Genetics, Social Behaviors, Social Environments and Aging

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These are exciting times for genetic and genomic studies of human sociality. Progress in understanding the causes and consequences of human social behavior is advancing through highly integrative science and predicated on the recognition that many social behaviors have a biological basis. Social behaviors, and the environments constructed by such behaviors, are central to the evolution of species. How patterns of social behaviors evolve has long been an intense area of research in its own right. In more recent years a significant literature has emerged documenting that human social environments, ranging from larger sociocultural factors and neighborhoods (Berkman & Kawachi, 2000; House et al., 1988; Marmot, 2006; Wen et al., 2006) to interpersonal relationships (Hawkley et al., 2006; Ryff et al., 2001), influence physical and psychological health throughout life. An extensive array of research has begun to identify biomarkers and elucidate pathways likely to be involved (Hawkley et al., 2006; Kiecolt-Glaser et al., 2005; McDade et al., 2006; Meyer-Lindenberg & Weinberger, 2006; Ryff & Singer, 2005; Uchino et al., 1996). This collection of work suggests that social environments may figure prominently in gene–environment interactions (Hernandez & Blazer, 2006; Ryff & Singer, 2005) and a growing number of studies are confirming this, particularly in the area of psychopathology (Rutter, 2007; Rutter et al., 2006).

Bringing cutting-edge behavioral genetics research to bear on questions of social behaviors, social environments and aging marks a high priority area of program development at the Behavioral and Social Research (BSR) program at the National Institute on Aging (NIA). This theme has been explored and promoted through a series of workshops and other activities (Harris, 2005).This special issue entitled *Genetics, Social Behaviors, Social Environments and Aging* is part of that initiative and features a range of research from various twin and nontwin studies investigating social behaviors and social environments.

In very broad strokes, three lines of inquiry are generating findings critical to understanding genes, social behaviors and social environments. First, concerns genetic influences on social behaviors; second, is the interplay between genes with social behaviors and social environments; and third, relies on the integration of biodemography, population genetics and evolution to explore how the social and demographic histories of populations have shaped gene pools and genomic structure. Detailing research in these three areas is beyond the scope of this introduction, but some important findings and directions are highlighted below to help frame how the field is moving forward.

Genetic Influences on Social Behaviors

Some of the most compelling research into the genetics of social behaviors derives from sociogenomics, a field of inquiry that integrates behavioral science with molecular and evolutionary biology, genetics, genomics and neurosciences in order to understand social life in molecular terms (Robinson et al., 2005). Research based on a number of species has already identified specific genes regulating a range of social behaviors associated with foraging, mate recognition and courtship, post-mating behavior, social hierarchies and dominance interactions. Newer analytic tools, such as transcriptomics, have yielded important insights showing that social stimuli affect gene expression levels in the brain which in turn, affect behavior (Robinson et al., 2005). Momentum is this field is gaining quickly as witnessed by the recent release of the draft honey bee (*Apis mellifera*) genome (Honey Bee Genome Sequencing Consortium, 2006); this highly social insect provides a model system for studying social interactions.

Important inroads have also been made in understanding biological influences on sociality and health through studies of the neuropeptides, oxytocin and vasopressin. A large animal literature documents the role of these neuropeptides in mediating complex social and affiliative behaviors including pair bonding, monogamy, maternal care and social attachment

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(Insel & Fernald, 2004; Keverne & Curley, 2004; Olazabal & Young, 2006; Young & Wang, 2004). Studies of social bonding in prairie voles have started to illuminate the role of oxytocin and cellular mechanisms of social attachment (Young & Wang, 2004) and rat studies indicate that the oxytocin receptor gene expression is associated with pathways whereby maternal care influences maternal behavior of female offspring (Meaney, 2001). Human research also points to a key role of oxytocin in affective and social processing (Kirsch et al., 2005) and trust (Kosfeld et al., 2005). Taken together, these findings open up new avenues for human studies by providing novel tools for probing genetic components affecting social behaviors that may be relevant, for example, to autism (Hammock & Young, 2006).

Heritable variation has been reported for a number of human social behaviors including loneliness (Boomsma et al., 2005), aggression (Eley et al., 2003; Hudziak et al., 2003), social cognition (Scourfield et al., 1999), and prosocial behavior (Knafo & Plomin, 2006). More recent focus in behavioral genetic studies of social behaviors has moved beyond heritability studies. Although efforts to find genes affecting human sociality are complicated by the typical challenges inherent in any complex phenotype (i.e., polygenic inheritance, gene-environment interactions, epistasis, age effects, and epigenetic factors), notable advances have been made. For example, the 5'-promoter polymorphism of the serotonin transporter gene (5-HTT) is one of the most widely studied common genetic variants underlying complex social behaviors in humans. The functional polymorphism shows a variable repeat sequence that encodes a short or long variant and carriers of the short allele are more likely to exhibit higher levels of anxiety-related personality traits (Lesch et al., 1996). A wide range of animal and human studies have associated 5-HTT gene variation with emotional regulation, including anxiety and stress-reactivity. Evidence to date implicates the amygdala in these processes and reveals greater amygdala reactivity to emotionally provocative stimuli among S carriers versus LL genotypes. Further research indicates that genetically influenced changes in 5-HTT function impacts the structure and function of corticolimbic pathways associated with the brain's ability to react to stress (Hariri & Holmes, 2006).

Another promising approach was adopted by scientists who recognized that the study of Willams syndrome (WS) could be critical in laying the foundation for studying genetic variants that influence complex social behaviors in humans (Meyer-Lindenberg et al., 2005, 2006). WS is a neuro-developmental disorder caused by the hemizygous deletion of approximately 28 genes on chromosome 7 (Meyer-Lindenberg et al., 2006). Among other characteristics, WS patients show hypersocial behavior, high empathy, and anxiety. Functional imaging studies examining the neural correlates of this genetic hypersociability and nonsocial fear revealed patterns of amygdala activation that mirrored findings from nonhuman primates (Prather et al., 2001) and provided a basis for studying genetic variants influencing human social behaviors (Meyer-Lindenberg et al., 2005).

Genetic Interplay and Social Environments

A key quest, given the large epidemiological literature linking social environments to health outcomes and biomarkers, is to explore gene–environment interplay between social worlds, genetic variation and health. Landmark studies by Meaney and colleagues provide evidence for behaviorally induced influences on gene expression in rats. They explored mechanisms by which natural variation in rat maternal care affects stress reactivity of offspring, a response that endures throughout the lifespan. Detailed analysis of the transmission of stress response from mother to offspring revealed differences in DNA methylation between the offspring of mothers who showed high versus low levels of care. Cross fostering studies revealed: (1) reversal of such early life effects (Francis et al., 2003), and (2) methylation changes in the offspring consistent with behavior of the foster mother (Weaver et al., 2004), indicating intergenerational, nongenomic transmission of maternal behavior and stress responses in the rat. Further analyses discovered that maternal nurturing behavior affects offspring stress reactivity by modifying the expression of the glucocorticoid receptor gene promoter in hippocampus of the offspring. These epigenetic influences conferred permanent and measurable effects on behavioral and endocrine responses of the pups (Weaver et al., 2004). This work eloquently illustrates how social environments can affect gene expression in the rat. Although the implications of these findings for human studies of social behavior and gene expression are still unknown, these findings are helping to reshape how we think about gene-environment dynamics (Gottleib, 2007) and may signify evolutionarily adaptive mechanisms. In his review of sociogenomics Robinson et al. (2005, p. 268) summarizes eloquently that 'our new-found appreciation for the responsiveness of the genome to social influence provides a biological basis for what observers of animal and human societies have long known: that flexibility is the hallmark of behavior'.

Building upon findings from neuroscience, a wave of human behavioral studies have explored interactions between specific gene variants and specific environments for psychopathology-related measures. Particular attention has focused on functional polymorphisms in the serotonin transporter gene to determine whether these variants modify the effects of stressful life events on depression. Evidence for this gene–environment interaction is reported by some (Caspi et al., 2003; Ely et al., 2004; Grabe et al., 2005; Kaufman et al., 2004; Kendler et al., 2005) but not confirmed by all (Gillespie et al., 2005; Surtees et al., 2006) studies. Similarly,

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mixed results are reported in studies analyzing gene by environment interaction between functional polymorphisms in the promoter region of the monamine oxidase A gene, childhood maltreatment and antisocial behavior (Caspi et al., 2002). Exciting and significant insights have emerged from research that explores these potential interactions through genomic imaging or other approaches to identify the brain regions and neural mechanisms underlying gene by environment interactions. For example, neural level analyses revealed that the differential effects of life stress on functional connectivity of the amygdala and hippocampus was dependent upon the serotonin transporter genotype (Canli et al., 2006).

Do Social Behaviors and Social Histories Shape Population Gene Pools?

The articles in this special issue fit into either of the two themes described above investigating genetic influences on social behaviors and gene–environment interplay. A third, quite nascent theme, related to population genetics, and of interest to future program development in BSR, is briefly mentioned here.

Evidence showing genetic influences on social behaviors implicates social behaviors as targets for evolution. This raises questions related to the evolutionary effect of social behaviors on gene pools. Sequence variation data has enabled researchers to map human demographic history and to address questions of evolution that weren't previously possible. Efforts to disentangle effects of demographic histories from selection on gene frequencies and genetic variation are revealing that demographic histories of human populations explain a substantial portion of genetic variation (Akey et al., 2004; Stajich & Hahn, 2005). From a population genetics perspective, demographic histories refer to events such as bottlenecks, population expansion, and subdivision. However, within the context of biodemography such histories may have social behavioral correlates related, for example, to survival and reproduction. In their analysis of 132 genes, Akey et al. found population differences in the strength of the signatures of selection and hypothesize that these differences may derive from recent selective pressures perhaps related to cultural environments, diets or climate. Have social behaviors or cultures detectably influenced the genomes of current populations? Although it is too early to know how fruitful this line of inquiry will prove to be, the tools to investigate such questions can now be harnessed drawing upon new resources in comparative genomics with population and molecular genetics and social behavioral science.

The collection of papers comprising this special issue represents current areas of interest, mainly from twin studies, exploring social behaviors and social environments of relevance to healthy aging. These works reflect a narrow cross-section of behavioral genetic studies of sociality, but a broad range of social behaviors and social environments are explored, either as modulating factors of health outcomes or as endpoints in themselves.

Maintaining functional abilities is a central theme in successful aging and several previous studies have examined genetic and environmental components of age trajectories for aspects of functional aging (see, *Behavior Genetics*, Special Issue on Aging, v. 33, nr 2, 2003). The first two papers in this issue take this work one step further by investigating age changes in the context of social environments. In their exploration of cognitive aging and social factors Reynolds and colleagues are interested in genotype–environment interactions that could affect change in memory abilities. They examine specific genotypes and specific nonshared environments associated with social support factors, stress, and depressive symptoms in Swedish twins. Their results have important implications for gene–social context interplay on cognitive aging. McGue and Christensen examine the relationship between social activity and late-life physical functioning, cognitive functioning, and depression symptomatology in Danish twins. They investigate genetic and environmental influences on initial status and change in status over a 12-year period, and study whether these influences are mediated by social activity. Their results help to shed light on questions of true causation versus selection effects whereby socially engaged individuals maintain higher functional levels.

Feelings of social isolation and loneliness are important, independent predictors of mortality and health outcomes among the aged. There are few published heritability studies of loneliness, but research shows that approximately half of the variation in feelings of loneliness is explained by genetic differences among children (McGuire & Clifford, 2000) and among adults (Boomsma et al., 2005). Further results are suggestive of a QTL on chromosome 12 influencing variation in loneliness (Boomsma et al., 2006). In this issue Boomsma and colleagues report results from 12-year longitudinal, loneliness data analyzed using full genetic growth models. This approach, which isolates time-specific from growth-specific sources of variation, yields important new information regarding the genetic and environmental variance structure of loneliness.

The importance of exercise for healthy aging across a wide array of physiological dimensions is well established, yet less is known about exercise effects on psychological functioning or why some people exercise and others do not. Johnson and Krueger explore psychological benefits of vigorous exercise using data from the National Survey of Midlife Development in the United States (MIDUS) study. This work employs a discordant identical twin design to help minimize confounding related to the selection of control groups. Their results are important for understanding the relationship between exercise and aspects of psychological wellbeing in aging.

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The next three articles share in common an analytic focus on larger social worlds, created by parents, peers and other key figures during development and investigate how these social-environmental factors interact with genetic influences. In their study on helping relationships and genetic propensities, Shanahan and colleagues approach the complex issue of gene by environment interactions and gene by environment correlation using data from the National Longitudinal Study of Adolescent Health. The questions at the heart of their study ask whether genetic propensity for behaviors that interfere with school continuation to university can be attenuated by helping relationships (G x E), but whether those with the predisposing genotype are less like to have helping relationships (rGE). The combinatoric approach they use offers a different method for studying gene–environment interplay by defining sets configured by multiple measures, including genetic, social, psychological, and other types of variables. Combinatoric analyses of a gene associated with dopamine receptor type 2 (DRD2 TaqIA), mentor-student relationships, and educational continuation beyond secondary school reveal a complex pattern of genotype–environment interplay. This work sheds light on the role of mentors in education and also illustrates that the complexities of modelling social context need to be addressed in order to understand gene-environment interplay.

Ganiban and colleagues study marital quality and parenting using an extended twin design to help disentangle the impact of individuals on relationships from the effects of relationships on individuals. Their analyses of parent-based genetic and environmental influences on the relationship between marital quality and maternal negativity and warmth explore a recurring theme in family research regarding the carry-over of affective quality from one relationship to another. Their findings have important implications for understanding family subsystems and the role of the individual in shaping the emotional climate of the family.

The research by Dick and colleagues tests for potential moderation effects of parenting and peers on the genetic and environmental factors on adolescent substance use. Previous research has established substantial environmental influences for adolescent substance use. This study builds upon previous findings in several important ways and examines the effects of specific parenting dimensions on smoking and drinking behaviors at two different ages, it investigates the extent to which parental substance use may mediate parenting effects, and also explores peer influences. Their results lend new insights into factors affecting vulnerability for substance abuse and illustrate the importance of studying the interplay of specific influences within a developmental framework.

Finally, Willemsen and Boomsma report on the effects that religious upbringing has on prevalence and variance structures of neuroticism in Dutch twin families. Their approach illustrates the importance of environmental contexts for studies of heritability. Effects of religion are likely to show age, cohort and country effects all of which have important implications for understanding personality and health with age.

As evidenced by the articles comprising this special issue, research on social behaviors and social environments is becoming more and more integrative. Building upon the work generated from a diverse range of genetic and genomic studies, the unique advantages of the twin design, coupled with new technological advances, provides creative and important avenues of scientific inquiry to help push this agenda forward and to understand the dynamic interplay between genes, social behaviors and social environments that affect healthy aging.

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