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Emotional vulnerability and cognitive control in patients with bipolar disorder and their healthy siblings: a pilot study

Scheuch K, Bräunig P, Gauggel S, Kliesow K, Sarkar R, Krüger S. Emotional vulnerability and cognitive control in patients with bipolar disorder and their healthy siblings: a pilot study.

Objective: There is evidence that, even in remission, patients with bipolar disorder (BD) have deficits in cognitive function and emotional regulation. Siblings of patients with BD are also reported to exhibit minor dysfunction in neuropsychological domains. In this study, we examined the interference of acute mood state with reaction time (RT) and response inhibition in euthymic patients with BD, in their healthy siblings and in healthy controls.
Methods: A total of 34 patients with bipolar I disorder, 22 healthy siblings and 33 healthy controls performed a stop-signal paradigm after induction of a transient intense sadness and a relaxed mood state. The differences in RT and the response inhibition were compared between the groups.
Results: Euthymic patients with BD displayed a higher emotional reactivity compared with their siblings and with controls. Compared with controls, patients with BD showed longer RTs in a relaxed mood state and a delay in response inhibition during emotional activation.
Conclusions: The present study provides evidence for the clinical observation that patients with BD have shorter RTs when in a state of emotional arousal rather than in a relaxed state. Inhibitory deficits in these patients may be because of a too strong emotional arousal. The results show that in patients with BD, relaxation and emotional arousal are inversely associated with performance in a neuropsychological task. This is in contrast to findings in healthy individuals suggesting a dysbalance in emotional regulation in these patients.

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Keywords: Bipolar Depression Rating Scale; bipolar disorder; cluster analysis; international studies; reliability; scale validation

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Introduction

There is growing evidence that even in remission, patients with bipolar disorder (BD) have dysfunctions in several cognitive areas, such as verbal memory, executive functions and attention (1–6). Patients with BD and a history of psychotic symptoms have more impaired executive function and verbal memory deficits (7) than those without psychotic episodes. Genetic studies indicate that BD is highly heritable (8,9). However, the specific susceptibility genes remain unknown. Endophenotypes are intermediate phenotypes that are considered a more promising index of underlying genetic liability than the illness itself. One criterion is that the marker is more frequently observed in unaffected relatives of patients in comparison with the general population (10). Only a few studies investigated cognitive deficits of unaffected relatives of patients with BD. The findings have been less consistent than those conducted in affected patients themselves. Recent meta-analysis studies showed that besides verbal learning/memory, set shifting and target detection impairments, an impaired response inhibition could be the most prominent cognitive endophenotype of BD (7,11).

Response inhibition is considered a key component of executive control (12–16). The ability to suppress

responses that are no longer required or inappropriate supports flexible and goal-directed behaviour in ever-changing environments. An abnormal response inhibition may underlie the increased impulsivity, which is a core component of BD, prominent across all phases of the illness (17). Recent findings have revealed a disrupted response inhibition brain network, involving the middle frontal gyrus, the middle and superior temporal gyri, and the striatum in euthymic patients with BD (18).

Besides the cognitive dysfunctions, BD is characterised by emotional instability and fluctuations of mood (19). Studies of emotion perception and affect generation in BD suggest that misinterpretation of neutral material as negative and impairments in the capacity to inhibit emotional material may evoke the generation of inappropriate and extreme emotional responses that are difficult to regulate (20–23). This unstable affective state is thought to contribute significantly to the vulnerability of patients with BD to external stressors, which may trigger new episodes. Mood induction paradigms where subjects are requested to draft autobiographical scripts detailing a sad event in their lives are frequently used in positron emission tomography (PET) studies to investigate dysfunction in the emotional network. After induction of a transient sadness, euthymic patients with BD were found to have a decreased blood flow in the orbitofrontal and inferior temporal cortices and an increased blood flow in the dorsal/rostral anterior cingulate and anterior insula (24,25). Interestingly, the blood flow changes in response to an emotional challenge of healthy siblings had a higher similarity to the patients with BD compared with the healthy controls, which may suggest that modified emotional processing is a familial 'trait marker'.

It has been suggested that emotional dysregulation accounts for cognitive disturbances by reciprocal interactions between cognitive and emotional brain networks (18,26). However, studies that have examined a direct cognitive-emotional interference are scarce. To investigate the interrelation between emotional regulation and cognitive function, we used an acute memory-evoked sad mood provocation and a relaxation induction with a stop-signal paradigm. The stop-signal paradigm is most suitable for the investigation of response inhibition in a laboratory setting (14,27–31). We measured reaction and inhibition times in patients with BD, their healthy siblings and healthy controls under an acute mood state and after induction of relaxation. We hypothesised that mood-related stress amplifies response inhibitory deficits in patients with BD and unmasks a vulnerability in unaffected siblings, which is similar to that seen in the patient group.

Materials and methods

Subjects

For this study, three groups of subjects were recruited: euthymic patients with BD, their healthy siblings and healthy controls. Subjects were recruited at the outpatient departments of the Clinic of Psychiatry and Psychotherapy of the University of Dresden and at the Clinic of Psychiatry in Chemnitz, Germany, which is a teaching hospital affiliated with the University of Dresden. All participants were assessed with the Structured Clinical Interview for *Diagnostic Statistical Manual*-IV (DSM-IV) (32). The following medications were permitted: lithium, valproate and carbamazepine. Exclusion criteria were other axis I or II diagnoses and severe internal or neurological disorders. Siblings and healthy controls also received an SCID for exclusion of any axes I and II disorders. Patients with BD and their siblings were randomised to the same emotional conditions (acute sadness or relaxation). Healthy controls were matched to patients with BD and healthy siblings regarding sex, age and school education level. Written informed consent was obtained from all subjects, and the study was approved by the local Ethics Committee.

Screening for emotional vulnerability

All subjects were assessed with the scale of experience of emotions (SEE), a self-administered questionnaire (33) that contains seven subscales (1. acceptance of own emotions, 2. emotional flooding, 3. lack of emotions, 4. somatic expression of emotions, 5. imaginative symbolisation of emotions, 6. regulation of emotions and 7. self-control). Results were compared with standard values for men and women expressed as T-values (a scaled score of the norm-referenced standardised test). A cut-off value was determined by >40. Furthermore, data were collected using the subscales for emotionality and impulsiveness of the Freiburger Persönlichkeitsinventar (personality questionnaire), revised version – FPI-R (34). FPI-R scores are given as stanine scores (a scaled score of the norm-referenced standardised test) with a median value of 5.

Study design

The three groups (patients with BD, healthy siblings and controls) were randomised to the two emotional conditions (acute sadness or relaxation). The design of the study is shown in Fig. 1. The choice task was to discriminate words presenting on the monitor according to their pleasant or unpleasant emotional

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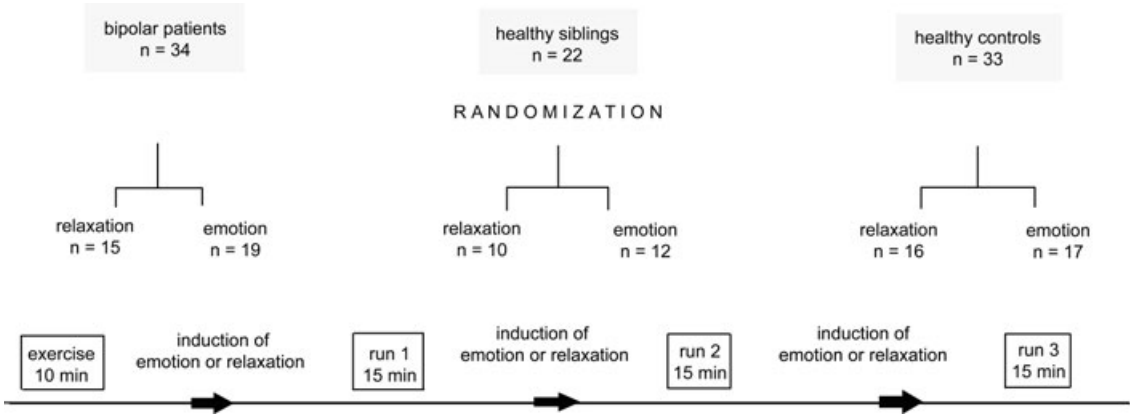

Fig. 1. Study design. Thirty-three healthy controls, 34 patients with BD and 22 healthy siblings were randomised to the two emotional conditions. Participants performed one practice block (10 min) after induction of acute sadness or relaxation. Between the three experimental blocks (15 min), the emotion/relaxation induction was repeated. The choice task in the stop-signal paradigm was to discriminate words presenting on the monitor according to their pleasant or unpleasant emotional content.

content. Participants performed one practice block (10 min) after induction of acute sadness or relaxation. After the practice block, participants performed three experimental blocks, each consisting of 300 trials. The stimulus was presented for 1000 ms. After an interval of 2000 ms the next trial started. The words have been validated in the study of Pratto and John (35). Between the three experimental blocks (15 min), the emotion/relaxation induction was repeated.

Mood induction and induction of relaxation

Induction of transient intense sadness was performed using a mood induction paradigm, which has successfully been validated in PET studies (36–38). In brief, subjects were requested to draft a short individualised autobiographical script describing a sad life event. Sad scenarios most commonly centred on loss of friends, relatives or significant relationships. In patients with BD, hospitalisation on an involuntary basis and forced medication were frequently used to provoke sad memories. One week before the actual experiment, the script was used during a test run to ascertain that it would cause transient sadness in the subjects. All subjects experienced sadness and all bipolar subjects cried. On the day of the experiment, the script was projected onto a PC screen and read by subjects before the initiation of the task. Intensity of sadness was quantified using a self-rating visual analogue scale (VAS) with a range of 0–100. For each subject, the paradigm was not performed unless the mood state reached a value over 50 on the VAS. Confounding emotions like anxiety, anger and agitation were excluded using additional VASs. Relaxation was induced using the standardised method of progressive muscle relaxation according to Jacobson (39). Intensity of relaxation was quantified using a self-rating VAS. Again, the paradigm was not performed unless a value >50 on the VAS was reached.

Stop-signal paradigm

Subjects performed the choice reaction time (RT) task by pressing the right or the left button on a PC with the preferred hand depending on the pleasant or unpleasant emotional content of the presenting word. For example, the word ‘flower’ was a word with a pleasant emotional content (pleasant trial) ‘nauseous’ was a word with a unpleasant content (unpleasant trial). Participants were seated approximately 50 cm in front of a computer screen. Occasionally, the go stimulus was followed by an auditory tone (the stop signal, 1000 Hz tone of 500 ms duration), which instructed subjects to withhold their response. The stop-signal delay was set by a staircase tracking algorithm, which adapts to the response rate. We used one staircase to adjust the delay in a way that participants could inhibit approximately 50% of all stop trials. This was done in the following way: if in a stop-signal trial the response was not inhibited, the stop-signal delay (SSD) was reduced by 50 ms the next time a stop signal occurred, thus increasing the chance of successful inhibition. Successful inhibition was followed by an increase of the delay by 50 ms. For all subjects p (respond/signal) was between 0.45 and 0.52. Therefore, the stop-signal reaction time (SSRT) represents the latency of the stop process as an index of inhibitory control and can be estimated by calculating the difference between the average reaction time (RT) on trials without stop signal and the average SSD. For a detailed description of the

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stop-signal task and its mathematical formulation, see reference Logan and Verbruggen (14,30,31).

Statistical analysis

Reaction and inhibition time data were analysed using SPSS for Windows version 12.0. Differences in the RT task between the three groups and the two conditions were carried out using three-way or two-way analysis of variance with repeated measures followed by Tukey or LSD *post hoc* test. Significance was accepted for $p < 0.05$. For the emotional screening questionnaires, standardisations are available and parametric tests were used to examine differences between the three groups.

Results

Subjects

A total of 34 euthymic patients with DSM-IV BD, type I in a euthymic mood state [Hamilton Depression Rating Scale (HDRS) score ≤6 and Young Mania Rating Scale (YMRS) ≤4], their healthy siblings ($n = 22$) and healthy controls ($n = 33$) were included in the study. The mean age was 41.7 ± 12.3 for the group of patients with BD, 35.6 ± 14.9 for the groups of healthy siblings and 33.1 ± 9.9 for the control group. The three groups did not differ significantly in HDRS or YMRS scores.

Emotional vulnerability

Results of the SEE scale are shown in Table 1. Patients with BD experienced their emotions more pronounced in the subscales 'emotional flooding', 'imaginative symbolisation of emotions' and 'lack of emotions', but self-evaluated their 'regulation of emotions' lesser. Analysis of the subscale T-values revealed significant differences in 'lack of emotions' ($F_{2,83} = 5.562$, $p < 0.005$) and 'regulation of emotions' ($F_{2,83} = 3.952$, $p = 0.023$) between the three groups. Patients with BD self-evaluated their emotional regulation lesser (45.0 ± 11.4) compared with their siblings (52.5 ± 11.2, $p = 0.030$) and healthy controls (50.4 ± 8.5, $p = 0.095$, *trend*). In contrast, patients with BD had higher values in the subscale 'lack of emotions' (53.2 ± 13.1) compared to controls (44.8 ± 7.6, $p = 0.004$).

In the variance analysis of the FPI-R values, significant differences in the subscale 'emotionality' between the three groups ($F_{2,83} = 4.523$, $p < 0.014$) were found, whereas patients with BD had higher values (4.94 ± 2.15) than controls (3.61 ± 1.77, $p = 0.025$) and their siblings (3.55 ± 2.24, $p = 0.047$) in this subscale (Table 2).

Table 1. Results of the SEE test are shown as means of the T-values and SD

Subscales	Control group	Bipolar group	Healthy siblings
Acceptance of own emotions	54.6 ± 6.3	51.5 ± 9.5	52.7 ± 10.9
Emotional flooding	44.7 ± 9.3	49.0 ± 11.0	44.1 ± 11.7
Lack of emotions	44.8 ± 7.6	53.2 ± 13.1	48.1 ± 8.2
Somatic expression of emotions	43.4 ± 8.4	45.2 ± 10.5	46.2 ± 10.5
Imaginative symbolisation of emotions	46.7 ± 7.5	49.0 ± 8.7	46.8 ± 10.8
Regulation of emotions	50.4 ± 8.5	45.0 ± 11.4	52.5 ± 11.2
Self-control	50.2 ± 9.8	52.1 ± 8.2	53.7 ± 10.7

Table 2. Results of the FPI-R subscales are shown as means of the stanine values and SD

Subscales	Control group	Bipolar group	Healthy siblings
Emotionality	3.61 ± 1.77	4.94 ± 2.15	3.55 ± 2.24
Impulsiveness	4.58 ± 2.15	4.97 ± 1.99	3.75 ± 1.45

All subjects reached the required sad state. The experiment had not to be repeated for anyone. During the mood induction paradigm, subjects with BD required on average 2 min to become sad after reading the script. Healthy controls required on average 5 min to achieve an adequately sad mood state. Siblings required a longer time to become sad than their siblings with BD, but the average time until the sad state was achieved (approximately 2–3 min) was still shorter than that required by controls. All subjects with BD cried, whereas only 10 controls and 5 siblings cried on reading their sad autobiographical script. No difference of time needed for sufficient relaxation and deepness of relaxation (self-evaluation) were observed between the three groups.

Reaction times

Mean RTs in the stop-signal task are presented in Fig. 2 and Table 3. Statistically significant differences were observed comparing RTs of patients with BD, siblings and controls independent of emotional state or word valence ($F_{2,78} = 3.734$, $p = 0.03$). Patients with BD exhibiting longer RTs compared with controls ($p = 0.034$). RTs differed highly significantly depending on the word valence, whereas longer RTs were observed presenting unpleasant go trials ($F_{1,78} = 62.65$, $p = 0.001$).

Comparing the six groups (control group/relaxed, control group/sad, bipolar group/relaxed, bipolar group/sad, sibling group/relaxed and sibling group/sad), we found significant longer RTs in the bipolar group under a relaxed mood state compared with controls in a relaxed mood state ($p = 0.01$).

Patients with BD in a relaxed mood state showed longer RTs than the control group in an acute negative mood state ($p = 0.031$). Interestingly, no

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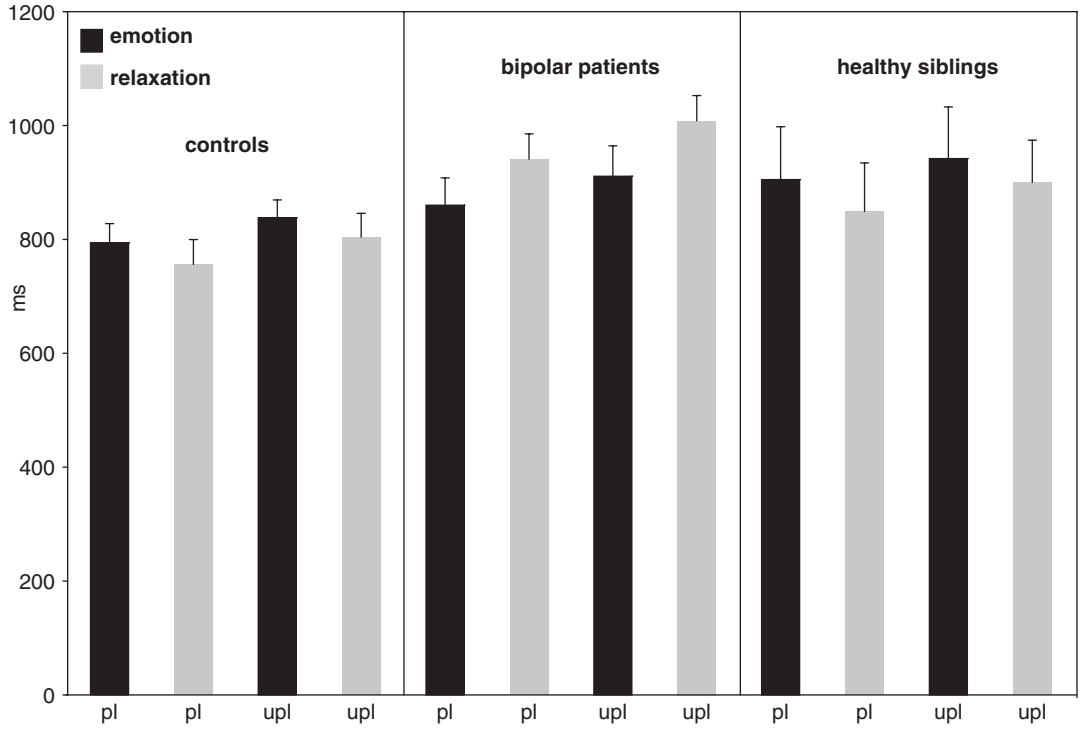

Fig. 2. Reaction time (RT) under acute mood state and relaxed state in patients with BD, healthy siblings and controls. The stimuli for the choice RT task were words with either a word with a pleasant emotional content (pl, pleasant trial; e.g. flower) or unpleasant content (upl, unpleasant trial; e.g. nauseous). Data are expressed as standard error of means (SEM).

Table 3. Results of the choice reaction time (RT) task. Subjects had to decide between 'pleasant emotional content' (pl trial) or 'unpleasant emotional content' (upl trial) of the presented word

	Control group ($n = 33$)		Bipolar group ($n = 34$)		Healthy siblings ($n = 22$)	
	Emotion ($n = 17$)	Relaxation ($n = 16$)	Emotion ($n = 19$)	Relaxation ($n = 15$)	Emotion ($n = 12$)	Relaxation ($n = 10$)
RT pl. trials	794 ± 139	756 ± 175	860 ± 198	941 ± 166	905 ± 308	849 ± 256
RT upl. trials	838 ± 129	804 ± 167	911 ± 220	1008 ± 167	942 ± 301	900 ± 223
SSD pl. trials	519 ± 160	473 ± 173	481 ± 171	591 ± 221	613 ± 303	513 ± 240
SSD upl. trials	539 ± 158	522 ± 203	511 ± 208	638 ± 219	634 ± 309	558 ± 219
SSRT pl. trial	233 ± 51	239 ± 52	307 ± 103	278 ± 119	250 ± 97	285 ± 102
SSRT upl. trial	275 ± 65	245 ± 101	348 ± 118	318 ± 134	282 ± 93	298 ± 107

Occasionally, the go stimulus was followed by a stop signal, which instructed subjects to withhold their response. Means and SDs of the RT, stop-signal delay (SSD) and stop-signal reaction time (SSRT) are shown (in ms). The SSRT represents the latency of the stop process as an index of inhibitory control.

differences were observed comparing RTs of subjects with BD in an acute sad mood state with controls under both emotion conditions. Healthy siblings showed a trend for longer RTs when in a sad mood state compared with controls under relaxation ($p = 0.070$). However, this effect was not statistically significant.

Inhibition time

Inhibition times (SSRT) were measured using a stop-signal task (Fig. 3; Table 3). Inhibition times differed significantly between the three groups independent of emotional state or word valence ($F_{2,78} = 3.959$, $p = 0.023$), whereas patients with BD exhibited longer inhibition times compared with controls ($p = 0.014$). Inhibition times differed highly significantly depending on the word valence, whereas longer inhibition times were observed presenting unpleasant go trials ($F_{1,78} = 18.19$, $p < 0.001$).

Comparing the six groups (control group/relaxed, control group/sad, bipolar group/relaxed, bipolar group/sad, sibling group/relaxed and sibling group/sad), we found that inhibition times were longer in the bipolar group after induction of transient sadness compared with controls in the same mood state ($p = 0.022$). Comparing the bipolar group in a sad

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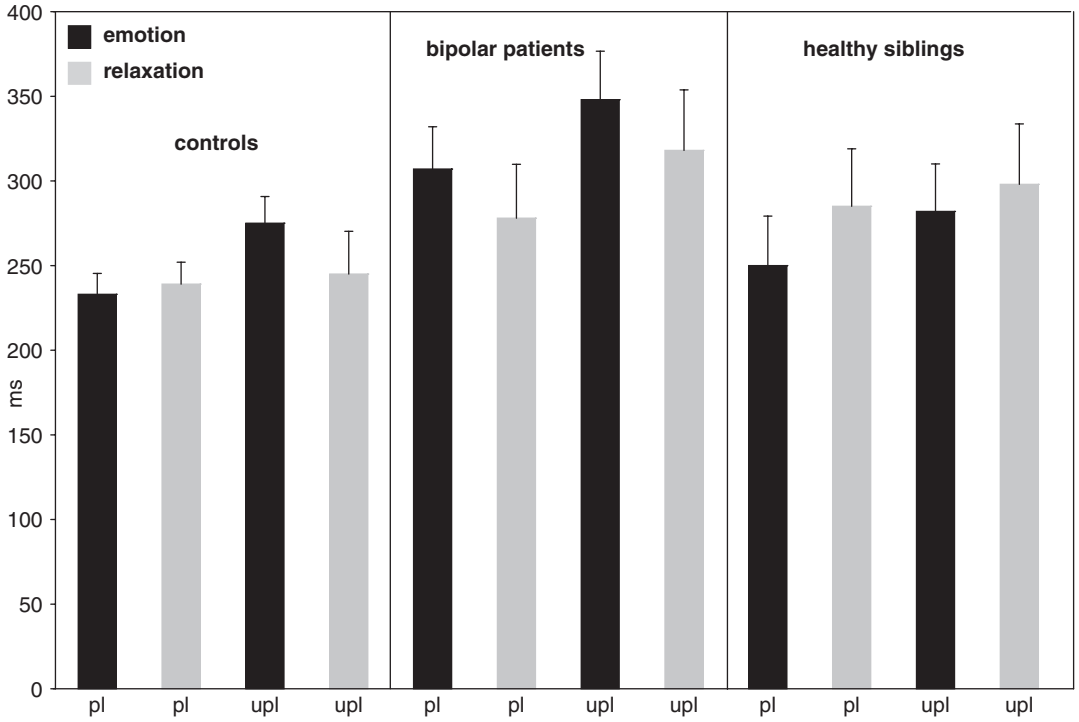

Fig. 3. Response inhibition time under acute mood state and relaxed state in patients with bipolar disorder, healthy siblings and controls. The stimuli for the choice reaction time task were words with either a word with a pleasant emotional content (pl, pleasant trial; e.g. flower) or unpleasant content (upl, unpleasant trial; e.g. nauseous). Data are expressed as standard error of means (SEM).

mood state with the control group after induction of relaxation revealed significantly higher inhibition times in the bipolars ($p = 0.009$). Healthy siblings showed longer inhibition times under relaxation compared with relaxed controls, but this was not statistically significant ($p = 0.203$).

Discussion

Euthymic patients with BD and their healthy siblings required less time to become sad and cried more frequently than the healthy controls in our mood induction paradigm. Our results confirm previous findings (40,41) and suggest that emotional vulnerability could be an endophenotype of BD. Krüger et al. investigated emotional challenge in euthymic bipolar patients and their healthy siblings using the same mood induction paradigm combined with PET and found that biological correlates of emotional vulnerability in patients and healthy siblings are decreased regional cerebral blood flow (rCBF) in the orbitofrontal cortex coupled with an increase in the dorsal anterior cingulate (25).

Our study provides evidence that a relaxed mood state may have a negative influence on RT in subjects with BD, whereas a state of heightened emotional arousal may improve cognitive functioning in this area. It is well known that optimal performance requires an intermediate level of emotional intensity – too little emotional intensity has negative effects on performance, whereas too much emotional intensity may lead to disorganisation of thinking and physical self-control (42,43). This implication forms the basis of the Yerkes-Dodson (YD) law which states that the relationship between arousal and performance resembles an inverted U (44–46).

The higher emotional arousal of subjects with BD in response to the emotion induction paradigm may lead to a better performance regarding the RT by moving to the right on the YD curve and convergence to the peak of the curve (optimum of performance). It is remarkable that patients with BD required this higher emotional arousal to react as fast as healthy people. Furthermore, relaxation induction methods could impair the RTs in patients with BD.

In contrast to the results regarding RT, we found longer inhibition times under acute emotional arousal in patients with BD suggesting that inhibitory deficits become more apparent under a high emotional arousal. An associated hypothesis to the YD law is that the optimal level of arousal is lower, the more complex is the task (46). As inhibitory function is more complex, it might be possible that the higher emotional arousal of patients with BD leads to

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surpassing the optimum peak of the YD curve and to an impaired inhibitory performance. A functional magnetic resonance imaging study combined with an emotional and non-emotional go/nogo task provided evidence for a cognitive-emotional interference in euthymic bipolar patients (47). On the non-emotional go/nogo task, bipolar patients and healthy controls performed similarly, and no activation difference has been detected between both groups. In contrast, they found a frontostriatal over-activation in patients with BD under emotional go/nogo conditions (47). These findings support the hypothesis of an altered emotional modulation of cognitive processing in euthymic bipolar patients. The fact that inhibitory deficits are also observable in patients with BD without emotional stimulation suggests that other variables besides the impaired emotional regulation impact on inhibitory function.

Response inhibition studied with stop-signal tasks requires inhibition of a prepotent motor response. Performance on these tasks is well modelled as a race between reflexive/prepotent go processes and volitional/controlled stop processes. Neurobiologically, response inhibition depends upon the interaction of frontal control systems with the basal ganglia and motor output regions. Failed attempts at response inhibition need not necessarily reflect a specific deficit in inhibitory mechanisms. Instead, they may be because of failures of executive control, for example, to maintain task goals in the working memory and rapidly recruit the inhibitory mechanisms underlie the stop process (48). A meta-analysis described deficits in verbal memory, sustained attention and psychomotor speed in euthymic patients with BD, which could have an influence on the performance in stop-signal task. It is not completely clarified if these deficits are illness-related impairments or a medication effect (11).

An alternative explanation for some of the findings could be that subjects develop response strategies to balance between going and stopping in the stop-signal paradigm (49,50). Thus, it cannot be ruled out that different mood states influence how the task is done and how different strategies are used. Although this most probably would only influence go trials, it could also possibly influence SSRT.

Frangou et al. examined euthymic patients with BD under different types of medication (antipsychotics, mood stabiliser antidepressants) and found that antipsychotic treatment predicted worse performance in executive function tests, particularly in general memory and working memory tests (51,52). Therefore, we excluded patients receiving antipsychotic medication. But we cannot completely rule out that the allowed medication in this study (lithium, valproate and carbamazepine) influences performance in the stop-signal paradigm. The literature on this is controversial, with one study by Hessen et al. finding that tasks of attention and RT revealed no difference between valproate-treated and valproate-untreated subjects with epilepsy (53). By contrast, Holmes et al. reported that subjects with bipolar depression treated with valproate or lithium exhibited greater response latency in affective processing tasks compared with a non-medicated group (54).

Although a variety of frontal regions are recruited by these tasks, right ventrolateral prefrontal cortex (VPFC) activity has been directly tied to inhibitory control across multiple paradigm (48). VPFC-related functions are detected as endophenotypes of BD (11,51,52). The more episodes patients have, the more pronounced are the cognitive deficits. We did not correlate number of episodes in our patients with the cognitive deficits we found; however, the finding of an inverse relationship between cognitive performance and emotional state may be independent of the number of episodes.

In all groups, performance in the stop-signal paradigm depended highly significantly on the word valence, in that longer reaction and inhibition times were observed in words with an unpleasant emotional content. Similar results were obtained in another emotional go/nogo task presenting fearful, happy and neutral facial expressions. RTs were slower for responses to fearful facial expressions suggesting that an unpleasant emotional content has a negative influence on behavioural performance (55). In contrast, Verbruggen has shown that the presentation of an emotional stimulus prolonged both response and stopping latencies regardless of the valence of the emotional stimulus, but in dependence of the arousing level of the pictures (56). These findings support the arousal hypothesis, which stated that high-arousal stimuli interfered more with responding and stopping than low-arousing stimuli. In our study, we have not measured the arousing level of the words. Therefore, it is possible that the negative words, presented in our study, induced higher arousing levels and lead to consequential prolonged reaction and inhibition times.

Even though we found evidence of higher emotional vulnerability in healthy siblings, we were not able to verify significant differences of cognitive performance depending on the emotional state in healthy siblings compared with controls. Presumably, the small sample size constrained our ability to find significant differences. Moreover, the complex design is a further limitation of the study.

In conclusion, our data provide evidence that patients with BD have faster RTs under strong emotional arousal. In contrast, under the same

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emotional arousal the inhibitory deficits become more apparent. It is possible that patients with BD will function best under a moderate emotional arousal. Psychotherapeutic strategies for emotion regulation could help patients with BD to deal better with their strong emotions and could improve inhibitory deficits.

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