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ORIGINAL CONTRIBUTION

Premenstrual mood symptoms: study of familiality and personality correlates in mood disorder pedigrees

Jennifer L. Payne · Sarah R. Klein · Rachel B. Zamoiski · Peter P. Zandi · Oscar J. Bienvenu · Dean F. MacKinnon · Francis M. Mondimore · Barbara Schweizer · Karen L. Swartz · NIMH Genetics Initiative Bipolar Disorder Consortium Raymond P. Crowe · William A. Scheftner · Myrna M. Weissman · Douglas F. Levinson · J. Raymond DePaulo Jr. · James B. Potash

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Abstract We sought to determine whether premenstrual mood symptoms exhibit familial aggregation in bipolar disorder or major depression pedigrees. Two thousand eight hundred seventy-six women were interviewed with the Diagnostic Interview for Genetic Studies as part of either the NIMH Genetics Initiative Bipolar Disorder Collaborative study or the Genetics of Early Onset Major Depression (GenRED) study and asked whether they had experienced severe mood symptoms premenstrually. In families with two or more female siblings with bipolar disorder (BP) or major depressive disorder (MDD), we examined the odds of having premenstrual mood symptoms given one or more siblings with these symptoms. For the GenRED MDD sample we also assessed the impact of personality as measured by the NEO-FFI. Premenstrual mood symptoms did not exhibit familial aggregation in families with BP or MDD. We unexpectedly found an association between high NEO openness scores and premenstrual mood symptoms, but neither this factor, nor NEO neuroticism influenced evidence for familial aggregation of symptoms. Limitations

J. L. Payne (✉) · S. R. Klein · R. B. Zamoiski · O. J. Bienvenu · D. F. MacKinnon · F. M. Mondimore · B. Schweizer · K. L. Swartz · J. R. DePaulo Jr. · J. B. Potash
Department of Psychiatry and Behavioral Sciences,
School of Medicine, Johns Hopkins University,
550 N. Broadway, Suite 305,
Baltimore, MD 21205, USA
e-mail: jpayne5@jhmi.edu

J. L. Payne · S. R. Klein · R. B. Zamoiski · O. J. Bienvenu · D. F. MacKinnon · F. M. Mondimore · B. Schweizer · K. L. Swartz · J. R. DePaulo Jr. · J. B. Potash
Department of Mental Health, Johns Hopkins University,
Baltimore, MD, USA

P. P. Zandi
Bloomberg School of Public Health, Johns Hopkins University,
Baltimore, MD, USA

R. P. Crowe
Department of Psychiatry and Mental Health Clinical Research Center, University of Iowa Carver College of Medicine,
Iowa City, IA, USA

W. A. Scheftner
Department of Psychiatry,
Rush-Presbyterian Medical Center,
Chicago, IL, USA

M. M. Weissman
Department of Psychiatry,
College of Physicians and Surgeons, Columbia University,
New York, NY, USA

M. M. Weissman
New York State Psychiatric Institute,
New York, NY, USA

D. F. Levinson
Department of Psychiatry,
Stanford University School of Medicine,
Palo Alto, CA, USA

include the retrospective interview, the lack of data on premenstrual dysphoric disorder, and the inability to control for factors such as medication use.

Keywords Premenstrual · Bipolar · Major depression · Genetics

Introduction

We have previously demonstrated familial aggregation of the trait of postpartum depressive symptoms in families with major depressive disorder (MDD) (Murphy-Eberenz et al. 2006) and bipolar disorder (BP) (Payne et al. 2008). These findings provide support for the hypothesis that there may be a genetic basis for the trait of postpartum mood symptoms. Still unresolved is the question of whether this finding is specific to the postpartum period or whether it reflects a sensitivity to times of hormonal change more generally. The latter hypothesis would suggest that premenstrual mood symptoms should also be genetically influenced in these samples.

There have been a number of previous studies examining whether premenstrual mood symptoms have a genetic basis, mostly in the general population. There have been two family studies with conflicting results. Widholm and Kantero (Widholm and Kantero 1971) showed that women with retrospective premenstrual complaints were more likely to have mothers with the same complaint. Later, Glick et al (Glick et al. 1993) examined both retrospective and prospective premenstrual symptoms in 80 sister pairs and concluded that premenstrual symptoms did not exhibit familiality.

A number of twin studies of premenstrual symptoms have generally suggested a genetic component to susceptibility. An early study in a small sample (Dalton et al. 1987) reported a much higher concordance rate of prospectively confirmed premenstrual symptoms in 15 monozygotic twins compared to 16 dizygotic twins. Kendler et al (Kendler et al. 1992) used conventional factor analysis in a study of 827 female twins and estimated a heritability of 35.1% for retrospectively reported premenstrual symptoms. They later performed a second factor analysis on a follow-up study of premenstrual complaints in the same sample, with 314 monozygotic twins and 181 dizygotic twins and found that premenstrual complaints were modestly stable over time, with heritability estimated at 56% (Kendler et al. 1998). Condon et al (Condon 1993) examined 157 monozygotic and 143 dizygotic female twin pairs for concordance rates on a retrospective self-report questionnaire about premenstrual symptoms. The concordance rate in monozygotic twins (0.55) was twice that of the dizygotic twins (0.28). Van den Akker et al (van den Akker et al. 1987) performed a factor analysis on retrospectively reported menstrual cycle characteristics in 462 female twin pairs and concluded that premenstrual symptom reporting may be heritable. However, in a later study they concluded, based on a multivariate analysis in 634 women, that premenstrual symptom reporting was instead associated with the personality trait of neuroticism and not genetic in and of itself (van den Akker et al. 1995). Treloar (Treloar et al. 2002) studied 720 Australian female twin pairs with retrospectively reported premenstrual symptoms and found that additive genetic influences explained 44% of the variance, although they could not distinguish between the liability to neuroticism and an independent genetic trait.

In this study, we sought to determine if premenstrual mood symptoms, like postpartum mood symptoms, show familial aggregation in MDD and BP pedigrees. We further examined whether familiality of these symptoms might be influenced by personality traits.

Methods

Sample

The sample consisted of women who participated in either of two multisite genetics studies. The first, the National Institute of Mental Health (NIMH) Genetics Initiative Bipolar Disorder Collaborative project was a ten-site collaborative that collected families with bipolar I disorder from 1999 to 2003. The sites included Johns Hopkins, Indiana University, Washington University in St. Louis, the NIMH Intramural Program, the University of California, San Diego, University of Iowa, University of Pennsylvania, University of Chicago, Rush-Presbyterian Medical Center, and University of California, Irvine. Inclusion criteria focused on BPI probands with at least one sibling with BPI disorder. Fifty-three percent of the affected subjects were female (Dick et al. 2003; McInnis et al. 2003). The sample was primarily Caucasian with African-Americans comprising 5.5% of the total and Hispanics 1.9%. The second project was the Genetics of Recurrent Early-Onset Depression (GenRED) study which collected 680 pedigrees with 971 affected sibling pairs with recurrent, early-onset MDD (Levinson et al. 2003). Six sites participated in the study, including: University of Iowa, Johns Hopkins University, New York State Psychiatric Institute, University of Pennsylvania, University of Pittsburgh, and Rush-Presbyterian Medical Center in Chicago. Criteria for enrollment included a proband with recurrent early-onset (≤30 yo) DSM-IV defined (American Psychiatric Association 1994) MDD with at least one sibling with recurrent MDD with onset ≤40 years old. Seventy-nine percent of the affected subjects were female. This sample was also primarily (95%) of European ancestry (Holmans et al. 2007).

Subjects were ascertained for both of the studies through various means including newspaper, magazine, radio advertising, Web announcements, and recruitment in clinical settings. After complete description of the study to the subjects, written informed consent was obtained. Diagnoses were based upon an interview conducted by trained research clinicians (masters or doctoral level) using the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al. 1994). Interrater reliability for the DIGS has been shown to be 0.85–0.96 for mood disorders (Nurnberger et al. 1994). Collateral information from family informants and medical records were obtained whenever possible. Final diagnoses were made at each site by two clinicians who reviewed all available data using a best-estimate diagnosis procedure based on the DSM-IV.

A total of 1130 women participated in the NIMH Bipolar Study, 665 of whom had a diagnosis of Bipolar I disorder. A total of 1746 women with a diagnosis of recurrent or single episode MDD participated in the GenRED study. Thus, the total sample size was 2876 women. Women and their families were excluded from the premenstrual analyses if they did not have at least one female sibling who also met criteria for either Bipolar I disorder (for the NIMH Bipolar study) or recurrent or single episode MDD (for the GenRED study). We completed familial aggregation analyses in the following subsets: 1) women and their siblings with Bipolar I disorder (N=435); 2) women and their siblings with recurrent MDD or long single episode (≥3 years) as defined by the GenRED study criteria (N= 1088). In the Bipolar I sample there were a total of 196 families included: 160 with 2 siblings, 32 with 3 siblings, 2 with 4 siblings, and one each with 5 or 6 siblings. In the GenRED sample, there were a total of 476 families: 376 with 2 siblings, 78 with 3 siblings, 13 with 4 siblings, 5 with 5 siblings, 3 with 6 siblings and 1 with 7 siblings.

Interview

The DIGS was used as part of the diagnostic process in both the NIMH Bipolar study and the GenRED study, though the former used the 3.0 version, while the latter used the 3.0 modified for MDD studies (3.0 GenRED). Both versions included the same question about mood symptoms prior to menstruation which was: "Have you ever noticed regular mood changes in the premenstrual or menstrual period?" Clinicians were allowed flexibility in their interview in order to obtain enough information to accurately answer the questions. In addition, the interviewer obtained a description of the reported symptoms which was included in the dataset.

A subgroup of women who participated in the GenRED study completed a NEO Five Factor Inventory (NEO-FFI) (N=838). This is a 60-item, self-rated, version of the longer Revised NEO Personality Inventory which gives a comprehensive measure of five domains of personality: neuroticism, extroversion, openness, agreeableness, and conscientiousness (Costa and McCrae 1988)

Statistical analysis

First, we examined the clinical characteristics of each of the samples including, among other characteristics, age of onset, number of major depressive episodes, and whether or not women reported that they were depressed at the time of the interview. Women with premenstrual symptoms were compared to women without premenstrual symptoms.

We then used the Generalized Estimating Equation (GEE) (Zeger and Liang 1986) to examine familial aggregation of the traits of premenstrual mood symptoms while controlling for any clinical characteristics that differed between those with and without premenstrual symptoms. The GEE uses logistic regression but also takes into account potential correlation between observations when multiple members of the same family are considered. We examined the odds that a family history of premenstrual mood symptoms positively predicted premenstrual mood symptoms in the individual. A positive family history of premenstrual mood symptoms was defined as having another member or members of the family who also gave a history of premenstrual mood symptoms by direct interview using the DIGS, while a negative family history was defined as having no family members who gave such a history. For each analysis, the same criteria were used to assign a positive family history as was used to assign a positive individual history. In these analyses, we used general family history of premenstrual mood symptoms to predict premenstrual mood symptoms rather than proband history since many of the probands were male. Each analysis was controlled for any clinical factor, such as age of onset, that was found to be significantly different (with a p value ≤0.05) between women with and without premenstrual symptoms in the sample under investigation (i.e. Bipolar I or MDD samples). All analyses were carried out using STATA 9.0.

Since neuroticism has been previously shown to influence the presence of premenstrual symptoms, we reanalyzed the sample of women who participated in GenRED and had completed the NEO-FFI personality inventory. T-scores were calculated using the standard population means and standard deviations for women. We compared the mean scores of each of the five personality factors between women with and without premenstrual symptoms. We also reran the familial aggregation analysis controlling for individual NEO scores.

Table 1 Clinical characteristics of the samples

	Number	Percent	X^2	*P* value
Total *N*				
Bipolar I				
PMS+	279	64.14%		
PMS−	156	35.86%		
MDD				
PMS+	769	70.68%		
PMS−	319	29.32%		
Married				
Bipolar I				
PMS+	142	50.90%	3.52	0.0605
PMS−	64	41.03%		
MDD				
PMS+	422	54.88%	0.96	0.3285
PMS−	164	51.41%		
Currently depressed				
Bipolar I				
PMS+	97	34.77%	0.77	0.3790
PMS−	47	30.13%		
MDD				
PMS+	265	34.46%	0.52	0.4722
PMS−	102	31.97%		
History of pregnancy				
Bipolar I				
PMS +	231	82.80%	2.30	0.1292
PMS−	119	76.28%		
MDD				
PMS +	560	72.82%	1.72	0.1886
PMS−	219	68.65%		
	Mean	SD	*t*-statistic	*P* value
Age at interview				
Bipolar I				
PMS+	41.01	9.41	3.69	0.0002
PMS−	45.01	12.99		
MDD				
PMS +	40.79	10.50	1.46	0.1444
PMS−	41.89	12.95		
Age at onset				
Bipolar I				
PMS +	18.30	7.77	3.49	0.0005
PMS−	21.35	10.25		
MDD				
PMS+	18.83	7.28	1.95	0.0516
PMS−	19.77	7.19		
Number of MDE				
Bipolar I				
PMS+	20.67	35.73	0.12	0.9041
PMS−	20.17	50.19		
MDD				
PMS+	7.29	11.50	2.56	0.0123
PMS−	5.55	7.29		
Number of manias				
Bipolar I				
PMS+	25.55	77.10	1.49	0.1374
PMS−	15.61	42.44		
Longest MDE (weeks)				
Bipolar I				
PMS +	50.52	71.58	0.47	0.6393
PMS−	54.11	84.78		
MDD				
PMS+	644.50	984.53	0.90	0.3676
PMS−	705.84	1107.04		
Number of years III				
Bipolar I				
PMS+	22.80	10.23	0.79	0.4301
PMS−	23.66	12.00		
MDD				
PMS+	21.96	11.02	0.79	0.4301
PMS−	22.18	12.60		
Years educated				
Bipolar I				
PMS+	14.45	2.69	0.22	0.8259
PMS−	14.39	2.79		
MDD				
PMS+	15.36	2.94	0.91	0.3625
PMS−	15.54	2.75		

Results

Table 1 shows the clinical and demographic characteristics of the 435 women with BPI disorder and the 1088 women with MDD. Analyses were also completed for the subset of women with MDD who had completed NEO-FFI questionnaires. Age at interview and age of onset in women with BP were found to be significantly different between women with and without premenstrual symptoms. In women with MDD, only age at onset and number of major depressive episodes showed a nominally significantly difference between women with and without premenstrual symptoms. Importantly, whether or not women reported being depressed at the time of the interview did not differ between women with and without premenstrual mood symptoms.

Table 2 shows the results of the familiality analyses for premenstrual mood symptoms. The overall rate of symptoms was 64.1% in the BP sample, and 70.7% in the MDD samples. In each case these were only marginally higher in those with a positive family history of premenstrual symptoms as compared to those with a negative history: for BP (65.0% vs. 62.1%) and in MDD (71.7% vs. 67.3%). The odds ratios shown derive from analyses that were controlled for clinical characteristics noted to be different between women with and without premenstrual mood symptoms (see Table 1). For the BP analysis, we controlled for age at interview and age at onset, whereas for the MDD analysis we controlled for age at onset and number of major depressive episodes. In addition, though the rate of being

Table 2 Familiality of premenstrual mood symptoms (PMS) in the NIMH bipolar disorder study and the GenRED study of major depression

	Number	*N* (%) with PMS Given a positive family history of PMS[a]	N (%) with PMS given a negative family history of PMS[b]	OR	*P* value	CI
NIMH bipolar study						
Bipolar I	435	197/303 (65.0%)	82/132 (62.1%)	1.13	0.56	0.74–1.73
GENRED						
MDDR and Long SE	1,088	598/834 (71.7%)	171/254 (67.3%)	1.22	0.20	0.90–1.65

PMS premenstrual mood symptoms, *MDDR* recurrent major depression, *Long SE* major depression, long (<2 years) single episode
[a] Numerator equals number of women who had premenstrual mood symptoms given a family history of premenstrual mood symptoms. Denominator equals total number of women with a family history of premenstrual mood symptoms
[b] Numerator equals number of women who had premenstrual mood symptoms given NO family history of premenstrual mood symptoms. Denominator equals total number of women without a family history of premenstrual mood symptoms

depressed at the time of the interview did not differ between women with and without premenstrual symptoms, we included this factor in the analysis given previous work showing that being depressed can affect the reporting of premenstrual symptoms. These results did not substantially differ from data which were not controlled for these characteristics (data not shown). Neither the odds ratio in the BP sample (1.13, $p=0.563$) nor that in the MDD sample (1.22, $p=0.198$) reached statistical significance.

We wondered whether neuroticism or other personality characteristics might influence our analyses, potentially giving us a false negative result. Table 3 displays the mean scores of each of the five personality factors (neuroticism, extroversion, openness, conscientiousness, and agreeableness) in women with and without premenstrual symptoms among MDD subjects who had completed the NEO-FFI and who were not depressed at the time of the interview.

Table 3 NEO-FFI scores in women with and without premenstrual mood symptoms

	Mean	SD	*T*-score[a]	*t*-statistic	*P*-value
Neuroticism					
PMS−(*N*=232)	29.20	7.76	61.1	0.216	0.829
PMS+ (*N*=606)	29.33	7.54	61.4		
Extroversion					
PMS−	23.07	5.97	41.5	0.063	0.950
PMS+	23.04	5.87	41.2		
Openness					
PMS−	27.00	5.90	50.1	3.053	0.002
PMS+	28.40	5.96	52.3		
Agreeableness					
PMS−	29.85	6.25	41.9	0.009	0.992
PMS+	29.84	5.79	41.8		
Conscientiousness					
PMS−	29.59	7.88	40.7	0.511	0.610
PMS+	29.27	8.17	40.1		

[a] The *T*-score reflects a transformation of the mean score based on standardized means and standard deviations for the female population. A score of fifty is equal to the general population mean

The only personality factor that was significantly different between the two groups was openness ($t=3.05$; $p=0.002$); neuroticism, in contrast, did not differ between the groups. The mean for openness in the premenstrual symptom negative group was almost exactly at the population mean ($T=50.1$) while that for the premenstrual positive group was slightly high at $T=52.3$.

Given that differences were found between groups for openness, and given previous work suggesting that neuroticism might underlie premenstrual symptoms, we reran the familial aggregation analysis for premenstrual symptoms controlling for both these factors. Once again, familial aggregation of premenstrual symptoms was not significant with odds ratios of 1.28–1.35 ($p=0.10$–0.17).

Because previous work from our group found that younger women were more likely to report perinatal mood episodes than older women (Murphy-Eberenz et al. 2006), we examined whether menopausal status influenced the current findings. We limited the sample to families that had two or more siblings who had not yet experienced menopause and reran the analyses of familial aggregation of premenstrual symptoms. The odds ratios remained non-significant at 0.64 ($p=0.221$) for the BP families and 1.38 ($p=0.088$) for the MDD families.

Discussion

In contrast to postpartum mood symptoms, premenstrual mood symptoms did not appear to run in families in our bipolar disorder sample. Similarly, no significant evidence for familiality was found for these symptoms in MDD, although we cannot rule out a very modest effect. Neither the personality factors of neuroticism and openness, nor the age of interview or current depressive symptoms influenced these results.

Prior studies in twins reported a genetic component to premenstrual mood symptoms, but also suggested that this could be mediated in part by neuroticism, which has been

shown to have a genetic component. We did not see an association between these symptoms and neuroticism in our MDD sample. We did find an unexpected correlation between openness and premenstrual mood symptoms, although we note this finding would not stand up to a Bonferroni correction for the 28 tests conducted here (corrected $p=0.056$). To our knowledge this correlation has not previously been reported. Elevated scores on the openness domain, defined both with the NEO-FFI and the longer NEO-PI-R, have been associated with Seasonal Affective Disorder (SAD) (Bagby et al. 1996; Enns et al. 2006; Jain et al. 1999), which, in turn, has been associated with PMDD (Praschak-Rieder et al. 2001; Praschak-Rieder et al. 2002). Elevated scores on the openness domain have also previously been reported in a sample of college freshmen with MDD using the NEO-FFI (Trull and Sher 1994). This correlation was not confirmed in a larger community sample using the NEO-PI-R (Bienvenu et al. 2004). While the relationship between openness and premenstrual mood symptoms may be a real one, we cannot rule out the possibility that for unknown reasons the shorter NEO-FFI may be more likely to exhibit a relationship between openness and depressed populations than the longer NEO-PI-R. Thus, our results should be interpreted with caution.

There are several possible explanations for the negative result in our study. We studied subjects with mood disorders while previous work has primarily been in the general population. The rate of premenstrual symptoms was very high (69%) in our sample. With a very high baseline, we may have had reduced power to detect a familial effect. Rates in the family and twin studies reviewed in the introduction ranged from 12.1–59% for moderate to severe symptoms. The high rate we obtained is perhaps not surprising in a sample of mood disordered subjects. It could reflect either a true positive rate that is substantially higher than in the general population and/or a high false positive rate given that current depression could increase the rate of endorsement of past mood symptoms. However, in our dataset women who were currently depressed were not more likely to report PMS. There might be a familial effect within our samples, but it could be restricted to a particular sub-group, such as those who meet criteria for pre-menstrual dysphoric disorder (PMDD), or those with additional PMS symptoms such as physical complaints. Unfortunately, we do not have data to define these subgroups. We note that the only other study to focus on siblings was also negative (Glick et al. 1993) though it was fairly small. In contrast, multiple twin studies have been positive. Most previous studies have used multiple questions to assess premenstrual symptoms and have included physical complaints. By contrast, we had only a single question available to define the presence or absence of symptoms. The reduced reliability associated with this method of assessing premenstrual mood symptoms would be expected to bias the results toward the null.

Investigators, hypothesizing that genetic variation contributes to the risk for premenstrual mood symptoms, have carried out several association studies with inconclusive results to date. Two studies were negative (Damberg et al. 2005; Magnay et al. 2006) for genes including the serotonin transporter. A third study found that women with both a seasonal component to their mood disorder and PMDD were more likely to be heterozygous for the short allele polymorphism of the serotonin transporter promoter gene (Praschak-Rieder et al. 2002) . Takeo et al. (Takeo et al. 2005) found an association between the estrogen receptor beta gene and both menopausal and premenstrual symptoms in 51 postmenopausal Japanese women. Most recently, Huo et al. (Huo et al. 2007) found that PMDD was associated with variation in the estrogen receptor alpha gene in the setting of the Val/Val genotype of the catechol-O-methyltransferase (COMT) Val158Met polymorphism.

There are several important limitations to consider in interpreting our findings. First, the sample was originally collected for other purposes and therefore does not provide all the information that we would like to include in our analyses. A second but related limitation was the retrospective nature of the interview. A number of studies have found that the reliability of retrospective recall of mood-related symptomatology such as premenstrual symptoms and PMDD in particular is questionable (Ainscough 1990; Halbreich and Endicott 1985; Rubinow et al. 1984). Prospective studies would likely provide more reliable data and specific diagnoses (such as PMDD) with which to address the familiality of premenstrual mood symptoms. We were also not able to control for medication use which could have influenced our results, since these data were not collected.

We obtained negative results for familial aggregation of premenstrual mood symptoms in two samples in which we have previously reported familial aggregation of postpartum mood symptoms. This suggests that the latter finding might be specific and encourages pursuit of the potential genetic underpinnings of postpartum mood symptoms.

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