

Trait anxiety and impoverished prefrontal control of attention

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Many neurocognitive models of anxiety emphasize the importance of a hyper-responsive threat-detection system centered on the amygdala, with recent accounts incorporating a role for prefrontal mechanisms in regulating attention to threat. Here we investigated whether trait anxiety is associated with a much broader dysregulation of attentional control. Volunteers performed a response-conflict task under conditions that posed high or low demands on attention. High trait-anxious individuals showed reduced prefrontal activity and slower target identification in response to processing competition when the task did not fully occupy attentional resources. The relationship between trait anxiety and prefrontal recruitment remained after controlling for state anxiety. These findings indicate that trait anxiety is linked to impoverished recruitment of prefrontal attentional control mechanisms to inhibit distractor processing even when threat-related stimuli are absent. Notably, this deficit was observed when ongoing task-related demands on attention were low, potentially explaining the day-to-day difficulties in concentration that are associated with clinical anxiety.

National surveys suggest that nearly 20% of the adult US population will meet criteria for one or more anxiety disorders in a 12-month period¹. Anxiety is hugely disruptive to everyday life, placing an emotional burden on both individuals and their families. Consequently, there is a great deal of interest in advancing our understanding of the mechanisms underlying anxiety and developing new approaches for treating it.

Cognitive studies from the 1980s and 1990s suggest that anxiety is characterized by increased attentional capture by threat-related stimuli^{2,3}. The predominant theoretical stance has been that this arises as a result of a hyper-responsive pre-attentive threat-detection system centered on the amygdala⁴. This account has been modified in recent years to incorporate an influence of prefrontal cortical mechanisms in the top-down control of selective attention to threat^{5,6}. However, these models have retained an emphasis on the need for competition between the processing of threat-related and neutral stimuli to be present for anxiety-related cognitive biases to be observed.

Here we test a more radical account; namely that trait anxiety may be characterized by impaired recruitment of prefrontal mechanisms that are critical to the active control of attention when the task at hand does not fully govern the allocation of attention. It is proposed that this deficit does not arise as a result of current or state levels of anxiety, but instead reflects an underlying trait characteristic that influences attentional processing regardless of the presence or absence of threat-related stimuli. This may interact with state anxiety influences on subcortical threat detection mechanisms^{7,8} to account for the threat-related attentional biases associated with clinical anxiety. It may, however, also account for observations that anxious individuals show deficits across a

range of non-affective tasks that place demands on attentional or cognitive control^{9–11}.

Neural models of attentional or cognitive control have implicated the dorsolateral prefrontal cortex (DLPFC) in both the sustained and flexible control of attention. In regards to the former, DLPFC is thought to support the establishment and maintenance of 'attentional sets', with sustained representation of current goals and task rules being used to facilitate task-related performance^{12,13}. DLPFC recruitment is also thought to be important in the active re-allocation of attentional resources in response to trial-by-trial changes in processing competition, with these changes being signaled by input from regions that are thought to monitor the occurrence of such competition, in particular dorsal anterior cingulate cortex (ACC)¹⁴. DLPFC involvement in the online trial-to-trial adjustment of attentional control has been demonstrated through tasks manipulating response conflict, where task-irrelevant stimuli promote a response that is either congruent (low conflict) or incongruent (high conflict) with that required by the current target^{15,16}. Proponents of the load theory of selective attention^{17,18} have argued that active recruitment of attentional control mechanisms is required, in particular, in response to processing competition under conditions of low perceptual load. When the perceptual load or processing requirements of the primary task is high, the task is thought to fully occupy attentional resources, with the processing of distractors being terminated at an early stage before they can compete for further processing, such as response selection and entry into working memory. Under conditions of low perceptual load, however, attentional resources are thought to be only partially occupied, allowing salient distractors to compete for further processing

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unless attentional control is actively recruited to support task-related processing and inhibit distractor-related processing. Consistent with this, groups characterized by weakened attentional control show increased disruption by target-incongruent distractors under such low perceptual-load conditions^{19–21}.

If trait anxiety is associated with impoverished active recruitment of prefrontal control mechanisms to govern the allocation of attention when it is not fully constrained by the task at hand, then we would predict that this would be observed under such conditions: that is, as a function of response conflict under conditions of low, but not high, perceptual load. Although trait anxiety has been demonstrated to be negatively associated with the prefrontal response to threat-related distractors under similar conditions⁸, it is not possible to establish whether disruption to cortical attentional mechanisms is secondary to increased subcortical responsivity to threat-related stimuli or vice versa with the attention-to-threat procedure that was used. A procedure that manipulates the need to exert attentional control in response to changes in processing competition in the absence of threat-related stimuli is required to avoid this problem.

The current study consequently investigated whether trait anxiety is associated with impoverished DLPFC recruitment when faced with response conflict under conditions of low perceptual load in the absence of threat. This was indeed observed, even after the effects of state anxiety were controlled for, supporting the proposal that an underlying trait component of vulnerability to anxiety involves impoverished active recruitment of prefrontal attentional mechanisms to control the allocation of attentional resources when they are not fully occupied by the task in hand. These results are not easily reconcilable with theoretical accounts, such as attentional control theory (ACT)²², a reformulation of processing efficiency theory¹¹, that predict that anxiety-related dysregulation of prefrontal attentional mechanisms will be primarily observed under conditions placing increased demands on processing resources. Instead, our findings suggest that trait anxiety-related deficits in recruitment of prefrontal attentional mechanisms are seen when external demands are low and active trial-to-trial conflict-responsive augmentation of attentional control is required to support task performance. This may help us to understand the day-to-day conditions under which anxious individuals report suffering from lapses in concentration and difficulties in work-related function.

RESULTS

We used a letter-search task to orthogonally manipulate response conflict and perceptual load. On each trial, participants viewed a brief (200 ms) visual display comprising a horizontal string of six letters that were centered at fixation and a task-irrelevant distractor letter that was presented centrally slightly above or below the letter string (see **Fig. 1** and Methods). The participants were asked to identify whether an X or an N was present in the letter string. We used a mixed block/event-related design²³, varying the level of perceptual load for the letter-search task (high or low) across blocks and varying distractor type within blocks on a trial-by-trial basis. In high perceptual-load blocks, the letter string comprised a single target letter (N or X) and five nontarget letters (H, K, M, W and Z) that were arranged pseudo-randomly (see Methods). In low perceptual-load blocks, the letter string comprised six Xs or six Ns, reducing attentional search requirements. Distractors could be the same letter as the target in the current display (response congruent), the target letter that was not present in the current display (response incongruent) or the nontarget letter C (neutral condition). By examining the effect of perceptual load on the neural response to incongruent versus congruent distractors in



Figure 1 Example stimuli. On each trial, a string of six letters was presented at fixation with a slightly larger distractor letter being presented just above or below the center of the string. Participants had to indicate whether the letter string contained an X or an N. The example here comes from the high perceptual-load block, with the letter string comprising six different consonants, only one of which is the target X, and illustrates an incongruent distractor trial. Only the central portion of the display is shown; the remainder of the screen was black.

individuals with varying levels of anxiety (as measured using the Spielberger State Trait Anxiety Inventory (STAI)²⁴, see Methods), it was possible to test the hypothesis that trait anxiety would be associated with reduced DLPFC recruitment to high response-conflict trials under conditions of low, but not high, perceptual load.

fMRI: PFC response to conflict by load and anxiety

We created spherical regions of interest (ROIs, 8-mm radius) for left and right DLPFC and other prefrontal cortical (PFC) regions that have been implicated in attentional control and conflict monitoring (see Methods). In these regions, we examined the neural response to incongruent versus congruent distractor trials under conditions of low versus high perceptual load and the modulation of activity associated with this contrast by trait and state anxiety.

Across volunteers, there was no significant interaction of distractor congruency by load ($P > 0.1$). Consistent with predictions, however, trait anxiety was inversely associated with DLPFC recruitment to incongruent (high conflict) versus congruent (low conflict) distractor trials under conditions of low versus high perceptual load ($x, y, z = -32, 32, 20$; $Z = 2.96$, $P = 0.05$ small volume corrected (svc); $r = -0.67$, $P = 0.002$ uncorrected; **Fig. 2a,b**). In particular, low levels of trait anxiety were associated with greater DLPFC activation to response conflict (incongruent versus congruent distractor trials) under low perceptual load ($r = -0.61$, $P = 0.004$ uncorrected; **Fig. 2c**). This effect was specific to DLPFC. No parallel relationship between state anxiety and differential prefrontal recruitment to incongruent versus congruent distractor trials under low versus high perceptual load was observed either in DLPFC or any of the other prefrontal ROIs ($P > 0.1$). Furthermore, the relationship between DLPFC recruitment and trait anxiety survived the partialling out of variance attributable to individual differences in state anxiety ($r_p = -0.64$, $P = 0.003$ uncorrected). Additional regression analyses also indicated that this relationship was not affected by either gender or age ($P > 0.1$).

fMRI: Testing predictions from processing efficiency models

Analyses at the block level, averaging across distractor trial types, revealed that performance of the high perceptual-load blocks relative to the low perceptual-load blocks was associated with increased activation across a network of frontal and parietal cortical regions (**Fig. 3**). This very characteristic pattern of fronto-parietal activation is typically observed when contrasting any task placing demands on executive or higher cognitive function with another version of the same task that is superficially similar, but less reliant on executive processes^{25–27}. Together with behavioral evidence of slower and less

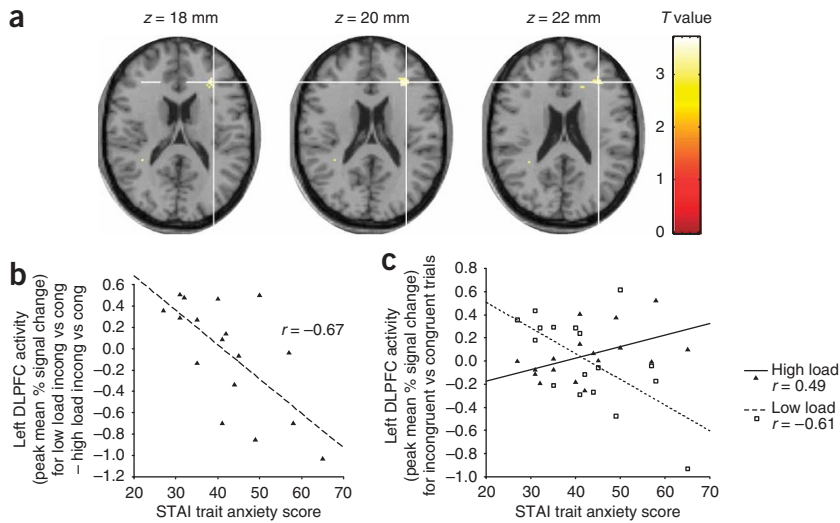


Figure 2 DLPFC activity to incongruent – congruent distractors under low versus high perceptual load against STAI trait anxiety. **(a)** Statistical map of the interaction, overlaid on the SPM 5 canonical single subject T1 image. Peak activation occurred at $-32, 32, 20$ (x, y, z) ($Z = 2.96, P = 0.05$ *svc*). For illustrative purposes, the map is thresholded at $P < 0.1$ *svc* ($P < .005$ uncorrected). Radiological convention is used (left lateralised activations are displayed on the right side as viewed). **(b)** Mean percentage signal change for the interaction of distractor congruency by load (incongruent – congruent distractors under low versus high perceptual load) is plotted against STAI trait anxiety for the peak voxel from **a**. **(c)** This interaction is broken down to show the mean percentage signal change associated with incongruent versus congruent distractors under low load and incongruent versus congruent distractors under high load against STAI trait anxiety for the peak voxel from **a**.

accurate search performance under the high load conditions (see below), this data is consistent with the high perceptual-load version of the task being more demanding of attentional resources than the low perceptual-load version of the task.

'Processing efficiency' accounts such as ACT²² argue that anxiety is associated with reduced 'efficiency' of performance of cognitively demanding tasks, with compensatory effort being expended to avoid actual decrements in effectiveness or accuracy. At a neural level, ACT predicts that high trait-anxious individuals will show increased prefrontal activation to achieve a given level of cognitive task performance, this being most notable when the executive or attentional demands of a task are increased. Consequently, we examined whether elevated levels of trait or state anxiety were associated with greater PFC recruitment (but equivalent task performance) during the high perceptual-load blocks relative to the low perceptual-load blocks.

Anxiety did not affect performance accuracy during either the high or low perceptual-load blocks (see below). Notably, there was also no evidence for differential PFC recruitment across high versus low perceptual-load conditions as a function of anxiety. Specifically, regression analyses showed no significant effect of trait or state anxiety on PFC activity associated with performance of the high versus low perceptual load–task blocks ($P > 0.1$). This held when the DLPFC and other prefrontal ROIs were considered separately and when the DLPFC, ventrolateral PFC (VLPFC) and dorsal ACC ROIs were collapsed to form a single composite prefrontal cortical ROI, with activation across this ROI associated with performance under high versus low perceptual-load conditions being extracted and covaried against individuals' anxiety scores (**Fig. 4a**). It should be noted that the rostral ACC ROI was not included in this composite, as activity in this region often does not track activation changes in dorsal ACC and lateral PFC regions in response to increasing executive processing demands. Additional analyses (data not shown) were conducted to confirm that inclusion of the rostral ACC region did not alter our results.

Behavioral data

Analysis of the behavioral data enabled us to determine whether the impoverished DLPFC recruitment shown by high trait-anxious individuals in response to high conflict (incongruent versus congruent) distractor trials under conditions of low (but not high) perceptual load was accompanied by slowed target detection under these conditions. In addition, we tested an alternate prediction derived from processing

efficiency theories such as ACT, namely that anxiety should primarily slow target detection during the more executive demanding high perceptual-load task blocks, in the absence of effects of anxiety on detection accuracy. The results of the analyses pertaining to this latter prediction are presented first.

Participants were faster to identify the target letter present and made fewer errors in the low perceptual-load blocks than in the high perceptual-load blocks ($t_{16} = 13.41$ and $t_{16} = 8.37$, respectively; $P < 0.001$). This is consistent with previous findings²⁸ and, together with our imaging results described above, suggests that the perceptual-load manipulation was effective, with the high perceptual-load task placing more demands on processing resources than the low perceptual-load task. There was a trend for both state and trait anxiety to be associated with slower target identification across conditions (state: $r = 0.45, P = 0.07$; trait: $r = 0.47, P = 0.06$), but neither measure differentially modulated target identification latencies under high versus low perceptual load ($P > 0.1$). Indeed, the effect of trait anxiety on target identification times was marginally greater for the low load condition (**Fig. 4b**). Similarly, we did not observe an interaction of

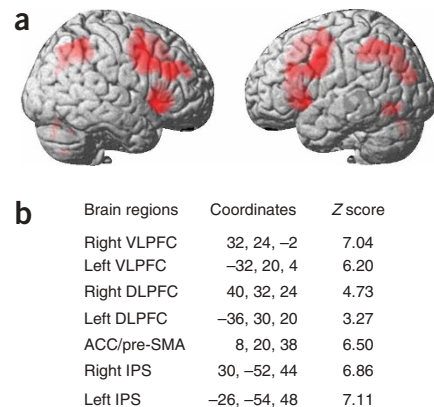
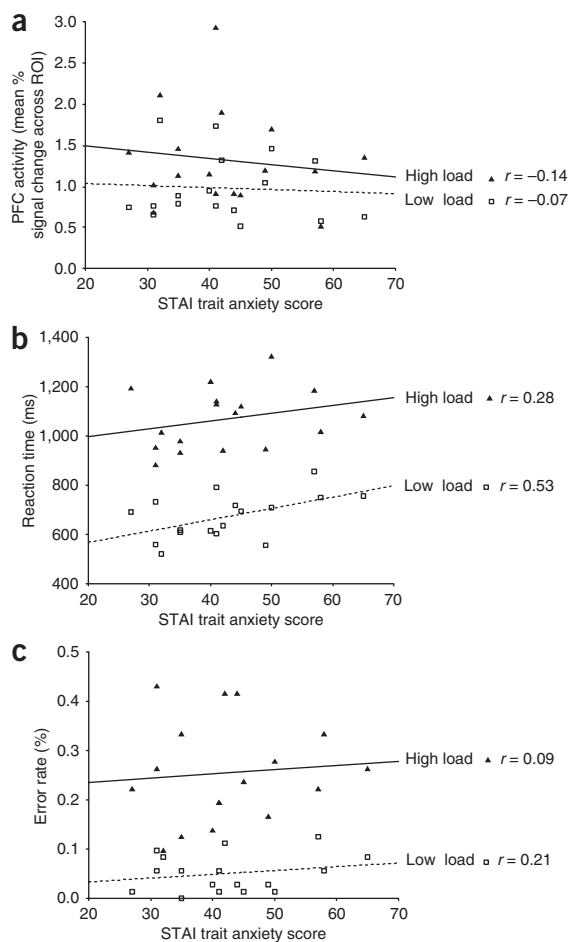


Figure 3 Neural regions showing increased activation under conditions of high versus low perceptual load. **(a)** Significant activations at a whole-brain false-detection rate threshold of $P < 0.05$ are shown, rendered onto the canonical single subject T1 image from SPM5. **(b)** Fronto-parietal activation peaks. Where clusters overlap the a priori-specified prefrontal ROIs, the table gives the peak voxel in the ROIs. IPS, intra parietal sulcus; pre-SMA, pre-supplementary motor area.



perceptual load by anxiety level on target identification times when we used a median split on either the trait or state anxiety subscale to divide participants into high and low anxious groups ($P > 0.1$). There were also no main effects of trait or state anxiety and no interaction of perceptual load by anxiety on target identification error rates ($P > 0.1$; Fig. 4c). This held true both when anxiety scores were entered as continuous covariates and when median splits were used to divide participants into high and low state and trait anxious groups. In other words, anxiety did not modulate task performance accuracy as a function of perceptual load. Contrary to processing efficiency theories,

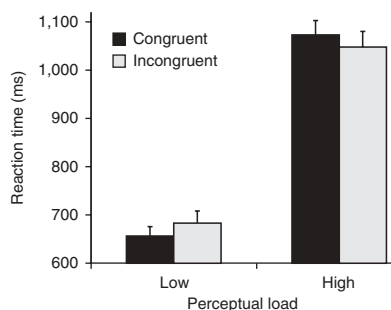


Figure 5 Participant mean reaction times as a function of distractor congruency (congruent, incongruent) and perceptual load (low, high). Error bars represent 1 s.e.m. Participant error rates by condition were 5.39 ± 0.78 (low load, congruent), 5.39 ± 1.46 (low load, incongruent), 25.74 ± 2.84 (high load, congruent) and 23.04 ± 3.30 (high load, incongruent).

Figure 4 PFC activity and target identification reaction times and error rates for the high and low perceptual-load blocks as a function of STAI trait anxiety. (a) PFC activity relative to baseline for high and low perceptual-load blocks was averaged across all voxels contained in the DLPFC, VLPFC and dorsal ACC ROIs. By this means, a single composite PFC activity score associated with each block type was extracted on an individual-by-individual basis and plotted against participant trait anxiety. (b) Participants' mean reaction times (correct trials only) for the high and low perceptual-load blocks are plotted against trait anxiety. (c) Participants' error rates for the high and low perceptual-load blocks are plotted against trait anxiety.

there was also no evidence for trait or state anxiety being differentially associated with reaction time slowing for the more attentionally demanding version of the task.

Turning to effects of response conflict, across participants, there were no significant effects of distractor congruency or distractor congruency by perceptual load on reaction times ($P > 0.1$). However, planned comparisons revealed that target identification was faster for trials with congruent distractors than for those with incongruent distractors under low perceptual load ($t_{16} = 2.1$, $P < 0.05$), with no parallel congruency effect being observed under high perceptual load ($t_{16} < 1$, $P > 0.1$) (Fig. 5).

When entered as continuous measures into analyses of covariance, neither state nor trait anxiety significantly interacted with load or distractor congruency to influence target identification times ($P > 0.1$). However, planned comparisons revealed that when participants were split into high and low anxious groups (using a median split on trait anxiety scores), high trait-anxious participants were slower to identify targets in the presence of incongruent versus congruent distractors under low perceptual load ($t_7 = 2.14$, $P < 0.05$). Low trait-anxious participants showed no such effect ($t_8 < 1$, $P > 0.1$), and neither group showed slowing for incongruent versus congruent distractor trials under conditions of high perceptual load ($P > 0.1$). A parallel pattern was observed when participants were divided into high and low anxious groups using a median split on state anxiety scores.

As a result of the non-normal distribution of target identification error rates when broken down by load and distractor type, we used nonparametric tests (Wilcoxon signed rank) to examine the effects of distractor congruency under high or low perceptual load for high and low anxious participants. The only effect revealed by these tests was a trend for low trait-anxious participants to be more accurate on trials with incongruent as opposed to congruent distractors under conditions of high perceptual load, which did not reach significance ($Z = 1.88$, $P = 0.06$).

As with the imaging data presented above, neither gender nor age significantly modulated any of the reported results ($P > 0.1$, analyses restricted to data for which parametric tests were possible).

DISCUSSION

The data reported here suggest that trait anxiety is associated with deficient recruitment of DLPFC mechanisms that are used to augment attentional control in response to processing conflict. Notably, this was only observed under conditions where the allocation of attentional resources is not fully governed by the primary task and where maintenance of task-oriented processing may require trial-by-trial modulation of attentional control as a function of response conflict. This impoverished recruitment of prefrontal attentional control mechanisms was observed using a purely cognitive task in the absence of threat-related stimuli. It should also be noted that this deficient recruitment was primarily associated with trait and not state anxiety, suggesting that it reflects a processing style or deficit that is associated with vulnerability to anxiety rather than a symptomatic outcome of altered mood state.

The behavioral data indicate that high trait-anxious individuals were slower to identify targets in the presence of incongruent (high response conflict) distractors under conditions of low perceptual load. This is also consistent with trait anxiety being associated with impoverished recruitment of the attentional control mechanisms required to prevent these distractors from competing for further processing resources under conditions where attentional resources are not entirely directed toward task-related processing. These data parallel previously reported findings showing increased effects of response competition under low perceptual load for individuals and groups characterized by impoverished attentional control, including young and elderly populations and individuals scoring highly on the cognitive failures questionnaire^{19–21}.

The results reported here support the proposition that trait anxiety is associated with impaired trial-by-trial recruitment of DLPFC attentional mechanisms in response to processing competition under conditions in which the primary task does not fully occupy attentional resources. In contrast, they are not so easily reconciled with theoretical accounts such as ACT²², which propose that high trait-anxious individuals will show decreased efficiency of prefrontal attentional mechanisms as demands on processing resources increase. Our finding that, across distractor trial types, neither trait nor state anxiety was differentially associated with increased prefrontal activity or longer target identification times during the more attentionally demanding high perceptual load–task blocks relative to the low perceptual load–task blocks is also problematic for these alternate efficiency-based accounts.

At a broad level of analysis, the account put forward here shares certain commonalities with ACT in suggesting that anxious individuals are characterized by deficient attentional control, particularly when inhibition of distractor processing is required. Contrary to ACT, however, we propose that this deficit is associated with reduced, rather than increased, DLPFC recruitment. In addition, we argue that the primary determinant for whether this deficit is observed may be the need for trial-to-trial alterations in attentional control when attentional resources are not fully occupied by the task at hand. This contrasts with the prediction from ACT that anxiety-related deficits will emerge as a task becomes more attentionally or executively demanding.

Our results raise a number of issues concerning the nature of the deficit in attentional control associated with trait anxiety and the probable effect of other empirical manipulations. First, there was no significant relationship between trait or state anxiety and dorsal ACC activity. A possible interpretation of this finding is that the attentional impairment associated with high trait anxiety does not involve impoverished detection of response conflict but rather involves impaired implementation of trial-to-trial adjustments of attentional control, the latter being thought to be more dependent on DLPFC than on dorsal ACC function^{14,15}. It should be noted, however, that our experiment did not manipulate conflict expectancy. Such manipulations are particularly effective in dissociating DLPFC and ACC activity^{5,29} and might potentially reveal a trait anxiety-related impairment in dorsal ACC-mediated conflict-detection in addition to the DLPFC deficit that we observed.

A second issue raised by our findings pertains to the relationship between attentional control and working memory. It has been argued that working memory capacity reflects individual differences in the ability to control attention, particularly in conditions where there is interference or distraction³⁰. Manipulations that occupy working memory resources can increase distractor interference in attentional tasks, although the circumstances under which these increases in interference effects are observed are still the subject of debate^{31–33}. One interpretation of these findings is that such working memory

manipulations may disrupt recruitment of the prefrontal mechanisms that are needed for the active re-allocation of attentional resources in response to trial-by-trial fluctuations in processing competition. Consistent with this, working memory is thought to recruit the same DLPFC regions implicated here in the active attentional regulation of response conflict under conditions of low perceptual load^{34,35}. An interesting question is whether high trait-anxious individuals would be expected to show greater or lesser effects of working memory–load manipulations than low trait-anxious individuals. It has been shown that individuals with low working-memory spans are less affected by such manipulations, possibly reflecting a failure to actively recruit PFC mechanisms in the first place³⁶, leading to the prediction that high trait-anxious individuals would be similarly less affected. However, a number of findings from the anxiety behavioral literature lead to the reverse prediction³⁷, calling for future empirical work on this issue.

Our data are of potential clinical relevance, suggesting that one of the predisposing factors to clinical anxiety may be a processing style or deficit that is characterized by the impoverished recruitment of prefrontal attentional control mechanisms in response to trial-by-trial changes in processing competition under conditions in which attentional focus is not fully determined by the task at hand. Selective attention under load models has proposed that attentional resources are not fully occupied under low perceptual-load conditions and active attentional control is required to inhibit salient distractors from competing for further processing, including response selection^{17,18}. These conditions are arguably akin to day to day conditions in which there are breaks in the demands of our work and our attention can wander. Being able to avoid distraction by task-irrelevant stimuli under such conditions is often necessary and clinically anxious individuals are anecdotally reported to struggle with this. Our current findings suggest that impoverished recruitment of prefrontal control mechanisms may contribute to these difficulties.

Our finding that high trait-anxious individuals showed as strong prefrontal recruitment and as accurate performance as low trait-anxious individuals during the more executively demanding high perceptual load–task blocks is potentially of importance. Under these conditions, high trait-anxious volunteers also resembled low trait-anxious volunteers in not showing any slowing on high response-conflict trials. This supports the proposition that trait anxiety may not be associated with a generic impairment in recruitment of prefrontal control mechanisms but, instead, may be primarily associated with a deficit in the active recruitment of these mechanisms when performance of the main task does not require attentional resources to continually be fully allocated to goal-oriented processing. In particular, problems may arise when salient stimuli compete to gain processing resources under such conditions. The suggestion that trait anxiety may be especially associated with a weakness in using information about changes in the levels of processing competition to regulate attentional control on a moment-to-moment basis is consistent with our previous findings regarding attentional control over threat⁵, but extends to cases in which the processing competition in question does not arise as a result of the threat-relatedness of distractor stimuli. One possibility is that this weakness may be a processing style rather than a processing deficit and that it may be possible to train high trait anxious individuals to maintain attentional focus more effectively under conditions of low external demands. Arguably, this could possibly relate to the apparent success of techniques such as mindfulness training. Clearly this is an important issue for further investigation.

There are both similarities and differences in the symptomatology experienced by clinically anxious individuals and other individuals

characterized by impoverished attentional control, such as individuals with attention deficit hyperactivity disorder and those suffering attentional problems subsequent to traumatic brain injury. Although clinically anxious individuals resemble these other groups in experiencing problems with maintaining concentration and staying focused on the task at hand, they also report symptomatology indicating extreme fear of particular objects or situations, a focus on negative concerns and worries, and enhanced attention to threat-related information. Equivalent levels of such symptoms are not consistently reported by individuals with attention deficit hyperactivity disorder or by patients with prefrontal damage as a result of traumatic brain injury, although there is some suggestion that symptoms of anxiety may be more prevalent in these groups than in the population at large^{38,39}. This suggests that impairment of prefrontal attentional control mechanisms alone is unlikely to be sufficient to lead to clinical anxiety.

We have previously reported that elevated state anxiety is associated with increased amygdala responsiveness to threat-related stimuli^{7,8}. Clinically anxious individuals typically show both high trait and high state anxiety and are therefore likely to be characterized by both impoverished active recruitment of prefrontal attentional control mechanisms and exaggerated amygdala responsiveness to threat-related stimuli. This double impact on the mechanisms involved in selective attention to threat may explain anxious individuals' particular problems with regulating attention to external threat-related stimuli and internal worries or concerns. State anxiety reflects a combination of both trait anxiety and current environmental influences on mood state. It is therefore possible that trait factors contributing to vulnerability to anxiety affect the function of the amygdala or related areas, such as the bed nucleus of the stria terminalis⁴⁰, as well as prefrontal function. It should be noted that we are not arguing against this, and indeed such factors may help to differentiate clinically anxious individuals from other groups with prefrontal dysregulation. Instead, we are emphasizing the need to recognize that, beyond any potential abnormality in threat-related processing, trait anxiety is also characterized by impoverished recruitment of the DLPFC mechanisms that are implicated in the active control of attention in response to changes in processing competition when attentional focus is not fully determined by the task at hand. This deficit in recruitment of the prefrontal mechanisms supporting attentional control may contribute not only to threat-related attentional biases, but may also underlie the more general day-to-day problems in concentration and work-related cognitive function that characterize clinical anxiety.

METHODS

Participants. 17 participants (seven females and ten males, all right-handed, aged 19–48 years, mean age = 27 years) performed a letter-search task while functional magnetic resonance imaging (fMRI) data were acquired. The study was approved by the Cambridgeshire Local Research Ethics Committee and was carried out in compliance with their guidelines. Written informed consent was obtained from all participants. Individuals with a history of inpatient psychiatric care, neurological disease or head injury were excluded, as were individuals on medication for anxiety or depression. Prior to the fMRI session, participants completed the STAI²⁴. Participants' state anxiety scores ranged from 20 to 53 (mean = 35, s.d. = 8), and their trait anxiety scores ranged from 27 to 65 (mean = 43, s.d. = 11). These scores are comparable to the published norms for this age group (state: mean = 36, s.d. = 10; trait: mean = 36, s.d. = 10)²⁴.

Stimuli and procedure. Visual stimuli were back projected onto a translucent screen positioned behind the bore of the magnet and were viewed via an angled mirror placed above the participant's head. The letter-search task used was based on previously reported experiments in the selective attention literature^{8,17,28}. Response conflict and perceptual load were orthogonally manipulated. On each trial, fixation was followed by the presentation for

200 ms of a horizontal string of six letters, centered at fixation, with a task-irrelevant distractor letter presented centrally slightly above or below the letter string (Fig. 1). The letters at each end of the string were at 1.4° eccentricity. Each letter in the string subtended a visual angle of 0.4° vertically × 0.4° horizontally. The distractor letter was presented at 0.7° eccentricity above or below fixation and was slightly larger than the letters in the main string, subtending a visual angle of 0.5° vertically × 0.5° horizontally. Participants were required to indicate whether the letter string contained an X or an N.

There were three imaging-acquisition runs, each comprising 12 blocks of four trials. In half of the blocks, the high perceptual-load condition, the string comprised a single target letter (N or X) and five nontarget letters (H, K, M, W and Z) arranged in a pseudo-random order (see below). In the other half of the blocks, the low perceptual-load condition, the letter string comprised six Xs or six Ns, reducing attentional search requirements. There was a 2-s interval between blocks. Within blocks, the interstimulus interval was randomly jittered using an exponential function with a mean of 4.5 s and a minimum of 3 s. We used a mixed block/event-related design²³, varying the level of perceptual load for the letter-search task (high or low) across blocks and varying the nature of the distractor within blocks on a trial-by-trial basis. Distractors could be the same letter as the target in the current display (response congruent; for example, current target = X and distractor = X), the target letter that was not present in the current display (response incongruent; for example, current target = X and distractor = N) or the nontarget letter C (neutral condition).

This task used broadly the same perceptual load manipulation as in two previous studies^{8,28} but with a number of important differences. Neither of these prior studies used a response-conflict manipulation; instead, both used face distractors, with one study⁸ including faces with threat-related expressions. Here, face stimuli were avoided, as these are known to activate the amygdala even when expressions are neutral in valence. In addition, we did not allow the target to appear in either of the most eccentric letter string positions (position 1 or 6) in the high perceptual-load conditions. These changes brought the mean error rates in the high perceptual-load condition down (from 34% to 24%) and led to performance accuracy (averaged across distractor types) being equated between high and low anxious volunteers.

fMRI data acquisition. Blood oxygenation level-dependent contrast functional images were acquired with echo-planar T2*-weighted (EPI) imaging using a Siemens Tim Trio 3T MR system with a 12-channel head coil. Each image volume consisted of 32 sequential 3-mm thick slices (interslice gap, 0.75 mm; inplane resolution, 3 × 3 mm; field of view, 192 × 192 mm; matrix size, 64 × 64; flip angle, 78°; echo time, 30 ms; bandwidth, 2,232 Hz; repetition time, 2.0 s). Slice acquisition was transverse oblique, angled to avoid the eyeballs and covered the whole brain. Data were acquired in three scanning runs of 5.5 min each. The first eight volumes of each run were discarded to allow for T1 equilibration effects.

fMRI data analysis. Data were analyzed using statistical parametric mapping (SPM) version 5 software (University College London). We conducted standard preprocessing, including realignment, slice timing correction and normalization of each participant's EPI data to the Montreal Neurological Institute International Consortium for Brain Mapping template. Images were resampled into this space with 2-mm isotropic voxels and smoothed with a Gaussian kernel of 10-mm full-width at half-maximum. Trials were modeled by step functions that were convolved with the canonical hemodynamic response function to form regressors. Realignment parameters for each session were included to account for residual movement-related variance. A high-pass filter of 128 s was used to remove low-frequency noise.

A random-effects analysis was used to analyze data at a group level, with modulations by anxiety being assessed by regression against state- and trait-anxiety scores from the STAI. Functionally defined ROIs for DLPFC, VLPFC and dorsal, and rostral ACC were used to constrain these analyses. Lateral prefrontal cortex (LPFC) and dorsal ACC activation has been associated with increasing executive or processing demands across a wide-range of cognitive tasks²⁶. LPFC regions have primarily been implicated in both sustained and transitory adjustments of attentional control. Dorsal ACC activation is thought to signal detection of processing competition and error commission^{12–15}. When processing competition arises as a result of the emotional valence of distractor

stimuli, activation of a more rostral ACC region is often observed^{5,8}. For completeness, all of these regions were included in the current analyses. To avoid *post hoc* bias, we defined the central points and spatial extent of these ROIs in accordance with the procedure adopted in two earlier studies^{5,8}. 8-mm radius spheres were used for all ROIs. The central coordinates for the LPFC ROIs were derived from reviews of tasks manipulating attentional control, including response-conflict protocols^{26,41}. Consistent with these reviews, the DLPFC ROIs (central coordinates: $\pm 34, 36, 24$) included parts of the middle frontal gyrus and inferior frontal sulcus, whereas the VLPFC ROIs (central coordinates: $\pm 38, 20, 0$) included parts of the frontal operculum and anterior insula. The central coordinates for the dorsal ACC ROI ($4, 14, 36$) and rostral ACC ROI ($-2, 44, 20$) were derived from a meta-analysis of studies examining response conflict and emotional conflict, respectively⁴². Here, the specific coordinates were provided directly by G. Bush (Massachusetts General Hospital) and converted from Talairach to MNI space.

We also conducted analyses to explore the effects of anxiety on activity in the amygdala and other regions outside of our prefrontal ROIs (Supplementary Note online). For both the fMRI and behavioral analyses, one-tailed tests were used for specific a priori predictions; otherwise, two-tailed tests were applied. All activations are reported using MNI coordinates.

Note: Supplementary information is available on the Nature Neuroscience website.

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