidence for early and late processing influences. *Cognitive, Affective & Behavioral Neuroscience* 7, 25–36.
- Lins, O.G., Picton, T.W., Berg, P., Scherg, M., 1993. Ocular artifacts in EEG and event-related potentials. I: scalp topography. *Brain Topography* 6, 51–63.
- Luck, S.J., Woodman, G.F., Vogel, E.K., 2000. Event-related potential studies of attention. *Trends in Cognitive Sciences* 4, 432–440.
- MacLeod, C., Mathews, A., Tata, P., 1986. Attentional bias in emotional disorders. *Journal of Abnormal Psychology* 95, 15–20.
- Mangun, G.R., 1995. The neural mechanisms of visual selective attention. *Psychophysiology* 32, 4–18.
- Mangun, G.R., Buck, L.A., 1998. Sustained visual–spatial attention produces costs and benefits in response time and evoked neural activity. *Neuropsychologia* 36, 189–200.
- Martinez, A., Anillo-Vento, L., Sereno, M.I., Frank, L.R., Buxton, R.B., Dubowitz, D.J., et al., 1999. Involvement of striate and extrastriate visual cortical areas in spatial attention. *Nature Neuroscience* 2, 364–369.
- Mathews, A., Mackintosh, B., 2000. Induced emotional interpretation bias and anxiety. *Journal of Abnormal Psychology* 109, 602–615.
- Miller, A., Tormarken, J., 2001. Task-dependent changes in frontal brain asymmetry: effects of incentive cues, outcome expectancies, and motor response. *Psychophysiology* 38, 500–511.
- Mogg, K., Bradley, B.P., 1998. A cognitive-motivational analysis of anxiety. *Behaviour Research and Therapy* 36, 809–848.
- Mogg, K., Bradley, B.P., 1999. Orienting of attention to threatening facial expressions presented under conditions of restricted awareness. *Cognition and Emotion* 13, 713–740.
- Mogg, K., Philippot, P., Bradley, B.P., 2004. Selective attention to angry faces in clinical social phobia. *Journal of Abnormal Psychology* 113, 160–165.
- Monk, C.S., Nelson, E.E., McClure, E.B., Mogg, K., Bradley, B.P., Leibenluft, E., et al., 2006. Ventrolateral prefrontal cortex activation and attentional bias in response to angry faces in adolescents with generalized anxiety disorder. *The American Journal of Psychiatry* 163, 1091–1097.
- Monk, C.S., Telzer, E.H., Mogg, K., Bradley, B.P., Mai, X., Louro, H.M.C., et al., 2008. Amygdala and ventrolateral prefrontal cortex activation to masked angry faces in children and adolescents with generalized anxiety disorder. *Archives of General Psychiatry* 65, 568–576.
- Mueller, E.M., Hofmann, S.G., Santesso, D.L., Meuret, A.E., Bitran, S., Pizzagalli, D.A., 2009. Electrophysiological evidence of attentional biases in social anxiety disorder. *Psychological Medicine* 39, 1141–1152.
- Navon, D., Margalit, B., 1983. Allocation of attention according to informativeness in visual recognition. *Quarterly Journal of Experimental Psychology: Human Experimental Psychology* 35, 497–512.
- Pine, D.S., Helfinstein, S.M., Bar-Haim, Y., Nelson, E., Fox, N.A., 2009. Challenges in developing novel treatments for childhood disorders: lessons from research on anxiety. *Neuropsychopharmacology* 34, 213–228.
- Posner, M.I., Snyder, C.R., Davidson, B.J., 1980. Attention and the detection of signals. *Journal of Experimental Psychology* 109, 160–174.
- Pourtois, G., Grandjean, D., Sander, D., Vuilleumier, P., 2004. Electrophysiological correlates of rapid spatial orienting towards fearful faces. *Cerebral Cortex* 14, 619–633.
- Pourtois, G., Dan, E.S., Grandjean, D., Sander, D., Vuilleumier, P., 2005. Enhanced extrastriate visual response to band-pass spatial frequency filtered fearful faces: time course and topographic evoked-potentials mapping. *Human Brain Mapping* 26, 65–79.
- Pourtois, G., Schwartz, S., Seghier, M.L., Lazeyras, F., Vuilleumier, P., 2006. Neural systems for orienting attention to the location of threat signals: an event-related fMRI study. *Neuroimage* 31, 920–933.
- Santesso, D., Meuret, A., Hofmann, S., Mueller, E., Ratner, K., Roesch, E., Pizzagalli, D., 2008. Electrophysiological correlates of spatial orienting towards angry faces: a source localization study. *Neuropsychologia* 46, 1338–1348.
- Schmidt, N.B., Richey, J.A., Buckner, J.D., Timpano, K.R., 2009. Attention training for generalized social anxiety disorder. *Journal of Abnormal Psychology* 118, 5–14.
- Schupp, H.T., Junghöfer, M., Weike, A., Hamm, A., 2003. Emotional facilitation of sensory processing in the visual cortex. *Psychological Science* 14, 7–13.
- Schupp, H.T., Öhman, A., Junghöfer, M., Weike, A.I., Stockburger, J., Hamm, A.O., 2004. The facilitated processing of threatening faces: an ERP analysis. *Emotion* 4, 189–200.
- Spilberger, C.D., Gorsuch, R.L., Lushene, R., Vagg, P.R., Jacobs, G.A., 1983. *Manual for the State-Trait Anxiety Inventory*. Consulting Psychologists Press, Palo Alto, CA.
- Stolarova, M., Keil, A., Moratti, S., 2006. Modulation of the C1 visual event-related component by conditioned stimuli: evidence for sensory plasticity in early affective perception. *Cerebral Cortex* 16, 876–887.
- Streit, M., Dammers, J., Simsek-Kraues, S., Brinkmeyer, J., Wolwer, W., Ioannides, A., 2003. Time course of regional brain activations during facial emotion recognition in humans. *Neuroscience Letters* 342, 101–104.
- Telzer, E.H., Mogg, K., Bradley, B.P., Mai, X., Ernst, M., Pine, D.S., Monk, C.S., 2008. Relationship between trait anxiety, prefrontal cortex, and attention bias to angry faces in children and adolescents. *Biological Psychology* 79, 216–222.
- Tottenham, N., Tanaka, J., Leon, A.C., McCarry, T., Nurse, M., Hare, T.A., Marcus, D.J., Westerlund, A., Casey, B.J., Nelson, C.A., 2009. The NimStim set of facial expressions: judgments from untrained research participants. *Psychiatry Research* 168, 242–249.
- Williams, J.M., Mathews, A., MacLeod, C., 1996. The emotional Stroop task and psychopathology. *Psychological Bulletin* 120, 3–24.
- Yong-Ku, K., Heon-Jeong, L., Jong-Chul, Y., Jung, A.H., Ho-Kyoung, Y., 2009. A tryptophan hydroxylase 2 gene polymorphism is associated with panic disorder. *Behavior Genetics* 39, 170–175.