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Genetic and environmental causes of variation in adolescent anxiety symptoms: A multiple-rater twin study

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ABSTRACT

Heritability estimates for adolescent anxiety vary across studies, partly depending on who is rating the symptoms. The goal of our study was to estimate genetic and environmental influences using a multi-informant design with responses from a population-based sample of adolescent twins, their mothers and their fathers ($N = 1394$ families).

Results from multivariate biometrical modeling indicated quantitative, but no qualitative sex differences in etiology. The best fitting model was an AE Common Pathway model, defining anxiety as a latent factor common to all informants. This model offers error free estimates of genetic and environmental influences explaining the latent factor variance.

Variation in the latent factor was highly genetic, with heritability estimates of 65% for boys and 74% for girls. Non-shared environmental effects explained the remaining variance. In addition, there were significant rater-specific genetic and environmental effects for both sexes.

The observed rater differences underline the importance of using several informants when studying adolescent anxiety.

1. Introduction

Most adolescents experience anxious feelings from time to time. However, the intensity of the anxiety symptoms and the adolescents' abilities to deal with them varies greatly. Individuals with high levels of symptoms may meet criteria for an anxiety disorder, ranging from simple phobias to panic disorder. Anxiety disorders comprise one of the most common disorders of adolescence (Rapee, Schniering, & Hudson, 2009), and studies indicate that 3–12% of children and adolescents meet criteria for an anxiety disorder at a given time (Rice & Thapar, 2009). The goal of the present twin study was to explore genetic and environmental causes for individual differences in anxiety symptoms in the general adolescent population.

Twin analyses are based on comparisons of co-twin similarity in a trait (e.g. anxiety symptoms) between monozygotic (MZ) twins who are (nearly always) genetically identical and dizygotic (DZ) twins who on average share half of their segregating genes (assuming additive genetic variance and no assortative mating for the trait). Under the crucial assumption that the environmental conditions for MZ twins raised in the same home are as similar as they are for DZ twins raised in the same home, a higher resemblance of MZ versus DZ twin pairs reflects the higher genetic similarity and indicates genetic influences on the trait. In the recent years, several twin studies have indicated that genetic influences play a major role in the etiology of adolescent and childhood anxiety, often explaining between 30% and 40% of the phenotypic variation in the population (for reviews see: Gregory & Eley, 2007; Rapee et al., 2009; Rice & Thapar, 2009). Moderate heritability is also suggested in an overlapping field in the literature, examining the broader phenotype internalizing problems (Rice & Thapar, 2009).

Due to variations in samples and study designs the magnitude of heritability estimates on adolescent anxiety varies widely across studies. Most studies focus upon symptoms of anxiety within the full range, while other studies use a clinical cut-off, or diagnostic information. Despite variation in definitions of the anxiety phenotype however, studies suggest that the level of genetic influence appears to be similar. The same genes seem to influence normal variation as well as high levels of symptoms (Eley, 2011). Similarly, research indicates little difference in heritability across specific anxiety disorders. All of the major DSM-IV anxiety disorders co-aggregate in families and are genetically correlated, suggesting a substantial common genetic risk to adolescent anxiety across the anxiety disorders (Gregory & Eley, 2007; Rapee et al., 2009; Smoller,

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Block, & Young, 2009), some of which may also be shared with depression (Arnold & Taillefer, 2011).

One possible reason for variation in heritability across studies is the age of the sample. The genetic influence on anxiety appears to increase with age (Eley, 1999). This increase may be most evident in the peripubertal transition, reflecting developmental changes in both brain structure and general functioning (Van Baal, Boomsma, & De Geus, 2001). Developmental changes in etiology could produce discrepant findings in samples with different age ranges (Eley, 1999).

However, the most consistently demonstrated cause of variation in heritability estimates across studies is based on who is rating the anxiety symptoms. There appears to be stronger estimates of heritability in studies that use parental ratings of children's anxiety symptoms rather than child self-reports (Boomsma, Van Beijsterveldt, & Hudziak, 2005; Burt, 2009; Eaves et al., 1997; Feigon, Waldman, Levy, & Hay, 2001; Gregory & Eley, 2007; Rapee et al., 2009; Rice, Harold, & Thapar, 2002; Thapar & McGuffin, 1995). Heritability estimates based on parental ratings often exceed 50%, as compared to estimates below 15% or close to zero when twins are reporting their own symptoms of anxiety. Due to this single informant bias, investigators have recommended the use of multiple informants for studies of childhood psychiatric disorders (Eaves et al., 1997; Simonoff et al., 1998).

Despite variability in estimates, twin studies have established the importance of genetic determinants in adolescent anxiety. But the heritability estimates do not tell anything about which genes or how many genes are directly involved in the emergence of anxiety. A heritability estimate of 40% could represent the additive effects of four loci each contributing 10% to risk or 100 loci each contributing 0.4% (Smoller et al., 2009). Over the past two decades, molecular genetic approaches, including linkage and association studies, have been applied to localize and identify the DNA sequences and specific genes that involve a risk for anxiety disorders. Association studies have identified links between serotonin and dopamine genes and different symptoms of anxiety, but few findings have been robustly replicated (Smoller et al., 2009). The largest effect sizes observed are very small and the sum of the influences of various markers only explain a small portion of the heritability estimates reported in twin studies (Trzaskowski et al., 2013). This phenomenon is termed 'the missing heritability problem' (Maher, 2008). A main reason for the missing heritability is thought to be genetic and phenotypic complexity (Smoller et al., 2009). Like other genetically complex traits, variety in anxiety symptoms most likely reflects the influence of multiple genes of small effect size. Moreover, the risk genes may require interactions with other genes or environmental factors to influence anxiety symptoms (Arnold & Taillefer, 2011). Complex traits are increasingly investigated by the means of genome-wide association studies (GWAS). Instead of limiting the search to pre-specified candidate genes, GWAS analysis provides hypothesis-free association tests on all common variants across the genome in a single experiment (Arnold & Taillefer, 2011; Smoller et al., 2009). In the first genome-wide association study on anxiety-related behaviors in childhood (Trzaskowski et al., 2013) the sum of the effect sizes (<5%) was still far from the one suggested by twin studies.

One of the values of twin methodology is that it can be used to estimate not only the genetic influences in which the effects of alleles combine additively (A) (or effects of genetic dominance, D), but also aspects of the environment (Eley & Lau, 2005). In quantitative genetics individual differences are assumed to arise from two distinct environmental sources. Shared environmental influences (C) include all environmental sources that in effect increase the similarity between twins within the same family beyond that explained by shared genetic liabilities, while non-shared environment (E) includes environmental experiences that make members of a family different from each other (and measurement error) (Eley, 1999). A recent meta-analysis (Burt, 2009) involving 23 twin and adoption studies on child and adolescent anxiety indicates that a significant proportion (10–30%) of the variance in anxiety symptoms can be attributed to C. The influence appears to be strongest in the youngest age groups and weaker in older groups (Bartels, van de Aa, van Beijsterveldt, Middeldorp, & Boomsma, 2011; Burt, 2009; Eley et al., 2003; Feigon et al., 2001; Topolski et al., 1997). This decrease with age is in line with the theoretical expectation that C from, for example parenting would account for most variance during the time when parents exert their strongest influence on offspring (Rapee et al., 2009). As individuals progress through adolescence, they spend less time with parents and more time with peers and typically gain greater independence, possibly increasing the influence of E on anxiety. Actually, in most adolescent twin studies the majority of variance in anxiety can be attributed to environmental factors that make siblings different from each other (Gregory & Eley, 2007). It is important to acknowledge that variance attributed to E in the univariate case is confounded by measurement error.

Symptoms of anxiety are not equally distributed among boys and girls. Epidemiological studies show that girls have almost twice the risk than boys to experience any anxiety disorder (Essau, Conradt, & Petermann, 2000; Lewinsohn, Gotlib, Lewinsohn, Seeley, & Allen, 1998; McLean & Anderson, 2009). Some studies have indicated that the female preponderance of anxiety disorders starts early in childhood with a steady increase throughout adolescence (McLean & Anderson, 2009). A dramatic shift in gender distribution following puberty, as observed for depression, is not demonstrated for anxiety (Rapee et al., 2009). The majority of studies with child and adolescent samples exploring sex differences in the etiology of anxiety observe higher heritability estimates for girls than for boys (Bartels et al., 2011; Eley, 2001; Feigon et al., 2001; Gregory & Eley, 2007; Topolski et al., 1999; Trzaskowski, Zavos, Haworth, Plomin, & Eley, 2012). Although the reported sex differences are relatively small (Franić, Middeldorp, Dolan, Ligthart, & Boomsma, 2010), this finding has been described as the most consistent result yet to appear from the literature of anxiety in children and adolescents (Eley, 1999). The impact of sex on genetics can be either qualitative (non-scalar) or quantitative (scalar). Qualitative sex-limitation implies that different genes or environments control the expression of a trait in males and females. Quantitative sex-limitation connotes that the same genes cause individual differences between males and females, but that the magnitude of their effect differs across sexes (Neale & Cardon, 1992). Results from studies assessing both qualitative and quantitative sex differences indicate quantitative differences, but not qualitative sex differences in the etiology of adolescent anxiety (Bartels et al., 2011; Boomsma et al., 2005; Topolski et al., 1999).

The main aim of the present study was to investigate the relative contribution of genetic and environmental etiological sources explaining variability of adolescent symptoms of anxiety using a large sample of adolescent twins. We add to previous knowledge by using a multi-informant approach, in which adolescent anxiety symptoms were reported by mothers, fathers, and the twins themselves. Epidemiological studies have emphasized the importance of using multiple informants for the assessment of psychopathology (Arseneault et al., 2003; Jensen et al., 1999). In addition to providing a more complete picture of adolescent anxiety, this design offers error-free estimates of the relative impact of the common etiological sources, as well as estimates of sources specific for each informant (Bartels, Boomsma, Hudziak, van Beijsterveldt, & van den Oord, 2007). Rater differences may reflect situation specificity or differences in perspective and type of exposure to the adolescents' emotions (Achenbach, McConaughy, & Howell, 1987). Based on results from earlier studies, our primary hypothesis was that