

New Segregation Analysis of Panic Disorder

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We performed simple segregation analyses of panic disorder using 126 families of probands with DSM-III-R panic disorder who were ascertained for a family study of anxiety disorders at an anxiety disorders research clinic. We present parameter estimates for dominant, recessive, and arbitrary single major locus models without sex effects, as well as for a nongenetic transmission model, and compare these models to each other and to models obtained by other investigators. We rejected the nongenetic transmission model when comparing it to the recessive model. Consistent with some previous reports, we find comparable support for dominant and recessive models, and in both cases estimate nonzero phenocopy rates. The effect of restricting the analysis to families of probands without any lifetime history of comorbid major depression (MDD) was also examined. No notable differences in parameter estimates were found in that subsample, although the power of that analysis was low. Consistency between the findings in our sample and in another independently collected sample suggests the possibility of pooling such samples in the future in order to achieve the necessary power for more complex analyses.

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KEY WORDS: anxiety disorders, panic disorder, genetics, segregation analysis

INTRODUCTION

Panic disorder (PD), a common psychiatric disorder with a lifetime prevalence estimated at 1–3.5% [Robins and Regier, 1991; Kessler et al., 1994], shows significant clustering within families [Crowe et al., 1983; Noyes

et al., 1986; Weissman et al., 1993; Mendlewicz et al., 1993; Maier et al., 1993]. Although the familial aggregation of PD and related anxiety conditions has been noted for over a century [Oppenheimer and Rothschild, 1918; Wood, 1941; Cohen et al., 1951; Beard, 1969; Noyes et al., 1978], the mechanism for this aggregation remains unclear. Estimates of relative risks of PD in first-degree relatives of PD probands compared to relatives of controls range from 3–21, with a median relative risk of 9.6 for the family studies cited. Twin studies suggest that a component of this aggregation may be genetic [Torgersen, 1983; Kendler et al., 1993]. However, the nature of underlying genetic factors is unknown.

Three published genetic studies have considered the involvement of a major gene. Pauls et al. [1980], in the first such analysis, examined 19 families of probands with DSM-III PD. Clinical diagnoses of PD in relatives were made using direct interviews of all available first-degree relatives and family history data on second-degree, third-degree, and the remaining first-degree relatives. Pauls et al. [1980] were unable to reject a dominant model. Their best-fitting model yielded the following parameter estimates: frequency of the disease allele = 0.014; penetrance for gene carriers = 0.75; and penetrance for noncarriers (phenocopy rate) = 0.

Crowe et al. [1983], in an extension of the earlier work of Pauls et al. [1980], carried out genetic modeling in a set of 41 families of probands with primary DSM-III PD that included the 19 families from the analysis by Pauls et al. [1980]. Only first-degree relatives were included in this study, with diagnosis by direct interview or by family history when the relatives were unavailable. Both single major locus (SML) and multifactorial polygenic models provided an acceptable fit to the distribution of PD in their sample. The best-fitting SML model included different penetrances for males and females and for heterozygotes and homozygotes, with a disease allele frequency of 0.05. Sex-averaged penetrances for individuals homozygous for the disease allele, heterozygous for the disease allele, and homozygous for the normal allele were 0.83, 0.35, and 0, respectively.

Vieland et al. [1993] performed simple segregation analyses using 30 families of probands with DSM-III PD without any lifetime major depression. Data for the analyses by Vieland et al. [1993] were collected by

Received for publication March 3, 1995; revision received October 4, 1995.

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Weissman et al. [1993]. Diagnoses in probands and relatives were obtained via best-estimate procedures that utilized information from direct interviews, family history data, and medical records when available. Segregation analyses were carried out with individuals with probable or definite DSM-III panic considered affected, and all other individuals treated as unaffected. They determined parameter estimates for single major locus models, but because of lack of power they were unable to test the fit of their SML models.

However, their results were of interest for several reasons. First, they reported that recessive and dominant models fit their data equally well. Second, they also reported nonzero phenocopy rates of 0.01 under both their best-fitting dominant and their best-fitting recessive models, in contrast to the earlier results of Pauls et al. [1980] and Crowe et al. [1983], which had both estimated phenocopy rates of 0.0. Third, 49% of all cases under the dominant model were estimated to be phenocopies, as were 26% of cases under the recessive model. Finally, the model obtained by Pauls et al. [1980] could be rejected for their data.

In this paper we present simple segregation analyses using a sample of families of probands with PD that is independent of those used in prior segregation analyses [Fyer et al., 1995]. Our primary goals were 1) to estimate parameters of SML models in the new data set, and 2) to assess the comparability of these data with the earlier reports mentioned above. Although this sample is larger than any of the previous samples analyzed, it was too small to test the fit of more complex models. However, if the results in this sample are comparable to those obtained in the study by Vieland et al. [1993], then in the future we may be able to combine these two data sets in order to obtain more power to test a broader range of models.

As is well-known, PD shows high rates of comorbidity with a number of diagnoses, including major depression [Breier et al., 1984; Stein et al., 1990; Angst et al., 1990]. Weissman et al. [1993] noted higher rates of familial aggregation of PD in families of probands without comorbid major depression, and suggested that the PD + major depression (MDD) group might be more heterogeneous than the families of PD probands without comorbid MDD. For this reason, Vieland et al. [1993] (but not the earlier studies of Pauls et al. [1980] and Crowe et al. [1983]) restricted their analyses to the families of probands without comorbid MDD. However, in a more recent analysis of the data from the family study by Weissman et al. [1993], Wickramaratne et al. [in press] found that source of proband ascertainment (depression clinic vs. anxiety clinic vs. epidemiologic catchment area study) had significant effects on rates of PD in relatives of PD + MDD probands, although source of ascertainment did not fully explain the difference in rates of PD between relatives of PD-only and PD + MDD probands. The family study data set which we used for these analyses [Fyer et al., 1993, 1995] consisted of 126 families of probands with PD, of whom 72 had no lifetime history of comorbid MDD (PD without MDD), while 54 had an episode of MDD (PD + MDD) [Mannuzza et al., 1995]. We initially present analyses

for the data set consisting of only the 72 families of PD probands without comorbid MDD. However, because all probands for this study were ascertained from an anxiety disorder clinic, and because there were no significant differences in rates of PD in relatives of PD-only vs. PD + MDD probands [Mannuzza et al., 1995], we also fit SML to the full data set of 540 adult first-degree relatives and spouses of all 126 probands with PD. We compare the models obtained from the full data set to those obtained using the subset of PD-only families.

SUBJECTS AND METHODS

Sample

Subjects came from a family study of anxiety disorders conducted at the Anxiety Disorders Clinic of the Columbia College of Physicians and Surgeons/New York State Psychiatric Institute [Fyer et al., 1995]. PD probands were recruited from the treatment and biological research programs of the clinic. All patients entering these studies between 1983–1988 and the last 6 months of 1989 who met DSM-III-R criteria for PD, and who were of European descent, English speaking, and had at least one living first-degree relative were asked to participate in the family study. Probands were recruited irrespective of lifetime history of major depressive disorder or alcohol or drug abuse, although since current MDD and drug and alcohol abuse were exclusion criteria in some clinic treatment studies, some potential probands with these disorders were excluded [Fyer et al., 1993]. In no cases was there more than one proband per family, nor is there any reason to suspect nonindependence of ascertainment across families. Thus the data appear to conform to single ascertainment [Morton, 1959].

All potential probands were directly interviewed using the Schedule for Affective Disorders and Schizophrenia-Lifetime Version modified for the study of anxiety disorders (SADS-LA) [Fyer et al., 1985]. Proband interviews were conducted by one of three specially trained senior clinicians who were not blind to the proband's participation in the clinic program. Clinical records for the 126 probands, including narrative case histories and interview forms, were reviewed by the principle investigator (A.J.F., who was also blind to diagnoses in relatives) in order to ensure conformance with DSM-III-R criteria. Of the probands, 91.3% were non-Hispanic whites and 8.7% were Hispanic. Mean age at interview was 34 years (SD = 8.6 years); 69.0% were female, and 45.2% were college graduates, while only 5.6% had not completed high school; 51.6% were currently married, 31.8% were never married, and 16.6% were widowed, separated, or divorced.

All available adult first-degree relatives and spouses were directly interviewed by interviewers blind to proband diagnosis using the SADS-LA. Family history data on all relatives were also obtained from every directly interviewed subject, using the Family Informant Schedule and Criteria (FISC) [Mannuzza et al., 1985]. In order that interviewers remained blind to proband diagnostic status, family history data about probands were not obtained from the relatives. Direct interviews

were done on 78% of all living or 66% of all total (living and dead) first-degree relatives.

The best-estimate procedure has been described in detail elsewhere [Fyer et al., 1995] and will only be reviewed here. Two senior clinicians blind to proband diagnosis independently reviewed all available information from direct and informant assessments of each relative. Best-estimate lifetime DSM-III-R diagnoses were arrived at in consensus meetings following independent review. For the purpose of these analyses, relatives with definite or probable DSM-III-R PD were considered affected, irrespective of the presence of comorbid DSM-III-R MDD.

In preparation for genetic modelling we also examined distribution of the ages of onset of the 170 subjects with PD. (Age of onset data could not be determined for 2 affected relatives and were treated as missing values.) Ages of onset appeared normally distributed, with a mean age of onset of 26.6 years (SD = 8.9 years) and a median age of onset of 24 years. As in the sample of Vieland et al., there was no gender difference in age of onset of PD, with a mean age of onset in females of 26.6 years (SD = 9.4 years), and in males of 26.7 years (SD = 7.7 years).

Genetic Modelling

All calculations were performed using the REGTN program as implemented in the Statistical Analysis for Genetic Epidemiology (SAGE) computer program [SAGE, 1992]. REGTN performs segregation analysis of a dichotomous trait with a variable age of onset where the age of onset is assumed to be normally distributed. We used REGTN's model 2, where each genotype is presumed to influence the susceptibility to developing the trait but not the age of onset, since we found no relationship between age of onset in the probands and rates of panic in the relatives, nor to the best of our knowledge has any such relationship been reported in the literature. Ascertainment was corrected for by conditioning likelihoods on the phenotypes of the probands [Cannings and Thompson, 1977; Vieland and Hodge, 1995].

The full model specifies 15 parameters: frequency of disease allele A = q; population frequencies of the three genotypes = $\psi_{AA}, \psi_{AB}, \psi_{BB}$; probabilities of transmitting

the A allele for the three parental genotypes AA, AB, and BB, respectively = τ_1, τ_2, τ_3 ; the mean μ and variance σ^2 of the age of onset distribution; and the penetrances (lifetime susceptibilities) for the three genotypes, separately for each sex = $\gamma_{AAf}, \gamma_{AAm}, \gamma_{ABf}, \gamma_{ABm}, \gamma_{BBf}, \gamma_{BBm}$. All analyses were carried out assuming Hardy-Weinberg equilibrium, thus making population genotype frequencies dependent on frequency of the disease allele. Transmission probabilities were also fixed at 1.0, 0.5, and 0.0, respectively, in order to correspond to Mendelian inheritance, except when explicitly testing the hypothesis $\tau_2 = 1/2$. Because we had convergence problems, even when we used the full sample of 126 families, we were forced to further constrain the models by requiring identical penetrances for males and females for each genotype. Using these restrictions we were able to estimate the remaining parameters (q, μ , σ^2 , γ_{AA} , γ_{AB} , and γ_{BB}) in the subset of PD without MDD families as well as in the full sample. We used several different sets of initial parameters for each model in order to ensure that the parameter estimates to which the program converged represented global and not local maxima.

We used the program to specify different models, i.e., no genetic transmission (NGT), dominant, recessive, and arbitrary SML, and we calculated the corresponding maximum likelihood estimates and the natural logarithm of the maximum likelihood (LnL). Nested models were tested against one another using the -2 times the LnL, which is asymptotically distributed as a chi-square statistic with degrees of freedom corresponding to the difference in the number of parameters between the two models.

RESULTS

PD Without MDD Families

Table I presents the maximum likelihood estimates and corresponding values of LnL for the four SML models (NGT, dominant, recessive, and arbitrary SML) for the 72 families of probands with PD and no lifetime history of major depression. Because the parameters of the age distribution were essentially identical across models ($\mu = [36.5-37.4]$, $\sigma^2 = [103.7-108.6]$), we omitted their values from the table. Testing the recessive,

TABLE I. Parameter Estimates and Corresponding Log-Likelihoods for Models Obtained Using Families of Probands With No Lifetime History of Major Depression*

	Arbitrary SML	Recessive	Dominant	NGT
q	0.100	0.180	0.021	NA ^a
γ_{AA}	1.000 ^b	0.806	0.485	0.126
γ_{AB}	0.057	[0.030]	[0.485]	[0.126]
γ_{BB}	0.002	0.030	0.052	[0.126]
Ln Likelihood	-353.17	-353.36	-354.39	-355.06
χ^2 ^c		0.38	2.44	3.88
d.f.		1	1	3
P		NS	NS	NS

* Numbers in brackets are either fixed in advance or determined by other parameters in the model.
^a Gene frequency is not applicable to NGT models.
^b Converged to boundary value. Note that χ^2 tests will tend to be conservative, since the d.f. are probably somewhat less than they would have been had this parameter not converged to the boundary.
^c χ^2 tests compare Ln Likelihoods for each model to Ln Likelihood for the arbitrary model.

dominant, and random models against the arbitrary model, we see that there are no significant differences between any of the models. However, we note that the arbitrary SML model is most similar to the recessive model. We also tested the arbitrary model against a model in which τ_2 was estimated, in order to test for Mendelian inheritance. We were unable to reject the hypothesis $\tau_2 = 1/2$ (estimate of $\tau_2 = 0.77$, $\chi^2 = 0.66$).

Table II compares the best-fitting SML model obtained with these data to the best-fitting models obtained by Pauls et al. [1980], Crowe et al. [1983], and Vieland et al. [1993]. The LnLs for the recessive and dominant models obtained by Vieland et al. [1993] do not differ significantly from the LnL for the best-fitting SML model. However, the models of Crowe et al. [1983] and Pauls et al. [1980] do not fit this sample ($\chi^2_{df=4} = 11.40$, $P < .05$, and $\chi^2_{df=4} = 41.08$, $P < .001$, respectively).

PD With or Without Comorbid MDD

Table III presents the maximum likelihood parameter estimates and corresponding values of the LnL for the four SML models for the full sample of 126 PD families. We again found minimal differences between models in age-of-onset parameters ($\mu = [33.8-34.4]$, $\sigma^2 = [102.9-106.5]$) and omitted them from the table. In this larger sample, the parameter estimates were similar to those obtained in the smaller samples, but we had more power to discriminate between models. Furthermore, when we applied the specific parameter estimates obtained from the subset of probands without comorbid MDD to this full sample, the LnLs were extremely close to those of the best-fitting models, with differences ranging from .04 for the arbitrary model to .23 for the dominant model (data not shown). Thus we did not find evidence that adding the additional 54 families of probands with PD + MDD changed the pattern of transmission obtained with the original sample, although the original 72 families comprised the majority of families in the combined data set and must accordingly induce some similarity between the two analyses. We were unable to fit models in the PD + MDD sample alone, due to the small number of families.

Table III shows that the arbitrary SML model is marginally superior to the dominant model ($\chi^2_{df=1} = 2.88$,

$P < .10$) and to the NGT model ($\chi^2_{df=3} = 7.22$, $P < .10$). Once again, the arbitrary and recessive models were similar, and their LnLs were not significantly different. We also see that the recessive model was significantly better than the model of no genetic transmission ($\chi^2_{df=2} = 6.32$, $P < .05$), while the dominant model was not ($\chi^2_{df=2} = 4.34$, $P = NS$). As before, when we tested the arbitrary model against a model in which τ_2 was estimated, we were unable to reject the hypothesis $\tau_2 = 1/2$ at the 0.1 level (estimate of $\tau_2 = 1.00$, $\chi^2 = 1.94$).

Table IV shows, using the full sample, the fit of the models obtained by other investigators. As in Table II, we see that the parameter estimates of Vieland et al. fit our data well, with the recessive model slightly closer to the best-fitting model than the dominant model. The estimates of Crowe et al. [1983] and Pauls et al. [1980] do not fit our data ($\chi^2_{df=4} = 16.76$, $P < .01$, and $\chi^2_{df=4} = 77.38$, $P < .001$, respectively).

We also tested the fit of "pure" Mendelian models with full penetrance and no phenocopies (results not shown). We were able to reject both the pure dominant ($P < .001$) and the pure recessive ($P < .05$) models. However, neither the hypothesis of full penetrance (with phenocopies) nor of no phenocopies (with reduced penetrance) could be rejected for either the dominant or recessive models.

DISCUSSION

The primary findings of this study are as follows:

- 1) When we restricted our analysis to the 72 families of probands with PD and no lifetime history of major depression, our best-fitting model was disease allele frequency $q = 0.100$, and lifetime susceptibilities for the three genotypes of $\gamma_{AA} = 1.000$, $\gamma_{AB} = 0.057$, $\gamma_{BB} = 0.002$. We were able to reject the earlier models of Pauls et al. [1980] and Crowe et al. [1983], but were unable to discriminate between arbitrary SML, recessive, dominant, and NGT models. We found comparable support for dominant and recessive models, as did the earlier report of Vieland et al. [1993] and obtained parameter estimates similar to theirs, including nonzero phenocopy rates.
- 2) The parameter estimates obtained from the fami-

TABLE II. Log-Likelihoods for Models Obtained by Other Investigators Applied to Families of Probands Without Comorbid Major Depression*

	Arbitrary SML ^a	Vieland [1993], recessive	Vieland [1993], dominant	Crowe et al. [1983]	Pauls et al. [1980]
q	0.100	[0.200]	[0.010]	[0.050]	[0.014]
γ_{AA}	1.000 ^b	[0.700]	[0.500]	[0.834]	[0.750]
γ_{AB}	0.057	[0.010]	[0.500]	[0.351]	[0.750]
γ_{BB}	0.002	[0.010]	[0.010]	[0.000]	[0.000]
Ln Likelihood	-353.17	-353.55	-355.37	-358.87	-373.71
χ^2		0.76	4.40	11.400	41.08
d.f.		4	4	4	4
P		NS	NS	<.05	<.001

* Note that Ln likelihoods in columns 2-4 are obtained by analyzing the present data set, but fixing the parameters at the estimates obtained by previous investigators in independent data sets. Thus they represent tests of the fit of previously reported models within our own data set.

^a Repeated from Table I for purposes of comparison.

^b Converged to boundary value.

TABLE III. Parameter Estimates and Corresponding Log-Likelihoods for Models Obtained Using Families of All Proband Irrespective of History of Major Depression

	Arbitrary SML	Recessive	Dominant	NGT
q	0.099	0.231	0.020	NA
γ_{AA}	1.00 ^a	0.586	0.491	0.134
γ_{AB}	0.064	[0.013]	0.491]	[0.134]
γ_{BB}	0.001	0.013	0.032	[0.134]
Ln Likelihood	-660.82	-661.27	-662.26	-664.43
χ^2		0.90	2.88	7.22
d.f.		1	1	3
P		NS	<.10	<.10

^a Converged to boundary value.

lies of PD-only (no MDD) probands were comparable to those obtained in the full sample of PD families irrespective of comorbid MDD in the probands. There thus did not appear to be any evidence of a different pattern of transmission in the full sample compared to the restricted sample. However, we were unable to fit models in the sample comprised of families of PD + MDD probands due to the small number (N = 54) of such families.

3) Using the full sample, our best-fitting model was $q = 0.099$, $\gamma_{AA} = 1.000$, $\gamma_{AB} = 0.064$, $\gamma_{BB} = 0.001$. While we could not reject a recessive model ($q = .231$, $\gamma_{AA} = 0.586$, $\gamma_{AB} = \gamma_{BB} = .013$), we found marginally less support for the dominant ($q = .020$, $\gamma_{AA} = \gamma_{AB} = 0.491$, $\gamma_{BB} = .032$) and NGT ($\gamma_{AA} = \gamma_{AB} = \gamma_{BB} = 0.134$) models. The recessive model also resulted in a significant improvement in fit over the model of random (nongenetic) occurrence. We again found that the parameter estimates of Vieland et al. fit our data, while the estimates of Pauls et al. [1980] and Crowe et al. [1983] did not. Although our best-fitting recessive and dominant models both included nonzero phenocopy rates, we could not reject a recessive model without phenocopies; we found marginally less support for a dominant model without phenocopies.

We note that our best-fitting arbitrary, recessive, dominant, and NGT models predict population lifetime prevalence of 2.2%, 4.4%, 5.0%, and 13.4%, respectively. The prevalence predicted by the NGT model differs markedly from what is found in population samples [Robins and Regier, 1991; Kessler et al., 1994], but the

others are within the range of what would be expected based on epidemiologic studies (reported rates of 1–4% are not adjusted for the age distribution of the population, so that lifetime prevalence such as we obtained should be somewhat higher than these rates). This suggests that the NGT model should be rejected as a plausible model for PD based on our data.

Epidemiologic studies have also consistently found higher rates of PD in females than in males [Robins and Regier, 1991; Kessler et al., 1994]. This observation holds for our sample as well, with 69% of probands being female. One possible explanation for the difference in rates in males and females is a polygenic threshold model. This model postulates an underlying continuous distribution of liability to illness, with individuals whose liability exceeds a certain threshold having the disorder. Under such a model, the difference in rates of PD between males and females is explained by a difference between the sexes in the threshold for PD. The polygenic model in this case implies that the threshold for PD is higher in males than females, accounting for the lower rates of PD in males.

One corollary of this model is that relatives of male probands should show higher rates of the disorder than relatives of female probands (because male probands must have higher underlying liabilities and hence greater genetic "loading" for PD than female probands). Both Crowe et al. [1983] and Vieland et al. [1993b] sought for but failed to find support for this model in their PD samples. We obtained findings similar to theirs, with no significant differences in rates of PD in siblings of male and female probands (5 of 67 = 7.5% of

TABLE IV. Log-Likelihoods for Some Specific Models Applied to the Full Data Set

	Arbitrary SML ^a	Vieland [1993], recessive	Vieland [1993], dominant	Crowe et al. [1983]	Pauls et al. [1980]
q	0.099	[0.200]	[0.010]	[0.050]	[0.014]
γ_{AA}	1.000 ^b	[0.700]	[0.500]	[0.834]	[0.750]
γ_{AB}	0.064	[0.010]	[0.500]	[0.351]	[0.750]
γ_{BB}	0.001	[0.010]	[0.010]	[0.000]	[0.000]
Ln Likelihood	-660.82	-661.51	-662.80	-669.20	-699.51
χ^2		1.96	3.96	16.76	78.38
d.f.		4	4	4	4
P		NS	NS	<.05	<.001

^a Repeated from Table III for purposes of comparison.

^b Converged to boundary value.

siblings of male probands are affected; 15 of 162 = 9.3% of siblings of female probands are affected; $\chi^2_{df=1} = 0.19, P = \text{NS}$). Thus, the data do not appear to support the polygenic threshold model.

Limitations

Under the SML models, the differences in rates of illness between males and females is attributed to differences in susceptibilities. A limitation of our study is that, due to lack of power, we were compelled to assume equal susceptibilities for males and females. Sex effects clearly do exist in PD, and one outstanding question is the extent to which our results may have been influenced by requiring that $\gamma_f = \gamma_m$. Resolution of this question will have to await the analysis of larger, more informative data sets.

We also note that the estimate of the mean age of onset obtained in these analyses (approximately 34 years) is somewhat different from the mean age of onset as calculated in the relatives within this sample (27 years), as well as from estimates generally reported [Breier et al., 1984; Klein, 1964; Von Korff et al., 1985] on the basis of epidemiologic samples. The discrepancy between mean age of onset in relatives and the estimated mean for our own sample is due to the ascertainment correction inherent in the analysis model. It is known that failure to adjust for ascertainment and the age structure of the population when estimating age-of-onset distributions can result in biased estimates, even in epidemiologic samples [e.g., see Faraone et al., 1994]. For this reason, the discrepancy between our estimated mean age of onset and the mean age of onset as reported for epidemiologic samples does not necessarily represent an error in the present study, but may be a cause for concern and should be pursued in future work.

Also, we have not examined more complicated models, e.g., a multifactorial model allowing for major gene, polygene, and environmental effects. The size of our sample precludes fitting such models, which require estimation of many additional parameters. However, Vieland et al. [1993], using a data set that was independently ascertained and assessed, reported results strikingly similar to ours. The similarity of our results to their earlier results is encouraging, and suggests the possibility of pooling the two data sets in the future. This would yield a substantially larger sample and possibly sufficient power to test more complex models.

ACKNOWLEDGMENTS

This work was supported in part by NIMH grants MH37592, MH30906, MH00884, MH48858, MH28274, and MH43878. D.W.G. was supported by a Research Fellowship from the DeWitt Wallace/New York Hospital Fund. The analysis was conducted using the program package S.A.G.E., which is supported by U.S. Public Health Service resource grant RR03655 from the National Center for Research Resources. We appreciate the helpful comments of Dr. Sal Mannuzza regarding this manuscript.

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