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ORIGINAL ARTICLE

Evidence for shared environmental contributions to attention-deficit/hyperactivity traits. A twin study

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Abstract
Background and objectives: Behavior-genetic analyses have shown that measurements of inattention and hyperactivity–impulsivity are genetically-influenced. In view of limited studies on ADHD (Attention deficit hyperactivity disorder) in Spanish samples, this study aims to explore the genetic architecture of ADHD symptoms; inattention and hyperactivity–impulsivity in a Spanish twin schoolchildren sample.
Methods: Participants were 258 pairs of adolescent Spanish twins. Symptoms of ADHD, inattention and hyperactivity–impulsivity were assessed by means of a sub-scale of the Strengths and Difficulties Questionnaire. Univariate twin models, according to sex, were run to assess the heritability of ADHD symptoms.
Results: Heritability of hyperactivity was 55% in girls, 57% in boys. Inattention showed a heritability of 26% in girls, and no genetic factors influence was found in boys. Environmental factors are prominent influences among these traits.
Conclusion: Our results highlight the magnitude of environmental effects among ADHD symptoms and therefore the importance of preventive programs that may modify the expression of these traits.

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Introduction

Attention deficit hyperactivity disorder (ADHD) is a common and prevalent condition that shows a worldwide variable prevalence estimate of 5.0–7.0% in school-age children.[1] The core symptoms of ADHD, inattention, impulsivity, and hyperactivity, are common daily behaviors of most preschool aged children, and tend to change with maturity.[2] These aspects are related to de difficulty in diagnosing the disorder (ADHD) in preschool children.

Behavior-genetic analyses have shown that measurements of inattention and hyperactivity–impulsivity are genetically-influenced, with estimates ranging from 56.0% to 87.0%.[3,4] There is a substantial amount of evidence to fully support that not only attention problems and hyperactivity–impulsivity are highly heritable, but also heritability estimates are similar across childhood.[5] Furthermore there is an overlap between genes influencing both behavioral traits, that is to say the two dimensions share in a large extent the same etiological genetic influences.[4] Regarding sex, even though ADHD symptoms are more prevalent among boys,[6] heritability estimates are shown to be similar for both genders.[5]

As we know, ADHD commonly appears comorbid to other psychiatric illness such as anxiety, mood, and disruptive disorders, as well as substance abuse.[7] Moreover, genes that influence ADHD symptoms may also be at play in these numerous comorbidities that usually entails this disorder. In this regard, it has been described that, ADHD and depression, show a genetic correlation over to 0.77, or in other words common genes confer liability to both conditions in children and adolescents.[8] Similar patterns have been demonstrated for conduct and disruptive problems with ADHD, which also show common underlying genetic risk.[9] Additionally, previous research has shown that genetic influences on reading difficulties may be stronger in those who also have a diagnosis for ADHD than subjects without.[10]

Even though the influence of gens has to be considered when stablishing a diagnosis of this complex condition, taking into account family history of ADHD, related conditions and comorbidities, we cannot fail to forget the main role that the environmental factors play. Research has continuously demonstrated that the environment may influence the development of ADHD. Numerous environmental factors have been epidemiologically associated with ADHD comprising psychosocial adversities, parents mental health, violence, stress and the exposure to tobacco smoke and alcohol in utero.[11] Moreover, twins studies have constantly suggest that ADHD and its symptoms are influenced by genes (A) and unique environmental influences (E).

The aforementioned variability in the prevalence of ADHD worldwide may be due to several reasons, firstly in could be related to the wide range of factors that affect accurate assessment of children and youth.[12] Secondly it could also be linked to the different patterns of genetic and environmental influences that vary across the different countries and cultures. The Gene–environment interplay involves variations in heritability according to environmental circumstances.[13] Accordingly, environmental constraints, such us rigid patterns of child raising or school educational childcare models, may reduce the role of genetic influences among the expression of ADHD. Thus, studying heritability estimates and cultural differences across different geographic and cultural areas is of interest and can lead to a better understanding of the complex syndrome ADHD.

The current investigation explores the genetic architecture of ADHD symptoms; inattention and hyperactivity–impulsivity in a Spanish twin schoolchildren sample. To our knowledge, this is the first study conducted in our country that assesses the heritability of ADHD symptoms and evaluates differences in gene–environmental influences according to sex.

Methods

Participants

Subjects were obtained from a study of risk factors, early detection and prevention of eating disorders, the DITCA-CV program (Programa de Detección e Intervención en Trastornos de la Conducta Alimentaria de la Comunidad Valenciana), that the Public Health and Education administrations of Valencia, Spain, have offered for many years to all compulsory secondary education schools in the region. The survey was approved by the Department of Public Health of the regional health administration. Passive informed consent from parents was obtained. The methods for the DITCA-CV have been reviewed elsewhere [see[14]]. The inclusion criteria were being 12–18 years old and attending class on the day in which the questionnaires were conducted. The global population sample comprised 57.997 schoolchildren (49.1% girls, 50.9% boys) obtained over four consecutive years. Although not a random sample, it included a moderate percentage (33%) of the school population of our community. From the population sample, 584 adolescent twins were identified by matching on family name, date of birth, school and year of the survey.[15] Opposite sex pairs were excluded from the univariate analysis. It's a convenience twin sample comprised of twin pairs to whom we were able to access through their school centers. There were no selection bias attributable to parents as children directors or tutors were those who permitted to stablish twin zygosity.

Zygosity determination

School teachers participated in the twin recruitment by confirming that pairs included in the sample were in fact siblings and by determining twins' zygosity. Teachers answered a twin physical similarity questionnaire, over 98% accurate to determine zygosity.[16] Questions are about childhood similarity (i.e., ''The siblings are as alike as two peas in a pod, or do they show a common resemblance between siblings?''). We validated teachers' determination of zygosity in 108 twin pairs, administrating the physical similarity questionnaire to the twins' mother or father and their teacher. Only in 8 cases there were discrepancies between answers from both sources. In those cases, the questionnaire was repeated and disagreement was solved in 6 cases, 5 in favor of teacher's first answer and one in favor of parents'. The Cohen kappa statistic was 0.94 ($p < 0.001$). This statistic measures the agreement between two or more observers when they are

measuring the same object. A kappa of 1 indicates perfect agreement, whereas a kappa of 0 indicates agreement equivalent to chance. Our results indicated a high agreement between teachers and parents and so, that our method to determine zygosity was accurate.[14]

ADHD symptoms measurement

Symptoms of ADHD, inattention and hyperactivity–impulsivity were assessed by means of a sub-scale of the Strengths and Difficulties Questionnaire (SDQ). The SDQ is an brief instrument for early detection of psychological problems, that can be administered to the parents and teachers of 4–16-year-olds and to 11–16-year-olds themselves.[17] For the current investigation, schoolchildren self-rated the questionnaire, wording is slightly different compared to the questionnaire completed by patents. The SDQ scale is composited of 25 items which can be divided in 5 sub-scales: ''emotional symptoms'', ''conduct problems'', ''hyperactivity-inattention'', ''peer relationship problems'' and ''prosocial behaviour''. The ''hyperactivity-inattention'' sub-scale assesses for the two core DSM-IV symptoms of ADHD. High scores do not determine the existence of an ADHD diagnosis, but suggest the presence of features or traits of ADHD.[17] We used the Spanish version of the scale. More information regarding the SDQ scale is available in the website www.sdqinfo.com.

Statistical analysis

Descriptive statistics

We analyzed the data with SPSS v. 17. Descriptive statistics of the traits measured were calculated and the differences between groups (according to sex and zygosity) were examined by means of the *t*-student test.

Equal environments assumption (EEA)

The EEA assumption holds that MZ (MZ) twins don't receive a more similar treatment from their environment when compared to dizygotic (DZ) twins, and even if they do it does not have an effect on twin similarity for the trait under heritability evaluation.[18] In other words, the EEA implies that the shared environmental influences are equally important in MZ and DZ twin pairs. The validity of the EEA has been debated.[19,20] If violated, increased MZ relative to DZ concordance for the trait under study may be due to environmental factors rather than (or in addition to) genetic factors.[21]

To evaluate de EEA the twin's parents were contact by telephone and answered to the questionnaire based on their children's differential experiences during childhood.[22] This questionnaire has been previously used in twin studies.[18,23,24] The questionnaire was translated into Spanish (firstly translated and then inversely translated into English).

We tested the EEA by calculating Pearson coefficient correlations (*r*) between the total value of co-socialization and childhood' treatment and the intra-pair difference in ''inattention'' and ''hyperactivity–impulsivity''. The childhood treatment is composed of 3 items regarding parents' treatment; ''Did your twins sleep together in the same room?'' ''Did your twins spend a lot of time together?'' And ''Did your twins dress the same?'' The co-socialization scale is composed of four items regarding differential experiences during childhood; ''Did your twins attend to the same school?'' ''Did your twins have the same school teacher?'' ''Did your twins play together?'' And ''Did your twins play sports together?'' A significant negative correlation ($p < 0.05$) would indicate greater similarities of these traits among those twins with a greater level of common experiences, and so, EEA violation.

Univariate models

Analyses on twin data assess factors influencing liability to a latent phenotype comparing the resemblance of MZ twins with the resemblance of DZ twins for that phenotype (covariation).[25] As we know, MZ twins share 100% of their genes, while DZ share, on average, 50%. Consequently, a higher phenotypic similarity between MZ compared to DZ points toward the presence of a genetic influence. Based on this knowledge, we used univariate structural equation modeling for ''inattention'' and ''hyperactivity–impulsivity''. This way, the variance of a trait can be decomposed into additive genetic effects (A), shared (common) environmental effects (C) and unique (non-shared) environmental effects (E). Initially, a full model (ACE) was fitted to the data, followed by an AE, a CE, and a model containing only E influences. The goal of model fitting is to explain the observed data as an optimal combination of goodness-of-fit and parsimony. Akaike's Information Criterion (AIC) states that the lower the value is, the better fitness the model has.[25] All statistical analyses were performed using OpenMx.

Results

The sample was composed of 584 twin pairs; 200 MZ twins (118 female twin pairs, 82 male twin pairs) and 384 DZ twin pairs; 102 same sex female twin pairs, 87 same sex male twin pairs and 195 discordant sex twin pairs. Mean age at the time of the study was of 14.2 ± 1.1 years. No statistical differences were found due to sex or zygosity.

Description of ADHD measures

Descriptive data for each outcome are reported in Table 1, according to sex and zygosity. Mean scores for the total Hyperactivity-inattention subscale ranged from 3.93 (S; 2.16) to 4.60 (S; 2.23). No statistical differences were found due to zygosity or sex.

Equal environments assumption (EEA)

There were no threshold differences in frequency and quality of contact with parents or measures of co-socialization between MZ and DZ twins. Moreover, there was no statistical negative association between measures of co-socialization and/or in frequency and quality of contact with parents with intra-pair resemblance for any of the constructs of ADHA. Therefore, no significant violation of the equal environments assumption (EEA) was found.

Table 1 Hyperactivity-inattention sub-scale of the Strengths and Difficulties Questionnaire (SDQ) mean scores in the twin sample ($N = 516$).

	Boys		Girls	
	Mz 164 X (s)	Dz 172 X (s)	Mz 234 X (s)	Dz 199 X (S)
SDQ	4.60 (2.236)	4.40 (2.099)	4.07 (2.039)	3.93 (2.164)
Hyperactivity	2.62 (1.583)	2.98 (1.631)	2.64 (1.502)	2.56 (1.503)
Inattention	6.24 (2.287)	6.85 (2.542)	6.56 (2.326)	6.47 (2.524)

DZ: Dizigotics.
MZ: Monozigotics.
SDQ: Strengths and Difficulties Questionnaire.
S: Standard deviation.
X: mean.

Univariate twin analyses

Table 2 shows Pearson correlation coefficients between members of the twin pair for the different ADHD subscales. The first step of the evaluation of heritability estimates is to compare the resemblance of MZ twins with DZ twins for a trait or disease.[26] As we know, MZ twins share 100% of their gens, while DZ twins share 50% of their genes on average. Thus, MZ correlations (rMZ) twice higher than the DZ twins (rDZ), suggests a genetic influence among the phenotype. Furthermore, if we compare separately the correlations between boys and girls, we would obtain specific information about quantitative differences in the heritability of the phenotype due to sex. For example, the ''Hyperactivity'' scale in girls, MZ twin correlations (0.534) were consistently much higher than DZ twin's (0.327) (Table 2). On the contrary, a MZ twin's resemblance similar to DZ twin's indicates a low heritability of the trait, as we can observe for inattention in boys (rMZ of 0.798 and rDZ of 0.740).

Tables 3 and 4 show results of fitting separate univariate ACE models to each ADHD subscale in girls and boys respectively. For the Hyperactivity trait, in both sexes, the AE model provided an appropriate fit to the data and its AIC showed the most parsimonious explanation. This model indicates the influence of genetic (A) and specific environmental factors (E) on its variance, and, at the same time, dismisses a common environmental influence (C). Heritability estimates were moderate and similar among boys and girls, being 57.0% and 55.0% respectively. While for the Inattention trait, the ACE model was the best-fitting model for girls, with genetic contribution accounting for 26.0% and common environmental factors accounting for 60.0% of the variance. Surprisingly, the best model in boys dismissed a genetic contribution for the inattention trait and indicated an influence of common environmental (C) and specific environmental factors (E) on its variance accounting for 80.0% and 20.0% respectively.

Table 2 Pearson correlation coefficients between members of the twin pair for the SDQ Hyperactivity-Inattention sub-scales according to sex.

	Hyperactivity–impulsivity		Inattention	
	MZ	DZ	MZ	DZ
Girls	.534	.327	.850	.739
Boys	.530	.396	.798	.740

DZ: Dizigotics.
MZ: Monozigotics.

Discussion

The present work is the first investigation conducted in a Spanish twin sample to evaluate the etiological influences among the core symptoms of ADHD. No violations on the EEA were found for each variable of interest.

Our results showed slightly higher mean scores of the SDQ Hyperactivity-Inattention subscale as other authors have reported by means of the self-reported scale in adolescent samples.[27]

We found moderate heritability estimates for hyperactivity–impulsivity among both sexes, while inattention showed a low heritability among girls, and genetic factors influences were dismissed among boys. Similarly, previous findings have shown higher heritability estimates for ratings of hyperactivity–impulsivity than inattention.[4]

Even though twin studies have revealed that measurements of inattention and hyperactivity–impulsivity are genetically-influenced, with estimates ranging from 56.0% to 87.0%,[3,4] we are not the first to note that ADHD symptoms show scarce genetic influences. Edwars et al. conducted a twin study that observed that the main symptoms of ADHD in males show low heritability estimates of 0.34 for inattention, 0.31 for hyperactivity/impulsivity and 0.29 for forgetfulness.[28]

The fact that we found low-moderate heritability estimates and even no genetic influences among the ADHD measures could be explained by the use of a community sample instead of a clinical sample composited of ADHD diagnosed subjects. In support of this hypothesis, a Swedish study conducted in a population representative sample of 2.143 twins concluded that low extreme ADHD traits were significantly influenced by shared environmental factors (23.0–35.0%) but were not significantly heritable. In contrast, high extreme ADHD traits showed significant heritability (39.0–51.0%) but no shared

Table 3 Univariate structural equation models in girls and boys of; hyperactivity. Goodness of fit statistic and relative contributions of genetic and environmental parameters.

	Variance components			Goodness of fit			
Model	A	C	E	Δ df	*p*	Δ-2LL	AIC
GIRLS							
ACE	0.33 [0,0.60]	0.20 [0,0.49]	0.47 [0.36, 0.58]	–	–	–	658.65
AE	0.55 [0.43, 0.64]	–	0.45 [0.36, 0.57]	1	0.27	1.20	657.85
CE	–	0.46 [0.34, 0.54]	0.54 [0.46, 0.66]	1	0.097	2.75	659.40
E	–	–	1	2	<0.001	52.15	706.80
Model	A	C	E	df	*p*	Δ-2LL	AIC
BOYS							
ACE	0.31 [0,0.6]	0.23 [0,0.48]	0.45 [0.33, 0.58]	–	–	–	562.88
AE	0.57 [0.45, 0.67]	–	0.43 [0.33, 0.55]	1	0.228	1.46	562.33
CE	–	0.46 [0.38, 0.54]	0.54 [0.47, 0.62]	1	0.154	2.03	562.91
E	–	–	1	2	<0.001	41.93	600.81

AIC = Akaike's Information Criterion.
dF: degree of freedom.
p: likelihood ratio χ^2 test.
A: additive genetic.
C: common environment.
E: unique environment.

Table 4 Univariate structural equation models in girls and boys of; inattention. Goodness of fit statistic and relative contributions of genetic and environmental parameters.

	Variance components			Goodness of fit			
Model	A	C	E	df	*p*	Δ-2LL	AIC
GIRLS							
ACE	0.26 [0.09, 0.43]	0.60 [0.42, 0.76]	0.14 [0.11, 0.18]	–	–	–	868.47
AE	0.86 [0.82, 0.89]	–	0.14 [0.11, 0.18]	1	<0.001	22.55	889.02
CE	–	0.80 [0.75, 0.83]	0.20 [0.17, 0.25]	1	<0.001	11.57	878.03
E	–	–	1	2	<0.001	225.54	1090.01
Model	A	C	E	df	*p*	Δ-2LL	AIC
BOYS							
ACE	0.10 [0,0.22]	0.72 [0.62, 0.82]	0.18 [0.13, 0.23]	–	–	–	699.14
AE	0.83 [0.79, 0.88]	–	0.17 [0.12, 0.22]	1	<0.001	31.26	728.40
CE	–	0.80 [0.76, 0.84]	0.20 [0.16, 0.24]	1	0.25	1.31	698.45
E	–	–	1	2	<0.001	168.42	863.56

AIC = Akaike's Information Criterion; dF: degree of freedom; P: likelihood ratio χ2 test; A: additive genetic
C: common environment
E: unique environment

environmental influences.[29] In contrast, a German study conducted by means of a clinical sample of patients diagnosed of ADHD found heritability estimates of 0.88 for males and 0.77 for females.[30]

An additional explanation that must be considered in relation to the low heritabilities observed in our sample resides in the fact that we used a self-rating scale, and children may not be reliable informers of their own behavior. Low reliability leads to under-power genetic effects because it entails to lower identical (MZ) within-twin correlations, and so increases measurement error.[31] In this regard, Morwood et al. used a large sample composited of 6372 twin pairs aged 11-12 years old to examine the genetic and environmental influences to individual differences in parent, teacher and self-ratings of ADHD symptoms evaluated by means of the SDQ. Their results showed that estimates were lower for self-ratings (48.0%) than for parent (82.0%) or teacher (60.0%) ratings.[27]

Heritability estimates derived from our sample showed remarkable differences according to sex. A possible explanation has been suggested by other authors that argue that there is a ''female protective effect'' against ADHD behaviors.[32] The ''female protective effect'' postulates that girls go through greater exposure to etiological

factors than boys in order to develop ADHD. These may occur not only throughout differences in the variances of the etiological factors, but throughout differences in the gene–environment interplay that involves variations in heritability according to environmental circumstances.[13] The gene–environmental relationship comprises three differentiated mechanisms. Firstly, in the ''additive'' model, influence due to genes and environment are viewed as independent factors. Secondly, the gene–environmental interaction model (GxE) entails that responsiveness to the environment is conditional to the genotype.[33] That is, environment factors influence is more prominent among those subjects who are at high genetic risk or, on the other hand, that the environmental factors modify the impact of genetic influences. Finally, the genotype-environmental correlation model (rGE) implies that genes influence the probability of subjects' exposure to the environment he encounters.[33] Accordingly, environmental constraints, such us rigid patterns of child raising or school educational childcare models, may modify the role of genetic influences among the expression of ADHD. Thus, studying heritability estimates, sex differences and cultural differences across different geographic and cultural areas is of interest and can lead to a better understanding of the complex syndrome ADHD. To date numerous studies have found evidence for different environmental factors moderating etiological influences on ADHD, such as parental involvement[34] or maternal stress during pregnancy.[35] Future research should seek to delineate if the protective female effect undergoes a gene–environmental interaction model, and if so which specific environmental experiences work as etiologic moderators, and to clarify how this gene–environment interplay might be sex specific related.

An original aspect of our study relies on the results related to the common environmental factors influences among the trait inattention in both girls and boys. One often replicated result and cited conclusion from twin studies has been that the key environmental influences are those ''non-shared'' between siblings, whereas environmental common influences that create similarities between the twin pair are indistinguishable from zero, and so do not contribute to the variance of ADHD.[36] However, other authors have suggested that these results may be partly due to methodological issues and that the effects of individual environmental factors could be higher than the effects of individual genes, as well as more immediately useful for intervention treatments, emphasizing the value of future environmental investigation.[37] In sum, our results highlight the magnitude of environmental effects among ADHD symptoms and therefore the importance of preventive programs that may modify the expression of these traits, at least in our community sample.

There are several limitations to the current study. First of all, we must point out that only twin pairs that participated in DITCA-CV eating disorders prevention program were included in the study. Therefore, recruitment was carried out in two steps, what usually entail more losses.[38] Secondly, our sample was relatively small for a twin study. We included 516 participants (258 twin pairs; 149 MZ twin pairs and 109 DZ twin pairs). Thus, this sample issue has the potential to underpower to discern C effects. However, we did manage to find common environmental influences. Finally, when behavioral and hyperactivity disorders are analyzed by means of the SDQ, self-reported data have less predictive value than when the questionnaire is answered by parents or teachers.[17] Our results may not be generalizable to other symptoms of ADHD measured throughout other scales.

Conclusions

Our investigation reveals that genetic influence among ADHD symptoms, inattention and hyperactivity–impulsivity, are low in our adolescence community sample. The fact that environmental factors are prominent influences among these traits, focus the attention upon the importance of prevention strategies that can have a powerful effect among their expression. Given that ADHD commonly appears comorbid to other psychiatric illness such as anxiety, mood, and disruptive disorders, as well as substance abuse,[7] and reading difficulties,[10] ADHD prevention programs may also be helpful in many other related conditions.

Future research will need to characterize the nature of the differences according to sex in the etiological factors underlying ADHD symptoms and to clarify the nature of the gene–environmental interplay and its possible relation to the ''protective female effect''.

Ethical statement

Subjects were obtained from a study of risk factors, early detection and prevention of eating disorders, the DITCA-CV program (Programa de Detección e Intervención en Trastornos de la Conducta Alimentaria de la Comunidad Valenciana), that the Public Health and Education administrations of Valencia, Spain, have offered for many years to all compulsory secondary education schools in the region. The survey was approved by the Department of Public Health of the regional health administration. Passive informed consent from parents was obtained.

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Conflict of interest

None of the authors have a conflict of interest. We all confirm full access to all aspects of the research and writing process, and take final responsibility for the paper.

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