Mechanisms of Selective Attention in Generalized Anxiety Disorder

(Invited Extended Paper)

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Abstract

A well-established literature indicates that there are different components of anxiety-related attentional bias, such as engagement and disengagement, and it has been suggested that these distinctions may have important clinical implications. However, this view relies heavily upon experimental work in subclinical populations. To determine whether this distinction is relevant for clinical populations we investigated, across two separate experiments, attentional orienting mechanisms in individuals diagnosed with Generalised Anxiety Disorder (GAD), healthy volunteers and people reporting high levels of trait-anxiety but not meeting diagnostic criteria for GAD. Experiment 1 showed that GAD patients, but not healthy volunteers or high trait-anxious individuals, were *faster* to disengage angry than neutral faces, an effect opposite to that expected on the basis of the subclinical literature. In Experiment 2 we used a more rigorous methodology and wider range of emotional expressions, to provide a second test of attentional orienting patterns in GAD patients versus healthy volunteers. Participants in both groups showed a selective attentional avoidance of affective stimuli (fearful, angry and happy facial expressions) as well as a non-spatial interference effect. Together these data challenge our current assumptions that we can generalize, to those with GAD, the pattern of selective attentional orienting to threat found in subclinical groups. This in turn raises important questions about the most appropriate attentional mechanisms to target for treatment. Our results highlight the need for further basic research into the mechanisms of biased attentional orienting in GAD. We offer some suggestions on the next steps needed to decisively advance our understanding in this field.

Experimental research suggests that dysfunctional forms of cognitive processing help to cause and maintain emotional disorders (Clark & Beck, 2010; Williams, Watts, Mathews & MacLeod, 1997). Successful cognitive therapies involve identifying and challenging these dysfunctional cognitions. One example is biased attentional processing of emotional information, which is particularly implicated in the anxiety disorders (Yiend, 2010). Anxious individuals (clinically disordered and subclinically anxious) typically prioritize processing of threatening information in the visual environment in preference to benign or positive information(see Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van Ijzendoorn, 2007, for meta-analysis of visual-spatial attentional "probe" tasks). This cognitive pattern is assumed to lead to exaggerated negative perceptions and evaluations, which helps maintain anxiety, establishing a vicious cycle of cause and effect (Mathews, 1990). Experimental findings to date have supported this view demonstrating that attentional biases toward negative information are associated with clinical and subclinical anxiety using a range of stimuli including words, faces and pictures (see Bar-Haim et al, 2007; Mathews & MacLeod, 1994; Yiend, 2010 for reviews).

This fundamental research in experimental psychopathology has emphasized that the direct targeting of dysfunctional biases in attention is an important strategy in the treatment of anxiety disorders. In particular, 'attentional training' (sometimes called 'attention bias modification procedures' or 'ABM') is aimed at reducing symptoms and behaviours associated with anxiety by systematically reducing negative attentional biases and training selective attention to orient away, or to disengage, from threat (Koster, Fox & MacLeod, 2009; Woud & Becker, 2014). For example, in one study (Amir, Beard, Cobb, & Bomyea, 2010), fourteen patients with Generalised Anxiety Disorder (GAD), were assigned to an active ABM procedure in which attention was systematically directed away from threat

words, while fifteen were assigned to a 'control' training procedure in which attention was directed to threat-related and neutral stimuli equally often. Following eight sessions of training there was a significant reduction in negative attention bias from pre- to post-ABM training in the active training group but not in the control group. Importantly, there was also a significant reduction in clinical symptoms in those who received the active training. Remarkably, 50% of those who had received active training no longer met diagnostic criteria for GAD following the eight sessions compared to just 13% of those who had received placebo training. These results suggest that negative attentional biases may indeed play a critical role in the maintenance of GAD symptoms. While subsequent studies have generally produced much smaller effect sizes, three meta-analyses support the view that ABM procedures show promise as a novel treatment for a variety of anxiety disorders (Hakamata, Lissek, Bar-Haim, Britton, Fox, Leibenluft, Ernst, & Pine, 2010; Hallion & Ruscio, 2011; Mogoașe, David, & Koster, 2014).

What has emerged in the recent literature is that the ability to manipulate attention biases is somewhat inconsistent and effect sizes on clinical outcome measures are generally lower than expected. In a useful overview, it has been noted that when a negative attention bias is successfully modified then a congruent impact on emotional reactivity occurs (Clarke, Notebaert & MacLeod, 2012). However, the majority of studies of ABM in clinical groups have failed to shift attentional biases (7 out of 11) and therefore it is not surprising that the overall impact of ABM on clinical symptoms is inconsistent (Clarke et al, 2012). Several investigators have suggested that there is now an urgent need to focus on maximising the efficacy of bias modification procedures (Clarke et al, 2012; Fox, Mackintosh & Holmes, 2014; Lester, Mathews, Davison, Burgess, & Yiend, 2011; Yiend et al., 2013). In order to

optimise such interventions it is, however, vital to have a clearer understanding of the nature of the mechanism of change in specific anxiety disorders such as GAD.

In order to improve our understanding of attentional bias mechanisms the field has borrowed from mainstream attentional research. There an important conceptual distinction is that between *selective attention (*selection*),* and *attentional orienting* (orienting)(Yiend, 2010). Bias in selective attention refers to certain material (threat, in the case of GAD) being prioritised over other material for further processing, and is typically measured by traditional attentional bias tasks, such as the so called attentional probe task. Attentional orienting, on the other hand, can be thought of as one possible mechanism by which attentional selection can be implemented. Orienting refers to the process of moving attention to a location, either in space (spatial orienting) or, less commonly, in time (temporal orienting)[1]. Orienting frequently uses Posner's distinction among shifting, engagement and disengagement of attention (Posner & Peterson, 1995). A long-standing concept in attention research, it has been of particular interest recently within psychopathology research as a means to further specify the cognitive mechanisms by which attentional biases operate.

While selective attentional bias favouring threat in GAD is well evidenced, research on the components of orienting (disengage, engage) which might underlie this effect, have, to date, been largely restricted to subclinical samples. A growing literature in subclinical anxiety has suggested that there are different components of anxiety-related attentional bias and that these may have different clinical implications. However, this has been assumed more often than tested in clinical populations. For example, it has been shown that participants reporting high levels of trait-anxiety take longer to disengage their attention

[1] Attention also may be oriented to particular stimulus dimensions which co-occur in the same spatial location at the same time (e.g., to the colour or content of a word)

from threat-related words and faces (Fox, Russo, Bowles, & Dutton, 2001; Fox, Russo & Dutton, 2002; Georgiou, Bleakley, Hayward, Russo, Dutton, Eltiti & Fox, 2005), affective pictures (Yiend & Mathews, 2001) and locations associated with negative outcomes (Derryberry & Reed, 2002). This suggests that anxiety-related attentional biases may be associated with problems in disengaging attention from negative material as well as enhanced engagement with threat (Fox, Mathews, Calder, & Yiend, 2007; Mathews, Fox, Yiend, & Calder, 2003). However, to our knowledge, attentional orienting mechanisms have not yet been investigated in clinical samples except once in social phobia (Amir et al., 2003), a disorder that can show attentional effects at odds with those of other anxiety disorders (Staugaard, 2010). In searching the literature we could find no studies investigating attentional orienting mechanisms in GAD patients.

An absence of relevant empirical evidence in GAD patients is especially critical due to the importance of identifying appropriate cognitive mechanisms to target in the treatment of GAD. Biases in different components of attentional orienting could have different clinical implications. For instance, if clinically anxious individuals show speeded engagement towards threat then detection and evaluation processes are implicated, suggesting that therapists might focus on reducing patients' sensitivity to threat. If disengaging from threat is impaired this suggests patients might derive more benefit from improving their ability to disregard negative information. Elucidating the involvement of these orienting mechanisms (engagement, disengagement or both) should therefore enhance the development of translational research, such as the attentional bias modification (ABM) training techniques described earlier. Indeed the notion that different attentional orienting mechanisms (e.g., engagement and disengagement) may underlie selective attentional bias, and therefore have different implications for psychopathology, has generated substantial interest since the

seminal publications introduced the idea to the field (Fox, Russo, Bowles, & Dutton, 2001; Fox, Russo, & Dutton, 2002; Yiend & Mathews, 2001). This is most strikingly evidenced by performing a simple literature search using topic keywords 'disengage*', 'attention' and 'anxiety'. For the 12 years leading up to 2001 this generates only 11 publications, whereas the same output for the 12 subsequent years (2001-13) yields over 200 peer reviewed articles. The primary aim of the present study was therefore to investigate the spatial attentional orienting mechanisms underlying threat-related selective attentional biases in GAD.

The data reported here comprised two separate experiments, both involving patients meeting diagnostic criteria for GAD. Both studies attempted to identify the specific components of attentional orienting underlying naturally occurring selective attentional bias to threat. While it is likely that GAD is characterized primarily by attention biases that are specific to personal concerns and worries, there is evidence that GAD patients, relative to matched controls, show attentional biases involving more general threat, for example involving angry facial expressions (Ashwin, Holas, Broadhurst, Kokoszka, Georgiou, & Fox, 2012; Bradley, Mogg, White, Groom, & de Bono, 1999). Therefore, in order to facilitate comparisons with previous studies in subclinical anxiety (Fox et al, 2001; Fox, Mathews, Calder & Yiend, 2007; Georgiou et al, 2005) we used emotional and neutral facial expressions in the current investigations.

In the first of two experiments, we assessed the disengagement of attention from angry, happy and neutral facial expressions in GAD patients and matched healthy volunteers using a task that we have previously used with subclinically anxious individuals (Georgiou et al, 2005). We assessed angry, rather than fearful, facial expressions since previous studies of

disengage processes in trait-anxiety (Fox et al, 2001) and biased attention in GAD (Ashwin et al, 2012; Bradley et al, 1999) have more typically used angry facial expressions. Experiment 1 also included a group of people reporting high levels of trait-anxiety, but not meeting diagnostic criteria for GAD, for comparison with the previously reviewed findings in subclinical anxiety. GAD patients and high trait-anxious groups were matched on self-reported trait-anxiety (although not on depression), but differed on clinical status. This design allowed us to more clearly determine whether the pattern of attentional bias apparent in GAD would be similar to that found previously in subclinical anxiety.

The attention task used in Experiment 1 assessed the spatial orienting components of anxiety related bias. The task involved the presentation of a face at the centre of a computer screen for over half a second followed by a target letter that was flashed on the screen very briefly (50 ms) either above, below, to the left or to the right of the centrally located face. In a previous study with this task we reported that a sub-clinical group with high trait-anxiety took longer to categorize the peripheral target letter when it was presented with a fearful face relative to when the centrally located face conveyed happiness, sadness or a neutral expression (Georgiou, et al, 2005) implying that high trait-anxiety is linked with a delay in disengaging from fear-related material. In Experiment 1 the aim was to assess whether the GAD group would show a delay in disengaging from threatening facial expressions as was expected in the high trait-anxious (sub-clinical) group. A delay was not expected in the matched control group.

EXPERIMENT 1

METHOD

Participants

Fourteen GAD patients, fourteen of their relatives (matched healthy volunteers), and fourteen people with high levels of self-reported trait-anxiety who did not pass criteria for GAD took part in the study. Patients were identified through clinician referrals for the North East Essex Mental Health Trust and most were on a waiting list for an appointment with a clinical psychologist at the Trust. Initial telephone screening was conducted using the SCID, a structured clinical interview for DSM-IV (First, Spitzer, Gibbon & Williams, 1996) by a researcher trained in clinical interviewing and the use of the SCID by an approved local trainer (ML). All patients were given the anxiety disorders modules and additional relevant modules were completed as necessary. Inclusion criteria were likely diagnosis of GAD on the SCID, aged between 18 and 65 years and native English speaking. Exclusion criteria (checked by telephone screening or at interview) were: significant psychiatric co-morbidity, addictions, or current major physical illness. Those in current receipt of psychological or pharmacological treatment were also excluded. Upon agreeing in principle to take part in the study patients were asked to nominate a close relative who could also take part in the study as a matched healthy volunteer. A further group of 14 people who had reported high levels of trait-anxiety (more that 45 on the STAI trait-anxiety scale) were also included in the study. These were recruited from the University of Essex campus and had responded to advertisements to partake in psychological studies. All healthy volunteers and high trait-anxious participants were given a short form of the SCID via either telephone screening or at interview and were excluded if they reported any previous or current major psychopathology, major physical illness or addictions.

Materials

Trait and State Anxiety: The State Trait Anxiety Inventory (STAI: Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983) is a well-validated self-report questionnaire. The trait-anxiety form of the STAI consists of 20-items developed to measure the degree of dispositional trait-anxiety. Participants score each item on a 4-point Likert type scale and the total score ranges from 20 (very low trait-anxiety) to 80 (very high trait-anxiety) with the population median being around 40. The state-anxiety form of the STAI is similar but measures "how you feel now".

Depression: The Beck Depression Inventory-II (BDI-II: Beck, Steer, & Brown, 1996) is a well-validated 21-item questionnaire that provides a measure of depression severity. Participants score each item on a 4-point Likert type scale and total scores of 0-13 are considered to be within the minimal range, 14-19 reflects mild depression, 20-28, moderate depression, while scores from 29-63 are considered severe.

Mill Hill Vocabulary Scale (MHVS). The MHVS (Raven, Court, & Raven, 1988) assesses verbal intelligence and consists of two lists of words divided into two sets (A and B) of 34 words, arranged in order of ascending difficulty, which those taking the test are asked to define. We used the multiple-choice version from set B. Participants were asked to select the correct synonym from a list of 6 alternatives and the maximum score was 33.

Attentional Task: For this reaction time task, three different photographs were selected from the Ekman and Friesen (1975) set of emotional facial expressions. All were of the same individual (PE), but displayed different expressions: anger, happiness and neutral. All photographs were presented in black and white, were matched for brightness, and measured 6.8 cm x 10.3 cm in size. In an earlier pilot study, 12 undergraduate students had rated the faces (among several other faces) in terms of whether they appeared to be "happy", "sad", "fearful", "angry", "surprised", "disgusted" or "neutral". It was found that 100% categorized the angry face as "angry", 100% categorized the happy face as "happy" and

83.3% categorized the neutral face as “neutral”, while 16.7% categorized this face as “sad”. The target letters were P and X and were presented in Geneva font 24. They were presented 8cm above, below, to the left or to the right of the centrally presented face. At a viewing distance of 60 cm this was 7.6 deg of visual angle from the face stimulus.

Procedure

Testing either took place in a quiet room at the North East Essex Mental Health Trust in Clacton or Colchester or at the University of Essex in Colchester. After consent procedures, participants completed the STAI-trait, BDI and STAI-state forms, followed by the Mill Hill Vocabulary scale. Participants were shown the computer and button-box and the attentional task was explained in detail. It was explained that they would see an asterisk at the centre of the screen and that they should keep their eyes focused on this location. It was explained that a face would shortly appear in this location followed by a letter (either X or P) above, below, to the left or to the right of the face. They were instructed to keep their eyes on the face, but categorize the letter as quickly and accurately as possible by pressing either the red or the green button on the response box. Response mappings were counterbalanced across participants so that half pressed the Red button for X while half pressed the Green button for X and vice versa. Every trial began with an asterisk at the centre of the computer screen for 1000 ms. One of the three facial expressions was then presented, and after 600 ms one of the target letters was presented in one of the four locations for 50 ms. The face remained on the screen until the participant responded or, if there was no response, after 2000 ms. There was a blank screen for 500 ms and then the next trial began.

Each participant completed a practice block of 28 trials and once they were happy with the procedure they started the main experiment. This consisted of 288 trials, which were divided equally into trials with targets above (72), below (72), to the left (72) or to the right

(72) of the face. For each location, the centrally presented face was equally often angry (96), happy (96) or neutral (96). Likewise, the actual target letter (X or P) appeared equally often with each facial expression and in each location. Each participant received a different randomized order of trials.

All stimuli were presented on a Power Macintosh 7200/90 computer with a 29 cm x 21 cm Sony Trinitron Multiscan screen. Presentation of stimuli and data collection was controlled by PsyScope software (Cohen, MacWhinney, Flatt, & Provost, 1993) and reaction times were recorded on a USB-based RB-834 response pad with a built in timer that allowed data to be collected with a 1-millisecond accuracy.

RESULTS

Participant Characteristics

Characteristics of the participants in the three separate groups are shown in Table 1. A series of 1-way ANOVAs showed that there were differences across the three groups on Age, F (2, 39) = 9.1, $p < .001$, trait-anxiety, F (2, 39) = 75.6, $p < .001$, BDI, F (2, 39) = 33.8, $p < .001$, and state-anxiety, F (2, 39) = 32.0, $p < .001$. As expected the GAD and Control groups were matched on age and on MHVS scores (t (26) < 1 for both), while the GAD group reported higher levels of trait and state anxiety, and depression on the BDI (all ps < .001). The GAD and High Trait Anxiety group were matched on trait and state anxiety (t (26) < 1 for both), while the GAD group reported higher levels of depression on the BDI, t (26) = 2.1, $p < .05$. The High Trait Anxiety group also reported higher levels of trait-anxiety, state-anxiety and depression on the BDI in comparison with the Control group (all ps < .001). Finally, the High Trait Anxiety group were significantly younger than either the GAD, t (26) = 3.5, $p < .002$, or the Control group, t (26) = 3.8, $p < .001$.

INSERT TABLE 1 HERE

Attentional Task

Reaction time data was prepared by removing trials on which errors occurred and eliminating high and low outliers (< 3.5 % of the data). Mean reaction times by condition are shown in Figure 1. Data were analyzed by means of a 3 x 3 ANOVA, with factors Group (GAD, Control, High Trait Anxiety) x Valence of Face (Angry, Happy, Neutral). There were no main effects for either Group, F (2, 39) = 1.9, or Valence of Face, F (2, 39) < 1, while the Group Valence of Face interaction did reach statistical significance, F (4, 78) = 3.6, MSe = 1828.8, partial eta squared = 0.155, $p < .01$. Follow-up 1-way ANOVAs were conducted on each Group separately for Valence of Face. For the GAD group, the main effect of Valence of Face was significant F (2, 26) = 5.7, MSe = 1404.7, partial eta squared = 0.305, $p < .009$. Further analysis using paired-contrasts showed that reaction times for this group were *faster* when the central face was angry compared to neutral, t (13) = 3.1, $p < .009$, 2-tailed. Reaction times for angry relative to happy face trials did not differ significantly, t (13) = 2.0, $p < .07$, 2-tailed, and neither did those of happy compared to neutral face trials , t (13) = 1.3, ns. The main effect of Valence of Face did not reach significance for either the matched control group (F (2, 26) = 1.5, MSe = 1499.5, partial eta squared = 0.104, $p = .240$) or for the High Trait Anxious group (F (2, 26) = 1.7, MSe = 2582.3, partial eta squared = 0.117, $p = .198$). Table 2 shows the relevant means and standard deviations for each group as a function of condition.

INSERT FIGURE 1 AND TABLE 2 HERE

DISCUSSION

The findings of Experiment 1 imply that the pattern of impaired disengagement from threatening expressions, previously reported in high trait-anxious subclinical samples, may not be directly generalizable to clinical anxiety. While we did not replicate previous findings of impaired disengagement in sub-clinical high trait-anxious individuals in the current study (Fox et al, 2001; Georgiou et al, 2005), we did find significant differences in the GAD group, in a direction opposite to that expected. Individuals with GAD were *faster* to respond to a peripheral target letter when a centrally presented face was angry relative to happy or neutral, a pattern not found in matched healthy volunteers. One explanation for these results is that GAD patients showed attentional *avoidance* of threatening facial expressions. Thus, rather than impaired disengagement of attention as expected, this patient sample appeared to show *enhanced* disengagement.

One problem with the task employed in Experiment 1 was that it is difficult to separate any effects of general interference from those specifically related to selective attention and attentional orienting. For instance, it is possible that patients were faster to respond on threat trials due to a generally increased arousal level in the presence of threat. Although randomly interspersing emotional and neutral trials might help protect against this, it remains possible that momentary fluctuations in physiological response to threat could account for a similar pattern of reaction times to that which we seek to attribute to attentional effects. We therefore sought to address this concern in Experiment 2 by using a methodology that provides a separate measure of 'general arousal', allowing us to more precisely isolate selective attentional effects. The paradigm chosen was the emotional adaptation of the so-called 'Posner peripheral cuing task' (Fox et al, 2001; Yiend & Mathews, 2001). This task involves using emotional cues (here facial expressions) presented in the periphery of the visual field that 'capture' attention at their location. The speed of identifying an arbitrary probe (such as a letter) at either the same, or a different, location from the cue, acts as an

indicator of the spatial orienting of attention and how orienting speed may vary according to the type of emotion depicted in the cue. On invalid trials attention must be disengaged from an emotional cue appearing in the periphery in order to detect a target occurring in a different location. By changing the emotion of the cue it is therefore possible to compare ease of disengaging attention from different types of emotional information.

Further limitations of Experiment 1 concerned the small sample size and the restricted range of facial expressions of emotion used in the study. With only fourteen participants per group, power to detect small effects was low, and the possibility of false positives relatively high. Experiment 2 was therefore based upon an a priori power calculation and tested groups of 21 GAD and 21 matched healthy volunteers. We also included a more comprehensive selection of facial expressions: fearful, angry, happy and neutral.

Finally, Experiment 2 added a second task, an adaptation of a gaze-direction cuing task, which has been used to assess the engagement component of spatial attentional orienting. Observing another person looking in a particular direction ('eye gaze') has the effect of directing and engaging the observer's attention to that same location (Driver et al., 1999; Langton & Bruce, 1999). Facial expression of emotion can therefore be used in combination with eye gaze to assess the effects of different emotional expressions on attentional engagement to a location cued by the direction of the gaze. On so called 'congruent' trials, if an emotional facial expression facilitates engagement to the location indicated by the averted eyes, that should lead to particularly fast (efficient) target identification compared to similar trials using neutral expressions with averted eye gaze. We have used this task in two previous studies with subclinical anxiety and found that those who reported high trait-anxiety did show enhanced orienting towards a location (ie engagement) indicated by the eye-gaze of a fearful facial expression relative to a neutral expression (Fox et al, 2007; Mathews et al, 2003). Interestingly, on centrally cued trials in which the eye-gaze

does not move (very similar to the task used in Experiment 1 here) fearful expressions did not hold attention any more than neutral faces (Fox et al, 2007; Mathews et al, 2003), but *angry* facial expressions did hold the attention of high trait-anxious participants to a disproportionate extent (Fox et al, 2007), indicating a difficulty in disengaging from angry facial expressions. We used just fearful and neutral expressions in the current investigation in order to determine whether a similar pattern of attentional orienting occurs in a group of patients diagnosed with GAD as we have observed in those reporting high levels of trait-anxiety (Mathews et al, 2003). Once again, this is important in order to establish whether results found with sub-clinically anxious groups can be generalized to clinical groups.

EXPERIMENT 2

METHOD

Participants

Power. Using 21 participants in each group this study had 80% power to detect a small effect size (f=0.1) on the Trial Type (2) x Cue Type (2) within – between interaction, assuming 6 levels of repeated measurement (Erdfelder, Faul & Buchner, 1996). A small effect on the task would equate to a difference of 20ms on reaction times of around 500ms, with standard deviation of 100ms.

Twenty one GAD patients and 21 healthy volunteers participated in the study. Patients were identified through clinician referrals from Oxfordshire and Buckinghamshire Mental Healthcare Trust staff. These included consultant psychiatrists, psychologists, primary care counsellors and patient response to poster advertisements in a local psychiatric outpatient department. Initial telephone screening using the GAD-Q (Roemer et al., 1995) was used to confirm likely GAD diagnosis. Exclusion criteria (checked by telephone

screening or at interview) were: significant psychiatric co-morbidity, in current receipt of psychological or pharmacological treatment, current major physical illness, current addictions and past serious head injury. Patients were not excluded if they had previously received an intervention for GAD but remained symptomatic at diagnostic level.

Healthy volunteers were recruited by responses to poster advertisement on local public notice boards, internet advertisement and local media publications. Exclusion criteria for healthy volunteers were checked during telephone screening and included past or present psychopathology as indicated by self-report, current major physical illness, current addictions and past serious head injury. Inclusion criteria (in both groups) were age (18-65) and native English speaking. Despite screening procedures, 4 control participants reported levels of trait anxiety within the clinical range (50 or above on the STAI-T; Spielberger et al. 1983). These participants were therefore ineligible to be included in the healthy control group and were replaced. This decision was made on a priori grounds, before any data analysis had been conducted, on the basis that all participants must meet the inclusion criteria for the relevant group in order to take part in the study. All participants had normal or corrected-to-normal vision.

Materials

All stimuli for the experimental tasks were taken from standardised sets. For the peripheral cuing task, Caucasian stimuli were selected from the JACFEE/JACNeuF sets of facial expressions (Matsumoto & Ekman, 1988). Eight identities of each emotion (happy, neutral, angry and fearful) were chosen based on the normative data provided, each being presented a total of 12 times during the task. For the central cuing task, stimuli were those used previously by Mathews et al, (2003). Eight identities of each emotion (neutral and fearful) were used from the Ekman series on the basis of the normative ratings provided

(Ekman & Friesen, 1976). Each identity had previously been digitally manipulated to produce eye gaze shift (left and right) for use on relevant trials. Stimuli were assigned to trial condition within each type of emotion according to a fixed random order.

Procedure

After completing consent procedures, healthy volunteers were asked to complete the General Health Questionnaire (GHQ; Goldberg & Williams, 1988). Patients were given the SCID, a structured clinical interview for DSM-IV (First et al., 1996) by a researcher experienced in clinical interviewing and specifically trained in its use by an approved local trainer. All patients were given the anxiety disorders modules and the SCID – screen was used to identify additional relevant modules which were completed as necessary. Participants then received the following two computerised experimental tasks in counterbalanced order.

Peripheral Cuing Task. This task used the method employed by Yiend and Mathews (2001) and Fox et al, (2001) to compare attentional disengagement from faces of different emotional expressions. Participants fixated a central cross while a face cue appeared either on the left or right. Their task was to identify a subsequent target letter (E or F) as quickly as possible but without making errors. Targets either appeared opposite (an invalid trial) or in the same location (a valid trial) as the face cue. A total of 384 trials were presented, using a valid: invalid ratio of 2:1. Cues were presented for either 200ms or 500ms, and four different emotional facial expressions were used as cues: happy, angry, fearful and neutral. The factors, Cue duration (2), Facial expression (4) and Validity (2: valid, invalid) were used in a fully crossed design with 16 trials in each invalid condition and 32 in each valid condition. Trials were presented in a randomised order generated automatically by the computer software with optional rest breaks. The task lasted around 20 minutes.

Central Cuing Task. This task used the method employed previously by Mathews et al (2003). Participants fixated a central cross after which a face cue appeared in the centre, replacing fixation. The eyes then shifted to the left or right, cueing attention to that location. The task was to identify a subsequent target letter (E or F) appearing in either the cued (congruent trials) or uncued (incongruent trials) location as quickly as possible but without making errors. A total of 384 trials were presented, using a congruent: incongruent ratio of 1:1. Cues were presented for 2 durations, 300ms or 700ms and depicted either fearful or neutral facial expressions. The factors Cue duration (2), Facial expression (2) and Congruency (3: valid, invalid, central – eyes do not move) were used in a fully crossed design with 32 trials per condition, presented in a randomised order. The task lasted around 20 minutes, with optional rest breaks.

At the end of the experimental tasks all participants completed the following questionnaire measures in an individually allocated random order: the Beck Depression Inventory (BDI; Beck, 1961); the Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987); the Hospital Anxiety and Depression Scale (HADS; Zigmond, 1983) and the state and trait versions of the Spielberger State-Trait Anxiety Inventory (STAI; Spielberger et al., 1983).

RESULTS

Participants

Table 1 shows participant characteristics. Patients and healthy volunteers differed significantly on all measures of mood state, trait and symptoms, but not on age.

Peripheral Cueing Task

Error trials totalled 2.9% of the data and outliers 0.8% (high outliers > 1370 ms; low outliers < 200ms). Mean reaction times to identify the target in the peripheral cuing task

were subjected to a mixed model ANOVA with one between subjects factor, Group (patient, control) and three within subjects factors, Cue Duration (200, 500ms), Facial Expression (anger, fear, happy, neutral) and Validity (invalid, valid). There was a main effect of Validity F (1, 40) = 30.67, $p < .001$, partial eta squared = 0.43, reflecting faster reaction times on valid than invalid trials (608ms, se = 14.7 vs. 660ms, se = 15.6, respectively). A main effect of Cue Duration, F (1, 40) = 29.79, $p < .001$, partial eta squared = 0.43, revealed that reaction times were faster when cues were presented for longer (624ms, se = 14.5, vs. 645ms, se = 14.6). No interactions involving Group approached significance, (all Fs < 2.5, largest partial eta squared = 0.06), nor was there a main effect of Group ($F < 1$, partial eta squared = 0.02). There was one significant interaction, Validity x Facial Expression, F(1,40) = 6.61, $p = .001$, partial eta squared = 0.15. Table 2 shows the relevant means.

To interpret this interaction according to our hypotheses about the effects of emotional compared to neutral expressions, we used reaction times to neutral trials as a baseline against which to subtract the effects of emotion cuing for valid and invalid trials separately, using the following equation:

Effect of emotional expressions on spatial orienting = Neutral Cue [reaction time] – Emotional Cue [reaction time].

Thus a negative index indicates that emotion cues slowed reaction times, whereas a positive index indicates that emotion cues speeded reaction times, compared to neutral. Slowing on valid trials can therefore be interpreted as slower engagement to emotion, while speeding on invalid trials can be interpreted as faster disengagement from emotion. Subsequent analyses were carried out on these index scores. Figure 2 illustrates these data. For completeness, hypothesis driven follow up t-tests were conducted comparing each index score to zero (no effect of emotion). After correcting for multiple comparisons two effects remained significant. Fear cues significantly slowed reaction times on valid trials, t (41) = 4.47, p<.001,

d = 0.69, and significantly speeded reaction times on invalid trials, $t(41) = 2.77$, $p < .01$, d = 0.43.

INSERT FIGURE 2 HERE

In the preceding analyses there were no significant group interactions, suggesting that the above pattern of orienting applied to GAD patients and healthy volunteers, alike. However, given the purpose of the experiment and the previous literature, a further hypothesis driven analysis was conducted as a stringent test of whether the above pattern of findings held true in the patient sample alone. The main analysis was repeated on the patient sample only, namely a repeated measures ANOVA of design Cue Duration (200, 500ms) x Facial Expression (anger, fear, happy, neutral) x Validity (invalid, valid). This revealed a significant Validity x Facial Expression interaction, F (3, 60) = 2.98, p = .04, partial eta squared = 0.13, as previously, with means following the same pattern as the main findings, reported above.

Central Cueing Task

Error trials totalled 1.8% of the data and outliers 2.1% (high outliers > 1160 ms; low outliers < 100ms). A mixed model ANOVA was conducted on mean reaction times to identify the target, with one between subjects factor, Group (patient, control) and three within subjects factors, Cue Duration (300, 700ms), Facial Expression (fear, neutral) and Cue Congruency (central, congruent, incongruent). There was a main effect of Cue Congruency, F (2, 80) = 20.11, $p < .001$, partial eta squared = 0.34, reflecting faster reaction times on congruent than central trials (556ms, se = 13.7, vs. 568ms, se = 13.3) and on central than incongruent trials (568ms, se = 13.3 vs. 572ms, se = 14). Thus the general effect of spatial attentional cuing on this task was as expected. A main effect of Cue Duration, F (2, 80) =

18.54, $p < .001$, partial eta squared = 0.32, revealed that reaction times were faster when cues were presented for longer (559ms, se = 13.8, vs. 572ms, se = 13.4). No interactions involving Group approached significance, (all Fs < 1.5, largest partial eta squared = 0.03), nor was there a main effect of Group ($F < 0.5$, partial eta squared = 0.004). There was one significant interaction, Cue Duration x Facial Expression, F (1,40) = 6.98, $p = .01$, partial eta squared = 0.15. Table 2 shows the relevant data. Follow up pairwise comparisons showed that at cue durations of 700ms (but not 300) participants were significantly slowed by fearful compared to neutral cues (t (41) = 2.55, p = 0.02, d = 0.40).

DISCUSSION

Despite patients and healthy volunteers being highly differentiated in their levels of psychopathology, the two groups did not differ significantly in their attentional processing of emotional expressions on either of the two tasks administered. Instead, on the peripheral cuing task both anxious patients and healthy volunteers showed relative speeding on invalid trials with emotional cues, especially when fear-related, compared to neutral cues were used. As in Experiment 1, this unexpected finding suggested faster, not slower, disengagement of attention from emotional expressions a pattern that was especially unexpected for the GAD group based on previous results in subclinical anxiety. In addition, reaction times on valid trials suggested slower, not faster, engagement of attention to emotional expressions, especially fear, which again was particularly unexpected for the GAD group on the basis of previous non-clinical research. On both valid and invalid trials, fear cues were particularly effective at eliciting this pattern of spatial attentional avoidance, as illustrated in Figure 2. Importantly there was no evidence of a general slowing effect of emotion, which can compromise the interpretation of cuing data (see Yiend 2010, p29 for details).

On the second task, an emotional adaptation of an eye-gaze cuing task, there was no evidence that spatial attentional orienting was influenced by the valence of the central cue. There was, as expected, a congruency or cue validity effect, but this did not interact with the emotional expression of the facial cue or participant group. In addition, irrespective of how attention was directed, participants showed a general slowing when fearful compared to neutral information was presented at the longer duration (700ms). These results are in marked contrast to our previous findings in subclinical anxiety where the facial expression of the cue did influence the allocation of attention and this enhancement was influenced by the degree of self-reported trait-anxiety. Specifically, fearful faces were more effective at eliciting a shift of attention to the gazed at location in high relative to low trait-anxious individuals (Fox et al, 2007; Mathews et al, 2003). The absence of this pattern in the current sample of GAD patients further emphasizes the difficulty of generalizing from subclinical studies to clinical populations.

GENERAL DISCUSSION

The general implication of these findings, across two experiments, are that previously reported anxiety-specific effects of impaired disengagement from, and speeded engagement towards, threatening information in subclinical samples may not be as relevant for clinical populations as has been widely assumed. Experiments 1 and 2 produced conceptually similar patterns of results in this regard. Experiment 1 found that individuals meeting diagnostic criteria for GAD showed faster disengagement from angry than from neutral facial expressions, a pattern that was quite different to that found in a group of people who did not meet diagnostic criteria for GAD but who were matched with the clinical group on the level of self-reported trait-anxiety. Experiment 2 showed spatial attentional orienting effects indicating avoidance of fearful facial cues that, once again, did not differ between GAD and

healthy volunteers. Both groups showed avoidance of fearful expressions, being faster to disengage from, and slower to engage to, fearful compared to neutral or happy facial cues. Moreover this pattern held up in a stringent hypothesis driven test of the GAD patient sample alone. Using a gaze-cueing task, the pattern of results found for our GAD sample was, once again, different to that previously found with the same task in people with subclinical levels of high trait-anxiety (Fox et al, 2007; Mathews et al, 2003).

These results have important implications for experimental psychopathology. It is widely assumed that studies in subclinical analogue samples can be generalised to the corresponding clinical disorder and this has particularly been the case for the phenomenon of impaired disengagement of attention in anxiety. However, there are insufficient published studies in clinical anxiety groups to validate this assumption. The present data with two samples of GAD patients underline the need for caution in generalising previous findings from subclinical samples. Rather than delayed disengagement and faster engagement with fear-relevant stimuli as expected we found faster disengagement and slower engagement with threat; a pattern indicative of attentional avoidance of threat-relevant material. Attentional avoidance of relatively mild levels of threat-relevant material has been reported elsewhere (Wilson & MacLeod, 2003; Mogg et al., 2000) and is integral to two current models of attentional orienting toward fear-relevant stimuli (Mogg & Bradley, 1998; Mathews & Mackintosh, 1998). It is proposed that this avoidance is an evolutionarily adaptive response allowing current goals to be pursued, unimpeded by relatively minor and insignificant environmental challenges. Importantly, however, the absence of this attentional avoidance of mild threat is considered to be an important cognitive component associated with high levels of trait-anxiety (e.g., Fox et al, 2001; Yiend & Mathews, 2001). While the present data are broadly consistent with this suggestion, the observation of this same pattern of avoidance in

the clinical anxiety groups runs counter to expectations. Taken together, these studies could indicate that impaired disengagement from threatening information is a specific attentional marker of vulnerable, subclinical samples, but does not extend to, or may even be reversed in, clinical anxiety.

The implications of the findings we report here are especially pertinent for translational research. For example, new experimentally based treatments are being developed for various disorders based on manipulations of cognitive biases (eg. Yiend, Savulich, Coughtrey & Shafran 2011; Lester, Mathews, Davison, Burgess & Yiend, 2011; Hayes, Hirsch & Mathews, 2010; Amir, Beard, Burns & Bomyea, 2009). Researchers applying these manipulations to clinical anxiety have generally assumed that it is necessary to correct the 'impaired disengagement' of attention from threat, given the findings in subclinical samples. However, the pattern of data we report suggests that this assumption may not be warranted. The present data challenge this assumption and suggest that generalising conclusions from subclinical to clinical anxiety may be premature. A more nuanced understanding of the pattern of spatial orienting to threat across clinical and subclinical anxiety may be required. Certainly, further work on the underlying mechanisms of spatial attention processing in GAD is now warranted.

As with all research, the studies reported here suffer from a number of limitations. For instance, our sample sizes were relatively small and may have been insufficient to detect between-group differences in the orienting of spatial attention. In the first experiment with only fourteen participants per group, power to detect small effects was low. However the second experiment was specifically powered to detect the necessary interaction effect, assuming a small effect size (see methods section for power analyses). Moreover, the fact that

both experiments found a broadly similar pattern of rapid disengagement, or avoidance, of threat-relevant cues that was *opposite* to that found in subclinical samples mitigates against issues of power being a parsimonious explanation of our findings. In addition, demonstration of the expected general emotion-related spatial orienting effects found in Experiment 2 suggests that those tasks were appropriately sensitive, but that the pattern of attentional processing on these tasks previously observed in subclinical anxiety (Fox et al, 2001; Fox et al, 2007; Mathews et al, 2003) was not observed in a GAD sample.

A more nuanced possibility, and one which the present data cannot speak to, is that attentional orienting effects (engagement and disengagement) may operate over different timescales in clinical and subclinical samples. The results of Ellenbogen and Schwartzman (2009) raise this possibility. They tested 36 patients with a variety of anxiety disorders (11 had GAD as a primary diagnosis) and reported that they were *fast* to disengage from supraliminal threatening pictures (similar to the effects seen in the present data) and that impaired disengagement was limited to pictures presented subliminally. They concluded that this pattern of results reflected early vigilance followed by effortful avoidance. However, as their investigation included other conditions and clinical groups, the impact of their findings for GAD are difficult to assess. Nevertheless, our finding of attentional avoidance in a GAD sample with supraliminal stimuli is consistent with this notion. It is possible that we would have found the anticipated pattern of enhanced engagement and impaired disengagement had we also examined subliminal effects.

Arguably, the most important limitation of the present research concerns the nature of the stimuli used to test for attentional effects. Early findings, reviewed by Mathews and MacLeod (1994, p36), indicated that attentional effects may depend critically on relevance of

the stimuli to the individual participant's current emotional concerns. For example, socially phobic patients are particularly likely to attend to socially threatening words, whereas panic disorder patients are more likely to attend to physically threatening words. Even in non-anxious groups, words matching current emotional concerns are differentially attended, whether negative or positive in valence (Reimann & McNally, 1995). Facial stimuli may not therefore have tapped the most appropriate content for GAD, because the major symptom, worry, is thought to be primarily verbal. Indeed the original finding of attentional bias in GAD (MacLeod et al., 1986) used word stimuli, as have some successful GAD attentional training studies (Amir et al., 2009). Against this, some studies *have* used facial expressions as stimuli and found attentional differences between GAD and healthy participants (Ashwin et al, 2012; Bradley et al, 1999; Mogg, Millar & Bradley, 2000; Waters, Mogg, Bradley, & Pine, 2008). This literature is somewhat difficult to interpret, however, as the number of studies are small and they use different measures of attention (e.g., eye movements; Mogg et al, 2000) or different samples (e.g., children; Waters et al, 2008). Another possible explanation for the mixed pattern of findings is that some GAD patients worry about social threats and therefore biased attention to threat-related facial expressions would be a reasonable expectation. However, for many GAD patients, whose worries relate to other dimensions, these stimuli would not necessarily trigger attentional bias. It seems clear that more information is required, not only on attentional mechanisms in GAD, but also on exactly what type of stimuli are associated with triggering these mechanisms.

In light of the findings we present here, it is useful to consider how the field of attentional bias in GAD should seek to move forward in order to decisively resolve the questions raised by our data. In our view, the link between the nature of the stimuli presented and the emotional concerns of the individual, discussed immediately above, is the issue most

in need of being addressed in future studies. We therefore advocate more precise specification of both the form and content of emotional cues that best match emotional concerns in clinical groups such as GAD, as a necessary precursor to revisiting the questions raised in the present experiments, such as the role of attentional engagement and disengagement, as well as of possible differences in this respect between clinical and high trait anxious groups.

The first necessary experimental step therefore involves establishing the type of stimuli that best evoke the primary emotional concerns of the target group (e.g., GAD patients), and determining how these stimuli differ from those in non-clinical groups, including those with high trait anxiety. This would determine whether specific concerns (e.g. about social disapproval) are less frequent or central in GAD patients than in high trait anxious groups, as discussed above. A related question concerns the way in which emotional concerns are typically represented: for example, in patients with social phobias, threats are typically represented in the form of images of oneself performing poorly in social situations, whereas in GAD patients, future threats are more often represented in quasi-verbal form (Hirsch, Hayes, Mathews, Perman, & Borkovec, 2012)

The second step would be to use this information to re-visit the questions addressed in the current experiments: namely, to test whether stimuli known to evoke relevant emotional concerns in clinical groups elicit differential attentional engagement, slowed disengagement, or both, in comparison with non-clinical high trait anxiety and health volunteer groups. An ideal study would include analysis of a wide time-scale of stimulus processing. Given the results of Ellenbogen and Schwartzman (2009), it would be important to assess attentional mechanisms with very fast (subliminal) presentation times up to much longer presentation

times. The ideal study would be powered, a priori, to detect small effects, using either these or other similar relevant data. The sample should compare GAD patients with sociodemographically matched healthy volunteers and with a subclinical participant group additionally matched to patients for their levels of trait-anxiety and depression. A study of this design would be well placed to provide essential new empirical data to guide future developments, not only in the field of attentional processing in anxiety per se, but also in the rapidly growing field concerned with the translational applications of this research.

Perhaps it will transpire that – given stimuli similarly evocative of individual emotional concerns – attentional (and other) effects are actually quite similar across clinical and subclinical anxiety, even if the form or content of the evocative stimuli differ. This finding would suggest that rather than the nature of attentional responding *per se*, it may be the type, intensity, or range of emotional concerns that is particularly characteristic of clinical conditions. Alternatively, it may be that the underlying pattern and direction of attentional processing does indeed differ across groups. Thus it may be the case that cues that are related to central emotional concerns do indeed elicit different degrees (or directions) of attentional engagement, or disengagement, in clinical than in comparison sub-clinical groups. Answering these questions is likely to be difficult, but addressing them is essential to throw light on the cognitive mechanisms that play a causal role in emotional disorders, as well as having obvious implications for identifying profitable targets for treatment.

In summary the two studies presented here suggest GAD patients may show a pattern of attentional biases opposite to that observed using similar methods in sub-clinical samples to date. Specifically, instead of *impaired* disengagement from threatening expressions, the data suggest selective attentional avoidance of threat-related facial expressions in GAD.

These results pose a challenge to assumptions made to date about the generic nature of attentional biases in GAD, indicating that it may be premature to generalize from existing sub-clinical studies of attentional biases. Further work is undoubtedly needed to resolve the questions the present studies raise, and we have attempted to make some concrete suggestions for how best the field can be further advanced. This is particularly important in the context of developing cognitive manipulations (Hertel & Mathews 2011) designed to modify specific biases that may be used in future treatments or treatment adjuncts. It will be important to have a deeper understanding of the nature and type of attentional biases that occur in GAD before we can be confident that reducing specific biases is likely to have clinical benefits. Our data point to a need for further basic research into patterns of attentional orienting in clinical anxiety.

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