Changes in Automatic Threat Processing Precede and Predict Clinical Changes with Exposure-Based Cognitive-Behavior Therapy for Panic Disorder

Andrea Reinecke, Lara Waldenmaier, Myra J. Cooper, and Catherine J. Harmer

Background: Cognitive behavioral therapy (CBT) is an effective treatment for emotional disorders such as anxiety or depression, but the mechanisms underlying successful intervention are far from understood. Although it has been a long-held view that psychopharmacological approaches work by directly targeting automatic emotional information processing in the brain, it is usually postulated that psychological treatments affect these processes only over time, through changes in more conscious thought cycles. This study explored the role of early changes in emotional information processing in CBT action.

Methods: Twenty-eight untreated patients with panic disorder were randomized to a single session of exposure-based CBT or waiting group. Emotional information processing was measured on the day after intervention with an attentional visual probe task, and clinical symptoms were assessed on the day after intervention and at 4-week follow-up.

Results: Vigilance for threat information was decreased in the treated group, compared with the waiting group, the day after intervention, before reductions in clinical symptoms. The magnitude of this early effect on threat vigilance predicted therapeutic response after 4 weeks.

Conclusions: Cognitive behavioral therapy rapidly affects automatic processing, and these early effects are predictive of later therapeutic change. Such results suggest very fast action on automatic processes mediating threat sensitivity, and they provide an early marker of treatment response. Furthermore, these findings challenge the notion that psychological treatments work directly on conscious thought processes before automatic information processing and imply a greater similarity between early effects of pharmacological and psychological treatments for anxiety than previously thought.

Key Words: Antidepressants, anxiety, cognitive-behavior therapy, emotional information processing, mechanisms of action, panic disorder

Cognitive-behavior therapy (CBT) is a well-established psychological treatment revolving around experimentation with alternative, more adaptive behaviors and cognitions (1), and it has been shown to be very effective in targeting emotional disorders such as depression or anxiety (2). However, treatments are cost-intensive (3), and a subgroup of patients does not achieve sustained improvement at all (4). To enhance interventions and their application it is important to identify the mechanisms underlying their efficacy. Recent research suggests that biased processing of emotional information might be a surrogate marker for the presence of affective disorders and for the effectiveness of interventions used to treat them (5). For example, research has shown that if a face with a negative expression and a face with a neutral expression are shown simultaneously, anxious patients are more likely than non-anxious people to automatically direct their attention to the negative face (6,7). Such a reduced threshold for processing negative information is believed to make anxiety attacks more likely (8). Studies have also found that first-line treatments for anxiety (9), CBT and pharmacological treatment with drugs such as serotonin reuptake inhibitors, bring this threshold back up to a normal level (10–12), suggesting that a normalization of threat bias might be a key mechanism underlying recovery with either treatment.

A methodological caveat of such studies is that by the end of treatment both processing bias and symptoms are resolved, making it impossible to disentangle these two effects and to draw conclusions with regard to their causal relationship. An acute-dose paradigm, established in pharmacological research, allows the investigation of the effects of drug treatment on cognitive bias and subjective symptoms separately. Research in healthy samples exploring the early effects of selective serotonin reuptake inhibitors or serotonin–norepinephrine reuptake inhibitors, routinely used in the treatment of anxiety disorders, show that emotional processing is already targeted during acute and short-term drug administration, before changes in anxiety or mood are seen (13–17). A similar cognitive neuropsychological approach used in depression revealed that such early changes in emotional processing with antidepressant administration were predictive of later changes in therapeutic effects measured 6 weeks later (5). Such results suggest that early changes in cognitive bias drive recovery during antidepressant treatment.

In contrast, it is usually assumed that CBT primarily targets more explicit and deliberate cognitive beliefs and control processes rather than automatic processes (5,18,19). Cognitive behavioral therapy would therefore be expected to reduce automatic threat processing only over time and only with repeated practice and learning. We have tested this hypothesis in panic disorder (PD), as a paradigm treatment target, with an acute-dose CBT paradigm. Our results fundamentally challenge the idea that CBT predominantly affects explicit, strategic processing aspects and suggest that, contrary to popular belief, change in automatic threat processing might be a key mechanism of CBT action.

From the Department of Psychiatry (AR, LW, CJH); and the Isis Education Centre (MJC), University of Oxford, Oxford, United Kingdom.

Address correspondence to Andrea Reinecke, Ph.D., University of Oxford, Department of Psychiatry, Warneford Hospital, Oxford OX37JX, UK; E-mail: andrea.reinecke@psych.ox.ac.uk.

Received Sep 5, 2012; revised and accepted Feb 4, 2013.

0006-3223/$36.00
http://dx.doi.org/10.1016/j.biopsych.2013.02.005

Methods and Materials

Participants

Twenty-eight patients with DSM-IV PD with or without agoraphobia, naïve to exposure-based CBT, were recruited. They were randomly assigned to one of two experimental conditions, either receiving a single session of exposure-based CBT (treatment group [TG]) or no intervention (until after the study procedures and assessments; waiting group [WG]). Diagnoses were assessed with the Structured Clinical Interview for DSM-IV Axis I Disorders Clinician Version (20). Patients had to present with at least moderate agoraphobic avoidance, panic-related safety behaviors (e.g., medication, or standing close to an escape exit to prevent panic attacks) and catastrophic panic cognitions (e.g., "If I stay here my heart will beat even faster, and I will suffer a heart attack"), assessed with a structured panic assessment interview (21). General exclusion criteria were lifetime history of epilepsy, psychotic disorders, bipolar disorder or substance abuse, primary depressive disorder, insufficient English skills, and psychopharmacological or psychotherapeutic treatment during the last 6 months. Occasional medication with benzodiazepines or β-blockers as needed was not an exclusion criterion. However, patients were required to be medication-free 48 hours before the test sessions to avoid any interference with experimental testing and CBT (benzodiazepine as needed: one TG, one WG; β-blocker as needed: three TG, two WG).

Clinical Symptom Questionnaires

At all three test times, general levels of anxiety and depression were assessed with the Hospital Anxiety and Depression Scale (22). Panic symptoms were monitored with: 1) the Body Sensations Questionnaire (BSQ) (23), assessing to what degree patients are afraid of specific physical symptoms such as heart palpitations or dizziness; 2) the Agoraphobic Cognitions Questionnaire (ACQ) (23), assessing the severity of explicit catastrophic beliefs occurring in such situations, such as "I am going to pass out"; and 3) the Mobility Inventory (MI) (24), determining agoraphobia severity by asking to what degree certain situations such as crowded places or public transport were avoided for fear of having a panic attack. During the first visit only, patients also completed the Panic Disorder Severity Scale (25), the Panic Attack Scale (26) and the National Adult Reading Test (27) to ensure that the two groups were matched with respect to baseline panic severity, panic frequency, and verbal intelligence.

Faces Dot Probe Task

Stimuli were colored photographs of 20 individual faces with a neutral, fearful, and happy facial expression each (28). In each trial, these were arranged in a neutral-neutral, neutral-happy, or neutral-fearful pair (64/condition, 192 in total), with stimuli appearing above and below a central fixation position. The probe was a double dot oriented either horizontally (..) or vertically (:). Eight blocks of unmasked trials versus masked trials each were presented in an alternating order. In the unmasked condition, a face pair was presented for 100 msec. In the masked condition, the face was presented for 16 msec, and then replaced by a mask (scrambled face) for 84 msec. Immediately afterward, a dot probe replaced one of the faces. Participants were instructed to report the orientation of the probe as quickly and accurately as possible. Position of an emotional face, probe position, and type were fully counterbalanced. Thus, this task design involved congruent trials (dot appears at the position of an emotional face) and incongruent trials (dot replaces a neutral face while an emotional face is present). Although previous research suggests no differences between panic disorder patients and control subjects in processing unmasked faces, patients show increased vigilance for masked fearful faces (7).

Manipulation Check (Stress Test)

To provide evidence for the efficacy of the CBT session given to half of the patients, responses to a stress test (29) were recorded. This involved 5 min of exposure to an individually chosen agoraphobic situation that would be likely to provoke panic-specific catastrophic cognitions and anxiety. For most participants, this involved being in an enclosed walk-in closet (TG = 10, WG = 9). Other tests included a bus or car drive through the city center (TG = 1, WG = 1), a walk through an open-spaced park (TG = 2, WG = 0), being in a crowded supermarket or shopping street (TG = 0, WG = 3), or being in a lift (TG = 1, WG = 1). There were no systematic differences in the distribution of test types between the two groups ($\chi^2 = 5.05$; $p = .28$). Immediately after the manipulation check, participants rated their degree of situational anxiety and catastrophic belief experienced during the test (for four time points: just before, after 1 min, after 3 min, at the end of the test), with 0–100 visual analogue scales. Baseline ratings were acquired during an earlier part of the experimental sessions, before the faces dot probe task and stress test.

Intervention

The treatment followed a previously published protocol (29) based on the well-established cognitive-behavioral theory of panic (21). This approach assumes that anxiety disorders develop as a consequence of neutral situations being misperceived as threatening and safety strategies (e.g., leaving situation, calling a friend) being developed to reduce the perceived danger. Safety behavior 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 single-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 (15 min), focusing on the role of safety strategies and exposure to an individually agoraphobic situation (stress test situation; 15 min) while dropping safety behavior (Supplement 1).

General Procedure

The study was approved by the local National Health Service research ethics committee, and informed consent was obtained. Patients were assessed on 3 test days, with the first two assessments taking place on 2 consecutive days, and the last assessment being carried out 4 weeks later. On all test days, clinical symptoms were assessed with the questionnaires detailed in the preceding text. Afterward, responses to the stress test were recorded at all three assessments to provide evidence for the efficacy of the CBT session. At the end of the first test day, half of the participants received one session of CBT. The following day, participants were given the Faces Dot Probe task to assess emotional information processing.

Statistical Analysis

All statistical tests (SPSS, version 20; SPSS, Chicago, Illinois) were two-tailed and based on an alpha-level of significance of .05. Effect sizes are reported as Cohen's *d*. Group differences in matching variables and clinical symptoms were analyzed with