Factorial structure and familial aggregation of the Hypomania Checklist-32 (HCL-32): Results of the NIMH Family Study of Affective Spectrum Disorders

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ABSTRACT

Background: There is substantial evidence that bipolar disorder (BD) manifests on a spectrum rather than as a categorical condition. Detection of people with subthreshold maifestations of BD is therefore important. The Hypomania Checklist-32 (HCL-32) was developed as a tool to identify such people.

Purpose: The aims of this paper were to: (1) investigate the factor structure of HCL-32; (2) determine whether the HCL-32 can discriminate between mood disorder subtypes; and (3) assess the familial aggregation and cross-aggregation of hypomanic symptoms assessed on the HCL with BD.

Procedures: Ninety-six probands recruited from the community and 154 of their adult first-degree relatives completed the HCL-32. Diagnosis was based on semi-structured interviews and family history reports. Explanatory factor analysis and mixed effects linear regression models were used.

Findings: A three-factor ("Activity/Increased energy," "Risk-taking/Irritability", "Novelty seeking") solution fit the HCL-32, explaining 11.2% of the total variance. The HCL Risk-taking/Irritability score was elevated among those with BP-I and BP-II, compared to those with depression and no mood disorders. Higher HCL-32 scores were associated with increased risk of BD-I (OR=1.22, 95%CI 1.14-1.30). The "Distractibility/Irritability" score was transmitted within families (β=0.15, p=0.040). However, there was no familial cross-aggregation between mood disorders and the 4 HCL factors.

Conclusions: Our findings suggest that the HCL-32 discriminates the mood disorder subtypes, is familial and may provide a dimensional index of propensity to BD. Future studies should explore the heritability of symptoms, rather than focusing on diagnoses.

Key words: Bipolar disorder; Hypomania Checklist-32; Familial aggregation; Familial cross-aggregation; Factor analysis; Major Depressive Disorder.

Abbreviations: BD = bipolar disorder; HCL-32 = Hypomania Checklist-32; MDD = major depressive disorder; NIMH = National Institute of Mental Health; NIH = National Institutes of Health; DIAS = NIMH Family Study Diagnostic Interview for Affective Spectrum Disorders; DIAS-FHX = NIMH Family Study Family History Interview; FH-RDC = Family History-Research Diagnostic Criteria; EFA = Explanatory Factor Analysis

1. Introduction

The spectrum concept of bipolar disorder (BD) has been widely demonstrated in both clinical and community samples [1, 2]. There is a substantial proportion of people who exhibit manic symptoms but fail to meet full criteria for mania or hypomania. Because most people with BD seek treatment for depression rather than for mania or particular hypomania, the presence of subthreshold mania symptoms is often neglected [3]. Detection of subthreshold bipolarity in the context of major depressive episodes is particularly important because it may lead to inadequate or inappropriate treatment [4]; specifically, the American Psychiatric Association and American Academy of Child and Adolescent Psychiatry both caution against the administration of antidepressant medication in people with – or at risk for – BD without a mood stabilizer [5, 6]. The threat of anti-depressant coincident mania calls attention to the need for a low burden way of assessing for hypomanic symptoms; major depressive disorder (MDD) is approximately 4-10 times more common than BD [7, 8], so administering a costly or time consuming mania assessment for everyone who experiences depressed mood is not feasible. A brief, self-report measure, on the other hand, could be a simple way to limit misdiagnosis and its consequences.

The Hypomania Checklist-32 (HCL-32) was developed specifically to improve detection of cases of BD that have a primarily depressed presentation [4]. The HCL-32 has demonstrated diagnostic efficiency, with a sensitivity of 80% and a specificity of 51% for distinguishing cases of BD from cases of MDD [4, 9]. The HCL-32 has also shown to be a reliable screening tool in community-based samples [10], in adolescents [11], and has been translated and validated in a number of languages [12-15].

Factor analyses of HCL-32 on clinical and nonclinical samples from different countries have mostly found a 2-factor (active/elated hypomania and risk-taking/irritable hypomania) solution [4, 9, 10, 16-18]. However, a few studies have shown either a 3-factor [11, 19, 20] or a 4-factor solution [13, 21]. These

inconsistencies may be related to differences in the age composition and clinical status of the samples. Identifying the structure of the HCL-32 is important, as research suggests that not only the severity, but also the type, of manic symptoms are related to impairment and prognosis [10, 17].

Because a family history of BD is one of the strongest risk factors for BD [22, 23], relatives of patients with BD may often manifest the full spectrum of BD ranging from hypomanic symptoms to severe BD. The HCL-32 may provide a powerful tool to test the familial liability for BD. To our knowledge, no previous study has examined the familial aggregation of subthreshold BD as measured by the HCL-32, nor whether the HCL-32 may provide an index of the familial liability to BD. Identification of the liability to bipolarity could have important clinical and etiologic relevance.

The major aims of this paper are to investigate: 1) the factor structure of HCL-32 in a nonclinical sample of adults; we hypothesize that, consistent with previous community studies, the HCL-32 will have a two-factor structure; 2) whether HCL-32 can be used as a tool to discriminate between BD-I, BD-II and MDD in a community-based sample; we expect that the HCL-32 will be able to distinguish between the diagnostic categories; and 3) if hypomanic symptoms assessed by the HCL-32 are familial, and if so, provide an index of familial risk for BD, we propose that the HCL-32 factors are familial and that they may be elevated among relatives of probands with BD who did not meet criteria for BD.

2. Methods and materials

2.1. Study population

The present study is a secondary analysis of data from the National Institute of Mental Health (NIMH) Family Study of Affective Spectrum Disorders, a large community-based, controlled family study of probands with mood disorders (i.e., BD-I, BD-II and MDD). The sample was derived from a community

screening of the greater Washington, D.C. metropolitan area, the National Institutes of Health (NIH) Clinical Center general volunteer referral core, from local health newsletters and announcements, and from people identified through the NIMH Mood and Anxiety Disorder Program. Inclusion criteria included: willingness to consent to have the research team contact at least two living, first-degree relatives and an ability to speak English. A total of 509 participants, consisting of both probands and relatives completed the HCL-32. Of these, 96 probands and 154 of their adult first-degree relatives were included in the familial transmission analyses (the remaining 259 participants, who did complete the HCL-32 questionnaire, were not be included in the family analyses). Recruitment is described in detail in Merikangas et al. [24].

The study was approved by the Combined Neuroscience IRB at the NIH and are in accordance with the Helsinki Declaration of 1975. All participants provided written informed consent.

2.2. Procedures

2.2.1. Interview

Standard family study methodology was employed including systematic enumeration of first degree relatives, direct interview of probands and relatives by experienced clinicians, and multiple informant family history reports about both probands and relatives [24].

2.2.2. Diagnostic assessments

The NIMH Family Study Diagnostic Interview for Affective Spectrum Disorders (DIAS) was based on the adaptation of the diagnostic interview used in our prior family studies of anxiety disorders and substance use disorders at the Yale University School of Medicine Genetic Epidemiology Research Unit based on the SADS/DIGS [25, 26]. The DIAS ascertains diagnostic criteria for current and lifetime DSM-IV-TR disorders, but does not adhere to strict diagnostic criteria for skip-outs based on frequency or

duration at the probe level in order to capture subthreshold phenomenology across the key domains of psychopathology for multiple diagnostic systems [27, 28]. The interview included all major mental disorders, including mood disorders and anxiety. For the present study, the mood disorder diagnostic categories included BD-I, BD-II, MDD, Other (all participants without mood disorders, but not excluding other psychopathology).

The NIMH Family Study Family History Interview (DIAS-FHX) was used to assess a family history of psychiatric disorders based on modifications of the family history interview from our previous family study research [25, 26]. The interview was based on the core structure of the Family History-Research Diagnostic Criteria (FH-RDC) developed for the collaborative family study of affective disorders [29]. Diagnoses for this study were based on all available information and were made by a team of experienced clinicians (psychologists and a psychiatrist) using a best estimate procedure [30]. The current analyses assess BD-I, BD-II, and MDD as defined by DSM-IV.

2.2.3. Hypomania Checklist (HCL – 32) questionnaire

The HCL-32 is a self-administered questionnaire for the assessment of hypomania (a previous version included an extra question, which was later omitted without any loss of information, Angst et al., 2010b). There are 32 yes/no items, each of which corresponds to a different emotion, behavior, or thought (e.g., "I feel more energetic and more active") [4]. The HCL-32 was first developed in German and different versions in several languages have been validated [9]. In our study, we used the English version [4].

2.3. Statistical Methods

Statistical analyses were completed using the Statistical Analysis System (SAS Institute Inc., Cary, NC, USA), version 9.3 for Windows. Descriptive analyses were conducted for demographic characteristics

(sex and age) for both probands and adult first degree relatives, and recruitment source and comorbidity for probands. Chi-square and ANOVA were used to test differences between the proband diagnostic groups (BD-I, BD-II, MDD, Other [anyone without a mood disorder diagnosis]).

An Explanatory Factor Analysis (EFA) was conducted for the 32 items of the HCL-32 with subsequent Varimax rotation with all participants. Initially, factors with Eigenvalues greater than 1 revealed 7 factors, and the decision on the number of factors to retain was based on the scree plot and the coherence of the factors. Items that were cross-loading ("Want to travel and do travel more"; "Take more risks in daily life"; "Am physically more active"; "Wear more colorful clothes"; "Think faster"; "Get into more quarrels"; "Drink more alcohol") were excluded and a second EFA with Varimax rotation was conducted. For subsequent analyses, a total score summing all 32 items of the HCL-32 was calculated. Additionally, we summed the items of each of the factors to create subscale scores.

Mean values with the Duncan test (a multiple comparison procedure) were assessed for the total HCL-32 and subscale scores among probands and relatives by their lifetime diagnosis. Only the 96 probands and their 154 adult first degree relatives were included in these analyses. Non-linear mixed models and logistic regressions were applied to determine the comorbidity between total HCL-32 and subscale scores and mood disorder subtypes in the overall sample adjusting for sex and age. The familial transmission of hypomanic symptoms, as assessed by the HCL-32, was tested using mixed effects linear regression models that evaluated the associations between proband and relative HCL-32 total and subscale scores, adjusting for sex and age of the relative. Familial cross-aggregation for the association between HCL-32 scores and BD was tested using mixed effects linear and logistic regression models, adjusting for sex, age, and BD in relatives (when the outcome was HCL-32 scores). All the mixed models included random intercepts to account for the within family correlation.

In additional analyses, we further tested current states of the mood episodes to evaluate differences between lifetime and current diagnoses and to examine whether HCL scores tap state vs. trait manifestations of mood disorders.

3. Results

The description of the sample by proband mood disorder diagnostic groups (BD-I, BD-II, MDD and Other) is presented in Table 1. Comorbid disorders among probands and age of first degree relatives varied by diagnostic groups.

3.1. Factor analysis

The degree of common variance of the EFA among the variables was "meritorious" bordering on "marvelous" (Kaiser's measure of sampling adequacy = 0.87), which means that the factors extracted accounted for a good amount of variance. Based on the scree test and on the coherence of the factors, we retained a 4-factor solution (Table 2), which explained 11.1% of the total variance. Factor 1 was labeled "Activity/Increased Energy", consisted of 10 items and accounted for 3.8% of the variance; factor 2 was labeled "Distractibility/Irritability", consisted of 7 items and accounted for 3.0% of the variance; factor 3 was labeled "Novelty seeking/Disinhibition", consisted of 5 items and accounted for 2.7% of the total variance; and finally, factor 4 was labeled "Substance use", consisted of 3 items and accounted for 1.6% of the total variance.

3.2. Distribution HCL scale scores by diagnostic group

The distributions of total HCL and subscale scores by diagnostic groups are presented in Figures 1a and 1b. The mean total HCL-32 score was higher in participants with BD-I compared to other mood disorder subgroups and Others, and among those with BD-II compared to those with MDD or Others. The MDD and Others groups did not differ with respect to the mean HCL-32 total score. Similar group differences

emerged for the HCL Distractibility/Irritability and the HCL Substance use subscale scores. The other HCL subscales also differed among those with BPI/BPII compared to those with MDD and Others.

3.3. Associations HCL scale scores and mood disorders

The associations between total HCL and subscale scores and lifetime mood disorder subtypes (BD-I, BD-II and MDD) in the overall sample adjusted for sex and age are presented in Table 3. The HCL total score and the HCL Distractibility/Irritability subscale were associated with an increased likelihood of BD-I and BD-II, and a decreased risk of MDD. Moreover, the HCL Activity/Increased energy subscale was associated with and increased likelihood of BD-II, whereas HCL Novelty seeking/disinhibitionand HCL Substance use subscales were not associated with lifetime mood disorders in the overall sample.

3.4. Familial associations of HCL-32 scale scores

HCL total, HCL Activity/Increased energy, HCL Novelty seeking/disinhibitionand HCL Substance use scores in probands were not associated with HCL scores in their relatives (β = -0.09, *p*-value = 0.263; β = -0.10, *p*-value = 0.288; β = -0.11, *p*-value = 0.154, β = -0.01, *p*-value = 0.829, respectively). The HCL Distractibility/Irritability subscale score was associated with an increased HCL Distractibility/Irritability subscale score in relatives (β = 0.15, *p*-value = 0.040). However, after controlling of bipolar comorbidity in relatives, the HCL Distractibility/Irritability subscale score was no longer significant (β = 0.06, *p*-value = 0.388). Similarly, after controlling for bipolar comorbidity in probands, the association between HCL Distractibility/Irritability subscale score did not remain significant (β = -0.00, *p*-value = 0.979).

3.5. Cross-transmission of HCL-32 scale scores and mood disorders

The associations between proband HCL total and subscale scores with lifetime mood disorders in relatives are presented in Table 4. The HCL Distractibility/Irritability subscale in probands was associated with an increased risk of BD-I in relatives. However, when we further adjusted the model for BD in probands, the association was no longer significant (OR=1.42, 95%CI 0.81-2.48). The Activity/Increased

energy subscale in probands was associated with a decreased risk of BD-I in relatives. No significant associations were found for HCL scale scores in probands and BD-II or MDD in relatives.

Finally, the association between proband BD-I and BD-II and HCL total and subscale scores in relatives adjusting for age, sex and BD in relatives are presented in Table 5. No significant associations of HCL subscale scores were observed among relatives of probands with BD. See Figure 2 for an illustration of the familiality of HCL-32 Distractibility/Irritability scores and BD-I in probands and relatives.

We repeated these analyses for current versus lifetime mood disorders and the findings for the lifetime mood disorders persisted.

4. Discussion

To our knowledge, this is the first study to examine the familial transmission of hypomanic symptoms in a large, contemporary community-based family study of mood disorders using the HCL-32. Consistent with some previous research, we found a 4-factor solution for the HCL-32, and demonstrated that it is a valid tool to distinguish adults who have BD-I or II from those who have MDD or no mood disorder diagnoses. We also found that the HCL Distractibility/Irritability factor was familial, suggesting that this factor may underlie the familial aggregation of BD.

4.1. Factor analysis

The majority of previous factor analysis studies of the HCL-32 reported a 2-factorial solution, with factor 1 being “Active/Elated” (the bright side) and factor 2 being “Risk-taking/Irritable” (the dark side) [4, 9, 16-18]. Three previous studies also proposed a 3-factorial solution, with the third factor being “Sexual activity” [10, 11, 20], and another previous study yielded a 4-factorial solution, with 2 positive and 2 negative dimensions of hypomania [13]. Apart from the separate factor 3 “Novelty seeking/

disinhibition" and factor 4 "Substance use", our findings are in agreement with previous studies showing a 2-factorial solution. Our third factor included items related to sexual activity, as well as other items related to novelty seeking ("meet more people" and "engage in lots of new things"). A fourth factor was related to substance use, confirming a previous study by Haghinghi et al. [13], with two positive dimension of hypomania (Activity/Increased energy and Novelty seeking/Disinhibition) and two negative dimensions (Distractibility/Irritability and Substance use). Importantly, the majority of studies (cf. [11]), including ours, report a risk-taking/irritability factor; given the relative consistency of this finding and the association of Distractibility/irritability scale scores with both proband BD-I diagnosis and relative HCL-32 scores, it may be that this aspect of hypomania is an endophenotype, whereas other symptoms we associate with hypomania result from heterogeneous factors. Other self-reports [31, 32] have been validated as tools to identify people at risk for BD in community [33] and in high-risk [34] samples. These measures, like the HCL-32, include items related to risk-taking and irritability. However, additional research is necessary to examine the specificity of these symptoms as predictors of the development of BD-I.

4.2. HCL-32 questionnaire as a valid tool to discriminate between mood disorder diagnostic groups

Consistent with previous studies, our findings showed that the HCL-32 questionnaire is a valid tool to distinguish individuals with BD-I or BD-II from those with MDD or no mood disorders in a nonclinical sample [4, 10]. The difference between BD-I and BD-II seemed to be attributable primarily to the factors "Distractibility/Irritability" and "Substance use", suggesting that the difference between BD-I and BD-II may be more driven by the "dark side" of hypomania [17]. Because the Distractibility/Irritability scores were related within families, this finding could provide evidence for differences in heritability between BD-I and II and may support the theory that BD-I and II result from different mechanisms [35-37].

4.3. Familial transmission

Even though we demonstrate the familial associations between HCL scores in probands and relatives, our goal of examining whether the HCL taps subthreshold bipolarity in relatives requires an elevation in HCL scores among those relatives who do not manifest BD. As shown in Table 5 and our summary figure, our findings do show an elevation in the Distractibility/Irritability score among relatives of probands with BD-I, but not after controlling for the relative BD. This suggests that the HCL does not detect propensity to BD-I in relatives who do not manifest threshold level BD-I. The lack of association between proband BD-II and relative HCL Distractibility/Irritability is of particular interest because our earlier findings at the diagnostic level did not yield a significant familial association between either Hypomania or BD-II in relatives [24]. Because the HCL was assessed outside of acute episodes in the majority of the sample, our findings further suggest that this HCL factor may comprise a trait marker of bipolarity (that is, an endophenotype) that may represent an intermediate form of expression of underlying genes. This would be particularly valuable as a tool in offspring of parents with BD in order to identify early manifestations of mania and institute preventive interventions. However, the lack of familial cross-transmission after adjustment for BD suggests that HCL scores do not detect symptoms beyond those already evident among those who manifest BD.

4.4. Limitations

These findings should be considered in the context of two major limitations. First, the participants reported on their symptoms retrospectively, which may have diminished the accuracy of the data due to recall biases. Second, the participants were evaluated at only one time point, so we cannot determine the stability of these factors, nor infer causal relations between the HCL-32 scores and later diagnoses. Third, although the factors extracted using the EFA accounted for a substantial amount of variance

(good Kaiser's measure of sampling adequacy), the 4-factor solution explained a modest total variance. Therefore, the results should be interpreted with caution.

5. Conclusions

In conclusion, our findings suggest that the HCL-32 questionnaire is a useful tool for discriminating BD-I and BD-II from MDD in a nonclinical sample. We also demonstrated the familiality of the Distractibility/Irritability subscale, which may comprise an index of liability to BD in relatives. The lack of familial aggregation of the HCL among those with BP-II provides evidence that BD-II is not on the same diathesis as BD-I disorder. Future studies should focus on evaluating the ability of the HCL-32 to predict BD prospectively, and should test whether symptoms of distractibility and irritability could be an endophenotype for mania, potentially shedding light on mechanisms of transmission of mania.

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Legend Figure 1

Figure 1 Distribution of total Hypomania Symtpom Checklist-32 (**Figure 1a**) and subscale scores (**Figure 2b**) by mood disorder diagnostic groups among probands and relatives (N = 509). A, B, C correspond to the Duncan grouping test. Means with the same letter are not significantly different. Abbreviations: MDD, Major Depressive Disorder; HCL, Hypomania Symptom Checklist-32.

Legend Figure 2

Figure 2 Familiality of Hypomania Symptom Checklist-32 Distractibility/Irritability subscale scores and bipolar I disorder. (**a**) Transmission of Hypomania Symptom Checklist-32 scores in probands and relatives, adjusted for age, sex in relatives. (**b**) Cross-transmission of Hypomania Symptom Checklist-32 scores and bipolar I and II in probands and relatives; ¶ Adjusted for age, sex in relatives and bipolar disorders in probands; § Adjusted for age, sex, bipolar disorders in relatives.