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Genetic influences on post-natal depressive symptoms: findings from an Australian twin sample

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ABSTRACT

Background. Conflicting evidence exists on causes of vulnerability to post-natal depression. We investigated genetic and environmental influences on variation in post-natal depressive symptoms (PNDS) following first live birth, and sources of covariation with the personality trait Neuroticism and lifetime major depression occurring post-natally (DEP-PN) and at other times (DEP-XPN) to test for shared genetic influences.

Method. Retrospective interview and questionnaire data from 838 parous female twin pairs (539 monozygotic, 299 dizygotic) from the Australian National Health and Medical Research Council volunteer adult twin register were used for multivariate genetic model-fitting. Data on PNDS were evaluated for consistency with diagnostic interview assessment.

Results. Genetic factors explained 38% of variance in PNDS (95% confidence interval 26–49%) and 25% of the variance in interview-assessed DEP-PN. The genetic correlation between PNDS and lifetime major depression (DEP-PN and DEP-XPN) was low ($r_g = 0{\cdot}17$, 95% confidence interval = 0·09–0·28), suggesting that the questionnaire was measuring a construct other than post-natally occurring major depression, possibly post-natal dysphoria. Associations between PNDS and obstetric factors were very modest.

Conclusions. Findings suggest modest genetic influences on major depression occurring post-natally. Independent and stronger genetic influences identified for post-natal symptomatology or dysphoria (PNDS) justify further investigation.

INTRODUCTION

There is perhaps even less understanding of the aetiology of post-natal psychiatric morbidity than there is agreement on its nosology. Post-natal mood disorders are common and the need for further research into their aetiology is still seen as critical (Wisner & Stowe, 1997). Certain research has challenged the view that post-natal depression is a distinct clinical diagnosis and suggests that it is an expression of depression, no different in character from depression occurring at other times (for example, Whiffen, 1991). A major quantitative review of a large number of studies has identified past history of psychopathology and psychological disturbance during pregnancy (O'Hara & Swain, 1996) as among the most important risk factors for post-natal depression. Personality (expressed in high interpersonal sensitivity and high neuroticism) has also been identified as a vulnerability factor to depression assessed post-natally (Boyce *et al.* 1991*a*, *b*). Cooper & Murray (1995), after comparing the course and recurrence of post-natal and other episodes of depression in two groups of primiparous women, selected according to whether the index episode of post-natal depression was the first episode or a recurrence of depression, affirmed a specific nosology for post-natal depression, reflecting a possibly different aetiology. Whether there is a difference between 'post-natal depression' (or dysphoria) and depression occurring post-natally is an important nosological and scientific question. Uncovering the common and specific causes of

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any such difference should contribute to clinical and scientific understanding.

Genetic influences on post-natal depression have been discussed (e.g. Atkinson & Rickel, 1984; Daw, 1988). Estimates of 'positive heredity' for 'mental morbidity' (puerperal psychosis) in the families of probands have varied from 32 to 65% (Thuwe, 1974). However, other researchers such as Baker *et al.* (1971) found no family loading for the development of post-natal depressions in their sample. That there may well be a distinct biological basis to post-natal depression has been suggested (Dennerstein *et al.* 1988; Martin *et al.* 1989). This biological predisposition may be expressed by any of the major changes in progesterone, oestrogen, cortisol and β-endorphin level reported as associated with parturition (Glover, 1992). Hormonal components have been identified as plausible for depression (Paykel, 1991), but evidence is equivocal. A hormonal component for post-natal depression has, on the other hand, been given increased plausibility (Harris, 1993, 1996; Harris *et al.* 1996), although it has been suggested that hormonal factors may affect only a small subgroup of post-natal depression sufferers (O'Neill *et al.* 1990). Post-partum thyroiditis, occurring in 5–9% of women, has been associated with depressive symptoms (Lazarus *et al.* 1997). However, cognitive impairment in post-natal depression has been found to be independent of thyroid antibodies and thyroid dysfunction (Mallett *et al.* 1995).

Phenotypic correlational analyses and risk factor identification have begun the process of establishing the reasons for association between post-natal depression and personality (Boyce *et al.* 1991*b*) and between post-natal depression and depression (Cooper & Murray, 1995). Post-natal depression has received little attention in genetic studies. The aim of the multivariate analyses described here is to clarify the relationships between recalled post-natal depressive symptoms reported by questionnaire (PNDS), the personality trait neuroticism, and major depression reported post-natally or at other times, by estimating their genetic and environmental covariation. The hypothesis to be tested in the first instance is that neither genetic nor environmental covariation exists between neuroticism, major depression and PNDS. i.e. that they are influenced not only by different environmental events and effects, but by different genes.

METHOD

Sample and assessments

The 1981 questionnaire survey

In 1980–1982, as part of a health survey by mailed questionnaire, information was obtained from 1231 monozygotic (MZ) female and 748 dizygotic (DZ) female twin pairs (1979 female pairs) in a total sample of 3808 adult (i.e. over 18 years) twin pairs from the Australian National Health and Medical Research Council Twin Register ('1981 survey') (Jardine *et al.* 1984; Martin & Jardine, 1986; Eaves *et al.* 1989). All twins were asked questions relating to personality, depressive symptoms and anxiety. Two items concerning similarity in appearance and being mistaken by others were included to determine zygosity. Pairs giving inconsistent responses were recontacted for clarification. Such questionnaires have been shown to give at least 95% agreement with diagnosis based on extensive blood-typing (Martin & Martin, 1975; Ooki *et al.* 1990). More recently, members of a subsample of 198 same-sex pairs from this group, who reported themselves to be MZ, were typed for 11 independent highly polymorphic markers in the course of an asthma study; no errors in our previous zygosity diagnosis were detected (Duffy, 1994, p. 366). Of 131 like-sex pairs (male and female) who reported themselves to be DZ and who had DNA available, five (3·8%) were concordant at the 11 loci, with a probability of monozygosity of over 0·9999. This gave a sensitivity for self-report monozygosity of 0·98 (exact 95% CI 0·94–0·99) and a specificity of 1·00 (0·97–1·00) in this sample (Duffy, 1994).

The 1989 questionnaire survey

The same twins were followed up 8 years later, between 1988 and 1990 when the minimum age of respondents was 25 years (Treloar *et al.* 1992; Heath *et al.* 1994). The 1989 questionnaire replicated most of the earlier questions and added new items on each delivery, including obstetric difficulties and feelings of depression following each birth. A 2-year follow-up was carried out following the 1989 second-wave survey in order to measure medium-term stab-

ility of reports over time. Identical questionnaires were mailed in 1990 to the first 500 female individual twins who responded to wave 2. The percentage of nulliparous individual respondents in 1981 was higher than in 1989 (52% compared with 28%), although the wording of the question in 1981 meant that pregnancies that had ended in abortion or stillbirth could not be accurately distinguished from live births.

The 1992–3 interview study

A third follow-up study of the same twins, including 3848 women, was conducted by telephone interview in 1992–3 (Heath *et al*. 1997*a*), using an instrument adapted for telephone administration from the SSAGA (Bucholz *et al*. 1994). Reliability of the SSAGA depression measures was good in both within- and cross-centre test–retest data in a multi-site genetic study (Bucholz *et al*. 1994). Questions were based in part on well-validated items used in other psychiatric research interviews (Bucholz *et al*. 1994; Slutske *et al*. 1998) and in part on DSM-III. Its validity was maximized by clinician review of interviews and interviewer notes. The semi-structured interview obtained diagnostic assessments of DSM-III-R alcohol dependence (American Psychiatric Association, 1987), depression and other psychiatric symptoms and disorders, but DSM-IV diagnosis of major depressive episode (American Psychiatric Association, 1994) was possible (Statham *et al*. 1998). Responding twin pairs where both had at least one live birth and met inclusion criteria numbered 950. Both members of 838 pairs (88%) provided information on all variables.

A subsample of female like-sex high-risk and control pairs, who received follow-up interviews between 1 and 4 years later, provides reliability data about diagnostic assessments.

The twin method relies on the assumption that the environments of MZ co-twins are no more similar than those of DZ co-twins – or if they are, that this does not influence intrapair similarity in the variable being analysed. Our study assessed environmental similarity in two ways. At both study waves, twins were asked how much they see and contact each other on a seven point scale, and in 1989 we also asked about four aspects of childhood 'environmental' similarity (sharing the same room, being dressed alike, sharing the same playmates and being in the same class), scored on a 4-point scale. Absolute differences in co-twins' reports were analysed by degree of contact and seeing each other (7 point scales) and childhood environmental similarity (4-point scale).

The five variables included in the multivariate analysis were postnatal depressive symptoms following first live birth (1989 survey: PNDS), Neuroticism assessed both at 1981 and 1989 surveys (N81, N89); DSM-IV major depression assessed at 1992–3 diagnostic interview, occurring either postnatally (DEP-PN) or at other times (DEP-XPN).

Post-natal depressive symptoms (PNDS)

Post-natal depressive symptomatology was reported retrospectively in the 1989 questionnaire. Twins were asked, for each delivery they reported 'Did you feel depressed after the birth of any of your children?' ('Yes/No'), and if 'Yes' 'How many weeks did this go on for?', and 'Did you need to seek help for the depression?'. Analysis was limited to parous twin pairs and to reports on the first live birth to avoid problems with data censoring, since women experiencing severe PNDS might be less likely to have further children. Reported depression following stillbirth was excluded to avoid confounding by distress related to the pregnancy outcome. In cases where the first birth was a stillbirth, the next live birth was used as the focus for analysis; four cases where no subsequent live births were reported were excluded from all analyses. A three-category scale was computed on the basis of number of weeks feelings of depression were reported to have lasted (no depression, depression lasting up to 2 weeks, and depression lasting > 2 weeks). This was done in order to distinguish between women who had felt no depression at all from those who, on the grounds of length of episode rather than specific symptomatology, experienced short-term 'maternity blues' (lasting up to 2 weeks post-partum), and those in whom depressive symptoms persisted for a longer period and might possibly be identified as having suffered 'post-natal depression'.

Neuroticism (N81 and N89)

Twenty-four items from the full Eysenck Personality Questionnaire were used to obtain the measure of neuroticism in the 1981 study; 12

items from the short form revised Eysenck Personality Questionnaire, the EPQ-R(S) (Eysenck *et al.* 1985), were used in the 1989 survey. We chose to use both 1981 and 1989 measures to assess whether genetic or environmental sources of any covariation with postnatal depression changed over this time period. Scores were recoded into 13 categories for computation of polychoric correlations.

Depression occurring non-post-natally and post-natally (DEP-XPN and DEP-PN)

The depression section of the interview included a detailed assessment of the respondent's most severe episode of depression, in order to determine whether it qualified as a major depressive episode according to DSM-IV criteria as well as information about episode length and, most importantly, whether the depression occurred around childbirth. For up to five other episodes of depression, brief information about episode duration, treatment, and whether or not the depression occurred around childbirth was also obtained. A variable was computed to reflect post-natal depression. DEP-PN was counted as an episode of depression, lasting two weeks or more, around the time of childbirth. Because precise dating was obtained only for the most severe depressive episodes, it was not possible to derive a 'first' DEP-PN measure from the interview data. Because there was no pregnancy-by-pregnancy questioning about possible episodes of depression during the interview, it is likely that major depressive episodes occurring postnatally will have been underreported. DEP-PN and episodes of depression not occurring postnatally (DEP-XPN) could be considered as subsets of DSM-IV depression episodes.

The interviews also included a non-diagnostic screen for a history of mania. Respondents were considered 'positive' for mania if they reported a week or more of euphoria and psychiatric treatment for this condition and if clinician review of interviewer notes confirmed an apparent history of bipolar disorder (Bierut *et al.* 1999). Such cases (and their co-twins) were excluded from further analyses.

Data analysis

Twin-pair matrices of polychoric correlations, and corresponding asymptotic covariance matrices, were computed separately for MZ and DZ twin pairs, using the Windows version of PRELIS 2.20 (Jöreskog & Sörbom, 1998). Genetic models were fitted by the method of asymptotic least squares to estimate the contributions of additive genetic, shared and non-shared environmental effects, using Mx (Neale, 1997). Multivariate models allowed estimation of variable-specific genetic and environmental effects, as well as genetic and environmental correlations. We proceeded by systematically testing the significance of dropping parameters in turn. In addition to the likelihood ratio chi-square test (LR), the Akaike Information Criterion (AIC, measured as $\chi^2 - 2$ df) was used as an additional indicator of fit. On the grounds of parsimony the model with the least number of parameters which offered a fit not significantly worse than the full model was chosen. Data analysis methods are described more fully in Kendler *et al.* (1992*a*), Neale & Cardon (1992) and Heath *et al.* (1997*a*).

We commenced model-fitting with an atheoretical Cholesky decomposition model for two triangular sets of factors which together explain 100% of the variance. Each comprised five additive genetic factors and five specific environmental factors. Variables were ordered as in Table 1. We then aimed to find a more parsimonious, theoretical model to best explain the sources of variance and covariance between PNDS, neuroticism and depression occurring post-natally and non-post-natally. Following the successful fit of a two genetic factor (neuroticism and depression) model, we then incorporated a correlation between these two factors on the basis of previous findings. Our final best-fitting and most parsimonious model to explain these relationships allowed for two correlated genetic factors. Specific genetic influences on each of the five measures were estimated in the model. We constrained the specific genetic influences on the two neuroticism measures to be equal; likewise for the two measures of depression. All specific environmental influences were allowed in the model as for a Cholesky decomposition (Neale & Cardon, 1992).

RESULTS

Reliability of reporting

Test–retest polychoric correlations ($\pm$standard errors), for the 385 parous respondents who

Table 1. *Summarized univariate twin pair correlations for N81, N89, DEP-XPN, DEP-PN and PNDS*

	Monozygotic ($N = 539$ pairs)		Dizygotic ($N = 299$ pairs)	
	r	S.E.	*r*	S.E.
N81	0·51	±0·04	0·29	±0·06
N89	0·47	±0·03	0·26	±0·05
DEP-XPN	0·41	±0·07	0·11	±0·11
DEP-PN	0·20	±0·15	0·08	±0·20
PNDS	0·42	±0·07	0·21	±0·09

N81 = Neuroticism (1981); N89 = Neuroticism (1989); DEP-XPN = lifetime history of non-post-natal DSM-IV major depression (1992–3); DEP-PN = lifetime history of DSM-IV major depression occurring post-natally (1992–3); PNDS = depressive symptoms after first birth (1989).

participated in the 2-year questionnaire reliability study, were $r = 0{\cdot}70 \pm 0{\cdot}06$ for depressive symptoms following first live birth (PNDS) and $r = 0{\cdot}81 \pm 0{\cdot}05$ for trait neuroticism (N89). For interview data, using combined Phase 1 and Phase 2 follow-up data sets, reliability was similarly high (DEP-PN $r = 0{\cdot}75 \pm 0{\cdot}05$, $\kappa = 0{\cdot}42$, 95% CI = 0·31–0·53) when respondents were restricted to those who were parous and had not had any additional children by the time of the phase 2 interview. For DEP-XPN, corresponding reliability was $\kappa = 0{\cdot}45$ (95% CI = 0·39–0·51) and tetrachoric correlation was $r = 0{\cdot}68 \pm 0{\cdot}04$. Some of the unreliability in DEP-XPN reflects new onsets of depression since phase 1.

Prevalence estimates

At the time of the 1981 survey the age range of the responding female pairs was 18 to 88 years, and the mean age was 36 ± 14 years (median 32 years). The mean age of the responding pairs in 1989 was 44 ± 13 years (median 40 years), range 26 to 88 years. Respondents were significantly younger than non-respondents. At the 1981 survey, the majority (52%) of twins were nulliparous; 48% of individual twins reported one or more pregnancies. By the 1989 questionnaire survey there were 954 (59%) responding female pairs where both members were parous; at 1992–3 interview survey in 978 female pairs (67%) both twins reported one or more biological children.

Of the 3248 individual members of female pairs who responded to the 1989 questionnaire survey, 918 (28·3%) were nulliparous, five reported only stillbirths, while the remaining 2325 (71·7%) reported one or more live births. Fifty-five of these twins reported a stillbirth as their first birth (five of these were twin births). In these cases the next live birth was used as the focus for analysis; four cases where no subsequent live births were reported were excluded from all analyses. Mean parity (including nulliparous women and stillbirths) was 1·9 births.

Six hundred and twenty-nine (27·1%) parous respondents who had given birth reported feeling some depressive symptoms following their first live birth, with the duration ranging from less than 1 week to 156 weeks. Transient episodes lasting 2 weeks or less were more common ($N = 379$, 16·3%) than episodes persisting for a longer period ($N = 250$, 10·8%), and only 4% reported that their depressive symptoms lasted 1 year or longer. Only 15% of women reporting post-natal depressive symptoms had sought help for their symptoms. A weak but significant association between reporting depressive symptoms following first birth and having fewer children was noted ($r = -0{\cdot}10 \pm 0{\cdot}04$).

The interview measure of lifetime DEP-PN yielded a positive history for 196 twins ($N = 2381$), a prevalence of 8·2%. A total of 2128 parous women who completed the 1989 questionnaire also completed the 1992–3 diagnostic interview assessment of lifetime major depression, based on DSM-IV criteria. Some 8·4% of women reported an episode of DEP-PN that lasted at least 2 weeks, compared with 11·0% of questionnaire respondents who reported an episode of greater than 2 weeks (this higher threshold was chosen to allow for rounding-up by questionnaire respondents).

Phenotypic associations

Modest phenotypic correlations were observed between PNDS and N81 (0·22), N89 (0·23), and DEP-XPN (0·18); there was a stronger correlation with DEP-PN (0·45, κ with binary PNDS = 0·06, 95% CI = 0·01–0·11). With the exception of a strong correlation between N81 and N89 (0·71), between DEP-PN and DEP-XPN ($r = 0{\cdot}53 \pm 0{\cdot}04$, $\kappa = 0{\cdot}17$, 95% CI = 0·12–0·22), and between N81 (and N89) and DEP-XPN (0·31), these variables were in turn only modestly intercorrelated (0·18–0·26).

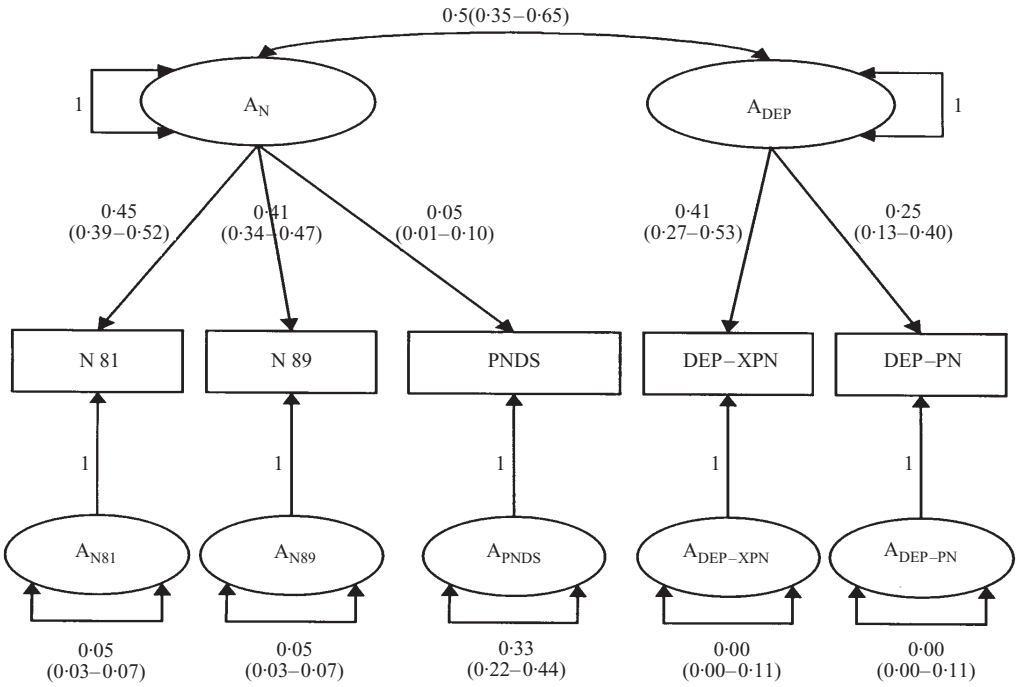

FIG. 1. Correlated genetic factor model showing genetic loadings.

Obstetric factors were tested in a simultaneous multivariate analysis that showed associations between PNDS and obstetric factors for first live birth to be negligible for Caesarean section, episiotomy, and prematurity of delivery; very modest associations were found with forceps delivery ($r = 0{\cdot}11 \pm 0{\cdot}04$), induction ($r = 0{\cdot}15 \pm 0{\cdot}04$), epidural anaesthetic ($r = 0{\cdot}11 \pm 0{\cdot}04$) and reported extreme difficulty or pain in labour ($r = 0{\cdot}17 \pm 0{\cdot}04$). The correlations between DEP-PN and obstetric factors were also negligible, with the exception of the latter two factors ($r = 0{\cdot}20 \pm 0{\cdot}06$ and $r = 0{\cdot}26 \pm 0{\cdot}05$ respectively).

Genetic influences on PNDS and DEP-PN

Greater MZ than DZ twin pair similarity was observed for questionnaire reporting of PNDS > 0 weeks after first live birth (MZ pairs, OR 4·81, 95% CI = 3·17–7·30; DZ pairs, OR 2·98, 95% CI = 1·73–5·13). The difference between the odds ratios for the two zygosity groups was not significant. When PNDS was analysed alone as a three-level variable (no problems; transient depressive symptoms lasting two weeks or less; depressive symptoms lasting more than 2 weeks), its estimated heritability was 42% (95% CI 28–55). Estimated twin pair similarity for DEP-PN was lower (MZ pairs, OR 2·29, 95% CI = 0·75–6·97; DZ pairs, OR 1·36, 95% CI = 0·30–6·25), with a univariate heritability estimate of 20% (95% CI 0–49). The odds ratio difference was again not significant; cell sizes were low for DZ pairs.

The greater concordance of MZ than DZ pairs could not be explained by greater sharing of environmental experiences. No association was found between twin pair concordance for PNDS and either current social contact or similarity of early environmental experiences.

Genetic relationships

Table 1 summarizes univariate MZ and DZ female like-sex twin pair correlations for N81, N89, DEP-XPN, DEP-PN and PNDS.[1] These confirm significant heritability of each of the four hypothesized personality and affective correlates of PNDS. In multivariate analyses,

[1] The full 10×10 matrices of correlations and cross-correlations can be obtained from the first author.

Table 2. *Genetic variances* * *and correlations* † *and their* 95% *confidence intervals* ‡

	N81	N89	DEP-XPN	DEP-PN	PNDS
N81	0·50 (0·43–0·50)				
N89	0·90 (0·86–0·94)	0·45 (0·39–0·52)			
DEP-XPN	0·47 (0·34–0·61)	0·47 (0·34–0·60)	0·41 (0·29–0·53)		
DEP-PN	0·47 (0·34–0·61)	0·47 (0·34–0·60)	1·00 (0·70–1·00)	0·25 (0·13–0·42)	
PNDS	0·33 (0·19–0·49)	0·33 (0·19–0·49)	0·17 (0·09–0·28)	0·17 (0·09–0·28)	0·38 (0·26–0·49)

* On diagonal.
† Lower triangle.
‡ 95% confidence intervals in parentheses.

comparison of Cholesky decomposition models revealed that neither an ADE model ($\chi^2_{15} = 3{\cdot}15$ (NS)) nor an ACE model $\chi^2_{15} = 2{\cdot}26$ (NS) gave a significant improvement in fit compared to an AE model ($\chi^2_{65} = 58{\cdot}331$, AIC $= -71{\cdot}669$), so subsequent model-fitting proceeded under an AE model, allowing for additive genetic and non-shared environmental effects only. Comparison of fit of genetic factor models identified a correlated two-factor model as the most parsimonious, with the first genetic common factor influencing neuroticism measured at 1981 and 1989 surveys together with PNDS, and the second influencing major depression, both post-natal and non-post-natal (see Fig. 1, which shows parameter estimates). We did not attempt to formulate a parsimonious model for the environmental factor structure, retaining a Cholesky structure for non-shared environmental effects. Model fit was $\chi^2_{71} = 67{\cdot}675$, AIC $= -74{\cdot}325$), suggesting this model to be the one of choice. Table 2 summarizes the genetic variances and genetic correlations estimated under this multivariate correlated genetic factor model.

The estimated genetic variance (heritability) for PNDS (0·38, 95% CI = 0·26–0·49) is close to that for DEP-XPN and greater than that for DEP-PN. The latter had the lowest heritability, although confidence intervals were wide. PNDS showed a low genetic correlation with the interview depression-post-natal (DEP-PN) measure (see Table 2). The genetic correlation between the neuroticism measures 8 years apart on average was less than unity (0·90), most probably reflecting the difference between using the full and the short versions of the EPQ. The genetic correlation with neuroticism (N81 and N89) was $r = 0{\cdot}33$, a stronger genetic association than that with depression. It is noteworthy that the specific genetic influences on PNDS, i.e. those not explained by the first genetic 'neuroticism' (emotionality) factor, are substantial in comparison with those allowed for the other variables, where they are clearly unimportant (see Fig. 1). Genetic effects that are specific to PNDS account for around one third of the total phenotypic variance, and $> 85\%$ of the overall genetic variance in risk of PNDS. The PNDS item was therefore measuring a construct distinct from personality or depression predisposition – a specific post-natal condition or state, with depressive symptomatology indictative of dysphoria, with its own genetic influences independent of those relating to neuroticism or major depression. The pattern of non-shared environmental loadings tells a similar story, with substantial specificity of non-shared environmental influences on PNDS, accounting for 38% of the total phenotypic variance.

DISCUSSION

We examined two research questions: whether there are important genetic influences on risk of post-natal depressive symptoms (PNDS), and whether any such influences are explained by the same genetic factors that influence risk of depression at other times, post-natally or non-post-natally. The estimated genetic contribution to PNDS (38% heritability) was similar to estimates typically reported for episodes of depression occurring in most cases outside the

context of childbirth: 21–45% depending on the definition of depression used (Bierut *et al.* in review, Kendler *et al.* 1992*a*, *b*) and for depressive symptoms 33–46% (Kendler *et al.* 1986) or 30–37% (Kendler *et al.* 1994). Higher heritability estimates have been reported using clinically ascertained samples, but such estimates are notoriously subject to serious biases when the model for ascertainment correction of twin data is misspecified (e.g. Heath, *et al.* 1997*b*). In spite of comparability of univariate estimates, our multivariate analyses suggested distinct genetic influences on PNDS and on DEP (-XPN and -PN) implying aetiological heterogeneity and supporting a specific nosology for a post-natal affective disorder other than major depression, not time-limited to less than 2 weeks. Our analyses give only a partial answer to the question of how such genetic differences in risk of post-natal PNDS may arise. It cannot be simply through genetic differences in vulnerability to child-birth complications: only modest associations were observed between reported childbirth complications and PNDS.

A significant genetic and environmental covariation between neuroticism and life-time history of major depression (Kendler *et al.* 1993) was confirmed in our data. For major depression there was no evidence for a genotype × environment interaction (e.g. Kendler & Eaves, 1986), whereby the importance of genetic predisposition might be increased during a period of vulnerability after childbirth.

Prevalence of post-natal depressive symptoms after first live birth (11%) was higher than prevalence of lifetime history of major depression occurring around the time of childbirth (8%), but comparable to the overall prevalence of 13% (95% CI = 0·123–0·134) based on estimates from 59 studies ($N = 12810$) reported from a meta-analysis by O'Hara & Swain (1996). The definition of post-partum depression used in the meta-analysis allowed for inclusion of depressive symptoms assessed by validated or standardized measure, which may not however have satisfied standard diagnostic criteria such as DSM-IV for syndromal depression. It is, therefore, not surprising that the prevalence estimated from interview data was lower.

Several limitations of these analyses must be borne in mind. Our single questionnaire item about feelings of depression following birth involved no detailed diagnostic assessment. The increased heritability that we observed for this measure was not observed for a diagnostic interview-based measure of DEP-PN. However, the latter assessment was not specifically designed to detect post-natal episodes, and may have led to under reporting of episodes that were not severe. The interview measure could not be accurately associated with a particular birth and could apply to any birth, not necessarily the first. Moreover, a diagnostic assessment that specifically probed for major depressive episodes occurring after childbirth might have yielded results more consistent with questionnaire-based findings. PNDS was defined by length of episode in an attempt to separate short-term 'blues' from 'depression', which might persist for a longer period. The question did not specifically ask about timing of symptom onset.

Questions could be raised about our approach of using a three-level measure of post-natal depressive symptoms in multivariate analyses. However, this is reinforced by the findings of Hannah *et al.* (1992), who reported a highly significant positive correlation between early post-partum mood and post-natal depression, with similar symptom profiles. Similarly, Fossey *et al.* (1997) found that post-natal blues were predictive of subsequent post-natal depression. Finally, the study was retrospective: the comparative rarity of twins renders a prospective study of pregnant twin mothers an infeasible strategy.

Our results, thus, suggest the existence of a post-natal dysphoric condition that is aetiologically independent from major depression occurring post-natally, with implications both for nosology, clinical practice and gene identification. The prospective investigation of pregnant siblings of a series of cases and controls using an accepted diagnostic scale, to confirm the evidence for a specific genetic contribution to risk of post-natal depressive symptomatology or dysphoria, would appear worthwhile.

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