



# Causes of Comorbidity: Pleiotropy or Causality? Shared Genetic and Environmental Influences on Migraine and Neuroticism

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Comorbidity — the clustered occurrence of two traits or disorders — may be studied in genetically informative designs such as the classical twin study, to test whether genetic and/or environmental factors underlying the two disorders are correlated. When a genetic correlation is found, this can be explained by several mechanisms, including pleiotropy (the same genes influencing multiple traits), and causality (one trait causing the other). With a cotwin control design, it can be investigated which scenario is most plausible. In this design, monozygotic twin pairs discordant for the first trait (i.e., one twin is affected, the other is not) are compared in terms of their risk for the second trait: under a causal model, only the twins affected for the first trait will be at increased risk for the second trait. Under genetic pleiotropy, this risk will be increased in both twins because they share the same risk genes. We first discuss the cotwin control design and then illustrate its application with data on migraine and neuroticism that were collected in 5,200 Dutch twins, including 1,648 complete twin pairs (981 monozygotic and 667 dizygotic pairs). There was a significant association between migraine and neuroticism, which could be attributed to genetic and environmental correlations ( $r_G = .27$  and  $r_E = .19$ ). In monozygotic and dizygotic twin pairs discordant for neuroticism, the risk of migraine was significantly higher in the twins with a high neuroticism score. This pattern of results is consistent with a causal relationship, suggesting that neuroticism increases the risk of migraine.

■ **Keywords:** Comorbidity, migraine, neuroticism, causality, pleiotropy

Comorbidity — the clustered occurrence of two traits or disorders — can be investigated in genetically informative designs such as the classical twin study, in which the resemblance for one or multiple traits in monozygotic (MZ) and dizygotic (DZ) twin pairs is compared. When two traits are studied simultaneously, in a so-called bivariate genetic model, it can be tested whether the association between the two traits is due to the same genetic and/or environmental factors influencing both traits. If the same set of genes influences both traits, this is reflected in a genetic correlation; if the same set of environmental factors affects the two traits, an environmental correlation will be observed.

One explanation for a genetic correlation is genetic pleiotropy: this is the case when the same genes affect multiple traits or disorders. The finding of a genetic correlation between two disorders is often translated into the conclusion that the disorders must be correlated because

they happen to share certain biological pathways. However, an important alternative explanation is that the two traits are causally related. As illustrated in Figure 1, causality is consistent with a genetic correlation, because if Trait A causes Trait B, all influences on Trait A, including genetic ones, will also affect Trait B, through the causal chain (de Moor, Boomsma, Stubbe, Willemsen, & de Geus, 2008). Importantly, the absence of a genetic correlation between two heritable traits excludes the possibility of a causal relationship. In other words, if the relationship is

RECEIVED 01 February, 2012; ACCEPTED 02 February, 2012.

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causal, and if the traits of interest are influenced by both genetic and environmental factors, there has to be both a genetic and an environmental correlation between them.

In the present paper, we show how the hypotheses of pleiotropy and causality can be distinguished based on analysis of discordant MZ and DZ twin pairs. This method is illustrated with data on migraine and neuroticism, collected in Dutch adult twins. There is a well-documented association between migraine and depression (e.g., Breslau et al., 2000; Merikangas, Risch, Merikangas, Weissman, & Kidd, 1988). Given the strong association between depression and neuroticism (e.g., Bienvenu et al., 2001), it is not surprising that neuroticism and migraine are also associated, although this relationship is not as well-studied. In the present study, we investigate whether migraine and neuroticism are influenced by the same genetic and environmental factors, as has been found previously for migraine and depression.

### The Cotwin Control Design

Pleiotropy and causality can be distinguished with a design based on discordant twin pairs, referred to as the cotwin control design (Cederlof, Friberg, & Lundman, 1977; Kendler et al., 1993). In this design, MZ and DZ twin pairs discordant for Trait A are compared in terms of their risk of Trait B. The same is done in a sample of unrelated individuals.

When two traits are causally related, it is expected that in the general population individuals affected with Trait A will be at increased risk of Trait B, compared to the risk of unaffected individuals. This increased risk is reflected in an odds ratio (OR) greater than 1 for Trait B, compared between individuals affected and unaffected for Trait A. The same will be observed in discordant MZ and DZ twin pairs: the twins affected with Trait A will be at increased risk of Trait B, compared to their unaffected cotwins (Figure 2A).

If genetic pleiotropy explains the association, the expectations for the general population are the same as described above ( $OR > 1$ ). However, in MZ twin pairs dis-

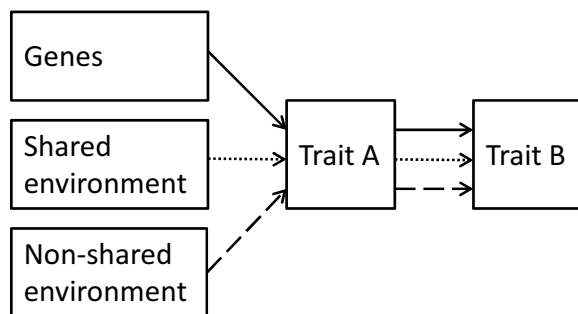
cordant for Trait A, we expect to observe that both twins have a similarly increased risk of Trait B ( $OR = 1$ ). This is because both twins have inherited the same risk genes that predispose to the two disorders, even though one of them has not yet developed, or may never develop, Trait A. The OR for discordant DZ twins is expected to be intermediate between the OR for the general population and the OR for MZ twins: because DZ twins share, on average, 50% of their segregating genes, they will resemble each other more than unrelated individuals, but less than MZ twins, who are genetically identical (Figure 2B).

These expectations are based on the assumption that the association is explained entirely by genetic factors, but environmental factors may also play a role. When two traits are both influenced by certain environmental factors that are shared between both members of a twin pair, MZ and DZ twins will have a similar OR, which is significantly lower than the OR in the general population (Figure 2C). In the present study, this is unlikely, because there is no evidence that either migraine or neuroticism is influenced by shared environmental factors (Jang, Livesley, & Vernon, 1996; Ligthart, Boomsma, Martin, Stubbe, & Nyholt, 2006; Mulder et al., 2003). Finally, if environmental factors not shared by twins explain the association between the two traits, only the twin exposed to these factors will be at increased risk of both traits, which results in a pattern that resembles the causal model (Figure 2A). Combinations of these scenarios are, of course, possible and will result in mixtures of the associated risk patterns.

### Migraine and Neuroticism

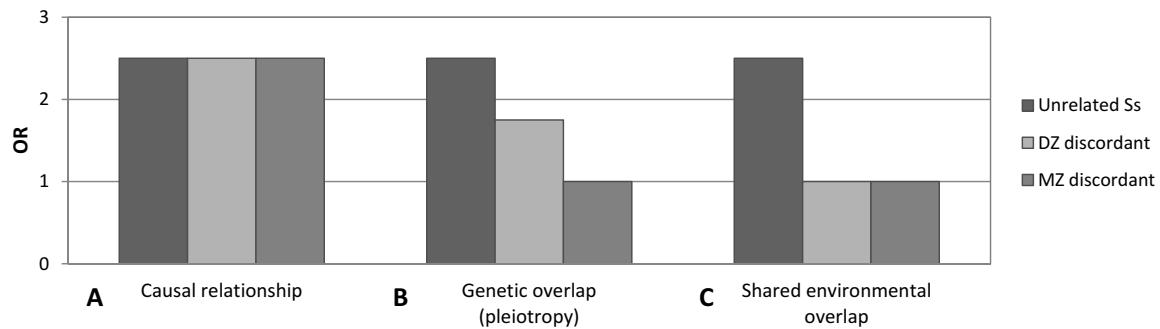
Migraine is a neurovascular disorder, characterized by recurrent attacks of moderate to severe headache, often unilateral, aggravated by physical activity, and typically accompanied by nausea or vomiting, photophobia and phonophobia (Headache Classification Committee of the International Headache Society, 2004). Neuroticism (sometimes also referred to as emotional instability) is a personality trait that can be described as the tendency to experience negative, distressing emotions (e.g., Costa & McCrae, 1987). It is strongly associated with depression and anxiety (Bienvenu et al., 2001).

There is a well-established comorbidity of migraine with depression, anxiety, and neuroticism (Breslau & Andreski, 1995; Breslau, Merikangas & Bowden, 1994; Breslau et al., 2000; Merikangas, Angst & Isler, 1990). In an earlier paper, we showed that migraine and anxious depression are partly influenced by the same genetic and nonshared environmental factors (Ligthart et al., 2010). It is often hypothesized that this comorbidity is due to genetic pleiotropy. Anxiety, depression, and migraine may be partly affected by the same biological pathways, for instance, the serotonergic and dopaminergic systems (Breslau, Davis, & Andreski, 1991; Frediani & Villani, 2007). Disturbances in these systems might therefore increase an individual's risk of any of these disorders.



**FIGURE 1**

Causality implies genetic and environmental correlations: if Trait A causes Trait B, genes and environmental factors influencing Trait A also affect Trait B.

**FIGURE 2**

Expected odds ratios under causality, genetic overlap (pleiotropy), and shared environmental overlap.

Note: Ss = subjects; DZ = dizygotic; MZ = monozygotic.

However, based on analysis of discordant twin pairs according to the cotwin control method, there was no evidence for pleiotropy (Ligthart, Nyholt, Penninx, & Boomsma, 2010).

In the present study, we investigate the comorbidity of migraine and neuroticism. Neuroticism is strongly associated with anxiety and depression. However, severe forms of anxiety and depression are classified as psychiatric disorders (American Psychiatric Association, 2001), which are typically episodic (although recurrence is common). Neuroticism, on the other hand, is more stable across the lifespan (e.g., Rantanen, Metsäpelto, Feldt, Pulkkinen, & Kokko, 2007; Steunenbergh, Twisk, Beekman, Deeg, & Kerkhof, 2005), because it is a personality trait. Therefore, the mechanism that links migraine and neuroticism may differ from the mechanism that causes the association between migraine and anxious depression.

We analyze data from the Netherlands Twin Registry to investigate the strength of the association between migraine and neuroticism, and to determine whether there are genetic and environmental factors that influence both traits. The cotwin control design is applied to test whether the association between migraine and neuroticism is more likely explained by a causal mechanism or by genetic pleiotropy. The results are discussed in the context of previous findings for migraine and anxious depression.

## Methods

### Subjects

All participants were volunteer members of the Netherlands Twin Registry (NTR), established at the department of Biological Psychology at VU University, Amsterdam (Boomsma et al., 2006). The NTR participants are twins and parents, and siblings, children, and spouses of twins, who take part in an ongoing longitudinal study on health, lifestyle, and personality. The analyses in this paper are based on data from a survey held in 2004 (Distel et al., 2007), which included questions on both migraine and neuroticism. The subjects were twins aged 18 years or

older (age range 18–86 years). Migraine diagnoses were available for 4,776 twins (1,416 [29.6%] male, 3,360 [70.4%] female, mean age 35.7 years,  $SD = 11.4$ ). Neuroticism scores were available for 5,211 twins (1,563 [30.0%] male, 3,648 [70.0%] female, mean age 36.0 years,  $SD = 12.48$ ). For 4,711 individuals (1,401 [29.7%] male, 3,310 [70.3%] female, mean age 35.6 years,  $SD = 11.3$ ), both migraine and neuroticism data were available.

### Measures

**Neuroticism.** Neuroticism was measured with the neuroticism subscale of the NEO Five Factor Inventory [NEO-FFI], a short version of the revised NEO Personality Inventory [NEO-PI-R] (Costa & McCrae, 1992). The neuroticism subscale consists of 12 items that are rated on a 5-point scale and sum to a scale score between 12 and 60.

**Migraine.** Migraine status was determined by a set of headache questions based on the ICHD-II diagnostic criteria for migraine (Headache Classification Committee of the International Headache Society, 2004). Participants who were positive for the screening question (Do you ever experience headache attacks, for instance migraine?) subsequently answered a set of more detailed questions about migraine symptomatology. The following criteria were covered by the questionnaire: at least five migraine episodes, duration 4–72 hours, pulsating quality, moderate-to-severe pain intensity, aggravation by physical activity, nausea or vomiting, photophobia and phonophobia, and visual aura.

### Statistical Analyses

**Latent Class Analysis.** Migraine diagnoses were made based on Latent Class Analysis (LCA) of the headache symptom data. LCA can be used to classify groups of individuals based on the pattern of symptoms they report (Lazarsfeld & Henry, 1968; McCutcheon, 1987). The empirical groupings resulting from this analysis, which primarily reflect differences in the severity of the migrainous headache, were used to classify participants as *affected* or *unaffected* for ‘migrainous headache’. The application of

LCA to migraine data has been described extensively in previous studies (Ligthart et al., 2006; Nyholt et al., 2004). LCA was performed with the software package Latent GOLD 4 (Statistical Innovations, Inc.). The number of classes was determined based on the Bayes Information Criterion (BIC; Schwarz, 1978), with a smaller BIC indicating a better model fit. The analysis was performed on the largest available migraine dataset, based on data from all participants of two surveys that included the same set of headache questions. The surveys were conducted in 2002 and 2004 (Boomsma et al., 2006; Distel et al., 2007). For individuals who participated in both surveys, the most recent report (2004) was included.

The best-fitting model (BIC = 51,428.19); had four classes, which represented different degrees of migraine severity. Class 0 included the individuals who screened negative and were therefore assumed not to have any migraine symptoms. Class 1 included individuals with mild 'nonmigrainous' headache. Class 2 can be described as individuals having a mild form of migraine, and Class 3 included the individuals with moderate-to-severe migraine. Individuals in classes 0 and 1 were treated as unaffected, whereas individuals in classes 2 and 3 were treated as affected for migraine.

**Structural Equation Modeling.** Genetic modeling was performed using the structural equation modeling package Mx (Neale, Boker, Xie, & Maes, 2003). Because Mx does not allow the joint analysis of a categorical variable (migraine) and a continuous variable (neuroticism), the neuroticism variable was recoded into quartiles and a liability threshold model was used in all analyses. First, univariate saturated models were tested for both variables, to test whether twin correlations and thresholds could be equated across zygosity and sex. Next, the relative contributions of genetic and environmental factors to the variance in migraine and neuroticism were estimated. Finally, neuroticism and migraine were analyzed in a bivariate model in which the genetic and environmental correlations between the traits were estimated. These analyses were based on all twin data. Twins with unknown zygosity ( $N = 76$ ) were excluded, leaving 5,200 individuals in the analysis (1,560 (30%) males, 3,640 (70%) females, mean age 36.1 years,  $SD = 12.5$ ). There were 1,648 complete twin pairs (981 MZ, 667 DZ) with migraine data, 1,809 (1,089 MZ, 720 DZ) complete twin pairs with neuroticism data, and 1,606 (964 MZ, 642 DZ) complete pairs with both migraine and neuroticism data.

**The Cotwin Control Design.** To test whether the association between migraine and neuroticism was more likely explained by pleiotropy or by a causal relationship, a cotwin control design was applied, in which the risk of migraine was compared between individuals high and low on neuroticism. This comparison was done in a sample of unrelated subjects, and in MZ and DZ twin pairs discordant for neuroticism. Twin pairs were defined as being discordant if one twin's neuroticism score was in the highest quartile and the other twin's neuroticism score was in one of the lowest three. However, if discordance is based only on a cutoff value, MZ twins classi-

fied as discordant may still resemble each other slightly more than DZ twins, who may, in turn, resemble each other more than randomly selected unrelated individuals. If this is not addressed, the results may falsely suggest a risk pattern consistent with pleiotropy (see Figure 2B), because if twin pairs resemble each other for neuroticism, they may also resemble each other with respect to migraine (due to the comorbidity of the two traits). This will result in a smaller OR compared to the OR of a sample of unrelated individuals. Therefore, to ensure a sufficient degree of discordance in both DZ and MZ twins, a between-twin difference of at least nine points on the NEO-FFI neuroticism scale was required.

A sample of unrelated subjects was obtained by selecting individuals from the remaining twins (i.e., those twins who were not part of a discordant pair). These individuals were classified as high or low on neuroticism, depending on whether their score was in the highest quartile or in the lowest three. To avoid any potential bias due to sex differences in migraine and neuroticism, the sample of unrelated subjects was selected such that the proportion of males and females in this group matched that in the discordant MZ and DZ twin pairs as much as possible. Opposite-sex twin pairs and individuals with missing migraine data were excluded from the analyses.

With these procedures, a total of 148 MZ and 95 DZ twin pairs (190 and 296 individuals, respectively), and 2,319 unrelated individuals (584 high and 1,735 low on neuroticism) were selected for the analysis. The selected samples were very similar in terms of average neuroticism scores in the high and low neuroticism groups, in mean age and in proportion of females (Table 1).

Figure 3 illustrates the expected migraine risk in individuals scoring low and high on neuroticism, under causality and under pleiotropy. In the unrelated individuals, we expect to see the same under both scenarios: a high risk of migraine in individuals with a high neuroticism score, and a low risk of migraine in individuals with a low neuroticism score ( $OR > 1$ ). In MZ twin pairs, the same will be observed under a causal scenario: the twins with high neuroticism scores will have a higher risk of migraine than their cotwins with low neuroticism scores (resulting in an  $OR > 1$  for migraine). However, if pleiotropy explains the association, the MZ cotwins low on neuroticism will also have an increased risk of migraine, because they share the underlying risk genes with the affected twins (resulting in a smaller OR than observed in the unrelated individuals).

## Results

### Bivariate Genetic Models: Estimating Genetic and Environmental Correlations

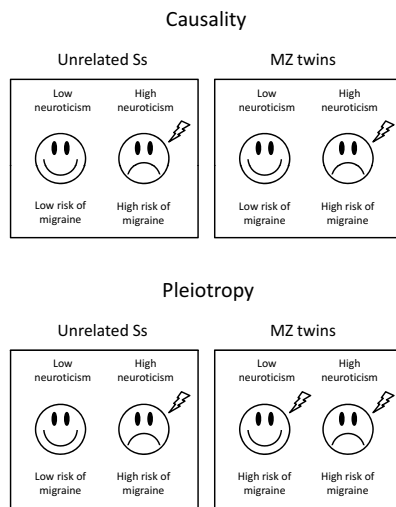
First, all thresholds and twin correlations for migraine and neuroticism were estimated and tested for equality across sex and zygosity groups. As expected, threshold values could be equated across zygosity groups, but not across sex, reflecting higher prevalence in females for both migraine and

**TABLE 1**

Mean Neuroticism Scores in Discordant Unrelated Subjects, and Dizygotic and Monozygotic Discordant Twin Pairs

	Low neuroticism			High neuroticism			Mean age (years)	Female (%)
	N	Mean score neuroticism	SD	N	Mean score neuroticism	SD		
Unrelated Ss	1735	26.61	4.81	584	40.09	4.73	35.2	82.3%
DZ discordant	95	26.00	3.80	95	40.61	4.35	34.7	82.1%
MZ discordant	148	26.65	4.19	148	40.39	4.14	37.2	82.4%

Note: Ss = Subjects, DZ = dizygotic, MZ = monozygotic.

**FIGURE 3**

Expected risk of migraine in individuals with high and low neuroticism in cotwin-control analyses, under a causal scenario and under pleiotropy.

neuroticism. Twin correlations (Table 2) could be equated across sex, suggesting a similar genetic architecture in males and females. Next, the relative contribution of genetic and environmental factors was estimated for both traits. Based on the twin correlations from the saturated models, there was no evidence for shared environmental influences on either trait, but some suggestion of genetic nonadditivity (dominance). Therefore, models including additive genetic (A), nonadditive genetic (D) and environmental (E) factors were tested for both variables. For migraine, there was some evidence for nonadditive genetic variance, although power was insufficient to distinguish the contributions from A and

**TABLE 2**

Twin Correlations for Neuroticism and Migraine as a Function of Sex and Zygosity

	Neuroticism	95% CI	Migraine	95% CI
rMZM	.58	[.47, .67]	.44	[.17, .66]
rDZM	.04	[-.17, .26]	-.02	[-.46, .43]
rMZF	.48	[.42, .55]	.53	[.43, .61]
rDZF	.23	[.11, .35]	.11	[-.08, .29]
rDOS	.34	[.20, .46]	.11	[-.14, .34]

Note: CI = confidence interval, MZM = monozygotic male, DZM = dizygotic male, MZF = monozygotic female, DZF = dizygotic female, DOS = dizygotic opposite sex.

D. For neuroticism, the nonadditive genetic factor was very small and nonsignificant. Therefore, the subsequent bivariate analyses were restricted to an AE model. The model included separate thresholds for males and females, and twin correlations were equated across sex.

Table 3 shows the estimates of heritability based on the bivariate AE model. Both neuroticism and migraine were moderately heritable, with additive genetic factors explaining 51% and 48% of the variance, respectively. The expected comorbidity of migraine and neuroticism was confirmed, with a significant phenotypic correlation of .23 (see Table 4). The covariance between the two traits was primarily explained by genetic factors (59%). The other 41% was explained by nonshared environmental factors (Table 3). The genetic correlation between neuroticism and migraine was estimated at .27, and the environmental correlation was .19 (Table 4). Both correlations were significant: dropping either of them from the model resulted in a significant worsening of the model fit ( $\chi^2(1) = 21.22, p < .001$  for  $rG$  and  $\chi^2(1) = 13.63, p < .001$  for  $rE$ ).

**TABLE 3**

Estimates of Percentages of Variance Explained by Additive Genetic and Environmental Factors for Neuroticism and Migraine, Based on Bivariate AE model

	A	95% CI	E	95% CI
Neuroticism	51%	[46, 56]	49%	[44, 54%]
Migraine	48%	[39, 57]	52%	[43, 61]
Covariance neuroticism-migraine	59%	[36, 80]	41%	[20, 64]

Note: A = additive genetic factors, E = nonshared environmental factors, CI = confidence interval.

**TABLE 4**

Estimates for Phenotypic Correlation Between Neuroticism and Migraine, Genetic Correlation and Nonshared Environmental Correlation

	<i>r</i>	95% CI
<i>r</i> P neuroticism–migraine	.23	[.19, .27]
<i>r</i> G	.27	[0.16, .39]
<i>r</i> E	.19	[.09, .29]

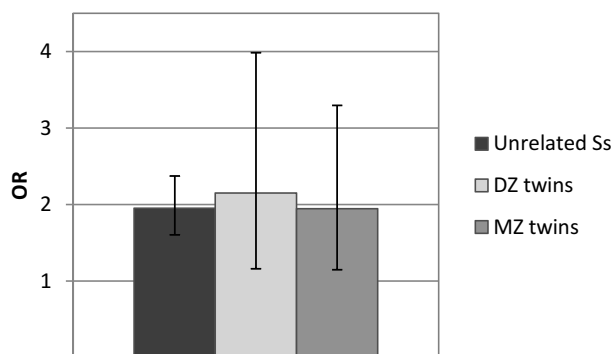
Note: *r*P = phenotypic correlation between neuroticism and migraine, *r*G = genetic correlation, *r*E = nonshared environmental correlation; CI = confidence interval.

### Cotwin Control Method

The results of the cotwin control analysis are presented in Figure 4, which shows the ORs for migraine compared between the high and low neuroticism groups. In both MZ twins and DZ twins, the OR was significantly larger than one, indicating that the twins with a high neuroticism score had a significantly increased risk of migraine compared to the risk of twins with a low neuroticism score. There was no evidence for pleiotropy: the ORs in MZ and DZ twins were very similar to the OR in the unrelated individuals. These data are therefore most consistent with a causal model.

### Discussion

The results of this study show that neuroticism and migraine are partly explained by the same genetic and nonshared environmental factors. Furthermore, the results of the cotwin control analysis favor a causal explanation over an explanation based on pleiotropy. It is important to note that the possibility that pleiotropy plays a role cannot be excluded based on these analyses. Given the wide confidence intervals around the ORs for MZ and DZ twins, there may be subtle differences between the three groups that were not detected due to a lack of power. For instance, it is possible that a combination of pleiotropy and non-

**FIGURE 4**

Observed odds ratios for migraine, compared between individuals high and low on neuroticism, in unrelated individuals and discordant monozygotic and dizygotic twin pairs.

shared environmental factors common to the two traits explain the observed pattern of ORs. However, the fact that the ORs in both types of twins were significantly greater than 1, combined with the absence of a trend towards a smaller OR in MZ twins, indicate that a mechanism based exclusively on pleiotropy is highly unlikely. The possibility of causality is further supported by the observation that both the genetic and the nonshared environmental factors influencing migraine and neuroticism were significantly correlated (see Figure 1), as expected under a causal model (De Moor et al., 2008).

These findings resemble our previous findings for migraine and anxious depression (Ligthart et al., 2010), which is not unexpected given the strong correlations observed between anxiety, depression, and neuroticism. However, we should be cautious in assuming that depression and neuroticism are related to migraine via the same mechanism. Given that neuroticism is a relatively stable aspect of an individual's personality, it seems likely that genetically predisposed individuals will show a certain level of neuroticism throughout their lives; and throughout their lives, and at some point may develop migraine, possibly under the influence of, for example, hormonal changes and environmental stressors. Anxiety and depressive disorders, on the other hand, are generally episodic, and the mechanism that causes their association with migraine may differ. An interesting hypothesis is that pain should, in fact, be viewed as a symptom of depression. This has been proposed based on the observation that not only migraine, but many pain symptoms have a remarkably high prevalence in depressed patients (Bair, Robinson, Katon, & Kroenke, 2003; Lépine & Briley, 2004; Stahl, 2002). If this hypothesis is true, the comorbidity of migraine and depression might not be due to causality: in a subgroup of patients, migraine and depression might in fact be manifestations of the same underlying pathology. This 'syndromic' type of relationship, which has been hypothesized previously by Merikangas, Merikangas, & Angst, 1993), would result in a risk pattern that resembles a causal model: twins with high depression scores will report an increased prevalence of migraine, but their nondepressed cotwins will not (Ligthart et al., 2010), and both genetic and environmental factors will be correlated between migraine and depression. Although the syndromic scenario resembles pleiotropy in the sense that the same genes are involved in two traits, there is an important difference: in the case of a strict syndromic relationship, the two disorders are not distinct; they are the result of the same underlying pathology, and the fact that they are diagnosed as two different disorders is a classification issue. In practice, however, it may be very difficult to distinguish between these two situations. Therefore, results should always be interpreted with caution.

In summary, our results suggest that migraine and neuroticism are partly explained by the same genes, but also by the same environmental factors. Based on the observed

risk patterns in discordant twin pairs, we conclude that a mechanism based exclusively on pleiotropy is unlikely to explain the association, but that a causal mechanism is plausible. These results suggest that having a neurotic personality may increase the risk of developing migraine.

## Acknowledgments

This work was supported by the EMGO<sup>+</sup> Institute of Health and Care Research and the European Research Council (ERC-230374).

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