Research paper

A mania-related memory bias is associated with risk for relapse in bipolar disorder[☆,☆☆]

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ABSTRACT

Objective: Previous work has shown that neuropsychological performance can predict outcome of psychotherapy. The present paper explores whether an affective bias in verbal memory is associated with recurrence of mood episodes in patients with Bipolar Disorder (BD).
Method: 76 euthymic adult patients with BD were randomly assigned to either 9 months of Cognitive Behavioral Therapy (CBT) or Support Therapy (ST), and followed up for 2 years after completing therapy. At baseline, affective learning memory (Emotional Auditory Verbal Learning Test; EMO-AVLT) and other measures were assessed. Recurrence of a mood episode was the primary outcome.
Results: The survival analyses revealed that the interaction between therapy condition, more specifically ST, and a recognition bias in favor of mania-related, but not depression-related words predicted recurrence of mania. Recurrence of depression was predicted by neither affective memory bias nor their interaction with treatment.
Conclusions: A mania-related memory bias emerged as a predictor of mania recurrence, specifically in an unstructured setting such as ST. Perhaps mania-related schemata are more salient or more easily activated in those at high risk for recurrence. Interventions targeting patients' insight into their internal states as potential indicators of prodromal manic symptoms could be the key to improve the outcome of psychological interventions in BD. Additional research in the role of cognitive factors in relapse prevention is warranted.

1. Introduction

The number of studies investigating the factors predicting the efficacy of psychological treatments in bipolar disorder (BD) is limited, and usually focuses on indices of illness progression such as age of onset or number of prior mood episodes (Lam et al., 2009; Reinares et al., 2014). Across psychiatric disorders, only a small number of studies have investigated the role of cognitive abilities in therapeutic outcomes more generally, and the evidence is mixed. Higher verbal intelligence scores and immediate verbal recall were associated with better treatment response to both CBT and fluoxetine in adults with OCD (D'Alcante et al., 2012), although others have not shown this effect (Braga et al., 2016). Lower intelligence scores were linked to poor treatment response to medication and behavioral therapy in unipolar depression (Fournier et al., 2009) and Post-traumatic Stress Disorder (Rizvi et al., 2009). Additionally, others have shown that the relationship between baseline cognitive abilities and treatment outcomes is associated with the type of psychotherapy delivered. For example, poor performance on

a spatial memory test predicted reduced treatment response to CBT in children with obsessive compulsive disorder (OCD) (Flessner et al., 2010). Elderly patients with anxiety disorders were found to benefit from CBT regardless of their intellectual functioning. However, only patients with high intelligence scores were found to benefit from less structured counseling therapy (Doubleday et al., 2002). Further, in a previous paper based on a subset of the dataset used for the current study (Bauer et al., 2017) euthymic BD patients with lower free recall performance were more likely to have a manic relapse, especially if randomly assigned to a less structured supportive therapy (ST). The link between cognitive performance and treatment response may, therefore, depend on the type of psychological treatment and mental health problem.

While the studies mentioned before provide some evidence that interindividual differences at baseline in non-emotion laden cognitive abilities ("cold cognition") might moderate the effects of psychotherapies, the question is whether emotionally relevant cognitive processes such as memory biases or dysfunctional attitudes ('hot

cognition') also predict treatment outcome given the established link between affective processing, mood, and cognition (e.g. Elliott et al., 2011). A few studies have looked at "hot cognition" and psychotherapy outcome. For example Segal et al. (2006) found that "cognitive re-activity" to a sad mood induction was related to relapse in depression. Cognitive reactivity was defined here as the propensity to dysfunctional attitudes due to current mood state (Wenze et al., 2007). When talking about an affective cognitive bias, research usually refers to an atten-tional or memory bias towards specific stimuli due to their intrinsic emotional significance. Such biases appear to be especially pronounced during the manic and depressive phases of BD (e.g. García-Blanco et al., 2013; Murphy et al., 1999; Roiser et al., 2009). The evidence is mixed with regards how strong such biases are still during euthymia (e.g. García-Blanco et al., 2017; Lex et al., 2011; Lex et al., 2008; Linke et al., 2011; Montel et al., 2014). Some findings suggest that such affective biases are mood-congruent but might persist during the euthymic states and might even indicate an increased risk for recurrence similar to what Segal et al. (2006) had found.

We therefore decided to specifically explore whether an affective memory bias measured during euthymic mood state was related to recurrence of mood episodes using data from BD patients who were followed up for 2 years after completing either cognitive behavioral therapy (CBT) or supportive therapy (ST) for a period of 9 months (Meyer and Hautzinger, 2012). We tested the hypothesis that memory bias towards mania-related words would be related to re-currence of mania, and that a memory bias for depression-related words would predict recurrence of depression. Specifically, we hy-pothesized that better memory for mania-related words would be associated with greater rates of relapse into mania. Accordingly, better memory for depression-related words would be linked to greater incidence of relapse into depression. We also examined two exploratory hypotheses testing 1) whether an affective memory bias would predict recurrence of a mood episode of opposite polarity and 2) whether biases would interact with treatment (ST or CBT) to predict recurrence.

2. Methods

2.1. Participants

Using Meyer and Hautzinger (2012)'s dataset we included clinical and cognitive data from 76 participants with BD Type I and II who were euthymic at the time of recruitment for the RCT (mean age: 43.96 ± 11.81, 38 women) (Meyer and Hautzinger, 2012). The study took place at the Department of Psychology, University of Tübingen, Germany, between August 1999 and September 2004. Participants were recruited by word-of-mouth and through clinicians' and hospital's re-ferrals. Participants were first invited to a screening session and eligible candidates were asked to give informed consent (Fig. 1). At baseline participants were administered clinical interviews (e.g. SCID-I and SCID-II) and self-ratings questionnaires (e.g. Beck Depression Inventory (BDI), Self-Report Mania Inventory (SRMI) (Shugar et al., 1992). Par-ticipants were included if 1) their primary diagnosis was BD based on the DSM-IV (APA, 1994), 2) they were aged between 18 and 65 years, and 3) open to continue or start new medication. Exclusion criteria were: 1) the primary diagnosis was a non-affective disorder including schizo-affective disorder; 2) participants currently suffered from a major affective episode as defined in DSM-IV (depressed, mixed or mania either defined by the SCID-I or Bech-Rafaelsen Mania or Mel-ancholia Scale (Bech and Rafaelsen, 1980); 3) participants suffered from a substance-induced affective disorder or an affective disorder due to a general medical condition; 4) current substance dependency re-quiring detoxification (abuse did not qualify for exclusion); 5) in-tellectual disability (IQ < 80), and 6) participants currently in psy-chological treatments [for further details see: Meyer and Hautzinger, 2012]. Participants were randomly assigned to CBT and ST

and the two treatment groups were matched for gender, BD I or II disorder, and age of onset. Therapists had at least 1 year postgraduate training in psychotherapy and had attended a specific 2-day workshop for CBT and ST for BD. All sessions were video-taped and supervised on a weekly basis.

2.2. Procedures and measures

At baseline an extensive assessment was undertaken including the SCID-I to assess DSM-IV diagnoses, mood questionnaires, as well as neuropsychological tests. A modification of the SCID was used during follow-up to assess recurrence of new mood episodes. During the treatment period hospitalizations and mood episodes were tracked based on the clinicians' notes and patients' mood diaries. The se-verity of mood episodes was evaluated using the Bech-Rafaelsen Melancholia Scale (BRMS), Bech-Rafaelsen Mania Rating Scale (BRMAS) and the Global Assessment Scale (APA, 1994; Bech and Rafaelsen, 1980; Bech et al., 1978). Self-rating mood measures in-cluded the Beck Depression Inventory (Beck and Steer, 1987) and the Self-Rating Mania Inventory (Shugar et al., 1992) [for further details see: Meyer and Hautzinger, 2012]. Throughout the study the parti-cipants' medication treatment was tracked using the Somatotherapy Index (Bauer, 2001). We used this index to aggregate patients' medications instead of reporting frequencies for individual medica-tion or their combinations. The CBT and ST groups did not differ with regard to medication treatment. After the initial clinical assessment participants were randomly assigned to the CBT or Supportive Therapy (ST) interventions including 20 sessions over 9 months. Follow-up assessments by raters blind to group allocation occurred at post-treatment, month 3, 6, 9, 12 and 24 (Please see for additional information about recruitment, procedures or measures: Bauer et al., 2017; Meyer and Hautzinger, 2012). Prior to treatment participants were administered a general intelligence measure – Leistung-sprüfsystem (LPS) and the Emotional Auditory Verbal Learning Test (described below) (Lex et al., 2011).

2.3. Affective memory bias

The Emotional Auditory Verbal Learning Test (EMO-AVLT, Lex et al., 2011) is an affective analogue version to the California Verbal Learning Test (Delis et al., 1987). The EMO-AVLT is a mea-sure of emotional processing which has been used both in patients with BD (Lex et al., 2011) and in individuals at risk for mood dis-orders (Lex and Meyer, 2013). As part of this test, participants are read a list of 21 words five times (List A, Trials 1–5). These words include 7 mania-related words (e.g. self-confident, talkative), 7 de-pression-related words (e.g. sad, pessimistic) and 7 neutral words (e.g. solid, normal). After each reading of the word list, there is a test of free recall of the list of words that has just been read. After the fifth trial the researcher reads to participants an interference list containing 21 words that are not related to mood (List B) followed by a free recall test of List B words (Free Recall). After testing the recall of the distraction list, subjects were asked to recall List A without reading this list to the participants again. The verbal learning curve was estimated by the sum of the number of words recalled during trials 1–5. After a 20-min interval, participants were presented with words from lists A, and B along with 20 distractors. They were then asked to which words they recognize originally presented in List A (Recognition). The test takes approximately 40 min.

As part of this study we focused on the variables 'Learning trials 1–5', 'Free recall' and 'Recognition' for neutral, mania and depression-related words. To eliminate the effect of general memory capacity and only capture affective bias for each EMO-AVLT variable, we generated two scores, separately for depression- and mania-related words by subtracting the number of correctly learnt, recalled, and recognized neutral words from the respective depression- and mania-related words.