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

Andrea Reinecke [a, *], Kai Thilo [b], Nicola Filippini [a, c], Alison Croft [d], Catherine J. Harmer [a]

[a] Department of Psychiatry, University of Oxford, UK
[b] Oxford Psychologists Ltd., Oxford, UK
[c] Centre for Functional Magnetic Resonance Imaging of the Brain, University of Oxford, UK
[d] Oxford Cognitive Therapy Centre, Warneford Hospital, Oxford, UK

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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.

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 & Marzol, 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

* Corresponding author. University of Oxford, Department of Psychiatry, Warneford Hospital, Oxford OX37JX, UK. Tel.: +44 1865 226471; fax: +44 1865 251076.
E-mail address: andrea.reinecke@psych.ox.ac.uk (A. Reinecke).

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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, Stuttgen, 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 ± 11.1, years of education 15.8 ± 2.5, verbal intelligence as measured using the NART (Nelson, 1982): 116.6 ± 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 ± 1.7, mean arousal ratings 6.0 ± 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

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