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Research Article

The Nature of Covariation between Separation Anxiety Symptoms and Obsessive Compulsive Symptoms in Developmental Age

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Abstract

In spite of the high rates of comorbidity between Obsessive Compulsive Symptoms and Separation Anxiety Symptoms, no previous study, to our knowledge, has explored the nature of the covariation between these two phenotypes in developmental age.

In three-hundred-ninety-eight twin pairs belonging to the population-based Italian Twin Registry, we investigated by behavioral genetics approach whether the phenotypic correlation between Obsessive Compulsive Symptoms and Separation Anxiety Symptoms could better be accounted for by direct, causal effect, or by the presence of latent causal factors, acting simultaneously as elements of risk for these two phenotypes.

Significant correlation was found between Obsessive Compulsive Symptoms and Separation Anxiety Symptoms. Results from Causal Analysis indicated that shared factors of liability, rather than direct causation, better explained the phenotypic correlation between these phenotypes. Bivariate analyses showed shared genetic factors that simultaneously influence Obsessive Compulsive Symptoms and Separation Anxiety Symptoms as the best explanation for the phenotypic covariation.

The same gene pools that influence high scores of Separation Anxiety symptoms cause also high level of Obsessive Compulsive symptoms. Although individual-specific experiences appear to play a significant role in accounting for the variance of all phenotypes under study, their influence on covariation was found to be negligible.

Keywords: Obsessive-compulsive disorder; Separation anxiety; Twin study; Heritability; Genes; Environment

Introduction

Obsessive-Compulsive Disorder (OCD) was once considered rare in childhood; however recent advances in diagnosis and treatment have led to recognize the disorder as a common cause of distress for children and adolescents [1]. In fact, recent studies indicated a lifetime prevalence ranging from 0.7 to 2.7% [2,3], with an earlier onset for males than females [4].

OCD is a pervasive disorder that rarely improves without treatment and it is frequently associated with significant impairment of quality of life and social and familial relationships [5]. Individuals with OCD often experience comorbid psychiatric disorders, including depressive disorders and anxiety disorders, such as Separation Anxiety Disorder (SAD). In particular, in the NIMH sample, 7% of the pediatric subjects present OCD in comorbidity with SAD [6]. A more recent contribution showed that the first comorbid disorder in a sample of children affected by OCD was SAD (17.5%) [7]. Data supporting this comorbidity came also from the study of Verduin and Kendall showing that the 4% of children with primary SAD have also OCD [8]. In addition, research in adult samples indicated that several patients with OCD report a history of SAD [9,10].

SAD in childhood is defined as a developmentally inappropriate and excessive worry about separation from home or from attachment figures, with onset before the age of 18 years (DSM V). Childhood SAD usually has an early age of onset, with a peak between 7 and 9 years of age, and a prevalence estimated to be approximately 4% [11,12].

OCD and SAD often have onset in childhood and phenomenological similarities. For instance, children with SAD often have worries that can take on obsession qualities [10].

SAD, which usually has an earlier onset than OCD [13], may influence the clinical course of OCD. Indeed, OCD adult patients with an history of SAD have an earlier age at onset, more severe OCD symptoms and a greater severity of the sexual/religious dimension [7,10].

Very little is known about the nature and the causes of the covariation between OCD and SAD in developmental age. In fact, to our knowledge, only one study investigated, by a behavioral genetics approach, this relationship in a pre-school children sample [14], providing evidence for phenotypic and environmental overlap.

This lack of studies in literature underlines the necessity to

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investigate the nature and the causes of this covariation and the character of latent, shared etiological factors that can simultaneously act as elements of risk for OCD and SAD in the developmental years.

The aim of this study concerns analyzing the relationship between Separation Anxiety (SA) symptoms and Obsessive-Compulsive (OC) symptoms.

By taking advantage of the twin method, we sought to address three main questions:

1) Assessing the direction and the size of the covariation between SA symptoms and OC symptoms.

2) Investigating whether the phenotypic correlation between SA symptoms and OC symptoms could better be accounted for by a direct, causal effect of SA symptoms on OC symptoms, or by the presence of a latent, "third etiological factor" orchestrating the observed covariation .

3) In absence of clear causal effects exploring, by fitting bivariate twin models, the nature of latent, shared etiological elements that can simultaneously act as elements of risk/protection for SA symptoms and OC symptoms in the developmental years.

Materials and Methods

Participants

This study is based on the responses provided by parents of children belonging to the population-based Italian Twin Registry (ITR). The procedures that led to the establishment of the ITR are described in detail elsewhere [15].

Subjects aged 8-17 (mean 13.06±2.59) living in the industrialized province of Milan and in the suburban province of Lecco were sampled from the ITR database for psychometric studies of different nature and aims [16-18]. The recruitment methods and the socio-demographic characteristics of participants are reported in detail elsewhere [17,18], and show that general factors such as the mean age of children and parents and the social and educational levels reflect population norms for Italy, without substantial differences between participants and non-participants in the psychometric survey. Moreover, the CBCL mean scores comprehensively reflect those found in a national probability sample [19].

There were 398 complete twin pairs who accepted to participate to this study, which accounts for a 54% acceptation rate among families who confirmed the presence of twins in the 8-17 age range [17,18]. Zygosity was assigned by the parent-rated Goldsmith questionnaire [20], which has an accuracy of determination of 99.4% [21]; according to its algorithm, there were 74 Monozygotic (MZ) male, 70 MZ female, 134 same-sex Dizygotic (DZS, 53 male, 81 female), and 120 unlike-sex Dizygotic (DZU) twin pairs. Zygosity distribution did not differ from that found in the larger ITR population, and the MZ/DZS/DZU ratio was 1.1/1.0/0.9. Due to the relatively small sample size, the analyses were not stratified by gender: DZS and DZU pairs were thus pooled together in the category of DZ pairs, and MZ male and female pairs were also pooled in one category.

The procedures were accepted by the ethical committee of each participating institution, and for all participants parents signed consent.

Measures

CBCL Obsessive compulsive scale (OCS)

The Child Behavior Checklist 6-18 (CBCL/6-18) was filled in by one of the parents for both twins; 77% percent of the questionnaires were completed by the mother and the remaining 23% by the father, without significant differences in the mean values of the CBCL scales rated by mothers versus those rated by fathers [17].

The CBCL is a standardized parent-report questionnaire, composed by 118 items, rating behavioral and emotional problem exhibited by their child in the past 6 months. Respondents rate each item on a 3-point scale: 0 = not true; 1 = somewhat or sometimes true; and 2 = very true or often true. These items have been factor-analyzed into eight empirically based syndrome scales [22]. The recent Achenbach System of Empirically Based Assessment (ASEBA; [22]) includes six DSM-oriented scales aimed at covering common childhood mental disorders. To generate the six DOS, 22 clinicians rated the degree of consistency of the items included in the CBCL scale for age 6-18 (CBCL/6-18; [22]) with corresponding DSM-IV criteria.

The psychometric characteristic of this questionnaire have been well studied [22].

The CBCL Obsessive-Compulsive Scale (OCS) was developed by Nelson et al. [23] using a factor analysis on 11 CBCL items that were thought to likely predict obsessions and compulsions. The best solution was a single-factor model in which 8 items were retained and were shown to have good internal consistency (Cronbach's Alpha = 0.84). The scale, ranging from 0 to 16, was created by adding the score of the 8 items (9. Can't get his/her mind off certain thoughts; obsessions; 31. Feels he/she might think or do something bad; 32. Feels he/she has to be perfect; 52. Feels too guilty; 66. Repeats certain acts over and over; compulsions; 84. Strange behavior; 85. Strange ideas; 112. Worries).

SCARED Separation anxiety scale (SAS)

Children filled in the Italian version of the 41-item Screen for Child Anxiety Related Emotional Disorders (SCARED) questionnaire [16], a screening instrument for childhood Anxiety Disorder (AD) based on the DSM-IV. The SCARED questionnaire was originally devised to screen AD in clinical samples [16,24-26], but it is also employed as valuable screening tool in community samples (e.g. [26,27]). Children were asked to rate the frequency with which they experience each symptom on a 3-point liker scale (0 = 'almost never', 1 = 'sometimes', 2 = 'often'). According to the original factorial structure of the SCARED questionnaire, the 41 items can be allocated into five subscales [25] 1) Panic/Somatic Anxiety, 2) General Anxiety, 3) Separation Anxiety (SAS), 4) Social Phobia and 5) School Phobia. The SAS, ranging from 0 to 16, includes the following items: 4. I get scared if I sleep away from home; 8. I follow my mother or father wherever they go; 13. I worry about sleeping alone; 16. I have nightmares about something bad happening to my parents; 20. I have nightmares about something bad happening to me; 25. I am afraid to be alone in the house; 29. I don't like to be away from my family; 31. I worry that something bad might happen to my parents.

When a cut-off point of 25 was applied to the total sum of items, endorsed by subjects across these five factors, data showed good

sensitivity (70%) and good ability to discriminate between children with AD versus those without AD (specificity: 67%), and between children with AD versus those with depression, or disruptive disorders (specificity: 61%) [25,28]. Specific cut-off points have been proposed also for the five subscales [25,28]; score majors to the cut-off point may indicate the presence of a Panic Disorder, General Anxiety Disorder, Separation Anxiety Disorder, Social Phobia and School Phobia.

Statistical analyses

Phenotypic and twin correlations: The correlation coefficient was calculated between the scores in SCARED SAS and CBCL OCS. Then, we calculated the Twin correlations (within-trait and cross-trait).

Causal analysis

To investigate the presence of a direct causal effect of SAS (continuously defined) upon OCS (continuously treated), the MZ Intrapair Differences Method [29] was applied. By this method, the MZ within–twin pair differences in SAS would be significantly associated with the within–twin pair differences in OCS, if the two phenotypes are causally linked. The presence of a significant regression coefficient, as tested by regression of within-pair differences on the SAS upon within-pair differences on the OCS, would argue in favor of such hypothesis, whereas the absence of causal evidence would speak against the hypothesis of a causal effect of SAS on OCS [29].

Model-fitting analyses

Bivariate twin model was implemented with Open Mx [30] to investigate the sources of covariation between scores in SAS and OCS.

Parameters were estimated by maximum-likelihood theory, with models fitted to quantitative raw data. The bivariate design allows for the separation of the total phenotypic variance and covariance of two traits into proportions due to i) additive genetic factors (A), ii) shared environmental factors (C, including socio-economic level, religion, style of parenting, etc.), and iii) unique (individual-specific) environmental factors (E, including illness, relationships with peers, etc.). The model compares MZ and DZ twin phenotypic resemblances, assuming a correlation between twins' additive genetic influences of 1.0 for MZ pairs (all genes are shared) and of 0.5 for DZ pairs (DZ twins share half of their segregating genes on average), a correlation between twins' dominance genetic influences of 1.0 for MZ pairs and of 0.25 for DZ pairs, and a correlation between twins' shared environmental influences of 1.0 for both MZ and DZ twin pairs (i.e., shared environmental influences are assumed to be of equal magnitude for MZ and DZ twins, as endorsed by the 'equal environments assumption' [31]).

Before genetic modeling, a saturated model requiring a free parameter for every observed statistic was fitted to the data; this model testes some fundamental assumptions such as equality of means and variances, excluding the effects of twin order, and/or zygosity. A bivariate Cholesky decomposition [31] was then applied (Figure 1), with the SA symptoms score entered as the first variable and the OC symptoms score as the second. For n variables, a Cholesky model includes n independent genetic and environmental factors: the first factor loads on all traits, the second loads on all traits except the first, the third loads on all traits except the first two, and so on. This model

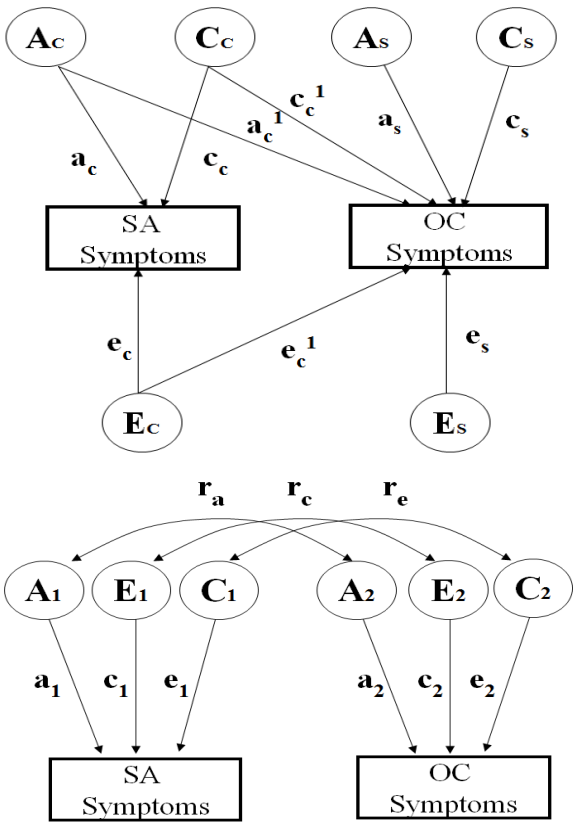

Figure 1: Bivariate Model for Separation Anxiety Symptoms and Obsessive Compulsive Symptoms. Observed phenotypes are shown in squares. Latent factors are shown in circles. Top, bivariate Cholesky model. A_c, C_c, E_c: additive genetic, shared environmental and unique environmental influences common to SA Symptoms and OC Symptoms. A_s, C_s, E_s: additive genetic, shared environmental and unique environmental influences specific to SA Symptoms. Bottom, correlated factors model (the standardized version of the Cholesky model depicted above) A1, C1, E1: additive genetic, shared environmental and unique environmental effects on SA Symptoms A2, C2, E2: additive genetic, shared environmental and unique environmental effects on OC Symptoms a_1, c_1, e_1: path coefficients representing the effect of the latent variables on SA Symptoms a_2, c_2, e_2: path coefficients representing the effect of the latent variables on OC Symptoms r_a, r_c, r_e: genetic, shared environmental, and unique environmental correlations.

provides the fullest explanation of data because it does not impose any restrictions to the genetic and environmental contributions to covariation. Additive genetic factor "A_c" influences both traits, while genetic factor "A_s" loads on the second trait only. Shared (C_c, C_s) and unique (E_c, E_s) environmental factors have a similar pattern of loadings.

Next, the bivariate results were represented as a Correlated Factors Models (Figure 1), which is the standardized version of the Cholesky decomposition [32].

According to this model, the observed phenotypic SAS-OCS correlation is the consequence of correlations between additive genetic (r_a), shared environmental (r_c) and unique environmental (r_e) factors. These correlations can be conceptualized as an indication of the extent to which genetic or environmental influences for the first and the second measure in the model overlap.

Given the limited power conveyed by this relatively small sample,

we did not test for sex or age differences in variance/covariance components. Our analyses began with a full model fitted to the MZ and DZ groups. By stepwise deletion of variance and covariance components, progressively more parsimonious models were applied to search for the best-fitting model. Sub models were compared by hierarchical χ2 tests: the difference between twice the negative Log-Likelihood (-2LL) for the reduced and the full models has a χ2 distribution, with degrees of freedom (df) given by the difference between the df for the two models [33]. Models were also compared on the basis of the Akaike Information Criterion (AIC = χ2-2df) [34], with the lowest AIC value reflecting a balance between goodness of fit and parsimony. Before model fitting, all of the scales were transformed by natural logarithm to approximate normal distributions.

Results & Discussion

Results

Phenotypic and twin correlations: Table 1 shows phenotypic and twin correlations for SA symptoms and OC symptoms.

Phenotypic correlation between SA symptoms and OC symptoms was .20, indicating that SA symptoms were moderately associated with symptoms scores in OCS.

For both phenotypes, the cross-twin/within-trait correlations (between twin 1 and twin 2 for the same trait) were higher in MZ than in DZ pairs, suggesting that SA symptoms and OC symptoms are to different extents influenced by genetic factors.

Likewise, the greater MZ than DZ cross-twin/cross-trait correlation (between SA symptoms in twin 1 and OC symptoms in twin 2, and vice versa) indicates that genetic influences play a role in explaining the covariance but also unique environment could account for part of the covariance.

Causal analysis

Regression of the MZ intrapair difference scores in SAS on the MZ intrapair difference scores in OCS were non-significant (beta= -.046, adjusted R^2= -.005, p=.594). Therefore, in genetically identical twin pairs, a twin who scored higher in SAS does not have more OC symptoms than his or her co-twin who scored lower in SAS. This excluded the hypothesis that the co-occurrence between SA symptoms and OC symptoms could be explained by a direct effect of one phenotype upon the other.

Table 1: Twin correlations by zygosity group for SAS and OCS scores.

Within-trait correlations			Cross-trait correlations	
Zygosity	SAS	OCS	Within-twin (Phenotypic Correlation)	Cross-twin
MZ	0.53	0.48	0.20*	0.16
DZ	0.28	0.38	0.20*	0.15

P < 0.05

Model-fitting analyses

Table 2 shows the results of model comparison under the saturated model. Means and variances could be equated across twin 1/twin 2 and MZ/DZ twins without significant fit deterioration, suggesting the absence of a significant effect of twin order (which was casually attributed in this sample) and/or zygosity on means and variances.

Table 3 shows the results of bivariate analyses between SA symptoms and OC symptoms.

The comparison between Full ACE Model and nested sub-models suggests that the best fitting model was an AE model, meaning that all variance and covariance could be explained by genetic and unique environmental factors.

Common environmental factors explained a negligible amount of the variance of both SA symptoms and OC symptoms and their covariation , and they were dropped without a significant fit deterioration.

Regarding the covariance, within the AE model it was also possible to drop the unique environmental correlation (r_e) without a significant fit deterioration. The final best model (Table 3, in bold) and the correspondent correlated factors solution (Figure 2) suggest genetic factors as the sole sources of covariation between SA symptoms and OC symptoms.

Overall, these analyses show a best fitting model that includes a common genetic factor to explain the covariance between SA symptoms and OC symptoms (r_a=.36), plus a specific genetic variance component for both SA symptoms and OC symptoms and specific unique environmental variance components for the two phenotypes to explain the residual variance.

Discussion

This study investigated whether the phenotypic correlation between SA symptoms and OC symptoms could better be accounted for by a direct, causal effect of one phenotype upon the other, or by the presence of a latent, "third etiological factor" causing the observed covariation between these two phenotypes. Our data suggest that etiological overlap can be a primary explanation for the association between SA symptoms and OC symptoms.

Univariate results showed moderate genetic and environmental influences for both SA symptoms and OC symptoms, in accordance with previous research [35-37].

For example, a recent meta-analysis on SAD meta-heritability showed that when SAD was assessed by self-reports, the proportion of variance explained by within-family factors (both A and C) was smaller than in parental report-based studies [38]. In addition, a review on twin studies on OCD by van Grootheest [39] showed

Table 2: Model comparisons under the saturated model.

Model	-2LL	df	ΔX²	Δdf	*P*	AIC
1- Grand means and variances freely estimated	-1324.54	1542	-	-	-	-
2- Equal means and variances across twin order	-1315.95	1550	8.59	8	0.38	-4415.95
3- Equal means and variances across twin order and zygosity	-1312.21	1554	12.33	12	0.42	-4420.21
4- Full ACE Cholesky Model	-1308.07	1556	16.47	14	0.29	-4420.07

–2LL minus twice the negative log-likelihood, df degrees of freedom
Δ_{x^2} : (–2LLsub-model) – (–2LLfull model); Δdf : (dfsub-model) – (dffull model); AIC : Δ_{x^2} – 2 Δdf

Table 3: Bivariate model fitting and model comparisons.

Model	Compared Model	–2LL	df	ΔX²	Δdf	p	AIC
1- FullACE	-	-1308.07	1556	-	-	-	-
2- AE	ACE	-1304.53	1560	3.54	4	0.47	-4424.53
3- CE	ACE	-1292.83	1560	15.24	4	0	-4412.83
4- E	AE	-1168.82	1564	135.71	4	0	-4296.82
5-AE drop r_e	**AE**	**-1304.2**	**1562**	**0.33**	**2**	**0.85**	**-4428.2**

–2LL minus twice the negative log-likelihood, df degrees of freedom

Δ_{χ^2} : (–2LLsub-model) – (–2LLfull model); *Δdf : (dfsub-model) – (dffull model); AIC : Δ_{χ^2} – 2 Δdf*

Best-fitting model is shown in bold

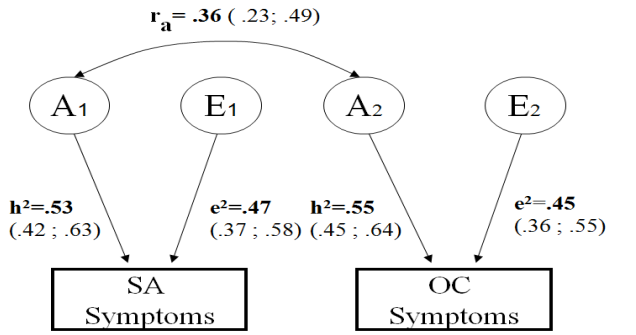

Figure 2: Final model with standardized variance estimates and confidence intervals.

A_1 additive genetic effects; E_1 unique environmental influences on SA Symptoms; A_2 and E_2 additive genetic and unique environmental influences on OC Symptoms, Respectively, r_a = genetic correlation.

that in children obsessive-compulsive symptoms are heritable, with genetic influences in the range of 45% to 65%. Moreover, in the study of Hudziak and colleagues [37], assessing OC symptoms with CBCL OCS in large samples of twins aged 7, 10 and 12 years, best-fitting models indicated a significant additive genetic influences ranged 45–58%, with significant shared environmental influence detected only in the Dutch 12-year-old cohort (16%).

Results from causal analysis seemed to indicate that direct causation is not the main explanation for the covariation between SA symptoms and OC symptoms.

Model fitting analyses showed that the source of this covariation is genetic in nature. This means that the same gene pools that influence high scores of SA symptoms also cause high level of OC symptoms. Although individual-specific experiences appeared to play a significant role in explaining the variance of all phenotypes under study, their influence on covariation was found to be negligible. The moderate genetic correlations (.36) indicate that about 36% of the genetic effects on the first phenotypes overlap with genetic effects on the second ones.

Our data are in disaccord with previously results by Eley and colleagues [14] that indicated that the covariance between Obsessive-Compulsive Behaviors and Separation Anxiety Behaviors was predominantly influenced by shared environmental factors (78%), while the proportion of the correlations due to shared genetic effects and unique environmental effects was respectively of 12%, and 10%. However, several differences were present between our and Eley's sample. First of all, Eley's sample included pre-school children whereas our sample mean age was 12, a decrease of shared environment effects is therefore expected [38,40]. In addition, in our study anxiety symptoms have been rated by children. Thus, several reports, including meta-analytic data, found higher estimates of C for the studies based on maternal and paternal reports than for the studies based on child reports [38,41].

Meanwhile our results seemed to be in accordance with the study of Bolton and colleagues [42] that found significant familial aggregation investigating the covariation between OCD and Anxiety disorder (considered as a total phenotype). In addition, several contributions demonstrated shared genetic effects between different Anxiety Disorders in adult and in developmental samples e.g. [43,44].

There are also several potential limitations that need be taken into account. First, the sample size is relatively small, yielding limited power to detect certain variance and covariance components. Our estimations showed modest power to decompose some sources of variance and covariance (particularly C), therefore some of our results should be considered cautiously. We had also reduced ability to adequately address important issues such as age and sex differences in the genetic and environmental effects. In fact, although several studies of the CBCL in literature found evidence of sex and age differences in the genetic architecture of behavior problems, we could not investigated the effect of these variables, [40,45,46]. Third, we do not test for rater bias effect. This effect could have influenced our result since the CBCL were filled in only by one parent.

Conclusion

Results indicated that direct causation is not the main explanation for the covariation between SA symptoms and OC symptoms. The same gene pools that influence high scores of Separation Anxiety symptoms cause also high level of Obsessive Compulsive symptoms. Although individual-specific experiences appeared to play a significant role in explaining the variance of all phenotypes under study, their influence on covariation was found to be negligible.

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