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# Impaired down-regulation of negative emotion in self-referent social situations in bipolar disorder: A pilot study of a novel experimental paradigm

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## ABSTRACT

Emotion dysregulation is a core feature of bipolar disorder (BD) that persists into periods of remission. Neuroimaging studies show aberrant neural responses during emotion regulation (ER) in patients with BD relative to healthy controls, but behavioural evidence for ER deficits is sparse and conflicting. This study aimed to explore ER in BD using a novel, personally relevant experimental paradigm. Twenty patients with BD and 20 patients with unipolar disorder (UD), in full or partial remission, and 20 healthy controls were given a novel computerised test. Participants were instructed to react naturally or dampen their emotional response to positive and negative social scenarios and associated self-beliefs. They were also given an established experimental task for comparison, involving reappraisal of negative affective picture stimuli, as well as a questionnaire of habitual ER strategies. BD patients showed reduced ability to down-regulate emotional responses in negative, but not positive, social scenarios relative to healthy controls and UD patients. In contrast, there were no between-group differences in the established ER task or in self-reported habitual reappraisal strategies. Findings highlight the novel social scenario paradigm as a sensitive test for detection of ER difficulties in BD.

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## 1. Introduction

Bipolar Disorder (BD) is a chronic disorder marked by recurrent affective episodes of mania and depression as well as considerable mood instability and functional impairment in-between affective episodes (e.g., Gershon and Eidelman, 2015). Emotion dysregulation in BD persists in periods of remission and is a key contributor to patients' emotional and socio-occupational impairments (Goodwin and Jamison, 2007; Van Rheenen and Rossell, 2013). Indeed, difficulty with emotion regulation (ER) in stressful social situations has been shown to interfere with appropriate social behaviours in adolescents with BD (Goldstein et al., 2006), and is associated with impaired social function (Van Rheenen and Rossell, 2014).

BD is frequently misdiagnosed as unipolar depression (UD) (e.g., Hirschfeld et al., 2003), which often leads to a delay of correct diagnosis and adequate treatment of 10 years (Bowden, 2001). This highlights a clinical need for markers of BD that can help

improve diagnostic accuracy by characterising pathophysiological processes that differ between BD and UD. Emerging neuroimaging evidence points to deficits in ER being a prominent feature of BD, while UD seems to be more consistently associated with negative processing biases (for reviews see Phillips et al., 2008; Almeida and Phillips, 2013; Miskowiak and Carvalho, 2014). Deficits in ER are thought to constitute a latent trait-related vulnerability mechanism of BD, but studies comparing ER in BD and UD include mainly patients in depressed states and produce conflicting findings (Almeida and Phillips, 2013). Neuroimaging studies point to differential patterns of neural activation during cognitive control of negative emotions between these groups (e.g., Taylor Tavares et al., 2008) and greater abnormalities in white matter tracts within the neural circuitry underlying ER in depressed patients with BD vs. UD (Versace et al., 2010). ER difficulties during depressive states occur in both UD and BD, but were recently shown to persist after clinical remission in BD patients only (Rive et al., 2015). This highlights ER difficulty as a diagnosis-specific trait-marker for BD.

Neuroimaging findings indicate that ER in BD is associated with increased activity in limbic regions implicated in emotion-generation paired with deficient lateral prefrontal top-down control of

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emotional responses (e.g., Phillips et al., 2008; Townsend et al., 2013). These neural changes may constitute an endophenotype of BD; a disease-associated trait that is highly heritable, associated with the illness, independent of the clinical state, and found in non-affected family members at a greater proportion than in the general population (Gershon and Goldin, 1986; Leboyer et al., 1998). Indeed, euthymic BD patients and individuals at familial risk of BD also show reduced functional coupling (correlation of activity over time) between prefrontal regions and amygdala during ER in response to affective stimuli (R.W. Morris et al., 2012; Heissler et al., 2014; Kanske et al., 2015), suggesting that emotion dysregulation may be an endophenotype for BD. However, studies in BD have generally failed to find any deficits in *behavioural* (i.e., task accuracy, reaction time) or *experiential* read-outs (i.e., subjective emotion intensity) of ER in response to wide range of emotional stimuli including emotion-laden film clips or aversive pictures (R.W. Morris et al., 2012; Gruber et al., 2014; Hay et al., 2014; Heissler et al., 2014; Kanske et al., 2015), highlighting the different degrees of sensitivity of these distinct units of analysis (S. E. Morris and Cuthbert, 2012). This discrepancy between neural and behavioural findings may be a result of aberrant neural responses being a more sensitive measure of abnormal brain function than overt behavioural and/or experiential subjective outcomes (e.g., Haas et al., 2007). Alternatively, this discrepancy between neural and behavioural measures may result from compensatory processes at the neural level that results in differences not being detectable at the behavioural level (Wheaton et al., 2014).

Nevertheless, it is disappointing that current behavioural paradigms are mostly unable to detect ER difficulties in BD given the impact of these difficulties on affective symptoms and psychological well-being in patients' daily lives. The scarcity of behavioural evidence for ER deficits in BD is likely to be related to the design of the current experimental paradigms: The paradigms were optimised for investigation of neural correlates of ER rather than to detect differences in behavioural and/or subjective measures of patients' ER success as reflected by differential behavioural response or change in the intensity of the resulting emotion. In particular, extant paradigms often involve static pictures or faces, which have little personal relevance (i.e., little to do with patients' real life, personal memories etc.), and provide patients with highly specific instructions on how to down-regulate their emotional responses (e.g., Heissler et al., 2014; Kanske et al., 2015; Morris et al., 2012; Townsend et al., 2013). Moreover, a limitation of these paradigms is that they generally do not tap into anxiety which is highly prevalent (observed in about 90% of BD patients) and thus possibly a core feature of BD (Simon et al., 2004; Merikangas et al., 2007).

Patients with BD may thus be successful in down-regulating emotion in the specific testing situations, but may be unable to regulate their emotions in their everyday life. In keeping with this, one study demonstrated that BD patients can successfully down-regulate their negative response to emotional film clips with rehearsed reappraisal strategies, but fail to effectively use these ER strategies when uninstructed (Gruber et al., 2012, 2014). Paradigms optimised for investigation of the explicit *experiential* rather than neural output of ER should therefore have more in common with real-world social situations in which patients receive no specific strategies or instructions to down-regulate their emotional responses.

The present study aimed to explore the ability of patients with BD in full or partial remission to down-regulate emotional responses with no specific instructions on how to regulate their emotions in a novel experimental test involving self-relevant social scenarios. The primary aim of the study was to assess the sensitivity of the novel paradigm (adapted from Goldin et al.,

2009) to measure ER difficulties in patients with BD relative to HCs. A secondary aim was to investigate whether the hypothesised ER impairment was more pronounced in BD than in UD (i.e., showed some specificity for BD) consistent with Rive et al. (2015). We hypothesised that fully or partially remitted BD patients would exhibit reduced ability to down-regulate negative and positive affect in social situations, in comparison with healthy, never-depressed individuals, and that this phenomenon would be specific to patients with BD.

## 2. Methods

### 2.1. Pilot study

Eight remitted patients with BD were recruited from the Copenhagen Affective Disorder Clinic for a pilot study that aimed to develop a task of novel social scenarios of high personal relevance for patients with BD. The task is a modified version of the social-cognitive experimental task used in Goldin et al.'s (2009) study on emotional reactivity and regulation in social anxiety disorder. Given the high rates of comorbid social anxiety in BD (Simon et al., 2004), and that the content of negative memories in BD patients are predominantly anxious in nature (Mansell and Lam, 2004), we hypothesised that negative social scenarios that provoke anxiety in patients with social anxiety disorder would also be highly prevalent for patients with BD. To construct social scenarios that were personally salient for patients with BD, we conducted 45-minute patient interviews at the Copenhagen Clinical for Affective Disorders, in which patients were asked to rate the social situation from Goldin et al.'s test for (a) personal relevance, and (b) ability to induce emotional responses. Patients were additionally asked about whether they had experienced any other highly emotional (positive and negative) social situations and, if so, to describe these and their related self-beliefs in detail. Based on these interviews, the social scenarios and associated self-beliefs that were rated as most personally relevant and emotional for the patients (four scenarios from the original task by Goldin et al. and five new social scenarios created in a collaboration between the experimenters and therapists at the Copenhagen Clinic for Affective Disorders; Table S1) were selected and used in the task. The purpose of the pilot study was solely to generate emotional social scenarios that are representative and common for patients with BD and estimate the ability of these scenarios to evoke emotional responses. Patients who participated in the pilot study were not included in the main study.

### 2.2. Participants and screening

Twenty patients with an ICD-10 diagnosis of BD and 20 patients with an ICD-10 diagnosis of UD between 18 and 60 years were recruited from the Copenhagen Affective Disorders Clinic. Twenty age and gender-matched healthy controls (HC) with no personal or first-degree family history of psychiatric illness were recruited at the University Hospital Blood Bank, Rigshospitalet. Patients were recruited at the outpatient Clinic for Affective Disorders, Psychiatric Centre Copenhagen for a validation study of new screening instruments for cognitive dysfunction in bipolar and unipolar disorder (Jensen et al., 2015; Ott et al., 2015) and subsequently asked to participate in the current study. All patients were in full or partial remission defined according to a score of  $\leq 14$  on the Hamilton Depression Rating Scale 17 items (HDRS-17; Hamilton, 1960). Patients with BD and HCs (but not UD) were also assessed with the Young Mania Rating Scale (YMRS; Young et al., 1978). Due to the latent effect on cognitive functions and potential confounds, exclusion criteria were a

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