VU Research Portal

Risk Factors for Childhood Problem Behavior: Studies in Twins and Triplets

Lamb, D.J.

2013

document version
Publisher's PDF, also known as Version of record

Link to publication in VU Research Portal

citation for published version (APA)
Lamb, D. J. (2013). *Risk Factors for Childhood Problem Behavior: Studies in Twins and Triplets*.

CHAPTER 1:

GENERAL INTRODUCTION
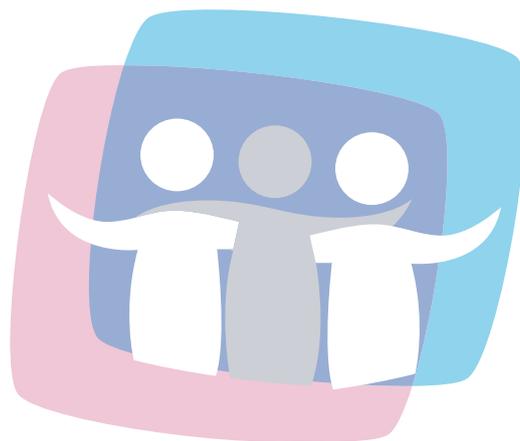
The nature-nurture debate has developed from a debate questioning whether nature or nurture is influencing a trait to a debate on how nature and nurture together influence a trait, including their additive effects, their interactions and their interdependencies. The objective of this thesis is to make a contribution to this debate in the field of child and adolescent problem behaviors, with a focus on Internalizing (INT) and Externalizing problems (EXT) in children and adolescents. The data on these dimensions of emotional and behavioral problems come from the Netherlands Twin Register (NTR) that has collected information from parents and teachers of twins and triplets, and from the young twins and triplets themselves. The children were registered by their parents as newborns (Beijsterveldt et al., 2013).

Child and adolescent behavioral and emotional problems
The most common behavior problems in children and adolescents can be roughly divided into 4 different types: anxious and depressive, inattentive and hyperactivity, autism related and disruptive behavior symptoms. These symptoms can be categorized into disorders according to, for example, the Diagnostic and Statistical Manual of DSM-IV disorders (APA, 2000). However, for research focusing on the etiology of problem behavior, it can be more useful to investigate continuous measures of problem behavior. Continuous measures contain more information regarding variation than a dichotomous trait and recent studies have suggested that the latent variables underlying the disorders are dimensional (Markon, Chmielewski and Miller, 2011; Haslam, Holland and Kuppens, 2012). In this thesis, we focus on *internalizing* and *externalizing* problem behavior, mostly measured with the age appropriate versions of the Achenbach System of Empirically Based Assessment (ASEBA, 2013). The Child Behavior Check List (CBCL)

assesses anxious depression, withdrawn behavior, somatic symptoms, attention problems, thought problems, social problems, aggressive behavior and rule breaking behavior. The first three clusters of symptoms comprise the INT broadband scale and the latter two the EXT broadband scale (the middle three types of problems are thus not included in the two broadband scales).

Twin studies

Twin studies comprise the most often used design to estimate the heritability of human traits. By now, there hardly is a phenotype of which the heritability has not been assessed in the classical twin design (Martin, Boomsma and Machin, 1997; van Dongen, Draisma, Martin and Boomsma, 2012). Initially, a problem with many twin studies was that they tended to be far too small; experimenters who were used to the sample sizes that are required to properly compare means, assumed that these were sufficient for the comparison of correlations between monozygotic (MZ) and dizygotic (DZ) twin pairs. In a series of papers by Jinks and Fulker (1970), and by Eaves and coworkers (Eaves, Last, Martin and Jinks, 1977; Eaves, Last, Young and Martin, 1978), power studies indicated that to obtain a reasonably accurate estimate of the degree of genetic influence on a quantitative trait, at least 200 pairs need to be studied for a trait of high heritability, whereas ten or twenty times this number is needed to study traits of intermediate or low heritability, especially if other influences such as shared family environment or genetic non-additivity (genetic dominance, epitasis) are also important (Martin, Eaves, Kearsey and Davies, 1978; Posthuma and Boomsma, 2000). For dichotomous traits, such as disease status (e.g. affected versus unaffected) in which information from a continuous measure is unavailable, even larger samples of unselected twins need to be studied - the rarer the trait the higher the number of twin pairs that needs to be included in the study (Neale, Eaves and Kendler, 1994).

These power calculations reinforced the value of the large population-based twin registers which for example existed in Scandinavia, and led to the establishment of large volunteer twin registers in other countries, including the NTR, that longitudinally follow large to very large numbers of twins and their families (Beijsterveldt et al., 2013; Willemsen et al., 2013).

Emotional and behavioral problems during childhood and adolescence are among the traits investigated in these large twin studies. The results have clearly indicated that all kinds of child and adolescent problem behaviors are partially heritable, but that estimates vary depending on the phenotype. Heritability estimates are fairly high for attention problems and EXT (between 40 and 70%) and moderate, but still substantial for INT such as anxiety and depression (in general around 30 to 60%). The common environment shared by twins explains some variation in INT (10 to 40%) in children and also some variation in attention problems and EXT (20 to 40%) in children, though during adolescence the effect of common environment mostly disappears for these phenotypes.

However, it has also been acknowledged that these estimates are not static, but are population- and time-specific "snapshots" (Kendler, 2001). It has been shown, for example, that heritability estimates of child and adolescent problem behavior can depend on factors like sex, age and the environment of the child, in other words gene x age, gene x sex and gene x environment (GxE) interaction (e.g. Bartels et al., 2004; Bergen, Gardner and Kendler, 2007; Hudziak et al., 2003; Hicks, South, DiRago, Iacono and Mcgue, 2009; Hicks,

DiRago, Iacono and Mcgue, 2009). Insight into differences in the etiology of problem behavior in different circumstances is important as it can facilitate the search for specific risk factors influencing a trait as well as tailored treatment for problem behavior in childhood and adolescence.

Factors interacting with heritability can be investigated by using advanced twin models. Especially GxE has received a renewed interest after the publication by Caspi et al. (2003) showing that the most investigated genetic variant for internalizing traits, the serotonin transporter length polymorphism (5-HTTLPR), only makes a difference in depressive symptoms when individuals were exposed to negative life-events. This has led to several studies trying to replicate this effect. So far, no conclusive results can be drawn from these studies given that meta-analyses come to different conclusions, which are followed by a still ongoing debate around the differences in conclusions (Munafo, Durrant, Lewis and Flint, 2009; Caspi, Hariri, Holmes, Uher and Moffitt, 2010; Duncan and Keller, 2011; Risch et al., 2009).

One of the problems with candidate GxE interaction studies is the selection of candidate genes. The knowledge about the biological mechanisms leading to psychiatric disorders or symptoms is limited. Furthermore, the field is plagued by publication bias for positive results (Duncan and Keller, 2011). As a consequence, candidate GxE studies might be followed up on insufficient grounds, just because the negative studies were not published.

Because of these problems in the candidate GxE studies, it is, at this moment, possibly better to (re)turn to twin studies when examining GxE. Twin studies can provide knowledge on GxE without the measurement of genetic variants by analyzing whether the heritability differs in certain environments. The first GxE studies compared the heritability in a group of twins exposed to an environmental factor with the heritability in a group of twins non-exposed to the environmental factor (e.g. Boomsma, de Geus, van Baal and Koopmans, 1999). After these first studies, the twin model has been extended to also include continuous moderators on the influences of additive genetic, common environmental and unique environmental factors enabling more extensive GxE analyses (Purcell, 2002).

An important issue to consider when investigating GxE is gene-environment correlation (rge), which means that an individual's genetic make-up influences the chance of being exposed to a certain environment by, for example, creating one's own environment (Kendler, 2001; Kendler and Baker, 2007; Scarr and McCartney, 1983). When environmental variables are in fact *correlated* with the genetic effects on the trait rather than *moderating* the genetic effects on the trait (i.e. GxE), this correlation can appear as interaction in typical analyses of GxE. Including the environmental factor as a fixed effect in the means model will effectively remove any genetic effects that are shared between the trait and the moderator from the covariance model (Purcell, 2002).

There are two other points that should be noted in the light of GxE research. First, there are different mechanisms leading to GxE (Dick (2011) for a review). The best known is the diathesis-stress model, which proposes that the environment works as a *contextual trigger*, such that stressors interact with personal predispositions to produce disease states, illness, and decrements in well-being (Rende and Plomin, 1992). The bio-ecological model states the opposite, i.e. genetic expression is higher in an enriched environment and thus lower in a disadvantaged environment (Shanahan and Hofer, 2005; Bronfenbrenner and Ceci, 1994). An example of this model is the social push hypothesis, which postulates that antisocial behavior in a disadvantageous environment is more environmentally driven while in an advantageous en-

vironment it is more genetically driven (Raine, 2002). Belsky and Pluess (2009) have proposed that some individuals have a genetic make-up that is relatively indifferent to the environment leading to rather stable trait scores over different environments. Other individuals, in contrast, are relatively susceptible to protective as well as risk environmental factors. They score lower on a trait when they are exposed to the protective environment but higher when they are exposed to the risk factors, compared to the indifferent individuals.

Second, differences in heritability in different environments cannot only be explained by GxE, but also by common environment x unique environment or unique environment by unique environment interaction. This is because the heritability is a ratio of the genetic variance and the total variance and thus can differ due to differences in the genetic variance as well as in the total variance. If the total variance is, for example, increased due to an increase in unique environmental variance, the heritability is decreased, even if the genetic variance remained the same.

Twin and higher-order multiples
The statistical power studies mentioned above also indicated the value of collecting data in relatives of twins (e.g. their parents and siblings) and also hint at the value of including higher-order multiples such as triplets and quadruplets. The birth of high-order multiples used to be a rare (or very rare) event, but this changed with the introduction of artificial fertility enhancing techniques. Before the introduction of In Vitro Fertilization (IVF) the rate at which triplets were born was the square of the twinning frequency in a population (e.g. if the twinning frequency is 1 in 80 births, the triplet frequency is 1 in 6400 births; Hellin, 1895; Fellman and Eriksson, 2009b; Fellman and Eriksson, 2009a). Twins can be MZ or DZ (born from one or two fertilized eggs), multiple-birth siblings are either MZ or polyzygotic; for example triplets can be mono-, di- or trizygotic. Most triplets born after Assisted Reproductive Technology (ART) are trizygotic.

Outline of this thesis
The NTR has recruited twins and triplets since its start in 1987 and now includes over 30,000 families with twins enrolled at birth and 677 families with triplets. In January 2013, 1756 persons from triplet families are active participants. A recent overview of the data collection procedures and the recruitment of families is given in van Beijsterveldt et al. (2013) which summarizes 25 years of NTR research in young twins and triplets.

The first three studies in this thesis use twin data on problem behavior collected between age 3 and age 16 and focus on gene x age, gene x sex and GxE interaction. Chapter 2 investigates differences in the impact of additive genetic influences (A), common environment (C) and unique environment (E) at ages 12, 14 and 16 years in a bivariate model of anxious depression and withdrawn behavior. Chapters 3 and 4 both examine GxE interaction. In chapter 3, teacher ratings of INT and EXT behavior of 7-, 10 and 12-year-old twins were analyzed. Heritability estimates were compared between groups of twins that were rated by the same teacher or by different teachers. If there would be differences in these heritability estimates, these could constitute evidence for gene x teacher/classroom interaction. In chapter 4, the effect of socio-economic status (SES) and formal child care attendance on the influences of A, C and E are investigated for INT and EXT at the ages of 3, 5 and 7 years.

The last two studies turn to the analysis of data from triplets. The average gestational

age of triplets is described in chapter 5 of this thesis. Gestational age is an important determinant of birth weight, and triplets are often born with a low birth weight. Chapter 5 describes the association of gestational age with birth weight and also assesses the influence of other factors, including genetic factors on birth weight in triplets. Next, chapter 6 describes a unique study in triplets that additionally assessed the effects of chorionicity on triplet birth weight. This assessment was possible because the triplet data from the NTR were linked to the data on chorionicity from PALGA, the nationwide network and registry of histo- and cytopathology in the Netherlands (Casparie et al., 2007). PALGA was founded in 1971 and has nationwide coverage since 1991. In addition, to investigate the representativeness of the sample, the data from triplets registered with the NTR were compared with the total Dutch triplet population, based on information from the Netherlands Perinatal Registry (PRN-foundation).