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Article

Twin Study of the Relationship between Childhood Negative Emotionality and Hyperactivity/Inattention Problems

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Abstract

The present study aimed to determine the genetic and environmental etiology of the association between childhood negative emotionality (NE) and hyperactivity/inattention problems (HIP) using South Korean elementary school twins (mean age = 10.19 years, *SD* = 1.79 years). Telephone interviews were given to mothers of 919 twins (229 monozygotic males: 112 pairs and 5 individuals; 148 dizygotic males: 73 pairs and 2 individuals; 180 monozygotic females: 87 pairs and 6 individuals; 103 dizygotic females: 50 pairs and 3 individuals; 259 opposite-sex dizygotic twins: 127 pairs and 5 individuals) to assess their children's NE and HIP. Consistent with prior studies, the phenotypic correlation between NE and the HIP was moderate ($r = .29$; 95% CI = .24, .34). Model-fitting analysis revealed that additive genetic and nonshared environmental influences on NE were .45 (95% CI [.34, .54]) and .55 (95% CI [.46, .66]), respectively, and that additive and nonadditive genetic, and nonshared environmental influences on HIP were .08 (95% CI [.03, .26]), .41 (95% CI [.21, .51]) and .51 (95% CI = .42, .61), respectively. In addition, the additive genetic correlation between NE and HIP was 1.0 (95% CI [.52, 1.00]), indicating that additive genetic factors are entirely shared between the two phenotypes. Nonadditive genetic influences were unique to HIP and not responsible for the NE-HIP association. Nonshared environmental correlation was significant but modest ($r_e = .18$, 95% CI [.06, .30]).

Keywords: Negative emotionality; hyperactivity/inattention; twin study; genetic correlation; heritability

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A recent meta-analysis has demonstrated that parental ratings of children's negative emotionality (NE) significantly predict various forms of psychopathology, including attention deficit hyperactivity disorder (ADHD) in children and adolescents (Kostyrka-Allchorne et al., 2020). NE is characterized by sadness, fear and irritability and is known to form a basis for later neuroticism, a general marker of adulthood psychopathology (du Pont et al., 2019; Rothbart & Bates, 2006). The mean correlation between NE and externalizing disorders in children and adolescents has been reported to be .34 (Singh & Waldman, 2010). The relationships remained significant even after removing the overlapping items between measures of NE and childhood externalizing psychopathology, suggesting that the associations were not due to measurement confounding (Lemery et al., 2002).

Heritability of childhood NE is well documented. Genetic variance for NE was primarily additive, and generally fell within the range of 20%−60%, with the remaining variance being mostly attributable to nonshared environmental effects (Saudino, 2005; Vertsberger et al., 2019). ADHD is characterized by hyperactivity, inattention and impulsivity symptoms (American Psychiatric Association, 2013). ADHD is substantially influenced by genetic factors. For example, Faraone et al. (2005) found that the mean heritability estimate across 20 twin studies of ADHD symptoms was .76. Evidence for nonadditive genetic effects is inconsistent in the literature of ADHD symptoms. While some studies detected the presence of nonadditive genetic effects (e.g. Singh & Waldman, 2010), others failed to detect them (e.g. McLoughlin et al., 2007; Taylor et al., 2013).

Despite well-documented phenotypic relationships between NE and ADHD symptoms, a surprisingly small number of twin studies have examined the genetic and environmental etiology of these associations, partly because most previous twin studies associated NE with the broad externalizing factor rather than specific ADHD traits. For example, Schmitz et al. (1999) examined genetic and environmental influences on the covariance between NE and externalizing problem behavior in a small longitudinal twin sample (<350 pairs). The phenotypic correlations ranged from .19 to .30 from 14 months to 4 years of age, and these correlations were largely due to substantial genetic overlap (genetic correlations: .70−.86), with environmental correlations being nonsignificant. Similar conclusions were drawn from a few twin studies that examined the genetic and environmental etiology of the associations between NE and ADHD traits alone. An early study (Gjone & Stevenson, 1997) showed that significant genetic factors mediated the relationship between the Attention Problems scale of the Child Behavior Checklist and NE in children and adolescent twins. Singh and Waldman (2010) found that NE was significantly correlated with Hyperactivity/Impulsivity at .38 and Inattention at .33 in 4- to 17-year-old twins. They further found that while additive genetic influences were completely overlapping ($r_g = 1.0$)

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between NE and Inattention and NE and Hyperactivity/Impulsivity, common nonadditive genetic influences were small: only 29% between NE and Inattention and 26% between NE and Hyperactivity/Impulsivity. Common nonshared environmental influences were also small: 13% for Inattention and 9% for Hyperactivity/Impulsivity.

Using Australian adult twins (mean age = 32.31 years, *SD* = 2.5 years), Park et al. (2017) found that the phenotypic correlation between the Neuroticism scale of the NEO Five Factor Inventory (Costa & McCrae, 1992) and the Adult ADHD Self-Report Scale (ASRS; Kessler et al., 2005) was .45. The Cholesky decomposition model of the data showed additive genetic and nonshared environmental correlations to be .56 and .37, respectively, indicating that 52% of the phenotypic correlation between the Neuroticism scale and the ASRS scale was explained by overlapping additive genetic influences, with the remaining correlation explained by overlapping nonshared environmental influences. Although male twins showed some evidence for nonadditive genetic influences on the Neuroticism and the ASRS scales, common nonadditive genetic influences did not attain statistical significance in the total sample of the Park et al. study.

The main objective of the present study was to investigate the genetic and environmental etiology of the relationship between NE and hyperactivity/inattention problems (HIP) in elementary school twins in South Korea. We attempted to elucidate underlying specific quantitative genetic structure for NE and ADHD symptoms by focusing only on ADHD symptoms rather than the general externalizing factor.

Materials and Methods

Participants

Participants in the present study were elementary school twins drawn from the South Korean Twin Registry (Hur et al., 2019). Twins ranged in age from 7 to 13 years (mean = 10.19 years; *SD* = 1.79 years). Telephone interviews were conducted with mothers of the twins to assess their children's temperament and behavior problems. Zygosity of twins was determined from mothers' responses to questions during the telephone interview about physical similarity of the twins and frequency of confusion by others (Ooki et al., 1993). As the questionnaire method is less accurate than DNA analysis in determining twins' zygosity, we excluded twin pairs whose zygosity was ambiguous from data analyses ($n = 11$ pairs). The final sample included 919 twins, consisting of 229 monozygotic male (MZM: 112 pairs and 5 individuals), 148 dizygotic male (DZM: 73 pairs and 2 individuals), 180 monozygotic female (MZF: 87 pairs and 6 individuals), 103 dizygotic female (DZF: 50 pairs and 3 individuals), and 259 opposite-sex dizygotic twins (OSDZ: 127 pairs and 5 individuals; Table 1).

Measures

Negative Emotionality (NE). To measure NE, we used the Emotionality scale of a Korean version (Cheon, 2002) of the Emotionality, Activity and Sociability (EAS) temperament survey (Buss & Plomin, 1984). The EAS temperament survey consists of the (negative) EAS scales that measure major dimensions of children's temperament. Psychometric properties of the EAS temperament survey have been well established (Buss & Plomin, 1984). The NE scale comprises five items assessing children's temperamental distress and the tendency to become upset easily and intensely. Example items include 's/he cries easily', 's/he gets upset easily' and 's/he reacts intensely when upset'. During the telephone interview, mothers of twins were asked to rate their children's behaviors on a 5-point Likert-type scale ranging from *not at all true* (1) to *certainly true* (5). The NE score was calculated by summing the scores of all five items so that higher scores indicate higher NE. Cronbach's alpha reliability of the five items was .71 in the present sample.

Hyperactivity/Inattention Problems (HIP). To measure ADHD symptoms of twins, we used five items of the HIP scale of the Korean version of the Strengths and Difficulties Questionnaire (SDQ; Ahn et al., 2003; Goodman, 1997). The SDQ is one of the most commonly used instruments for screening psychopathology in children and adolescents aged from 3 to 17 years and has been translated into over 70 languages worldwide. It includes 25 items to represent five scales: Emotional Problems, Peer Problems, HIP, Conduct Problems and Prosocial Behavior. Psychometric properties of the five scales have been shown to be satisfactory across different age groups and sexes (Stone et al., 2010). The HIP scale includes two inattention, two hyperactivity and one impulsivity item. Mothers of the twins were asked to rate their children's behaviors on a 3-point Likert-type scale ranging from *not true* (0) to *certainly true* (2) through a telephone interview. The HIP score was computed by summing the scores of the five items. Higher scores represented greater symptoms of ADHD. Cronbach alpha reliability estimates of the five items were .78 in the present sample.

Statistical Analyses

To fulfill the goal of the present study, maximum likelihood twin correlations were computed for five zygosity groups, and a bivariate Cholesky model-fitting analysis was conducted. Monozygotic (MZ) twins who share all segregating alleles are assumed to be genetically identical, whereas dizygotic (DZ) twins, on average, share 50% of their segregating alleles, and are thus assumed to have 50% genetic resemblance. Genetic influences are implied when MZ twin correlation is greater than DZ twin correlation. When DZ twin correlation is lower than half the MZ twin correlation, this would be indicative of nonadditive genetic effects. On the other hand, when DZ twin correlation is greater than half the MZ twin correlation, this would indicate the presence of shared environmental influences. In twin correlational analysis, age was treated as a covariate.

In the bivariate Cholesky model-fitting analysis, the phenotypic variances and covariances of NE and HIP were partitioned into additive genetic (A1, A2), nonadditive genetic (D1, D2) and shared (C1, C2) and nonshared environmental (E1, E2) variance components. Measurement error was confounded with nonshared environmental variances and covariances. In the model, NE was entered first because we were interested in the extent to which the genetic factor for NE also influences the second genetic factor for HIP, assuming that NE may developmentally precede ADHD symptoms. As C and D effects cannot be estimated simultaneously in a model with twin data alone, we fit the ACE and the ADE models separately and compared the model-fit statistics to determine the full model. The bivariate Cholesky model provides additive genetic (r_a), nonadditive genetic (r_d), shared environmental (r_c) and nonshared environmental correlation (r_e) between NE and HIP. These correlations indicate the extent to which the same set of additive and nonadditive genes or shared and nonshared environments influence two phenotypes. Bivariate heritability,

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Table 1. Sample size and mean (SD) for age, Negative Emotionality (NE) and Hyperactivity/Inattention Problems (HIP) by zygosity and sex

	MZM	DZM	MZF	DZF	OSDZ	Total
N (individuals)	229	148	180	103	259	919
Age	10.42 (1.80)	10.15 (1.74)	10.33 (1.78)	10.41 (1.80)	9.83 (1.77)	10.19 (1.79)
NE	11.41 (4.24)	11.49 (4.42)	11.80 (4.39)	12.22 (4.52)	11.88 (4.46)	11.69 (4.39)
HIP	3.72 (2.73)	3.41 (2.68)	2.30 (2.07)	2.13 (2.15)	2.90 (2.69)	2.96 (2.60)

MZM, monozygotic male twins; DZM, dizygotic male twins; MZ; monozygotic female twins; DZF, dizygotic female twins; OSDZ, opposite-sex dizygotic twins; Age, age in years.

the contribution of common genetic factors to the phenotypic correlation, is calculated by the product of the square root of both heritabilities multiplied by the genetic correlation ($\sqrt{a1} \times r_a \times \sqrt{a2}$). The same logic can be applied to the calculation of bivariate environmentality (e.g. $\sqrt{e1} \times r_e \times \sqrt{e2}$), the contribution of common nonshared environmental factors to the phenotypic correlation. Because our sample size was not sufficiently large to adequately test sex differences in genetic and environmental correlations, males and females were combined to conduct bivariate model-fitting analysis, where age and sex were treated as covariates to control their main effects.

Mx (Neale et al., 2003) was used to compute maximum likelihood twin correlations and carry out model-fitting analysis. Mx produces −2 log-likelihood (−2 LL), and the difference between −2 LL of two nested models is distributed as a chi-square (χ^2), with degrees of freedom (*df*) equivalent to the difference in the number of parameters between the two models. The relative goodness of fit of various nested models was compared to that of the full model to determine the best-fitting, most parsimonious model for the data. Parameter estimates were then calculated with 95% confidence intervals using the maximum-likelihood method. The best-fitting model was selected on the basis of the log-likelihood ratio test (LRT) and the Akaike's information criteria (AIC; Akaike, 1987). The model with the lowest AIC value is considered to be the most parsimonious based on this criterion (Akaike, 1987).

Results

Descriptive Statistics and Twin Correlations

As the distributions of the NE and HIP scores were not seriously skewed (.30 for NE and .86 for HIP), data transformation was not necessary for any of the two scales. Means and standard deviations of HIP and NE for five zygosity groups are presented in Table 1. HIP was not significantly correlated with age ($r = .01$, $p = .78$). NE was significantly negatively correlated with age, but the size of the correlation was inconsequential ($r = -.07$, $p < .05$). The mean and variance of HIP were significantly higher in males than in females ($t = 9.0$, $p < .01$; $F = 58.4$, $p < .01$), although there was no significant sex difference in the mean or variance of NE ($t = .87$, $p = .39$; $F = .30$, $p = .58$). Within each sex, twins were not significantly different across zygosity groups in the mean or variance of HIP, indicating the absence of zygosity effects.

Figure 1 shows maximum likelihood twin correlations and their 95% confidence intervals for NE and HIP. The correlations for NE were, respectively, .50 for MZM, .20 for DZM, .41 for MZF, .18 for DZF and .27 for OSDZ twins. The corresponding correlations for HIP were .55, .04, .37, .06 and .12, respectively. As can be seen from confidence intervals in Figure 1, all MZ twin correlations were significant, whereas all of DZ twin correlations were not significant except for the OSDZ correlation for NE. Higher MZ than DZ twin correlations for both traits in both sexes suggested substantial genetic influences. DZ twin correlations for NE were only slightly lower than half the MZ correlations in both sexes, indicating that genetic variance may be additive for NE. However, DZ twin correlations for HIP were much lower than half the MZ twin correlations in both sexes, which suggested that genetic variance may be largely nonadditive for HIP.

The phenotypic correlation between HIP and NE adjusted for age and sex was .29 (95% CI [.24, .34]), indicating a significant relationship between the two traits. The phenotypic correlation was not significantly different between boys and girls ($r = .30$ for boys, $r = .28$ for girls). The sex- and age-adjusted cross-twin, cross-trait correlations between NE and HIP were .19 (95% CI [.05, .32]) for MZ and .14 (95% CI [.15, .26]) for DZ twins. Higher MZ than DZ cross-twin, cross-trait correlation suggested that genetic influence might mediate the relationship between NE and HIP. MZ cross-twin, cross-trait correlation lower than the phenotypic correlation suggested the presence of nonshared environmental influences on the relationship between HIP and NE.

Bivariate Model-Fitting Analysis

Table 2 presents the results of bivariate model-fitting analysis. AIC was much lower in model 1 than in model 2 (AIC = 1362.03 vs.1372.42), indicating that the ADE model is better than the ACE model. In model 3, all nonadditive genetic variances and covariance for HIP and NE were removed from the ADE model. The resulting chi-square difference was significant ($\Delta\chi^2 = 10.39$, $\Delta df = 3$, $p = .02$), indicating that nonadditive genetic effects are important. Model 4 allowed nonadditive genetic variance for HIP only, whereas model 5 allowed nonadditive genetic variance for NE only. A significant difference in chi-square occurred in model 5 ($\Delta\chi^2 = 8.90$, $\Delta df = 23$, $p = .01$) but not in model 4 ($\Delta\chi^2 = .58$, $\Delta df = 2$, $p = .75$), suggesting that nonadditive genetic variance was significant only for HIP. In model 6, additive genetic correlation was eliminated from model 4, whereas in model 7, nonshared environmental correlation was dropped. Significant poor fit occurred in both models 6 and 7. Thus, on the basis of LRT, model 4 was chosen as the best-fitting one. AIC agreed with the decision made from LRT because model 4 had the lowest AIC.

Parameter Estimates in the Best-Fitting Bivariate Model

Figure 2 shows the parameter estimates in the best-fitting model. Additive genetic and nonshared environmental influences on NE were .45 (95% CI [.34, .54]) and .55 (95% CI [.46, .66]), respectively. Genetic influences on HIP were primarily nonadditive: Additive and nonadditive genetic and nonshared environmental influences on HIP were .08 (95% CI [.03, .26]), .41 (95% CI [.21, .51]) and .51 (95% CI [.42, .61]), respectively. Figure 2 also shows that the additive genetic correlation between HIP and NE was 1.0 (95% CI [.52, 1.00]), suggesting that although the additive genetic variance component of HIP was modest (.08), it completely overlapped with

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Table 2. Bivariate model-fitting results for the relationship between Negative Emotionality (NE) and Hyperactivity/Inattention Problems (HIP)

	Model	−2 LL	*df*	AIC	$\Delta\chi^2$	Δdf	*p*
1	ADE for NE, HIP	5020.03	1829	1362.03			
2	ACE for NE, HIP	5030.42	1829	1372.42			
3	AE for NE, HIP	5030.42	1832	1366.41	10.39	3	.02
4	AE for NE, ADE for HIP	5020.60	1831	1358.60	.58	2	.75
5	AE for HIP, ADE for NE	5028.93	1831	1366.93	8.90	2	.01
6	AE for NE, ADE for HIP, Drop r_a	5041.16	1832	1377.16	21.13	3	.00
7	AE for NE, ADE for HIP, Drop r_e	5029.37	1832	1365.37	9.34	3	.02

Models were compared with the ADE model. The best-fitting model is shown in bold. −2 LL, −2 log-likelihood; A, additive genetic influences; C, shared environmental influences; D, nonadditive genetic influences; E, nonshared environmental influences including measurement error; r_a, additive genetic correlation; r_e, nonshared environmental correlation.

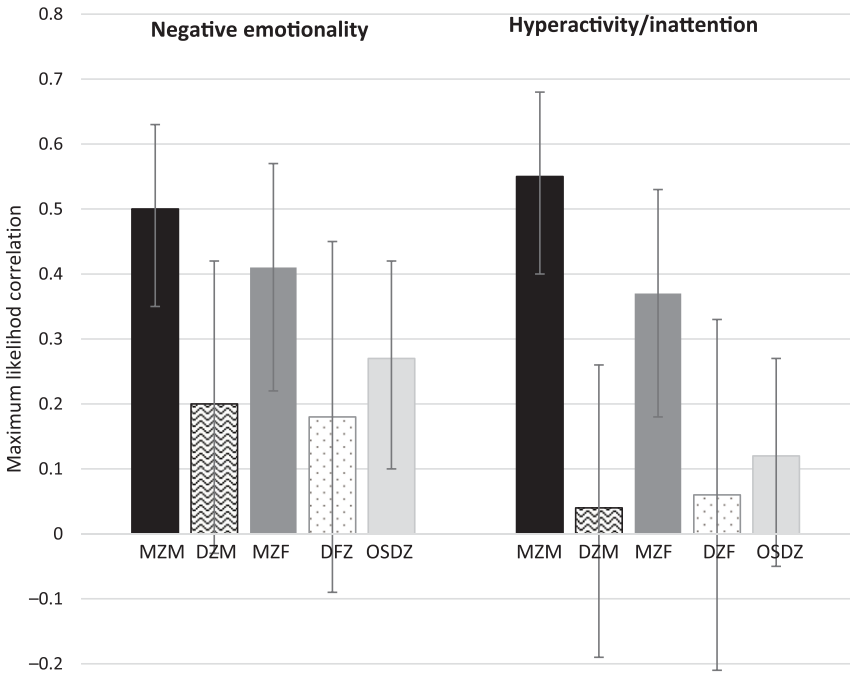

Fig. 1. Maximum likelihood twin correlations for Negative Emotionality and Hyperactivity/Inattention problems for monozygotic male twins (MZM), dizygotic male twins (DZM), monozygotic female twins (MZF), dizygotic female twins (DZF), and opposite-sex dizygotic twins (OSDZ).

genetic influences on NE. Nonadditive genetic variance was unique to HIP and was not responsible for the NE-HIP association. The nonshared environmental correlation between NE and HIP was significant but small ($r_e = .18$; 95% CI [.06, .30]). The bivariate heritability and environmentality calculated from these estimates were .19 (1.0*√.45 *√.08) and .10 (.18*√.55*√.51), respectively. These suggest that 66% (.19/.29) of the phenotypic correlation ($r = .29$) between NE and HIP can be explained by shared genes that act additively, and the remaining 34% (.10/.29) can be accounted for by common no-shared environmental influences and measurement error.

Discussion

The etiology of the relationship between NE and HIP was examined in South Korean elementary school twins. Our finding that the NE-HIP phenotypic association was largely due to genetic overlap was in line with prior studies (Park et al., 2017; Singh & Waldman, 2010). Especially, a complete overlap of additive genetic factors between NE and HIP found in our study corroborated the results from the Singh and Waldman study (2010). However, our study differed from the Singh and Waldman (2010) study and the Park et al. (2017) study in that while we found no overlap in nonadditive genetic variance, the Singh and Waldman study found small but significant overlap in nonadditive genetic variance between NE and two ADHD symptoms (26% and 29%) and the Park et al. study showed a significant amount of additive genetic variance unique to ADHD symptoms (25%) in addition to the shared additive genetic variance between ADHD symptoms and NE. As the Singh and Waldman study included twins with a wide range of age (preschoolers to late adolescents), and the Park et al. study contained adult twins, age differences in twins among the studies may partly explain the discrepancies in findings. Heritability estimates of ADHD symptoms were found to be lower in adults than in children (Boomsma et al., 2010; Faraone et al., 2005). For this reason, several researchers have suggested that childhood ADHD, adulthood

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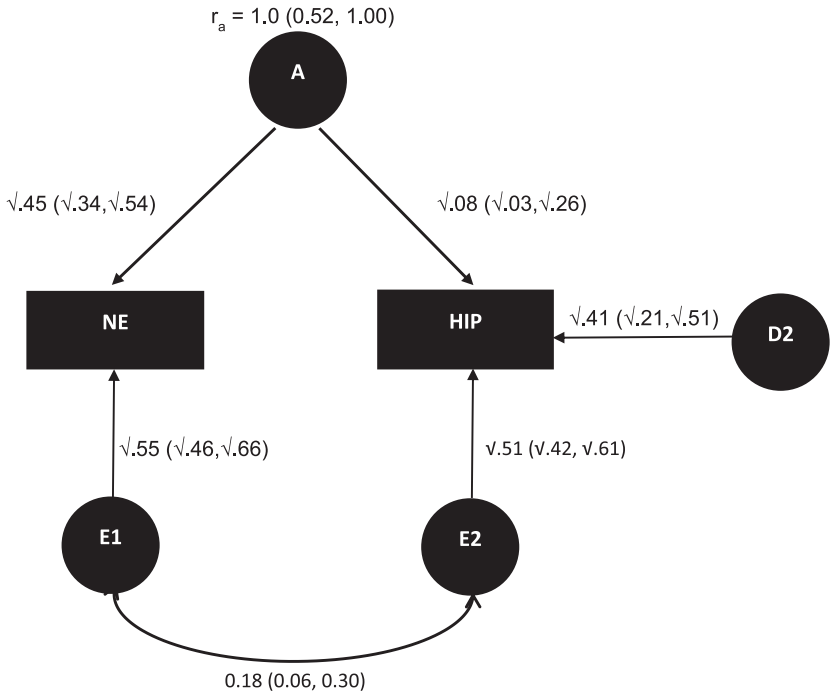

Fig. 2. Parameter estimates in the best-fitting bivariate model for the relationship between negative emotionality (NE) and hyperactivity/inattention (HIP) problems. A, additive genetic variance; D2, nonadditive genetic variance unique to HIP; E1, nonshared environmental variance including measurement error unique to NE; E2, nonshared environmental variance including measurement error unique to HIP; r_a, additive genetic correlation; r_e, nonshared environmental correlation. The path coefficients should be squared to determine variance components.

ADHD and persistent ADHD may be genetically distinct subtypes that need to be analyzed separately (Palladino et al., 2019).

Our findings support the developmental propensity model (Lahey & Waldman, 2003), where early developing disposition such as NE plays an important etiological role in later manifestation of externalizing disorders. However, as we assessed our twins contemporaneously, future studies should examine the etiological associations between NE and ADHD symptoms prospectively using a longitudinal design. Recently, Caspi et al. (2014) proposed that as a parallel to the g factor in cognitive abilities, there exists a single general factor (P factor) that influences hundreds of psychiatric symptoms, which aggregate into externalizing versus internalizing domains, and the thought disorder domain. Caspi et al. further maintained that the P factor is characterized by high neuroticism and low agreeableness and conscientiousness. Our finding of the significant positive association between NE and ADHD symptoms generally fits well with the concept of the P factor.

Genomewide association studies (GWAS) to date suggest that ADHD is a highly polygenic trait in which many common variants of small effect size make up the polygenic component (Faraone & Larsson, 2019). Recently, a meta-analysis of 12 GWAS demonstrated that 12 independent genetic loci mostly involved in neurodevelopmental processes were associated with ADHD (Demontis et al., 2019). Our finding of genetic overlap between NE and HIP suggests that genetic variants associated with NE are likely to also affect variations in ADHD symptoms and vice versa. Consistent with our finding, Demontis et al. (2019) found significant genetic correlation ($r = .26$) between neuroticism and ADHD in a GWAS meta-analysis. However, Gale et al. (2016) failed to detect evidence of pleiotropy in associations between neuroticism and ADHD, suggesting that more work is necessary to draw a firm conclusion on genetic correlation between NE and ADHD symptoms.

Our study has several limitations that need to be addressed. First, our data were based on mothers' report only. If we had employed multiple informants, the results may have been somewhat different. However, agreement among raters of children's temperament tends to be low (Achenbach et al., 1987). For this reason, focusing on the common variance among raters can lead to low heritability, explaining only a fraction of the variance of the construct (Burt et al., 2005). Second, it has been argued that parents tend to exaggerate dissimilarity of DZ twins (sibling-contrast effects). If contrast effects are present but not detected, then nonadditive genetic variance can be overestimated, while additive genetic variance and/or shared environmental variance can be underestimated (Rietveld et al., 2003; Saudino et al., 2000). In twin studies, sibling-contrast effects are difficult to detect without including additional biologically unrelated relatives raised together (e.g. step siblings). However, larger DZ than MZ twin variances are indicative of sibling contrast effects (Saudino et al., 2000). As we noted above, the variances of MZ and DZ twins in NE and HIP in our sample were not significantly different, suggesting that our estimates of genetic influences may not be seriously biased due to sibling contrast effects. Third, the present study relied on the screening questionnaire rather than diagnostic interviews to assess ADHD symptoms. Prior twin studies found a strong genetic link between the extreme and the subthreshold variation of ADHD symptoms, suggesting that etiological factors involved in ADHD may be largely the same across the full range of symptoms (Larsson et al., 2012; Levy et al., 1997). Fourth, the HIP scale in our study is a short measure including only five items. Future twin studies may employ a more comprehensive measure to determine how NE is genetically related to each of the three specific components of ADHD, that is, hyperactivity, inattention and impulsivity. Fifth, although additive genetic correlation between NE and HIP found in the present study was 1.0, the phenotypic correlation (r

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= .29) and the common additive genetic variance (8%) between the two traits were both modest. Thus, caution has to be exercised in interpreting the practical significance of the findings. Finally, bivariate analysis in the present study was based on a combined sample of males and females. The phenotypic correlations between NE and HIP were almost the same in males and females in our sample. However, prior studies have shown that although the magnitudes of genetic and environmental influences are the same in boys and girls, genes for ADHD may be expressed differently between two sexes (Derks et al., 2007). Thus, future twin studies should increase the sample size to examine sex differences in the etiology of the association between NE and ADHD symptoms.

In summary, using bivariate genetic model-fitting analysis, we found that shared additive genetic factors largely mediated the phenotypic relationship between NE and ADHD symptoms in elementary school twin children in South Korea. Nonshared environmental factors also significantly contributed to the phenotypic association, but the magnitude was small. These results highlight possible overlap in genetic variants between NE and ADHD symptoms, aiding gene identification studies for ADHD symptoms and neuroticism.

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