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Threat expectancy bias and treatment outcome in patients with panic disorder and agoraphobia

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ABSTRACT

Background and objectives: Previous studies suggest that patients with panic disorder and agoraphobia (PD/A) tend to overestimate the associations between fear-relevant stimuli and threat. This so-called threat expectancy bias is thought to play a role in the development and treatment of anxiety disorders. The current study tested 1) whether patients with PD/A ($N = 71$) show increased threat expectancy ratings to fear-relevant and fear-irrelevant stimuli relative to a comparison group without an axis I disorder ($N = 65$), and 2) whether threat expectancy bias before treatment predicts treatment outcome in a subset of these patients ($n = 51$).
Methods: In a computerized task, participants saw a series of panic-related and neutral words and rated for each word the likelihood that it would be followed by a loud, aversive sound.
Results: Results showed higher threat expectancy ratings to both panic-related and neutral words in patients with PD/A compared to the comparison group. Threat expectancy ratings did not predict treatment outcome.
Limitations: This study only used expectancy ratings and did not include physiological measures. Furthermore, no post-treatment expectancy bias task was added to shed further light on the possibility that expectancy bias might be attenuated by treatment.
Conclusions: Patients show higher expectancies of aversive outcome following both fear-relevant and fear-irrelevant stimuli relative to the comparison group, but this does not predict treatment outcome.

1. Introduction

Panic disorder with agoraphobia (PD/A) is characterized by recurrent and unexpected panic attacks and situational avoidance (American Psychiatric Association, 2013; Brown, Campbell, Lehman, Grisham, & Mancill, 2001; Kessler et al., 2006). One model for the development and treatment of panic disorder (PD) is derived from Pavlovian fear conditioning and extinction (Mineka & Oehlberg, 2008; Pavlov, 1927). Meta-analyses have shown that patients with anxiety disorders demonstrate enhanced fear acquisition and reduced fear extinction relative to comparison groups without axis I disorder (Duits et al., 2015; Lissek et al., 2005). However, it is not clear whether these impaired fear conditioning processes are necessarily based on fear conditioning abnormalities or whether they involve more general biases towards threat expectancy. Indeed, studies that compared patients with PD to a comparison group without axis I disorder have found increased (subjective) threat expectancy ratings in patients to stimuli that were only verbally associated with a shock (Grillon et al., 2008) as well as to stimuli which were not explicitly associated with a shock (Lissek et al., 2009, 2010). These findings suggest a more general bias towards threat in patients with PD, which may be independent of fear conditioning processes.

The phenomenon of overestimating associations between fear-

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relevant stimuli and threat is known as 'threat expectancy bias'. Threat expectancy bias (i.e., overestimating the *forthcoming* stimulus-threat association) may play a causal role in the origin and maintenance of anxiety disorders (e.g., Beck & Clark, 1997). Interestingly, threat expectancy bias may originate from *pre-experimental* expectancies, rather than from learning threat contingencies in fear conditioning studies (e.g., Davey, 1992; McNally & Heatherton, 1993). An experimental study demonstrated that patients with PD, relative to a healthy comparison group, show a priori threat expectancy bias: they overestimate associations between fear-relevant stimuli and threat (Wiedemann, Pauli, & Dengler, 2001). One longitudinal study found that increased a priori threat expectancy ratings predict the persistence of PTSD symptoms in soldiers deployed to Iraq, even after controlling for earlier PTSD symptoms (Engelhard, de Jong, van den Hout, & van Overveld, 2009).

Threat expectancy bias may contribute to the development and maintenance of anxiety disorders by intensifying pre-existing anxiety and reducing extinction learning (e.g., Davey, 1997, 2006; McNally, 1990; Öhman & Mineka, 2001; Tomarken, Mineka, & Cook, 1989; Vroling & De Jong, 2013). Extinction learning is considered to be a core mechanism underlying exposure therapy (e.g. Craske, Treanor, Conway, Zbozinek, & Vervliet, 2014). Therefore, it could be hypothesized that threat expectancy bias before treatment predicts worse outcome of exposure therapy in patients with PD/A.

So far, the predictive value of threat expectancy bias on treatment outcome has not been investigated. One study investigated covariation bias, which is an overestimation of random associations between fear-relevant stimuli and *actual* aversive consequences (rather that an a priori bias), and demonstrated that high covariation bias measured directly after treatment predicted relapse after two years in patients with spider phobia (de Jong, Van Den Hout, & Merckelbach, 1995). In the current study, we tested whether high threat expectancy ratings before treatment predict poor treatment outcome in patients with PD/A using fear-relevant and fear-irrelevant stimuli. Although increased threat expectancies are most pronounced when fear-relevant (instead of fear-irrelevant) stimuli are used (e.g., Wiedemann et al., 2001), results from fear conditioning studies in patients with PD suggest that increased threat expectancy ratings may also be associated with fear-irrelevant stimuli. That is, patients with PD, relative to comparison groups, have demonstrated stronger fear responses to both threat cues and safety cues (Lissek et al., 2009, 2010).

In the current study, a threat expectancy task was administered in patients with PD/A and a comparison group without axis I disorder. Patients with PD/A completed the expectancy task before participating in exposure therapy. The aim of the current study was to replicate and extend previous findings by examining 1) whether patients with PD/A relative to the comparison group demonstrate higher threat expectancy ratings to panic-related as well as to neutral words before treatment, and 2) whether threat expectancy ratings measured before treatment would predict treatment outcome in patients with PD/A. We hypothesized that 1) the patient group would show a stronger threat expectancy bias to fear-relevant stimuli than the comparison group and that 2) higher threat expectancy ratings before treatment would be associated with worse treatment outcome in patients with PD/A. To extend earlier findings, we also explored whether the hypothesized increased threat expectancy ratings in patients with PD/A were not only related to fear-relevant stimuli but also to fear-irrelevant stimuli.

2. Method

2.1. Participants

Ninety-seven patients with PD/A were invited for the current study through three mental health care organizations in the Netherlands: Altrecht Academic Anxiety Centre (Utrecht), GGZ inGeest (Amsterdam), and GGZ Centraal (Ermelo). Twenty-six patients refused to participate. Seventy-one patients with PD/A (39% male) participated in the threat expectancy paradigm before they started exposure therapy with response prevention (ERP). The current study was part of a multi-center randomized controlled trial, in which the added value of D-cycloserine (DCS) administration in patients with PD/A was examined (Klein Hofmeijer-Sevink et al., in preparation). Sample size calculations were based on a power analysis comparing three groups (DCS before treatment versus DCS after treatment versus placebo), with a 0.05 significance level (two-tailed), power of 80% and Cohen's effect size of 1.1 (based on previous work by Otto et al., 2010). Calculations resulted in a recommended sample size of 20 patients per condition. To take into account the attrition rate (estimated to be approximately 20%), we included 71 patients. Exclusion criteria for the current study were 1) dependence and/or abuse of alcohol/drugs in the past three months; 2) current comorbid psychotic disorder; 3) current severe major depressive disorder; 4) current bipolar disorder; 5) mental deficiency (verbal IQ < 80 as assessed with the Dutch Adult Reading test; Schmand, Bakker, Saan, & Louman, 1991); and 6) insufficient ability to speak or read Dutch. Diagnosis of PD/A and any comorbid diagnoses were established with the Dutch version of the structured clinical interview for DSM-IV Axis-I disorders (SCID-I; First, Spitzer, Gibbon, & Williams, 1994; Groenestijn, Akkerhuis, Kupka, Schneider, & Nolen, 1998). Thirty-eight patients (54%) had no comorbid diagnosis, 15 patients (21%) were diagnosed with one comorbid other anxiety disorder, 10 patients (14%) with an additional mood disorder and 8 patients (11%) were diagnosed with both a comorbid other anxiety disorder and a mood disorder. Thirty-two patients (45%) used at least one psychotropic medicine at the time of participation, including the use of serotonin reuptake inhibitors ($N = 23$), benzodiazepines ($N = 13$) and tricyclic antidepressants ($N = 2$). Medication dosage was kept stable throughout the ERP.

Sixty-five healthy control subjects (48% male) were recruited through advertisements (posters and flyers) and via contacts of the researchers. The comparison group was matched with the patient group on age, sex and highest attained educational level. Table 1 provides the demographics and clinical characteristics of the patient and comparison group. Absence of a lifetime DSM-IV Axis I disorder in the comparison group was confirmed by using the Mini International Neuropsychiatric Interview (Lecrubier et al., 1997; Sheehan et al., 1997). None of the subjects from the comparison group used psychotropic medication.

This study was approved by the Medical Research Ethics Committee of the University Medical Centre Utrecht. Subjects were first informed about the study, both orally and by written information, and then provided written informed consent.

2.2. Procedure

At baseline, prior to the first treatment session, the threat expectancy task was administered to patients with PD/A. The task was developed by Engelhard et al. (2009), and based on Davey, 1992; exp 2 and 4), and was adapted for the current study, i.e., the deployment-(un)related images used by Engelhard et al. (2009) were replaced by panic-related and neutral words for this study. Participants were seated in a quiet room and completed the threat