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Genetic thinking in the study of social relationships: Five points of entry

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Abstract

For nearly a generation, researchers studying human behavioral development have combined genetically informed research designs with careful measures of social relationships: parenting, sibling relationships, peer relationships, marital processes, social class stratifications and patterns of social engagement in the elderly. In what way have these genetically informed studies altered the construction and testing of social theories of human development? We consider five points where genetic thinking is taking hold. First, genetic findings suggest an alternative scenario for explaining social data. Associations between measures of the social environment and human development may be due to genes that influence both. Second, genetic studies add to other prompts to study the early developmental origins of current social phenomena in mid-life and beyond. Third, genetic analyses promise to bring to the surface understudied social systems, such as sibling relationships, that have an impact on human development independent of genotype. Fourth, genetic analyses anchor in neurobiology individual differences in resilience and sensitivity to both adverse and favorable social environments. Finally, genetic analyses increase the utility of laboratory simulations of human social processes and of animal models.

For the past thirty years geneticists and social scientist have collaborated on a series of studies exploring the links between social relationships and normal and pathological human development. Has this changed the way think about social relationships? For clues, we examine—briefly—a history of the encounters between social science and genetics and suggest five points of entry for genetic analyses to influence social science thinking about social relationships and their impact. We conclude by forecasting the likely impact of entry at each of these five points.

Genetics and the science of human relationships: a note on confrontation and collaboration across time

Understanding the role of genetics in social science depends on understanding the circumstances under which they have come. For example, there is a widespread belief that of the two strands of science, social science is by far the older. This leads to a misperception that genetics is the current, 21st century express with the potential to set aside, correct or undermine older theories of social causation. A fair read of the history of science and of the literature over the last century yields a different picture: genetics and social science are two strands of science with distinctive and traceable roots in the distant past that have come together repeatedly both in epic struggles and for mutual benefit. Developments in the last three decades, which provide the bulk of evidence considered here, are a modern-day

extension of this process. Preliminary efforts at writing a history of behavioral genetics are now available (Gottesman 2008; McGue 2010). However, for present purposes we require a history of encounters between social science and behavioral genetics. Here we provide an initial sketch.

Few serious scholars would doubt the long and productive history of the social and behavioral sciences. In larger perspective, the only dispute might be when informal observations of social relationships and human nature became systematic enough to be designated as “science.” Some might argue that the exceptionally penetrating and recurrent attention to sibling relationships in the stories of Genesis, originally redacted before 1000 BC and considered as penetrating “qualitative analysis”, has not been surpassed in the centuries since. Others might nominate a later starting point when the Greeks distinguished three perspective for study human psychology: social, psychological and biological factors that influenced both mental life and human relationships (Simon 2008).

The same perspective can extend backwards in time to the early roots of the genetics of behavior. By 1868 Darwin was able to document the centuries of widespread use of practical genetics in the domestication of plants and animals (Darwin 1920 (1868)). For example, dog and cattle breeders had a clear understanding of animal fertility, cross breeding, inbreeding, and heritability so much so that, even in antiquity, high prices could be obtained for very young animals on the basis of well-documented pedigrees. However, it was not until systematic science rediscovered the work of Gregor Mendel, a re-discovery at the very end of the 19th century that a formal theory of genetics could explain and extend the practice of plant and animal breeding. At the same time, a more mechanistic understanding of genetics shed new light on Darwin's earlier observations on heritability and natural selection.

Early in the 20th century many model systems were constructed to explore genetic hypotheses about behavior. These included studies of fruit flies, sophisticated mathematical models and the studies of isolated human and animal populations in natural settings (Maxson 2007). However, the most powerful tool for exploring genetic influences on human development was the twin method: specifically the comparisons of *correlations* or *concordances* between monozygotic (MZ) and dizygotic (DZ) twins. Although Galton was the first to explore the use of the twin method to examine the influences of divergent environments on the life course of MZ twins, the fundamental discovery of the modern twin method was reported in 1922 by a graduate student of Lewis Terman named Curtis Merriman. In an investigation of intelligence he compared within-sib correlations for identical twins with a sample of twins of varying zygosity. In 1924, the German dermatologist Herman Siemens was the first to use the twin method in its current form: a direct comparison between identical and fraternal twins which he used to investigate the role of genetic factors in both dermatologic conditions as well as behavioral differences such as school performance (Rende, Plomin et al. 1990).

The twin method was widely applied in ensuing years to many domains of human activity but its use stimulated a challenge from the social sciences. One area of dispute was twin studies of schizophrenia. Kallmann (Kallmann 1946) had reported that MZ twins showed consistently higher concordance rates than DZ twins. He concluded that genetic factors

played a major role in schizophrenia. Family process researchers did not accept this conclusion. They enumerated many ways in which identical twins were treated more similarly than fraternal twins by their parents and by others (e.g. (Jackson 1960). Criticism of this sort has continued to the present (Joseph 1998; Joseph 2001). Over time, behavioral geneticists recognized the validity of these broad critiques and responded by developing more critical designs. For example, to deal with the critiques of the Kallmann twin studies (Kallmann 1946), Leonard Heston, while a psychiatric resident, and Seymour Kety, Paul Wender and David Rosenthal applied the adoption method to study the prevalence of schizophrenia in the biological and adoptive relative of index cases (Kety, Rosenthal et al. 1967; Heston and Denney 1968; Rosenthal and Kety 1968; Rosenthal, Wender et al. 1968) which confirmed Kallman's essential findings. Robert Plomin and Nancy Pedersen developed a population-based sample of Swedish MZ and DZ twins some reared apart and others reared together. They showed that differences in concordances or correlations between MZ and DZ twins in a sample of reared apart twins could replicate MZ-DZ differences in those reared together. The findings in reared apart twins cannot be due to the special treatment of MZ twins by parents and others (Bergeman, Plomin et al. 1991; Pedersen, McClearn et al. 1991).

Thus, by the early 1980s, after a generation of conflict, the field of behavioral development and social processes had a strengthened set of methods for exploring the role of genetic influences. However, it is not the case that methodological disputes are over. For example, estimates of heritability from twin methods may be seriously over-estimated if the interaction between environments and genetic factors are not taken into account. New analytic techniques have been developed to estimate these interactions (Purcell 2002). Likewise, there are recent challenges to the adoption design. When, these designs were presented to address the twin studies of schizophrenia it was assumed that resemblances between a birth parent and child placed for adoption early in life could be attributed to genetic factors. However, recent research has suggested that maternal substance use and nutrition as well as high levels of maternal anxiety may influence fetal development and subsequent behavioral development of the child (O'Connor, Heron et al. 2002; Costello, Worthman et al. 2007; Van Den Bergh, Van Calster et al. 2008). Collectively, these intrauterine influences are often termed "behavioral teratogens" and require a measure of caution about genetic inferences from adoption designs.

These controversies have led to refined use of twin and adoption designs, in the past two decades. This, in turn, has encouraged a growing synthesis of research drawn from several streams of genetic research and from the long a productive lines of research on behavioral development and family, group and larger scale societal processes. On the one hand, behavioral geneticists such as David Rowe, Robert Plomin, Matt McGue, Kenneth Kendler and Richard Rose have recognized the importance of including measures of parenting, sibling relationships, peer relationships and rural and urban distinctions in well-crafted twin studies and adoption studies. (Rowe 1983; Plomin and Daniels 1987; McGue and Lykken 1992; Plomin and Neiderhiser 1992; McGue and Sharma 1995) (Kendler 1996) (Rose, Dick et al. 2001). Likewise, and at approximately the same time, established behavioral and social scientists such as Judy Dunn, David Reiss, Mavis Hetherington Xiaojia Ge. Theodore Jacob and Lea Pulkkinen used twin and adoption studies to clarify and test psychological and

social theories of normal and pathological development (Dunn and Plomin 1986; Pike, McGuire et al. 1996; Reiss, Neiderhiser et al. 2000) (Ge, Conger et al. 1996) (Rose, Dick et al. 2001) (Jacob, Waterman et al. 2003).

While these bridges were being built, using twin and adoption designs, a second line of potential cooperation grew rapidly. Geneticists and social scientists could collaborate in studies of measured genes: specific alterations of DNA that have implications for behavioral and social development. This historical line begins in 1903 with Walter Sutton, a graduate student at the University of Kansas who clarified the role of chromosomes in Mendelian inheritance (Crow and Crow 2002) and 51 years later Watson and Crick clarified the molecular structure of the chromosomal nucleic acids (Watson 1952). A torrent of innovation followed allowing investigators to identify variation among individuals in the structure of specific genes and to begin to establish the molecular basis of many human diseases. A gene that has varying structural form with consequences for function is called a polymorphism and each of its various forms is called an allele. Some early success in the molecular genetics of behavior was achieved in mental retardation, early onset Alzheimer's disease and Rett's syndrome. Progress in delineating the molecular bases of more complex disorders with very high heritabilities--such as ADHD, schizophrenia and autism--have been much slower.

Several strategies have emerged that may help move this field forward. For example, the biological psychiatrist Daniel Weinberger has proposed parsing the complex thought disorder of schizophrenic patients into simpler, more biologic homogenous components (Goldberg and Weinberger 2004); this strategy searches for genes associated with these parsed components which Weinberger refers to as "intermediate phenotypes." The developmental psychologists, Avshalom Caspi and Terrie Moffitt have shown that the effects of allelic variation of some polymorphic genes are recognizable only under conditions of high social stress (Caspi, McClay et al. 2002; Caspi, Sugden et al. 2003)..

Genetics in the construction and revision of social science theory

There are still obstacles in the way of a full collaboration between social and genetic science. Among them are three misconceptions that many social scientists seem to hold implicitly. To advance collaboration they need to be made explicit and examined in the light of empirical findings.

The first misconception is an assumption of additivity: important outcomes in human development, according to this assumption, are a sum of genetic influences and social influences. This misconception has fostered the belief that social scientists can study "their portion" of influences and leave the "rest" up to the geneticists. However, as analytic methods have improved many studies show that genetic and environmental factors mix in much more complex combination from conception onwards. Three concepts illustrate these combinations.

The first is *gene x environment interaction*. This refers to variations in the expression of genetic influences that depends on variation in the social environment. A second form of combination is *gene-environment correlation*. At its simplest, the term implies that, in any

population, genotype and environmental influences are correlated. Two basic mechanisms account for this correlation. First, each parent shares 50% of their genes with each offspring. Thus, a common set of genes may lead a parent to behave against the best interest of the child and the same genes, in the child, may lead to disruptive behavior. A second mechanism reflects heritable characteristics of the child that evoke or select particular environments. Leve and her colleagues review these two concepts in this issue (Leve, Harold, et al, *this issue*).

A third concept is *genetic contribution to covariance* between measures of the social environment and measures of behavioral development. For example, genetic factors that influence antisocial behavior in adolescents also influence hostile and critical interaction between parents and children. In one study nearly 60% of this covariance between child behavior and parental style was accounted for by genes common to both (Reiss, Neiderhiser et al. 2000). Growing evidence suggests that the underlying mechanism for findings of this kind involves, in part, evocative processes in the child that evoke adverse parenting which, as a consequence of this evocation, further shapes the child's development. The reverse also happens as well: genetic influences on children's adverse behavior lead to reactive, equally adverse parental behavior (Burt, McGue et al. 2005; Larsson, Viding et al. 2008).

The empirical basis for these three basic ideas moots imprecise distinctions between measures of the social “environment” and genetic factors. For example, positivity in parent-child relationships has for decades been seen as index of the child's social “environment.” However, child's genes evoke parental positivity (e.g. Reiss (Reiss, Neiderhiser et al. 2000) and parent's genes influence their positive responses to their children (Neiderhiser, Reiss et al. 2004). Moreover, the association between positive mothering and, for example, adolescent autonomy is accounted for mainly by *genes common to both* (Reiss, Neiderhiser et al. 2000).

A second misconception concerns the timing of influences: genetics have their influence early before the “environment takes hold.” Again, this assumption—implicitly held—suggests it is “safe” for social scientists to study later phases of development where genetic influences may have already “died out.” Current evidence does not support this assumption either. For cognitive development, for example, the social environment--particularly factors that distinguish among families--has distinctive effects early in development and genetic influences grow and then remain stable in adolescence and adulthood (see, for example, recent studies of cognitive development (Price, Dale et al. 2004; Davis, Haworth et al. 2009). Moreover, genetic influences vary not only in amount but also in kind across the life span. For example, the genetic influences on temperament, emotion and language, at the end of the toddler period, are uncorrelated or poorly correlated with those that influence these same variables early in the toddler period (Plomin, Emde et al. 1993); early genetic influences go “off line” and new genetics influence come “on line.” Later in development, genetic factors are responsible for stability in both cognitive and personality measures across broad spans of time (see a recent review (Reiss and Leve 2007).

A third misconception is perhaps an over-simplification of Durkheim's conceptions of “social facts” that are independent of the motive and characteristics of individuals. The

operations of social systems, so this argument goes, reflect enduring laws of social process and organization that can influence individual action and development but cannot be observed or understood by examining individuals. Behavioral genetics is, par excellence, a science of individual differences in psychological and social functioning. Durkheim's focus on the properties of social systems *qua* systems spawned a century of highly productive research but it is not a barrier to combining this tradition with genetic analyses. For example, in a series of analyses Rose and his colleagues showed that genetic influences on adolescent alcohol use were stronger in urban than rural areas; their data suggested that this effect was due in part to greater cohesion and less in and out migration in rural communities (Dick, Rose et al. 2001; Rose, Dick et al. 2001). Durkheim's perspective has often been carried over to studies of small social systems including marriage where, it has been assumed, that the pattern of partner interaction must be studied on the level of the dyad. However, evidence suggests otherwise. For example, heritable characteristics of children can evoke conflict in the marital process of their parents (Reiss, Neiderhiser et al. 2000). These and other studies argue there is something to be learned about the causes and consequences of social integration, a prime focus of work in the Durkheim tradition, from genetic analyses and, more important, a preoccupation with "social facts" is not a barrier to genetic thinking in the study of social relationships.

We turn now to five points of entry of genetic thinking into the study of social relationships.

Counterfactuals and alternate scenarios

The most important entry point of genetics is that its findings suggest alternate explanations for well-established findings. Research on social relationships, for example, have studied carefully how maternal depression alters a mother's relationships with her child and such an altered relationship might affect the child's subsequent psychological development. However, these studies are invariably carried out with mothers and their biological offspring (e.g., (Network 1999; Coyne, Low et al. 2007; Maughan, Cicchetti et al. 2007; Foster, Garber et al. 2008). Thus, any association between mother's depression or her parenting, on the one hand, and her child's development, on the other, could be due to the genes they share, not to any effects of her parenting.

This underscores the importance of a recent study by, Tully and her associates (Tully, Iacono et al. 2008). They used an adoption design to provide the strongest evidence to date that maternal (but not paternal) depression is associated with child psychopathology for environmental reasons. She reported that child psychopathology was as likely among adopted offspring of depressed mothers as among biological offspring of depressed mothers. Thus, genes common to parent and child could not explain the link between maternal depression and child psychopathology.

A substantial impact of genetic research on social theory is that it has made possible an alternative scenario: maternal depression is not an adverse social environment for the child but an indicator of the child's heritable risk for a range of psychopathologies. For example, variations among individuals in depression, in self worth and in parenting practices have all shown notable genetic influences (McGuire, Manke et al. 1999; Neiderhiser, Reiss et al. 2004); hence, parents' self concepts and parenting practices might be influenced by the same

genes that, when passed on to their children, influence the child's psychopathology as well. The alternative (genetic) scenario is driven home by a starkly contrasting set of findings from the same adoption study used by Tully for her analyses. When parental alcoholism is the "environmental" variable it is associated with impulsive and disinhibited behavior in offspring; however that association is found *only in biological offspring* (King, Keyes et al. 2009). Thus, genes common to parents and children account for all of the transmission raising questions about interpreting many studies that have assumed parental alcoholism is a pathogenic environmental risk for children.

Imagining plausible alternative explanations always strengthens causal reasoning in the social sciences. The philosopher David Lewis first formalized this approach to causal reasoning through the imagination of possible worlds whose plausibility was established by *counterfactuals* (Lewis 1973). This approach to causal analysis has been systematically applied to the analysis of social systems (e.g. (Durand and Vaara 2009) and to the psychological study of how most people reason about causality.

Alternate, genetic scenarios for parent-offspring transmission are easier to imagine and provide more intuitively compelling reasons for designing studies to directly test their plausibility. However, there are other domains of social process where the alternate genetic scenario might be more difficult to imagine unless genetic analysis prods the investigator's imagination. For example, marital processes involve intimate reciprocity, both loving and hating, to which children often bear witness. Surely, one might think, the links between the marriage of child's parents and the child's psychological development rest exclusively on environmental mechanisms of covert learning, imitation as well as arousal, anxiety and fear. A sizable literature on the relationship of marital conflict and child adjustment appears to assume that association reflects social and psychological (see, for example, the review by Rhoades (Rhoades 2008).

However, recent, genetically informed research provides important counterfactuals: evidence suggesting a scenario where genetic factors, not environmental ones, account for the apparent impact of marital discord on at least some aspects of child development. For example, Harden and her colleagues used a "children of twins" design where parents who are twins are recruited along with their children. For children of MZ women (or men) their aunts (or uncles) are genetically identical to their mothers (or fathers). However, in most families, these children have much less exposure to aunts or uncles than to parents. The design yields particularly interesting results when the MZ twin parents are discordant for a trait (for environmental reasons). For these families, we can focus on children where the parent does not have the trait but the aunt (or uncle) does have the trait. If an environmental mechanism of parent-child transmission is important we should expect, for each pair of parents who are twins, to find the child's trait only among the children of the twin parent who has the trait. However, if a genetic mechanism is important we would expect to see the trait in children of the twin parents who have the trait as well as the children of the twin parents who do not. This conclusion would be reinforced if the child's risk is greater when the aunt (or uncle) was an MZ twin of the parent rather than a DZ twin. Harden and her colleagues used this method to study marital conflict as the parental trait and child antisocial behavior. Harden's data suggested a genetic mechanism linking marital conflict and

antisocial behavior (Harden, Turkheimer et al. 2007). An earlier study, with far less statistical power, hinted at the same counterfactuals (O'Connor, Caspi et al. 2000). The genetic “possible scenario” is supported by genetically informed studies of marital quality and marital breakdown, both of which show notable genetic influence (McGue and Lykken 1992; Jocklin, McGue et al. 1996; Spotts, Neiderhiser et al. 2004).

These data are important for their probative value: they suggest that a heritable personality trait in the parents, perhaps antisocial behavior, contributes to their marital conflict and, when transmitted to their offspring, influences their conduct problems as well. However, the larger importance of these data is that provide counterfactuals for an alternate scenario for explaining observed links between marital process and child development. As a set of counterfactuals these data suggest that *all* research on the impact of marriage on child development must consider the possibility that all or part of the effect is genetically, not socially, transmitted. In this sense counterfactuals operate differently than facts. They need only to establish the plausibility of an alternate scenario, not its probability. The concept of plausibility is interactive: it derives not only from the weight of surprising findings but also from the readiness of any particular investigator to be roused by them.

Moving social theories upstream

Most current behavioral and social theories are complex. Often, they posit early causal influences, subject to mediating and moderating influences for social and behavioral outcomes of interest. For some decades, efforts to unravel causal links among variables relied heavily on longitudinal observations. Variables occurring earlier in complex models were likely to be given causal priority in models of this kind. However, for some time, researchers have recognized that the major probative value of longitudinal studies is *disproving* some causal theories. Many hypothesized causes of behavioral outcomes could be shown to occur after rather than before the outcome of interest. For example, the impact of divorce on children's behavior problems was thrown into question long before genetic studies of marriage when it became clear that for divorcing couples the child's behavior problems preceded, often by many years, the divorce—particularly for boys (Cherlin, Furstenberg et al. 1991). In the causal chain linking marital difficulties to child outcomes, the legal status of divorce was clearly not the beginning of the sequence; matters began more upstream, presumably in the dysfunction and deterioration of the marital relationship or in the genetic transmission of risk.

Social theory has often provided a place marker for these “upstream” processes and termed them *selection effects*. The emphasis in the analysis of selection effects is precautionary. Results from many studies suggest, for example that social class differences among individuals contributes to differences in their physical health. For decades it has been routine, in interpreting findings of this kind, to be sure that variations in physical health, occurring before investigators obtained measures of social class, are not responsible for “selecting” individuals into different class levels. Even without genetics, powerful analytic tools, particularly econometrics, have successfully addressed this issue (see a significant example in the current issue (Conti, Heckman and Urzua, *this issue*).

However, genetic data provide an added tool not only for examining these selection effects but a strong incentive to construct theories of social class effects that move far upstream. For example, Lichtenstein and colleagues—in large sample of Swedish twins (mean age 58.6) some reared together and other reared apart—observed notable genetic effects on several measure of social class and also on measures of illness burden and of self reported health. Most important they found that genetic factors common to both measures of social class and illness accounted for a substantial portion of the observed correlation between class and health (Lichtenstein, Harris et al. 1993). The findings also supported a social class effect on health independent of genotype but an effect smaller than the observed correlations between class and health would suggest.

The genetic findings in the Lichtenstein study and can be interpreted in two ways. First, genetic influences might have impacted health earlier in life with a subsequent impairment of educational and occupational performance and hence a drift into lowers social status. It is equally likely that genetic effects impacted some critical capabilities earlier in development, ones not identified in the Lichtenstein study. These inherited capabilities could have enhanced or impeded social mobility with a consequent impact on health. Lichtenstein and colleagues used twin data to identify heritable cognitive capabilities as a source for subsequent differences in both education and occupational status (Lichtenstein and Pedersen 1997). However, their data suggested there were other capabilities not yet then identified. These findings prompt a search for the cumulative influence of genetics on social mobility, influences that may start at a very early age. How are these effects first manifest and how much do evocative or active gene-environment correlations play in amplifying these earliest manifestations in educational and occupational attainment?

Recently, molecular genetic techniques have helped pushed these analyses further upstream. For example Shanahan and colleagues, in an adolescent sample, reported notable effects for a polymorphism in a gene regulating a dopamine receptor: the DRD2 gene, A1+ and A1- alleles. The A1+ allele has been associated with novelty and sensation seeking, aggressiveness and is a risk allele for conduct problems. In Shanahan's work with adolescents it was associated with curtailed educational attainment, which, for many adolescents, sets a major constraint on maintaining or improving social class status (Shanahan, Erickson et al. 2007). Intriguingly, the same polymorphism was associated with the decreased likelihood of the teen attracting a mentoring teacher suggesting an inherited social capability is also important in social class position. Intriguingly, this same DRD4 polymorphism was associated with maternal sensitivity in a study of infants by Mills-Koonce and colleagues; those infants with the A1- allele attracted more maternal sensitivity (Mills-Koonce, Propper et al. 2007). Genetic analysis, then, prompts an early inquiry about selection into social classes: a child capacity to recruit support that might start in infancy.

Rising submerged social systems

The Tully et al study cited earlier suggested the social impact on children of a depressed mother. However, mother-child relationships—including many studies of depressed mothers—have been at the center of the study of social relationships. The findings were notable only because the study design addressed an alternate, genetic scenario for explaining

associations of maternal depression and child psychopathology not because it played any role in highlighting mother-child relationships. However, genetic analyses plays an important role in delineating the impact of social relationships that have received far less attention, highlighting—in three distinctive ways—their effects on human development that are independent of genotype.

The first is to underscore the important etiologic roles of social systems that have been mostly overlooked by mainstream theory. One clear example is that of siblings. The literature on the importance of sibling relationships on the socialization of children and adolescents is relatively small. Brody has reviewed the earlier literature, a literature to which he was the major contributor, on the apparent effect (no genetic analyses were involved) of sibling relationships on cognitive and emotional development as well as on aggression (Brody 2004). More recent studies, again small in number and not genetically informed, have continued to explore—for example—the role of sibling relationships in the development of substance abuse (Scholte, Poelen et al. 2008), academic competence and perverse adult sexual behavior (Santtila, Mokros et al. 2010). However, as Natsuaki and colleagues pointed out, many of these studies are flawed by failure to take into account special statistical problems of non-independence among siblings reared in the same family, potentially confounding variables such as parenting and its overlapping role in influencing child development and, most important for our purposes, the genetic relatedness of siblings (Natsuaki, Ge et al. 2009). Thus, with notable exceptions (particularly a rich literature on siblings of persons with severe chronic illness and disability; see for example (Bluebond-Langner 1996; Lobato and Kao 2002; Houtzager, Grootenhuis et al. 2004; Barlow and Ellard 2006)), genetically uninformed research on siblings has had less than modest impact on both theory and practice.

However, several genetically informed studies are now highlighting the important role of sibling relationships on child, adolescent and adult development that is independent of child genotype but highly dependent on the quality of the sibling relationship. These studies control for statistical artifacts and for genetic relationships between sibs and, in some cases, significant third variable confounds. These studies have delineated important roles for siblings in the development of smoking and substance abuse (McGue and Sharma 1995) (Rende, Slomkowski et al. 2005; Slomkowski, Rende et al. 2005), and of depression, social responsibility, sociability and autonomy (Reiss, Neiderhiser et al. 2000). Using multi-level modeling in a twin and sibling design, Natsuaki and colleagues specifically confirmed the idea, first advanced by the social systems researcher Gerald Patterson, that siblings train each other in delinquent behavior (Patterson 1986).

Genetic analysis of social systems acts in a second way to elevate submerged social systems: they can distinguish among social systems that appear to be similar. An example is relationships between parents and adolescents that, by self-report and direct observation, are warm, supportive and pleasurable. In one study, the heritable characteristics of the adolescent account for about 25 to 50% of the variance among families in these relationships. However, the heritable factors in an adolescent that elicit warmth for mothers are *completely uncorrelated* from those that elicit warmth in fathers (Reiss, Neiderhiser et al. 2000). These genetically informed data suggest distinctively different dynamics in mother-

child and father-child positive relationship in adolescence and commend follow-up study, as yet not accomplished. Third, and finally, genetic analysis allows a disambiguation of social systems operating independently of parent and/or child genotype and those where genotype is of central importance. For example, prenatal exposure of infants to the products of maternal substance abuse has been a research focus of immense practical importance. Just how does maternal use of potential behavioral teratogens during pregnancy influence the short and long term development of her children? This question is addressed by a recent, genetically informed innovation in design. This design makes use of natural variation in *in vitro* fertilization practices. In some cases, mothers bear children with their own eggs and donated sperm; in other cases the fertilized egg is also donated. In the former case mother and child share the usual 50% of their individual difference genes; in the latter case they share no genes with their offspring. If fetal exposure to a potential behavioral teratogen, such as the products of cigarette smoke, causes subsequent problems in aggression or attention and behavioral self-control then the risk of subsequent aggressive behavior in the child should be equal for both groups of mothers. However two recent reports suggest they are not: only where mothers have offspring from their own eggs is the risk of subsequent behavioral and attentional disorders greater. However, low birth weight—and the many health consequences that may follow --is equal for both groups of mothers (Rice, Harold et al. 2009; Thapar, Rice et al. 2009)

Neurobiological anchoring of sensitivity and agency

The study of individual differences in response to major social forces is a major theme in social science research. The tradition is well established in studies of child and adolescent development. First, there are studies they focus on the *agency* of the child and adolescent. What factors in the child allow them to push back against adverse physical and social circumstances or fully grasp favorable circumstances and grow into productive, content and healthy adults? For example, the work of Emmy Werner has identified features of children and adolescents that enabled them to survive adverse childhood circumstances: an engaging temperament in early childhood, scholastic competence, intelligence, self esteem, autonomy and an engaging social style during the school years and a relationship with a least one adult who cheered them on their way (Werner and Smith 1982; Werner and Smith 1992; Werner 1993; Werner 1994; Werner 1995).

An alternate mode of theorizing about individual differences in response to adversity focuses not on active agency but on a more receptive or passive *sensitivity*. Children vary in their sensitivity to both adverse and to favorable aspects of the social environment. For example, Susan Crockenberg and her colleagues have shown that maternal insensitivity, as a parenting style, is likely to lead to the development of anxiety in infants who react adversely to novelty and withdraw (Crockenberg and Leerkes 2006).

Studies of genetic factors regulating individual sensitivity to adverse social circumstances have flowered in recent years, a subject we return to in a subsequent section below. An illuminating earlier example, using adult twins, was reported by Kendler. He showed that twin sisters of depressed women were more likely to develop depression themselves in response to stress of they were MZ rather than DZ twins (Kendler and Karkowski-Shuman

1997). The report of Caspi and colleagues, cited earlier, began to lay the grand work for understanding the genetic neurobiology of this inherited sensitivity to stress (Caspi, Hariri et al. 2010).

In both studies of individual differences in agency and in sensitivity, genetic studies remove a fundamental ambiguity in interpreting results from studies that are not genetically informed. In the case of non-genetic studies of agency we cannot know the earliest origins of these agentic properties. For example, despite the high levels of adversity in Werner's Kauai studies, it is plausible that very supportive microenvironments, early in the child's development, may have shaped their engaging temperaments, their capacity to elicit peers and adults and their sturdy sense of esteem and efficacy. Two genetic analyses may be informative. Manke and her colleagues (Manke, McGuire et al. 1995) reported notable genetic influences on children's capacity to develop warm, and positive relationships with close friends. They also reported environmental effects but these were environments specific to siblings rather than shared between them, the so-called "nonshared effects." Hansson, in adults, reported a similar finding for characteristics of resilience, many that seem to overlap with those identified by Werner including self-esteem, optimism and self directedness. In both studies, the genetic influences provide some clues to the origins of Werner's resilient features encouraging a search, in understanding their development, for intermediate neurobiological processes. Beyond genetics, the type of environmental influences reported by both studies, environmental effects specific to siblings, also provides helpful evidence. A substantial literature suggests these "nonshared effects" are almost universally short term and are likely to reflect relatively transient differences between siblings in their current life circumstances, not some early feature of their childhoods whose effects persist over time (Turkheimer and Waldron 2000; McGue 2010)). Thus, these data argue against the importance of lasting effects of an early microenvironment for Werner's resilient children, particular an effective environment (such as the family) that is shared with other siblings.

Genetically influenced agentic characteristics of children and adults can have an enduring effect on their social world, either by evoking responses from that world or by changing it. For example, data suggest that heritable properties of adolescents evoke strong hostile and critical responses from parents and that the stability of these parent-child relationship patterns are maintained by constant genetic influence (Reiss, Neiderhiser et al. 2000). Or, heritable properties of children may lead them to chose or avoid particular environments. This seems to be the case for peer relationships (Cleveland, Wiebe et al. 2005; Fowler, Shelton et al. 2007; Harakeh, Neiderhiser et al. 2008; Gillespie, Neale et al. 2009). Preliminary data suggest that, in turn, these evoked or selected relationships, have an effect on the child, perhaps to amplify the earlier genetically influenced behavioral characteristic. Thus it is plausible to argue that sequences such as these play a substantial role in the evolution of some lines of psychological development:

Gene → heritable child trait → evoked or selected social relationships → amplification of trait (which, if adverse, may result in diagnosable psychopathology)

In this instance, the social relationship may be said to *mediate* the expression of genetic factors. Scarr (Scarr and McCartney 1983) and Reiss and his colleagues (Reiss, Neiderhiser

et al. 2000) have made empirically-based arguments for the role of this sequence in child and adolescent development but the evidence is best suggestive. Appropriate, genetically informed longitudinal designs, with statistical modeling of mediation are crucial (Burt, McGue et al. 2006; Larsson, Viding et al. 2008). A more critical test is an experimental intervention to interrupt the environmental mediation that should reduce genetic expression. A study of that kind is entirely feasible. Reiss has described the use of the adoption method for such a study (Reiss, Neiderhiser et al. 2000) but, thus far, no such studies have been reported.

The molecular studies of genetically influenced sensitivity to adverse environments provided an even firmer neurobiological anchor for understanding individual differences. As we will describe, the identification of specific genes links laboratory models of the neurobiology of affect to an understanding of differential sensitivity to stress and form one of the firmest bridges now traveled between neurobiology and the social sciences.

Simplified working models of social processes

Modeling social processes has a long tradition across the social sciences. For example, laboratory-based studies in social psychology designed games, tasks and simulations to examine a wide range of social processes from racism and stereotyping, to empathic processes to economic decision making (see three very recent examples (Goodwin, Williams et al. 2010; Gutsell and Inzlicht 2010; Lin, Keysar et al. 2010). In the current era of studies of brain function, laboratory models of social processes have been particularly attractive: laboratory paradigms allow subjects to be presented with highly specific social stimuli at intervals and exposure times that can be precisely calibrated. For example, in an initial set of brain imaging studies investigators have explored brain mechanisms involved in maternal care. While their brain function is visualized, mothers are shown pictures of their infants or hear their cries or, for adult offspring, investigators play recordings of their mothers (Leibenluft, Gobbi et al. 2004; Ranote, Elliott et al. 2004; Hooley, Gruber et al. 2005; Noriuchi, Kikuchi et al. 2008). These approaches are static: the investigator focuses on the brain's response to a simple stimulus or contrasts among stimuli. Moreover, the significant other in the relationship is typically represented by an auditory or visual image. However, more complex laboratory models promise a more dynamic exploration of brain function during simulated or actual social process. Examples may now be found in dynamic laboratory models of economic decision making (Carter, Meyer et al. 2010), interactions with a stranger (Redcay, Dodell-Feder et al. 2010) and marital support processes (Coan, Schaefer et al. 2006). Further developed, these paradigms will allow simultaneous monitoring of social and neural processes.

Likewise, social behavior among animals—in both laboratory circumstances and in the wild—have attracted wide attention. Social processes are more transparent in these models for three reasons. First, they can be more completely observed. Very few human studies could match the access to ongoing social interaction that John Gottman achieved in his Apartment Lab where observed couples (with ethical restrictions) 24 hours a day (Driver and Gottman 2004). Second, in the laboratory of animals we can conduct true experiments by manipulating social circumstances, such as rearing conditions, or biological

characteristics such as genotype (e.g. (Cases, Self et al. 1995). Third, laboratory animals have, for the most part, much shorter life spans than humans so that aging and trans-generational processes can be studied economically. Many biological assays as well as post mortem examinations, impossible in most human research, yield a rich harvest of neurobiological findings in these models systems. For example, substantial programs of field and laboratory studies of voles have explored sustained pair bonding (Insel and Hulihan 1995; Nair and Young 2006). Suomi and his colleagues have carried out life-span studies of rhesus monkeys in both the laboratory and the wild where they studies the effects of variations in maternal and peer relationship on the development of aggressive and anxious behavior across broad spans of the monkeys lives (Suomi, Eisele et al. 1973; Champoux, Metz et al. 1991; Champoux, Byrne et al. 1992; Higley, Suomi et al. 1996; Suomi 2000; Barr, Newman et al. 2003).

Molecular genetic tools have made three important contributions to this tradition of building simplified models of social process. First, it is had strengthened the *backward utility* of laboratory models. In this instance laboratory models are used to explicate a finding already obtained in clinical or field research with humans. For example, a series of laboratory models have demonstrated the role of the limbic system, particularly the amygdale, in moderating an individual's response to threatening stimuli (see for example, (Phelps, O'Connor et al. 2001; Davidson 2002; Haxby, Hoffman et al. 2002)). Hariri and colleagues were the first to report that variation among individuals in the amygdale response to threatening stimuli was associated with a polymorphism in the promoter of the serotonin transporter gene (Hariri, Mattay et al. 2002). This work, and a long series of subsequent experiments in "imaging genetics" became a useful set of models for explaining the important findings of Caspi and colleagues (Caspi, Sugden et al. 2003); they reported the interaction between this same polymorphism and stressful life circumstances in a prospective field study of human depression. The Caspi prospective study assessed both childhood maltreatment and significant adult stressful circumstances arising from calamities in personal relationships, health, employment, housing and finances from age 21 to 26. The laboratory model simulated stress by asking subjects to match the emotion of a test photograph with one of two subsequent photos. The relationship between Hariri's photos and the major stressors of the Caspi study might seem tenuous although the photo technique had a rich psychometric history. The laboratory model became a compelling cue about the mechanisms of the gene x environment interaction reported by Caspi. The fact that the identical alleles were involved in both the field study and the laboratory model added to this explanatory or backward utility.

Second, molecular genetic tools have enhanced the *forward utility* of laboratory models. That is, observations in model systems, such as animal social behavior, suggest novel field or clinical studies of human social relationships. For example, pair bonding in voles has attracted wide attention. Prairie voles are monogamous while the closely related montane voles are not. The distinction between the two is strongly influenced by a single polymorphism in *males* in the gene regulating the distribution of receptors for vasopressin in the brain. Detailed laboratory study of pair bonding of prairie voles coupled with inbreeding techniques and transgenic mice clarified the causal role of this single polymorphisms in pair

bonding and the neuroregulatory mechanisms arising from its regulation of vasopressin receptor density in the lateral septum and related structures (see a review by Nair and Young (Nair and Young 2006). This work encouraged Walum, a doctoral student at the Karolinska Institute, and colleagues (Walum, Westberg et al. 2008) to test the role of an analogous polymorphisms in human marriage. Though effects sizes were small, it was of considerable theoretical interest that they reported associations of a vasopressin gene allele and the bonding process in adults. Specifically the allele in *men* was associated with their *wives'* report of the level of affection, consensus and cohesion in their marriage; the allele was also associated with whether or not the couple was married or cohabiting.

Finally, the use of molecular genetics has enhanced *cross model* utility. An instructive example comes from current research in schizophrenia. As we have noted, Weinberger and colleagues have achieved considerable progress in identifying genes linked to this complex disorder by parsing this syndrome into carefully specified components. One component is a deficit in shifting sets. A brief description of this skill is important to appreciate the role of molecular genetics and laboratory and animal models. Effective set shifting is measured as a rapid response to changing rules for card comparisons in the widely used Wisconsin Card Sorting Test (WCST). There is an analog to this test used in young children: the Dimensional Change Card Sorting (DCCS). This cognitive capacity has important social ramifications, which makes it relevant for our illustration here. For example, the WCST predicts adults' capacity to function in complex social situations such as cooperativeness in the work environments (Lysaker, Bell et al. 1995; Kurtz, Wexler et al. 2004). In children, impaired functioning on the DCCS is associated with impaired capacity to see events from another's perspective (Kloo and Perner 2003)..

The *val* allele of the COMT is a risk factor for schizophrenia. The clear identification of this allele facilitates the integration of laboratory models of set shifting and brain function in humans and strong inference from animal models, particularly transgenic mice. For example, in the human laboratory model, the *val* allele was associated with impaired set shifting and with reduced blood flow in the dorsolateral prefrontal cortex (Egan, Goldberg et al. 2001). However, even with its precision in delineating brain regions the human model is inexact. For example, genes can interact with other genes; thus it is difficult to interpret precisely the allele-brain association. Is the observed allele sufficient to produce the result or does it require an interaction with another, unmeasured allele? The transgenic mouse helped resolve this dilemma. The human *val* allele can be transferred to a mouse strain. In the transgenic strain, this single allele is distinctively associated with impaired set shifting in the transgenic mouse strain (Papaleo, Crawley et al. 2008).

In sum, the identification of a specific allele with well-known effects on specific metabolic steps in equally specific regions of the brain allows a firm link between clinical studies of specific impairments in a serious psychiatric disorder, human laboratory models of this impairment using a laboratory simplification of a cognitive and socially relevant process (the WCST) and an animal model that more precisely delineates the effect of the specific allele under study.

Summary and Tentative Conclusion

Of these five entry points, where might genetic thinking prove revolutionary, opening up entirely new avenues of investigation?

Molecular genetics provides strength in the integration of clinical and field studies of human relationships and human and laboratory models. Nonetheless, these are methods of investigation, which set an agenda for training investigators but do not guarantee revolutionary results. Likewise, the study of social relationships has had many prods to move theory construction upstream. The psychoanalysts Freud, Blos and Erikson long ago mapped out a life-span approach to understand the interplay of relationships and human development (Freud 1933; Blos 1962; Erikson 1963). Subsequently a series of studies on the life-long impact of trauma provided more prods (e.g. (Dube, Anda et al. 2001; Nelson, Heath et al. 2002; Nemeroff, Heim et al. 2003). Barker (Barker and Osmond 1988) stimulated two decades of research on the impact of fetal nutrition on long term risk for both medical and mental illness (Costello, Worthman et al. 2007). The life span perspective reinforced by genetic analyses will be revolutionary only if it fleshed out with innovative substantive research.

A third entry point is the use of genetic analysis to raise submerged social systems. What might it yield? The importance of genetic analysis to more accurately estimate behavioral teratogens, for example, cannot be overestimated. However, some of the yield so far, at this entry point, suggests this use of genetic analyses—such as in the distinction between father-child and mother-child relationships—helps provide more nuance but not revolution in the study of social systems. We don't need genetics, really, to alert us to differences between mothers and fathers but it will be intriguing to follow the question: “what do the child's genes have to do with this?” The importance of this entry point undoubtedly lies with its combination with others, particularly as we note below. For example the genetically-informed studies of siblings, if it is to push beyond the book of Genesis, will take on significance as it is added to a broader effort to integrate social and genetic theory.

A genuine revolution does seem possible from a potentially generative combination: the role of genes in both agentic processes molding the social environment and genetic factors shaping sensitivity to it. These two process are closely linked in both analysis and, and probably in social development as well. From the standpoint of measurement it is impossible to know whether a particular allele renders an individual more sensitive to an adverse environment unless we know, and control for, the influence that the same allele has had (through its impact on agentic processes) in shaping that environment. Moreover, environments may be differentially sensitive to agentic processes in individuals, a potentially important mechanism for gene x environment interaction. For example, a depressed mother may become more irritable with a fussy baby than a non-depressed mother. Genetically influenced agentic and sensitivity process may both be involved in development, as has already been suggested for depression (Lau and Eley 2008); a child's genes can evoke harsh parental discipline and lead to greater exposure to stressful events while at the same time variation in the child's genotype make them more or less sensitive to

these circumstances. The same pattern of results has been reported for peer relationships and adolescent substance use (Harden, Hill et al. 2008).

Studies of this kind are harbingers of specific developmental studies of social relationship and human development across the life span and are bound to improve the reach and precision of social theories. Beyond their impact on the construction and testing specific theories of development, these studies serve as a fabric of counterfactuals outlining a possible world of theories of social relationships and development that are significant blends of genetic and social processes. Social science is now imagining this possible world. This vision is likely to propel a major reorganization of scientific collaboration, training and funding. It is within the nexus of this social reorganization of the behavioral sciences, broadly conceived, that a revolution is possible. This nexus continues to encourage research teams that combine social and genetics researchers. It must also give space and support to students in the tradition of Sutton (chromosomes), Merriman (twin method), Heston (adoption study of schizophrenia) and Walum (vasopressin and human marriage) who will no longer seek to combine two distinguishable fields of research but see their combination as an obvious and unified catapult for innovative investigation.

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