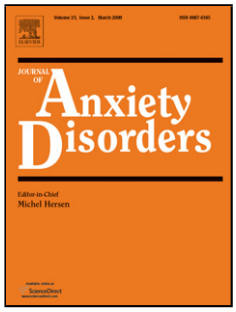

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Changes in neural activation underlying attention processing of emotional stimuli following treatment with positive search training in anxious children

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Highlights

Assessed neural correlates of treatment outcome following positive search training

Found pre- to post-treatment reductions in anxiety symptoms and neural reactivity to emotional faces within a broad neural network

Neural reactivity to the threat-bias contrast reduced from pre- to post-treatment in the mid/posterior cingulate cortex

Abstract

Prior research indicates that positive search training (PST) may be a promising home-based computerised treatment for childhood anxiety disorders. It explicitly trains anxious individuals in adaptive, goal-directed attention-search strategies to search for positive and calm information and ignore goal-irrelevant negative cues. Although PST reduces anxiety symptoms, its neural effects are unknown. The main aim of this study was to examine changes in neural activation associated with changes in attention processing of positive and negative stimuli from pre- to post-treatment with PST in children with anxiety disorders. Children's neural activation was assessed with functional magnetic resonance imaging (*f*MRI) during a visual-probe task indexing attention allocation to threat-neutral and positive-neutral pairs. Results showed pre- to post-treatment reductions in anxiety symptoms and neural reactivity to emotional faces (angry and happy faces, relative to neutral faces) within a broad neural network linking frontal, temporal, parietal and occipital regions. Changes in neural reactivity were highly inter-correlated across regions. Neural reactivity to the threat-bias contrast reduced from pre- to post-treatment in the mid/posterior cingulate cortex. Results are considered in relation to prior research linking anxiety disorders and treatment effects with functioning of a broad limbic-cortical network involved in emotion reactivity and regulation, and integrative functions linking emotion, memory, sensory and motor processes and attention control.

Keywords: attention bias; anxiety; children; fMRI; attention bias modification

Anxiety disorders are prevalent and debilitating psychiatric conditions characterized by excessive worry, hypervigilance, and apprehension about future events (American Psychiatric Association, 2000). They are associated with life impairment (Ezpeleta et al. 2001) and predict later psychopathology and poor outcomes (Kessler et al. 2008; Pine et al. 1998). Cognitive-behavioural therapy (CBT) is a well-established psychological treatment for youth anxiety disorders, yet only about 60% of children achieve post-treatment remission of whom about one half relapse over time (Ginsburg et al., 2014; James et al., 2013). This highlights the need for novel treatment approaches that target underlying mechanisms of youth anxiety disorders and a greater understanding of the brain circuitry changes associated with their therapeutic effects (Sanislow et al., 2010).

Neuroimaging evidence suggests that childhood anxiety disorders relate to dysfunction of a neural 'threat circuit' involving the amygdala and prefrontal cortex (PFC), (e.g., Monk et al., 2006, 2008; see review by Blackford & Pine, 2012), as anxious children show increased amygdala and PFC activation on emotion-cognitive tasks (see meta-analysis by Mana et al., 2010). Key functions of the amygdala are to detect motivationally salient stimuli, such as threat cues, and to modulate activity in cortical regions to prioritise their processing (Pessoa & Adolphs, 2010). The PFC modulates amygdala response to threat cues and, together with other regions such as the insula, temporal and parietal cortex, supports subjective emotional experience, working memory, attention control and goal-directed activity (Corbetta & Shulman, 2002; LeDoux & Pine, 2016; Miller & Cohen, 2001). Research in adult anxiety disorders, such as generalised anxiety disorder (GAD) and social anxiety disorder (SAD), indicates abnormal reactivity to emotional stimuli in a widespread neural network including not only the amygdala, insula, anterior cingulate, and medial and dorsolateral PFC (e.g., reviews by Bruhl et al., 2014; Greco & Liberzon, 2016), but also temporal, parietal and occipital regions, including the posterior cingulate, precuneus and cuneus (Bruhl et al., 2014;

Fonzo et al., 2014). This limbic-cortical network is implicated in emotion reactivity, regulation and experience, self-related processing, integrative functions linking emotion, memory, sensory and motor processes, and attention control (Bruhl et al., 2014; LeDoux & Pine, 2016).

The modification of attention to threat stimuli, which is widely known as *attention bias modification* (ABM) training, has received considerable attention as a novel therapeutic strategy in the past decade (see MacLeod & Clarke, 2015; Mogg & Bradley, 2016, for reviews). Most ABM studies have focused on implicitly training attention orienting away from threat stimuli (i.e., *threat avoidance training*). Although several studies report clinical efficacy of threat-avoidance training (e.g., Bar-Haim et al., 2011; White et al., 2017), recent reviews indicate inconsistent effects on anxiety and attention biases to threat, and poor efficacy outside laboratory settings (Cristea et al., 2015; MacLeod & Clarke, 2015; Mogg & Bradley, 2016).

Positive search training (PST) is a form of attention regulation training that involves training explicit, goal-directed attention towards positive/adaptive stimuli while inhibiting goal-irrelevant threat distractors (Dandeneau et al., 2007; Waters et al., 2013; 2015; 2016). This approach employs repeated practice of a visual search task, which presents arrays of pictures that contain positive and neutral target stimuli embedded among threat distractor stimuli. Participants are required to search for ‘good’ and ‘calm’ targets among negative distractors which encourages stimulus appraisal differentiation based on perceptual and categorical features and inhibition of attention to negative distractors. Arrays are presented in grouped and spaced formats to encourage attention flexibility and the number of targets displayed and required to be found within each array varies across blocks to promote greater cognitive control. Verbalisation of explicit attention-search strategies (e.g., “look for good”, “look for calm”) enhances memory consolidation of the search strategies to promote generalisation and maintenance. Three studies to date have confirmed that home-delivered PST is effective in reducing anxiety symptoms in anxious children (Waters et al., 2013; 2015; 2016). The

therapeutic effect of PST is posited to target multiple cognitive regulatory processes to strengthen the control of attention to goal-relevant stimuli and inhibit the processing of goal-irrelevant stimuli (Mogg & Bradley, 2016; Waters & Craske, 2016). Thus, it is informative to examine whether PST is modifying widespread neural network functioning underpinning emotion reactivity and regulation when processing emotional cues (Bruhl et al., 2014).

Neuroimaging research on the neural effects of psychotherapy and novel therapeutics for anxiety disorders in children specifically is sparse. Maslowsky et al. (2010) examined effects of CBT and medication on neural reactivity to angry faces in youth with GAD, who were assessed using functional magnetic resonance imaging (fMRI). The study used fMRI with an emotional-face visual-probe task, completed before and after treatment (n=14, half received CBT, half received fluoxetine). Region of interest (ROI) analyses showed increased right ventrolateral PFC activation by threat cues following both treatments.

ABM-threat-avoidance training with adults has mixed effects on *f*MRI measures of emotion reactivity (see review by Wiers & Wiers, 2016). For example, in socially anxious adults, one session of ABM-threat-avoidance training decreased reactivity to emotional faces in the amygdala and insula, and increased reactivity in ventromedial PFC regions (Taylor et al., 2013). Multi-session ABM-threat-avoidance training and CBT had differing neural effects in adults with SAD: CBT decreased reactivity to emotional and neutral faces in the dorsolateral PFC, anterior cingulate, caudate, putamen and cerebellum; whereas ABM increased reactivity in superior temporal, parietal (postcentral gyrus), putamen and supplementary motor area (Mansson et al., 2013). Multi-session ABM-threat-avoidance training increased amygdala reactivity in socially anxious adults to the threat-bias contrast on the visual-probe task which indexes attention bias to threat, described later (Britton et al., 2015). In another study of non-anxious adults, single-session ABM-threat-avoidance training modified neural reactivity on an emotion-attention contrast in frontal (dorsolateral and ventrolateral PFC, anterior cingulate)

regions, but not the amygdala (Browning et al., 2010). Comparison of results across studies is complicated by variation in methods (e.g., differing fMRI assessment tasks and contrasts, ROIs, anxious/non-anxious samples, and amount of ABM training) and a paucity of studies of neural correlates of treatment outcomes following other forms of attention control training.

To date, no studies have examined the modification of neural reactivity to emotional stimuli as a function of PST. Thus, as this is the first study to address this question, we hypothesised based on prior research (e.g., Bruhl et al., 2014), that anxious children trained via PST (to strengthen multiple cognitive regulation processes by attending to positive and calm stimuli and ignoring threat distractors) would show modification of neural reactivity to emotional stimuli (angry and happy faces) from pre- to post-treatment in an extended neural network, involving amygdala, frontal, temporal, parietal and occipital regions associated with change in cognitive control. Secondary analyses examined correlations between measures of neural reactivity to emotional stimuli, behavioural (RT-based) measures of attention bias for emotional stimuli, and anxiety symptoms. We hypothesised that changes in anxiety symptoms would relate to changes in neural reactivity to emotional stimuli, and that behavioural and neural indices of attention bias to threat would be inter-related.

Method

Participants

Seventeen children with anxiety disorders were recruited for this study based on established referral pathways including advertisements in local newspapers, school newsletters and radio as well as referrals from local health and school community professionals. However, the final sample consisted of 15 anxious children (8 females; *M* age= 10.7, *SD* = 0.3); two children were excluded because they did not complete the post-intervention scan. Table 1 contains descriptive characteristics of the 15 children with usable data.

Materials

Diagnostic status. The Anxiety Disorders Interview Schedule for DSM-IV, Parent and Child Interviews (ADIS-IV-C/P; Silverman & Albano, 1996) were used to assess children's diagnostic status. Children received diagnoses that were assigned a clinician severity rating (CSR) of four or higher (scale 0-8). The diagnosis with the highest CSR was deemed the principal (i.e., most severe) diagnosis. The ADIS-IV-C/P was administered over the telephone with parents (all mothers) and face-to-face with children. The telephone version of the ADIS-IV-C/P is as reliable as face-to-face administration (Lyneham & Rapee, 2005) and has excellent reliability and strong concurrent validity with other measures of childhood anxiety (Silverman, Saavedra & Pina, 2001; Wood, Piacentini, Bergman, McCracken & Barrios, 2002). The ADIS-IV-C/P interviews were administered by four graduate clinical students trained by clinical psychologists experienced in anxiety assessment and ADIS-IV-C/P administration. Independent assessors were blind to the assessment occasion and children's diagnostic profile at previous assessment. The outcomes of the two interviews were reviewed with the project team (blinded to child identifying details, assessment occasion and prior diagnostic profile) during weekly consensus meetings to arrive at consensus diagnoses and CSRs. Twenty percent of interviews were digitally recorded and coded by an independent rater blinded to children's diagnostic status. Inter-rater reliability showed excellent agreement (e.g., principal diagnosis $\kappa = .96$; second diagnosis $\kappa = 0.88$; third diagnosis $\kappa = 0.92$).

Global functioning. The Children's Global Assessment Scale (CGAS; Shaffer et al., 1983) is a 0-100 clinician-rated measure of change in severity of overall disturbance in functioning (Shaffer et al., 1983). The CGAS has been shown to be reliable between raters and across time and has demonstrated both discriminant and concurrent validity (Dyrborg et al., 2000; Rey, Starling, Wever, Dossetor, & Plapp, 1995; Shaffer et al., 1983). This measure was completed by independent assessors at pre- and post-treatment and reviewed in consensus meetings.

Symptoms. The Spence Children's Anxiety Scale, Parent and Child version (SCAS-P & SCAS-C; Spence, 1998) are 39-item (parent report) and 45-item (child self-report; 6 positive filler items) questionnaires that both contain 4-point response scales (0 = never true to 3 = always true), yield total scores reflecting symptom severity, and possess sound psychometric properties. Mean SCAS-P total scores of 14.2 and 31.8, and mean SCAS-C total scores of 18.8 and 32.2 are reported for non-clinical and clinically-anxious children, respectively (Nauta et al., 2004; Spence, 1998). The SCAS-P and SCAS-C were completed at pre- and post-treatment.

The Short Mood and Feelings Questionnaire, Parent and Child versions (SMFQ-P and SMFQ-C; Angold, Costello, & Messer, 1995) were used to assess children's depressive symptoms. Both versions of the SMFQ comprise 13 items which ask the respondent to rate the child's feelings and actions (0 = not true; 1 = sometimes true; 2 = always true) over the preceding two-week period. A score of 8 or more is considered significant (Angold et al., 1995). The SMFQ-P and SMFQ-C were completed at pre- and post-treatment.

Visual probe task

A visual probe task was used to assess behavioural (RT) and neural responses to threat and positive cues. Each trial presented a pair of faces (angry-neutral, happy-neutral, or neutral-neutral) side-by-side for 500 ms. The probe (an asterisk) replaced one of the faces, and children were required to press a 'left' or 'right' key to indicate the location of the probe. On trials presenting an emotional-neutral face pair (angry-neutral or happy-neutral), the probe was presented either in the same spatial location after the emotional face ('congruent' trials; i.e., probe location is congruent with location of emotional face) or after the neutral face ('incongruent' trials; i.e., probe location is incongruent with location of emotional face). This resulted in five trial types: angry-incongruent, angry-congruent, happy-congruent, happy-incongruent, and neutral-neutral trials presented in intermixed random order. The task included

four blocks of 72 trials (24 trials per angry-neutral, happy-neutral, and neutral-neutral condition), yielding a total of 288 trials (96 trials in total per condition).

Scanning parameters

The visual probe task was completed in a 3 Tesla Siemens Trio MRI scanner with 32-channel head coil. Gradient-echo echo-planar images (EPI) were acquired with 37 axial slices from the top of the vertex covering most of the brain with parameters: 3.0 x 3.0 voxels at 3.0 mm resolution, 3 mm slice thickness with 10% inter-slice gap, repetition time (TR): 2.3 sec, echo time (TE): 30 ms, flip angle (FA): 85^{o}. For each participant, 436 volumes were obtained (4 runs x 109 scans each). High-resolution anatomical images were acquired using 3D T1-weighted image and 0.9x0.9mm voxel resolution. Data pre-processing and analysis was performed with SPM8 (The Wellcome Trust Center for Neuroimaging, London, UK). Slice timing correction was used first to correct images for inter-slice timing differences (Sladky et al., 2011).

Treatment program: Positive search training

The treatment was identical to that used by Waters et al. (2015; 2016). Briefly, the intervention was programmed in Java and completed on a PC with headphones and a microphone in the family home. Picture stimuli depicted a wide range of emotionally pleasant, negative and neutral stimuli to form a database of over 375 pictures. The program involves 12 treatment sessions, each including nine blocks of trials (four blocks of 20 trials, four blocks of 26 trials, one block of 40 trials; total 224 trials). Each trial consisted of either a 3x3 or 4x4 picture array containing unpleasant distractor images (e.g., house on fire, person in hospital) and between one and three positive targets, which are either ‘good’ targets (e.g., happy children; cute animals) or ‘calm’ targets (e.g., a vase; a book). Half the trials in each block were 3x3 picture arrays, the other half were 4x4 arrays; and in half the trials, pictures were closely

grouped together and in the other half they were spaced apart to promote search over a varying visual field. Trials were randomly ordered within each block.

At the start of the program, children received instructions that the program was designed to help them learn important skills, namely, to 'look for good', to 'look for calm', to 'use both options' and to 'never give up' doing this. Children were informed that they would see picture panels showing a mixture of good, calm and unpleasant pictures, and to use the mouse to click on a good or calm picture. Feedback (pleasant tone) was given on each trial for correct detection of positive and calm cues, and then the next trial was presented. Children completed six practice trials. Prior to each block, children received instructions about which type of and how many target pictures (i.e., good or calm) would be shown in each picture panel and that they were to click on one target. Then each attention-search strategy was presented over the headphones and a jingle and children repeated the jingle out loud. Attention-search goals (e.g., look for good or calm) varied between blocks of trials to encourage cognitive flexibility. In the final block of 40 trials, children received instructions to 'use both options' of 'look for good' and 'look for calm' by clicking on one good and one calm target in each picture panel. They were told that there would be more picture panels in this final game because it was important to 'never give up' using these attention-search strategies even when circumstances are challenging.

Children completed one of three short intermission games after blocks two and six in each session. The three computer games involved (i) popping balloons which triggered one of the four jingles to play over the headphones, (ii) clicking on happy face icons among various emotional face icons as they cascaded down the screen; or (iii) remembering between two and four happy cartoon faces and then clicking on the correct faces when they reappeared amongst distracting faces.

After each session, children said out loud what they were learning and answered four treatment-rating questions. RT and number of mouse clicks to correctly detect targets for all 224 trials, plus the treatment ratings and verbalization data were recorded in output files and automatically sent back to the project coordinator (for further task details, see Waters et al., 2015). This confirmed that each participant completed the 12 PST sessions.

Procedures

All procedures were approved by the Griffith University and The University of Queensland Human Research Ethics Committees. Parents provided written consent and participants provided written assent. Following diagnostic assessments conducted at Griffith University and reviewed in clinical supervision, participants attended the *f*MRI scanning session at the Queensland Brain Institute at the University of Queensland where they completed symptom questionnaires and a short practice visual probe task outside the scanner, they were settled in the scanner and completed the visual probe task. Within the following week, the treatment package was mailed to them at home, a telephone set-up call was conducted between a parent and our research coordinator, and children completed the treatment sessions over the following three weeks. After treatment completion, the diagnostic assessment was completed by an independent clinician blind to time-point and the *f*MRI assessment repeated as per the pre-treatment procedure. The mean time between pre- and post-treatment assessments was 6.1 weeks.

Data analysis

Treatment outcome data. Treatment outcome data were analysed using descriptive statistics and *t*-tests and included the percentage of children free of their principal and all diagnoses as well as change in symptom measures from pre- to post-treatment.

Behavioural data. Incorrect trials and trials with RT <200 ms or >1000 ms and then >3 SD above the participant's mean RT were not included in the RT or *f*MRI analyses. The

main analyses used RT data from the angry-neutral and happy-neutral trials. Attention bias towards angry faces is reflected by faster RTs to probes which appear in the same (congruent) rather than opposite (incongruent) location as angry faces on angry-neutral trials (i.e., threat bias score = mean RT on angry-incongruent trials minus mean RT on angry-congruent trials; positive values indicate attention bias towards angry faces, and negative values indicate bias away from angry faces). An attention bias score for happy faces was similarly calculated. Pre-post treatment change in bias scores was assessed using *t*-tests. As the task was considerably longer for fMRI analyses than that typically used to obtain behavioural measures of attention bias, analyses also examined behavioural attention bias scores calculated for the first half of the task.

***f*MRI data.** To achieve optimal alignment of individual EPI images in a common template space, participant images were first aligned in a study-specific template space and then subsequently transferred into MNI space, using the registration procedure below. Pre-treatment images from 14 participants were skull-stripped using BET (Smith, 2002) and then normalized to create an average template brain using the open-source deformable registration tool ANTS. One subject was omitted from template creation due to abnormal brain morphology. Before template creation, linear (rigid-body) registration as well as bias field correction of inputs was performed. The study-specific template was then generated by iteratively registering images to the current template estimate (Avants et al., 2010). This template generation procedure was repeated iteratively (I = 4). The registration between each participant's pre-treatment image and the study-specific template was performed using the nonlinear Greedy-SyN algorithm and the image match metric was the cross-correlation between the images using a 4x4x4 voxel window. Registration was performed in a multi-resolution scheme, with a maximum of 30 iterations at 4x subsampling, 50 iterations at 2x

subsampling and 20 iterations at full resolution. The final template was registered to the MNI (2mm) standard template brain using the nonlinear SyN algorithm.

Next, linear (rigid-affine) registration of participants' mean EPI images to their corresponding pre-treatment images was performed. Then, nonlinear registration of the pre-treatment images to study-specific template space, of the participant omitted from template creation, was performed. Finally, EPI time-series data from each participant was transformed from individual participant space into MNI space in the following order, using transforms resulting from the processing steps performed previously: 1. Forward transform from participant EPI to participant pre-treatment space, 2. Forward transform to study-specific template space and 3. Inverse of the forward transform to MNI (2mm) space. Once images were transferred to MNI space, smoothing of EPI data was conducted using a 6mm full width at half maximum (FWHM) Gaussian kernel.

Hypotheses were tested by examining pre-post changes in neural responses to four contrasts: (1) threat-cue reactivity (angry vs neutral faces; Browning et al., 2010; Monk et al., 2008), (2) positive-cue reactivity (happy vs neutral faces) to assess emotion-specificity, (3) threat-bias reactivity (angry-incongruent vs angry-congruent trials), which reflects differential neural responses when attention is directed away from angry faces (i.e., towards the location of neutral faces vs toward the location of angry faces; Britton et al., 2013; 2015; Price et al., 2014; White et al., 2017) and (4) positive-bias reactivity (happy-incongruent vs happy-congruent trials).

Data analysis was performed with SPM8 (The Wellcome Trust Center for Neuroimaging, London, UK). For first-level data analysis, event-related neural responses to the face pairs were modelled as 6 separate conditions (angry-incongruent/angry-congruent trials, happy-incongruent/happy-congruent trials, neutral trials, and error trials) convolved with the canonical hemodynamic response function. The six motion correction parameters were also

added as regressors to the first-level models. These first-level analyses were conducted separately for pre- and post-treatment sessions.

Group-level analyses were conducted using flexible factorial models, with conditions being set as dependent to each other (repeated measures). Analyses of emotion-cue reactivity used data entered into a 3x2 model including first-level contrasts of angry (incongruent + congruent), happy (incongruent + congruent) and neutral, each pre- and post-treatment. To examine threat-cue reactivity, we calculated a t-contrast for angry trials pre- versus post-treatment and masked inclusively with the interaction t-contrast of angry minus neutral trials pre- versus post-treatment. With this masked contrast, areas reported as significant satisfied both criteria that: (1) activity for angry trials decreased significantly from pre- to post-treatment; and (2) the pre-post decrease in activity for angry trials was significantly greater than any pre-post difference for neutral trials. To examine positive-cue reactivity, we calculated the same masked contrast of happy trials pre- versus post-treatment masked inclusively by the interaction contrast of happy minus neutral trials pre- versus post-treatment.

Analysis of threat-bias reactivity was conducted using a separate 2x2 flexible factorial model including first-level contrasts of angry-incongruent and angry-congruent trials pre- and post-treatment. We calculated a t-contrast for the interaction effect of angry incongruent minus congruent trials pre- versus post-treatment. Similarly, analysis of positive-bias reactivity was conducted the same way using another 2x2 flexible factorial model including first-level contrasts of happy-incongruent and happy congruent trials pre- and post-treatment.

Results from these whole-brain analyses were reported at a cluster-level threshold of $P_{FWE} < .05$, corrected for multiple comparisons, with clusters formed by the voxel-level height threshold of $P_{uncorrected} < .001$. For masked contrasts, we applied the same voxel-level threshold for both the contrast of interest and the inclusive mask at $P_{uncorrected} < .001$ and applied correction for multiple comparisons conservatively based on the whole brain volume (i.e. not

restricted only to the masked regions). Anatomical names for brain areas showing significant effects were identified using the Automated Anatomical Labelling toolbox of SPM8 (Tzourio-Mazoyer et al., 2002).

For regions showing significant neural plasticity (i.e., pre-post changes in reactivity, which are the main focus of this study), we examined correlations between neural, behavioural and anxiety symptom measures. Beta parameter estimates were extracted at the peak of each significant cluster and entered into SPSS for correlations using a $p < .01$ significance level.

Results

Anxiety diagnoses and symptoms

At post-treatment, 77% of children were free of their principal diagnosis and 66% were free of all diagnoses. Children's mean principal diagnosis severity, number of diagnoses, and global functioning all improved significantly from pre- to post-treatment, $t(14) = 7.9$, $p < .001$, $t(14) = 4.6$, $p < .001$, $t(14) = 6.3$, $p < .001$, respectively (see Table 1 for means). Similarly, parent-reported and child-reported SCAS total anxiety symptom scores and child-reported SMFQ depression total scores reduced significantly from pre- to post-treatment, $t(14) = 4.3$, $p = .001$, $t(14) = 3.3$, $p = .006$, $t(14) = 2.2$, $p = .04$, respectively (change in parent-reported SMFQ total scores was not significant, $t(14) = 1.8$, $p = .09$).

Behavioural results

Mean behavioural (RT-based) attention bias scores on the visual probe task are presented in Table 1. There were no significant pre- to post-treatment changes in bias scores (results were similar for bias scores obtained from the first half of the task).

Insert Table 1

Whole-brain fMRI analysis

Threat-cue reactivity (angry-neutral versus neutral-neutral contrast). There were significant reductions in activation by angry (relative to neutral) faces from pre- to post-

treatment in several regions identified by the following clusters: (1) the left supplementary motor area, extending to the left mid cingulate cortex and left superior frontal gyrus; (2) right calcarine fissure, extending to cuneus and right lingual gyrus; (3) left rolandic operculum, extending to the left Heschl gyrus, left putamen, left insula, left superior temporal gyrus, and left inferior frontal gyrus; (4) left superior and inferior parietal gyrus, extending to the left superior and middle occipital gyrus; and (5) right precentral gyrus, extending to the right superior, middle and inferior frontal gyrus (see Table 2 for all peak co-ordinates and statistical value and Figure 1). There were no significant pre-post increases in threat-cue reactivity. Thus, neural reactivity declined within a broad neural network from pre- to post-treatment when picture-pairs contained an angry face compared to those that contained neutral faces.

Insert Table 2

Positive-cue reactivity (happy-neutral versus neutral-neutral contrast). From pre- to post-treatment, there were significant declines in activation by happy (relative to neutral) faces in many regions including: (1) the bilateral supplementary motor area, extending to the mid and anterior cingulate cortex and bilateral medial superior frontal gyrus; (2) left superior and inferior parietal gyrus, extending to the left precuneus, left precentral and postcentral gyrus, and the left superior and middle occipital gyrus; (3) right precentral gyrus, extending to the right superior, middle and inferior frontal gyrus, and right insula; (4) left middle and inferior frontal gyrus (opercular and triangular parts), extending to the left precentral gyrus; (5) right superior and middle temporal gyrus; (6) right calcarine fissure, extending to bilateral cuneus, bilateral lingual gyrus and left precuneus; (7) right middle occipital gyrus, extending to the right calcarine and right cuneus; (8) right angular gyrus, extending to the right supramarginal gyrus, right superior occipital gyrus, and right inferior and superior parietal gyrus; (9) left precentral gyrus, extending to the left superior and middle frontal gyrus (see Table 2 for all peak co-ordinates and statistical values and Figure 1). There were no significant pre-post

increases in positive-cue reactivity. Thus, neural reactivity declined within a broad neural network from pre- to post-PST when picture-pairs contained a happy face compared to those that contained only neutral faces.

Insert Figure 1

Threat-bias reactivity (angry-incongruent versus angry-congruent contrast). There was significant reduction between pre- and post-treatment in activation to the angry-bias contrast in the mid cingulate cortex extending to the left posterior cingulate cortex (see Table 2), and no other significant changes. Thus, neural reactivity in these regions reduced from pre- to post-treatment more so on incongruent trials (i.e., attending to the neutral face in threat-neutral pairs) compared to congruent trials (i.e., attending to the angry face in threat-neutral pairs).

Positive-bias reactivity (happy-incongruent versus happy-congruent contrast). There were no significant pre-to post-treatment differences for this contrast.

Correlations between neural and symptom measures

Pre-post change in overall emotion-cue reactivity was not associated with treatment outcome (indexed by pre-post changes in symptoms). However, the overall index of pre-treatment emotion-cue reactivity positively correlated with pre-treatment parent-report of child anxiety symptoms, $r = .76$, $p = .001$ (see Figure 2). Thus, greater neural reactivity to emotional cues was significantly associated with greater parent-reported child anxiety symptoms prior to treatment.

Insert Figure 2

Correlations with behavioural attention bias measures

Pre-post change in behavioural attention bias was unrelated to pre-post changes in emotion-cue reactivity, threat-bias reactivity, or symptoms. Before treatment, initial behavioural attention bias for threat cues (first half of task) showed a trend to correlate

negatively with neural reactivity to the threat-bias contrast in the mid/posterior cingulate, r = -.51, p = .05 (non-significant at p = .01 level). That is, greater pre-treatment neural reactivity on angry-incongruent compared to angry-congruent trials tended to be related to greater behavioural threat avoidance, that is, faster RT on neutral-probed compared to angry-probed trials.

Discussion

The present findings must be considered as preliminary in light of study limitations, in particular, a small sample size with no comparison group. Nevertheless, few prior studies in youth examined treatment-related changes in brain function. Moreover, the study did find several potentially interesting results. First, before treatment, neural reactivity to emotional faces averaged across multiple regions positively correlated with parent-report of child anxiety symptom severity. Second, reactivity to both angry and happy faces declined between pre- and post-treatment; such changes occurred within a broad neural network linking frontal, parietal, temporal and occipital regions. Third, from pre- to post-treatment, there was reduction in reactivity of the mid/posterior cingulate cortex to the threat-bias contrast. Finally, pre- to post-treatment change in brain function was unrelated to pre- to post-treatment change in anxiety symptoms.

Emotion-cue neural reactivity. The present study reported pre- to post-treatment *reduction* in reactivity across a wide cortical network when processing emotional relative to neutral cues. Such findings contrast with results of an earlier study of treatment effects on neural emotional reactivity in anxious youth. Maslowsky et al. (2010) found *increased* activation of the right ventrolateral PFC from pre- to post-treatment (with CBT and fluoxetine) in response to angry relative to neutral faces. Inconsistent results across studies may relate to methodological differences, such as differing interventions and analysis parameters (e.g., whole brain analyses as conducted here vs ROIs). As noted earlier, research with anxious adults

has indicated inconsistent effects of ABM-threat-avoidance training and CBT on neural reactivity to emotional stimuli (Mansson et al., 2013), so further research could usefully compare neural effects of PST and CBT in anxious individuals.

Despite some inconsistencies discussed earlier, research into adult anxiety disorders indicated treatment-related changes in neural emotion-cue reactivity, which occurred in widespread brain regions similar to those showing pre- to post-treatment reductions in the present study, including frontal (anterior cingulate, insula, frontal gyrus, e.g., Fonzo et al., 2014; Klumpp et al., 2013), as well as temporal (superior and middle temporal gyrus), parietal (superior and inferior parietal gyrus, posterior cingulate, precuneus) and occipital regions (cuneus, occipital gyrus) (see review by Messina et al., 2013).

Of note, changes in symptoms and neural reactivity during treatment were not correlated, but pre-treatment neural reactivity to emotional faces did positively correlate with parent-report of child anxiety symptom severity. Further research is required with a larger sample and the inclusion of a healthy comparison group and a clinical wait list control group to clarify whether pre-treatment neural reactivity to emotional cues is abnormal and normalised by treatment with PST in anxious children.

Despite limitations, the present study suggests a broad network that exhibits anxiety-related responsivity to threat and positive cues. This may comprise multiple overlapping component networks such as the amygdala-frontal *valuation network* and frontal-parietal *attention network* (Pessoa, 2009, 2014). The valuation network integrates information from other networks and modulates their processing to facilitate detection of motivationally salient stimuli such as threats and rewards (Pessoa, 2009, 2014). While the amygdala may play a key role in the valuation network, its small, deep structure makes it difficult to detect reliably with *f*MRI (Lipp et al., 2014). Further research (e.g., using larger samples, graph theory and

network analysis, Pessoa, 2014) is required to clarify the effects of treatment on network activity underlying emotion-attention processing in anxiety.

Threat-bias neural reactivity. There was also significant pre-post reduction in neural reactivity to the threat-bias contrast in the mid/posterior cingulate region of the parietal cortex. Previous studies have found effects of ABM training on neural reactivity to threat-bias contrasts, albeit in differing brain regions. In healthy non-anxious adults, ABM-threat-avoidance training modified neural reactivity on a conceptually similar threat-bias contrast in frontal regions (dorsolateral and ventrolateral PFC, anterior cingulate; Browning et al., 2010). In socially anxious adults, ABM training (using the visual-probe task to increase attention to happy vs neutral faces) increased amygdala reactivity to the threat-bias contrast (Britton et al., 2015). Comparison of results across studies is complicated by methodological differences (e.g., differing ABM methods, assessment tasks, ROIs, anxious/non-anxious samples). Nevertheless, the present finding of reduction in threat-bias neural reactivity reflects greater reduction when attending to neutral more so than angry faces in threat-neutral pairs. Given that treatment with PST aims to encourage attention to adaptive, goal-relevant stimuli (i.e., neutral and positive cues), the finding of reduction in neural reactivity on the threat-bias contrast in the mid/posterior cingulate is notable, given key roles of the mid cingulate in linking motivation and action (e.g., linking aversive/reward cue processing with avoidance/approach behaviour) and the posterior cingulate in regulating the focus of attention (see reviews by Leech & Sharp, 2014; Vogt, 2016). The present findings may suggest a reduction in neural reactivity when regulating the focus of attention upon and approach behaviour towards neutral cues which become motivationally salient during treatment with PST due to the emphasis on attending and responding to neutral and positive stimuli. Indeed, that both neutral and positive stimuli are targets in PST may contribute to the absence of significant pre-post changes in neural reactivity on the positive-bias contrast.

Furthermore, before treatment, there was a trend (p = .05) for threat-bias reactivity in the mid/posterior cingulate to correlate negatively with behavioural attention bias to threat; that is, anxious children with greater neural threat-bias reactivity (angry-incongruent> angry-congruent) tended to show greater behavioural threat avoidance (i.e., faster RT to probes following neutral compared to angry faces in threat-neutral pairs). Previous *f*MRI studies have found associations between behavioural attention bias (RT) and neural reactivity to threat in anxiety disorders. In youth with mixed anxiety disorders, behavioural attention bias to fearful faces (presented for 2000 ms) positively correlated with threat-bias reactivity in the left posterior insula and parietal regions, that is, right angular gyrus and precuneus (which adjoins the posterior cingulate) (Price et al., 2014). In adults with panic disorder, behavioural attention bias to angry faces (presented for 500 ms) negatively correlated with threat-cue reactivity in the ventrolateral PFC, dorsal anterior cingulate, medial frontal gyrus, insula, precentral gyrus, caudate, parahippocampal gyrus, and parietal regions including the precuneus (Fani et al., 2012). In youth with GAD, behavioural attention bias to masked angry faces positively correlated with threat-cue reactivity in the amygdala (Monk et al., 2006). Although studies examine different fMRI contrasts, threat-cue exposure durations, ROIs, anxiety disorders and adult/child samples, together they broadly suggest that anxiety disorders are associated with aberrant neural reactivity in limbic-cortical regions which underpin attention processing of threat stimuli. The present study suggests that PST may modify functioning in this emotion-attention neural network in anxious children by reducing neural reactivity associated with focusing attention upon neutral cues when threat cues are present. Thus, PST may reduce neural reactivity during goal-directed regulation of attention to adaptive stimuli. Of note, however, was the finding that change in pre- to post-neural reactivity was not significantly correlated with change in anxiety symptoms. It is possible that the pre- to post- changes in neural reactivity are due to other factors such as habituation or the passage of time. However,

methodological factors may also explain the lack of association; prior findings of significant pre- and post-intervention associations between neural reactivity and symptom change have been based on therapist-rated continuous symptom measures (White et al., 2017) rather than parent and child self-report measures as used in the present study. Further research with larger sample sizes, appropriate comparison conditions, and therapist-rated continuous measures are required to elucidate these possibilities.

Other study limitations must be considered in addition to the small sample size and absence of comparison groups. As recent work highlights the importance of imaging research on the stability of brain functions engaged by attention bias tasks (e.g., White et al., 2017), future studies with larger sample sizes should further examine the stability of brain functioning on the dot-probe task. Also, as PST is designed to engage multiple cognitive regulatory processes, it is possible that the visual probe task is not an adequate index of the behavioural effects of this training. Future studies should examine whether behavioural tasks assessing higher order attentional control processes are sensitive to behavioural changes following PST. Larger studies are needed that compare effects of PST and other active treatments (e.g., CBT) on neural reactivity to emotional and neutral cues, anxiety symptoms, and behavioural attention bias. Nevertheless, the present study represents the first step in determining the neural effects of treatment with PST in anxiety disorders and thus informs future research.

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Table 1: Descriptive, clinical and behavioural attention bias measures at pre- and post-treatment

Measure	Pre-Treatment	Post-Treatment
Percent principal diagnosis free (N)	0% (15)	78% (11)
Percent all diagnoses free (N)	0% (15)	66% (10)
Principal diagnosis severity (0-8)	5.5 (0.64)	2.8 (1.5)
Number of diagnoses	3.0 (1.3)	0.7 (1.2)
CGAS Global functioning	60.6 (2.6)	76.0 (9.1)
SCAS-Parent total anxiety score	27.4 (7.9)	19.0 (6.4)
SCAS-Child total anxiety score	36.1 (9.4)	26.6 (11.4)
SMFQ-Parent total score	3.9 (3.2)	2.2 (2.1)
SMFQ-Child total score	4.8 (2.9)	3.1 (2.7)
Visual-probe task		
Angry Bias score (ms)	3 (22)	-2 (26)
Angry-congruent trials, RT (ms)	623 (64)	604 (70)
Angry-incongruent trials, RT (ms)	626 (64)	602 (65)
Happy Bias score (ms)	7 (20)	-3 (27)
Happy-congruent trials, RT (ms)	627 (64)	603 (74)
Happy-incongruent trials, RT (ms)	634 (61)	600 (65)

Note. CGAS= Children's Global Assessment Scale; SCAS= Spence Children's Anxiety Scale; SMFQ= Short Mood and Feelings Questionnaire

Table 2: Brain regions showing significant reduction in threat-cue reactivity (angry pre- vs post-treatment), positive-cue reactivity (happy pre- vs post-treatment), and threat-bias reactivity (angry incongruent minus congruent, pre- vs post-treatment). No regions showed significant increases in reactivity from pre- to post-treatment for these contrasts.

Area	Cluster peak co-ordinate	Brodmann Area	Peak z score	Cluster size	Cluster level P_{FWE}
Threat-cue reactivity (Angry pre- versus post-treatment)					
Left supplementary motor area	(-4, 0, 54)	6	5.92	202	0.011
Bilateral calcarine fissure	(-2, -72, 8)	30	5.33	677	0.000
Right precentral gyrus	(30, -8, 50)	6	4.94	308	0.001
Left sup & inf parietal gyrus	(-22, -56, 44)	7	4.83	232	0.006
Left insula and putamen	(-30, -2, -4)	13	4.58	220	0.008
Positive-cue reactivity (Happy pre- versus post-treatment)					
Left supplementary motor area	(-4, 0, 54)	6	6.33	622	0.000
Right precentral gyrus	(30, -8, 48)	6	5.80	647	0.000
Right mid & sup temporal gyrus	(48, -40, 14)	22	5.50	187	0.015
Left sup & inf parietal gyrus	(-22, -60, 44)	7	5.50	1133	0.000
Right calcarine	(10, -68, 8)	30	5.16	636	0.000
Left inferior frontal gyrus (opercular)	(-42, 18, 32)	9	4.88	507	0.000
Left precentral	(-26, -10, 52)	6	4.86	180	0.017
Right middle occipital gyrus	(22, -88, 18)	18	4.76	211	0.009
Right angular gyrus	(30, -54, 44)	7	4.66	235	0.006
Threat-bias reactivity (Angry incongruent vs congruent, pre- versus post-treatment)					
Left mid cingulate cortex	(-4, -16, 34)	23	4.66	283	0.005

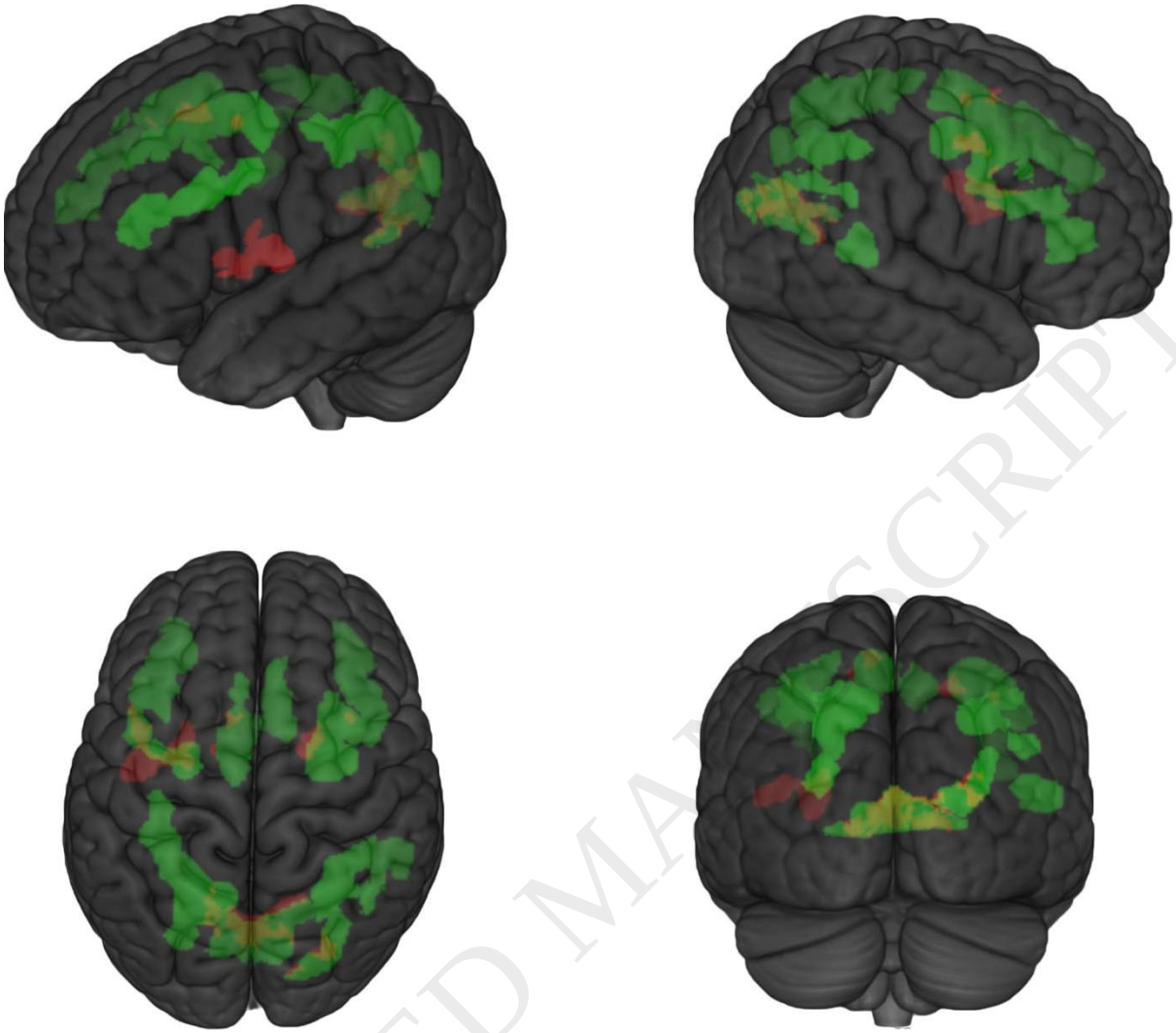

Figure 1. Rendered brains showing activation maps for pre- to post-treatment reduction in threat-cue reactivity (shown in red) and positive-cue reactivity (shown in green). Overlapping areas that were involved in both conditions are shown in yellow.

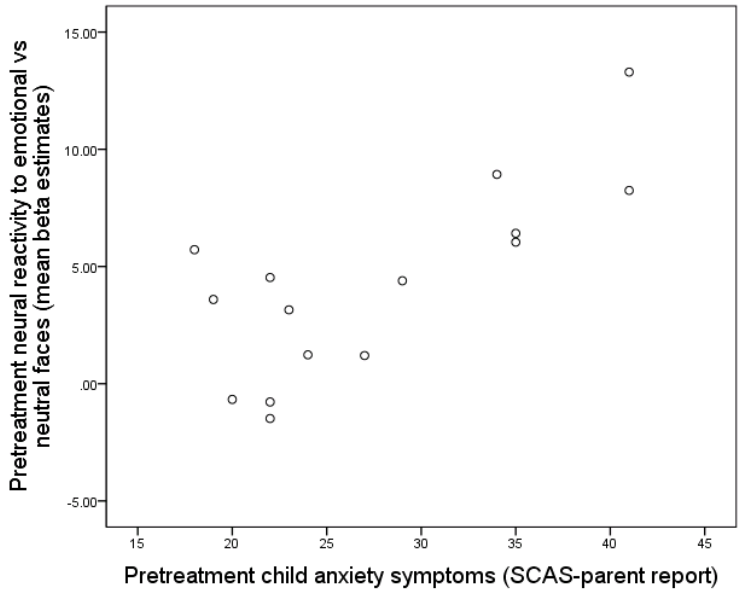

Figure 2. Significant positive relationship between pre-treatment parent-report of child anxiety symptoms and pre-treatment neural reactivity to emotional cues (combined angry and happy faces, vs neutral faces), r = .76, p = .001 Estimates of emotion-cue reactivity are averaged across a widespread neural network of frontal, temporal, parietal and occipital regions, which showed reduction in reactivity between pre- and post-treatment with PST.