Familiality of Symptom Dimensions in Depression

Ania Korszun, PhD, MD, MRCPsych; Valentina Mosklevina, PhD; Shyama Brewster, BSc Joint (Hons); Nick Craddock, MB, PhD, MRCPsych; François Ferrero, MD; Michael Gill, MD, MRCPsych, FTCD; Ian Richard Jones, MB, PhD, MRCPsych; Lisa Anne Jones, BSc (Hons), PhD; Wolfgang Maier, MD; Ole Mors, MD, PhD; Michael J. Owen, PhD, FRCPsych; Martin Periseg, MD, MPH; Theodore Reich, MD; Marcella Rietschel, MD; Anne Farmer, MD, FRCPsych; Peter McGuffin, MB, PhD, FRCP, FRCPsych

**Background:** Depression is a clinically heterogeneous disorder thought to result from multiple genes interacting with environmental and developmental components. A dimensional rather than a categorical approach to depressive phenotype definition may be more useful for identification of susceptibility genes.

**Objectives:** To perform an exploratory factor analysis on a range of depressive and anxiety symptoms in a large, well-defined sample of depressed siblings, as well as a confirmatory factor analysis in a separate large group of unrelated depressed subjects, and to analyze correlations of identified symptom dimensions between depressed siblings.

**Design:** Subjects (N = 1034), including 475 sibling pairs, with a history of at least 2 depressive episodes were recruited from the Depression Network Study, a large-scale multicenter collection of families affected by recurrent unipolar depression. Subjects were interviewed using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) and diagnosed according to the DSM-IV and the International Classification of Diseases, 10th Revision, using a computerized scoring program (CATEGO5). Factor analysis was carried out on 26 depression symptom items, including 4 anxiety screening items. Confirmatory factor analysis was performed on an independent sample of 485 depressed individuals.

**Results:** Four interpretable factors were identified: (1) mood symptoms and psychomotor retardation; (2) anxiety; (3) psychomotor agitation, guilt, and suicidality; and (4) appetite gain and hypersomnia. For each symptom group, a quantitative scale was constructed, and correlations between siblings were calculated. There was a moderate degree of sibling homotypia for some depressive symptoms, and factors 1, 2, and 3 showed significant positive familial correlation (0.145 [P = .001], 0.335 [P < .001], and 0.362 [P < .001], respectively).

**Conclusions:** This is the first study of large, well-defined samples of depressed subjects in whom symptom dimensions have been derived and then confirmed using independent material. The significant correlations between siblings for 3 of the dimensions suggest substantial familial, perhaps genetic, etiologies.

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interpretation. Confirmatory factor analysis, on the other hand, is used to confirm or reject an assumed factor structure by testing it against independent data.

In the past, the construct of depression has been subjected to various factor analytic studies exploring different concepts of subtypes of depression, ranging from a 2-factor model of neurotic vs endogenous depression to a 10-factor model, with more recent focus on the atypical depressive subtype. This approach has renewed potential in light of current understanding of a genetic contribution to the etiology of depression. For instance, a particular symptom dimension might represent the action of a contributory gene or group of genes, and a particular combination of such genes may result in a characteristic phenotype. Identification of symptom dimensions could thus lead to definition of a more appropriate classification system for depression, particularly for genetic studies.

Subsequent demonstration that symptom dimensions identified in this way are correlated in pairs of affected relatives would provide external validation of the proposed factor structure and suggest usefulness for genetic studies. This type of approach has been used to explore the classification and heritability of schizophrenia, but there have been fewer studies of the familiality of symptom dimensions in unipolar depression. Although previous work has shown familiality between categorical subtypes of major depression, to our knowledge, there has not been a large systematic study of sibling correlations of depressive dimensions derived by factor analysis.

The aims of this study were therefore (1) to identify depressive symptom dimensions by performing an exploratory factor analysis on a range of depressive and anxiety symptoms in a large, well-defined sample of depressed siblings diagnosed using accepted standardized criteria; (2) to perform a confirmatory factor analysis in a separate large group of unrelated depressed subjects assessed using the same clinical research methods to validate the results of the exploratory factor analysis; and (3) to provide further validation of the identified symptom dimensions by analyzing their correlations between depressed siblings.

METHODS

SUBJECTS

The main part of the analysis was carried out on subjects recruited for a large international multicenter genetic study of siblings with depression (depression network study [DeNT]) conducted at the following 8 clinical centers: St Louis, MO, London, England, Cardiff, Wales, Birmingham, England, Dublin, Ireland, Lausanne, Switzerland, Aarhus, Denmark, and Bonn, Germany. Confirmatory factor analysis was carried out on subjects recruited from a multicenter case-control depression study (depression case-control study [DeCC]) conducted in Birmingham, Cardiff, and London. Ethical approval was first obtained from the appropriate local ethics committees in each of the countries involved, and every participant gave written informed consent.

Both studies used similar methods for subject ascertainment. Subjects were identified from psychiatric clinics, hospitals, and general medical practices and from volunteers responding to media advertisements. White subjects older than 18 years were included if they had experienced 2 or more episodes of unipolar depression of at least moderate severity, separated by at least 2 months of remission, as defined by DSM-IV and ICD-10. In the DeNT study, subjects were included if they had at least 1 full sibling older than 18 years meeting the same inclusion criteria. Subjects were excluded if either sibling was adopted or if they were the monozygotic twin of any other sibling in the study.

Exclusion criteria for the DeCC and DeNT included a history of psychotic symptoms that were mood incongruent or present when there was no evidence of a mood disturbance, intravenous drug use with a lifetime diagnosis of dependency, depression occurring solely in relation to alcohol or substance abuse, or depression secondary to medical illness or medication. Subjects were also excluded from both studies if there was a clear diagnosis of bipolar disorder, schizophrenia, schizoaffective disorder, or transient psychotic disorders in first- or second-degree relatives.

CLINICAL ASSESSMENT

All subjects were interviewed using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN), a set of instruments validated in assessing, measuring, and classifying the symptoms of major adult psychiatric disorders. Subjects identified their 2 worst episodes of depression, and SCAN items were rated from the worst and second worst episodes. Most items are coded on an ordinal scale indicating the presence and severity of items (general rating of anxiety, general rating of phobia, sleep problem with depressed mood, and morning depression, 0-1; hypersomnia and appetite gain, 0-2; suicide or self-harm, 0-4; and the remainder of items, 0-3). The ratings from the SCAN interviews were entered into a computerized scoring program, CATEGO5, which provides diagnoses according to DSM-IV and ICD-10 operational definitions.

AGREEMENT BETWEEN RATERS ACROSS SITES

All interviewers from each site undertaking the DeNT study attended a 4-day SCAN training course in the United Kingdom. Additional interrater reliability meetings were held regularly at each site, and annually the interviewers from all sites took part in a joint interrater reliability exercise, with a mean across centers of 0.77 (range, 0.63-0.89), giving a substantial level of interrater agreement. Rates from the 3 United Kingdom sites undertaking the DeCC study also participated in a 4-day SCAN training program and regular local interrater reliability meetings. In addition, intersite joint audiotape rating sessions were undertaken via telephone conferencing.

DATA ANALYSIS

Correlation of Symptoms Between Episodes

Spearman rank correlation coefficients were calculated for depressive symptoms between worst and second worst episodes.

Correlation of Symptoms Between Siblings

To remove the effects of sex and age on the depressive symptoms, each symptom was adjusted by age and sex in the DeCC and DeNT samples. The SAS PROC MIXED (SAS Institute, Cary, NC) procedure was used to fit a linear model with age as a covariate and sex as a fixed effect. The residuals were considered as continuous variables and used for further analysis. Data were also analyzed with symptoms adjusted for the age at first onset of depression; however, as no significant effect of age at onset was found, all results are presented based on age and sex adjustment only.

Intraclass correlations were calculated for adjusted depressive symptoms between affected sibling pairs. Intraclass correlations were derived as (Msb − MSw)/(MSb + [k−1]MSw), where MSb and MSw are mean squares between and within siblings, respectively, obtained using analysis of variance for the
random-effects model,\(^1\) and \(k\) is the number of subjects in the class (\(k=2\) for sib pairs). In families with more than 2 members, each sibling pair contributed 1 independent pair, each trio (proband, sibling 1, and sibling 2) contributed 2 independent pairs (proband-sibling 1 and proband-sibling 2), each quartet contributed 3 independent pairs, and so on.

EXPLORATORY FACTOR ANALYSIS

Factor analysis was performed on 26 adjusted depression symptom items from the SCAN interview questions, representing a broad range of depressive symptoms, and 4 screening questions for the presence of anxiety disorders, using SAS PROC FACTOR. To assess the effect of latent dependencies between sib pairs stemming from the same family, we adjusted each symptom for the family (random) effect in addition to the sex and age adjustment. The SAS PROC MIXED procedure was used to fit a mixed model with age as a covariate, sex as a fixed effect, and family effect as a random effect. The residuals were used for the factor analysis. Initial factors were extracted using the principal components method, and rotations were then performed by the PROMAX method. To simplify interpretation, different rotations are used: orthogonal rotation is used if the assumption is that factors are uncorrelated, and oblique (including PROMAX) rotation is used if the factors are correlated with each other, as in the present analysis. The number of meaningful factors was determined by the scree plot.

CONFIRMATORY FACTOR ANALYSIS

Confirmatory maximum likelihood factor analysis, using structural equation modeling, was performed to test the factor construction obtained from the DeNT data against the DeCC data (Figure). The PROC CALIS in SAS was used to carry out the confirmatory factor analysis. Several goodness-of-fit measures were used to assess different versions of the construction: the goodness-of-fit index (GFI) and the GFI adjusted for degrees of freedom,\(^1\) comparative fit index,\(^1\) nonnormed fit index,\(^1\) and root-mean-square error of approximation.\(^1\) To prove that a model fits the data, the accepted standard requirements for the goodness-of-fit indices are as follows: GFI, GFI adjusted for degrees of freedom, and comparative fit index greater than 0.95; nonnormed fit index greater than 0.9; and root-mean-square error of approximation less than 0.05.\(^1\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(\ldots\)
DEPRESSION CASE-CONTROL STUDY

Four hundred eighty-five depressed individuals (31.9% men and 68.1% women) were recruited from the 3 United Kingdom sites. The age range at assessment was 18 to 82 years (mean ± SD age, 47 ± 12 years). Both studies were designed for genetic analysis. Therefore, to simplify later linkage and association analyses, subjects were restricted to those with white parents and grandparents. The frequency and severity of clinically significant depressive symptoms (as defined by SCAN) in all subjects are shown in Table 2. The severity was calculated as the ratio of the mean score to the maximum score for each symptom.

DATA ANALYSIS

Correlations of Symptoms Between Episodes

Spearman rank correlation coefficients for all symptoms between episodes in the DeNT sample were highly significant (P<.001). Therefore, further analyses were carried out on symptoms reported during the worst episodes.

Correlations of Symptoms Between Siblings

For the between-siblings correlation analysis, the data consisted of 346 pairs, 46 trios, 8 quartets, 2 quintets, and 1 sextet. The number of independent pairs from sibling pairs, trios, quartets, quintets, and sextets was therefore 346, 92, 24, 8, and 5, respectively. Table 3 shows the correlation coefficients for depressive symptoms, corrected for age and sex effect, between siblings. Restlessness (0.307), anxiety symptoms (0.260-0.306), loss of libido (0.295), and irritability (0.238) showed the highest correlations.

EXPLORATORY FACTOR ANALYSIS

To ensure that artifactual groupings did not result from the selection of several SCAN items that address similar symptoms (eg, initial insomnia and middle sleep period insomnia, problems with thinking, and problems with concentration), only one item was used for each type of symptom. Psychotic symptoms (delusions of guilt or worthlessness, delusions of catastrophe, hypochondriacal delusions in the context of depression, and auditory hallucinations with affective state) were excluded from the analysis because they occurred in too few subjects.

All 1034 subjects were used for the exploratory factor analysis. The scree plot indicated 4 substantive factors, which accounted for 39% of the variance. The 4 symptom dimensions are shown in Table 4 and comprised the following symptom groupings. Factor 1 comprises the mood symptoms, including depressed mood, anhedonia, loss of hope, loss of reactivity, loss of interest, and low self-esteem. It also includes psychomotor retardation symptoms, with inefficient thinking and loss of energy and libido. Factor 2 comprises the anxiety dimension, including general rating of anxiety, free-floating anxiety, anxious foreboding with autonomic symptoms, and general rating of phobias. Factor 3 comprises psychomotor agitation with restlessness and irritability, pathological guilt and guilty ideas of reference, suicidality, and morning worsening of depressed mood.

Table 1. Sex and Age of Subjects Recruited at Each Site

<table>
<thead>
<tr>
<th>Site</th>
<th>Male-Female Ratio</th>
<th>Age, Mean (SD), y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aarhus, Denmark</td>
<td>17:22</td>
<td>41 (9)</td>
</tr>
<tr>
<td>Birmingham, England</td>
<td>40:83</td>
<td>48 (13)</td>
</tr>
<tr>
<td>Bonn, Germany</td>
<td>36:113</td>
<td>49 (13)</td>
</tr>
<tr>
<td>Cardiff, Wales</td>
<td>39:84</td>
<td>44 (10)</td>
</tr>
<tr>
<td>Dublin, Ireland</td>
<td>49:126</td>
<td>40 (11)</td>
</tr>
<tr>
<td>Lausanne, Switzerland</td>
<td>48:107</td>
<td>45 (12)</td>
</tr>
<tr>
<td>London, England</td>
<td>51:103</td>
<td>46 (10)</td>
</tr>
<tr>
<td>St Louis, Mo</td>
<td>41.75</td>
<td>46 (11)</td>
</tr>
<tr>
<td>Total (N = 1034)</td>
<td>321:713</td>
<td>45 (12)</td>
</tr>
</tbody>
</table>

Table 2. Frequency and Severity of Symptoms in Depression Network Study (DeNT) and Depression Case-Control Study (DeCC) Samples

<table>
<thead>
<tr>
<th>Symptom</th>
<th>DeNT Frequency, %</th>
<th>DeNT Severity, %</th>
<th>DeCC Frequency, %</th>
<th>DeCC Severity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressed mood</td>
<td>98.84</td>
<td>0.93</td>
<td>98.97</td>
<td>0.94</td>
</tr>
<tr>
<td>Loss of reactivity</td>
<td>96.81</td>
<td>0.94</td>
<td>99.38</td>
<td>0.93</td>
</tr>
<tr>
<td>Anhedonia</td>
<td>96.62</td>
<td>0.89</td>
<td>99.59</td>
<td>0.91</td>
</tr>
<tr>
<td>Loss of interest</td>
<td>95.84</td>
<td>0.85</td>
<td>95.05</td>
<td>0.82</td>
</tr>
<tr>
<td>Loss of energy or drive</td>
<td>95.16</td>
<td>0.85</td>
<td>95.26</td>
<td>0.87</td>
</tr>
<tr>
<td>Hopelessness</td>
<td>91.01</td>
<td>0.82</td>
<td>93.40</td>
<td>0.86</td>
</tr>
<tr>
<td>Loss of self-esteem</td>
<td>88.39</td>
<td>0.78</td>
<td>88.04</td>
<td>0.79</td>
</tr>
<tr>
<td>Subjectively inefficient thinking</td>
<td>88.01</td>
<td>0.74</td>
<td>90.31</td>
<td>0.80</td>
</tr>
<tr>
<td>Fatigability and exhaustion</td>
<td>70.31</td>
<td>0.62</td>
<td>59.79</td>
<td>0.51</td>
</tr>
<tr>
<td>Suicidality</td>
<td>62.09</td>
<td>0.25</td>
<td>64.95</td>
<td>0.25</td>
</tr>
<tr>
<td>Subjective feeling of retardation</td>
<td>61.70</td>
<td>0.49</td>
<td>61.44</td>
<td>0.50</td>
</tr>
<tr>
<td>Irritability</td>
<td>58.99</td>
<td>0.40</td>
<td>53.61</td>
<td>0.35</td>
</tr>
<tr>
<td>General rating of anxiety</td>
<td>57.54</td>
<td>0.58</td>
<td>55.26</td>
<td>0.55</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>57.45</td>
<td>0.50</td>
<td>66.45</td>
<td>0.61</td>
</tr>
<tr>
<td>Pathological guilt</td>
<td>56.96</td>
<td>0.44</td>
<td>65.57</td>
<td>0.49</td>
</tr>
<tr>
<td>Subjectively described restlessness</td>
<td>52.51</td>
<td>0.42</td>
<td>42.89</td>
<td>0.34</td>
</tr>
<tr>
<td>Morning depression</td>
<td>50.77</td>
<td>0.51</td>
<td>45.98</td>
<td>0.46</td>
</tr>
<tr>
<td>Early waking</td>
<td>50.58</td>
<td>0.39</td>
<td>52.37</td>
<td>0.39</td>
</tr>
<tr>
<td>Loss of weight</td>
<td>50.58</td>
<td>0.23</td>
<td>54.02</td>
<td>0.24</td>
</tr>
<tr>
<td>Loss of libido</td>
<td>47.10</td>
<td>0.39</td>
<td>42.89</td>
<td>0.36</td>
</tr>
<tr>
<td>Preoccupation with death or catastrophe</td>
<td>42.75</td>
<td>0.34</td>
<td>36.49</td>
<td>0.17</td>
</tr>
<tr>
<td>Free-floating anxiety</td>
<td>38.30</td>
<td>0.29</td>
<td>49.69</td>
<td>0.38</td>
</tr>
<tr>
<td>Hypersomnia</td>
<td>32.21</td>
<td>0.26</td>
<td>27.84</td>
<td>0.22</td>
</tr>
<tr>
<td>General rating of phobias</td>
<td>29.21</td>
<td>0.29</td>
<td>35.05</td>
<td>0.35</td>
</tr>
<tr>
<td>Guilty ideas of reference</td>
<td>26.20</td>
<td>0.20</td>
<td>29.48</td>
<td>0.22</td>
</tr>
<tr>
<td>Anxious foreboding with autonomic symptoms</td>
<td>23.21</td>
<td>0.16</td>
<td>31.55</td>
<td>0.24</td>
</tr>
<tr>
<td>Gain of weight</td>
<td>20.50</td>
<td>0.15</td>
<td>18.56</td>
<td>0.13</td>
</tr>
<tr>
<td>Gain of appetite</td>
<td>13.64</td>
<td>0.13</td>
<td>9.90</td>
<td>0.09</td>
</tr>
<tr>
<td>Delusions of guilt or worthlessness</td>
<td>2.22</td>
<td>0.01</td>
<td>1.44</td>
<td>0.01</td>
</tr>
<tr>
<td>Hypochondriacal delusions</td>
<td>1.64</td>
<td>0.01</td>
<td>1.24</td>
<td>0.01</td>
</tr>
<tr>
<td>Auditory hallucinations</td>
<td>1.23</td>
<td>0.01</td>
<td>2.89</td>
<td>0.01</td>
</tr>
<tr>
<td>Delusions of catastrophe</td>
<td>0.77</td>
<td>0.01</td>
<td>0.82</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Factor 4 includes appetite gain and hypersomnia negatively correlated with appetite loss and early waking.

There was cross-loading of suicidality between factors 1 and 3 and cross-loading of hypersomnia between factors 1 and 4.

**CONFIRMATORY FACTOR ANALYSIS**

Subjects from the DeCC sample (n=485) were used in the confirmatory factor analysis of the hypothesized factor structure derived from the exploratory factor analysis of the DeNT data set. The best fit (GFI, 0.99; GFI adjusted for df, 0.9; comparative fit index, 0.99; nonnormed fit index, 0.87; and root-mean-square error of approximation, 0.036) was obtained for the 4-factor model, which included cross-loadings, correlations between factors, and error covariances. The improvement in model fit after including the error covariances suggests that some of the errors are correlated and indicates that the data may also contain a nonlinear finer structure. Nevertheless, the linear modeling yields acceptable fit results and provides a good approximation.

**FAMILIARITY OF SYMPTOM DIMENSIONS**

Intraclass correlations between siblings for factor 4 was 0.075 (P = .052). The correlation between siblings for factor 4 was 0.075 (P = .052).

Both samples were from genetic studies designed to ascertain individuals with moderate to severe recurrent depression. This is reflected by the type and frequency of symptoms occurring in this study group, with a 62% frequency of suicidality and a high frequency of depressive cognitions and disturbances in thinking. Depressed mood, loss of mood reactivity, and anhedonia were almost ubiquitous symptoms, which would be expected as these are core symptoms occurring in the worst episodes. Kendler and colleagues have shown that, although there are limitations to using retrospectively acquired data, depression that tends to be more memorable and therefore more relati-
ably reported. Furthermore, it has been demonstrated that ratings from a past episode of depression are comparable to contemporary accounts derived from case notes. On the other hand, memories of symptoms that occurred during a severe episode of depression may confound memory of other episodes, resulting in recall of the same features for all episodes. Therefore, in the present study, the use of data from only the worst episodes produced a more robust analysis.

Reliability was further increased by inclusion of only those individuals who had experienced 2 or more depressive episodes. In this sample, there was a slightly greater preponderance of women (2.2:1) than is usually found in community samples, in which a 1.7 times greater depression risk for women has been reported. This probably also reflects recruitment methods and the fact that women are more likely to volunteer to participate in research studies. The higher mean age of 45 years in this study reflects the fact that only subjects with recurrent depression were included. Overall, the samples used in the present study were representative of moderate to severe nonpsychotic depression.

After eliminating the possible effects of age, age at onset of depression, and sex, factor analysis of a range of SCAN items identified 4 interpretable factors. The first factor (18% of the variance) comprised depressed mood symptoms that are almost ubiquitous among individuals with depression, as well as symptoms associated with psychomotor retardation and loss of libido and self-esteem. The second factor, consisting of the anxiety symptoms, formed an independent dimension of depression accounting for 9% of the variance. There is considerable overlap between depressive and anxiety symptoms, and anxiety as a symptom is the norm rather than the exception in major depression; 58% of individuals with depression, as well as symptoms associated with psychomotor retardation and loss of libido and self-esteem. The second factor, consisting of the anxiety symptoms, formed an independent dimension of depression accounting for 9% of the variance. There is considerable overlap between depressive and anxiety symptoms, and anxiety as a symptom is the norm rather than the exception in major depression; 58% of individuals with lifetime episode of major depression also meet criteria for an anxiety disorder.

In this study, the frequency of anxiety symptoms ranged from 23% (anxious foreboding) to 58% (general rating of anxiety). Interestingly, there was no cross-loading between the anxiety factor and any other dimension.

The third factor identifies a strong grouping of signs of agitation, such as irritability and restlessness, with suicidality and other depressive cognitions, in particular, guilt. Morning worsening of depressed mood is also part of this dimension. The association of suicidality and agitation is interesting; although ideally psychomotor agitation needs to be documented by an observer, irritability and subjective restlessness are indicators of its presence. Parker has proposed a hierarchical model of depression in which there are separate neurobiological processes generating differing clinical features. He further postulates that psychomotor disturbance is a distinct component associated with "melancholic" and more severe depression. Suicidality is an indicator of more severe depression, at least in the sense that it increases the risk of mortality from depression, and recognition of this suicidality-agitation dimension has important clinical implications if the presence of agitation predicts suicide.

The fourth factor comprised increased appetite and hypersomnia negatively correlated with early awakening and appetite loss. There has been recent interest in the atypical depressive subtype (ie, hypersomnia with increased weight and appetite) and a study of subtypes of depression in twins found appetite and weight to be among the most discriminating symptoms and findings and identified an atypical depressive subgroup. In our analysis, we focused on appetite changes rather than weight changes, as the former is a more reliable measure and not as dependent on the length of a depressive episode. The strong separation of increased appetite and sleep into a separate dimension adds some support to the existence of a separate atypical dimension.

Three of the 4 symptom dimensions showed a significant correlation between siblings, adding validation of this factor structure. Factor 1 showed a low level of correlation, but as this largely comprises a group of symptoms that are obligatory for a diagnosis of depression and thus almost ubiquitous in this sample and in any sample defined under our present classification systems, this dimension may be more indicative of severity rather than representing a particular phenotypic component, and, whereas heritability contributes to the latter, severity is not familial.

Factors 2 (anxiety) and 3 (psychomotor agitation, guilt, and suicidality) showed a highly significant moderate degree of correlation (0.335 and 0.362, respectively) between siblings. There was also significant correlation between siblings of several individual symptoms (Table 2), but with lower correlations overall than for symptom dimensions, suggesting that dimensions could be more robust phenotypic markers. However, although our findings support the existence of an atypical symptom dimension, it does not appear to have a familial etiology. This dimension and the individual symptoms of hypersomnia and appetite gain show low sibling correlation.

The correlations between siblings for symptom dimensions reported herein are much higher than those found in similar factor analyses of schizophrenia and are more likely to reflect genetic or environmental factors shared between the depressed siblings, rather than modifying factors. Genetic effects are the most important contributor to familial aggregation, and if the factor structure shown in this study represents different components of genetic liability, then such factors could be used in genetic studies to identify more homogeneous subgroups of depression.

Limitations of this study are that subjects were ascertained in different ways at the various sites, relying on advertisement in some centers, and in others being mainly recruited from psychiatric clinics; therefore, findings cannot necessarily be generalized to other studies. This study was carried out on white subjects only; therefore, results cannot be extrapolated to other ethnic groups. Furthermore, there are potential sources of bias in that volunteering may be more likely in sibling pairs who have more similar types of depressive symptoms, and that subjects came from families with more than 1 sib with depression. However, the confirmatory analysis demonstrated similar findings in an independent group of single depressed subjects (DeCC). A further limitation, as already discussed, is that we made cross-sectional assessments of psychiatric symptoms; although a longitudinal...
or repeated assessment would have been preferable, assessments were retrospective and therefore subject to memory bias.

There has been a long-standing and largely unresolved debate as to whether depression is best classified as a collection of syndromes or as a single entity in which cases differ mainly in terms of severity. In this study of large, well-defined samples of depressed subjects, symptom dimensions have been derived and then confirmed using independent material. We also found highly significant correlations between siblings. Caution is required when interpreting correlation between siblings, but recent twin studies suggest that shared environmental effects in depression are small or nonexistent. We can therefore conclude that the dimensions corresponding to factors 1, 2, and 3 have substantial familial, perhaps genetic, etiologies. Although this is not the same as finding 2 causally distinct syndromes, the identification of depressive symptom dimensions provides the potential for a more refined phenotypic definition for molecular genetic studies of depression using a quantitative trait locus approach. Furthermore, such dimensions may prove useful in psychopharmacological research, in which it has been pointed out that the development of new drugs to treat depression would be facilitated by dissecting the current “monolithic” definition of the disorder into component symptom complexes.

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From the Department of Psychological Medicine, University of Wales College of Medicine, Cardiff (Dr Korszun, Moskvina, Craddock, and Owen), GlaxoSmithKline Medical Genetics, Middlesex (Ms Brewster), Department of Psychiatry, University of Birmingham, Birmingham (Dr I. R. Jones and L. A. Jones), and Medical Research Council Social Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, King’s College, London (Drs Farmer and McGuffin), England; Department of Psychiatry, University of Geneva, Geneva (Dr Ferrero), and Departement Universitaire de Psychiatrie Adult, Prilly-Lausanne (Dr Preissig), Switzerland; Department of Psychiatry, Trinity Centre for Health Sciences, St James’ Hospital, Dublin, Ireland (Dr Gill); Department of Psychiatry, University of Bonn, Bonn (Dr Maier), and Division of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Mannheim (Dr Rietschel), Germany; Department of Psychiatric Demography, Psychiatric Hospital in Aarhus, Aarhus, Denmark (Dr Mars); and Department of Psychiatry, Washington University School of Medicine, St Louis, Mo (Dr Reich).

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Corresponding author and reprints: Ania Korszun, PhD, MD, MRCPsych, Department of Psychological Medicine, University of Wales College of Medicine, Heath Park, Cardiff CF14 4XN, United Kingdom (e-mail: akorszun@umich.edu).

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