Objectives: Recent neuroimaging studies support the contention that depression, pain distress, and rejection distress share the same neurobiological circuits. In two recently published studies we confirmed the hypothesis that the perception of increased pain during both treatment-refractory depression (predominantly unipolar) and difficult-to-treat bipolar depression was related to increased state rejection sensitivity (i.e., rejection sensitivity when depressed). In the present study, we aimed to compare the correlates of pain and rejection sensitivity in individuals with bipolar versus unipolar depression and test the hypothesis that bipolar disorder may be distinguished from unipolar depression both by an increased perception of pain and heightened rejection sensitivity during depression.

Methods: We analyzed data from 113 bipolar and 146 unipolar depressed patients presenting to the Black Dog Institute, Sydney, Australia. The patients all met DSM-IV criteria for bipolar disorder or unipolar depression (major depressive disorder).

Results: Bipolar disorder predicted a major increase in state rejection sensitivity when depressed ($p = 0.001$), whereas trait rejection sensitivity (i.e., a long-standing pattern of rejection sensitivity) was not predicted by polarity. A major increase in the experience of headaches ($p = 0.007$), chest pain ($p < 0.001$), and body aches and pains ($p = 0.02$) during depression was predicted by a major increase in state rejection sensitivity for both bipolar and unipolar depression.

Conclusions: State, but not trait, rejection sensitivity is significantly predicted by bipolar depression, suggesting that this might be considered as a state marker for bipolar depression and taken into account in the clinical differentiation of bipolar and unipolar depression.

Reports on pain in bipolar disorder are scant. There is epidemiologic evidence of an increased prevalence of migraine in this condition (1) and clinical evidence that a variety of painful conditions occur more frequently in those with bipolar disorder compared to controls (2, 3). Further, in another epidemiological survey, the prevalence of pain interference was found to be elevated in bipolar disorder, even compared to those with major depressive disorder (unipolar depression) and anxiety disorders (4).

For unipolar depression, pain has been reported to be a prevalent comorbid condition. For example, in a predominantly unipolar depressed sample, about 50% of patients reported suffering from physical pain, three to four times the prevalence of that in non-depressed individuals (5). Pain occurring during depression is frequently more difficult to manage (6) and appears to be associated with both a worse outcome for the depression and a higher cost of care (7). Although the biological mechanisms remain to be...
clarified, it has been hypothesized that depression and pain may share common neural substrates, possibly involving serotonin and noradrenaline (8, 9). Depression and pain are also associated with the same early childhood predisposing factors, and may be perpetuated by similar cognitive processes (10). Furthermore, neuroimaging studies have suggested that pain, depressive mood, and rejection distress may be regulated in similar neurobiological circuits, including the anterior cingulate cortex (ACC) and right ventral prefrontal cortex (11). Functional magnetic resonance imaging (fMRI) has revealed that the dorsal anterior cingulate cortex (dACC), which is associated with the ‘unpleasantness’ of physical pain [i.e., the emotional experience of pain rather than the physical perception of pain (12)], is also activated during the distressing experience of social rejection, and that this activation correlates strongly with self-reported social distress (11). The subgenual anterior cingulate cortex (sACC) has been shown to be activated in humans experiencing depressive symptoms and is thought to be involved in the regulation of depression and sadness (13, 14). These findings suggest that the ACC region is not only involved in the perception of pain and social rejection, but is also an important region for depressed mood (15). In line with these findings, in two recently published studies (16, 17) we have confirmed our hypothesis that the perception of increased pain during depression (both treatment-resistant depression, predominantly unipolar, and mainly difficult-to-treat bipolar depression) is related to increased state rejection sensitivity.

The symptom of trait rejection sensitivity is included as a DSM-IV criterion for atypical depression (18). Trait rejection sensitivity is defined as a long-standing pattern of extreme sensitivity to perceived interpersonal rejection and is argued by some authors to be a ‘soft’ bipolar II disorder feature which would make atypical depression a diagnosis included in the bipolar spectrum disorders (19). State rejection sensitivity, on the other hand (i.e., the sensitivity to perceived interpersonal rejection during depression), has not been clearly differentiated from trait rejection sensitivity in the research findings of bipolar disorder.

The aim of the present study was to compare the relationship between pain and state- as well as trait rejection sensitivity in bipolar versus unipolar depression. Increased emotional reactivity, and consequently a higher degree of mood lability, has been reported to be a core clinical feature of bipolar disorder and has been demonstrated to be more prominent in bipolar depressed subjects than in those with major depressive disorder (20). In the present study, we proposed that bipolar disorder, in addition to being characterized by greater emotional reactivity, may also be distinguished from unipolar depression by both an increased perception of pain and heightened rejection sensitivity during depression.

**Materials and methods**

**Participants**

The sample involved two datasets comprising a total of 259 outpatients (107 males and 152 females; aged 16–77 years). The first dataset [which has been previously described (16)] was a treatment-refractory depressed sample, comprising 146 attendees of a tertiary referral Mood Disorders Unit Clinic (now the Black Dog Institute) at the Prince of Wales Hospital, Sydney, Australia, who had been diagnosed with a unipolar DSM-IV major depressive disorder. The second dataset comprised 113 attendees of the Black Dog Institute Bipolar Disorders Clinic with a DSM-IV-defined bipolar disorder. Most patients are referred to this clinic because of treatment resistance, with the majority demonstrating persistent and recurrent bipolar depressive episodes. Of these subjects, 72.6% (n = 82) met the criteria for bipolar I disorder, 25.7% (n = 29) for bipolar II disorder, and 1.8% (n = 2) for bipolar disorder not otherwise specified. This bipolar disorder dataset included some patients reported in our prior bipolar disorder paper, but with the addition of more recently recruited subjects. Further details of the recruitment and assessment of unipolar and bipolar samples are available in our two prior reports (17). All subjects in both datasets completed the same two probe questions within a general symptom self-report questionnaire: one assessing bodily pain when depressed (currently or in the past) and the other assessing rejection sensitivity while depressed. Written informed consent was obtained from all participants in accordance with the University of New South Wales Human Research Ethics Committee requirements.

**Assessment of pain and rejection sensitivity**

In both the unipolar and bipolar depressed datasets, patients completed a self-report questionnaire on state and trait rejection sensitivity, trait anxiety, and pain. The two questions assessing traits asked patients to rate how they ‘usually or generally feel or behave’ (over the years and not just recently), using a four-point scale (not true at all, slightly
true, moderately true, or very true). The first question (‘I am concerned about being rejected’) was considered as an index of trait rejection sensitivity. The second question (‘I’m generally a worrier about things’) was considered as an index of sensitivity to stress and high trait anxiety (21).

The third question was considered as an index of state rejection sensitivity and asked patients to rate whether they had ‘noticed any increase in sensitivity to feeling rejected by people’ when they became depressed (currently or in the past), on a four-point scale (no increase, some increase, moderate increase, or major increase).

A series of questions asked whether different specific bodily pains – headaches, chest pain, body aches, and pains – either became more noticeable or more of a problem while depressed, and were rated using four-point scales (not at all, slightly, moderately, or distinctly).

A number of items were collapsed into dichotomous variables for use as predictors in subsequent ordinal regression analyses. Depressive state rejection sensitivity was dichotomized as a ‘low increase in state rejection sensitivity’ (including no increase, some increase, and moderate increase) and a ‘high increase in state rejection sensitivity’. Trait rejection sensitivity was dichotomized as ‘low trait rejection sensitivity’ (including not true, slightly true, and moderately true) and ‘high trait rejection sensitivity’. Finally, trait anxiety was dichotomized as a ‘low anxiety trait’ (including not true, slightly true, and moderately true) and a ‘high anxiety trait’.

Negative childhood experiences

Structured researcher-administered questions from the measure developed by Gladstone et al. (22) were used to assess experiences of physical or sexual abuse in childhood (up to 16 years of age in the unipolar study and 18 years of age in the bipolar disorder study), and aggregated as ‘yes’ or ‘no’ responses. Measured experiences included traumatic physical aggression as well as traumatic unwanted sexual contact by parents or others. These questions were explored as previous studies have shown correlations between childhood abuse and both later chronic pain and trait rejection sensitivity and depression (23, 24).

Depression severity

As the bipolar and unipolar depressed datasets used different clinician-rated depression severity measures [the Hamilton Rating Scale for Depression (HRSD-17) (25) for the unipolar sample and the Montgomery–Asberg scale (MADRS) (26) for the bipolar disorder sample], we used severity cutoff recommendations developed by Rush et al. (27) and Trivedi et al. (28) to categorize depression severity (None: HRSD-17 scores 0–7, MADRS scores 0–6; Mild: HRSD-17 scores 8–13, MADRS scores 7–19; Moderate: HRSD-17 scores 14–19, MADRS scores 20–34; Severe/very severe: HRSD-17 scores 20–52, MADRS scores 35–60). These four categories of depressive severity were entered as predictors in subsequent ordinal regression analyses.

Statistical analyses

Data were analysed using SPSS for Windows version 20.0 (Armonk, NY, USA). At a simple descriptive level, we examined for linear-by-linear associations – that is, whether there was a significant component of any association which was due to higher scores on one variable being associated with higher scores on the other (or lower if the association was negative). Chi-square analyses (for dichotomous variables) and Mann–Whitney tests (for continuous variables) were used to compare variables. Our primary analyses used ordinal regression to model the categorical ratings of pain. The results from the regression are expressed as odds ratios (OR), indicating the degree to which a higher rating of pain is more likely for different levels of (or unit changes in) the predictors. For example, an OR = 2 for males versus females (with females as the reference category) means that the odds of a higher rating by males are twice the odds for females. We examined a series of models (multivariate ordinal regression analyses): (i) three predicting the different types of pain during depression; (ii) one predicting depressive state rejection sensitivity; and (iii) the other predicting trait rejection sensitivity.

Results

Demographics

As detailed earlier, 113 subjects (43.6% of the total study sample) were diagnosed with a DSM-IV bipolar disorder and 146 (56.4%) with a unipolar major depressive disorder. The mean age of the 259 outpatients (107 male and 152 female) was 41.2 [standard deviation (SD) = 13.7] years. The vast majority (88.2%) had had at least ten years of education. A minority (25.1%) were engaged in full-time employment and 34.0% were either unemployed or in receipt of government benefits. There were no significant differences in demographic variables between unipolar and bipolar disorder subjects. In terms of depression severity,
the mean score ± SD on the MADRS for the bipolar depressed patients was 13.4 ± 9.9 (indicating mild depression), while the mean HDRS–17 for the unipolar disorder patients was 15.7 ± 6.9 (indicative of moderate severity) (27, 28).

State and trait rejection sensitivity

We first examined individual experiences of depressive state rejection sensitivity (i.e., the sensitivity to perceived interpersonal rejection during depression). For depressive state rejection sensitivity, 11.6% of the total sample reported 'no increase', 18.6% 'some increase', 22.1% a 'moderate increase', and 47.7% a 'major increase'. Patients with bipolar disorder, compared to depressed patients with unipolar disorder, showed a tendency towards a greater increase in feeling major rejection sensitivity; however, the test for a linear trend was not significant ($\chi^2 = 2.52, df = 1, p = 0.11$). There were no gender differences with regard to state rejection sensitivity.

We then examined the experience of trait rejection sensitivity (i.e., the long-standing pattern of rejection sensitivity to perceived interpersonal rejection). For trait rejection sensitivity, 7.4% of the total sample reported long-standing rejection sensitivity to be 'not true at all', 23.4% as 'slightly true', 25.0% as 'moderately true', and 44.1% 'as very true'. There were no differences between unipolar and bipolar depressed patients, and no gender differences.

As defined in the Methods section, patients were dichotomized into low- and high-increase subsets for both depressive state and trait rejection sensitivity. In the bipolar disorder sample, the low- and high-increase subsets were able to be compared on the current MADRS. There were no significant differences between subsets based on either of the two measures of sensitivity. In the unipolar disorder sample, these subsets were able to be compared on the HRSD-17. Only the subsets based on depressive state showed a significant difference [mean ± SD = 14.9 ± 6.8 (n = 75) for low increase and 16.7 ± 6.9 (n = 67) for high increase; Mann–Whitney test: $U = 1,914.50; p = 0.020$].

For the total sample, trait rejection sensitivity was strongly associated with state rejection sensitivity during depression ($\chi^2 = 54.01, df = 9, p < 0.001$). There was no difference between the unipolar and bipolar groups.

Pain during depression

We then examined the experiences of different degrees of three kinds of pain during depression (headaches, body aches and pains, and chest pain). During depression, 32.4% of the study group experienced headaches as being ‘not at all’ a problem, 26.3% as being ‘slightly’ more of a problem, 22.8% as being ‘moderately’ more of a problem, and 18.5% as being ‘distinctly’ more of a problem. The percentages of the study sample experiencing body aches and pains ‘not at all’, ‘slightly’, ‘moderately’, and ‘distinctly’ more of a problem during depression were 33.2%, 26.6%, 20.1%, and 20.1%, respectively. The corresponding figures for chest pain were 59.8%, 22.0%, 11.2%, and 6.9%, respectively. There were no significant differences between the patients with unipolar and the bipolar disorder, and no gender differences regarding the experience of pain during depression.

As migraines have been reported in epidemiological studies to be more prevalent in bipolar disorder patients compared to the general population (1), we also investigated whether previous episodes of migraine in patients with bipolar disorder were associated with increased headaches when depressed. Eight of the 113 patients with bipolar disorder reported suffering from migraine but we found no significant relationship with state dependent headaches within this subset.

Rejection sensitivity and pain

In order to examine the relationship between state rejection sensitivity and pain, we analyzed state rejection sensitivity in relation to each of the three categories of pain (headaches, body aches and pain, and chest pain) for the bipolar and unipolar disorder groups, respectively. For patients with bipolar disorder, state rejection sensitivity was highly significantly linearly associated with headaches ($\chi^2 = 13.33, df = 1, p \leq 0.001$); body aches and pains ($\chi^2 = 4.88, df = 1, p = 0.027$); and chest pain ($\chi^2 = 9.27, df = 1, p = 0.002$). For patients with unipolar disorder, state rejection sensitivity was significantly linearly associated with headaches ($\chi^2 = 5.69, df = 1, p = 0.017$), body aches and pains ($\chi^2 = 3.98, df = 1, p = 0.046$), and chest pain ($\chi^2 = 6.78, df = 1, p = 0.009$). There was no significant linear association between trait rejection sensitivity and increased pain during depression, for either the unipolar or bipolar samples.

Predictors of increased pain during depression

As detailed earlier, there was a significant linear association between increased state rejection sensitivity and all three forms of increased pain during depression in patients with bipolar disorder as well as in patients with unipolar disorder, indicating...
that the greater the increase in rejection sensitivity, the greater the increase in headaches, body aches and pains, and chest pain during depression.

We then examined, using ordinal regression analyses, whether increased perception of pain during depression was dependent on any of the following nine variables: the unipolar/bipolar distinction, age, gender, childhood physical abuse, childhood sexual abuse, increase in state rejection sensitivity, trait rejection sensitivity, trait anxiety, and depressive severity (categorized as none to severe/very severe).

The overall models for headaches, body aches and pain, and chest pain during depression were significant ($\chi^2 = 45.7$, $p < 0.001$; $\chi^2 = 27.2$, $p = 0.00$; and $\chi^2 = 44.2$, $p < 0.001$, respectively; for details see Tables 1–3). A large increase in state rejection sensitivity was a significant predictor of increased depressive state rejection sensitivity and other study variables in ordinal regression analyses.

Table 1. Headaches increasing during depression (measured as not at all, slightly, moderately, and distinctly) predicted by increased depressive state rejection sensitivity and other study variables in ordinal regression analyses

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>OR</th>
<th>SE</th>
<th>Wald test</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>State rejection sensitivity</td>
<td>−0.719</td>
<td>0.487</td>
<td>0.265</td>
<td>7.378</td>
<td>0.007</td>
</tr>
<tr>
<td>(low, high)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trait rejection sensitivity</td>
<td>0.373</td>
<td>1.452</td>
<td>0.276</td>
<td>1.822</td>
<td>0.177</td>
</tr>
<tr>
<td>(low, high)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical abuse (no, yes)</td>
<td>−0.896</td>
<td>0.408</td>
<td>0.284</td>
<td>9.937</td>
<td>0.002</td>
</tr>
<tr>
<td>Trait anxiety (low, high)</td>
<td>−0.536</td>
<td>0.585</td>
<td>0.265</td>
<td>4.084</td>
<td>0.043</td>
</tr>
<tr>
<td>Depression severity none</td>
<td>−0.758</td>
<td>0.469</td>
<td>0.420</td>
<td>3.257</td>
<td>0.071</td>
</tr>
<tr>
<td>Depression severity mild</td>
<td>−1.090</td>
<td>0.336</td>
<td>0.381</td>
<td>8.183</td>
<td>0.004</td>
</tr>
<tr>
<td>Depression severity moderate</td>
<td>−0.471</td>
<td>0.624</td>
<td>0.362</td>
<td>1.696</td>
<td>0.193</td>
</tr>
<tr>
<td>Depression severity severe/very severe</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Age (increasing)</td>
<td>−0.017</td>
<td>0.983</td>
<td>0.009</td>
<td>3.359</td>
<td>0.067</td>
</tr>
<tr>
<td>Unipolar/bipolar distinction (unipolar, bipolar)</td>
<td>0.120</td>
<td>1.127</td>
<td>0.271</td>
<td>0.197</td>
<td>0.657</td>
</tr>
<tr>
<td>Gender (male, female)</td>
<td>−0.586</td>
<td>0.557</td>
<td>0.256</td>
<td>5.246</td>
<td>0.022</td>
</tr>
</tbody>
</table>

Analysis of log likelihood: $\chi^2 = 45.686$, $p < 0.001$. Test of parallel lines: $\chi^2 = 17.198$, $p = 0.752$. OR = odds ratio; SE = standard error.

*Positive (negative) values indicate higher (lower) odds of greater pain for direction, category in bold or relative to reference category (−).

Table 2. Body aches and pains increasing during depression (measured as not at all, slightly, moderately, and distinctly) predicted by increased depressive state rejection sensitivity and other study variables in ordinal regression analyses

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>OR</th>
<th>SE</th>
<th>Wald test</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>State rejection sensitivity</td>
<td>−0.628</td>
<td>0.534</td>
<td>0.263</td>
<td>5.681</td>
<td>0.017</td>
</tr>
<tr>
<td>(low, high)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trait rejection sensitivity</td>
<td>0.553</td>
<td>1.738</td>
<td>0.276</td>
<td>4.009</td>
<td>0.045</td>
</tr>
<tr>
<td>(low, high)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical abuse (no, yes)</td>
<td>−0.542</td>
<td>0.582</td>
<td>0.279</td>
<td>3.761</td>
<td>0.052</td>
</tr>
<tr>
<td>Sexual abuse (no, yes)</td>
<td>−0.054</td>
<td>0.947</td>
<td>0.287</td>
<td>0.036</td>
<td>0.850</td>
</tr>
<tr>
<td>Trait anxiety (low, high)</td>
<td>−0.318</td>
<td>0.728</td>
<td>0.263</td>
<td>1.462</td>
<td>0.227</td>
</tr>
<tr>
<td>Depression severity none</td>
<td>−0.757</td>
<td>0.469</td>
<td>0.416</td>
<td>3.302</td>
<td>0.069</td>
</tr>
<tr>
<td>Depression severity mild</td>
<td>−1.077</td>
<td>0.341</td>
<td>0.378</td>
<td>8.102</td>
<td>0.004</td>
</tr>
<tr>
<td>Depression severity moderate</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Depression severity severe/very severe</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Age (increasing)</td>
<td>0.008</td>
<td>1.008</td>
<td>0.009</td>
<td>0.864</td>
<td>0.353</td>
</tr>
<tr>
<td>Unipolar/bipolar distinction (unipolar, bipolar)</td>
<td>−0.143</td>
<td>0.867</td>
<td>0.269</td>
<td>0.284</td>
<td>0.594</td>
</tr>
<tr>
<td>Gender (male, female)</td>
<td>−0.281</td>
<td>0.755</td>
<td>0.252</td>
<td>1.244</td>
<td>0.265</td>
</tr>
</tbody>
</table>

Analysis of log likelihood: $\chi^2 = 27.212$, $p = 0.004$. Test of parallel lines: $\chi^2 = 18.238$, $p = 0.692$. OR = odds ratio; SE = standard error.

*Positive (negative) values indicate higher (lower) odds of greater pain for direction, category in bold or relative to reference category (−).
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Table 3. Chest pain increasing during depression (measured as not at all, slightly, moderately, and distinctly) predicted by increased depressive state rejection sensitivity and other study variables in ordinal regression analyses

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Estimatea</th>
<th>OR</th>
<th>SE</th>
<th>Wald test</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>State rejection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sensitivity (low, high)</td>
<td>−1.123</td>
<td>0.325</td>
<td>0.302</td>
<td>13.847</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Trait rejection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sensitivity (low, high)</td>
<td>0.356</td>
<td>1.428</td>
<td>0.309</td>
<td>1.327</td>
<td>0.249</td>
</tr>
<tr>
<td>Physical abuse (no, yes)</td>
<td>−0.767</td>
<td>0.464</td>
<td>0.304</td>
<td>6.353</td>
<td>0.012</td>
</tr>
<tr>
<td>Sexual abuse (no, yes)</td>
<td>−0.099</td>
<td>0.906</td>
<td>0.318</td>
<td>0.097</td>
<td>0.755</td>
</tr>
<tr>
<td>Trait anxiety (low, high)</td>
<td>−0.804</td>
<td>0.448</td>
<td>0.304</td>
<td>7.000</td>
<td>0.008</td>
</tr>
<tr>
<td>Depression severity none</td>
<td>0.005</td>
<td>1.005</td>
<td>0.474</td>
<td>0.000</td>
<td>0.991</td>
</tr>
<tr>
<td>Depression severity mild</td>
<td>−0.093</td>
<td>0.911</td>
<td>0.430</td>
<td>0.047</td>
<td>0.083</td>
</tr>
<tr>
<td>Depression severity moderate</td>
<td>0.240</td>
<td>1.271</td>
<td>0.399</td>
<td>0.362</td>
<td>0.548</td>
</tr>
<tr>
<td>Depression severity severe/very severe</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (increasing)</td>
<td>0.026</td>
<td>1.026</td>
<td>0.010</td>
<td>6.265</td>
<td>0.012</td>
</tr>
<tr>
<td>Unipolar/bipolar distinction (unipolar, bipolar)</td>
<td>−0.292</td>
<td>0.747</td>
<td>0.304</td>
<td>0.921</td>
<td>0.337</td>
</tr>
<tr>
<td>Gender (male, female)</td>
<td>−0.218</td>
<td>0.804</td>
<td>0.284</td>
<td>0.585</td>
<td>0.444</td>
</tr>
</tbody>
</table>

Analysis of log likelihood: $\chi^2 = 44.232, p < 0.001$. Test of parallel lines: $\chi^2 = 25.528, p = 0.273$. OR = odds ratio; SE = standard error.

*aPositive (negative) values indicate higher (lower) odds of greater pain for direction, category in bold or relative to reference category (−).

when depressed ($p = 0.045$). The unipolar/bipolar distinction did not predict an increase in any kind of pain when depressed.

Predictors of state and trait rejection sensitivity

Using ordinal regression analyses (see Table 4), we finally examined whether increased sensitivity of feeling rejected when depressed (i.e., state rejection sensitivity) was dependent on any of the following eight variables: the unipolar/bipolar distinction, age, gender, childhood physical abuse, childhood sexual abuse, trait rejection sensitivity, trait anxiety, and depressive severity. The overall model was significant ($\chi^2 = 60.636, p < 0.001$), with highly significant predictors being trait rejection sensitivity ($p < 0.001$), bipolar disorder ($p = 0.001$), and trait anxiety ($p = 0.008$). Prediction of trait rejection sensitivity (i.e., a long-standing sensitivity to rejection) was also examined using ordinal regression analysis with the same predictors. The overall model was significant ($\chi^2 = 87.922, p < 0.001$), with significant predictors being depressive trait rejection sensitivity ($p < 0.001$) and trait anxiety ($p < 0.001$).

Discussion

The principal finding of the present study was that bipolar depression, compared to unipolar depression, significantly predicted an increase in state rejection sensitivity (i.e., rejection sensitivity when depressed), supporting one of our original
hypotheses. *Trait* rejection sensitivity, by contrast (i.e., a long-standing sensitivity to rejection), was not predicted by polarity. This suggests that increased rejection sensitivity when depressed may be a further clinical feature assisting clinicians in distinguishing bipolar from unipolar depression (20, 29, 30).

State and trait rejection sensitivity were associated, but shown to be distinct. Trait rejection sensitivity was predicted only by state rejection sensitivity and trait anxiety, whereas state rejection sensitivity was predicted by bipolar depression, trait rejection sensitivity, trait anxiety, age, and depressive severity. These results point towards the importance of separating state from trait rejection sensitivity in further research. Interestingly, some researchers have found trait rejection sensitivity, a criterion for atypical depression according to DSM-IV, to relate to the bipolar spectrum (19), whereas other researchers question the whole concept of atypical depression by suggesting a weak correlation between trait rejection sensitivity and mood reactivity (31). In both of these lines of research, only trait, not state, rejection sensitivity has been explored. Furthermore, we showed that an increase in *state* rejection sensitivity predicted a significantly increased likelihood of headaches, body aches and pains, and chest pain during depression – in both bipolar and unipolar depression. By contrast, *trait* rejection sensitivity predicted only an increase in body aches and pains during depression; there was no difference between the bipolar and unipolar groups.

The findings with state rejection sensitivity are consistent with neuroimaging studies which have investigated pain, state rejection sensitivity, and depression. In an fMRI study of healthy volunteers, Eisenberger and colleagues (11) demonstrated that certain brain regions (including the dACC) which are activated during the distressing experience that accompanies physical pain are also activated during the perception of social rejection. The greater the feeling of social exclusion, the greater was the dACC activation. The ACC has also been shown to be involved in depressive states and behavior (32) – specifically, the sACC (13). The findings that aversive feelings associated with social exclusion and physical pain arise, in part, from the same brain regions are mirrored in studies of separation distress and pain regulation in animals (33, 34). Because of the adaptive value of mammalian social bonds, the social attachment systems which keep the young near their caregivers may have become associated with the physical pain system to promote survival (35), alerting humans to when they have sustained ‘injury’ to their social connections and, thus, allowing restorative measures to be taken. The same teleological argument may be made when discussing the link between pain and depression: in order to promote the survival of depressed individuals who behaviorally tend to socially withdraw (36), the mood systems may also have become associated with pain systems, alerting these individuals to reconnect socially. This putative evolutionary hypothesis of depression and pain is further supported by recent clinical studies in which a high proportion of males who attended general practitioners for chest pain were later found to be depressed (37), suggesting that it was the symptoms of pain that prompted these individuals to seek help. This may explain why we did not find any difference between bipolar and unipolar depression in predicting pain; the survival value of experiencing pain when depressed might be high regardless of polarity.

Findings from the present study should be interpreted with caution, and the first and most prominent limitation of our results is that the questions regarding rejection sensitivity and pain during depression were all retrospective. Another important limitation is that we used different measures of depressive symptom severity for the unipolar and bipolar disorder groups. A further possible limitation was that our data regarding rejection sensitivity and pain during depression was obtained via self-report questionnaires rather than clinical interview. Finally, despite our well-defined bipolar and unipolar disorder cohorts, our diagnostic subsets were largely tertiary referral patients. Therefore, the sample may have represented a more severely affected selection of patients compared to patients within the general population.

Nonetheless, to our knowledge, this was the first study to compare subjects with bipolar and unipolar depression regarding the relationship between rejection sensitivity and pain. The findings of the present study have a number of important clinical implications. First, we found that depressive state rejection sensitivity is highly significantly predicted by bipolar disorder; this clinical feature may potentially serve [with others (20, 29, 30)] as a differentiating state marker for bipolar depression. Individuals with bipolar disorder frequently present to clinical services when depressed, but are often misdiagnosed with unipolar depression, leading to inadequate treatment and poor outcomes (20). Increased accuracy in diagnosing bipolar disorder, especially during depression, is therefore a key long-term goal to improve the mental health of individuals with the disorder. Second, as state and trait rejection sensitivity were predicted by different variables, it will be critical to distinguish between
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these two distinct rejection sensitivity variables in future research into bipolar disorder as well as unipolar depression. Finally, for most pain sufferers with depression for whom an organic cause is not evident, the use of terms such as ‘unexplained’, ‘functional’, and ‘psychosomatic’ to describe painful symptoms generates frustration and distress, offering few pointers towards appropriate treatment (38). Educating patients and clinicians about the links between depression, rejection sensitivity, and pain during depression, and thereby normalizing these related experiences, might in itself help to reduce pain symptoms. Having unduly negative thoughts about pain is known to increase the perception of pain (39). A reduction in catastrophic beliefs about the serious consequences of pain has been strongly associated with both less intense pain and improved mental health (40). Furthermore, it is well known that social support provides a buffer for depression (41), although it is perhaps insufficiently recognized that social support also reduces the perception of pain (42). The nature of the link between pain and social support is not yet understood, but we propose that increased social support may be one means of decreasing the feeling of rejection during depression.

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Disclosures

AE has received remuneration for lectures from Eli Lilly & Co. in the last five years; and has not been a member of an industry advisory board since 2008. PBM has not accepted remunerations from pharmaceutical companies for more than three years; and has not been a member of an industry advisory board for more than five years. CL has received remuneration for lectures from Pfizer/Wyeth, Servier, Eli Lilly & Co., and AstraZeneca in the last five years. DH-P,GP,AF,MB,AW,GR,PL, and TP declare no conflict of interest in regard to this study.

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