

The Association of Anxiety Disorders and Obsessive Compulsive Personality Disorder with Anorexia Nervosa: Evidence from a Family Study with Discussion of Nosological and Neurodevelopmental Implications

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ABSTRACT

Background: To investigate the association of anorexia nervosa with anxiety disorders through use of a case-control family study design.

Method: Lifetime prevalence of anxiety disorders and obsessive compulsive personality disorder was determined among 574 first-degree relatives of 152 probands with anorexia nervosa and compared to rates observed among 647 first-degree relatives of 181 never-ill control probands.

Results: Adjusting for comorbidity of the same illness in the proband, relatives of probands with anorexia nervosa, had a significantly higher prevalence of generalized anxiety, obsessive compulsive disorder, separation anxiety disorder, social phobia, panic disorder, and obsessive compulsive personality disorder

compared to relatives of never-ill control probands.

Conclusion: Anorexia nervosa may share familial liability factors in common with various anxiety phenotypes. In suggesting that a transmitted propensity for anxiety is a key aspect of vulnerability in anorexia nervosa, the findings point to research developments in the affective neurosciences, specifically the neurocircuitry of fear and anxiety, as a heuristic framework in which to interpret aspects of premorbid temperamental anxieties and clinical symptoms. © 2007 by Wiley Periodicals, Inc.

Keywords: anxiety disorders; obsessive compulsive personality; family study; fear neurocircuitry

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Introduction

At least four lines of evidence support the idea that the frequent co-occurrence of eating and anxiety disorders within individuals¹ might be explained by genetic, neural, and behavioral mechanisms they share in common. First, the association has face validity inasmuch as fear-laden cognitions, heightened vigilance, and defensive avoidance are central to the phenomenology of eating disorders, in particular, anorexia nervosa (AN). Second, anxiety

disorders among individuals with AN usually begin before signs of dietary preoccupation and weight loss,² and heritable traits linked to anxiety proneness (e.g., neuroticism, harm avoidance, and low novelty seeking)^{3,4} are characteristic of the premorbid state in persons who develop AN.^{5,6} Third, subthreshold features of anxiety often persist long after recovery of normal body weight.⁷ Fourth, several twin studies^{8–11} have produced evidence of a modest genetic correlation between eating disorders and certain anxiety and depressive disorders, suggesting they comprise a spectrum of inherited phenotypes.^{12,13}

The objective of the present study was to inform this hypothesis by comparing the lifetime prevalence of seven anxiety disorders, in addition to obsessive compulsive personality disorder (OCPD), among biological first-degree relatives of probands with AN with the prevalence among relatives of never-ill controls (NICs): generalized anxiety disorder, obsessive compulsive disorder (OCD), social phobia, simple phobia, panic disorder, separation anxiety, and agoraphobia. We included OCPD in

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this analysis on heuristic grounds, because its clinical features closely resemble premorbid traits associated with AN,⁶ it has been shown to have a statistically unique association with OCD compared to other axis I psychiatric disorders,¹⁴ and because recent speculation¹⁵ has argued that similarities between obsessional phenomena and AN, and their strong correlation within individuals, stems from overlapping abnormalities in neuronal circuits that regulate habit patterns and the appraisal of affect relevant stimuli. If transmission of anxiety proneness plays a role in vulnerability to AN, it can be expected that anxiety disorders would aggregate significantly in family members of probands with this illness.

Method

Participants and Diagnostic Procedures

The data described herein were obtained as part of a previously published family study that examined the familial transmission of eating disorders.¹⁶ Readers are referred to this report for a description of procedures used in the recruitment of case and control probands, of interview measures, and of best-estimate diagnostic methods applied to the relatives. There were a total of 504 women probands between 18 and 28 years of age: 152 with pure restricting subtype of AN for a minimum of 5 years before study entry, 171 with bulimia nervosa (BN), and 181 without any lifetime psychiatric illness. This report is based only on the comparison of familial prevalence of anxiety illness among AN and NIC probands. Data regarding familial associations with BN will be the subject of a future report.

All probands with at least one first-degree relative available for direct interview were recruited from consecutive admissions to the eating disorders program of Resnick Neuropsychiatric Hospital at UCLA. NIC probands were persons free of any current or past history of DSM-III-R defined major psychiatric illness (the nomenclature in place at the inception of this study) and were selected randomly from lists of acquaintances generated by ill probands. Acquaintances were deemed eligible for participation as a NIC proband if they were free of lifetime axis I psychiatric illness and if they had at least one adult first-degree relative available for direct interview. Informed consent was obtained from all participating probands and interviewed relatives.

Information for best-estimate lifetime psychiatric diagnoses was sought on all first-degree relatives 12 years and older using face-to-face and telephone interview and family informant data. Only diagnoses made at the

definite or probable level of certainty were rated as positive. All diagnostic information was cleansed of identifying proband and relative information and then blindly evaluated, although interviewers could not be kept blind to proband status. The final sample included 574 relatives of AN probands and 647 relatives of NIC probands.

Statistical Analysis

The unadjusted lifetime prevalence of disorders among relatives of the two groups of probands was compared using Fisher's exact test with two-tailed probability values. Odds ratios (ORs) of illness in relatives of AN versus relatives of NIC probands were estimated using logistic regression with generalized estimating equations to account for within-family correlated observations and adjusted for the relative's gender, age, and relation to the proband (parent vs. sibling), age and age of onset of illness in the AN proband, and interview format (direct vs. phone). A second logistic regression was conducted, including the proband's specific comorbid anxiety disorder in the model to control for possible independence of the familial transmission of certain disorders.

Results

Characteristics of Probands and Relatives

As noted previously,¹⁶ there were no differences between AN and NIC probands, or between the two groups of relatives, in demographic characteristics. A significantly greater proportion of relatives of NIC probands was interviewed by telephone, but there were no statistically significant differences in the prevalence of any disorder obtained from face-to-face compared to telephone interview.

Ninety-four of the 152 AN probands (61.8%) had a lifetime history of at least one anxiety disorder and 55 (36.2%) met criteria for OCPD.

Rates of Disorder in Relatives of Probands

The unadjusted lifetime prevalence of individual anxiety disorders and of OCPD among relatives of AN and NIC probands are shown in **Table 1**. With the exception of agoraphobia, a statistically significant higher prevalence of each disorder was observed among relatives of AN probands. Simple risk ratios were greatest, and nearly equivalent, for obsessive compulsive disorder and generalized anxiety disorder (relative risk = 3.6 and 3.3, respectively), with remaining relative risks ranging from 1.3 for simple phobia to 2.2 for panic disorder. At least one lifetime anxiety disorder was assessed in 223 of the 574 (38.9%) relatives of AN probands

TABLE 1. Lifetime rates of anxiety disorders and obsessive compulsive personality disorder among relatives of probands with anorexia nervosa (AN) and relatives of never-ill control (NIC) probands

Diagnosis in Relative	Relatives of Probands with AN (<i>n</i> = 574)	Relatives of NIC Probands (<i>n</i> = 647)	<i>p</i> Value
Obsessive compulsive disorder	8.2	2.3	.0001
Generalized anxiety disorder	17.1	5.3	.0001
Social phobia	15.9	11.0	.014
Separation anxiety disorder	11.7	7.7	.025
Simple phobia	17.2	12.8	.036
Panic disorder	6.8	3.1	.003
Agoraphobia	4.2	3.9	NS
Any anxiety disorder	38.9	23.0	.0001
Obsessive compulsive personality	20.7 ^a	7.0 ^a	.0001

^aComparison based only on interviewed relatives 17 years and older. For relatives of AN relatives, *n* = 473; for relatives of NIC probands, *n* = 489.

compared to 149 of the 647 (23.0%) relatives of NIC probands (*p* = .0001). For OCPD, a threefold higher prevalence was found among relatives of AN probands compared to relatives of NIC probands, 20.7% vs. 7.0%, respectively, a highly significant difference (*p* = .0001).

Odds Ratios

Table 2 gives ORs for the significant pairwise comparisons shown in **Table 1** in a multivariate regression model that adjusted for potentially confounding proband and relative characteristics. The odds of having any lifetime anxiety disorder was two times greater in relatives of an AN proband compared to relatives of an NIC proband (OR = 2.10, 95% confidence interval (CI) = 1.70–2.80, *p* < .005). It can be seen that the ratios are significant for each disorder, and their magnitude follows the pattern of relative risks just noted.

The results of the second regression model, shown in the right-hand column of **Table 2**, controlled for the simultaneous presence of the same anxiety disorder in the AN proband. Differentially elevated ORs among relatives of AN probands remain for four disorders after the effect of proband comorbidity is removed, including obsessive compulsive disorder, generalized anxiety disorder, separation anxiety, and panic, thus suggesting a common source of familial liability for AN and these disorders; the same was true for OCPD. Concerning the latter, there was no effect on the OR when the diagnosis of obsessive compulsive disorder in both proband and relative was added to the model.

Because we showed previously¹⁶ that relatives of AN probands had elevated lifetime risks for full and partial syndromes of AN and BN, and since anxiety and eating disorders co-occur, it could be argued

TABLE 2. Odds ratios of diagnoses in relatives of AN probands compared with relatives of NIC probands

Diagnosis	Unadjusted OR ^a	Adjusted for Dx in AN Proband OR ^a
Obsessive compulsive disorder	3.8 (2.1–6.9) ^{b****}	2.5 (1.5–4.9)*
Generalized anxiety disorder	3.7 (2.4–5.7) ^{b****}	3.5 (2.4–5.4) ^{b****}
Social phobia	1.5 (1.1–2.2)*	1.5 (1.1–2.90)*
Separation anxiety disorder	1.6 (1.2–2.4)*	1.5 (1.1–2.3)*
Simple phobia	1.5 (1.1–1.90)*	1.2 (0.9–1.8)
Panic disorder	2.2 (1.3–4.0) ^{b***}	2.1 (1.2–3.9) ^{b***}
Obsessive compulsive personality	3.3 (2.2–5.0) ^{b****}	3.1 (2.1–4.9) ^{b****}

Notes: Dx = diagnosis; CI = confidence interval.

^aAdjusted for relative's age, gender, and relation to proband; age and age of onset of illness in AN proband; interview format (direct vs. phone).

^bValues in parentheses indicate 95% CIs.

p* < .05; *p* < .005; ****p* < .002; *****p* < .001.

that the differentially increased familial risk of anxiety in AN probands was a consequence of the cosegregation of eating disorder and anxiety disorder among their relatives. However, including lifetime diagnosis of eating disorder in relatives of AN probands in a third logistic regression model had no effect on any of the ORs.

Discussion

Main Findings

Anxiety is, arguably, the most common diagnostic comorbidity in AN.¹ To our knowledge, this is the largest case-control study to date to explore the role of familial transmission as a potential explanatory mechanism for this association. There are two main findings. First, relatives of probands with AN were shown to have a threefold greater risk of obsessive compulsive disorder, generalized anxiety disorder, and OCPD compared with relatives of NICs, and a more modestly elevated risk of panic disorder, social phobia, separation anxiety, and simple phobia. Second, except for simple phobia, familial aggregation of each disorder remained significant when regression models were adjusted for the same disorder in the proband, and for lifetime presence of eating disorder in the relatives.

Although our study was not designed to investigate familial transmission models of anxiety, the main findings are in agreement with previous research showing common genes underlying multiple anxiety phenotypes,^{17,18} substantial comorbidity among the anxiety disorders,¹⁹ familial-genetic correlations among eating, mood, and anxiety disorders,^{8–11,13} and animal and human data^{20–23} showing similar patterns of dysfunction in neural

systems mediating the acquisition and extinction of fear learning across a range of anxiety phenotypes. As such, the findings lend support to the notion that AN is part of a spectrum of disorders that share in common a transmitted, presumably inherited, propensity for extreme anxiety and fear learning.

Limitations

Our study had the following limitations. First, since AN probands were recruited from a specialty treatment setting and NIC controls were acquaintances agreeing to participate in a study of familial psychiatric illness, the results are possibly skewed by selection factors. A further limitation of the NIC group is that in having screened for psychopathology we may have accentuated the association between AN and anxiety disorders. Second, since we obtained only a single assessment of lifetime psychiatric illness and future onsets of anxiety disorder among the probands may yet occur, measurement error and reliability of the logistic regression models controlling for anxiety comorbidity are unknown. Third, nonblind interviewers may have been biased in their assessments; however, we believe that such biases were minimized by rating all case material blind to proband status and pedigree identity and using best-estimate diagnoses based strictly on operationalized diagnostic criteria. Fourth, because our family study was designed to recruit only diagnostically pure probands with restricting type AN, the present findings may not generalize to probands with binge eating or purging behavior.

Implications for Nosology and Models of Pathophysiology

While the need for independent replication of these findings is understood, we suggest two potential implications. First, the findings might be viewed as supporting an argument for reformulating the nosological status of AN in DSM-V. Relevant to this notion are recently proposed taxonomies of mood/anxiety disorders (e.g., see Watson²⁴) that are hierarchically structured, defined at the highest level by broad, genetic vulnerability factors (e.g., “negative affect/emotional distress”) which branch to more narrowly defined clinical phenotypes, whose distinguishing features express specific genetic, neural, and socioenvironmental mechanisms of symptom formation. Whether or not the present findings argue for incorporating AN in a general taxon of emotional disorders, whether or not it shares genetic, neurobiological, and environmental risk factors in common with so-called fear

disorders,²⁵ or if risk factors for AN are sufficiently unique to justify its placement outside the anxiety–fear spectrum, are questions of theoretical importance with direct implications for DSM-V.

Second, the findings may also aid in the search for candidate genes and neural endophenotypes causally related to fundamental characteristics of AN. An area of research we believe to have particular relevance to our findings is the affective neuroscience perspective on motivated behavior, a literature that has strongly implicated dysfunction in neural circuits mediating anxiety and fear learning in a range of pathological anxiety states. Specifically, in both human and animals studies, a wide range of anxiety phenotypes have been linked to overactivity of the amygdala, a key structure mediating innate fear proneness and the acquisition of learned fear, and of the hippocampus, which mediates the organism’s defensive adaptation to novelty and plays a critical role in emotional memory^{21,26–28}; dysfunction in frontal systems that regulate amygdala activation by threatening stimuli^{29,30}; altered morphometry in brain areas underlying the regulation of anxiety and fear-related behaviors^{29,31–35}; and specific genetic variants that moderate the engagement of these circuits by threat stimuli.³⁶ Accordingly, behavioral manifestations of amygdaloid and hippocampal structures that are hypersensitive, or abnormally modulated—biased attention to novelty and threat, inhibition of appetitive behavior upon confrontation by novel or aversive environments, enhancement of fear learning, and poor retention of fear extinction (see Gray and McNaughton,²¹ and Lang et al.²² for background)—may be a heuristic framework for exploring genetic and neurobiological underpinnings of the anxious premorbid temperament and anxiety-related diagnostic features of AN. While a speculative notion, we suggest the intuitive hypothesis that dysfunction of emotion regulating circuitry is mechanistically associated with these aspects of AN, potentially explaining why pubertal changes in body weight and shape in persons with AN elicit extreme levels of arousal and negatively biased attention, and why defensive tendencies in this population are so pronounced and long-lasting.³⁷

Also germane to this explanatory model, we believe, is an animal and human literature describing persistent adverse effects of early life stress on brain function and structure. For example, multiple lines of evidence (see Ref. 38–40 for detailed summaries) show that the development of emotion regulating circuitry is highly sensitive to environmentally induced plasticity, and that multiple properties of cognition, fear conditioning, and memory

consolidation can be impacted by stressful events. Interestingly, evidence is strong that chronic stress can induce atrophy of hippocampal neurons, whereas this same condition of stress exposure accelerates growth of dendrites and synaptic connections in the amygdala, where the effects persist well after stress has terminated.⁴¹ Notably, this contrasting effect of stress mediated plasticity—hippocampal atrophy (theoretically, impairing the processing of novel stimuli and discrimination of what is safe from a threatening environment) versus remodeling of amygdaloid architecture (theoretically, enhancing both the reaction to threat-related cues and speed of fear learning)—has been proposed recently by Vyas et al.⁴¹ as a cellular mechanism of enhanced fear learning and persistence of aversive memories. The potential relevance to AN might be as follows: Given that persons with behavioral inhibition, aversion to novelty, and neuroticism (traits which, as noted earlier, occur pre-morbidly in AN) are prone to low self-regard and thus experience higher than normal levels of perceived stress, these findings collectively support the intriguing possibility that vulnerability to AN is expressed neurodevelopmentally; specifically, that risk unfolds in a manner that is dynamic and progressive, involving a heritable inclination to extreme anxiety and fear, and then compromise of emerging cognitive and affective processes by corticolimbic circuitry that is, in effect, “locked” in a state of chronic activation by life events that are perceived and experienced by these temperamentally “at risk” children as uncomfortably novel and anxiogenic.

Conclusion

Our findings suggest that vulnerability to AN is associated with heritability of anxiety and fear proneness. A key implication is that the neurocircuitry of anxiety and fear can serve as a useful framework in which to interpret both the expressions of anxiety that occur pre-morbidly in AN, and the rapid escalation of fear, vigilance, and avoidance that is apparently triggered by emergent anxieties conditionally associated with body weight and shape via social learning. We offer the speculation that inherited variations in the circuitry mediating anxiety and fear learning, coupled with plasticity to stress, may explain why pubertal maturation, with its various social and psychological elements and the period around which most onsets of AN cluster, arouses fear of such great magnitude,

is rapidly imbued with inflated emotional salience, elicits affectively elaborated vigilance, and, as if a localized source of unmitigated “danger,” is defensively avoided. The findings also invite speculation on a possible nosological relationship of AN to anxiety states. There are certain to be objections to these notions, and questions for new lines of study remain; importantly, what factors contribute uniquely, or selectively, to weight and shape concerns among those who are anxiety prone?

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