The role of genes and environment in shaping co-occurrence of DSM-IV defined anxiety dimensions among Italian twins aged 8–17

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A B S T R A C T

This study investigated the ultimate causes of co-variation between symptoms of four common DSM-IV anxiety dimensions – Generalized Anxiety, Panic, Social Phobia and Separation Anxiety disorder – assessed with the Italian version of the Screen for Child Anxiety-Related Emotional Disorders questionnaire in a sample of 378 twin pairs aged 8–17 from the population-based Italian Twin Register. Genetic and environmental proportions of covariance between the targeted anxiety dimensions were estimated by multivariate twin analyses. Genetic influences (explaining from 58% to 99% of covariance) and unique environmental factors were the sole sources of co-variation for all phenotypes under study. Genetic influences associated with different anxiety dimensions coincide remarkably, as indicated by genetic correlations ranging from 0.40 to 0.61, while unique environmental overlap is less substantial. Thus, while additive genetic effects are important in explaining why children report symptoms from multiple anxiety disorders, environmental idiosyncratic factors seem to play a marginal role in shaping the co-occurrence of different anxiety dimensions in childhood.

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1. Introduction

Childhood and adolescence are critical for the development of anxiety disorders (AD), the most frequent form of psychopathology in the developmental years (Beesdo, Knappe, & Pine, 2009). Lifetime prevalence of AD in children and adolescents is about 15% to 20%, with 1-year or 6 month rates that do not differ greatly from lifetime estimates (Beesdo et al., 2009; Kessler et al., 2005). The most frequent diagnosis is Separation Anxiety Disorder which typically manifests before age 12 with estimates that vary from 2.8% in childhood to 8% in adolescence, while Agoraphobia and Panic Disorder have low prevalence (1% and 3–4% respectively, see Beesdo et al., 2009 for Review). Girls usually report more symptoms than boys, with a ratio that varies from 2:1 to 3:1 depending on data collection methodology and age (Beesdo et al., 2009; Kessler et al., 2005).

Several studies have already suggested that anxiety disorders (AD) are highly comorbid with each other, both in the developmental age (Beesdo et al., 2009; Essau, Conradt, & Petermann, 2000; Last, Strauss, & Francis, 1987; Otto et al., 2001) and in adulthood (Merikangas & Angst, 1995). This could be due to symptoms’ overlapping among different anxiety disorders and/or to the artificial nature of the categorical classification (Angold & Costello, 1993; Maser & Cloninger, 1990), so that high rates of comorbidity could be ultimately connected to poor discriminant validity (Brown & Barlow, 1992). Comorbidity can also originate from the fact that one disorder is part of, or is caused by, another disorder (Perrin & Last, 1995). More sophisticated concepts and approaches to comorbidity encompass the hypothesis of shared etiological factors (genetic and/or environmental) and shared underlying disease processes. In contrast to a large body of literature that examined the causes of comorbidity between anxiety disorders and depression in adulthood (Hettema, Prescott, Myers, Neale, & Kendler, 2005; Kendler et al., 1995), the origin of the co-occurrence between different AD in youth has rarely been addressed. Behavioral genetic strategies can clarify the causes of comorbidity. While univariate approaches estimate the role of genes and environment in the expression of a single phenotype, multivariate designs address how genetic and environmental risk factors influence the covariation of different disorders. Information derived from multivariate studies is then
useful to understand the etiology in term of risk factors of multiple AD, could influence classification and facilitate research into the development of prevention or early interventions programs of AD in children and adolescence.

Univariate studies consistently found evidence for genetic influences on AD (see for a review Gregory & Eley, 2007) in children and adolescents. Although genetic factors often explain a substantial amount of variance for different anxiety phenotypes, the contribution of genetic and environmental effects vary across different studies (Rice, Harold, & Thapar, 2002), possibly depending on heterogeneous factors such as the type of rater/informant (Foley et al., 2005; Kendler et al., 1991), age (Eley & Stevenson, 1999; Legrand, McGue, & Iacono, 1999; van Baal, Boomsma, & de Geus, 2001), sample size and power to detect shared environmental influences (Martin, Eaves, Kearsey, & Davies, 1978), format of the instruments employed for symptoms' collection (Verhulst & Van der Ende, 2001) and also phenotype definition (personality trait, number of symptoms, diagnosis) (Gregory & Eley, 2007).

To date, there are only four published multivariate studies of AD in the developmental years (Eley et al., 2003; Eley, Rijsdijk, Perrin, O'Connor, & Bolton, 2008; Hallett, Ronald, Rijsdijk, & Eley, 2009; Silberg, Rutter, & Eaves, 2001). Overall, these studies showed that both genetic and shared environmental effects are important in shaping the co-occurrence between different anxiety dimensions, but the estimates of their relative contributions vary, probably depending on the several factors mentioned above. The co-occurrence of mother-rated anxiety-related behaviors (general distress, separation anxiety, fear symptoms, obsessive-compulsive behaviours and shyness/inhibition) in 4-year-old twins (Eley et al., 2003), and self-reported anxiety-related behaviors (negative cognitions, negative affect, fear, obsessive-compulsive behaviours and social anxiety) in twins aged 7–9 (Hallett et al., 2009) are best explained by genetic and shared environmental factors (Eley et al., 2003; Hallett et al., 2009). Silberg et al. (2001) showed that the relationships between overanxious disorder, separation anxiety and simple phobia during middle childhood are explained by genetic factors, while one shared environmental factor best explains the covariation between separation anxiety and simple phobia during middle childhood and adolescence. Eley et al. (2008) found that common shared environmental effects explain the comorbidity between Specific Phobia and Separation Anxiety, while both idiosyncratic environmental effects and familial influences (genetic or shared environmental) shape the comorbidity between Specific Phobia and Social Phobia (Eley et al., 2008).

While the bulk of these studies broadly concord in finding genetic influences among the causes of covariation, they map heterogeneous psychometric constructs that relate to variable degrees to current clinical categories. In particular, there are no published efforts to systematically investigate the causes of covariation between common DSM-IV-defined AD based on children's self-reports. Moreover, the four multivariate studies reviewed above broadly indicate that the effects of shared environmental influences on covariance of AD phenotypes are more likely to be found in children up to the age of 7–8 years, and when mothers—more than children themselves—are the raters of AD symptoms. Here, we investigated the ultimate causes of covariation between symptoms of four common DSM-IV AD—Generalized Anxiety (GAD), Panic (PD), Social Phobia (SP), and Separation Anxiety (SAD)—assessed in a sample of Italian twins aged 8–17 with the 41-item version of the Screen for Child Anxiety Related Emotional Disorders child version (SCARED) originally developed by Birmaher et al. (Birmaher et al., 1997; Birmaher et al., 1999). While previous univariate results relying on the same sample used in the present paper (Ogliari et al., 2006) have shown moderate-to-high heritability (0.53–0.60) for the empirically derived Italian SCARED subscales, this multivariate study investigates the causal factors that are relevant to the co-occurrence of multiple AD. Compared to the majority of previously published multivariate studies of AD, in view of the fact that we relied on self-assessments of older children, we hypothesized a stronger role of genetic and unique environmental influences in explaining covariation of DSM-IV phenotypes.

2. Methods

2.1. Study participants

The study sample was derived from the Italian Twin Registry (ITR). The procedure that led to the establishment of the ITR is described in details elsewhere (Stazi et al., 2002). Currently, the ITR contains information on approximately 20,000 twins, and is involved in both general population- and clinical-based studies on various complex phenotypes, some of which conducted within large European consortia (Fagnani et al., 2006). The present study is part of a larger project regarding health-related characteristics and behaviors in Italy (Ogliari et al., 2006; Pesenti-Gritti et al., 2008; Sapatola et al., 2007). Parents of all “possible twins” born between 1986 and 1995 and resident in the Italian provinces of Milano and Lecco were contacted by mail in 2003. Out of 2015 families contacted, 973 (48.3%) answered confirming the presence of a twin pair in their offspring. Of the 973 families, 707 were willing to participate in various surveys, and 380 of these (53.7%) agreed to be involved in the psychometric survey. The exclusion of two twin pairs with missing data left a total of 378 pairs with complete data for all measures.

The mean age of children and parents did not differ between families who agreed to participate in the psychometric survey versus the remaining families (respectively, 13.06 ± 2.60 vs. 13.11 ± 2.31, p = 0.62 for children; 46.06 ± 0.23 vs. 46.71 ± 0.35, p = 0.10 for parents), and mothers of twins participating in the psychometric survey were slightly, but not significantly, more educated than mothers in the families who did not participate in the psychometric survey (University degree: 17.7% vs. 16.3%, p = 0.65). The study procedures were accepted by the Ethical Committee of the involved Institutions. Given that all twins were minor at the time of the survey, parents signed an informed consent form.

2.2. Zygosity assessment

The parent-rated Goldsmith (1991) questionnaire was mailed at home at the first mail contact and employed to assign zygosity. This instrument consists of items about physical similarity and frequency of confusion of the twins by family members and strangers, and it allows zygosity identification by a mathematical algorithm. Recent data (van Beijsterveldt, Verhulst, Molenaar, & Boomsma, 2004) show an accuracy of zygosity determination of over 94% with this algorithm.

According to the Goldsmith questionnaire, there were 135 monozygotic (MZ) pairs (70 male and 65 female) and 243 dizygotic (DZ) pairs (50 male, 78 female, 115 unlike sex) in our sample. The MZ/DZ same sex/DZ opposite sex ratio was 1.1/1.0/0.9, which is not substantially different from the expected 1/1/1 population distribution.

2.3. Behavioral measures

Each twin filled in, independently of the co-twin, the Italian version of the 41-item SCARED questionnaire (Ogliari et al., 2006), a screening instrument for childhood AD based on the DSM-IV. The SCARED questionnaire was originally devised to screen AD in clinical samples (Birmaher et al., 1997; Birmaher et al., 1999), but it is also employed as valuable screening tool in community samples (Crocetti, Hale, Fermani, Raaijmakers, & Meeus, 2009; Hale,
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