Relationship between disabling fatigue and depression in children

Genetic study

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Background Medically unexplained disabling fatigue in young people is familial and frequently associated with depressed mood.

Aims To examine the degree of sharing of genetic and environmental influences on the symptoms of depression and fatigue in this age group.

Method The parents of twins aged 8–17 years, derived from a population-based register, completed a questionnaire regarding lifetime-ever disabling fatigue in both twins. Twins aged 11 years or over completed the Mood and Feelings Questionnaire. The genetic and environmental influences on fatigue and the relationship with depression were examined using bivariate genetic analysis.

Results Parent-rated data were obtained for 1468 twin pairs (65%) and self-rated data from 930 older twin pairs (58%). Bivariate analysis of fatigue and depression suggested that genetic and environmental influences on disabling fatigue were mainly specific to fatigue.

Conclusions Unexplained disabling fatigue in childhood is substantially familial and has mainly an independent aetiology from depression.

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Chronic fatigue in young people can be disabling and is the main illness-related reason for prolonged absence from school (Dowsett & Colby, 1997). Despite this, to date there has only been one study that has specifically examined the genetic aetiology of disabling fatigue in children (Farmer *et al*, 1999). Symptoms of disabling fatigue and depression commonly co-occur (Marshall, 1999; Garralda & Rangel, 2002), and studies have shown that children suffering from chronic fatigue syndrome have significantly higher rates of depression than those with other chronic illness (Walford *et al*, 1993; Carter *et al*, 1999; Brace *et al*, 2000). Consequently, it is important to examine whether the co-occurrence of these two disorders arises because of shared genetic and/or environmental influences. We set out to examine the genetic and environmental aetiology of disabling fatigue and its relationship with depressive symptoms, using a twin study design.

METHOD

Participants

The participants were identified from the Cardiff Study of All Wales and North West of England Twins (CASTANET), a population-based twin register covering two geographical areas, South Wales (Scourfield *et al*, 1999) and nine health districts in Greater Manchester and Lancashire (Thapar *et al*, 2000). Earlier studies have shown the register to be representative of the local population (Thapar & McGuffin, 1994; Scourfield *et al*, 1999; Thapar *et al*, 2000).

The study design included some twin pairs (*n*=439) from South Wales who participated in the earlier study on fatigue by Farmer and colleagues (1999). However, our analyses were based on data obtained from a population-based extended sample of twins, the majority of whom had not previously been studied, and the focus is on comorbidity with depression.

Initially 2259 twin pairs, aged 8–17 years, were identified from the register if their current addresses could be verified through a British Telecommunications telephone database and/or the electoral role. Of these, 656 twin pairs were aged between 8 and 10 years and 1603 were aged between 11 and 17 years. The general practitioners (GPs) of all the twins were first approached to check for any contraindications to contact by the study team. Twins who had emigrated and pairs where one twin had died or suffered from a serious illness or was no longer living in the same household were excluded (*n*=34). Twin families who did not wish to take part were also excluded (*n*=19).

Measures

The parents of all twins were sent questionnaires by post, with three reminders. As there is evidence that self-reports of depression are not valid in children under the age of 11 years (Meltzer *et al*, 2000), self-ratings were obtained for children over the age of 11 years (adolescents) only. Zygosity was assigned using a standard twin similarity questionnaire that has been shown to have over 90% accuracy in distinguishing between monozygotic and dizygotic twins (Cohen *et al*, 1975). A questionnaire measure of environmental sharing was also included (Loehlin & Nichols, 1976). This consisted of items asking, for example, whether the twins dressed the same or shared the same friends, and was used to test the equal environment assumption that underlies twin analyses.

Fatigue was rated by asking parents if there had ever been a period of fatigue lasting several days or weeks where a twin felt very tired and was unable to go to school, college, work or out. If the response to this was 'yes', parents were asked to indicate how long the fatigue had lasted on a 5-point scale:

1. a few days of disabling fatigue;
2. more than 1 week but less than 1 month of disabling fatigue;
3. more than 1 month but less than 3 months of disabling fatigue;
4. more than 3 months but less than 6 months of disabling fatigue;
5. 6 months or more of disabling fatigue.

This is the measure of disabling fatigue used by Farmer *et al* (1999). All analyses were conducted using parental report of fatigue in the twins.

With regard to the validity of the measure of disabling fatigue, the parents of all individuals for whom there had been reported fatigue of more than 1 week were asked to complete a telephone interview about the period of fatigue. Questions were asked about the duration of the fatigue and associated characteristics, including those symptoms also necessary for a diagnosis of chronic fatigue syndrome (Fukuda et al, 1994). The nature and degree of impairment associated with the fatigue were assessed by enquiring about whether the twin needed to rest for at least 1 h daily specifically because of fatigue, and whether there was interference with school attendance and/or usual leisure activities and with family and peer relationships. To be classed as having disabling fatigue, the twin was required to need to rest for at least 1 h daily and for there to be a report of some interference in at least one of these life areas. A more detailed description of the composition of this interview is reported elsewhere (Farmer et al, 2004; Fowler et al, 2005).

Of those parents who agreed to take part (78%), all confirmed the questionnaire report of a period of disabling fatigue that lasted at least 1 week and was disabling and impairing in at least one of the following areas: family interactions, social interactions and school. The associated demographic characteristics of this group resembled those of clinical samples of children with chronic fatigue syndrome (Farmer et al, 2004; Fowler et al, 2005). This suggests that the questions on fatigue were assessing disabling fatigue in children and adolescents.

Because of the effects of categorical analysis, and the rarity of disabling fatigue when defined in its more extreme state, analysis was only undertaken for disabling fatigue of more than 1 week (short duration of fatigue) and for disabling fatigue of more than 1 month (prolonged fatigue). These cut points had the advantage of having been used previously in behavioural genetic research on fatigue in both children (Farmer et al, 1999) and adults (Hickie et al, 1999; Sullivan et al, 2003). Furthermore, Fukuda and colleagues (1994), when proposing a framework for examining fatigue as a disorder (which includes the definition of chronic fatigue syndrome), also proposed a broad category of disabling fatigue of greater than 1 month (prolonged fatigue). There is evidence from the interview data that using broader definitions for disabling fatigue is still clinically relevant. No significant difference in terms of impairment, comorbidity with depression, male:female ratio, age of onset and days per week affected was found between individuals who just fulfilled the broader definitions of disabling fatigue and those who fulfilled the criteria for chronic fatigue syndrome (Fowler et al, 2005).

Self-reports of depressive symptoms were used and depression was rated using the long version of the Mood and Feelings Questionnaire (MFQ; Costello & Angold, 1988). The MFQ is a 34-item questionnaire that has been well validated in community-based samples (Cooper & Goodyer, 1993; Wood et al, 1995). Each item is rated on a three-point scale (0, never; 1, sometimes; 2 often) and a total score is obtained by summing each item score. Individuals were asked to score each item with regard to how they had been feeling in the previous 3 months. No reliability or validity data for the MFQ were collected on this sample. However, previous reports from the CASTANET cohort have shown validity of the MFQ with diagnoses of depressive disorder derived from the Child and Adolescent Psychiatric Assessment (CAPA; Thapar & McGuffin, 1998) and stability of MFQ symptoms over a 3-year period (Pearson's $r=0.5$) (Scourfield et al, 2003).

Genetic analyses

Univariate models

A liability threshold model of disabling fatigue was assumed whereby the liability to disabling fatigue is considered as normally, or approximately normally, distributed in the population, and only those above a certain threshold of liability display the symptoms of fatigue (Falconer, 1965). Tetrachoric correlations and concordance rates were calculated initially to assess genetic and environmental influences on disabling fatigue as defined by increasingly more stringent periods of disabling fatigue. Monozygotic twins share 100% of their genes in common, whereas dizygotic twins share on average 50%. Thus, for genetically influenced disorders, we would expect higher monozygotic than dizygotic correlations. Standard univariate analysis using contingency tables and the maximum likelihood fit function, assuming bivariate normal liability, were undertaken using the structural equation modelling programme Mx (Neale, 1999). This estimated the contribution of additive genetic (A), shared environment (C) and non-shared environment (E) to the variance of liability of disabling fatigue. This analysis was further extended by fitting a general-effects gender-limitation model, a common-effects gender-limitation model and gender-homogeneity model to test for possible gender differences in aetiology (Neale & Cardon, 1992). By comparing a general-effects gender-limitation model to a common-effects gender-limitation model it is possible to test whether there are distinct genetic influences in males and females. By comparing the common-effects gender-limitation model to a gender-homogeneity model (which equates the separate male and female estimates), it is possible to test whether there are significant differences in the magnitude of the influences on the underlying aetiology of the disorder in males and females.

Bivariate models examining fatigue and depression

We set out to examine whether there are distinct genetic and environmental influences on disabling fatigue that are separate from those contributing to depression. A bivariate Cholesky decomposition allows this to be tested and has been used to do so in adults with disabling fatigue (Hickie et al, 1999). By placing depression first in the analysis, the first latent factors A1, C1 and E1 (Fig. 1) load on both variables, and the second latent factors A2, C2 and E2 load specifically on disabling fatigue. This allows the examination of the extent to which a common set of genetic and environmental factors account for the covariation between the two phenotypes: disabling fatigue and depression.

In this analysis, depression was also treated as a continuum of liability. As this type of analysis requires a certain number of twins in each category, the depression scores were grouped into six categories, as this was the maximum number of equally sized categories that ensured at least one individual in each category. As previous analysis of the depression data (Rice et al, 2002) demonstrated the importance of shared environment, it was hypothesised that shared environmental factors might be important in the covariation between disabling fatigue and depression. However, in bivariate analyses where the same informant rates both variables, shared method variance could explain a finding of shared environmental factors contributing to
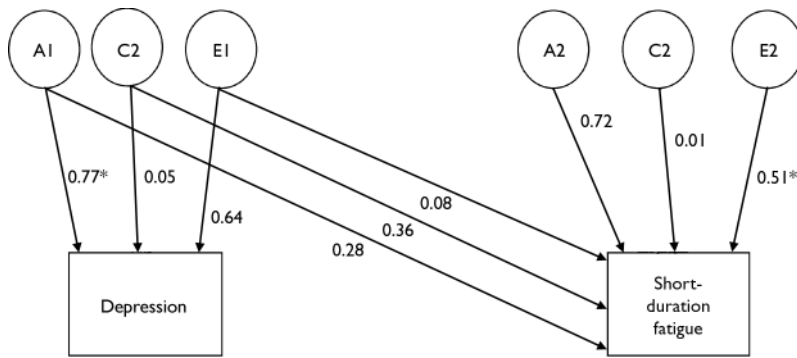
Fig. I Path diagram showing latent genetic and environmental influences on twin-rated depression and parent-rated short-duration fatigue. A, additive genetic; C, shared environment; E, non-shared environment; *significant at $P=0.05$. Standardised path coefficients are provided. These must be squared to obtain proportions of variance of the measured variable accounted for the latent variable.

covariance (Rutter *et al*, 2001). To avoid such a confound, bivariate analysis was undertaken across rater using parental ratings of disabling fatigue and twin self-ratings of depression.

For the bivariate analysis, a raw data analysis approach was taken. This allows information from twin pairs with missing data to be included in the analysis by estimating the missing values. This is particularly useful in multivariate analysis, where missing values can substantially reduce the sample size. Conventional tests of fit are not appropriate for this type of analysis; however, as the relative difference in the fit of minus twice the log-likelihood between submodels is distributed as χ^2, it is possible to compare the bivariate model to a perfect-fitting model in which there are no constraints. This perfect-fitting model is also referred to as a saturated model. If the bivariate model is not significantly different from this saturated model, it represents a good fit of the data (Rijsdijk *et al*, 2003).

RESULTS

Response rate and sample characteristics

Parent-rated questionnaires were returned for 1468 pairs of twins, representing a response rate of 65% of these returned questionnaires, 1052 were for twins aged between 11 and 17 years. Of the 1603 twins aged between 11 and 17 years, who were asked also to complete self-report questionnaires, 930 (58%) returned them. Parent-report suggested 129 individuals (monozygotic=53, dizygotic=73, zygosity unassigned=3) could be categorised as

suffering from short duration of fatigue and 73 individuals (monozygotic=26, dizygotic=45, zygosity unassigned=2) from prolonged fatigue. The mean self-rated MFQ scores for the twins was 11.26 (s.d.=9.89) for monozygotic twins and 11.90 (s.d.=10.28) for dizygotic twins (Rice *et al*, 2002).

Of the individuals for whom parental interview data were available (i.e. 77% of all individuals classed as suffering from disabling fatigue in the genetic analysis), approximately two-thirds were female (67%), the average age of onset for the fatigue was 11 years and 3 months and, although the majority did not fulfil the duration criteria for chronic fatigue syndrome, 80% had four or more associated symptoms also required for that diagnosis (Fukuda *et al*, 1994). There was no significant difference in any of these characteristics between those who were classed as suffering from short-duration fatigue and those classed as suffering from prolonged fatigue. There was a significant difference ($t=-1.97$, $P=0.05$) between MFQ scores for individuals categorised as suffering from short-duration fatigue only (mean=15.31, s.d.=10.16) and those who suffered from prolonged fatigue (mean=20.54, s.d.=14.05).

There were no significant differences between those who replied and those who did not, in terms of ecological socio-demographic indices that could be obtained by comparing the postcodes of responders and non-responders ($t=1.71$, $P=0.09$). Social class information was available only for the Manchester twins. For these twins, the percentage of families from the various social class groups (I, II,

III, IV, V) were in keeping with those expected from the Manchester population (Public Health Common Data Set, 1993; Rice *et al*, 2002).

Environmental sharing

Monozygotic twins scored significantly higher on the environmental sharing ($t=17.62$, $P=0.01$), but this did not account for the monozygotic similarity in short-duration fatigue (OR=0.935, 95% CI 0.747–1.169, $P=0.553$) or prolonged fatigue (OR=0.946, 95% CI 0.670–1.336, $P=0.752$), nor did it account for the depression scores ($R^2=0.003$, $F=2.866$, $P=0.091$) (Rice *et al*, 2002).

Genetic analysis

Univariate analysis

The concordance rates for short-duration fatigue were monozygotic=35%, dizygotic =14%; the tetrachoric correlations were monozygotic=0.66 (95% CI 0.45–0.83), dizygotic=0.33 (95% CI 0.07–0.56). For prolonged fatigue the concordance rates were monozygotic=25%, dizygotic=19%; the tetrachoric correlations were monozygotic=0.62 (95% CI 0.27–0.85) dizygotic=0.50 (95% CI 0.20–0.72).

The tetrachoric correlations for the data suggest that there is an important additive genetic component (A) for short-duration fatigue. The similar monozygotic and dizygotic tetrachoric correlation coefficients for prolonged fatigue suggest an increase in the importance of the shared environmental contribution. This is confirmed by the model fitting. ACE models were fitted to the data, as shown in Table 1; full models with confidence intervals are reported. For short-duration fatigue, genetic factors contributed the most and the shared environmental contribution was estimated at zero. For prolonged fatigue the full ACE model showed mainly environmental influences but modest genetic variance (25%). There was no significant difference between the general gender-limitation model and the common gender-limitation model for either short-duration fatigue ($\Delta\chi^2_1=0.01$) or prolonged fatigue ($\Delta\chi^2_1=0.19$), suggesting no gender-specific genetic influences. Neither was there a significant difference between the common gender-limitation models and the gender-homogeneity models (short-duration fatigue, $\Delta\chi^2_3=0.90$; prolonged fatigue, $\Delta\chi^2_3=4.28$), suggesting no gender

Table I Univariate genetic model-fitting for parent-rated short-duration fatigue and prolonged fatigue using full and nested models

Threshold of disabling fatigue	a^2 (95% CI)	c^2 (95% CI)	e^2 (95% CI)	χ^2	d.f.	P	AIC
Short-duration fatigue							
ACE model	0.67 (0.04–0.82)	0.00 (0.00–0.51)	0.33 (0.18–0.55)	1.10	2	0.58	−2.90
AE model	0.67 (0.47–0.82)	[0]	0.33 (0.18–0.53)	1.10	3	0.78	−4.90
CE model	[0]	0.50 (0.33–0.65)	0.50 (0.35–0.67)	5.43	3	0.14	−0.58
E model	[0]	[0]	1.00 (1.00–1.00)	34.80	4	0.00	26.80
Prolonged fatigue							
ACE model	0.25 (0.00–0.84)	0.37 (0.00–0.71)	0.38 (0.15–0.66)	1.41	2	0.49	−2.59
AE model	0.69 (0.41–0.87)	[0]	0.31 (0.13–0.59)	2.74	3	0.43	−3.27
CE model	[0]	0.55 (0.33–0.72)	0.45 (0.28–0.67)	1.77	3	0.62	−4.22
E model	[0]	[0]	1.00 (1.00–1.00)	22.43	4	0.00	14.43

A, additive genetic; C, shared environment; E, non-shared environment; a^2, additive genetic variance; c^2 shared environmental variance; e^2, non-shared environmental variance; [0], parameter set at zero; d.f. degrees of freedom; AIC, Akaike's information criterion (Akaike, 1987).

differences in the magnitude of the genetic and environmental influences.

Bivariate analysis

As previous work suggests a gender difference for twin-rated depression (Rice *et al*, 2002) MFQ scores were first standardised according to gender.

As statistical power is affected by the categorical data and the relatively small number of individuals with disabling fatigue, full models are reported with confidence intervals.

Short-duration fatigue

The phenotypic correlation between short-duration fatigue and depression was relatively small (polychoric correlation=0.28). The Cholesky decomposition for three sources of variance-additive genetics (A), shared environment (C) and non-shared environment (E) (Fig. 1), when compared with a saturated model was not significantly different ($\Delta\chi^2_5$=3.87) suggesting the model was a good fit. The majority of the variance in disabling fatigue appeared to be distinct from that of depression (Table 2, Fig. 1) with only 22% of the variance of disabling fatigue explained by factors common to both phenotypes. Of that 22%, shared environment accounted for the largest proportion of variance (13%), with genetic factors explaining only 8%.

Prolonged fatigue

The phenotypic correlation between prolonged fatigue and depression (polychoric correlation=0.30) was slightly higher than that between short-duration fatigue and depression. For disabling fatigue defined as greater than 1 month, a much higher percentage of the variance was explained by factors common to both disabling fatigue and depression (46%). The fit of the model was not significantly worse than the saturated model ($\Delta\chi^2_5$=7.01). Full models with confidence intervals are reported (Table 2, Fig. 2). Just over half of the variance was specific to disabling fatigue (54%). Of the remaining variance, shared environment accounted for the largest proportion (36%), with genetic factors accounting for 28%.

Cross-rater analyses were undertaken to control for the possibility of shared rater effect. Additional within-rater bivariate analysis of parent-rated fatigue and parent-rated depression showed that the majority of the variance for both short-duration fatigue and prolonged fatigue was specific to the fatigue (76% and 63% respectively). The remaining variance was accounted for by environmental factors (both shared and non-shared), with genetic factors accounting for a negligible amount (<1%).

DISCUSSION

This investigation has examined the genetic and environmental influences on disabling fatigue, using a community sample of 2259 twin pairs aged 8–17 years. It has also examined the overlap between disabling fatigue and depression in those twin pairs (1052) aged 11–17 years.

The genetic aetiology of disabling fatigue

The results suggest that the aetiology of short-duration fatigue in children and adolescents is heritable (67%). In addition, the present results suggest that prolonged fatigue is familial. These findings are in accordance with earlier findings on a smaller sample of twins reported by Farmer and colleagues (1999), which suggested disabling fatigue of greater than 1 week and disabling fatigue of greater than 1 month were both familial.

The results of the genetic analysis suggest that shared environment plays a more important role in prolonged fatigue than in the genetic aetiology of short-duration fatigue. This raises the question as to why there is an increase in the influence of shared environment in prolonged fatigue. It may be that individuals who are classed as experiencing a short period of fatigue have a propensity to being fatigued and that this is a genetically influenced trait. On the other hand, those with prolonged fatigue more resemble individuals with a specific disorder that may have a greater variety of aetiological factors.

Gender differences in aetiology

Interestingly, no significant differences in the magnitude of genetic and environmental effects between the genders were found. This is despite reports of clinical samples of chronic fatigue syndrome (Marshall, 1999; Garralda & Rangel, 2002), in which there is generally a preponderance of females, which might suggest aetiological

Table 2 Bivariate genetic model-fitting for twin-rated depression and parent-rated disabling fatigue using full models

Threshold of disabling fatigue	Phenotype	A1 (95% CI)	C1 (95% CI)	E1 (95% CI)	A2 (95% CI)	C2 (95% CI)	E2 (95% CI)	Difference in fit from saturated model $\Delta\chi^2_5$
Short-duration fatigue	Depression	0.59 (0.37–0.66)*	0.00 (0.00–0.17)	0.41 (0.34–0.50)*				3.87
	Disabling fatigue	0.08 (0.00–0.21)	0.13 (0.00–0.63)	0.01 (0.00–0.07)	0.52 (0.00–0.80)	0.00 (0.00–0.63)	0.26 (0.11–0.49)*	
Prolonged fatigue	Depression	0.59 (0.37–0.63)*	0.00 (0.00–0.17)	0.41 (0.34–0.49)*				7.01
	Disabling fatigue	0.11 (0.00–0.28)	0.34 (0.00–0.75)	0.01 (0.00–0.09)	0.30 (0.00–0.81)	0.00 (0.00–0.70)	0.24 (0.09–0.51)*	

Standardised parameter estimates for the sources of variation in liability to depression and disabling fatigue are provided.
A1, A2, additive genetic variance; C1, C2, shared environmental variance; E1, E2, non-shared environmental variance.
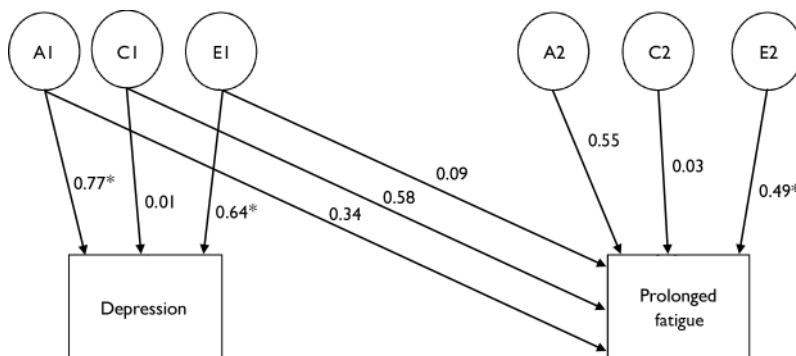*$P<0.05$.

Fig. 2 Path diagram showing latent genetic and environmental influences on twin-rated depression and parent-rated prolonged fatigue. A, additive genetic; C, shared environment; E, non-shared environment; *significant at $P=0.05$. Standardised path coefficients are provided. These must be squared to obtain proportions of variance of the measured variable accounted for the latent variable.

differences between males and females. However, in view of the relatively large confidence intervals reported from the univariate analysis, these results should be interpreted with caution.

The relationship between fatigue and depression

The bivariate analyses suggest that for the more extreme definition of disabling fatigue there are greater shared aetiological influences with depression. However, for both short-duration fatigue and prolonged fatigue, the majority of the genetic and environmental variance is specific to disabling fatigue and distinct from depression. This suggests that fatigued states in children should be considered as valid entities in their own right and not as variants of depression. Hickie et al (1999) also found evidence that implies depression has a distinct aetiology from disabling fatigue of greater than 1 month, in a sample consisting of twins over the age of 50 years. Thus, a similar pattern for the aetiology of chronic fatigue has been found at both extremes of the life span. Williamson et al (2005), in an analysis of sibling pairs (aged 20–55 years) also suggested that a substantial proportion of both familial and environmental aspects of the aetiology of fatigue were specific to fatigue.

Perhaps one of the most interesting findings was that, of the aetiology common to both phenotypes, shared environment had the greatest influence on disabling fatigue lasting at least 1 month. In standard bivariate genetic analysis, shared-method variance owing to the same rater reporting on both phenotypes may be partitioned into shared environmental effects. What is so striking in our study is that, since the analysis was cross-rater, this could not explain the shared environmental findings. As interview data had been collected on parental opinion as to the causes of the disabling fatigue and on parental report of GPs' explanation as to the cause of the disabling fatigue, this was also examined. Viral infection was the most common explanation of the fatigue, given by GPs when consulted. Viral infections were also an important cause according to parents, as was stress caused by a negative life event (Farmer et al, 2004). These negative life events consisted of such things as parents splitting up, parental illness or death, school exams, increased workload at school or moving schools: life events that were probably shared by both twins. It should, however, be noted that these events may impact differently on each twin. Although viral infections are not thought to be necessary or sufficient to cause disabling fatigue, they have been implicated as possible triggers (Garralda & Rangel, 2002). Individuals with chronic fatigue syndrome also appear to show higher levels of stressful life events just before the onset of the disorder (Hatcher & House, 2003). Considering that these are also risk factors for depression in young people (e.g., Goodyer et al, 1993; Monroe et al, 1999), it is possible that the increase in the importance of shared environment may be owing to the impact of viral illness and shared life events on making both twins more vulnerable to prolonged fatigue and depression.

Seeing that the results from the genetic analysis suggest that shared environment may be more important in people with longer periods of fatigue, future research should concentrate on both environmental and genetic risk factors. In view of the possible importance of shared life events and viral infections in explaining the relationship between fatigue and depression, both longitudinal and prospective studies examining these factors are called for, it also seems plausible that, in part, the high levels of depression seen may be the person's response to a disabling disorder. The most appropriate method with which to test this would be longitudinal genetically sensitive studies. These would examine the direction of the relationship between fatigue and depression and whether the relationship is owing to shared genetic and environmental risk factors.

In summary, disabling fatigue and depression co-occur but appear to have distinct genetic and environmental aetiologies.

Limitations

There are a number of limitations to this study. First, for the bivariate analysis, the measure of disabling fatigue was lifetime-ever, whereas the MFQ measured depressive symptoms in the previous 3 months. This is likely to have reduced the comorbidity between depression symptoms and disabling fatigue, and may have led to an underestimate of shared aetiological factors. However, there is longitudinal evidence from within the twin sample that levels of depressive symptoms are relatively stable over time, with a correlation of 0.5 between depression scores collected 3 years previously and the present wave of data collection (Scourfield et al, 2003). Furthermore, over 40% of parents interviewed reported that their child's fatigue was ongoing at the time of interview (and therefore current). As the depression section of the parent version of the Child and Adolescent Psychiatric Assessment (CAPA; Angold & Costello, 2000) was also undertaken, a measure of depressive symptoms during the disabling fatigue was available. There was no significant difference in the correlation coefficients between the twins MFQ scores and the number of depressive symptoms during the period of fatigue for those with ongoing disabling fatigue ($r=0.44$) and those who previously suffered from disabling fatigue ($r=0.45$) (Fisher $z=0.47$, $P=0.33$). The small numbers available precluded any model fitting for those individuals currently fatigued, but cross-twin cross-trait polychoric correlations were approximately the same for those currently fatigued and those previously suffering from fatigue. Although it is almost certain that the differences in time scale of the measures for disabling fatigue and depressive symptoms will lead to an underestimate of the phenotypic correlation, the evidence from the interview data suggests that this is likely to have been a small effect.

Second, the measure of disabling fatigue was based on self-report questionnaire data and was therefore fairly broad and imprecise. In what ways the measure relates to the clinical definition of chronic fatigue syndrome remains uncertain, although the interview data do suggest that it represents a fairly good indication of disabling fatigue.

Third, the study represents a partial resampling of those contacted originally in the Farmer et al (1999) paper and therefore is not entirely independent. Nonetheless, it does represent a new wave of data collection, and the twin register has been markedly increased by combining the original South Wales register with the Greater Manchester twin register. The results from a reanalysis of univariate data excluding the twins previously sampled gave broadly the same results but with larger confidence intervals. This study has also undertaken further analyses, namely the examination of the genetic contribution to gender differences in fatigue and the bivariate analysis of depression and fatigue.

Finally, because of the categorical nature of the data, the analyses have almost certainly lacked power. This is reflected in the wide confidence intervals in both univariate and bivariate analyses.

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