A Review and Meta-Analysis of the Genetic Epidemiology of Anxiety Disorders

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Objective: The authors conducted meta-analyses of data from family and twin studies of panic disorder, generalized anxiety disorder, phobias, and obsessive-compulsive disorder (OCD) to explore the roles of genetic and environmental factors in their etiology.

Method: MEDLINE searches were performed to identify potential primary studies of these disorders. Data from studies that met inclusion criteria were incorporated into meta-analyses that estimated summary statistics of aggregate familial risk and heritability for each disorder.

Results: For family studies, odds ratios predicting association of illness in first-degree relatives with affection status of the proband (disorder present or absent) were homogeneous across studies for all disorders. The calculated summary odds ratios ranged from 4 to 6, depending on the disorder. Only for panic disorder and generalized anxiety disorder could the authors identify more than one large-scale twin study for meta-analysis. These yielded heritabilities of 0.43 for panic disorder and 0.32 for generalized anxiety disorder. For panic disorder, the remaining variance in liability could be attributed primarily to nonshared environment. For generalized anxiety disorder, this was true for men, but for women, a potentially significant role for common familial environment was also seen.

Conclusions: Panic disorder, generalized anxiety disorder, phobias, and OCD all have significant familial aggregation. For panic disorder, generalized anxiety disorder, and probably phobias, genes largely explain this familial aggregation; the role of family environment in generalized anxiety disorder is uncertain. The role of nonshared environmental experience is significant, underscoring the importance of identifying putative environmental risk factors that predispose individuals to anxiety.

Anxiety disorders are common; lifetime prevalence for the group of disorders is estimated to be as high as 25% (1). They are highly comorbid with each other and with other psychiatric conditions (2), particularly mood disorders (3). Anxiety disorders carry a substantial burden of distress and impairment that is comparable to that of chronic "medical" disorders, such as diabetes (4–8). As such, their etiology has been, and continues to be, a major target of investigation.

A long history of primary studies has sought to determine whether anxiety disorders are familial and to estimate their heritability. A number of excellent, detailed reviews of the genetic epidemiology of anxiety disorders have also appeared (e.g., reference 9). Much knowledge has been amassed in this area; however, to date, there has been no attempt to summarize the information quantitatively. Therefore, a meta-analytic treatment of the data is timely, particularly as many research groups have begun to search for "anxiety genes."

We have attempted to answer, by means of a meta-analysis of selected epidemiological studies, the following two questions for major anxiety disorders: 1) what is the magnitude of the familial aggregation of anxiety disorders?

2) what is the relative contribution of genetics and environment to their etiology?

We applied this method to the following anxiety disorders: panic disorder, generalized anxiety disorder, phobias, and obsessive-compulsive disorder (OCD). We were limited to family and twin studies, as we know of no available adoption studies of anxiety disorders.

Method

The basic goals of meta-analysis, as applied in this study to the genetic epidemiology of anxiety disorders, are 1) to determine the consistency between differing results by testing for heterogeneity across studies and 2) to combine data from multiple primary studies for the purpose of synthesizing the information, thus providing more reliable, precise, and less biased aggregate estimates of familial risk and heritability.

We performed a keyword-driven MEDLINE search to identify all potential primary studies for inclusion in our analyses. In addition, we searched the reference sections of these manuscripts and existing reviews for additional sources. We limited our analyses to studies involving adult subjects that estimated the risk in relatives for the same anxiety disorder as that diagnosed in the proband. Although some of the studies included in this analysis examined the question of familial and genetic sources of the co-

morbidity of anxiety disorders, this important issue is outside of the scope of this study.

We used the following inclusion criteria for the studies: 1) use of operationalized diagnostic criteria, to the exclusion of studies assessing only anxiety symptoms and older studies of anxiety neuroses; 2) systematic ascertainment of probands and relatives; 3) direct interviews with the majority of subjects, to the exclusion of family history studies; 4) diagnostic assessment of relatives performed with investigators blind to proband affection status; and 5) for family studies, inclusion of a comparison group. For some disorders, in which fewer studies were available, we relaxed the criterion for blind ascertainment of diagnosis only to increase our data pool for comparison. Many primary studies identified in the literature were rejected for failing one or more of these criteria. In particular, twin studies meeting the inclusion criteria were limited to, at most, one or two large independent samples per disorder.

Family studies may be thought of as a type of case-control study design, in which the patients are affected probands and the comparison subjects are individuals without a history of the disorder (10). The measure of interest is the binary outcome of a relative diagnosed as affected or unaffected, which allows construction of 2×2 contingency tables of affected versus unaffected relatives of patients and comparison subjects. We reported the odds ratio as the measure of association, owing to its desirable statistical property of invariance under study design (10) and greater familiarity to readers than, e.g., the tetrachoric correlation, which is less sensitive to prevalence (11). In addition, stratifying by study allows one to test for homogeneity across studies by means of the Breslow-Day statistic (12) and to calculate a summary odds ratio by means of the Mantel-Haenszel method (13). The SAS routine proc freq (14) was used to make these calculations. For panic disorder and OCD, for which the most data exist, we also calculated an aggregate risk by combining raw data from each of the studies.

For the twin studies, we were limited by the scarcity of studies that met our inclusion criteria; only two large twin samples that met our criteria and were used to study anxiety disorders exist: the Virginia Twin Registry (15) and the Vietnam Era Twin Registry (16). Data from the Virginia Twin Registry have been reported regarding panic disorder, generalized anxiety disorder, and phobias; data from the Vietnam Era Twin Registry have been published on panic disorder and generalized anxiety disorder. Therefore, we attempted meta-analysis using twin data for panic disorder and generalized anxiety disorder only, but we tabulated twin data for the other disorders where it was available.

We report several measures of twin resemblance, depending on availability. The proband-wise concordance is the proportion of affected co-twins of affected index twins. The tetrachoric correlation is between the members of a twin pair regarding their liability for the disorder; it assumes an underlying continuous trait with a threshold that distinguishes between unaffected and affected twins. Structural equation modeling provides estimates of variance in liability to a disorder that are attributable to additive genetic (a^2), common familial environmental (c^2), and individual-specific environmental (e^2) factors (17).

For panic disorder and generalized anxiety disorder, we performed structural equation modeling by combining data from the two large twin studies using the statistical package Mx (18). To this end, we created 2×2 contingency tables of affection status for twin 1 versus twin 2 from the reported sample parameters for each study. The output of the modeling provided the fit of the model and the component estimates of variance. The fit of submodels created by placing limiting assumptions on the model (such as testing the significance of one of the variance components) was then compared to that of the full (saturated) model. Data from the Vietnam Era Twin Registry come from same-sex

male twin pairs, whereas data from the Virginia Twin Registry come from same-sex female twins for panic disorder and male-male, female-female, and opposite-sex twin pairs in the most recent assessment of generalized anxiety disorder. Therefore, the most saturated models allowed for differing proportions of genetic and environmental variance between men and women, whereas the submodels tested the hypothesis that these were the same for the two genders. In setting up the model, significant differences in prevalence in the various groups required that different thresholds be assigned.

Finally, for panic disorder and generalized anxiety disorder, we attempted to perform an overall structural equation modeling of the combined twin and family data. In comparison to the population-based twin data, data from all of the family studies were from clinically ascertained probands. Therefore, some restrictive assumptions had to be made in order to combine them. Owing to differing prevalence estimates among the family studies that were obtained by use of unequal comparison groups, a threshold for each family study was not calculated from the sample characteristics as it was for the twin data, but, rather, it was assigned from a base prevalence rate obtained from National Comorbidity Survey data (1). In addition, because the family study data were not reported separately by gender or type of relative, we had to make the rather broad assumption that all of the first-degree relatives in these studies could be modeled as if they had the same genetic and environmental correlations as did their siblings (or dizygotic twins). We tested the validity of this assumption by including a special twin environmental parameter that differentiated between dizygotic resemblance in twin pairs and all first-degree relatives in the family studies. We also had to test the hypothesis that model parameters from clinical and community samples could be equated to obtain aggregate estimates. Since all of the family studies used clinical study groups and the larger twin studies were community-based, it was not possible to test these last two assumptions separately. For several studies, partially or wholly overlapping samples were studied in more than one report. In most cases, we chose the studies that contained the largest sample sizes or the most recent results.

Results

Panic Disorder

Five family studies of panic disorder, all from clinical populations, met our criteria for inclusion (Table 1). Studies excluded from our analysis are cited in the References (29–32). (For detailed reviews, refer to references 33–36). All five studies support the familial aggregation of panic disorder. Except for the study by Mendlewicz et al. (20), all of the odds ratios are similar; in no instance do they significantly differ from each other. The results of our meta-analysis show that there is a significant association between panic disorder in the probands and panic disorder in the first-degree relatives (Mantel-Haenszel statistic= 47.8, df=1, p<0.0001); the hypothesis that the odds ratios for the five studies were homogeneous could not be rejected (Breslow-Day χ^2=2.69, df=4, p=0.61). The summary odds ratio across the five studies was 5.0 (95% confidence interval [CI]=3.0–8.2), which strongly supports a familial component in liability to panic disorder. The unadjusted aggregate risk based on 1,356 total first-degree relatives of panic disorder probands was 10.0%, compared to 2.1% in 1,187 comparison relatives.

TABLE 1. Family Studies of Panic Disorder That Met Criteria for Possible Inclusion in Meta-Analysis

Study	Year	Diagnosis of Proband	Patients			
			Group Type	Number of Probands	Number of First-Degree Relatives	Morbidity Risk (%)[a]
Noyes et al. (19)[b]	1986	DSM-III panic disorder	Clinical	40	241	17.3
Mendlewicz et al. (20)[c]	1993	DSM-III panic disorder	Clinical	25	122	13.2
Maier et al. (21)	1993	DSM-III-R panic disorder with or without agoraphobia	Clinical	40	174	7.9
Horwath et al. (22)[d]	1995	DSM-III-R panic disorder with or without agoraphobia	Clinical	107	583	11.0
Fyer et al. (23)[e]	1996	DSM-III-R panic disorder with or without agoraphobia	Clinical	79	220	9.5
Mantel-Haenszel summary odds ratio						

[a] Values were uncorrected in the study by Fyer et al., were age corrected by Kaplan-Meier analysis in the study by Horwath et al., and by Strömgren method in the other studies.
[b] Analyzed with combined data from Crowe et al. (24) and Harris et al. (25).
[c] Four diagnostic groups included patients with panic disorder, generalized anxiety disorder, and major depression and non-mentally-ill comparison subjects.

TABLE 2. Twin Studies of Panic Disorder That Met Criteria for Possible Inclusion in Meta-Analysis

Study	Year	Group Type	Diagnostic Criteria
Torgersen (39)[b,c]	1983	Clinical	DSM-III panic disorder with or without agoraphobia
Skre et al. (30)[b]	1993	General population, clinical	DSM-III-R panic disorder
Perna et al. (37)	1997	General population	DSM-IV panic disorder with or without agoraphobia
Kendler et al. (38)[d]	1993	General population	DSM-III-R panic disorder with or without agoraphobia
Scherrer et al. (16)[e]	2000	General population	DSM-III-R panic disorder with or without agoraphobia
Summary of Perna, Kendler, and Scherrer[f]			

[a] Genetic and environmental factors were classified as additive genetic factors (a^2), common familial environmental factors (c^2), and individual-specific environmental factors (e^2).
[b] Not included in meta-analysis.
[c] Patients had symptoms of panic disorder plus agoraphobia with panic attacks.

Three twin studies of panic disorder met our inclusion criteria (Table 2). We also tabulated two other (nonblind) studies but did not include them in the meta-analysis. The first three smaller studies support a role for genetic factors in the etiology of panic disorder. The two larger twin studies, performed on different samples and opposite genders, are consistent with each other in attributing 30%–40% of the variance in liability to additive genetics; the remaining variance in liability comes from individual-specific environments. The twin studies do not support a role for common family environment in the etiology of panic disorder. Combining the three blinded studies by means of structural equation modeling in Mx produced a best-fitting model that included only additive genetics and individual environmental factors, which is consistent with the results of the primary studies. In addition, we could constrain the genetic variance to be equal across the studies without a significant deterioration in model fit ($\Delta\chi^2=3.43$, df=2, p>0.10), which suggests that genes affect panic disorder similarly in men and women. The parameters of the best-fitting model are provided at the bottom of Table 2.

We then tested the broader model, combining the family study data with the twin data. We found that the special twin environmental parameter that differentiated between dizygotic twins and other first-degree relatives could be made equal to zero with no degradation in fit ($\Delta\chi^2=0.003$, df=1, p=0.95), which allowed us to equate parameters across studies. This combined data produced a best-fitting model that required only additive genetics and individual environment to account for liability to panic disorder, with a heritability estimate of 0.48 (95% CI=0.41–0.54).

Generalized Anxiety Disorder

Only one family study of generalized anxiety disorder met all of our inclusion criteria (20). In order to expand our sample, we included one additional study, that of Noyes et al. (40), which met all criteria except blind assessment. As indicated in Table 3, both studies supported the familial aggregation of generalized anxiety disorder, with an odds ratio greater than 1, and together they showed a significant association between generalized anxiety disorder in the probands and in their first-degree relatives (Mantel-Haenszel statistic=19.1, df=1, p<0.0001). A Breslow-Day test supported homogeneity of the odds ratio (Breslow-Day $\chi^2=0.69$, df=4, p=0.61), and we calculated the Mantel-Haenszel summary odds ratio as 6.1 (95% CI=2.5–14.9), which supports familial aggregation of generalized anxiety disorder.

	Comparison Subjects				
Group Type	Number of Probands	Number of First-Degree Relatives	Morbidity Risk (%)[a]	Odds Ratio	95% CI
Not anxious	20	113	4.2	4.8	1.6–13.8
Never mentally ill	25	130	0.9	15.6	2.0–121.0
Unscreened general population	80	309	2.3	3.6	1.3–10.2
Never-mentally-ill general population	45	255	1.8	6.7	2.1–21.7
Never mentally ill	77	231	3.0	3.4	1.4–8.1
				5.0	3.0–8.2

[d] Four diagnostic groups included patients with panic disorder with and without major depression and early-onset major depression and non-mentally-ill comparison subjects. Data from the first two panic disorder groups were combined. Other analyses of this data set were reported by Weissman et al. (26) and Goldstein et al. (27, 28).

[e] Four diagnostic groups included patients with panic disorder, panic disorder with social phobia, and social phobia and non-mentally-ill comparison subjects. Data from the first two panic disorder groups were combined.

			Twin Resemblance for Monozygotic (MZ) and Dizygotic (DZ) Pairs									
			Proband-Wise Concordance (%)		Tetrachoric Correlation		Parameters of Best-Fitting Model[a]					
N	Blind	Sex	MZ	DZ	MZ	DZ	a^2	95% CI	c^2	95% CI	e^2	95% CI
598	No	Male, female	30.8	0.0								
81	No	Male, female	41.7	16.7								
120	Yes	Male, female	73.0	0.0								
2,163	Yes	Female	20.7	14.5	0.36	0.20	0.37		—		0.63	
6,724	Yes	Male	—	—	0.47	0.05	0.43		—		0.57	
							0.43	0.32–0.53	—	—	0.57	0.47–0.68

[d] Subjects from the Virginia Twin Registry. Parameters of best-fitting model are from a computer-generated, broadly defined diagnosis of panic disorder.

[e] Subjects from the Vietnam Era Twin Registry. Bivariate analysis included panic disorder and generalized anxiety disorder. Panic disorder was defined by panic attacks with or without phobia. Parameters of the best-fitting model are from univariate modeling of panic disorder.

[f] Data and Mx script used in this analysis are available at ftp://views.vcu.edu/pub/mx/examples/adreview.

Two large twin studies met our inclusion criteria (16, 41), and we included one smaller controlled nonblinded study (30) in Table 4. The twin studies excluded are listed in the References (43, 44). The excluded study by Roy et al. (44) reported a bivariate analysis of major depression and generalized anxiety disorder in a sample of 1,484 male and female twins originally ascertained for affective illness from a combination of clinical and population sources. Although it met our inclusion criteria, because this study employed a complex ascertainment scheme, we chose not to use this data in our meta-analysis. Similar to what was done with the twin studies regarding panic disorder, we combined the two larger studies of generalized anxiety disorder by means of structural equation modeling. For consistency with the Scherrer et al. study (16), we used the definition of generalized anxiety disorder of 1 months' minimum duration from a report by Hettema et al. (41) without diagnostic hierarchy. The best-fitting model predicted that 31.6% (95% CI=24%–39%) of the variance for liability to generalized anxiety disorder was attributable to additive genetics in both genders and that the same genes predispose men and women to generalized anxiety disorder. The model also estimated a small role for common familial environment in the women only, with the remaining variance due to individual-specific environment. Although not included in the meta-analysis, the study by Roy et al. (44) estimated an additive genetic variance of 14.3% and 49% for their narrow and broad definitions of generalized anxiety disorder, respectively, no role for common environmental factors, and no gender differences. Since we could not equate the model parameters across genders as was possible for panic disorder, we were unable to combine the twin and family data into one model.

Although only a few family and twin studies of generalized anxiety disorder exist that were appropriate for our analyses, they provided convincing evidence for familial aggregation. In addition, the twin studies suggested at least a modest role of genetics in familial aggregation and an uncertain role of common environment. (For a review of genetic studies of generalized anxiety disorder, see Woodman [35].)

Phobias

For the purposes of this meta-analysis, specific phobias, social phobia, generalized social phobia, and agoraphobia were grouped together owing to the scarcity of these studies in each of the individual categories. Four family studies of phobias met our criteria for inclusion in this analysis; they are listed in Table 5. All studies support the familial

TABLE 3. Family Studies of Generalized Anxiety Disorder That Met Criteria for Possible Inclusion in Meta-Analysis

Study	Year	Diagnostic Criteria	Blind	Patients			
				Group Type	Number of Probands	Number of First-Degree Relatives	Morbidity Risk (%)[a]
Noyes et al. (40)	1987	DSM-III	No	Volunteer	20	123	19.5
Mendlewicz et al. (20)[b]	1993	DSM-III	Yes	Clinical	25	102	8.9
Mantel-Haenszel summary odds ratio							

[a] Values were uncorrected in the study by Noyes et al. and age corrected according to the Strömgren method in the study by Mendlewicz et al.

TABLE 4. Twin Studies of Generalized Anxiety Disorder That Met Criteria for Possible Inclusion in Meta-Analysis

Study	Year	Group Type	Diagnostic Criteria	N	Blind	Sex
Skre et al. (30)[b]	1993	General population, clinical	DSM-III-R	81	No	Male, female
Scherrer et al. (16)[c]	2000	General population	DSM-III-R	6,724	Yes	Male
Hettema et al. (41)[d]	2001	General population	DSM-III-R	6,200	Yes	Male
						Female
Summary of Scherrer and Hettema[e]						
Male						
Female						

[a] Genetic and environmental factors were classified as additive genetic factors (a^2), common familial environmental factors (c^2), and individual-specific environmental factors (e^2).

[b] Not included in meta-analysis.

[c] Subjects from the Vietnam Era Twin Registry. Bivariate study included generalized anxiety disorder and panic disorder. Generalized anxiety disorder was defined as 1 month of worry plus six of 18 associated symptoms not associated with an organic factor, without the hierarchical exclusion of major depression. Parameters of the best-fitting model are from univariate modeling of generalized anxiety disorder.

aggregation of phobias. Except for the Stein et al. study (47), all of the odds ratios are similar, and they are statistically consistent with each other. The results of our meta-analysis show that there is a significant association between phobias in probands and in their first-degree relatives (Mantel-Haenszel statistic=52.3, df=1, p<0.0001), and the hypothesis that the odds ratios for the five studies were homogeneous could not be rejected (Breslow-Day χ^2= 4.03, df=4, p=0.40). The summary odds ratio across the studies was 4.1 (95% CI=2.7–6.1), which strongly supports a familial risk for phobic disorders. (The family studies reviewed that did not meet the inclusion criteria are references 32, 50, and 51.)

The only twin studies of phobias that met our inclusion criteria were reported by our group for the Virginia Twin Registry sample, which was described earlier. Included in Table 6 are the results from a report by Carey and Gottesman (52) of a nonblinded assessment of 49 twin pairs from the Maudsley Twin Registry made up of twins hospitalized for obsessional neurosis, obsessional personality disorder, or phobic neurosis. It is not clear whether DSM-III criteria for phobias or OCD were used in the study, and the authors provided concordance rates for various levels of treatment criteria. We chose to include their data for twins who had a treatment episode involving phobias (Table 6), as this appeared to be the definition most consistent with a DSM phobic disorder. (The twin studies we excluded are references 43, 56–60.)

The following discussion focuses on data from the Virginia Twin Registry. Kendler et al. (53) reported best-fitting models for social phobia, agoraphobia, and animal pho-

bias that suggested additive genetics is responsible for twin resemblance in women and that there is no role for common environment. In situational phobias and phobias involving blood, needles, hospitals, or illness, reported in Neale et al. (54), the best-fitting models suggested just the opposite. This may not represent a real difference, however, since there may not have been sufficient power to differentiate between these two sources of variance (61). In fact, in a subsequent analysis that included measurement reliability from two assessments 8 years apart, the models predicted that twin resemblance was due solely to additive genetics for all but animal phobia and that when fears and phobias were combined by using a multiple threshold model, additive genetics alone accounted for twin resemblance in all of the phobic categories (62). We recently obtained similar results in a twin sample of men; the results are displayed in the bottom of Table 6 (55).

Although we know of only one large adult twin sample in which phobia diagnoses were examined, it predicted that additive genetics is largely responsible for the familial aggregation seen in the family studies, which represents roughly 20%–40% of the variance seen, depending on the type of phobia. Its results are supported by a large population-based adolescent twin study of social phobia, major depression, and alcoholism (63), in which additive genetics accounted for 28% of the variance in risk for social phobia, with the remainder due to nonshared environment. (Refer to Carey [64] for a general review of phobias and Fyer [65] for a review of social phobia.)

| | Comparison Subjects | | | | |
Group Type	Number of Probands	Number of First-Degree Relatives	Morbidity Risk (%)[a]	Odds Ratio	95% CI
Not anxious	20	113	3.5	6.6	2.2–19.7
Never mentally ill	25	130	1.9	5.0	1.0–24.3
				6.1	2.5–14.9

[b] Four diagnostic groups included patients with panic disorder, generalized anxiety disorder, and major depression and non-mentally-ill comparison subjects.

| Twin Resemblance for Monozygotic (MZ) and Dizygotic (DZ) Twins | | | | | | | | | |
| Proband-Wise Concordance (%) | | Tetrachoric Correlation | | Parameters of Best-Fitting Model[a] | | | | | |
MZ	DZ	MZ	DZ	a^2	95% CI	c^2	95% CI	e^2	95% CI
60.0	14.3								
—	—	0.39	0.13	0.37		—		0.63	
22.9	19.5	0.24	0.10	0.22		—		0.78	
38.1	40.6	0.42	0.44	0.22		0.25		0.53	
				0.32	0.24–0.39	—	—	0.68	0.61–0.76
				0.32	0.24–0.39	0.17	0.03–0.29	0.51	0.41–0.64

[d] Subjects from the Virginia Twin Registry, in which female-female twin pairs overlap those of Kendler et al. (42). Generalized anxiety disorder was defined as 1 month of worry plus six of 18 associated symptoms, without the hierarchical exclusion of major depression. Model fitting was performed by combining all five gender-zygosity groups.

[e] Data and Mx script used in this analysis are available at ftp://views.vcu.edu/pub/mx/examples/adreview.

OCD

There were four family studies of OCD that met our inclusion criteria, plus one more that we included in Table 7, although its assessment of relatives was not blind to proband status. Separately, the family study data provided mixed support for the familial aggregation of OCD. Taken together, however, there was a significant association between OCD in the probands and OCD in their first-degree relatives (Mantel-Haenszel statistic=25.1, df=1, p<0.0001). In addition, the hypothesis that the odds ratios across the five studies were homogeneous could not be rejected (Breslow-Day χ^2=4.48, df=4, p=0.34), which allowed us to calculate the Mantel-Haenszel summary odds ratio across the five studies, 4.0 (95% CI=2.2–7.1), which lent further support for the familial aggregation of OCD. The unadjusted aggregate risk based on 1,209 total first-degree relatives of the probands with OCD was 8.2%, compared to 2.0% in 746 comparison relatives. The family studies not meeting our inclusion criteria are cited in the References (71–84).

We could not identify any twin studies of OCD that met our inclusion criteria. The study by Carey and Gottesman (52), mentioned in the Phobias section of this report, included twin concordance rates for treatment of obsessive and compulsive symptoms. Other twin studies of obsessive-compulsive symptoms, obsessive-compulsive neurosis, or OCD were found (30, 39, 43, 85–89). Although these studies provided insight into the potential genetic basis of variables that are related to the OCD phenotype, speculations on the common genetic basis between these variables

and OCD are outside of the scope of this article. (For reviews of the genetics of OCD, see references 68, 90–93.)

Discussion

Results

The results of this meta-analysis strongly support the following conclusions:

1. Panic disorder, generalized anxiety disorder, phobias, and OCD aggregate in families; the strongest evidence exists for panic disorder, for which the most data exist. The summary odds ratios are similar across the disorders, ranging from about 4 to 6.

2. The major source of familial risk is genetic. This is supported by two large-scale twin studies of panic disorder and generalized anxiety disorder and one of phobias. Since we know of no adoption studies on anxiety disorders, twin studies are the only available means of differentiating potential genetic versus common familial environmental etiologies for their familial aggregation. The models used to proportion the variance in liability into either genetic or familial environmental sources are based on the assumption that greater intrapair resemblance of monozygotic versus dizygotic twins for a phenotype is due to their greater genetic resemblance rather than any greater similarity of their environment, also known as the equal-environments assumption. Our studies from the Virginia Twin Registry included examination of various measures of common environment as possible sources of violation of this assumption; we came to consistently negative conclusions. Also, there have been several direct in-

TABLE 5. Family Studies of Simple Phobias, Social Phobia, Generalized Social Phobia, and Agoraphobia That Met Criteria for Possible Inclusion in Meta-Analysis

Study	Year	Diagnosis of Proband	Patients			
			Group Type	Number of Probands	Number of First-Degree Relatives	Morbidity Risk (%)[a]
Noyes et al. (19)[b]	1986	DSM-III agoraphobia	Clinical	40	241	11.6
Fyer et al. (45)[c]	1995	DSM-III-R simple phobias	Clinical	15	49	31.0
		DSM-III-R agoraphobia	Clinical	49	131	10.0
Mannuzza et al. (46)[d]	1995	DSM-III-R generalized social phobia	Clinical	33	96	16.0
Stein et al. (47)[e]	1998	DSM-IV generalized social phobia	Clinical	23	106	26.4
Mantel-Haenszel summary odds ratio						

[a] Values in the study by Noyes et al. were age corrected according to the Strömgren method; values were uncorrected in the other studies.
[b] Analysis with combined data from Crowe et al. (24) and Harris et al. (25).
[c] Patients overlap with those of Fyer et al. (48, 49); results for social phobia subsumed under Mannuzza et al. (46).

TABLE 6. Twin Studies of Simple Phobias, Social Phobia, and Agoraphobia That Met Criteria for Possible Inclusion in Meta-Analysis

Study	Year	Group Type	Diagnostic Criteria	N	Blind	Sex
Carey and Gottesman (52)[b]	1981	Clinical	DSM-III simple phobias	98	No	Male, female
Kendler et al. (53)[c]	1992	General population	DSM-III social phobia	2,163	Yes	Female
			DSM-III agoraphobia	2,163	Yes	Female
			DSM-III simple phobia, animal	2,163	Yes	Female
			DSM-III simple phobia, situational	2,163	Yes	Female
Neale et al. (54)[c]	1994	General population	DSM-III simple phobia, medical[d]	1,858	Yes	Female
Kendler et al. (55)	2001	General population	DSM-III social phobia	2,396	Yes	Male
			DSM-III agoraphobia	2,396	Yes	Male
			DSM-III simple phobia, animal	2,396	Yes	Male
			DSM-III simple phobia, situational	2,396	Yes	Male
			DSM-III simple phobia, medical[d]	2,396	Yes	Male

[a] Genetic and environmental factors were classified as additive genetic factors (a^2), common familial environmental factors (c^2), and individual-specific environmental factors (e^2).
[b] Subjects from the Maudsley Twin Registry. It is unclear whether subjects had DSM-III phobia or phobic neurosis; concordance rates are for treatment involving phobias. Not included in meta-analysis.

TABLE 7. Family Studies of Obsessive-Compulsive Disorder That Met Criteria for Possible Inclusion in Meta-Analysis

Study	Year	Diagnostic Criteria	Blind	Patients			
				Group Type	Number of Probands	Number of First-Degree Relatives	Morbidity Risk (%)[a]
McKeon and Murray (66)	1987	ICD-8, Research Diagnostic Criteria	No	Clinical	50	149	0.7
Black et al. (67)	1992	DSM-III	Yes	Clinical	32	120	2.6
Fyer et al. (as referenced in Rasmussen [68])[b]	1993	DSM-III	Yes	Clinical	50	148	7.0
Pauls et al. (69)	1995	DSM-III-R	Yes	Clinical	100	466	10.3
Nestadt et al. (70)	2000	DSM-IV	Yes	Clinical	80	326	11.7
Mantel-Haenszel summary odds ratio							

[a] Values were uncorrected in the studies by McKeon and Murray, Fyer et al., and Nestadt et al.; values were age corrected according to the Strömgren method in the study by Black et al. and by survival analysis in the study by Pauls et al.

vestigations of the equal-environments assumption in twin studies supportive of its validity (94–96).

3. Estimated heritabilities across the disorders are in the modest range, 30%–40%, significantly lower than for disorders such as schizophrenia and bipolar disorder. This leaves the largest proportion of the variance in liability to be mostly explained by individual environmental factors. This value, however, most likely represents an underestimation of true heritability. This is owing to the fact that measurement error (including diagnostic reliability and stability) and gene-environment interactions not accounted for in the models lead to inflation of estimates of

the impact of specific environment. For example, our group recently performed an analysis of phobias that took into account measurement error by including data from two assessments of the same sample 8 years apart (62). The resulting estimated heritabilities across the phobias were in the 50%–60% range, compared to the point estimates of 30%–40% displayed in Table 6.

We limited our analysis to studies involving anxiety *disorders*. The relationship between anxiety symptoms seen in unselected individuals compared to those affected with an anxiety disorder is unclear. If symptoms and disorders exist on a single quantitative continuum based on

	Comparison Subjects				
Group Type	Number of Probands	Number of First-Degree Relatives	Morbidity Risk (%)[a]	Odds Ratio	95% CI
Not anxious	20	113	4.2	3.0	1.0–8.9
Never mentally ill	77	231	9.0	4.4	2.1–9.4
Never mentally ill	77	231	3.0	3.5	1.4–9.1
Never mentally ill	77	380	6.0	2.9	1.4–5.7
Never mentally ill	24	74	2.7	12.9	2.9–56.2
				4.1	2.7–6.1

[d] Reanalysis of social phobia patients of Fyer et al. (45) for rates of social phobia in relatives of patients with generalized social phobia and nongeneralized social phobia and comparison probands.

[e] Rates of social phobia subtypes in relatives of patients with generalized social phobia and comparison probands were examined; elevated rates of generalized social phobia subtype only were found.

Twin Resemblance for Monozygotic (MZ) and Dizygotic (DZ) Twins						
Proband-Wise Concordance (%)		Tetrachoric Correlation		Parameters of Best-Fitting Model[a]		
MZ	DZ	MZ	DZ	a^2	c^2	e^2
13.0	8.0					
24.4	15.3	0.31	0.12	0.30	—	0.70
23.2	15.3	0.41	0.15	0.39	—	0.61
25.9	11.0	0.38	0.04	0.32	—	0.68
22.2	23.7	0.27	0.27	—	0.27	0.73
—	—	0.33	0.32	—	0.32	0.68
12.6	9.8	0.21	0.13	0.20	—	0.80
12.2	12.2	0.32	0.25	0.37	—	0.63
15.9	7.7	0.36	0.10	0.35	—	0.65
21.2	6.5	0.31	−0.11	0.25	—	0.75
15.6	4.1	0.31	−0.04	0.28	—	0.72

[c] Overlapping subjects from the Virginia Twin Registry were used in the studies of both Kendler et al. and Neale et al.

[d] Blood, needles, hospitals, or illness.

	Comparison Subjects				
Group Type	Number of Probands	Number of First-Degree Relatives	Morbidity Risk (%)[a]	Odds Ratio	95% CI
Never-mentally-ill surgical patients	50	151	0.7	1.0	0.1–16.3
Never-mentally-ill volunteers	33	129	2.4	1.1	0.2–5.4
Never mentally ill	—	—	2.0	3.9	0.5–31.9
Never-mentally-ill volunteers	33	113	1.9	5.9	1.4–24.8
General population	73	297	2.7	4.8	2.2–10.3
				4.0	2.2–7.1

[b] Preliminary results (personal communication).

number, severity, duration, and the like, then studies of anxiety symptoms may be informative regarding the genetics of anxiety disorders. Twin studies have indeed found genetic contributions to nonspecific anxiety symptoms (97), fears (53, 54, 56, 57, 60, 62, 98–100), symptoms of panic-phobia (101), and obsessions and compulsions (52, 88, 102).

Limitations

There are several potential limitations on the interpretation of these results. First, we may not have included all primary studies, owing either to their unavailability in the literature or to our exclusion criteria. It is unclear what impact this choice of quality versus quantity of information had on our summary statistics, but we predict that correlations between relatives would be diluted by using less rigorous standards, lowering estimates of familial aggregation and heritability. Second, because of the scarcity of twin studies for phobias and OCD, the validity and generalizability of the data for these disorders are limited compared to data for panic disorder and generalized anxiety disorder. Third, the relative contribution of genetic verses family environment is based on twin studies only, as adoption studies were not available and family studies do not

provide these estimates. Finally, as previously discussed, since our genetic information is limited to twin samples, any undetected violations of the equal-environments assumption might lower the heritability estimates from those presented.

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