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Evidence of Overlapping Genetic Diathesis of Panic Attacks and Gastrointestinal Disorders in a Sample of Male Twin Pairs

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Abstract

We explored the comorbidity between panic attacks (PA), whose symptoms can include gastrointestinal discomfort, and gastrointestinal disorders (GD). Structural equation modeling was used to analyze data from 1,874 MZ and 1,498 DZ male–male twin pairs from the Vietnam Era Twin Registry. PA and GD were associated (relative risk for GD = 2). The percentage of liability due to genetic factors was estimated to be 37% for PA and 31% for GD. There was significant correlation between the genetic risk factors for PA and GD (estimated r = .55, 95% CI of 34% to 82%) and no evidence of correlation between the environmental causes of PA and GD. Therefore, PA and GD comorbidity can be explained by overlapping genetic factors and not overlapping environmental factors. Although these data cannot identify a biological pathway for such a shared liability, it suggests the presence of GD may be informative for genetic studies of panic.

Keywords

Panic disorder; panic attacks; gastrointestinal disorders; irritable bowel syndrome; peptic ulcer

The fact that anxiety and gastrointestinal function are linked is widely known. The experience of ‘butterflies in the stomach’ as a result of stress is nearly universal. Studies have also shown that anxiety and negative affectivity are linked with increased endorsement of gastrointestinal symptoms (Elklit & Christiansen, 2009; Johnson, 2003; Watson & Pennebaker, 1989). However, the degree to which anxiety and affective disorders are associated with organic — as opposed to ‘functional’ — gastrointestinal disorders (GD), is perhaps under appreciated. That is, while elevated rates of psychological disorder are common in individuals with unexplained gastrointestinal symptoms, higher rates of anxiety and affective disorder are also associated with peptic ulcer (PUD) and Crohn’s disease (CD), both of which are defined by observable organic damage. In one prospective study (Bowen et al., 2000), the authors found that anxiety disorder patients were 1.4 times more likely to develop gastrointestinal disorder — defined as the presence of duodenal ulcer, peptic ulcer, gastritis, and duodenitis— than controls.

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Although somatic symptoms are noted across anxiety and affective disorders, panic disorder (PD) is the anxiety disorder most closely associated with physical distress. PD is a heritable disorder associated with physical (nonpsychiatric) disorders such as mitral valve prolapse, migraine headaches, asthma, and hypertension (see Muller et al., 2005; Zaubler & Katon, 1996 for review of medical comorbidity and Hettema et al., 2001 for a review of heritability). While respiratory symptoms are the most common symptom of panic attacks (PA; Barlow, 2002), they may also include a variety of gastrointestinal symptoms (Barlow, 2002; American Psychiatric Association, 1987, 1994). Panic has also been associated with gastrointestinal disorders. In Harter et al. 2003 (Harter et al., 2003), gastrointestinal problems — defined as the presence of a range of conditions, including Hepatitis, liver disease, ulcer, gallbladder problems, colitis, constipation, chronic enteritis, and indigestion/nausea/nervous stomach — were present at a higher rate in PD or generalized anxiety disorder (GAD) probands than controls, with an estimated odds ratio of 3.14. In both clinical and population samples, panic disorder has been linked to increased rates of irritable bowel syndrome (IBS), Crohn's disease, and peptic ulcer disease (Blewett et al., 1996; Irwin et al., 1996; Kaplan et al., 1996; Katon, 1984; Kumano et al., 2004; Lydiard et al., 1991; Lydiard et al., 1993; R. Noyes et al., 1978; R. Noyes Jr. et al., 1980; Rogers et al. 1994; Tarter et al., 1987; Walker et al., 1995; Walker et al., 1992; Walker et al., 1990; Walker et al., 2008). Although the presence and nature of organic damage in these three disorders differs substantially, they do share some commonalities: all three are associated with negative affectivity, all three are moderately heritable, and they all have a complex etiology with multiple risk factors including smoking and alcohol abuse (Addolorato et al., 2008; Bengtson et al., 2006; Farnam et al., 2008; Farnam et al., 2007; Goodwin et al., 2006; Goodwin & Stein, 2003; Levy et al., 2001; Malaty et al., 2000; Morris-Yates et al., 1998; Raiha et al., 1998; Robertson et al., 1989; Sheffield & Carney, 1976; Talley et al., 1998; Tysk et al., 1988).

There are sound biological reasons to expect comorbidity between psychiatric disorders and GD. The enteric nervous system (ENS) is a complex, semi-autonomous local nervous system that regulates gastrointestinal function (Gershon, 1981). It consists primarily of two layers of neurons within the wall of the digestive tract. The nerves of the ENS are responsible for stimulating the motility (movement) of food through the gut and regulating a variety of functions including secretion of acid and enzymes, blood flow, and inflammation in the gastrointestinal tract (Gershon, 1981). Functioning of the ENS is mediated by a diverse array of neurotransmitters including serotonin, corticotrophin-releasing factor (CRF), urocortin, and cholecystokinin (Gershon, 1981). Overlapping diathesis of panic and GD is quite plausible based on the functional relationships and biological similarity between the central nervous system (CNS) and the ENS. Elements of the ENS regulate specific parts of the immune response and can have pro- and anti-inflammatory (Barbara et al., 2008). Much of research into the ENS and its association with GD has focused on neural disregulation associated with irritable bowel disease (IBD) as a function of inflammation, and the further effects of that disregulation on gastrointestinal function (Barbara et al., 2008; Mawe et al., 2009). Another area of interest has been specific brain structures associated with the interpretation of pain and gastrointestinal distress in individuals with IBS. It has been noted that the limbic system plays a central role in both emotional regulation and the interpretation of signals from the ENS (Jones et al., 2006). This presents another pathway by which psychiatric disease and gastrointestinal perception and function may be linked. Therefore, given the similarities in structure and function, and the interaction between the CNS and ENS, it is quite possible that there are genes whose function might have an impact on both anxiety and gastrointestinal function. For example, it is reasonable to hypothesize that a gene involved in serotonin transport would have implications for IBS (Van Kerkhoven et al., 2007). Alternately a gene that helped regulate CRF as part of the stress response in the

hypothalamic-pituitary-adrenal (HPA) axis of the CNS, might also have an effect on motility (Lydiard, 2001).

In this article, we examine panic attacks, the key feature of panic disorder and the co-occurrence of gastrointestinal disorders in a sample of male–male veteran twin pairs from the Vietnam Era Twin Registry (VETR). While several studies of IBS and IBD suggest that anxiety disorders generally (but not universally) precede GD (Dewsnap et al., 1996; Lydiard et al., 1993; Sykes et al., 2003; Tarter et al., 1987), the temporal relationship is not conclusive evidence that one disorder generally causes the other. We used the Neale-Kendler models of comorbidity (described in Table 1) to rigorously assess evidence of directional effects (e.g., GD causes PA or vice-versa) and other relationships of liability between PA and GD (Neale & Kendler, 1995). We additionally used a co-twin analysis to establish whether or not the presence of PA increased the rate of GD in a co-twin without PA. This would indicate any observed cross-twin cross-trait correlation was the effect of shared underlying susceptibility rather than direct causation (PA causes GD or vice-versa) for two independently heritable traits.

Next, we fit a series of genetic twin models to the data. These models test for evidence of genetic determinants shared between PA and GD. While it has been noted that those suffering from unexplained gastrointestinal distress and IBS should be screened for anxiety disorders in clinical settings (Alpers, 2008; Bray et al., 2006; Choung et al., 2009), establishing a shared genetic vulnerability would argue that their relatives are also at higher risk for anxiety disorders. The presence of a PA-GD link would also be relevant to those performing studies to map genomic variants underlying susceptibility to panic and anxiety. Incorporating GD information may yield novel candidate genes that could be examined for joint panic-GD effects. The incorporation of additional health information in the analysis of PD has already been used in a genetic linkage study to gain additional insight into the genetics of PD. A group at Columbia University has used an expanded panic-syndrome phenotype, which includes panic disorder and panic-associated physical diseases, to obtain increased evidence of the role of a region on Chromosome 13 in panic susceptibility (Hamilton et al., 2003; Talati et al., 2008; Weissman et al., 2000). This region has been implicated in psychological vulnerability for bipolar disorder, schizophrenia, and recurrent major depression (Blouin et al., 1998; Detera-Wadleigh et al., 1999; Lin et al., 1997; McGuffin et al., 2005; Shaw et al., 1998). Establishing that GD shares genetic overlap with panic would suggest that similar analyses should be performed incorporating GD into genetic studies of PD. It would also suggest that plausible risk loci for anxiety and anxiety disorders be considered as possible GD candidate genes.

To our knowledge, this is the first study to jointly consider the co-occurrence of PA and GD in twin pairs. However, the possibility of a genetic link between anxiety and GD has previously been examined in a family study, at least in the case of IBS (Woodman et al., 1998). Woodman et al. compared the rates of psychiatric illness in first-degree relatives of 20 IBS probands and 20 gall-bladder surgery patients and found elevated rates of anxiety disorder in the relatives of IBS patients, indicating that anxiety disorder and IBS share overlapping genetic influences. The rate of PD was higher in relatives of IBS patients versus controls (12% vs. 8%); however, this difference was not significant.

Materials and Methods

The data used was obtained from the VET registry and consisted of male–male twin pairs. Registry twins served during the Vietnam War era, between 1965 and 1975 (Eisen et al., 1987; Goldberg et al., 1987). This sample of individuals has been extensively characterized elsewhere (Goldberg et al., 1987). Twin-pair zygosity was determined using a method

shown to have 95% accuracy (Eisen et al., 1989). The presence of DSM III-R definition panic attacks was assessed using the diagnostic interview schedule (DIS) version III-R as part of the 1992 Harvard Twin Study of Substance Abuse (Tsuang et al., 2001). Of the 8,152 individuals assigned a PA status, 309 (3.8%) were diagnosed as having panic attacks. PD was present in 143 individuals (1.8%). As the number of individuals with PD in our sample is low, we focused on panic attacks for the remainder of the article to retain adequate power. The presence of gastrointestinal disorders (GD) was assessed as part of a 1987 health survey (Henderson et al., 1990). GD is defined here as a positive response to the question, 'Since 1975 or your discharge from active duty (if that was earlier), have you ever had any of the following health problems? … Stomach or digestive disorders such as ulcers, inflammations, etc.' Of the 10,731 valid responses to the GD question, 1,720 (16%) responded yes. A subset of the subjects were subsequently questioned about specific GD as a part of the Vietnam Era Twin Study of Aging (VETSA). Here, due to the reduced sample size and loss of power in this sample to analyze PA and GD in structural equation modeling (SEM), we only use the VETSA data descriptively, to relate GD and PA to specific diagnoses of gastritis, ulcer, IBS, CD, and ulcerative colitis. The relationship between the 5 gastrointestinal disorders examined in VETSA and the presence of GD, as assessed in the survey of health (SOH) for VETSA participants is presented in Table 2. We included data from 11,288 individuals from the VET registry with at least 1 diagnosis for either PA or GD contained in 6,194 twin pairs. Mx-based SEM analysis was performed on the 3,372 VET registry pairs with unambiguous zygosity status (1,874 MZ and 1,498 DZ).

Mx (Neale et al., 2006) was used to fit structural equation models to the twin data. These models assume a threshold over a normally distributed underlying vulnerability for both traits. First, we examined the Neale-Kendler (NK) models of comorbidity (Neale & Kendler, 1995). In small or moderate sample-sized datasets (like the one examined here), these models are most useful for finding models that are not compatible with the observed data rather than for identifying one particular 'correct' model (Rhee et al., 2004). Next, we used Mx to estimate tetrachoric correlations and to fit a series of genetic models to the data. Using this genetically motivated model, along with the assumption that shared environmental influences on the twin pair are equal for MZ and DZ twins, allows us to factor the variance of liability for these two traits into three categories: variance due to additive genetic factors (A), variance due to environmental factors that the twins share in common (C), and variance due to environmental factors that are unique to each twin (E). Estimates are obtained for the A, C, and E components of the variance in liability for each of the diagnoses (A_{PA}, C_{PA}, E_{PA}, A_{GD}, C_{GD}, E_{GD}). The correlation between these components of variance is also assessed (r_A, r_C, r_E). The final ACE model for the data is the most parsimonious model that still has an adequate goodness of fit, as indicated by a nonsignificant χ^2 likelihood ratio tests. In the event that two ACE models fit the data approximately evenly, the model with the lowest Akaike's information criterion (AIC) would be selected as the best fitting model.

Results

Responses for the 7,595 individuals with non-missing values for both GD and PA are contained in Table 3. Of the individuals with PA, 30% (89/293) were diagnosed with GD, while the rate of GD was only 15% (1,102/7,302) in individuals not affected with PA. Using a Fisher's Exact Test yields a p value on the order of 10^{-10}, strongly rejecting the null hypothesis that PA and GD were unrelated in this sample. Table 3 further summarizes the percentage of specific GD as assessed in the VETSA study by diagnosis of PA. The percentages of gastritis, ulcer, and IBS were much higher in those with PA than those without PA, however, these differences were not significant due to the small sample size of PA individuals who participated in VETSA.

The results of fitting the 13 NK comorbidity models are summarized in Table 4. We were unable to reject any of the models except for independence of the two factors. The most likely model, as indicated by the smallest AIC, is the excess co-occurrence of PA and GD is due to a shared underlying liability (model 10). However, the data were consistent with many of the other models listed, so that the results of fitting the NK models were largely inconclusive. A co-twin analysis also indicates that shared risk factors, either genetic or shared between twins, are a likely explanation for comorbidity between PA and GD. The rate of GD in PA-free co-twins of index twins with PA-only was 20%, while the rate of GD in PA-free co-twins of index twins unaffected with either PA or GD was 13%. This increased rate of GD (estimated odds ratio of 1.7, Fischer's exact *p* value of .02) in the co-twins demonstrates that PA, by itself, is enough to increase the rate of GD in relatives, even if those relatives have not developed panic.

Next, we fit a saturated model (unconstrained correlation estimates), and a series of genetic models to the data. An examination of the saturated model indicates that equating all of the thresholds for a given phenotype across twins 1 and 2 and across MZ/DZ pairs did not significantly worsen the fit of our model ($p = .40$). We observed increased twin 1–twin 2 correlation for MZ pairs compared to DZ pairs for both PA (.37 vs. .15) and GD (.33 vs. . 09), which indicates that some of the liability for both PD and GD is due to genetic risk factors. The possibility of a shared heritability for PA and GD was explored as a part of the genetically based ACE model described below.

Table 5 presents a summary of all of the twin-models that were tested to arrive at the 'best fitting' bivariate-genetic model (in bold). Imposing the constraints of the ACE model — with increased correlation for MZ twins compared to DZ twins — also did not significantly worsen the fit of the model ($p = .34$). Table 6 presents the parameter estimates from a standard bivariate ACE model and the associated 95% confidence intervals. Consistent with existing literature, common environmental factors did not explain a significant proportion of the variation in PD liability. Estimates of the common environmental variance for both PA and GD were equal to 0. Therefore, dropping the C component of the ACE model did not reduce the quality of the fit ($p = 1$). Any model that excluded the additive genetic component was rejected (CE model $p = .02$, E model $p = .000$). The correlation between the unique environmental components to the two disorders (r_E) was nonsignificant (estimate = .09, 95% CI of −.07 to .26, $p = .28$). In contrast, we could not drop the correlation between additive genetic components for PA and GD (r_A) from the model ($p = .004$). Therefore, our best fitting model is a bivariate AE model in which the twin-specific environmental risk factors for PA and GD are assumed to be uncorrelated.

The estimates of the best-fitting structural equation model and the 95% confidence intervals on the parameters are represented in Figure 1. Consistent with results from other studies, the ACE model indicates that both PA and GD are moderately heritable traits. We estimate that the additive genetic component of PA explains 37% of the variance in underlying PA susceptibility and that additive genetic factors explain 31% of underlying GD susceptibility. Perhaps the most interesting result to emerge from the bivariate ACE model is the substantial correlation between the genetic components of PA and GD risk. The bivariate AE model estimates that the correlation between the additive genetic component of PA and GD susceptibility, $r_A = .55$ (95% CI of .34 to .82). Because our best-fitting model does not include a common environmental component to PA and GD susceptibility and because there is no correlation between the environmental components of PA and GD, our data are consistent with a susceptibility model in which all of the comorbidity between PA and GD is due to shared underlying genetic factors.

Discussion

In this sample of male Vietnam-era veterans, panic attacks and gastrointestinal disorder co-occur more often than their individual rates would predict if PA and GD were unrelated. Not surprisingly given the sample size and prevalence rates, the results of fitting the 13 Neale-Kendler models of comorbidity were inconclusive. While the data were not sufficient to reject any model other than independence between PA and GD, the best fitting NK model suggests that PA-GD comorbidity is due to correlated liability. The hypothesis of correlated liability was also supported in a co-twin analysis which indicated that the presence of PA was enough to raise GD rates in relatives that were panic-free. We then examined these traits together in a bivariate genetic (ACE) model and obtained evidence that the comorbidity between PA and GD was entirely due to overlapping genetic liability. Even if some underlying correlation between the environmental components exists and we simply have too little power to detect it, this study indicates that genetic covariation is the primary source of PA and GD comorbidity.

Based on these data, it is not possible to identify a particular biological or psychological mechanism by which putative joint risk genes influence PA and GD. As we discussed briefly in the introduction, it is possible that GD and psychiatric disorders are correlated due to underlying abnormalities in nerve functioning and signaling affecting both the CNS and ENS, or an abnormality that affects communication between the CNS and ENS. It is also possible that the association is due to a heritable personality factor that makes an individual more likely to report somatic symptoms consistent with both diagnoses.

The results presented here are clearly preliminary and there are several limitations that should be kept in mind. The sample we examined consisted of only males. While the underlying structure of genetic liability for PD has not been found to differ substantially between males and females (Hettema et al., 2006), differences in somatization styles between males and females (Cain et al., 2009) may cause differences in the relationship between PD and GD. Given the small number of individuals affected with PD in this sample, we focused our analysis on the occurrence of panic attacks rather than panic disorder in order to retain adequate power. However, as a follow-up analysis we also examined PD for association with GD. Likely due to the reduced power, the model $r_A=0$ could not be rejected ($p = .08$) unless first assuming $r_E = 0$. If we similarly assume an AE model with $r_E = 0$, we obtain an estimate of $r_A = .52$ for PD and GD, similar to what we received for our initial PA-GD model.

Perhaps the most serious limitation of the current study is the lack of screening for specific GD as a part of the survey of health. While some specific GD were assessed in a subset of participants as a part of the VETSA study (as presented in Table 3), the smaller number of participants in VETSA and the low rates of relevant diagnoses leave us with too little power to detect correlation between PA and specific GD. The low rate of GD in VETSA for those who reported the presence of GD in the SOH (58%) could lead one to question our characterization of GD as gastrointestinal disorder, and instead characterize it as a measure of simple gastrointestinal distress. However, we note that a response of GD on the survey of health is significantly associated with increased rates of gastritis, IBS, and ulcers. Additionally, as only five specific GD were assessed as part of VETSA it is possible that many of those not reporting a specific GD in VETSA still suffer from a serious gastrointestinal disorder. We also note that of those responding positively to the question ‘Since 1975 or your discharge from active duty (if that was earlier), have you ever had any of the following health problems? … Stomach or digestive disorders such as ulcers, inflammation, etc.’, 80% also reported positively to the question ‘Since 1975 or your discharge from active duty (if that was earlier), have you seen a physician for any of the

following health problems? … Stomach or digestive disorders such as ulcers, inflammation, etc.', which we will refer to as GD_2. That is, for the vast majority of those respondents that reported GD, their symptoms were serious enough that they obtained medical care. Moreover, when we examine GD_2 in a bivariate ACE model with PA, we get almost identical results to our initial analysis: that there is no significant contribution of common environmental variance to the fit of the model, and that we can drop the r_E parameter from the model ($p = .10$) but not the r_A parameter ($p = .02$). The AE model with $r_E = 0$ yields an estimate of r_A that is nearly identical to our original estimate: $r_A = .58$ with a 95% CI of .35 to .89. That is, we received a nearly identical answer whether or not we require that subjects received medical care for their gastrointestinal disorder (GD_2) rather than simply report its presence (GD).

These results support the notion that panic-associated physical disorders (and GD in particular) should be taken into account when investigating the genetic underpinnings of PA and PD. There may be specific liability genes associated with the combination of panic disorder and stomach disorders, and GD diagnoses and symptomatology may be useful in linkage and association studies for PD. Whether or not specific GD should be incorporated into the PD syndrome identified by Columbia University researchers in their genetic linkage study (Hamilton et al., 2003; Talati et al., 2008; Weissman et al., 2000) remains to be seen. However, any anxiety disorder risk locus identified on chromosome 13 should also be considered a viable GD risk locus. Researchers designing future PD association studies should consider collecting gastrointestinal diagnosis information, along with a careful reporting of the gastrointestinally-related PA symptoms, such as nausea and abdominal distress. This information may be invaluable in identifying PD risk loci, either by identifying genetic subtypes of PD or by better characterizing the genetic components of anxiety underlying PD susceptibility. As most of the genetic liability for anxiety disorders is shared (Hettema et al., 2006; Hettema et al., 2005), this genetic relationship may not be panic-specific. Further study should be performed to validate this possible genetic link between panic attacks and gastrointestinal disorders. In particular, these results need to be replicated in samples including females and also replicated for specific GD diagnoses.

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References

Addolorato G, Mirijello A, D'Angelo C, Leggio L, Ferrulli A, Abenavoli L, Vonghia L, Cardone S, Leso V, Cossari A, Capristo E, Gasbarrini G. State and trait anxiety and depression in patients affected by gastrointestinal diseases: Psychometric evaluation of 1641 patients referred to an internal medicine outpatient setting. International Journal of Clinical Practice. 2008; 62:1063–1069. [PubMed: 18422970]

Alpers DH. Multidimensionality of symptom complexes in irritable bowel syndrome and other functional gastrointestinal disorders. Journal of Psychosomatic Research. 2008; 64:567–572. [PubMed: 18501256]

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 3 rev. ed. Washington, DC: Author; 1987.

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4 ed. Washington, DC: Author; 1994.

Barbara G, Stanghellini V, Cremon C, De Giorgio R, Corinaldesi R. What is the effect of inflammation on intestinal function? Inflammatory Bowel Disease. 2008; 14 Suppl. 2:S140–S144.

Barlow, DH. Anxiety and its disorders: The nature and treatment of anxiety and panic. 2nd ed. New York: The Guilford Press; 2002.

Bengtson MB, Ronning T, Vatn MH, Harris JR. Irritable bowel syndrome in twins: Genes and environment. Gut. 2006; 55:1754–1759. [PubMed: 17008364]

Blewett A, Allison M, Calcraft B, Moore R, Jenkins P, Sullivan G. Psychiatric disorder and outcome in irritable bowel syndrome. Psychosomatics. 1996; 37:155–160. [PubMed: 8742544]

Blouin JL, Dombroski BA, Nath SK, Lasseter VK, Wolyniec PS, Nestadt G, Thornquist M, Ullrich G, McGrath J, Kasch L, Lamacz M, Thomas MG, Gehrig C, Radhakrishna U, Snyder SE, Balk KG, Neufeld K, Swartz KL, DeMarchi N, Papadimitriou GN. Dikeos DG, Stefanis CN, Chakravarti A, Childs B, Housman DE, Kazazian HH, Antonarakis S, Pulver AE. Schizophrenia susceptibility loci on chromosomes 13q32 and 8p21. Nature Genetics. 1998; 20:70–73. [PubMed: 9731535]

Bowen RC, Senthilselvan A, Barale A. Physical illness as an outcome of chronic anxiety disorders. Canadian Journal of Psychiatry. 2000; 45:459–464.

Bray BD, Nicol F, Penman ID, Ford MJ. Symptom interpretation and quality of life in patients with irritable bowel syndrome. British Journal of General Practice. 2006; 56:122–126. [PubMed: 16464326]

Cain KC, Jarrett ME, Burr RL, Rosen S, Hertig VL, Heitkemper MM. Gender differences in gastrointestinal, psychological, and somatic symptoms in irritable bowel syndrome. Digestive Diseases and Sciences. 2009; 54:1542–1549. [PubMed: 18979200]

Choung RS, Locke GR 3rd, Zinsmeister AR, Schleck CD, Talley NJ. Psychosocial distress and somatic symptoms in community subjects with irritable bowel syndrome: a psychological component is the rule. American Journal of Gastroenterologyl. 2009; 104:1772–1779.

Detera-Wadleigh SD, Badner JA, Berrettini WH, Yoshikawa T, Goldin LR, Turner G, Rollins DY, Moses T, Sanders AR, Karkera JD, Esterling LE, Zeng J, Ferraro TN, Guroff JJ, Kazuba D, Maxwell ME, Nurnberger JI Jr, Gershon ES. A high-density genome scan detects evidence for a bipolar-disorder susceptibility locus on 13q32 and other potential loci on 1q32 and 18p11.2. Proceedings of the National Academy of Science USA. 1999; 96:5604–5609.

Dewsnap P, Gomborone J, Libby G, Farthing M. The prevalence of symptoms of irritable bowel syndrome among acute psychiatric inpatients with an affective diagnosis. Psychosomatics. 1996; 37:385–389. [PubMed: 8701018]

Eisen S, Neuman R, Goldberg J, Rice J, True W. Determining zygosity in the Vietnam Era Twin Registry: An approach using questionnaires. Clinical Genetics. 1989; 35:423–432. [PubMed: 2736790]

Eisen S, True W, Goldberg J, Henderson W, Robinette CD. The Vietnam Era Twin (VET) Registry: Method of construction. Acta Geneticae Medicae et Gemellologiae(Roma). 1987; 36:61–66.

Elklit A, Christiansen DM. Predictive factors for somatization in a trauma sample. Clinical Practice and Epidemiology in Mental Health. 2009; 5:1. [PubMed: 19126224]

Farnam A, Somi MH, Sarami F, Farhang S. Five personality dimensions in patients with irritable bowel syndrome. Neuropsychiatric Disease and Treatment. 2008; 4:959–962. [PubMed: 19183786]

Farnam A, Somi MH, Sarami F, Farhang S, Yasrebinia S. Personality factors and profiles in variants of irritable bowel syndrome. World Journal of Gastroenterology. 2007; 13:6414–6418. [PubMed: 18081232]

Gershon MD. The enteric nervous system. Annu Rev Neurosci. 1981; 4:227–272. [PubMed: 6111979]

Goldberg J, True W, Eisen S, Henderson W, Robinette CD. The Vietnam Era Twin (VET) Registry: Ascertainment bias. Acta Geneticae Medicae et Gemellologiae (Roma). 1987; 36:67–78.

Goodwin RD, Cox BJ, Clara I. Neuroticism and physical disorders among adults in the community: Results from the National Comorbidity Survey. Journal of Behavioral Medicine. 2006; 29:229–238. [PubMed: 16724279]

Goodwin RD, Stein MB. Peptic ulcer disease and neuroticism in the United States adult population. Psychotherapy and Psychosomatics. 2003; 72:10–15. [PubMed: 12466633]

Hamilton SP, Fyer AJ, Durner M, Heiman GA, Baisre de Leon A, Hodge SE, Knowles JA, Weissman MM. Further genetic evidence for a panic disorder syndrome mapping to chromosome 13q. Proceeding of the National Academy of Sciences USA. 2003; 100:2550–2555.

Harter MC, Conway KP, Merikangas KR. Associations between anxiety disorders and physical illness. European Archives of Psychiatry and Clinical Neuroscience. 2003; 253:313–320. [PubMed: 14714121]

Henderson WG, Eisen S, Goldberg J, True WR, Barnes JE, Vitek ME. The Vietnam Era Twin Registry: A resource for medical research. Public Health Reports. 1990; 105:368–373. [PubMed: 2116638]

Hettema JM, Neale MC, Kendler KS. A review and meta-analysis of the genetic epidemiology of anxiety disorders. American Journal of Psychiatry. 2001; 158:1568–1578. [PubMed: 11578982]

Hettema JM, Neale MC, Myers JM, Prescott CA, Kendler KS. A population-based twin study of the relationship between neuroticism and internalizing disorders. American Journal of Psychiatry. 2006; 163:857–864. [PubMed: 16648327]

Hettema JM, Prescott CA, Myers JM, Neale MC, Kendler KS. The structure of genetic and environmental risk factors for anxiety disorders in men and women. Archives of General Psychiatry. 2005; 62:182–189. [PubMed: 15699295]

Irwin C, Falsetti SA, Lydiard RB, Ballenger JC, Brock CD, Brener W. Comorbidity of posttraumatic stress disorder and irritable bowel syndrome. Journal of Clinical Psychiatry. 1996; 57:576–578. [PubMed: 9010120]

Johnson M. The vulnerability status of neuroticism: Over-reporting or genuine complaints? Personality and Individual Differences. 2003; 35:877–887.

Jones MP, Dilley JB, Drossman D, Crowell MD. Brain-gut connections in functional GI disorders: Anatomic and physiologic relationships. Neurogastroenterology and Motility. 2006; 18:91–103. [PubMed: 16420287]

Kaplan DS, Masand PS, Gupta S. The relationship of irritable bowel syndrome (IBS) and panic disorder. Annals of Clinical Psychiatry. 1996; 8:81–88. [PubMed: 8807032]

Katon W. Panic disorder and somatization. Review of 55 cases. American Journal of Medicine. 1984; 77:101–106. [PubMed: 6377887]

Kumano H, Kaiya H, Yoshiuchi K, Yamanaka G, Sasaki T, Kuboki T. Comorbidity of irritable bowel syndrome, panic disorder, and agoraphobia in a Japanese representative sample. American Journal of Gastroenterology. 2004; 99:370–376. [PubMed: 15046231]

Levy RL, Jones KR, Whitehead WE, Feld SI, Talley NJ, Corey LA. Irritable bowel syndrome in twins: Heredity and social learning both contribute to etiology. Gastroenterology. 2001; 121:799–804. [PubMed: 11606493]

Lin MW, Sham P, Hwu HG, Collier D, Murray R, Powell JF. Suggestive evidence for linkage of schizophrenia to markers on chromosome 13 in Caucasian but not Oriental populations. Human Genetics. 1997; 99:417–420. [PubMed: 9050933]

Lydiard RB. Irritable bowel syndrome, anxiety, and depression: what are the links? Journal of Clinical Psychiatry. 2001; 62 Suppl 8:38–45. discussion 46-37. [PubMed: 12108820]

Lydiard RB, Fossey MD, Ballenger JC. Irritable bowel syndrome in patients with panic disorder. American Journal of Psychiatry. 1991; 148:1614. [PubMed: 1928500]

Lydiard RB, Fossey MD, Marsh W, Ballenger JC. Prevalence of psychiatric disorders in patients with irritable bowel syndrome. Psychosomatics. 1993; 34:229–234. [PubMed: 8493304]

Malaty HM, Graham DY, Isaksson I, Engstrand L, Pedersen NL. Are genetic influences on peptic ulcer dependent or independent of genetic influences for Helicobacter pylori infection? Archives of Internal Medicine. 2000; 160:105–109. [PubMed: 10632311]

Mawe GM, Strong DS, Sharkey KA. Plasticity of enteric nerve functions in the inflamed and post-inflamed gut. Neurogastroenterology and Motility. 2009; 21:481–491. [PubMed: 19368664]

McGuffin P, Knight J, Breen G, Brewster S, Boyd PR, Craddock N, Gill M, Korszun A, Maier W, Middleton L, Mors O, Owen MJ, Perry J, Preisig M, Reich T, Rice T, Rietschel M, Jones L, Sham P, Farmer AE. Whole genome linkage scan of recurrent depressive disorder from the depression network study. Human Molecular Genetics. 2005; 14:3337–3345. [PubMed: 16203746]

Morris-Yates A, Talley NJ, Boyce PM, Nandurkar S, Andrews G. Evidence of a genetic contribution to functional bowel disorder. American Journal of Gastroenterology. 1998; 93:1311–1317. [PubMed: 9707057]

Muller JE, Koen L, Stein DJ. Anxiety and medical disorders. Current Psychiatry Reports. 2005; 7:245–251. [PubMed: 16098277]

Neale, MC.; Boker, SM.; Xie, G.; Maes, HH. Mx: Statistical Modeling. 7 ed. Richmond, VA: 2006.

Neale MC, Kendler KS. Models of comorbidity for multifactorial disorders. American Journal of Human Genetics. 1995; 57:935–953. [PubMed: 7573055]

Noyes R, Clancy J, Hoenk PR, Slymen DJ. Anxiety neurosis and physical illness. Comprehensive Psychiatry. 1978; 19:407–413. [PubMed: 679674]

Noyes R Jr, Clancy J, Hoenk PR, Slymen DJ. The prognosis of anxiety neurosis. Archives of General Psychiatry. 1980; 37:173–178. [PubMed: 6101536]

Raiha I, Kemppainen H, Kaprio J, Koskenvuo M, Sourander L. Lifestyle, stress, and genes in peptic ulcer disease: a nationwide twin cohort study. Archives of Internal Medicine. 1998; 158:698–704. [PubMed: 9554675]

Rhee SH, Hewitt JK, Lessem JM, Stallings MC, Corley RP, Neale MC. The validity of the Neale and Kendler model-fitting approach in examining the etiology of comorbidity. Behavior Genetics. 2004; 34:251–265. [PubMed: 14990866]

Robertson DA, Ray J, Diamond I, Edwards JG. Personality profile and affective state of patients with inflammatory bowel disease. Gut. 1989; 30:623–626. [PubMed: 2731754]

Rogers MP, White K, Warshaw MG, Yonkers KA, Rodriguez-Villa F, Chang G, Keller MB. Prevalence of medical illness in patients with anxiety disorders. International Journal of Psychiatry in Medicine. 1994; 24:83–96. [PubMed: 8077085]

Shaw SH, Kelly M, Smith AB, Shields G, Hopkins PJ, Loftus J, Laval SH, Vita A, De Hert M, Cardon LR, Sherrington R, DeLisi LE. A genome-wide search for schizophrenia susceptibility genes. American Journal of Medical Genetics. 1998; 81:364–376. [PubMed: 9754621]

Sheffield BF, Carney MW. Crohn's disease: a psychosomatic illness? British Journal of Psychiatry. 1976; 128:446–450. [PubMed: 1276548]

Sykes MA, Blanchard EB, Lackner J, Keefer L, Krasner S. Psychopathology in irritable bowel syndrome: support for a psychophysiological model. Journal of Behavioral Medicine. 2003; 26:361–372. [PubMed: 12921009]

Talati A, Ponniah K, Strug LJ, Hodge SE, Fyer AJ, Weissman MM. Panic disorder, social anxiety disorder, and a possible medical syndrome previously linked to chromosome 13. Biological Psychiatry. 2008; 63:594–601. [PubMed: 17920564]

Talley NJ, Boyce PM, Jones M. Is the association between irritable bowel syndrome and abuse explained by neuroticism? A population based study. Gut. 1998; 42:47–53. [PubMed: 9505885]

Tarter RE, Switala J, Carra J, Edwards KL, Van Thiel DH. Inflammatory bowel disease: Psychiatric status of patients before and after disease onset. International Journal of Psychiatry in Medicine. 1987; 17:173–181. [PubMed: 3610483]

Tsuang MT, Bar JL, Harley RM, Lyons MJ. The Harvard Twin Study of Substance Abuse: What we have learned. Harvard Review of Psychiatry. 2001; 9:267–279. [PubMed: 11600486]

Tysk C, Lindberg E, Jarnerot G, Floderus-Myrhed B. Ulcerative colitis and Crohn's disease in an unselected population of monozygotic and dizygotic twins. A study of heritability and the influence of smoking. Gut. 1988; 29:990–996. [PubMed: 3396969]

Van Kerkhoven LA, Laheij RJ, Jansen JB. Meta-analysis: A functional polymorphism in the gene encoding for activity of the serotonin transporter protein is not associated with the irritable bowel syndrome. Alimentary Pharmacology and Theraputics. 2007; 26:979–986.

Walker EA, Gelfand AN, Gelfand MD, Katon WJ. Psychiatric diagnoses, sexual and physical victimization, and disability in patients with irritable bowel syndrome or inflammatory bowel disease. Psychological Medicine. 1995; 25:1259–1267. [PubMed: 8637955]

Walker EA, Katon WJ, Jemelka RP, Roy-Bryne PP. Comorbidity of gastrointestinal complaints, depression, and anxiety in the Epidemiologic Catchment Area (ECA) Study. American Journal of Medicine. 1992; 92:26S–30S. [PubMed: 1531168]

Walker EA, Roy-Byrne PP, Katon WJ, Li L, Amos D, Jiranek G. Psychiatric illness and irritable bowel syndrome: A comparison with inflammatory bowel disease. American Journal of Psychiatry. 1990; 147:1656–1661. [PubMed: 2103735]

Walker JR, Ediger JP, Graff LA, Greenfeld JM, Clara I, Lix L, Rawsthorne P, Miller N, Rogala L, McPhail CM, Bernstein CN. The Manitoba IBD cohort study: A population-based study of the prevalence of lifetime and 12-month anxiety and mood disorders. American Journal of Gastroenterology. 2008; 103:1989–1997. [PubMed: 18796096]

Watson D, Pennebaker JW. Health complaints, stress, and distress: Exploring the central role of negative affectivity. Psychological Review. 1989; 96:234–254. [PubMed: 2710874]

Weissman MM, Fyer AJ, Haghighi F, Heiman G, Deng Z, Hen R, Hodge SE, Knowles JA. Potential panic disorder syndrome: Clinical and genetic linkage evidence. American Journal of Medical Genetics. 2000; 96:24–35. [PubMed: 10686548]

Woodman CL, Breen K, Noyes R Jr, Moss C, Fagerholm R, Yagla SJ, Summers R. The relationship between irritable bowel syndrome and psychiatric illness. A family study. Psychosomatics. 1998; 39:45–54. [PubMed: 9538675]

Zaubler TS, Katon W. Panic disorder and medical comorbidity: A review of the medical and psychiatric literature. Bulletin Menninger Clinic. 1996; 60:A12–A38.

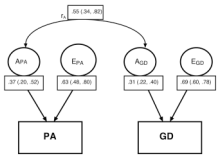

FIGURE 1.

Parameter estimates (and 95% CIs) of the components of variance from the best-fitting bivariate ACE model of PA and GD.

Note: PA = panic attack. GD = gastrointestinal disorder. A = proportion of risk attributable to additive genetic components. E = proportion of risk attributable to non-shared environmental effects. r_A and r_E = correlation between the A and E components of risk.

TABLE 1

Thirteen N-K Comorbidity Models, as Applied to Panic Attacks (PA) and Gastrointestinal Disorder (GD)

Model	Description
1. Chance	The disorders are independent
2. Alternate Forms	Both disorders share a single liability dimension.
3. Random multiformity	Independent liability dimensions, but a random subset of those with PA will manifest the symptoms of GD and vice-versa.
4. Random multiformity of PA	A random subset of those with PA will manifest the symptoms of GD.
5. Random multiformity of GD	A random subset of those with GD will manifest the symptoms of PA.
6. Extreme multiformity	Independent liability dimensions, but those with extreme liability for PA will develop GD and vice-versa.
7. Extreme multiformity of PA	Those with extreme liability for PA will develop GD.
8. Extreme multiformity of GD	Those with extreme liability for GD will develop PA.
9. Three indep. disorders	Apparent comorbid cases represent a third disorder with independent liability.
10. Correlated liabilities	Excess comorbidity occurs because the liabilities are not independent.
11. PA causes GD	Having PA increases the liability for GD
12. GD causes PA	Having GD increases the liability for PA.
13. Reciprocal causation	PA and GD cause each other in a feedback loop.

TABLE 2

Presence of Specific Gastrointestinal Disorders (GD) in VETSA by GD Response From the Survey of Health

	GD *n* = 1,720*	No GD *n* = 9,011*	Fisher's exact test
Gastritis	12%	3%	$p < .0001$
Stomach or duodenal ulcer	29%	3%	$p < .0001$
Irritable bowel syndrome	6%	2%	$p = .001$
Crohn's disease	1%	0.1%	$p = .07$
Ulcerative colitis	2%	0.4%	$p = .09$
None of the above	58%	92%	$p < .001$

Note:

*Denominator for particular GD may vary slightly due to missing values.

TABLE 3

Frequency of Gastronintestinal Disorder (GD) for Those With and Without Panic Attacks (PA) and for Specific Diagnoses in VETSA Subjects

	Affected with PA (*n* = 293)	**Unaffected with PA (*n* = 7,302)**	**Relative Risk**	**Fisher's exact test**
Percent GD In VETSA	**30%** **Affected with PA (*n* = 41*)**	**15%** **Unaffected with PA (*n* = 1,194*)**	**2.0**	***p* < .0001**
Gastritis	7%	4%	1.7	*p* = .42
Stomach or duodenal ulcer	15%	7%	2.1	*p* = .11
Irritable bowel syndrome	5%	2%	2.5	*p* = .20
Crohn's disease	0%	.2%	0.0	*p* = 1
Ulcerative colitis	0%	.7%	0.0	*p* = 1
None of the 5 above GD	80%	87%	0.9	*p* = .23

Note:

* Denominator for particular GD may vary slightly due to missing values.

TABLE 4

Fit Statistics for Thirteen N-K Comorbidity Models (Best-Fitting Model in Bold)

Model	x^2	df	p	AIC
1. Chance	37.094	12	< .001	13.094
2. Alternate Forms	14.714	13	.326	−11.286
3. Random Multiformity	6.590	10	.764	−13.410
4. Random Multiformity of PA	10.583	11	0.479	−11.417
5. Random Multiformity of GD	6.503	11	0.838	−15.497
6. Extreme Multiformity	5.855	10	0.827	−14.145
7. Extreme Multiformity of PA	5.839	11	0.884	−16.161
8. Extreme Multiformity of GD	11.593	11	0.395	−10.407
9. Three Indep. Disorders	14.714	9	0.326	−11.286
10. Correlated Liabilities	**3.799**	**9**	**0.975**	**−18.201**
11. PA causes GD	5.864	11	0.882	−16.136
12. GD causes PA	6.316	11	0.851	−15.684
13. Reciprocal Causation	5.692	10	0.840	−14.308

TABLE 5

c2 Tests and AICs Used to Determine the Best-Fitting Bivariate PA-GD ACE Model (in bold)

Model	# Par	−2LogL	AIC	DIF χ^2	DF	*P*	Vs. model
SAT	20	7566.9	−18587.1	—	—	—	—
SAT-ALL=CO	12	7574.3	−18595.7	7.5	8	0.48	SAT
ACE	11	7577.1	−18598.9	10.2	9	0.33	SAT
AE	8	7577.1	−18604.9	0.0	3	1.00	ACE
AE, $r_E = 0$	**7**	**7578.3**	**18605.7**	**1.2**	**1**	**0.28**	**AE**
AE, $r_A = 0$	7	7585.3	−18598.7	8.2	1	0.004	AE
CE	8	7587.3	−18594.7	10.2	3	0.017	ACE
E	5	7639.6	−18548.4	62.5	36	<0.001	AE,ACE

Note: PA = panic attack. GD = gastrointestinal disorder. A = proportion of risk attributable to additive genetic components. E = proportion of risk attributable to non-shared environmental effects. r_A, and r_E = correlation between the A and E components of risk.

TABLE 6

Parameter Estimates (and 95% CIs) of the Components of Variance From the Full Bivariate ACE Model

Parameter	Estimate and (95% CI)
A_{PA}	0.37 (0.00, 0.52)
A_{GD}	0.31 (0.12, 0.40)
r_A	0.43 (−1.00, 1.00)
C_{PA}	0.00 (0.00, 0.37)
C_{GD}	0.00 (0.00, 0.15)
r_C	0.54 (−1.00, 1.00)
E_{PA}	0.63 (0.48, 0.81)
E_{GD}	0.69 (0.60, 0.78)
r_E	0.09 (−0.07, 0.26)

Note: PA = panic attack. GD = gastrointestinal disorder. A = proportion of risk attributable to additive genetic components. C = proportion of risk attributable to shared (common) environmental effects. E = proportion of risk attributable to non-shared environmental effects. r_A, r_C, and r_E = correlation between the A, C, and E components of risk.