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Genetically Sensitive Sample Designs

Frank M. Spinath

November 2008

Working Paper Series of the Council for Social and Economic Data (RatSWD)

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Genetically Sensitive Sample Designs

Frank M. Spinath

Saarland University (f.spinath[at]mx.uni-saarland.de)

Abstract

Understanding the sources of individual differences beyond social and economic effects has become a research area of growing interest in psychology, sociology, and economics. A quantitative genetic research design provides the necessary tools for this type of analysis. For a state-of-the-art approach, multigroup data is required. Household panel studies, such as BHPS (Understanding Society) in the UK or the SOEP in Germany, combined with an oversampling of twins, provide a powerful starting point since data from a reasonably large number of non-twin relatives is readily available. In addition to advances in our understanding of genetic and environmental influences on key variables in the social sciences, quantitative genetic analyses of target variables can guide molecular genetic research in the field of employment, earnings, health and satisfaction, as combined twin and sibling or parent data can help overcome serious caveats in molecular genetic research.

1.   Motivation (Research questions)

The present report[1] argues that household panel studies which were initiated for the analysis of household incomes offer a unique opportunity to study the importance of genetic and environmental influences on variation across individuals in key areas of social, economic, and psychological research. It should be noted that, from a genetic point of view, the "environment" includes all influences other than inheritance, a much broader use of the term than is usual in the behavioral sciences. By this definition, environment includes, for example, prenatal events and biological events such as nutrition and illness, not just family socialization factors. Similarly, in this paper the term environment encompasses a wide variety of biological, natural, social, and economic environments.

Research questions like the origin of earnings variation, life satisfaction, health, and their interrelation with psychological variables such as personality can be addressed. By disentangling the interplay of genes and environmental factors (social scientist may call those effects "socio-economic"), the analyses of genetically informative samples make it possible to derive more accurate estimates of social and economic effects on behavior than social and economic studies, which ignore the influence of genes. A recent Special Issue on Society and Genetics in the journal *Sociological Methods & Research* illustrates the growing interdisciplinary readiness to stop treating the differences across individuals at birth as a black box (Guo 2008). In a similar vein, Diewald (2008) argues that genetically sensitive research designs can be of immense value to sociological research in providing evidence to test sociological hypotheses against competing explanations. As a result, more sophisticated methodological approaches in the social sciences should become best-practice, acknowledging and involving genetically informative samples.

Since the inherent design of household panels includes participants of varying genetic and environmental similarity (biological full siblings, biological half-siblings, parent-child dyads, and to a smaller extent adoptive children, twins, and triplets) such panel studies are an ideal - and up to now underutilized - starting point for state-of-the-art quantitative genetic analyses. This report illustrates how household panel studies enriched with an oversampling of twin participants can even address dynamic gene-environment interplay.

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[1]   Written within and for the project "Developing the Research Data Infrastructure for the Social and Behaviorial Sciences in Germany and Beyond: Progress since 2001, Current Situation, and Future Demands" of the German Council for Social and Economic Data (RatSWD) (http://www.ratswd.de/ver/veranstaltungen.php).

This report focuses on the quantitative genetic approach. Molecular genetic research strategies (e.g., genetic association and candidate gene studies) constitute a different methodological approach that is not addressed here (for an outlook on possible combinations of both methods, see Section 5 below). Due to the fact that genetically sensitive sample designs are a relatively new topic in the discussion of the research infrastructure and future needs in social and economic research, this report also provides a basic theoretical and methodological background to the understanding of quantitative genetic analyses.

The benefit of utilizing genetically informative data is not limited to research of a predominantly psychological nature, and the number of studies on the etiology of key variables in economic and social research is growing. For example, twin data indicates that basic political attitudes like liberalism and conservatism are likely to be heritable (Hatemi et al. 2007). In two further independent twin studies, Fowler, Baker, and Dawes (2008) showed that voter turnout and political participation have very high heritabilities.

In a recent multigroup analysis, Björklund, Jäntti, and Solon (2005) studied the influences of nature (genes) and nurture (socio-economic characteristics) on earnings variation using observed sibling correlations in earnings for nine types of sibling pairs: monozygotic twins reared together, monozygotic twins reared apart, dizygotic twins reared together, dizygotic twins reared apart, non-twin full siblings reared together, non-twin full siblings reared apart, half-siblings reared together, half-siblings reared apart, and adoptive siblings. On the basis of this variety of sibling types in the analyses, the authors were able to estimate models that involved less restrictive assumptions and provided opportunities to examine the sensitivity of their results to variation in modeling assumptions, namely the introduction of nonzero GE correlation, of estimates for the genetic relatedness of DZ twins, non-twin full siblings, half-siblings, and adoptive siblings, and varying sibling correlation in environmental influences. The results turned out to be sensitive to flexibility in modeling the variation across types of sibling pairs in the similarity of their environments. Even the smallest estimate of the genetic component of earnings variation, however, suggested that it accounts for about 20 percent of earnings inequality among men and more than 10 percent among women. The largest environmental influence was of the nonshared variety, which is in line with the results of many quantitative studies on personality. In the present study, even among MZ twin brothers, an estimated 64 percent of their earnings variation was explained by neither genetic nor shared environmental resemblance.

The latter study is also a good example of how quantitative genetic methods can be used to target key research topics in labor economics, that is, understanding the sources of earnings

inequality and accounting for the rise in earnings inequality that has occurred in most developed countries over the last quarter-century (Katz and Autor 1999). Inequality research focusing on the role of family and community origins ties in particularly well with the quantitative genetic understanding of shared and nonshared environmental factors. The basic idea is that if family and community origins account for a large portion of earnings inequality, siblings will show a strong similarity in earnings; if family and community background hardly matters at all, siblings will show little more resemblance than would randomly selected unrelated individuals.

2.   Theoretical and methodological background

Results from classical twin studies have made a remarkable contribution to one of the most dramatic developments in psychology during the past few decades: the increased recognition of the important contribution of genetic factors to virtually every psychological trait (Plomin et al. 2008). However, enriching classical twin studies by data from additional dyads (non-twin siblings, parents-children, etc) can improve behavioral genetic analyses for the following reasons.

The classical twin design compares the phenotypic resemblances of identical or monozygotic (MZ) and fraternal or dizygotic (DZ) twins. MZ twins derive from the splitting of one fertilized zygote and therefore inherit identical genetic material. DZ twins are first-degree relatives because they develop from separately fertilized eggs and are 50% genetically identical on average. It follows that a greater within-pair similarity in MZ compared to DZ twins suggests that genetic variance influences the trait under study.

To disentangle and to quantify the contributions that genes and the environment make to human complex traits, data are required either from relatives who are genetically related but who grow up in unrelated environments ("twin adoption design"), or from relatives who grow up in similar environments but are of differing genetic relatedness ("twin design"). Most twin studies that have been conducted over the past 80 years are of the latter type. Only two major studies of the former type have been conducted, one in Minnesota (Bouchard et al. 1990) and one in Sweden (Pedersen et al. 1992). These studies have found, for example, that monozygotic twins reared apart from early in life are almost as similar in terms of general cognitive ability as are monozygotic twins reared together, a result suggesting strong genetic influence and little environmental influence caused by growing up together in the same family. These influences are typically called **shared environment** because they refer to

environmental factors contributing to the resemblance between individuals who grow up together. **Nonshared environmental influences**, on the other hand, refer to environmental factors that make individuals who grow up together different from one another.

One reason why a predominant number of twin studies have utilized the twin design instead of the twin adoption design is that twins typically grow up together, thus it is much easier to find a large number of participants for the classic twin study. In humans, about 1 in 85 live births are twins. The numbers of identical and same-sex fraternal twins are approximately equal. That is, of all twin pairs, about one-third are identical twins, one-third are same-sex fraternal twins, and one-third are opposite-sex fraternal twins. The rate of twinning differs across countries, increases with maternal age, and may even be inherited in some families. Greater numbers of fraternal twins are the result of the increased use of fertility drugs and in vitro fertilization, whereas the rate of identical twinning is not affected by these factors.

Comparing the phenotypic resemblance of MZ and DZ twins for a trait or measure under study offers a rough estimate of the extent to which genetic variance is associated with phenotypic variation of that trait. If MZ twins resemble each other to a greater extent than do DZ twins, the heritability (h^2) of the trait can be estimated by doubling the difference between MZ and DZ correlations, that is, $h^2 = 2(r_{MZ} - r_{DZ})$ (Falconer 1960). **Heritability** is defined as the proportion of phenotypic differences among individuals that can be attributed to genetic differences in a particular population. It should be noted that for a meaningful interpretation of twin correlations in the described manner, a number of assumptions have to be met: the absence of assortative mating for the trait in question, the absence of G(enotype) × E(nvironment) correlation and interaction, and the viability of the Equal Environments Assumption. A more detailed discussion of these assumptions as well as the effects of variation attributable to chorionicity differences is available elsewhere (Spinath 2005), so a short introduction should suffice here:

Assortative mating describes nonrandom mating that results in similarity between spouses and increases correlations and the genetic similarity for first-degree relatives if the trait under study shows genetic influence. Assortative mating can be inferred from spouse correlations which are comparably low for some psychological traits (e.g., personality), yet are substantial for others (e.g., intelligence), with average spouse correlations of about. 40 (Jensen 1998). In twin studies, assortative mating results in underestimates of heritability because it raises the DZ correlation but does not affect the MZ correlation. If assortative mating is not taken into account, its effects are attributed to the shared environment.

Gene-Environment (GE) correlation describes the phenomenon that genetic propensities can be correlated with individual differences in experiences. Three types of GE correlations are distinguished: passive, evocative, and active. Previous research indicates that genetic factors often contribute substantially to measures of the environment, especially the family environment (Plomin 1994). In the classic twin study, however, GE correlation is assumed to be zero because it is essentially an analysis of main effects.

Gene-Environment (G × E) interaction is often conceptualized as the genetic control of sensitivity to the environment. Heritability that is conditional on environmental exposure can indicate the presence of a G × E interaction. The classic twin study does not address G × E interaction and the classic twin model assumes the equality of pre- and postnatal environmental influences within the two types of twins.

Finally, the classic twin model assumes the equality of pre- and postnatal environmental influences within the two types of twins. In other words, the **Equal Environments Assumption (EEA)** assumes that environmentally caused similarity is roughly the same for both types of twins reared in the same family. Violations of the EEA in the sense that MZ twins experience more similar environments than DZ twins would inflate estimates of genetic influences.

3.   Methodological advances and new research questions

The comparison of correlations between MZ versus DZ twins can be regarded as a reasonable first step in our understanding of the etiology of particular traits. To model genetic and environmental effects as the contribution of unmeasured (latent) variables to phenotypic differences, Structural Equation Modelling (SEM) is required. Analyzing univariate data from MZ and DZ twins by means of SEM offers numerous advances over the mere use of correlations, including an overall statistical fit of the model, tests of parsimonious submodels, and maximum likelihood confidence intervals for each latent influence included in the model.

The true strength of SEM, however, lies in its application to multivariate and multigroup data. During the last decade powerful models and programs to efficiently run these models have been developed (Neale et al. 2003). Extended twin designs and the simultaneous analysis of correlated traits are among the most important developments that go beyond the classic twin study (Plomin et al. 2008).

Multigroup designs using a wider variety of sibling types bring more power to bear on quantitative genetic analyses (e.g., Coventry and Keller 2005). For example, it is useful to

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include non-twin siblings in twin studies to test whether twins differ statistically from singletons, and whether fraternal twins are more similar than non-twin siblings.

Multigroup designs also enable the application of more general (i.e., less restrictive) models, such as relaxation of the EEA or the introduction of GE correlation and to examine the sensitivity of results to variations in modeling assumptions. Furthermore, results from multigroup analyses are less prone to systematic method bias and sampling error.

4.   Status quo: data bases and access

More than 5,000 papers on twins were published during the five years from 2001 to 2006, and more than 500 of these involve behavior (Plomin et al. 2008). The value of the twin method explains why most developed countries have twin registers (Bartels 2007).

About a decade ago, Boomsma (1998) published the first paper in a series aimed at giving an overview of existing twin registers worldwide. A short description of 16 registries in nine European countries was presented. At the time, these registries had access to over 350,000 pairs providing a resource for genetic–epidemiological research. In the years 2002 and 2006, special issues of the scientific journal Twin Research and Human Genetics documented further progress in this field. Currently, worldwide registers of extensive twin data are being established and combined with data from additional family members offering completely new perspectives in a refined behavioral genetic research (Boomsma et al. 2002).

However, data sets required for multigroup analyses are typically not readily available, especially in countries without official twin or extensive population registers such as Germany. Even in Sweden, home of one of the most extensive twin register in the world, samples for multigroup data have to be matched from different sources (Björklund et al. 2005). In the study described in the introduction, data on non-twin siblings came from random samples of the Swedish population drawn by Statistics Sweden whereas the twin sample came from the Swedish Twin Registry (Medlund et al. 1977).

The situation in Germany is even more complicated because a central twin register is not available. When the Bielefeld Longitudinal Study of Adult Twins (BiLSAT; Spinath et al. 2002), the first large scale twin in Germany, was initiated in 1993, twins were recruited through newspaper and media announcements as well as twin organizations. A telephone hotline was installed and twins who expressed their interest in the BiLSAT were informed about the aims of the study and the approximate time required to complete the questionnaire sets. Names, addresses, date of birth and self-reported zygosity of twin pairs who decided to

participate were entered into the database. Within six months, approximately 1,500 twin pairs were enrolled in the BiLSAT and questionnaire data was collected for approximately 75% of the initial sample. The twins' age varied between 14 and 80 years (M = 32, SD = 13 years) and the sample was heterogeneous with regard to education and employment status. As it is typically observed with voluntary twin samples, females participated more frequently than males and MZ twins participated more frequently than DZ twins.

In two more recent twin studies (Spinath and Wolf 2006), a different recruitment procedure aimed at reducing self-selective sampling was applied: Through individual inquiries at registrations offices in two German federal states (North Rhine-Westphalia and Thuringia), contact information on persons with the same birth name, the same birthday, and also the same birthplace was gathered. These requests resulted in 36,574 addresses of potential twin pairs – adult twins as well as parents of twins. From this list, people in the relevant age-groups for the planned projects (birth cohorts 1995-1998 and 1955- 1970) were selected. After matching the provided addresses with data found in public telephone directories, 1,014 adult twins and 715 families with children twins were contacted by phone in 2005. An additional 3,832 households were contacted via mail. First contact by phone turned out to be more efficient, because almost two-thirds of all personally contacted twins agreed to participate as compared to only 26% (children sample) and 10% (adult sample) participations when first contact was made by mail. The total number of false positive contacts (people born on the same day and with the same surname who claimed not to be twins) was relatively small, yielding 2.4% for the children sample and 4.3% for the adult sample and rendering the chosen way of recruitment feasible.

5. Future developments

Interdisciplinary efforts to collect data of relevance to psychologists, sociologists, and economists alike and using genetically sensitive designs are highly desirable since the challenges of recruiting a multigroup sample can be met with greater ease in a collaborative effort combining household panel study data and data from traditional twin samples.

Studies such as the British Household Panel Study (BHPS) and the German Socioeconomic Panel (SOEP), representative longitudinal studies of private households providing information on all household members and covering a range of topics including employment, earnings, health and satisfaction indicators, are ideal for many reasons:

First of all, household panels naturally include biological full-siblings, biological half-siblings, parent-child dyads, and to a smaller extent adoptive children, twins and triplets.

An explorative analysis showed that with nearly 11,000 households, and more than 20,000 persons sampled in SOEP, data from a reasonably large number of non-twin relatives is readily available. In the SOEP data collected in 2007, for example, it was possible to identify 2,209 individuals from 983 families who have at least one sibling as well as 179 adopted children. With 47 individuals in twin or triplet pairs from 20 families, the number of twins who are already enrolled in SOEP is not large enough for a multigroup analysis. However, the recruitment of twins who participate in the assessment of SOEP variables and who could ultimately be enrolled in the regular longitudinal assessment is a unique opportunity to enrich an already powerful dataset to allow for quantitative genetic analyses.

Studying the families of identical twins, for example, has come to be known as the families-of-twins method (D'Onofrio et al. 2003). When identical twins become adults and have their own children, interesting family relationships emerge. For example, in families of male identical twins, nephews are as related genetically to their twin uncle as they are to their own father. Furthermore, the cousins are as closely related to one another as half siblings are. Studying twins and their family members is a powerful method in differentiating and quantifying environmental and genetic processes underlying associations between family-level risk factors and child adjustment to environmental stimuli. In addition to refined modeling opportunities for estimating genetic and environmental influences on target variables in such samples, repeated measurements provide the opportunity to address genetic and environmental influences to stability and change over time as well as covariance among variables of interest. To summarize: In principle, household panel studies which trace individuals with their families and households for decades are ideal data bases for such studies. However, up to now the number of twins assessed in such studies is too small.

Finally, twin and multigroup samples are valuable for determining behavioral areas in which molecular genetic research efforts and candidate gene studies are more likely to be fruitful. As an example, Fowler and Dawes (2008) recently reported that a polymorphism of the MAOA gene significantly increases the likelihood of voting. Additional household information as well as twin and parent data combined (also known as the Nuclear Twin Family Design, NTFD), allow for a separation of environmental factors shared only between siblings (S) and familial environmental factors passed from parents to offspring (F).

Two possible ways to establish an oversampling of twins, i.e. to arrive at a sufficiently large number of twin participants, in Germany have already been outlined above. These

possibilities can be combined with a third recruitment strategy: the screening of people by survey research. In cooperation with TNS Infratest, a feasibility check was carried out in which a random sample was contacted via telephone.[2] As part of a larger interview, respondents were asked whether they happened to be a member of a twin pair. If that was the case a second question addressed the willingness to be contacted and informed about a twin research project. A total of 17,529 interviews yielded 312 members of twin pairs (1.8%). From this sample, 149 individuals (48%) agreed to be contacted by phone or mail. The twins' age varied between 14 and 75 years (M = 43, SD = 16 years). In contrast to the voluntary twin sample in BiLSAT mentioned above, male and female twins agreed to be contacted with equal frequency.

The fact that twin and non-twin sibling pairs need to be matched in a pairwise fashion requires the introduction of suitable pointer variables into the data set. Quantitative genetic analyses also require zygosity information for same-sex twin pairs. The best way to determine twin zygosity is by means of DNA markers (polymorphisms in DNA itself). If a pair of twins differs for any DNA marker, they must be fraternal because identical twins are identical genetically. If a reasonable number of markers are examined and no differences are found, it can be concluded that the twin pair is identical. Physical similarity on highly heritable traits such as eye color, hair color, or hair texture as well as reports about twin confusion are also often used for zygosity determination. If twins are highly similar for a number of physical traits, they are likely to be identical. Using physical similarity to determine twin zygosity typically yields accuracy of more than 90% when compared to genotyping data from DNA markers (e.g., Chen et al. 1999).

6. Conclusions and recommendations

Understanding the sources of individual differences - compared to social and economic effects - has become a research area of growing interest in psychology, sociology, and economics. A quantitative genetic research design provides the necessary tools for this type of analyses. For a state-of-the-art approach, multigroup data is required. Household panel studies, such as the SOEP in Germany or BHPS in UK,[3] combined with an oversampling of twins, provide a powerful starting point since data from a reasonably large number of non-twin relatives is readily available.

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3   Where the new panel "Understanding Society" with a larger number of households will provide even better research opportunities.

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Quantitative genetic analyses of target variables can guide molecular genetic research in the field of employment, earnings, health and satisfaction, and combined twin and sibling or parent data can help overcome serious caveats in molecular genetic research.

It is recommendable to carry out a pilot assessment of key socio-economic variables in a special sample of MZ and DZ twins which is comparable to BHPS or SOEP. Initial data collection in the twin sample including zygosity diagnosis can be realized online to minimize attrition. A total of approximately 400 twin pairs of each group of twins (that is, MZ, same-sex DZ, and opposite-sex DZ twins) enrolled in such a pilot assessment can provide a meaningful basis for the development of a more refined strategic plan, such as the integration of a twin cohort into the regular interview-based assessment in BHPS (Understanding Society) and SOEP.

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