Sex Differences in Genetic and Environmental Contributions to Depression Symptoms in South Korean Adolescent and Young Adult Twins

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It has been reported that prevalence estimates, symptom presentation, and sociocultural risk and protective factors for depression differ between Caucasian and East Asian populations. But, nonetheless, as the vast majority of twin studies of depression symptoms have been carried out using Caucasians, genetic and environmental influences on depression symptoms in East Asians remain poorly understood. In the present study, the Center for Epidemiologic Studies — Depression Scale (CES-D) was administered to 490 pairs of South Korean adolescent and young adult twins (ages: 13–23 years) by telephone interview. In males, monozygotic (MZ) and dizygotic (DZ) twin correlations were similar (.44 vs. .41), suggesting the importance of shared environmental factors in depression symptoms. In females, however, MZ twin correlation was much greater than DZ twin correlation (.40 vs. .23), indicating the importance of genetic influences. The total phenotypic variance for the CES-D was greater in females than in males. Variance components model confirmed sex differences in the magnitude of genetic and environmental influences on depression symptoms: Additive genetic, shared environmental, and individual specific environmental effects in the full model were, respectively, 12% (95% CI: 0–54%), 32% (95% CI: 0–53%), and 56% (95% CI: 44–70%) in males, and 41% (95% CI: 0–52%), 0% (95% CI: 0–36%), and 59% (95% CI: 48–72%) in females. Similar results were observed when 'culturally biased' items of the CES-D were separately analyzed. These variance components estimates for depression symptoms in East Asians overlap those observed in Caucasians.

Depression is one of the most common diseases and estimated to become the second most debilitating disease worldwide in 2020 (Murray & Lopez, 1996). Self-reported symptoms of depression have shown to be stable over time (Duncan-Jones et al., 1990) and strongly predict a clinical diagnosis of depression (Myers & Weissman, 1980; Roberts & Vernon, 1983). Twin studies of depression symptoms have suggested that genetic factors explain approximately 20% to 40% of the variance, with most of the remainder being attributed to individual specific environmental factors (Agrawal et al., 2004; Kendler et al., 1994; Jansson et al., 2004; Silberg et al., 1999; Sullivan et al., 2000). However, as twin studies of depression symptoms to date almost entirely employed Caucasian samples, it is necessary to understand whether the results can be generalized to other ethnic groups, especially to a genetically and culturally markedly different group such as South Koreans.

Cross-national epidemiological survey data have generally identified a lower rate of major depression in East Asian countries as compared to that in other countries. For example, the lifetime prevalence rates of major depression have been reported to be 1.5% in Taiwan, compared to 19.0% in West Germany and 5.8% in New Zealand (Weissman et al., 1996). Among South Koreans, the lifetime prevalence rate of major depression has been estimated to be 3.4% (Lee, 1994). It has been suggested that sociocultural factors in East Asian societies provide some protection against becoming depressed, leading to a lower prevalence of depression. These factors include characteristics of the collectivist culture such as strong family social support and interdependence, values for the maintenance of group harmony, and collective responsibility. Confucian values in most East Asian societies such as high tolerance for distressing circumstances and emotional control can also reinforce individuals to successfully cope with stress that may precipitate depression (Tseng & Wu, 1985; Xu, 1987).

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While some investigators have argued that there exist factors that protect against depression in East Asian societies, others have suggested that differences in reporting symptoms of depression between East Asians and Caucasians may have led to lower prevalence estimates of depression in East Asian countries compared to those in Caucasian countries. For example, after a review of the literature, Parker et al. (2001) concluded that East Asians tended to deny depression and express it somatically in psychiatric interviews perhaps because the social stigma of mental illness was high and complaints of physical problems were more socially acceptable than those of emotional distress in most East Asian societies.

Interestingly, when symptoms of depression were measured as specific questions rather than as open-ended psychiatric interviews, East Asians often scored higher than did North Americans (e.g., Takeuchi et al., 1994). In compariing the Japanese and Americans, Iwata and his colleagues (1994, 1995, 2002) found that on positively worded items of the depression questionnaire, the Japanese had a tendency to inhibit the expression of positive affect, whereas Americans tended to express positive affect without hesitation; on negatively worded items, however, response patterns were comparable in the two groups. Similar response tendencies in the psychiatric rating scales have been reported for Koreans in South Korea (Cho & Kim, 1998) and Korean immigrants in Canada (Noh et al., 1998). Iwata et al. (1998) examined scores of the depression scale in Japanese psychiatric patients and normal controls and concluded that the high scores of the Japanese in the depression scale were more likely due to their control of expression of positive affects than to their lacking in positive feeling. Iwata et al. (1998) argued that Japanese had been taught since childhood to understate their own virtues and not to behave assertively, resulting possibly in being less sensitive to positive self-relevant information.

The higher prevalence of depression symptoms in females than males is very well established in psychiatric literature worldwide. However, whether genetic and environmental factors exert a similar magnitude of influence in males and females is still inconclusive. For example, Rice et al. (2002) and Eley and Stevenson (1999) found that genetic effects were more substantial in adolescent boys than in adolescent girls, and shared environmental effects were more important for adolescent girls than for adolescent boys. However, these findings contrasted with results of the twin study by Silberg et al. (1999) and Scourfield et al. (2003), where genetic influences were found to be higher in girls than in boys during adolescence. Mixed results have been reported from the adult and elderly twin samples also. For example, whereas Kendler et al. (1994) and Agrawal et al. (2004) found no significant sex differences in genetic and environmental factors in depression symptoms among adults, Kendler et al. (2006) and Jansson et al. (2004) showed that genetic factors in depressive symptoms were higher in females than in males. These inconsistent findings point to a need for further studies on gender differences in genetic and environmental effects on depressive symptoms. If the etiology of depression symptoms is quite different between the two sexes, this has important implications for gene identification studies as well as for research aimed at development of strategies for prevention and treatment of depressive symptoms in males and females. The major goal of the present study, therefore, was to estimate genetic and environmental effects on depression symptoms in South Korean adolescent and young adult twins, with a special emphasis on sex difference.

Materials and Methods

Sample

The present sample was drawn from the South Korean Twin Registry (SKTR; Hur et al., 2006). The SKTR is a nationwide volunteer twin registry that includes twins from infants to young adults. In 2006, as part of the SKTR mental health project, a Korean version of the Center for Epidemiologic Studies — Depression Scale (CES-D; Radloff, 1977) was given to the twins who were aged 13 years or older and living in the greater Seoul area at the time of interview.

Twins' zygosity was determined from mothers' responses to a zygosity questionnaire that includes questions regarding physical similarities and frequency of confusion of the twins by family members and others. When compared to the analysis of DNA markers, this questionnaire method to determine zygosity has yielded over 90% accuracy in Asian twin samples (Ooki et al., 1993). To minimize misclassification of zygosity, however, 28 pairs of the twins who were ambiguous in zygosity were excluded from data analyses.

The final sample for the present analyses included 490 pairs of twins consisting of 197 monozygotic female (MZF), 56 dizygotic female (DZF), 145 MZ male (MZM), 41 DZ male (DZM), and 51 pairs of opposite-sex DZ (OSDZ) twins. Lower rates of DZ as compared to MZ twins in the present study reflect low DZ twin birth rates in South Korea (Hur & Kwon, 2005). The age of the present sample ranged from 13 to 23 years, with a mean of 16.8 years and standard deviation of 2.6 years.

Measure

The CES-D is a well-established self-report measure of symptoms of depression in the general population. It consists of 20 items representing symptoms of depressive disorder. Respondents were asked to rate the frequency with which they experienced each of the 20 symptoms during the week prior to the interview. Responses ranged from 'rarely or none of the time' to 'most or all of the time'. Answers for the 20 items were summed to calculate a total. Prior to calculating a total, four items stated positively were reverse scored. The reliability and validity of the Korean version of the CES-D have been well established (Cho & Kim, 1993,

1998). The internal consistency reliability for all 20 items was .86 in the present sample.

Statistical Analyses

To fulfill the goals of the present study, twin correlations for the five groups of twins were computed and the general sex-limitation model (Neale & Cardon, 1992) was fit to the twin data using the raw data option in Mx (Neale et al., 2003). For correlational and model-fitting analyses, age was treated as a covariate to control its main effect.

In the general sex-limitation model, the phenotypic variance of the depression score is decomposed into three sources: additive genetic (A), shared environmental (C), and individual specific environmental (E) factors. Measurement error is confounded with the E factors. The A factors, the sum of the average effect of all genes that influence a trait, correlated at 1.0 and .5 for MZ and same-sex DZ twins, respectively. For OSDZ twins, however, the correlation for the A factors was allowed to vary between 0 and .5, assuming that some of the genes that determine depressive symptoms may be qualitatively different between males and females. The C factors, those environmental factors that the two members of a twin pair share, correlated at 1.0 for both MZ and DZ twins. Finally, the E factors, environmental factors that are unique to each member of a twin pair and measurement error, do not contribute to the twin similarity and therefore, represent the remaining variance not explained by additive genetic and shared environmental factors. In the general sex-limitation model, A, C, and E parameters were allowed to differ between males and females ($A_m \neq A_f$, $C_m \neq C_f$, & $E_m \neq E_f$), assuming that the magnitudes of additive genetic and shared and individual specific environmental influences on depression symptoms may vary in males and females.

To choose the best fitting, most parsimonious model, two major steps were taken. First, the fit of the general sex-limitation model was compared to that of the saturated model where variances and means of the first- and the second-born MZ and DZ twins were allowed to vary. Next, the fit of the general sex-limitation model was compared to the fit of a series of reduced models. Three different kinds of constraints were made in the reduced models. First, the additive genetic correlation for OSDZ twins was fixed to .5 to examine the presence of the sex-specific genes for depression symptoms. Second, the magnitudes of A, C, and E parameters were equated across sexes to test sex difference in the estimates of genetic and environmental influences on depression symptoms. Finally, the A or C parameter was eliminated from the full model to determine the significance of each parameter in males and females. The E parameter was not removed because measurement error was confounded with the E parameter.

Two criteria were used to choose the best fitting, most parsimonious model: the likelihood ratio test (LRT) and the Akaike information criterion (AIC = $\chi^2 - 2df$). The raw data option in Mx calculates twice the negative log-likelihood (–2LL) of the data. As the difference in –2LL is chi-square distributed with degrees of freedom equal to the difference in degrees of freedom, LRT was applied to evaluate the significance of the constraint when two models were nested. A nonsignificant change in chi-square between the full and constrained models suggests that the reduction in parameter is acceptable, whereas a significant change indicates that the parameter should be retained in the model. AIC quantifies the information content of a model in terms of the joint criterion of fit and parsimony (Akaike, 1987). Thus, the smaller the AIC, the better the fit of the model to the data. When two models were not nested, the model that yielded a lower AIC was chosen as a more parsimonious model.

Results

Descriptive Statistics and Twin Correlations

Table 1 presents means, standard deviations, and maximum likelihood correlations and their 95% confidence intervals (CI) for CES-D for the five twin

Table 1

Sample Size, Mean, Standard Deviation, and Maximum Likelihood Correlations[1] and their 95% Confidence Intervals for the CES-D in the Five Groups of Twins

	MZM	DZM	MZF	DZF	OSDZ	Total
N (pairs)	145	41	197	56	51	490
Age range (years)	13–23	13–23	13–23	13–22	13–21	13–23
CES-D						
Mean	14.3	15.6	17.7	18	16.2	16.4
SD	8	8.9	9.1	10.8	8.1	9
r	.44 (.3–.56)	.41 (.13–63)	.40 (.27–.51)	.23 (–.03–.46)	.01 (–.26–.28)	

Note: 95% confidence intervals are in parenthesis. CES-D = Center for Epidemiologic Studies-Depression Scale.

MZM = male monozygotic twins, DZM = male dizygotic twins, MZF = female monozygotic twins,

DZF = female dizygotic twins, OSDZ = opposite-sex DZ twins. 95% CI for twin correlations are in parenthesis.

[1]Twin correlations were corrected for age.

groups. In spite of the predominance of low frequency symptoms, there were sufficient variability in the moderate and upper ranges of the distribution to permit analysis without a transformation of the scale (skewness = .88).

The first-born twins were not different from the second-born twins in terms of mean or variance, suggesting no birth order effects on CES-D. In both males and females, MZ twins were not significantly different from DZ twins in the mean score of CES-D. Variances were not significantly different between MZ and DZ twins in males, but they were different in females (DZ > MZ). Age was significantly positively correlated with CES-D (r = .21), suggesting that depression symptoms increase with age. Consistent with the literature of depression, females were significantly higher than males in the mean score of CES-D. The variance for CES-D was also higher in females than in males.

In males, MZ and DZ twin correlations were similar, suggesting the importance of shared environmental factors in depression symptoms for males. In females, however, the MZ twin correlation was much greater than the DZ twin correlation, indicating the importance of genetic influences. These results provided suggestive evidence for sex differences in the magnitude of genetic and environmental influences on depression symptoms. The OSDZ twin correlation was consistently lower than either the male or female same-sex DZ twin correlation, suggesting some indication of sex-specific genes for depression symptoms. These observations from correlational analyses were tested in model-fitting analyses below.

Model-Fitting Analyses

Table 2 provides model-fitting results for CES-D. The difference in fit between the saturated and general sex-limitation model was not significant (χ^2_{16} = 21.8, p > .10), suggesting that the data do not depart significantly from the general sex-limitation model. In the full model, additive genetic, shared environmental, and individual specific environmental factors were, respectively, 12% (95% CI: 0–54%), 32% (95% CI: 0–53%), and 56% (95% CI: 44–70%) for males, and 41% (95% CI: 0–52%), 0% (95% CI: 0–36%), and 59% (95% CI: 48–72%) for females. Consistent with correlational analyses, these results suggested that additive genetic factors were higher and shared environmental factors were lower in females than in males.

When the additive genetic correlation for the OSDZ twin correlation was set at .5, a nonsignificant change in chi-square occurred (Model 2). When additive genetic and shared and individual specific environmental factors were equated across sexes, however, a significant change in chi-square occurred (Model 3), suggesting that the magnitudes of these factors may be different between two sexes. Elimination of additive genetic factors for males and females simultaneously from Model 2, while equating individual specific environmental factors across two

Table 2

Model-Fitting Results for CES-D[1]

		Goodness of fit indices						Parameter Estimates					
Model	Description	–2LL	df	$\Delta\chi^2$	Δdf	p	AIC	A_m	C_m	E_m	A_f	C_f	E_f
1	General sex-limitation	6944.8	970				5004.8	.12	.32	.56	.41	.00	.59
2	r_aO= .5 for OSDZ twins	6944.9	971	0.1	1	.86	5002.9	.10	.33	.56	.39	.02	.59
3	r_aO = .5 for OSDZ twins; Am = Af, Cm = Cf, & Em = Ef	6959.6	974	14.8	4	.00	5011.6	.42	.00	.58	.42	.00	.58
4	r_aO = .5 for OSDZ twins; Drop Am & Af; Em = Ef	6963.2	974	18.4	4	.00	5015.2	—	.27	.73	—	.39	.61
5	r_aO = .5 for OSDZ twins; Drop Cm & Cf ; Em = Ef	6954.0	974	9.2	4	.06	5006.0	.34	—	.66	.47	—	.53
6	**r_aO = .5 for OSDZ twins; Drop Am & Cf; Em = Ef**	**6950.2**	**974**	**5.4**	**4**	**.25**	**5002.2**	**—**	**.34**	**.66**	**.47**	**—**	**.53**

Note: The results for the general sex-limitation and the best fitting model are indicated in bold. OSDZ = opposite-sex dizygotic twins.

r_a = additive genetic correlation, A = additive genetic factors, C = shared environmental factors, E = individual specific environmental factors. Subscripts, m and f indicate males and females, respectively. CES-D = Center for Epidemiologic Studies-Depression Scale: fixed to zero.

[1] Age was treated as a covariate in all models.

sexes resulted in a significant worsening of fit (Model 4); removing of shared environmental factors, however, produced a nonsignificant change in chi-square, although the *p* value for the chi-square was borderline (Model 5). In Model 6, additive genetic factors for males and shared environmental factors for females were dropped from Model 2, while individual specific environmental factors were equated across sexes. The chi-square change in Model 6 was not significant. These results suggested that both Models 5 and 6 were acceptable but since the AIC was lower in Model 6 than in Model 5, Model 6 was judged to be the best fit. Under Model 6, additive genetic, shared environmental, and individual specific environmental factors were, respectively, 0%, 34% (95% CI: 24–45%), and 66% (95% CI: 55–76%) for males, and 47% (38–56%), 0% and 53% (44–62%) for females.

Discussion

This study is the first to report genetic and environmental influences on depression symptoms using the general population sample of South Korean twins. In spite of the differences in symptom presentation, prevalence estimates of depression, and sociocultural risk and protective factors between East Asian and Western societies, the estimates of genetic and environmental contributions to depression symptoms found in the present sample were broadly in the range of those estimated from Western twin samples. As mentioned earlier, the CES-D includes four items worded positively. The sum of the four items in the present sample was normally distributed (skewness = .01, Kurtosis = –.45) and ranged from zero to 12, suggesting that there are sufficient variations in responses to these four items in spite of the contention that East Asians tend to suppress the expression of positive affects. Model-fitting analyses were conducted using the four items only. A similar pattern of sex difference in variance components was observed in the full general sex-limitation model and its various reduced models. Additive genetic, and shared and individual specific environmental influences on the sum of the four items in the same reduced model used for the full scale were, respectively, 0, .30, and .70 in males, and .26, .0, and .74. The slightly lower heritability estimate in females and the lower shared environmental influences in males found from these four positively scored items are probably due to the lower reliability associated with the reduction in the number of items. It is interesting to note that genetic influences emerge even when depression symptoms are measured by culturally biased items.

Sex differences in genetic and environmental influences on depression symptoms found in the present study were consistent with the results of twin studies by Silberg et al. (1999), Scourfield et al. (2003), and Jansson et al. (2004), but not with those by Kendler et al. (1994) and Agrawal et al. (2004). The results of this study showed that the total phenotypic and unstandardized genetic variances were greater in females than in males, suggesting that some of the genetic mechanism for depression symptoms may differ across two sexes.

For the last two decades, numerous studies have attempted to locate genes contributing to depression. So far, the 5-HT (serotonin) system has received the most attention for its involvement in depressive symptoms. Staley et al. (2006) found that diencephalon 5-HT transporter availability was decreased more markedly in female than in male depressed patients, suggesting that serotonergic mechanisms mediating depressed mood may differ between males and females. Another possibility is that some factors like hormonal changes in females enhance gene expression, resulting in higher genetic factors in females than in males. Seeman (1997) argued that the cyclic fluctuation of off-and-on binding to intranuclear estrogen receptors in the brain may render females vulnerable to stress, which confers susceptibility to depression.

Shared environmental factors known to contribute to depression symptoms include cold parenting, low level of family social support, family conflicts, and other disturbed family environments (Goldberg, 2006). The results of the present study suggest that these family environmental risk factors have more powerful impacts on the expression of depression in males than in females during adolescence and young adulthood. If replicated in a larger sample, these results will call for future research to investigate what those male-specific shared environmental factors are and how those factors exert influences on depression symptoms in males during adolescence and young adulthood.

The largest variance component found to explain individual difference in depressive symptoms in the present study was individual specific environmental factors. Examples of individual specific environmental risk factors for depression symptoms during adolescence and young adulthood include stressful life events such as separation from friends and mates. Several investigators have suggested that genes interact with these environmental risk factors (G × E) in developing depression (Eaves et al., 2003; Rice et al., 2003). For example, Caspi et al. (2003) demonstrated that as compared to carriers of the long alleles of the 5-HT polymorphisms, those of the short alleles exhibited increased vulnerability to depression in relation to stressful life events. According to Eaves et al. (2003), failures to take account of G × E interaction effects in the twin model may lead to an overestimation of the individual specific environmental variance component (Eaves et al., 2003; Rice et al., 2003). Thus, some of the variances of individual specific environmental factors in males and females found in the present study may include a G × E component. It would be interesting in future study to explore environmental risk factors specific to South Korean adolescents and young adults and investigate how these risk factors interact with genetic vulnerability to express depression symptoms.

There are some limitations in this study that deserve mention. First, twins who participated in the present

study were volunteers residing in the greater Seoul area, and thus, may not be a representative sample of South Korean adolescents and young adults. The mean score of the CES-D in the present sample was higher than that reported by Kim et al. (2000) who studied the CES-D in a nationwide singleton sample aged between 15 and 19 years (16.4 vs. 12.8). However, given that the CES-D data were collected in 1995 in the Kim et al. study, while the present data were collected in 2006, the mean difference between the Kim et al. and the present study is likely to reflect a secular increase in reporting symptoms of depression in South Korean population (Ohayon & Hong, 2006).

Second, as the sample size was limited, the present analyses were carried out in a combined sample of adolescents and young adults, controlling for the main effects of age. Lau and Eley (2006) examined continuities and changes in genetic and environmental influences on depressive symptoms across adolescence and young adulthood in a longitudinal twin sample. The authors found that although new genes and individual specific environmental factors emerged with age, overall, the magnitudes of genetic and environmental effects were fairly consistent across adolescence and young adulthood.

Third, although sex differences in genetic and environmental influences were detected in the present study, the sample, especially the DZ twin sample was relatively small to draw a firm conclusion. The absence of genetic effects in males in the best fitting model was somewhat inconsistent with results from prior studies, and is likely to reflect insufficient statistical power in the present study. Thus, replication of the present findings in a larger East Asian twin sample is clearly needed. Fourth, in the present study, depressive symptoms were measured by a questionnaire, the CES-D. The CES-D is more of a 'state' than 'trait' measure, as responses reflect frequency of experiencing a symptom during the last week. Although the CES-D has been shown to predict a clinical diagnosis of depression (Myers & Weissman, 1980; Roberts & Vernon, 1983), caution is necessary when the results of the present study are generalized to depressive disorders in clinical settings. Finally, the CES-D data in the present sample were collected through telephone interviews. Although face-to-face interview methods are often considered best in assessment of psychiatric illnesses, prior studies have supported the comparability of telephone and face-to-face interviews in assessment of mental illnesses (Rohde et al., 1997; Sobin et al., 1993).

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