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# Predicting rapid response to cognitive-behavioural treatment for panic disorder: The role of hippocampus, insula, and dorsolateral prefrontal cortex

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## ABSTRACT

Although cognitive-behavioural therapy (CBT) is an effective first-line intervention for anxiety disorders, treatments remain long and cost-intensive, difficult to access, and a subgroup of patients fails to show any benefits at all. This study aimed to identify functional and structural brain markers that predict a rapid response to CBT. Such knowledge will be important to establish the mechanisms underlying successful treatment and to develop more effective, shorter interventions. Fourteen unmedicated patients with panic disorder underwent 3 T functional and structural magnetic resonance imaging (MRI) before receiving four sessions of exposure-based CBT. Symptom severity was measured before and after treatment. During functional MRI, patients performed an emotion regulation task, either viewing negative images naturally, or intentionally down-regulating negative affect by using previously taught strategies of cognitive reappraisal. Structural MRI images were analysed including left and right segmentation and volume estimation. Improved response to brief CBT was predicted by increased pre-treatment activation in bilateral insula and left dorsolateral prefrontal cortex (dlPFC) during threat processing, as well as increased right hippocampal gray matter volume. Previous work links these regions to improved threat processing and fear memory activation, suggesting that the activation of such mechanisms is crucial for exposure-based CBT to be effective.

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## Introduction

Panic disorder (PD) is one of the most prevalent and severe anxiety disorders (Barlow et al., 1997). The illness is associated with significant impairments in life quality and psychosocial functioning (Mendlowicz & Stein, 2000; Pollack & Marzoli, 2000), but it also poses an enormous economic burden (Otto, Pollack, & Maki, 2000). Although cognitive-behavioural therapy (CBT) is an effective first-line intervention approach, only a minority of patients has access to treatment, with courses being long and cost-intensive, and a significant percentage of treated patients relapsing during treatment follow-up (Otto et al., 2000; Sharp et al., 1996). A number of studies have aimed to identify demographic and symptom severity variables that predetermine treatment success (Aaronson et al.,

2008; Dow et al., 2007; O'Rourke, Fahy, Brophy, & Prescott, 1996; Roy-Byrne et al., 2006), yet reliable predictors of clinical response have not been established. Determining the predictors of treatment response would not only have financial implications when prescribing cost-intensive interventions, but it might also elucidate key mechanisms of CBT action that will help to further refine treatment ingredients and application.

Although more costly, recent neuroscience approaches suggest that prediction models based on neural biomarkers rather than demographic and clinical data have the potential to drastically improve accuracy in predetermining treatment response (Ball, Stein, Ramsawh, Campbell-Sills, & Paulus, 2014). Improved knowledge about which neural properties predict enhanced CBT benefit has implications for the development of novel CBT combination approaches, as it establishes key mechanistic treatment targets that may guide treatment modification. For instance, identification of overlapping mechanisms of CBT and drug action might lead to combination interventions that logically integrate

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several treatment ingredients based on their key effects. This would be in accordance with a recent initiative published in *Nature*, calling for an improvement of psychological treatments by integrating basic neuroscience approaches (Holmes, Craske, & Greybiel, 2014).

Preliminary results indicate that increased pre-treatment functional activation in brain areas associated with threat processing, such as visual and occipital areas, the amygdala and the insula, is predictive of enhanced clinical response to CBT for anxiety disorders (Doehrmann et al., 2013; Klumpp, Fitzgerald, & Phan, 2013; McClure et al., 2007; Olatunji et al., 2013). Such observations are in line with the emotional processing account of fear reduction that proposes thorough processing of threat stimuli as an essential mechanism for exposure treatment to be successful (Foa & Kozak, 1986). Further support of this model comes from research showing that experimental procedures interfering with threat processing severely reduce the effect of CBT, while manipulations encouraging threat processing have facilitative effects (Craske, Street, & Barlow, 1989; Kamphuis & Telch, 2000; Salkovskis, Hackmann, Wells, Gelder, & Clark, 2007; Taylor & Alden, 2010). On the other hand, there is evidence suggesting that pre-treatment activation in prefrontal-cortical areas of emotion regulation in response to threat might play an important role in whether a patient with anxiety will or will not benefit from CBT. However, results remain inconclusive, with one study suggesting increased and one study proposing decreased activation in areas of cognitive control as a predictor of anxiety treatment success (Klumpp et al., 2013; Olatunji et al., 2013). Taken together, these results indicate the potential of neurofunctional markers in the prediction of treatment response, although the mediating role of prefrontal brain areas associated with cognitive control remains to be clarified.

Furthermore, although this has not been explored directly, there is some preliminary evidence pointing to the possibility that structural brain parameters, such as hippocampus gray matter volume, might also represent potential predictors of treatment response. The hippocampus has been implicated in fear memory, conditioning and extinction (Anagnostaras, Gale, & Fanselow, 2001; Quirk & Mueller, 2008). Increased right hippocampal volume has been shown to predict enhanced contextual fear conditioning in humans (Pohlack et al., 2012). Furthermore, transient pharmacological inactivation of the hippocampus in animals during extinction has been shown to impair later extinction retrieval, emphasizing a key role of this brain area in extinction learning (Lengersdorf, Stutgen, Uengoer, & Gunturkun, 2014; Sotres-Bayon, Sierra-Mercado, Pardilla-Delgado, & Quirk, 2012). Such findings might translate to human response to cognitive-behaviour treatment for anxiety, which, similar to extinction, largely depends on exposure to the threatening stimulus without aversive outcomes (Hofmann, 2008).

In this study, we aimed to identify both functional and structural neuromarkers of early response to exposure-based CBT for panic disorder. Patients underwent a brain scan before receiving four weekly sessions of CBT, and symptom severity of panic and agoraphobia was assessed before and after treatment. To identify potential neurofunctional predictors of treatment outcome, we used an emotion regulation task that we have recently shown to sensitively establish neural markers of anxiety in patients with panic disorder versus healthy volunteers (Reinecke et al., under review). The task allows to simultaneously measure emotional processing and regulation, mechanisms that are both thought to be affected in panic disorder. In this task, patients view blocks of threat-laden images. In half of the blocks, patients view images naturally, while in the other half of blocks they are instructed to use strategies of cognitive reappraisal to intentionally down-regulate negative affect. We additionally explored whether structural brain parameters, including left and right hippocampal gray matter

volume, were predictive of CBT response. A predictive signal from structural MRI measures would have key advantages for future clinical development. These measures are more readily accessible in clinical practice, less dependent on compliance or training and are less confounded by current medication compared to fMRI which detects vascular effects. We hypothesised that enhanced CBT response would particularly be associated with increased pre-treatment hippocampal volume, and that it would be predicted by increased activation in areas involved in threat processing in response to negative images.

## Methods and materials

### Participants

Fourteen patients with panic disorder (PD; 8 with/6 without agoraphobia; gender: 10 female/4 male, age in years:  $37.2 \pm 11.1$ , years of education  $15.8 \pm 2.5$ , verbal intelligence as measured using the NART (Nelson, 1982):  $116.6 \pm 5.6$ ) were recruited from the general public. Diagnoses were assessed by a clinical psychologist with expertise in the diagnosis and treatment of anxiety disorders (AR), using the Structured Clinical Interview for DSM-IV Axis I Disorders SCID-CV (First, Spitzer, Gibbon, & Williams, 1996). Three patients fulfilled criteria for comorbid specific phobia and one for social phobia, with panic disorder being the primary diagnosis. General exclusion criteria were left-handedness, contraindications for MRI, epilepsy, current or past psychotic disorder, bipolar disorder, or substance abuse, and antidepressant or psychological treatment during the last 6 months. Three patients had reported occasional benzodiazepine or propranolol intake but were medication free 48 h before scanning. Ethical approval was obtained from the local research ethics committee. All participants gave written informed consent.

### Clinical symptoms

At baseline and three days after the last session of their 4-week treatment, participants completed the following self-report questionnaires: i) Hospital Anxiety and Depression Scale (HADS; each subscale ranging from 0 to 21) assessing trait anxiety and depression (Zigmond & Snaith, 1983), ii) the Panic Disorder Severity Scale (PDSS-SR; range 0–28) assessing panic frequency and severity, avoidance behaviour and impact on social and professional life (Houck, Spiegel, Shear, & Rucci, 2002), and iii) the Agoraphobic Cognitions Questionnaire (ACQ; range 1–5) assessing the severity of explicit catastrophic beliefs occurring during panic attacks, such as “I am going to pass out” (Chambless, Caputo, Bright, & Gallagher, 1984).

### fMRI task design

Patients were brain scanned prior to 4-week treatment using an emotion regulation task (Phan et al., 2005; Reinecke et al., under review). Stimuli were 40 negatively valenced coloured IAPS images (Lang, Bradley, & Cuthbert, 1997) picturing characteristic panic-related catastrophic expectations, such as accidents, hospital treatments, or funerals (mean valence ratings  $2.8 \pm 1.7$ , mean arousal ratings  $6.0 \pm 2.2$  on 9-point Likert scales ranging from 1 = unpleasant/low arousal to 9 = pleasant/high arousal). These were presented in 8 blocks of 5 images, one after another for 5 s each, separated by 1 s blank screen interstimulus intervals. Picture blocks alternated with grey fixation baseline blocks of 30 s, and experiments started with a baseline block. For half of the blocks, participants were instructed to naturally experience the emotional state evoked by the images, without attempting to regulate or alter

it (Maintain blocks). For Reappraisal blocks, they were instructed to down-regulate the provoked negative affect by using strategies of cognitive reappraisal (e.g. reframing, rationalising). Valence and arousal ratings as well as scene content were matched between the two experimental conditions Maintain and Reappraisal. The order of picture blocks remained constant across all participants, with half of the subjects starting with a Maintain and half starting with a Reappraisal block. Prior to each picture block, instructions were given, presenting the word MAINTAIN or REAPPRAISE on the screen for 4 s. At the end of each picture block, a 4-point rating scale (1 = neutral, 4 = negative) was presented for 4 s, and participants indicated the intensity of negative affect experienced throughout the block using a keypad.

Prior to the scan, participants completed the Emotion Regulation Questionnaire that assesses the habitual use of the two emotion regulation strategies cognitive reappraisal and suppression (Gross & John, 2003). They were then trained to use Reappraisal strategies effectively, using images different from those presented during the experiment. It was emphasized not to look away from the images and not to provoke thoughts unrelated to the images as means of distraction. Regulation strategies were introduced by the experimenter presenting two example images and verbal reappraisal, such as positive reframing (e.g. interpreting a middle-aged woman in a hospital waiting room in a way that she is waiting for her first grandchild to be born rather than her ill husband undergoing difficult surgery) or rationalising (e.g. interpreting the tears of a child as signs of tiredness instead of grief). This was followed by the participant attempting to reinterpret three images aloud. In addition, complete example Maintain and Reappraisal blocks were presented and afterwards discussed for practise reasons.

#### Image acquisition

Images were obtained using a 3 T Siemens Sonata scanner. T<sub>2</sub>\*-weighted functional data were acquired for a whole-brain field-of-view (64 × 64 × 40 matrix, voxel resolution 3 mm<sup>3</sup>, repetition time (TR) = 3000 ms, echo time (TE) = 30 ms, flip angle = 90°). Field maps were acquired using a dual echo 2D gradient echo sequence with echos at 5.19 and 7.65 ms, and a repetition time of 500 ms. High-resolution T1-weighted images were obtained using a 3 T Siemens Sonata scanner at the Oxford Centre for Clinical and Magnetic Resonance Research. We used an MPRAGE sequence with the following parameters: voxel resolution 1 mm<sup>3</sup>, 174 × 192 × 192 matrix, TR = 2040 ms, TE = 4.7 ms, inversion time (TI) = 900 ms.

#### Image analysis

Individual left and right hippocampal gray matter volumes were obtained in mm<sup>3</sup>, using FSL's Integrated Registration and Segmentation Tool (FIRST; FMRIB Software Library; [www.fmrib.ox.ac.uk/fsl](http://www.fmrib.ox.ac.uk/fsl)), an automatic subcortical segmentation program (Patenaude, Smith, Kennedy, & Jenkinson, 2011). ROIs were visually inspected in the coronal plane to ensure accuracy.

Functional imaging data were analysed using a whole-brain approach in FSL FEAT (fMRI Expert Analysis Tool) 6.0. Z-statistic images were thresholded at  $Z > 2.3$ , with a cluster threshold of  $p < .05$ , including multiple-comparison corrections. Pre-processing included motion correction (Jenkinson, Bannister, Brady, & Smith, 2002), non-brain removal (Smith, 2002), spatial smoothing (Gaussian kernel FWHM = 5.0 mm), grand-mean intensity normalisation of the entire 4D dataset by a single multiplicative factor, registration of the functional space template to the anatomical space and the MNI 152 space, highpass temporal filtering (Gaussian-weighted least-squares straight line fitting, with

sigma = 50.0 s), fieldmap correction. At the first-level, data were analysed using a general linear model approach with local autocorrelation correction (Woolrich, Ripley, Brady, & Smith, 2001). Two regressors of interest (Maintain, Reappraise) and two regressors of no interest (instruction/rating periods) were included. Fixation blocks, presented between picture blocks, were the implicit baseline reference. Contrast images were calculated for picture blocks in general, Maintain blocks, Reappraisal blocks, Maintain versus Reappraisal, and Reappraisal versus Maintain.

These individual activation maps were then entered into second-level general linear model random-effects analysis across the whole brain. To identify predictors of treatment response, lower-level contrasts were entered into two separate whole-brain analyses of covariance, regressing a) baseline to post-treatment PDSS-SR change while controlling for baseline PDSS-SR scores as a regressor of no interest, and b) baseline to post-treatment ACQ change while controlling for baseline ACQ scores as regressor of no interest. This is a well-validated analysis approach (e.g. Klumpp et al., 2013) that allows insight into the role of variability between patients in a small sample.

Due to strong evidence implicating the amygdala in threat processing (Etkin, 2010; Hofmann, Ellard, & Siegle, 2012; Reinecke & Harmer, in press), we were also interested in whether pre-treatment amygdala BOLD activation was predictive of CBT induced changes on the PDSS-SR and ACQ, respectively. Therefore, these two higher-level analyses were repeated using a small volume correction region of interest analysis approach, within an anatomical left versus right amygdala mask.

#### Cognitive-behavioural treatment

Therapists were psychology graduates who were intensely trained in delivering one-on-one protocol-driven CBT through the Lupina initiative, an outreach service for panic disorder with or without agoraphobia developed at the Oxford University Department of Psychiatry. Evaluation data show that these young therapists perform similarly well as experienced clinical psychologists in the treatment of panic disorder (Croft & Hackmann, 2013). Training and supervision were provided by an experienced clinical psychologist executive involved in the development of the initiative (AC). Treatment involved four weekly sessions of exposure-based CBT and was based on the well-established cognitive-behavioural theory of panic (Clark et al., 1997). This approach assumes that anxiety disorders develop as a consequence of neutral situations (e.g., increased heart rate) being misperceived as threatening, and safety strategies (e.g., leaving situation, calling a friend) being developed to reduce the perceived danger. Safety behaviour in turn prevents patients from making corrective experiences (e.g. realizing that they will not die of a heart attack if they remain in a crowded supermarket when physical symptoms start). Our four-session treatment was a very condensed version of psychological intervention recommended for delivery in routine clinical care. It involved explanation of the learning mechanisms underlying the maintenance and treatment of panic, focussing on the role of safety strategies, and exposure to individually agoraphobic situations while dropping safety behaviours.

#### Results

##### Clinical symptoms

After having received treatment, patients showed significant improvement compared to their baseline scores in trait anxiety and depression (HADS) and panic severity (PDSS-SR), all  $t(13) > 2.80$ ; all

**Table 1**

Self-reported symptom severity at baseline and after 4-weeks of cognitive-behaviour treatment ( $M \pm SD$ , paired-samples  $t$ -test/ $p$ -scores).

|                     | Baseline       | Post-CBT      | $p$ -score |
|---------------------|----------------|---------------|------------|
| HADS-anxiety        | 13.4 $\pm$ 3.7 | 9.8 $\pm$ 3.8 | .03        |
| HADS-depression     | 9.1 $\pm$ 3.7  | 5.8 $\pm$ 3.5 | .04        |
| PDSS-SR (raw score) | 10.5 $\pm$ 6.3 | 4.2 $\pm$ 4.0 | .007       |
| ACQ                 | 2.3 $\pm$ .6   | 2.0 $\pm$ .7  | .13        |

Note: HADS = Hospital Anxiety and Depression Scale; PDSS-SR = Panic Disorder Severity Scale Self-Report; ACQ = Agoraphobic Cognitions Questionnaire.

$p < .03$ , but only a trend-improvement in agoraphobic cognitions (ACQ),  $t(13) = 1.66$ ;  $p = .13$  (Table 1).

#### Prediction of treatment success

##### Hippocampus volume

To establish whether left and right hippocampus (left:  $3894 \pm 349 \text{ mm}^3$ ; right:  $3988 \pm 342 \text{ mm}^3$ ) volumes were predictive of treatment response, hierarchical multiple regression analyses (forced entry) were run, separately for each of these two potential predictors and separately for pre-post treatment change scores on the dependent panic-specific outcome measures PDSS-SR and ACQ (2 predictors  $\times$  2 outcome measures = 4 analyses). In each analysis, we controlled for baseline panic symptom severity that potentially affects clinical outcome as well. We also controlled for baseline depression (HADS-D), as previous research indicates an association between depression and reduced hippocampal volume (Kasper & McEwen, 2008). We entered the baseline panic score in a first step, baseline panic and depression scores in a second step, and baseline panic and depression scores and the gray matter volume parameter in a third step. Bonferroni correction was applied by dividing the alpha-level of significance of .05 by the number of computed regression analyses, leading to a required significance level of  $p < .013$ .

Baseline PDSS-SR scores but not ACQ scores predicted symptom change during treatment on the same measure (step 1), PDSS-SR:  $R^2 = .71$ ,  $p < .001$ , ACQ:  $R^2 = .13$ ,  $p = .20$ , with those patients showing higher PDSS-SR scores at baseline reaching larger decrease on the same measure during treatment. Baseline depression scores were not associated with treatment outcome on ACQ or PDSS-SR (step 2), both  $\Delta R^2 < .07$ , both  $p > .36$ . Left hippocampus volume was not predictive of symptom change during treatment on any of the two self-report measures (step 3), both  $\Delta R^2 < .13$ , both  $p > .19$ . However, right hippocampal volume significantly predicted

treatment-induced changes on the ACQ,  $\Delta R^2 = .60$ ,  $p < .001$ , but not the PDSS-SR:  $\Delta R^2 = .03$ ,  $p = .32$ , explaining an additional 60% of variance in treatment outcome over and above baseline symptom severity. Remarkably, those patients showing the largest right hippocampal gray matter volume prior to CBT showed the most pronounced reduction in agoraphobic cognitions (Fig. 1).

##### Functional MRI activation

Valence ratings were significantly lower in Reappraisal ( $2.0 \pm .9$ ) versus Maintain ( $2.7 \pm 1.0$ ) blocks,  $t(14) = 2.19$ ;  $p < .05$ . Patients showed widespread BOLD responses to images versus baseline in general, with activation increase in both lateral occipital cortices, left and right thalamus, amygdala, hippocampus, putamen, and bilateral OFC, dlPFC, dmPFC, and vmPFC (cluster 1: 83,971 voxels, MNI 36, -86, 14,  $Z = 6.79$ ; cluster 2: 478 voxels, MNI 2, 48, -16,  $Z = 4.81$ ), and activation decrease in bilateral precuneus extending lingual gyrus (382 voxels, MNI 10, -54, 34,  $Z = 4.13$ ) (Fig. 2A). In Reappraisal > Maintain conditions, they showed increased BOLD activation in the paracingulate/anterior cingulate gyrus (1509 voxels, MNI -6, 32, 38,  $Z = 3.48$ ) and left and right dlPFC (left: 2093 voxels, MNI -52, 8, 46,  $Z = 3.74$ ; right: 834 voxels, MNI 40, 8, 44,  $Z = 3.63$ ) (Fig. 2B).

Controlling for baseline panic severity (PDSS-SR), greater pre-treatment BOLD response to images (versus baseline) in general in left and right insula (left: 1318 voxels, MNI -36, 10, 0,  $Z = 4.19$ ; right: 963 voxels, MNI 52, 10, 6,  $Z = 4.35$ ) was associated with greater symptom improvement on the PDSS-SR during 4-weeks CBT (Fig. 3). In addition, greater treatment-induced reductions in agoraphobic cognitions (ACQ) corresponded significantly with greater pre-treatment activation in the left dlPFC (408 voxels, MNI -36, 54, 12,  $Z = 3.58$ ; Brodmann areas 46, 10, 45) in response to images in the Maintain > Reappraisal contrast (Fig. 4). The predictive value of these clusters was maintained when adding individual scores on the Reappraisal subscale of the ERQ (Gross & John, 2003) as a regressor of no interest to the prediction models, suggesting that inter-individual differences in reappraisal skills were not confounding prediction results. BOLD activation in left versus right anatomical amygdala (in whole brain or small volume correction) was not predictive of treatment induced changes on the PDSS-SR or ACQ.

##### Discussion

This study simultaneously explored structural and neurofunctional biomarkers that predict early clinical response to exposure-

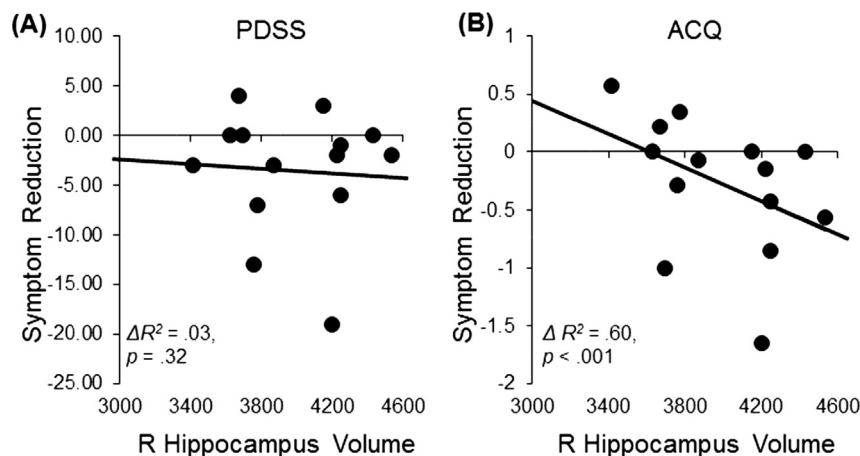


**Fig. 1.** (A) Larger right hippocampus was not predictive of enhanced response to brief exposure-based CBT as measured with the Panic Disorder Severity Questionnaire (PDSS-SR), but (B) predicted enhanced improvement on the Agoraphobic Cognitions Questionnaire (ACQ), over and above baseline symptom severity.

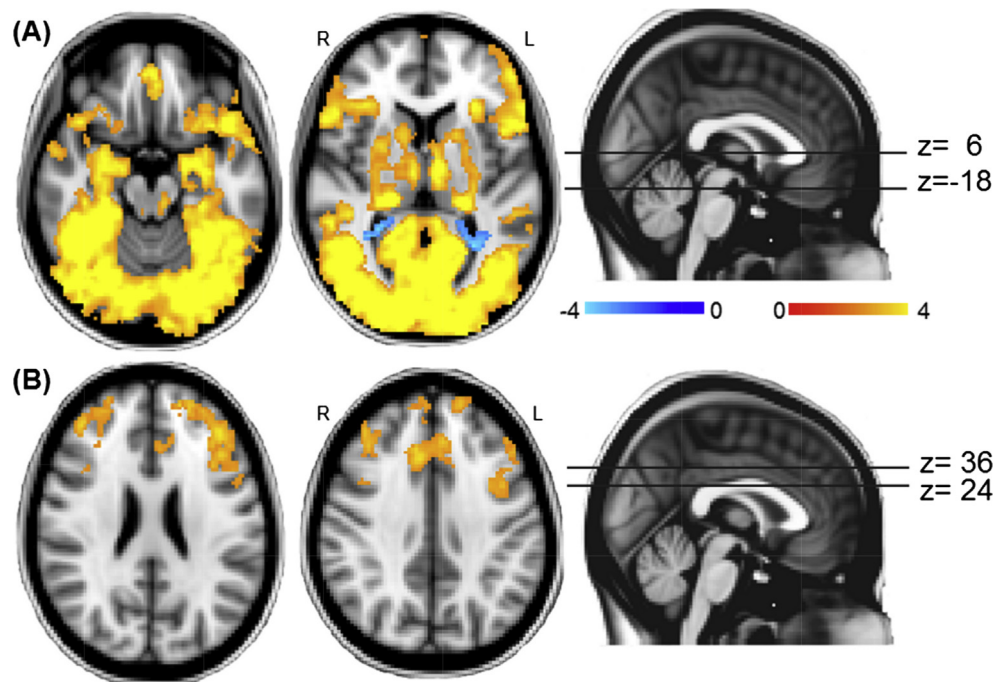


**Fig. 2.** (A) The presentation of negative IAPS images (versus fixation baseline) lead to a bilateral increase in activation in limbic areas (including amygdala, hippocampus, thalamus), occipital cortices, and prefrontal areas (including both OFC, dlPFC, dmPFC, and vmPFC), and a decrease in bilateral precuneus. (B) Reappraisal (versus Maintain) lead to greater BOLD signal response in the paracingulate gyrus and anterior cingulate gyrus and bilateral dlPFC. Images thresholded at  $Z > 2.3$ ,  $p < .05$ , corrected.

based CBT for panic disorder in unmedicated patients. Our results indicate that larger pre-treatment right hippocampal gray matter volume was predictive of greater reduction in panic symptom severity during CBT as measured using the agoraphobic cognitions questionnaire (ACQ), explaining an additional 60% of variance in treatment outcome over and above baseline symptom severity. Furthermore, greater pre-treatment activation in response to threatening images in bilateral insula was predictive of greater improvement in panic severity during brief CBT, as measured on the panic disorder severity scale (PDSS-SR). Also, greater activation in the left dorsolateral PFC in Maintain versus Reappraisal conditions was predictive of more pronounced symptom reduction on the ACQ. Taken together, these results provide evidence that the prediction of CBT response can potentially be improved when not only including baseline symptom severity but also functional and structural brain markers. Furthermore, these observations

highlight hippocampal volume as well as the ability to activate the insula and dlPFC during threat processing as essential mechanisms to achieve a rapid response to CBT.

Previous work had already implicated hippocampal volume and function as potentially relevant in anxiety disorders and psychological treatment action. Results from animal studies suggest that inactivation of the hippocampus impairs extinction learning and facilitates the return of fear (Lengersdorf et al., 2014; Sotres-Bayon et al., 2012). One proposed mechanism of this relationship is that hippocampal activity is essential to disambiguate extinguished cues into safe versus unsafe (Bouton, 2002; Tsetsenis, Ma, Lo Iacono, Beck, & Gross, 2007). Furthermore, a study in healthy humans suggests that smaller hippocampal volume is associated with impaired learning during fear conditioning (Pohlack et al., 2012). Interestingly, the cognitive enhancer cycloserine, which can improve CBT outcome if taken prior to exposure (Hofmann

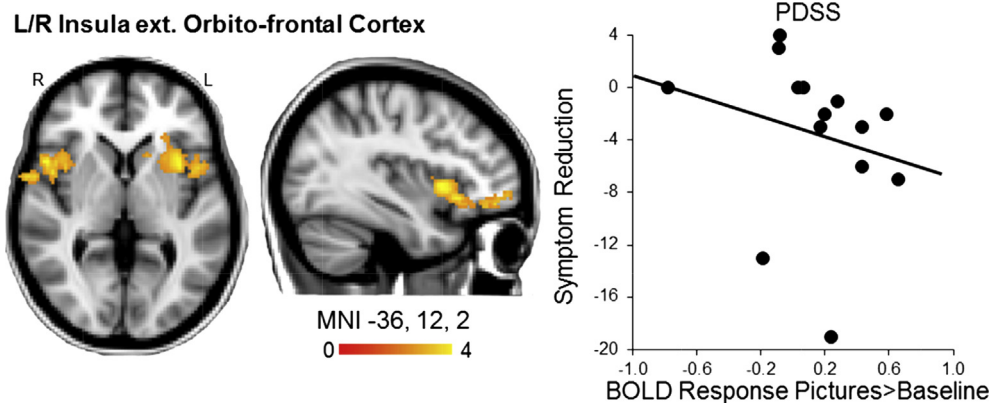


**Fig. 3.** Greater pre-treatment BOLD response to images (versus baseline) in bilateral insula ext. orbitofrontal cortex predicts larger symptom reduction during brief CBT on the Panic Disorder Severity Scale (PDSS-SR), over and above baseline symptom severity. Images thresholded at  $Z > 2.3$ ,  $p < .05$ , corrected.

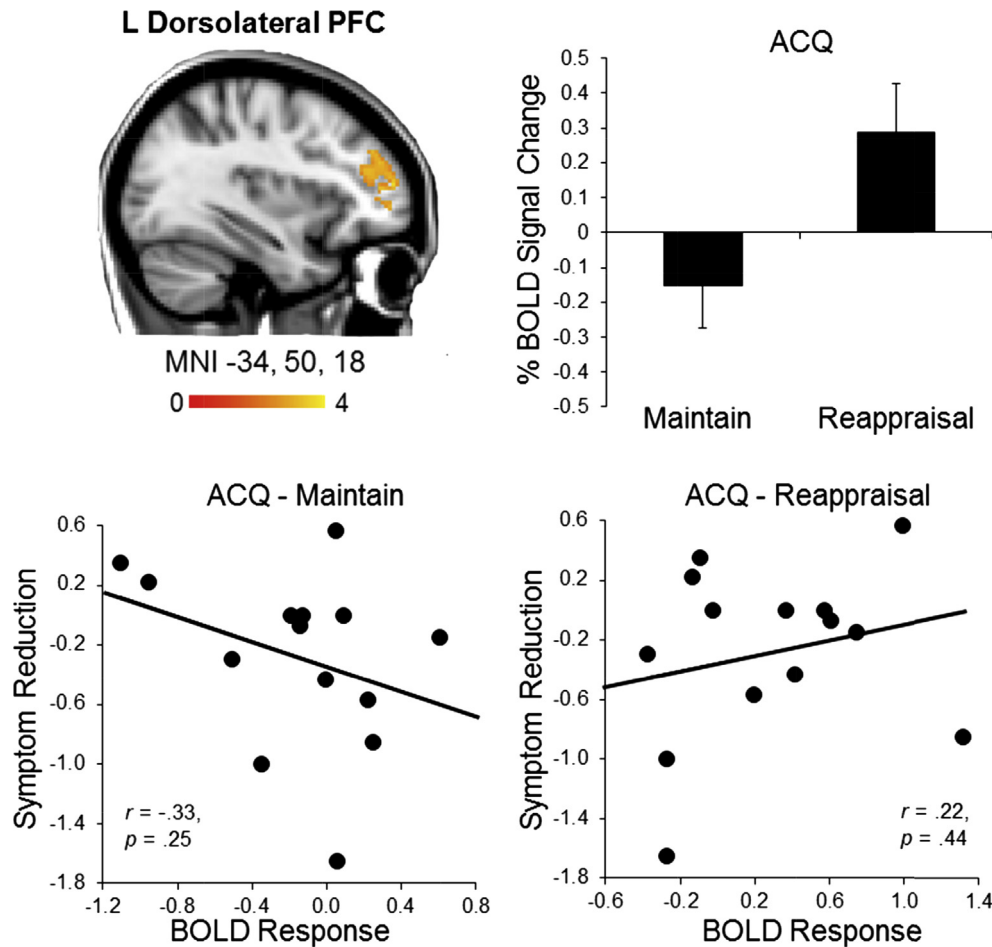


**Fig. 4.** Greater pre-treatment response in the left dorsolateral prefrontal cortex when maintaining negative affect naturally (versus Reappraisal) predicts enhanced response to brief CBT as measured on the Agoraphobic Cognitions Questionnaire (ACQ), over and above baseline symptom severity. Lower symptom reduction scores indicate stronger improvement. Images thresholded at  $Z > 2.3$ ,  $p < .05$ , corrected.

et al., 2013; de Kleine, Hendriks, Kusters, Broekman, & van Minnen, 2012; Kushner et al., 2007; Otto et al., 2010; Ressler et al., 2004), has been shown to lead to increased hippocampal activity in response to conditioned fear stimuli in humans (Kalisch et al., 2009), further supporting the idea that hippocampal involvement might be relevant for successful exposure. Our observations complement previous findings from animal research by translating them to human anxiety, suggesting that the hippocampus might be important for extinction-based treatment. Future research will have to disentangle whether the exact mechanism underlying this mediating relationship between hippocampal size and CBT response is in fact improved learning and integration of new associations, an improved activation of fear memory during exposure, or a combination of both.

Our results also indicate that increased bilateral insula activation and left dlPFC activation in response to threat images predict rapid CBT response. The insula has previously been implicated in awareness of internal physiological states and emotional experience (Craig, 2009; Critchley, Wiens, Rotshtein, Ohman, & Dolan, 2004; Zaki, Davis, & Ochsner, 2012). Increased insula activation during threat processing has been associated with a range of anxiety disorders, and it has been shown to reduce through the course of CBT (Ball et al., 2012; Etkin & Wager, 2007; Goossens, Sunaert, Peeters, Griez, & Schruers, 2007; Klumpp et al., 2013; Sakamoto et al., 2005; Schienle, Schafer, Hermann, Rohrmann, & Vaitl, 2007; Stern et al., 2011). Impairment of the insula has also been

suggested to cause impairments in aversively based learning (Rodriguez-Ortiz, Balderas, Saucedo-Alquicira, Cruz-Castaneda, & Bermudez-Rattoni, 2011), pointing towards a potential role of the insula in threat processing. Our observation that increased insula activation is related to improved treatment outcome is in line with previous research highlighting increased activation in brain areas of threat processing as relevant for treatment response. For instance, greater baseline amygdala response to threat stimuli has been shown to predict better clinical outcome at the end of CBT in generalised anxiety disorder (McClure et al., 2007), and increased amygdala and insula signal have been associated with improved CBT response in obsessive-compulsive disorder (Olatunji et al., 2013). Similarly, enhanced baseline responsivity in visual and occipital areas appears to be essential for clinical improvement during CBT in social anxiety disorder (Doehrmann et al., 2013; Klumpp et al., 2013). The emotional processing theory postulates that thorough threat processing is essential for exposure-based CBT to be effective (Foa & Kozak, 1986). This account is supported by a range of studies demonstrating that distraction from threat processing during exposure-based CBT significantly dampens clinical response (Craske et al., 1989; Kamphuis & Telch, 2000; Salkovskis et al., 2007; Taylor & Alden, 2010). Furthermore, yohimbine, an alpha(2)-adrenergic receptor antagonist known to improve CBT outcome if taken before exposure (Powers, Smits, Otto, Sanders, & Emmelkamp, 2009; Smits et al., 2013), has been shown to increase attention bias for threat (Vasa et al., 2009). It is possible that such

an increase in threat processing is the key mechanism underlying the facilitative effects of the drug on CBT. Attention bias towards internal physiological changes is a defining feature of panic disorder (Craske, Lang, Tsao, Mystkowski, & Rowe, 2001; De Cort, Griez, Buchler, & Schruers, 2012; Ehlers, Breuer, Dohn, & Fiegenbaum, 1995). Based on these observations, we propose that increased insula activation as observed here reflects increased attention towards interoceptive fear triggers, resulting in improved threat processing and fear extinction.

Our results also identified increased response in the dlPFC in Maintain versus Reappraisal conditions as predictive of enhanced, rapid response to CBT. Those who showed particularly increased activation in this area when viewing threat images naturally (Maintain blocks) but managed to reduce recruitment of this area during voluntary reappraisal benefitted notably more from treatment. This activation pattern is in line with previous work showing increased dlPFC activation during symptom provocation in anxiety disorders, and a reduction of such activation patterns following CBT (Goldin, Manber, Hakimi, Canli, & Gross, 2009; Paquette et al., 2003; Straube, Glauer, Dölger, Mentzel, & Miltner, 2006). Furthermore, increased prefrontal-cortical activation during threat processing has recently been identified as relevant for enhanced clinical response to CBT for social phobia (Klumpp et al., 2013). The dlPFC has extensively been linked with working memory processes, particularly with visual working memory, monitoring and vigilance (Barbey, Koenigs, & Grafman, 2013; Shackman, McMenamin, Maxwell, Greischar, & Davidson, 2009), but also with explicit verbal retrieval (Morro, Cutini, Ursini, Ferrari, & Quaresima, 2013). Furthermore, down-regulation of the left dlPFC using repetitive transcranial magnetic stimulation (rTMS) or transcranial direct-current stimulation (tDCS) has been shown to impair working memory for fear-related words (Weigand et al., 2013), and to impair fear memory consolidation (Asthana et al., 2013). The emotional processing theory of fear (Foa & Kozak, 1986) suggests that successful exposure not only depends on thorough processing of and attention towards the fear stimulus, but also on a full activation of fear memory associations and cognitive representations, including stimuli, responses, and their meaning. The importance of fear memory activation for extinction to be successful is well supported by research in animals, demonstrating that experimental activation of the fear memory through symptom provocation prior to extinction leads to drastically improved outcome (Monfils, Cowansage, Klann, & LeDoux, 2009). Based on these findings, it is possible that increased dlPFC activation as seen in our study mediates treatment success through facilitated fear memory activation, involving a more detailed cognitive representation of the fear experience.

However, neurobiological accounts of emotion regulation propose that recruitment of prefrontal-cortical activation is associated with down-regulation of negative affect through an attenuation of threat signalling in limbic areas (Beauregard, 2007; Ochsner, Silvers, & Buhle, 2012). More recent accounts of anxiety suggest that such regulation strategies might not only involve adaptive forms of regulation, but also maladaptive, dysfunctional mechanisms characteristic for anxiety disorders (Hofmann et al., 2012; Reinecke & Harmer, in press; Shin & Liberzon, 2010). These safety behaviours, such as counting in one's mind, trying to mentally talk oneself out of the anxiety, or holding on to something, are thought to maintain the anxiety disorder by preventing the patient from making corrective experiences when confronted with a threat situation. It is possible that patients who use a range of dysfunctional regulation strategies when confronted with threat but are able to successfully drop these when given alternative, more functional strategies, are those who will benefit best from CBT. Future research

will have to carefully disentangle the exact function of increased dlPFC activation in promoting CBT response.

Taken together, this study has identified structural and neuro-functional brain markers that have the potential to predict whether a patient with panic disorder will benefit from exposure-based CBT. Such knowledge may ultimately help to improve overall treatment outcomes by individually allocating patients to an optimal treatment before its cost intensive application. In particular, the results provide some preliminary evidence that a brief, structural brain scan that allows patients to maintain their medication regime may, similar to more elaborate and more interference-prone functional scans, provide reliable information regarding future CBT response. More importantly, however, our findings highlight brain areas relevant for CBT response. Such results might drive the development of more accessible, more compact treatment formats targeting these mechanisms more effectively. Recent work suggests that panic disorder may potentially be treated using much briefer CBT courses than previously thought – with one third of patients already reaching recovery status after only a single session of exposure (Reinecke, Waldenmaier, Cooper, & Harmer, 2013). It appears plausible that these early responders are patients who are able to draw on fear circuit brain areas associated with thorough threat processing and fear memory activation much more readily and successfully, leading to a stronger habituation experience. Identifying add-on CBT components such as pharmacological compounds that improve threat processing and fear memory activation prior to exposure may have great potential to ultimately develop ultra-brief CBT into a standard-of-care treatment.

While these results are promising, there are several limitations to their interpretation. First, brain areas predicting immediate treatment outcome may differ from brain areas predicting stability of treatment gains during follow-up. Additional studies including information on follow-up symptom severity will be essential to elucidate brain areas relevant in the prevention of relapse. Second, in clinical reality, patients also often present for CBT while being on anxiolytic or antidepressant treatment. As previous work suggests that CBT response might differ in these patients (e.g., Barlow, Gorman, Shear, & Woods, 2000), future studies will have to explore whether predictive associations found here generalize to medicated patient samples. It also remains to be tested whether identified predictors of treatment success are specific to CBT, or whether they can be generalized to pharmacological treatments such as selective serotonin reuptake inhibitors that have also been shown to be effective in a subgroup of patients with panic disorder (Clum, Clum, & Surls, 1983). Previous research in depression identified the insula as a treatment-specific biomarker that differentially predicted response to CBT versus medication (McGrath et al., 2013). Similar work in anxiety will have to establish whether specific brain activation patterns are differentially associated with response to different treatment options, which would significantly contribute to the development of algorithms to guide treatment allocation.

Third, it will be important to distinguish the predictive associations found here from brain response to neutral or positive images, to establish that brain activity to images (versus fixation baseline) is indeed related to the threat value of the images rather than the processing of images in general. Furthermore, interpretation of results is limited by the fact that the two measures used to monitor treatment response (PDSS-SR, ACQ) were differentially associated with pre-treatment hippocampal volume and neural activation in response to threat. This observation raises the question as to how to reliably define treatment response in anxiety treatment studies. However, it appears plausible that brain areas that are thought to be differentially associated with different roles in threat processing and fear memory activation are differentially associated with more

automatic-physical (PDSS-SR) versus more strategic-cognitive (ACQ) symptoms of panic. Future studies embracing the multiple phenomenological facets of anxiety may, in fact, improve our knowledge of the mechanisms underlying successful CBT.

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