The shared genetics of migraine and anxious depression

Abstract

Objectives: To investigate 1) whether shared genetic factors influence migraine and anxious depression, 2) whether the genetic architecture of migraine depends on anxious depression, and 3) whether the association between the traits is causal. Background: Migraine and anxious depression frequently co-occur, but little is known about the mechanisms causing this association.

Methods: A twin study was conducted to model the genetic architecture of migraine and anxious depression and the covariance between them. Anxious depression was also added to the model as a moderator variable to examine whether anxious depression affects the genetic architecture of migraine. Causal models were explored with the co-twin control method.

Results: Modest but significant phenotypic (rP = .28), genetic (rG = .30) and non-shared environmental (rE = .26) correlations were found between the two traits. Interestingly, the heritability of migraine depended on the level of anxious depression: migraine was less heritable in subjects with high anxious depression scores. The observed risk patterns in discordant twins are most consistent with a bidirectional causal relationship.

Conclusions: These findings confirm the genetic association between migraine and anxious depression and are consistent with a syndromic association between the two traits. This highlights the importance of taking comorbidity into account in genetic studies of migraine, especially in the context of selection for large-scale genotyping efforts. Genetic studies may be most effective when migraine with and without comorbid anxious depression are treated as separate phenotypes.
INTRODUCTION

Migraine and depression consistently show an association, which may be explained by a shared etiology, for instance, genetic risk factors. Several authors have suggested that disturbances in the serotonergic and dopaminergic systems, involved in both migraine and depression, might explain the association between the two traits (Breslau et al., 1991; Frediani & Villani, 2007).

Two recent studies investigated the association between migraine and depression and found that the two traits were genetically correlated (Schur et al., 2009; Stam et al., 2010). This may reflect the existence of genetic risk factors that can cause migraine as well as depression (pleiotropy). Alternatively, if there is a causal relationship between two traits, genetic factors contributing to the first trait will also explain variance in the second trait. Thus, a causal relationship is also consistent with a genetic correlation. Whether traits are related causally or through an underlying shared etiology, can be examined using family data (Kendler et al., 1993; Merikangas & Stevens, 1997).

In the present study, we investigated the shared genetics of migraine and anxious depression in three different ways. A twin design was used to (1) test whether the previously reported genetic correlation between migraine and depression could be replicated in migraine and anxious depression data from a large number of Dutch twins; (2) investigate whether the genetic architecture of migraine was the same in individuals with high and low anxious depression scores. Finally, to address the question of causality, the co-twin control method (Kendler et al., 1993) was applied to investigate whether the association between migraine and anxious depression is more likely explained by a causal model or a shared underlying etiology.

METHODS

SUBJECTS

The participants in this study were volunteer members of the Netherlands Twin Registry (NTR), based at the department of Biological Psychology of the VU University in Amsterdam. NTR participants receive mailed questionnaires every two to three years, in the context of an ongoing study of health, lifestyle and personality. The migraine and anxious depression data used in this study were collected in the 2002 and 2004 surveys. When a participant answered the headache section in both surveys, the most recent (2004) survey was used. Data
collection procedures are described in detail elsewhere (Boomsma et al., 2006; Distel et al., 2007). The study was approved by the Central Ethics Committee on Research Involving Human Subjects of the VU University Medical Center, Amsterdam. All subjects provided written informed consent.

The analysis performed to assign affection status for migraine to each individual was based on the largest possible sample with migraine data available, including twins, parents, singleton siblings and spouses [N = 14,904, including 12,303 participants from the NTR and 2,601 from NESDA (Penninx et al., 2008)]. Further analyses were based on the data of twins only (N = 5,535; 2,072 complete pairs and 1,391 individuals from incomplete pairs). Migraine data were available for all 5,535 individuals; 4,320 twins also provided data on anxious depression, resulting in a total of 1,491 complete twin pairs with information on both migraine and anxious depression (223 monozygotic (MZ) male, 100 dizygotic (DZ) male, 602 MZ female, 286 DZ female, and 280 DZ opposite sex pairs). In total, the sample consisted of 1,774 (32%) male and 3,761 (68%) female participants and the mean age was 34.33 years (SD = 11.35, range 14-86 years).

**Measures**

The subjects completed a questionnaire that included items relating to the diagnostic criteria for migraine of the International Headache Society (Headache Classification Committee of the International Headache Society, 2004; see Table 7.1). Migraine status was assigned to each subject based on a latent class analysis (LCA; Lazarsfeld & Henry, 1968; McCutcheon, 1987), which empirically classifies individuals according to their pattern of reported migraine symptoms. For simplicity, LCA-derived migrainous headache will be referred to as ‘migraine’ throughout the remainder of the paper. The application of LCA in migraine studies has been described in more detail elsewhere (Ligthart et al., 2006; Ligthart et al., 2008; Nyholt et al., 2004; Nyholt et al., 2005). LCA was performed in Latent Gold 4.0 (Statistical Innovations Inc., Belmont, MA). The correct number of classes was determined based on the Bayes Information Criterion (BIC; Schwarz, 1978) with a lower BIC indicating a better fit to the data.
The analysis performed to assign affection status for migraine to each individual was based on the largest possible sample with migraine data available, including twins, parents, singleton siblings and spouses \[N = 14,904, including 12,303 participants from the NTR and 2,601 from NESDA (Penninx et al., 2008)\]. Further analyses were based on the data of twins only (N = 5,535; 2,072 complete pairs and 1,391 individuals from incomplete pairs). Migraine data were available for all 5,535 individuals; 4,320 twins also provided data on anxious depression, resulting in a total of 1,491 complete twin pairs with information on both migraine and anxious depression (223 monozygotic (MZ) male, 100 dizygotic (DZ) male, 602 MZ female, 286 DZ female, and 280 DZ opposite sex pairs). In total, the sample consisted of 1,774 (32%) male and 3,761 (68%) female participants and the mean age was 34.33 years (SD = 11.35, range 14-86 years).

**MEASURES**

The subjects completed a questionnaire that included items relating to the diagnostic criteria for migraine of the International Headache Society (Headache Classification Committee of the International Headache Society, 2004; see Table 7.1). Migraine status was assigned to each subject based on a latent class analysis (LCA; Lazarsfeld & Henry, 1968; McCutcheon, 1987), which empirically classifies individuals according to their pattern of reported migraine symptoms. For simplicity, LCA-derived migrainous headache will be referred to as ‘migraine’ throughout the remainder of the paper. The application of LCA in migraine studies has been described in more detail elsewhere (Ligthart et al., 2006; Ligthart et al., 2008; Nyholt et al., 2004; Nyholt et al., 2005). LCA was performed in Latent Gold 4.0 (Statistical Innovations Inc., Belmont, MA). The correct number of classes was determined based on the Bayes Information Criterion (BIC; Schwarz, 1978) with a lower BIC indicating a better fit to the data.

**Table 7.1**

<table>
<thead>
<tr>
<th>Item in survey</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you ever experience headache attacks, for instance migraine? (yes/no)</td>
<td>-</td>
<td>Screening question</td>
</tr>
<tr>
<td>How often do you have these headache attacks? *</td>
<td>A</td>
<td>&gt;= 5 episodes</td>
</tr>
<tr>
<td>How long do these headache attacks usually last?</td>
<td>B</td>
<td>4-72 hours</td>
</tr>
<tr>
<td>The headache is usually pounding or stabbing (yes/no)</td>
<td>C2</td>
<td>Pulsating quality</td>
</tr>
<tr>
<td>How intense is the headache during most attacks? (mild/moderate/severe)</td>
<td>C3</td>
<td>Moderate or severe pain intensity</td>
</tr>
<tr>
<td>During a headache attack, do you experience:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>acceleration of headache by physical activity?</td>
<td>C4</td>
<td>Aggravation by physical activity</td>
</tr>
<tr>
<td>nausea or vomiting?</td>
<td>D1</td>
<td>Nausea and/or vomiting</td>
</tr>
<tr>
<td>aversion of light, sound or smell? †</td>
<td>D2</td>
<td>Photo- and phonophobia</td>
</tr>
<tr>
<td>partial loss of vision, seeing flashes of light or (zigzag) patterns? Aura</td>
<td></td>
<td>Visual aura</td>
</tr>
</tbody>
</table>

* An attack frequency of ‘several times a year’ or more was assumed to be equivalent to ‘>= 5 episodes’.
† The official criteria do not include osmophobia and require both photo- and phonophobia, however, from these data it was not possible to determine whether both were present.
Chapter 7

The anxious depression measure consisted of a factor score based on several measures of anxiety, depression and neuroticism that was calculated using an algorithm developed in previous research on anxious depression (Boomsma et al., 2000). This factor score was recoded into quartiles, with quartile 1 indicating a low anxious depression score and quartile 4 indicating a high score.

Genetic modeling

In the classical twin study, the resemblance between twins is used to estimate to what extent a trait is influenced by additive genetic factors (A), shared (or common) environment (C) and non-shared environment (E). MZ twins share 100% of their segregating genes, whereas DZ twins share on average 50%. Differences between MZ twins reflect E. Greater resemblance in MZ compared to DZ twins reflects genetic influences, with an MZ correlation (rMZ) equal to twice the DZ correlation (rDZ) indicating A, and an rMZ which is less than twice the rDZ indicating A and C. Based on these principles, the total variance in a trait can be decomposed into variance due to A, C and E. Estimation of the relative contributions of A, C and E can be accomplished with structural equation modeling (SEM). Figure 7.1 shows a path diagram of the model tested here. Since there was no evidence for shared environmental effects based on the observed twin correlations or the literature (Mulder et al., 2003; Sullivan et al., 2000), an AE model was tested for both traits.

To investigate whether the genetic and environmental factors influencing migraine and anxious depression were correlated, a bivariate genetic model was tested (Figure 7.1). This model included genetic and environmental factors for both traits, partly unique to each trait (the a_{11}, a_{22}, e_{11} and e_{22} paths), and partly shared (a_{21} and e_{21}). The shared part represents the covariance between the two traits, which can be decomposed into covariance explained by genetic and environmental factors. This is done based on the cross-trait cross-twin correlations (i.e. the correlation between one trait in the first twin and the other trait in the second twin). The cross-twin cross-trait correlations are interpreted in the same way as the within-trait twin correlations, with correlations higher in MZ than DZ twins indicating genetic factors influencing both traits. By standardizing the parts of the covariance due to A and E, genetic and environmental correlations can be calculated. The significance of these correlations was tested by dropping the a_{21} and e_{21} paths from the model and comparing the fit of the restricted and full models.

A liability threshold model was tested for both migraine and anxious depression. A threshold model assumes that the observed categorical data (e.g.,
The anxious depression measure consisted of a factor score based on several measures of anxiety, depression and neuroticism that was calculated using an algorithm developed in previous research on anxious depression (Boomsma et al., 2000). This factor score was recoded into quartiles, with quartile 1 indicating a low anxious depression score and quartile 4 indicating a high score.

**GENETIC MODELING**

In the classical twin study, the resemblance between twins is used to estimate to what extent a trait is influenced by additive genetic factors (A), shared (or common) environment (C) and non-shared environment (E). MZ twins share 100% of their segregating genes, whereas DZ twins share on average 50%. Differences between MZ twins reflect E. Greater resemblance in MZ compared to DZ twins reflects genetic influences, with an MZ correlation (rMZ) equal to twice the DZ correlation (rDZ) indicating A, and an rMZ which is less than twice the rDZ indicating A and C. Based on these principles, the total variance in a trait can be decomposed into variance due to A, C and E. Estimation of the relative contributions of A, C and E can be accomplished with structural equation modeling (SEM). Figure 7.1 shows a path diagram of the model tested here. Since there was no evidence for shared environmental effects based on the observed twin correlations or the literature (Mulder et al., 2003; Sullivan et al., 2000), an AE model was tested for both traits.

To investigate whether the genetic and environmental factors influencing migraine and anxious depression were correlated, a bivariate genetic model was tested (Figure 7.1). This model included genetic and environmental factors for both traits, partly unique to each trait (the $a_{11}$, $a_{22}$, $e_{11}$ and $e_{22}$ paths), and partly shared ($a_{21}$ and $e_{21}$). The shared part represents the covariance between the two traits, which can be decomposed into covariance explained by genetic and environmental factors. This is done based on the cross-trait cross-twin correlations (i.e. the correlation between one trait in the first twin and the other trait in the second twin). The cross-twin cross-trait correlations are interpreted in the same way as the within-trait twin correlations, with correlations higher in MZ than DZ twins indicating genetic factors influencing both traits. By standardizing the parts of the covariance due to A and E, genetic and environmental correlations can be calculated. The significance of these correlations was tested by dropping the $a_{21}$ and $e_{21}$ paths from the model and comparing the fit of the restricted and full models.

A liability threshold model was tested for both migraine and anxious depression. A threshold model assumes that the observed categorical data (e.g., a variable with values 1-4 indicating severity of migraine) are an imperfect measurement of an underlying normal distribution of liability with a mean of zero and a variance of one. This distribution is divided into discrete categories by one or more threshold values, expressed as $Z$-scores. The area under the curve between two thresholds represents the prevalence of each category. The categorized anxious depression variable was already adjusted for sex; therefore the thresholds for both sexes were equated in the model. Migraine, as expected, had a higher prevalence in females. Thus, the thresholds for migraine were estimated separately for males and females.

To test whether the heritability of migraine depends on anxious depression, anxious depression was specified as a moderator of the path coefficients $a_{ii}$ and $e_{ii}$ (which represent the variance shared by migraine and depression) and $a_{22}$, and $e_{22}$ (which represent the variance unique to migraine). In other words, the effects of the genetic and environmental factors affecting migraine were allowed to vary depending on depression status. The significance of the moderation effect was evaluated by dropping the beta parameters $\beta_{AC}$, $\beta_{AU}$, $\beta_{EU}$ and $\beta_{EC}$ from the model and assessing the difference in model fit.

To ensure identification of the model, the total variance in a threshold model has to be constrained to one. However, in the model used here the variance of migraine depends on the value of the moderator (anxious depression). Therefore, the moderator variable was converted to a $Z$-score; the variance was constrained to be one at the mean value of the moderator, as proposed by Medland and colleagues (Medland et al., 2009). All genetic modeling was performed in Mx (Neale et al., 2003).
Figure 7.1

The bivariate moderator model. AD = anxious depression, mig = migraine. The A and E factors influencing migraine are moderated by anxious depression (M). Regression betas are estimated for the genetic factors unique to migraine ($\beta_{AU}$) and common to migraine and anxious depression ($\beta_{AC}$), and the same for the non-shared environmental factors ($\beta_{EU}$ and $\beta_{EC}$). The moderator variable (anxious depression) affects both the variance unique to migraine (path coefficients $a_{22}$ and $e_{22}$) and the variance shared with anxious depression (path coefficients $a_{21}$ and $e_{21}$).
**Co-twin control method**

The co-twin control method (Kendler et al., 1993) was applied to test the hypothesis that 1) migraine causes anxious depression, and 2) anxious depression causes migraine. In this design, an odds ratio (OR) is calculated for trait A, given the presence or absence of trait B. This is done in three groups of individuals: MZ and DZ twin pairs discordant for trait B, and a case-control population sample. Under a *causal* model, all three groups are expected to show a similarly increased prevalence of A, given the presence of B, i.e., all three groups will have an OR > 1. Under a *non-causal* model, where shared underlying genetic factors explain the association, the OR in MZ twins is expected to equal one, because MZ twins are exposed to the same genetic risk factors, and should therefore have the same risk of trait A regardless of the presence of trait B. DZ twins will show an intermediate pattern (Figure 7.2).

For this analysis, anxious depression was dichotomized; individuals in the highest scoring quartile were treated as cases, the lowest three quartiles were treated as controls. A ‘general population’ sample was obtained by randomly selecting one individual from each family in the NTR sample (total N = 12,303), excluding the discordant twins. The sample included 358 MZ and 418 DZ pairs discordant for anxious depression, and 454 MZ and 510 DZ pairs discordant for migraine. The general population sample consisted of 2,838 unrelated individuals. ORs were calculated in SPSS 17.

**Results**

Four classes of individuals were identified, based on the patterns of reported migraine symptoms. The 4-class LCA model provided a better fit to the data (BIC = 60139.87) than a 3 or a 5-class model (with a BIC of 60185.03 and 60233.40, respectively). Figure 7.3 shows the pattern of symptoms in each class. The two most severe classes were treated as affected for migrainous headache, the remaining individuals were treated as unaffected. In the twin sample used in all subsequent analyses, 14% of the male and 35% of the female participants were classified as affected, which is comparable to the combined prevalence of migraine and probable migraine, according to IHS criteria (Merikangas et al., 1990).

A clear comorbidity of migraine and depression was observed, with a migraine prevalence of 20% in the lowest anxious depression quartile and 43% in the highest scoring quartile. The phenotypic correlation between migraine and anxious depression was estimated at .28 (95% CI = .20 - .36).
Table 7.2 shows an overview of the correlations across twins and traits. The twin correlations for both migraine and anxious depression were clearly higher in MZ than DZ twins, reflecting genetic influences on both traits. Genetic modeling results indicated that the variance in migraine could be explained by a combination of genetic (45%) and non-shared environmental factors (55%). For anxious depression, genetic factors explained 55% and non-shared environment explained 45% of the variance.

<table>
<thead>
<tr>
<th>Correlation matrices for MZ and DZ twins</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MZ</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>AD twin 1</td>
</tr>
<tr>
<td>mig twin 1</td>
</tr>
<tr>
<td>AD twin 2</td>
</tr>
<tr>
<td>mig twin 2</td>
</tr>
<tr>
<td><strong>DZ</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>AD twin 1</td>
</tr>
<tr>
<td>mig twin 1</td>
</tr>
<tr>
<td>AD twin 2</td>
</tr>
<tr>
<td>mig twin 2</td>
</tr>
</tbody>
</table>

MZ = monozygotic, DZ = dizygotic, AD = anxious depression, mig = migraine
Table 7.2 shows an overview of the correlations across twins and traits. The twin correlations for both migraine and anxious depression were clearly higher in MZ than DZ twins, reflecting genetic influences on both traits. Genetic modeling results indicated that the variance in migraine could be explained by a combination of genetic (45%) and non-shared environmental factors (55%). For anxious depression, genetic factors explained 55% and non-shared environment explained 45% of the variance.

<table>
<thead>
<tr>
<th></th>
<th>AD twin 1</th>
<th>mig twin 1</th>
<th>AD twin 2</th>
<th>mig twin 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>MZ twin 1</td>
<td>1.00</td>
<td>0.28 (.20-.36)</td>
<td>1.00</td>
<td>0.28 (.20-.36)</td>
</tr>
<tr>
<td>MZ twin 2</td>
<td>0.55 (.49-.60)</td>
<td>0.15 (.08-.22)</td>
<td>1.00</td>
<td>0.45 (.35-.55)</td>
</tr>
<tr>
<td>DZ twin 1</td>
<td>0.27 (.25-.30)</td>
<td>0.08 (.04-.11)</td>
<td>0.23 (.18-.27)</td>
<td>1.00</td>
</tr>
<tr>
<td>DZ twin 2</td>
<td>0.08 (.04-.11)</td>
<td>0.28 (.20-.36)</td>
<td>1.00</td>
<td>0.28 (.20-.36)</td>
</tr>
</tbody>
</table>

MZ = monozygotic, DZ = dizygotic, AD = anxious depression, mig = migraine

Figure 7.2
Expected patterns of odds ratios (OR) for general population and discordant DZ and MZ twins under the assumptions of causality and non-causality. Under the causal hypothesis, trait A and B are associated in all three groups. Under the non-causal hypothesis, where genetic factors explain the association, discordant MZ twins have an OR of 1, because they are genetically identical and are thus exposed to the same genetic risk factors. The DZ twins, who share on average 50% of their segregating genes, show an intermediate pattern. Finally, if the association is non-causal but explained by shared environment, all discordant twins are expected to have an OR of one. However, in this case, this is unlikely because there is no evidence that shared environment affects migraine or depression.
Chapter 7

Figure 7.3
Profile plot for the best fitting latent class model, showing the symptom prevalence in each of the empirically estimated classes. The migraine symptoms are on the x-axis, the y-axis shows the probability that a symptom is present given class membership.

The cross-twin cross-trait correlations were also higher in MZ than DZ twins, suggesting the correlation between migraine and anxious depression is at least partly explained by genetic influences. Most of the covariance between the two traits was indeed explained by shared genetic factors (54%), while non-shared environment was responsible for the remaining covariance (46%). The genetic correlation (rG) between anxious depression and migraine was estimated at .30 (95% CI = .18 - .43) while the non-shared environmental correlation (rE) was .26 (95% CI = .15 - .37). Both correlations were significant: dropping a_{si} and e_{si} from the model both resulted in a significant deterioration in model fit ($\Delta \chi^2(1) = 17.834, p < .001$ for a_{si}, $\Delta \chi^2(1) = 15.535, p < .001$ for e_{si}).

Figure 7.4
The heritability of migraine at different values of anxious depression. The proportion of variance in migraine explained by additive genetic factors (A) and non-shared environmental factors (E) across a range of depression scores, based on the estimates obtained from the moderator model. The higher the depression score, the lower the relative contribution of genetic factors to the individual differences in migraine susceptibility. Low = anxious depression score 2 SD below the mean, high = anxious depression score 2 SD above the mean.

The next step was to test the significance of the moderation effect of anxious depression on the heritability of migraine, by dropping the moderator betas from the model and assessing the resulting deterioration in model fit. The power to test the significance of these parameters individually was low (as reflected by confidence intervals that included zero; Table 7.3). However, dropping all four $\beta$ parameters from the model at once resulted in a significant deterioration of the model fit ($\Delta \chi^2(4) = 12.478, p = .014$), indicating that, overall, the moderator variable is of importance in explaining the observed data.

Figure 7.4 shows the effect of anxious depression on the genetic and environmental factors influencing migraine. The heritability of migraine was lower at a higher level of anxious depression. In other words, migraine is most heritable in the absence of anxious depression.
Figure 7.3
Profile plot for the best fitting latent class model, showing the symptom prevalence in each of the empirically estimated classes. The migraine symptoms are on the x-axis, the y-axis shows the probability that a symptom is present given class membership.

The cross-twin cross-trait correlations were also higher in MZ than DZ twins, suggesting the correlation between migraine and anxious depression is at least partly explained by genetic influences. Most of the covariance between the two traits was indeed explained by shared genetic factors (54%), while non-shared environmental was responsible for the remaining covariance (46%). The genetic correlation ($r_G$) between anxious depression and migraine was estimated at .30 (95% CI = .18 - .43) while the non-shared environmental correlation ($r_E$) was .26 (95% CI = .15 - .37). Both correlations were significant: dropping a $A^2$ and $e^2$ from the model both resulted in a significant deterioration in model fit ($\Delta \chi^2 (1) = 17.834, p < .001$ for $A^2$, $\Delta \chi^2 (1) = 15.535, p < .001$ for $e^2$).

Figure 7.4
The heritability of migraine at different values of anxious depression. The proportion of variance in migraine explained by additive genetic factors ($A$) and non-shared environmental factors ($E$) across a range of depression scores, based on the estimates obtained from the moderator model. The higher the depression score, the lower the relative contribution of genetic factors to the individual differences in migraine susceptibility. Low = anxious depression score 2 SD below the mean, high = anxious depression score 2 SD above the mean.

The next step was to test the significance of the moderation effect of anxious depression on the heritability of migraine, by dropping the moderator betas from the model and assessing the resulting deterioration in model fit. The power to test the significance of these parameters individually was low (as reflected by confidence intervals that included zero; Table 7.3). However, dropping all four $\beta$ parameters from the model at once resulted in a significant deterioration of the model fit [$\Delta \chi^2 (4) = 12.478, p = .014$], indicating that, overall, the moderator variable is of importance in explaining the observed data. Figure 7.4 shows the effect of anxious depression on the genetic and environmental factors influencing migraine. The heritability of migraine was lower at a higher level of anxious depression. In other words, migraine is most heritable in the absence of anxious depression.
**Table 7.3**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Point Estimate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>a_{21}</td>
<td>0.21</td>
<td>(0.11 - 0.30)</td>
</tr>
<tr>
<td>a_{22}</td>
<td>0.64</td>
<td>(0.56 - 0.71)</td>
</tr>
<tr>
<td>e_{21}</td>
<td>0.19</td>
<td>(0.10 - 0.29)</td>
</tr>
<tr>
<td>e_{22}</td>
<td>0.71</td>
<td>(0.64 - 0.78)</td>
</tr>
<tr>
<td>(\beta_{GC})</td>
<td>0.07</td>
<td>(-0.03 - 0.16)</td>
</tr>
<tr>
<td>(\beta_{EU})</td>
<td>0.00</td>
<td>(-0.13 - 0.12)</td>
</tr>
<tr>
<td>(\beta_{AC})</td>
<td>0.04</td>
<td>(-0.05 - 0.13)</td>
</tr>
<tr>
<td>(\beta_{AU})</td>
<td>-0.07</td>
<td>(-0.19 - 0.06)</td>
</tr>
</tbody>
</table>

**Figure 7.5**

Observed pattern of odds ratios (OR) in general population and discordant DZ and MZ twin pairs, for both possible directions of causality between migraine and anxious depression (AD). The error bars represent the 95% confidence intervals around the ORs. In both situations, all ORs are significantly larger than 1, and have roughly the same size for each group. This is most consistent with the causal hypothesis and excludes an entirely non-causal hypothesis, because in that case the OR for MZ twins would not be significantly larger than one (see Figure 7.2).
Finally, Figure 7.5 shows the results of the co-twin control analysis. The OR is roughly the same for MZ, DZ and general population, under both hypotheses (migraine causes anxious depression and anxious depression causes migraine). The 95% confidence intervals indicate that both in MZ and DZ discordant twin pairs the ORs were significantly larger than 1. These results are most consistent with a bidirectional causal relationship between migraine and anxious depression.

**DISCUSSION**

The results of this study are interesting in several aspects. First, they confirm the presence of a genetic correlation between migraine and anxious depression. This is consistent with the findings of two other recent studies on this topic (Schur et al., 2009; Stam et al., 2010).

A second important outcome of this study is that migraine was more heritable when not accompanied by comorbid depression. A possible explanation for this finding would be that some neurological disturbance in the brain, associated with depression, also makes patients more vulnerable to migraine. Thus, depressed individuals without a severe genetic predisposition to migraine might still develop migraine attacks regularly. Clearly, this theory is speculative and needs further investigation; interestingly, however, various studies have shown that depressed patients report several different types of pain (headache, low back pain, abdominal pain, etc.) more frequently than non-depressed individuals, suggesting that depression increases an individual’s vulnerability to pain conditions (Bair et al., 2003). It has been argued that pain should in fact be considered a symptom of depression (Lépine & Briley, 2004). It is unclear whether there is a specific association of depression with migraine (beyond the general increase in pain symptoms associated with depression), because to date, studies of migraine and depression have not accounted for the phenomenon of comorbid pain in depressed individuals.

A third important finding is that migraine and depression are most likely causally related in two directions. In MZ twin pairs discordant for anxious depression, the non-depressed twin did not have an increased risk of migraine, and in MZ twin pairs discordant for migraine, the twin without migraine did not have an increased risk of anxious depression. Similar results were obtained when the analysis was restricted to female subjects only (results not shown). Males were not analyzed separately, due to the relatively low number of male discordant twin pairs.
These findings are consistent with an earlier study by Merikangas et al. (1993), who reported that rates of anxiety/depression in relatives of migraineurs were only elevated in the presence of migraine in the relatives. Interestingly, a similar risk pattern can be observed in a series of prevalence diagrams published by Schur and colleagues (2009), which showed that the co-twins of individuals with ‘pure’ depression (i.e. depression but not migraine) were not at increased risk of ‘pure’ migraine, and vice versa. Further support for causality comes from a model proposed by de Moor et al. (2008), who argued that if a relationship is causal, all factors influencing the first trait should also affect the second trait. This was indeed the case in our study: genetic and non-shared environmental factors each explained roughly half of the variance in both traits, and genetic and non-shared environmental factors each also explained approximately half of the covariance between migraine and anxious depression.

At present we can only speculate what kind of mechanism might explain a causal relationship between migraine and anxious depression. Possible explanations at the psychological level are that frequent severe migraines might cause depressive or anxious symptoms, or that depressed or anxious patients might over-report pain as a result of their mood disorder. Alternatively, there might be a syndromic association between migraine and anxious depression, as previously suggested by Merikangas et al. (1993). This would indeed be consistent with the theory discussed above, that migraine might be part of the spectrum of symptoms associated with depression. If, in a subgroup of patients, comorbid migraine and depression were aspects of the same disorder, this would provide a good explanation for the pattern of risks we observed in the discordant twin pairs.

LIMITATIONS

One potential limitation of this study is the relatively limited power to detect the moderation of migraine heritability by depression. The effects of the moderator were small and only significant when dropped all at once. This indicates an overall moderation effect, but a larger sample is needed to determine whether genetic variance decreases, or whether non-shared environmental variance becomes larger in depressed individuals.

A second potential limitation is the fact that this study used broad definitions of migraine and anxious depression, based on self-report. While this limits comparisons to clinical populations, this strategy has some advantages. First, it is generally not feasible to obtain clinical diagnoses in the large numbers of subjects required for these analyses. Second, in population-based
These findings are consistent with an earlier study by Merikangas et al. (1993), who reported that rates of anxiety/depression in relatives of migraineurs were only elevated in the presence of migraine in the relatives. Interestingly, a similar risk pattern can be observed in a series of prevalence diagrams published by Schur and colleagues (2009), which showed that the co-twins of individuals with 'pure' depression (i.e. depression but not migraine) were not at increased risk of 'pure' migraine, and vice versa. Further support for causality comes from a model proposed by de Moor et al. (2008), who argued that if a relationship is causal, all factors influencing the first trait should also affect the second trait. This was indeed the case in our study: genetic and non-shared environmental factors each explained roughly half of the variance in both traits, and genetic and non-shared environmental factors each also explained approximately half of the covariance between migraine and anxious depression.

At present we can only speculate what kind of mechanism might explain a causal relationship between migraine and anxious depression. Possible explanations at the psychological level are that frequent severe migraines might cause depressive or anxious symptoms, or that depressed or anxious patients might over-report pain as a result of their mood disorder. Alternatively, there might be a syndromic association between migraine and anxious depression, as previously suggested by Merikangas et al. (1993). This would indeed be consistent with the theory discussed above, that migraine might be part of the spectrum of symptoms associated with depression. If, in a subgroup of patients, comorbid migraine and depression were aspects of the same disorder, this would provide a good explanation for the pattern of risks we observed in the discordant twin pairs.

LIMITATIONS

One potential limitation of this study is the relatively limited power to detect the moderation of migraine heritability by depression. The effects of the moderator were small and only significant when dropped all at once. This indicates an overall moderation effect, but a larger sample is needed to determine whether genetic variance decreases, or whether non-shared environmental variance becomes larger in depressed individuals.

A second potential limitation is the fact that this study used broad definitions of migraine and anxious depression, based on self-report. While this limits comparisons to clinical populations, this strategy has some advantages. First, it is generally not feasible to obtain clinical diagnoses in the large numbers of subjects required for these analyses. Second, in population-based genetic studies there are clear advantages to using broad, questionnaire-based measures, rather than strict clinical diagnoses only.

CONCLUSIONS AND IMPLICATIONS

Our finding that migraine is less heritable in severely depressed individuals has important implications for research, because it suggests that it may be important to treat migraine with and without comorbid anxiety or depression as separate phenotypes in genetic studies. This is especially worth taking into account when individuals are selected for expensive genotyping efforts. A similar conclusion follows from our findings with respect to causality. If migraine and anxious depression are causally related, ‘pure’ migraine and migraine associated with anxious depression may not have the same etiology, which could cause considerable genetic heterogeneity.

Comorbidity with migraine has been reported for a wide range of psychiatric (Merikangas et al., 1990) and non-psychiatric conditions (Merikangas et al., 1997; Nyholt et al., 2009; Ottman & Lipton, 1994). Whether our findings extend to other traits beside anxious depression requires further investigation.

Finally, it is worth emphasizing the importance of further research into the nature of migraine in depressed patients. A better recognition and understanding of this phenomenon, resulting in more effective treatment and pain relief, could improve the quality of life of many individuals.
Chapter 7

References


