2007

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Genetic and Environmental Contributions to Pathological Gambling Symptoms in a 10-Year Follow-Up

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Problem (P) and pathological gambling (PG) symptoms wax and wane. Past symptoms are a risk for future symptoms even after controlling for familial influences. To address the genetic architecture of lifetime PG and current PG symptoms, we tested for common and unique genetic factors to lifetime PG symptoms at baseline and past year PG symptoms at 10-year follow-up. *Diagnostic and Statistical Manual of Mental Disorders* (3rd ed., Rev.; DSM-III-R; American Psychiatric Association, 1987) lifetime criteria of one or more PG symptoms were derived in 1992 and past year PG symptoms in 2002 from 1675 individual twins from the Vietnam Era Twin Registry. Cholesky decomposition models were fit to baseline and past year PG symptoms. Under the best fitting model we observed that 49% of the risk for one or more baseline PG symptoms in 1992 was due to a genetic factor and 51% of the risk was due to a unique environmental factor. All of the genetic variance (57.5%) in risk to past year PG symptoms in 2002 was common with baseline PG symptoms. Unique environment accounted for the remaining variance in past year PG symptoms with 13% common to baseline and 30% specific to past year PG symptoms. The genetic contributions to lifetime and past year gambling symptoms 10 years later are similar. There is no evidence for genetic contributions unique to past year PG symptoms. However, most of the unique environmental influences to past year PG are not shared with lifetime PG. This may reflect the changed social–cultural environment between 1992 and 2002, characterized by increasing access to legalized gambling.

In several previous studies that analyzed data from members of the Vietnam Era Twin Registry (VETR), we reported substantial additive genetic contributions to pathological gambling (PG) symptoms. Among veterans who responded to the 1992 Diagnostic Interview Schedule, Third Edition, Revised (DIS3R), Eisen et al. (1998, 2001) found the total variance in risk due to genetic contributions to gambling symptoms ranged from 40% to 54% (Eisen et al., 1998, 2001). In the same cohort, Slutske and colleagues (2000, 2001) estimated a 50% genetic contribution to PG. Gambling symptoms in these studies were derived according to the *Diagnostic and Statistical Manual of Mental Disorders* (3rd ed., Rev.; DSM-III-R; American Psychiatric Association, 1987) criteria.

Recently (Scherrer et al., in press), we reported co-twin control analyses that suggest lifetime DSM-III-R PG symptoms in 1992 were associated with increased risk of past year symptoms in 2002. This association between baseline symptoms in 1992 and past year symptoms in 2002 remained after controlling for genetic and shared environmental factors. This previous analysis included both monozygotic (MZ) and dizygotic (DZ) twins; therefore, we were not able to control for 100% of the genetic influence on lifetime and past year PG symptoms. Because the association existed after accounting for the majority of familial influences, there are likely unique environmental factors and some genetic variance not shared between lifetime PG symptoms and current PG symptoms at 10-year follow-up. Thus we sought to test if, and to what degree, the genetic and unique environmental contributions to 1992 PG symptoms and to past year 2002 PG symptoms overlap or are specific to each phenotype.

Tests of genetic contributions to longitudinal studies of addictive behavior and depression and anxiety have produced varying results. Rose et al. (2001) and Penninkilampi-Kerola et al. (2005) found

Received 18 September, 2006; accepted 20 September, 2006.

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that the genetic contributions to frequency of drinking were partly unique to the behavior in young adulthood as compared to adolescence. In an Australian cohort, genetic influence on depression and anxiety were mostly stable in an adult cohort (Gillespie et al., 2004). Taken together, there is some evidence that a variable highly sensitive to the environment, such as frequency of drinking, will change in genetic architecture as availability presumably increases from adolescence to young adulthood. Because access to legalized gambling (e.g., casinos, lottery) has dramatically increased in the United States between 1992 and 2002, it is plausible that greater access to gambling would result in more twins developing problem gambling symptoms and exacerbate the course of those with a history of PG. A greater environmental contribution to PG may be accompanied by a smaller genetic influence to PG phenotypes in 2002 as compared to 1992 when legal gambling was less available. Thus the past year gambling phenotype may have genetic and environmental contributions that are not shared with a lifetime diagnoses of PG.

We hypothesize that additive genetic and nonshared environmental contributions will partly overlap 1992 lifetime baseline and 2002 past year PG symptoms and that there will also be genetic and environmental contributions that are specific to current PG symptoms in 2002. To test this hypothesis, we fit bivariate Cholesky decomposition models to past year and current PG symptoms using data obtained from 1675 male twins who participated at both time points.

Methods

Subjects

The VETR consists of 7375 male MZ and DZ twin pairs born between 1939 and 1955 in which both siblings served on active military duty during the Vietnam War era (1965–1975). The characteristics of the VETR and method of zygosity determination have been reported elsewhere (Eisen et al., 1987, 1989; Henderson et al., 1990).

To be eligible for interview in 1992, twins must have had a Department of Defense military record, and identifying and locating information had to be available. Of 10,300 eligible individuals (5150 pairs) from the VETR, 8169 (79.3%) were successfully interviewed (pair-wise response rate 66.1%, 3372 pairs). Pairs and singletons responded to a computer-assisted telephone interview (CATI) that contained the DIS3R (Robins et al., 1988). A portion of the DIS3R contained questions used to derive diagnoses of DSM-III-R criteria PG symptoms.

In 2002, 2400 members (1200 twin pairs) of the VETR were invited to participate in a National Institutes of Health (NIH) study funded to examine the course and correlates of PG. The target sample for the 2002 gambling study consisted of all twin pairs in the 1992 sample (410 twin pairs) for whom at least one twin had endorsed at least one DSM-III-R PG symptom during the 1992 DIS3R interview, and 790 randomly selected twin pairs for whom neither twin had endorsed any DSM-III-R PG symptoms. Interviews were completed for 1675 twins, yielding a response rate of 70%. The mean interval between the baseline and follow-up interviews was 11.1 years, $SD \pm 0.7$ years. The mean age of participants at follow-up was 53 (range 45 to 60 years). Trained, experienced staff from the Institute for Survey Research, Temple University conducted the interviews. Interviewers contacted twins and began interviewing after verbal informed consent was obtained, a method approved by the Institutional Review Boards at participating institutions.

1992 Baseline and 2002 Follow-Up Assessment of Pathological Gambling

Respondents to the baseline survey were asked: 'Have you ever gambled or bet or bought a lottery ticket or used a slot machine?', 'Have you done these things more than five times in your life?', and 'Have you ever gambled or bet or bought a lottery ticket or used a slot machine 25 or more times within one year?'. Only VETR members who answered yes to each of the three preceding questions were asked items to assess the nine symptoms of PG according to DSM-III-R criteria.

For consistency with the baseline interview, in the follow-up respondents were asked again if they had gambled 25 or more times within 1 year before assessing DSM-III-R PG symptoms.

Pathological Gambling Phenotypes

Because the 2002 target population was selected based on a lifetime history of experiencing one or more PG symptoms, we used this phenotype in our bivariate analyses to account for the sampling design. Importantly, Slutske et al. (2000) had demonstrated that the genetic architecture of one or more PG symptoms does not significantly differ from the twin model for full DSM-III-R criteria PG (i.e., four or more symptoms). In their analyses, the authors concluded that a normal liability threshold underlying no PG symptoms, one to three, and four or more symptoms could not be rejected. Thus, to have a sufficiently large sample size for our analyses we utilized one or more symptoms of PG with the expectation that results would be applicable to full criteria PG. We did not use a continuous symptom count measure because the distribution of the number of symptoms was highly skewed.

Biometrical Models

Cholesky decomposition models were fit to twin data to test the degree of genetic and environmental overlap between having one or more symptoms of PG at baseline and at 10-year follow-up. Variance in phenotypes is decomposed into additive genetic (notated A), shared family environment (notated C) and unique environmental factors (notated E). Bivariate models compared the fit of the full ACE model to that of reduced models, which removed one or more genetic (A) or environmental parameters (C, E). In the case of

lifetime PG symptoms, we have previously found an AE model provides the best fit for the data (Eisen et al., 1998). Because we are accounting for a two-stage sampling design and using missing data techniques, in the present analyses, we did not assume an AE model for the 1992 phenotype. Therefore, the bivariate model fitting began by allowing for a full model which contained A, C and E terms specific and common to lifetime and past year PG, respectively, and allowed for A, C and E terms specific to past year PG.

The difference between –2log-likelihood values for two models follows a chi-square distribution and is used to determine the better fitting model. If two or more reduced models are not significantly different from the full model based on the chi-square value, the model with the lowest Akaike Information Criterion (AIC; Akaike, 1987) is accepted as the best fitting model. Mx software (Neale et al., 2002) was used for genetic modeling.

Genetic Model Fitting to Raw Data

The following is a brief summary of the methods used for analyzing twin data. More detailed descriptions have been published (Neale & Cardon, 1992). Models were fit using raw data instead of the conventional method of fitting models to covariance matrices. The raw data option in Mx permits computation of variance and covariance when data are missing for an individual (Neale et al., 2002). Mx uses maximum likelihood methods to fit model parameters which include genetic and environmental parameters and threshold values. This is done to account for the missing data structure resulting from the high risk sampling design (i.e., sampling subjects from 1992 survey who had one or more PG symptoms). Fitting models using raw data does not produce a chi-square goodness-of-fit statistic. Instead, log-likelihood statistics are computed which are used to compare the relative fit of submodels to the full model.

Results

Among the subjects in these analyses, 137 (8.2%) met criteria for one or more DSM-III-R PG symptoms in the year preceding interview (i.e., current PG symptoms). Among the 2002 respondents, 331 met criteria for one or more lifetime DSM-III-R PG symptoms in 1992. Among subjects with current symptoms, 64 had not met lifetime criteria in 1992 and 73 had met lifetime criteria for one or more PG symptoms in 1992. Of the 331 respondents with lifetime 1992 DSM-III-R PG, 206 reported that they had never had a lifetime symptom of PG in the 2002 interview. These 206 subjects were removed from analyses because of this data discrepancy.

Bivariate model fitting results are shown in Table 1. The first reduced Model 2 removed family environmental influences common to baseline PG and current PG. The observed improvement in fit (AIC = –3.83) of this model and the subsequent Model 3 which removed all family environment (AIC = –4.16) suggests shared family environment does not contribute to baseline or current PG symptoms. In Model 4, the specific A to current PG symptoms was removed, which resulted in the most parsimonious model (AIC = –5.31). Model 4 fit the data with the fewest number of parameters without a significant decrease in goodness-of-fit. Models that allowed for genetic contributions specific to current PG symptoms gave significantly worse fit to the data as compared to the full Model 1. Specifically, Model 5 (AIC = 4.50) did not allow for genetic contributions common to lifetime and current PG. And Model 6 (AIC = 43.07) did not allow for genetic and family environmental contributions common to lifetime and current PG, and it did not allow for family environmental contributions specific to current PG.

Figure 1 shows the variance component estimates for baseline and current PG symptoms under the best fitting model. Of the total variance in risk of lifetime DSM-III-R PG symptoms at baseline, 48.9% was due

Table 1

Bivariate Model Fitting Results for One or More Symptoms of Pathological Gambling at 1992 Baseline[a] and One or More Current[b] Symptoms

	Bivariate model				Fit of model		Parsimony
Model #	Baseline PG	Current PG common	Current PG specific	*df*	–2 log-likelihood	Δ –2log-likelihood	AIC[c]
1	ACE	ACE	ACE	7983	3092.42	—	
2	AE	AE	ACE	7985	3092.59	0.17	–3.83
3	AE	AE	AE	7983	3094.26	1.84	–4.16
4	**AE**	**AE**	**E**	**7983**	**3095.11**	**2.69**	**–5.31**
5	ACE	CE	ACE	7984	3098.92	6.50	4.50
6	ACE	E	AE	7987	3143.49	51.07	43.07

Note: PG = pathological gambling

[a]data obtained according to DSM-III-R criteria in 1992

[b]one or more DSM-III-R criteria symptoms within the year preceding follow-up in 2002

[c]Akaike Information Criterion

A = additive genetic factor, C = family environment factor, E = unique environment factor

Bold text indicates best fitting model — fits data with fewest parameters

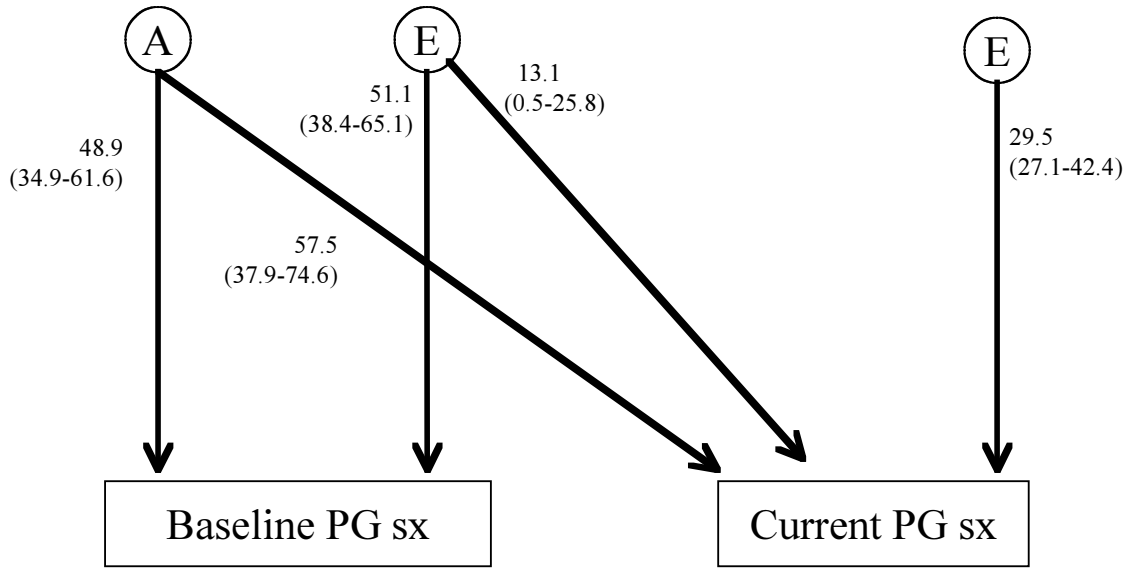

Figure 1

Variance component estimates for best fitting bivariate model for common and specific genetic and environmental contributions to one or more symptoms of PG at 1992 baseline and one or more symptoms of current PG at 10-year follow-up.

Note: PG sx = pathological gambling symptoms, A = additive genetic, C = shared family environment, E = unique environment

to genetic factors and the remainder to unique environmental influences. Of the total variance in risk due to one or more current PG symptoms at the 10-year follow-up in 2002, 57.5% was accounted for by genetic factors common to baseline PG symptoms. The remaining variance in current PG symptoms was attributed to unique environmental influences partially common to baseline PG (13.1%) and partially specific to current PG symptoms (29.5%).

Discussion

Bivariate analyses did not support our hypotheses that the genetic architecture of current DSM-III-R PG symptoms in 2002 differs from that underlying the risk for one or more symptoms of DSM-III-R PG in 1992. Model fitting results indicate all genetic variance for the 2002 gambling phenotype overlaps with the genetic risk for baseline PG symptoms. Despite the increase in legalized gambling and the increasing age of the twins, our results suggest that the genetic contributions to these phenotypes are stable across a 10-year period. We did find partial evidence of unique environmental influences, 30% of total variance, specific to past year gambling symptoms in 2002 and only 13% unique environmental factors common with baseline PG. It is possible that the unique environmental pathway is an expression of the increased availability of legalized gambling; however, we note that the nonshared environment includes measurement error.

Our results for lifetime PG symptoms at baseline are consistent with previous analyses of VETR twins by Eisen et al. (1998), who reported a 48% genetic contribution to one or more PG symptoms in 1992 with the remaining variance due to the unique environment. The similarity of results support the conclusion that the present two-stage sampling design and missing data technique is a valid method to model data collected from a cohort sampled for past gambling history. The stability of the genetic contribution to PG symptoms is consistent with another twin study of anxiety across adulthood (Gillespie et al., 2004). From this previous report and our current findings, there is evidence that genetic architecture may be stable in adult psychopathology. Data outside the addictions also suggest adult phenotypes are 'genetically' stable. In a separate study of VETR twins, Romeis and colleagues (2004) report that body mass index was explained by 63% to 69% genetic factors from young to late middle age despite the rapid societal changes (fatty fast foods, decreased use of public transportation, decreased labor) in the past 40 years which are likely to contribute to weight gain.

Limitations

Because the prevalence of full criteria past year PG in 2002 provided insufficient power for model fitting, we utilized a more liberal phenotype of one or more PG symptoms. However, importantly, Slutske et al. (2000) have previously demonstrated in the 1992 baseline data that liability for one or more symptoms of PG does not significantly differ from models for full criteria PG. Therefore, our results are likely to apply to full DSM-III-R criteria PG. Results may not generalize to females or to adolescent and elderly populations.

Under-report of past gambling problems was observed in 206 subjects. These respondents were removed from analyses because they met DSM-III-R

criteria in 1992, but denied lifetime symptoms in 2002. Lifetime prevalence of gambling problems has been previously reported to be conservative because of under-reporting in longitudinal studies (Abbott et al., 2004). It is possible that the phenotypes in the current study do not apply to all persons with symptoms of PG.

Strengths

Standardized, structured interviews were used to obtain data on PG symptoms in both the 1992 baseline and 2002 follow-up interviews. Trained interviewers who had no prior knowledge of the psychiatric status of participants conducted data collection. The community-based, national distribution of the sample increases generalizability. Because the VETR is a population-based cohort, our analyses avoid bias inherent in clinical studies. The raw data model fitting method utilizes all available data and accounts for potential bias due to missing data.

Conclusions

The vulnerability for past year problem gambling symptoms among men in 2002 can be explained by the same genetic factors that influenced lifetime problem gambling symptoms in 1992. Specific unique environmental contributions to past year gambling may be associated with increased access to legalized gambling. To the degree that this is true, approximately one quarter to one third of the variance in current gambling may be attributable to environmental changes. In our study, we did not collect data about availability to legalized gambling such as distance to a casino or presence of a state lottery. Future data collection with twin cohorts should consider the utility of collecting data that can be used to characterize such unique environmental influences. Research is warranted to test for changes from adolescence to adulthood and from midlife to late life behavior.

Acknowledgments

This study was supported by the Department of Veterans Affairs Health Services Research and Development Service and National Institute of Mental Health, Pathological Gambling: Courses, Consequences and Causes, MH60426.

The United States Department of Veterans Affairs has provided financial support for the development and maintenance of the Vietnam Era Twin (VET) Registry. Numerous organizations have provided invaluable assistance in the conduct of this study, including Department of Defense; National Personnel Records Center, National Archives and Records Administration; the Internal Revenue Service; National Opinion Research Center; National Research Council, National Academy of Sciences; the Institute for Survey Research, Temple University. Most importantly, the authors gratefully acknowledge the continued cooperation and participation of the members of the VET Registry and their families. Without their contribution this research would not have been possible.

References

Abbott, M. W., Williams, M. M., & Volberg, R. A. (2004). A prospective study of problem and regular nonproblem gamblers living in the community. *Substance Use and Misuse, 39,* 855–884.

Akaike, H. (1987). Factor analysis and AIC. *Psychometrics, 52,* 317–333.

American Psychiatric Association. (1987). *Diagnostic and statistical manual of mental disorders* (3rd ed., Rev.). Washington, DC: Author.

Eisen, S. A., Lin, N., Lyons, M. J., Scherrer, J., Griffith, K., True, W. R., Goldberg, J., & Tsuang, M. T. (1998). Familial influences on gambling behavior: An analysis of 3,359 twin pairs. *Addiction, 93,* 1375–1384.

Eisen, S., Neuman, R., Goldberg, J., Rice, J., & True, W. (1989). Determining zygosity in the Vietnam Era Twin Registry: An approach using questionnaires. *Clinical Genetics, 35,* 423–432.

Eisen, S. A., Slutske, W. S., Lyons M. J., Lassman, J., Xian, H., Toomey, R., Chantarujikapong, S., & Tsuang, M. T. (2001). The genetics of pathological gambling. S*eminars in Clinical Neuropsychiatry, 6,* 195–204.

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

Gillespie, N. A., Kirk, K. M., Evans, D. M., Heath, A. C., Hickie, I. B., & Martin, N. G. (2004). Do the genetic or environmental determinants of anxiety and depression change with age? A longitudinal study of Australian twins. *Twin Researc*h, *7,* 39–53.

Henderson, W. G., Eisen, S., Goldberg, J., True, W. R., Barnes, J. E., & Vitek, M. E. (1990). The Vietnam Era Twin Registry: A resource for medical research. *Public Health Report, 105,* 368–373.

Neale, M. C., Boker, S. M., Xie, G., & Maes, H. H. (2002). *Mx: Statistical modeling* (6th ed.). Richmond, VA: Department of Psychiatry, Virginia Commonwealth University.

Neale, M. C., & Cardon, L. R. (1992). *Methodology for genetic studies of twins and families*. Dordrecht, the Netherlands: Kluwer.

Penninkilampi-Kerola, V., Kaprio, J., Moilanen, I., & Rose, R. J. (2005). Co-twin dependence modifies heritability of abstinence and alcohol use: A population-based study of Finnish Twins. *Twin Research and Human Genetics, 8,* 232–244.

Romeis, J. C., Grant, J. D., Knopik, V. S., Pedersen, N. L., & Heath, A. C. (2004). The genetics of middle-age spread in middle-class males. *Twin Research and Human Genetics, 7,* 596–602.

Rose, R. J., Dick, D. M., Viken, R. J., & Kaprio, J. (2001). Gene-environment interaction in patterns of adolescent drinking: Regional residency moderates longitudinal influences on alcohol use. *Alcoholism: Clinical and Experimental Research*, *25,* 637–643.

Scherrer, J. F., Slutske, W. S., Xian, H., Waterman, B., Shah, K. R., Volberg, R., & Eisen, S. A. (in press). Factors associated with pathological gambling at 10 year follow-up in a national sample of middle-aged men. *Addiction.*

Slutske, W. S., Eisen, S., True, W. R., Lyons, M. J., Goldberg, J., & Tsuang, M. (2000) Common genetic vulnerability for pathological gambling and alcohol dependence in men. *Archives of General Psychiatry, 57,* 666–673.

Slutske, W. S., Eisen, S., Xian, H., True, W. R., Lyons, M. J. Goldberg, J., & Tsuang, M. (2001). A twin study of the association between pathological gambling and antisocial personality disorder. *Journal of Abnormal Psychology, 110,* 297–308.