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Genetics of Social Cognition in the Laboratory: Definition, Measurement, and Association

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[–] Abstract and Keywords

This chapter examines recent advances in the genetics of social cognition, discussing evidence from twin studies that confirm the relevancy of genetic hard wiring in understanding many social phenotypes, with important implications for the social sciences and for genome-wide association studies (GWAS) that may identify specific genes contributing to a wide range of social phenotypes, genoeconomics, and individual and social decision making. Stressing the importance of phenotype definition and precise measurement as key to success in GWAS, the authors argue that laboratory-based behavioral economic paradigms using ethnically homogenous student populations generate the best prospects for successful GWAS. Also discussed are the neurochemical/neurogenetic architecture of behavioral economic games that measure individual and social decision making and the considerable progress made in unraveling the neurogenetics of human parenting and the beginning of a political attitudes neuroscience. The authors' own GWAS is used to present a set of guidelines for future research directions.

Keywords: Decision making, social cognition, behavioral economics, genetics, genoeconomics, neuroeconomics

Human beings are not only predictive machines of conspecific behaviors but also chart their own course with marvelous accuracy through the maze of social relationships that constitute the social world. Our social brains are in tune and often synchronous with the social brains of other humans, allowing us to infer and communicate our and other's intentions to a remarkable degree. We not only infer the actions of other individuals, but we also infer the actions of groups of individuals, allowing us a latitude of behavioral actions surpassing all other species on the planet. Notably, we need to respond appropriately to the intention and actions of others so that we respond to trust by displaying trustworthiness and are willing to help others in times of need by displaying altruism toward other people. In exchange, we expect others to reciprocate our good acts. Moreover, when we observe acts of unfairness and perceived selfishness, we are willing to punish others at a cost to ourselves with no apparent accruing of personal benefit. We are not, however, perfect, and we also often display considerable envy, spite, and jealousy when observing the good fortune of our compatriots. How do we manage to negotiate the sea of social relationships that surround us, to make the right choices, and to emerge from all these complex encounters in a manner that maximizes our own resources but also allows others to benefit?

The molecular brain mechanisms underpinning our ability to navigate the complex relationships that embrace our environment remain largely unknown. Indeed, a major challenge to neuroscience is to understand the biology of individual and social decision making from genomics to mental constructs. In this postgenomic era when the human genome has been sequenced, we ask how the DNA code translates into the ability to maintain and foster complex decision-making processes that often include the social relationships that so uniquely characterize *Homo sapiens*. This question is the focus of this chapter: an attempt to gain an inkling of understanding of how the sequence of four bases in DNA partially account not only for dyadic human relationships but for the very structure of human

societies across the globe. Human beings, despite their ability to learn from parents, teachers, and peers and to adjust their behaviors during a long developmental period from birth throughout adolescence, are not, however, a tabula rasa. To a not inconsiderable extent, we are hard-wired toward achieving a level of individual and social decision-making skills that allow us to interact successfully with conspecifics, to find a mate, to parent our offspring, and to achieve our goals even in a complex, globalized economy. When these skills are inadequate due to both environmental and genetic deficits, human beings fail to function effectively, and such deficits in decision-making processes lead to considerable cost to individuals and society as a whole.

This review first discusses the overall evidence from twin studies that heredity significantly contributes to human variation on how individual and social decisions are made. We then move on to discuss current research strategies (candidate genes and genome-wide association) employed to identify specific genes associated with individual and social phenotypes. Most importantly, we discuss novel approaches to defining decision-making phenotypes and how such phenotypes can be measured by the paradigms from behavioral and experimental economics. Of particular interest are the phenotypes relevant to other-regarding or social behaviors such as altruism, trust, sense of fairness, and competitiveness. Social psychology focuses on parenting, mate selection, and pair bonding, and we give due mention to some recent advances in understanding their genetics.

Genetics has recently made some notable incursions into the world of business and management. Heredity partially explains individual differences in financial risk-taking behavior, leadership qualities, and even consumer behavior. Moreover, specific genes have been provisionally identified for some of those phenotypes. In the meantime, political science is also coming under the influence of genomics, and political attitudes (liberal vs. conservative) as well as the nature of society itself (individualistic vs. collectivist) are being scrutinized using the tools of molecular genetics. Indeed, we suggest that the social sciences (economics, political science, and sociology) could be informed by the genomics revolution in the life sciences, and much can be learned about human behavior, both singularly and aggregately, by incorporating genes. That being said, we are not suggesting a *reductio ad absurdum* scenario whereby human beings are slaves to their genes and genetic heritage. But, similar to all other species on the planet, our behaviors have evolved, and genetic mechanisms have been selected for that enable us to efficiently function as a species exquisitely fine-tuned to render decisions that maximize our fitness as both individuals and social creatures designed to interact with conspecifics. These genetic mechanisms can be studied, and we believe this study will inform a deeper understanding of the nature of man and his relationship to society.

I. Twin Studies

A. Estimating Heritability

Heritability is the proportion of the phenotypic variance in the population that is attributed to genetic variation. Heritability is usually studied by comparing monozygotic (MZ, identical) and dizygotic (DZ, fraternal) twins. Extensive twin studies leave little doubt that genes make a significant contribution to the molding of the human social brain and that heredity explains a good deal of the differences between people. Quantitative behavioral studies can estimate the proportion of variance in a trait due to genetic (heritability) and shared and nonshared environmental factors. Shared environmental factors those influences that, for example, make children in the same family similar to one other, presumably due to parental and home influences. Nonshared environmental factors are what make children in the same family different from each other. The main way to study this is to examine MZ and DZ twins. Monozygotic twins share their entire DNA, whereas DZ twins share on the average 50 percent of their DNA. If MZ twins are more similar than DZ, there is evidence for a role for genes in determining the trait. If MZ twins are not exactly the same, there is evidence for nonshared environment.

For prosociality (Knafo & Plomin, 2006) and empathy (Knafo, Zahn-Waxler, Van Hulle, Robinson, & Rhee, 2008; Rushton, 2004), church attendance and religiosity (Kendler & Myers, 2009), propensity to marriage (Johnson, McGue, Krueger, & Bouchard, 2004), values (Knafo & Spinath, 2011; Schermer, Vernon, Maio, & Jang, 2011), and parenting style (Harlaar et al., 2008; Kendler, 1996; Neiderhiser et al., 2004), it is shown that genes clearly matter (Ebstein, Israel, Chew, Zhong, & Knafo, 2010). Genes also clearly matter for individual decision making, such as in attitudes to financial risk taking (Cesarini, Dawes, Johannesson, Lichtenstein, & Wallace, 2009; Le, Miller, Slutske, & Martin, 2010; Zhong, Chew et al., 2009).

B. Social Attitudes to Abortion and Gay Rights

Just how informative the twin method can be in uncovering the role of genes in shaping our social brains is especially revealed when this approach is used to estimate the contribution of heredity to attitudes at the heart of many sociological and political science studies. Religiosity and attitudes to politically "hot" topics such as abortion and gay rights are potent topics in the news, and quantitative behavioral analysis is a powerful tool toward understanding individual differences. Longitudinal twin studies show that the variance in religiosity during the teen years, as measured by church attendance as well as by more detailed pencil-and-paper questionnaires, is largely due to shared environment. However, as we age, the role of genetic factors increases, and the role played by the shared environment shrinks to just about zero (Kendler & Myers, 2009; Koenig, McGue, & Iacono, 2008). Altogether, as individuals mature and become adults, they moderate their social milieu mostly due to their genes. As children and teens, parents have a greater influence on religiosity, and genes take a back seat; but their influence emerges strongly in early adulthood to explain a substantial portion of the variance in variables such as church attendance, including elements of prayer and faith.

Twin studies also identify genetic and environmental interaction (G×E interactions), and a good example is the moderating effect of religiosity on smoking and alcohol use (Kendler, Gardner, & Prescott, 1997; Kendler & Myers, 2009; Koopmans, Slutske, van Baal, & Boomsma, 1999; Timberlake et al., 2006). High levels of religiousness were found to attenuate the additive genetic component for smoking initiation and were associated with lower prevalence of smoking initiation. Genetic influences accounted for 40 percent of the variance in alcohol use initiation in nonreligious females, compared to 0 percent in religiously raised females; shared environmental influences accounted for 54 percent of the variance for nonreligious females and 88 percent of the variance in religious females (Koopmans et al., 1999).

In the United States, attitudes toward abortion and gay rights continue to play a salient role in local and national politics, and twin studies provide important insights into how such opinions are formed and how difficult they may be to change. The traditional social science model attributes similar family attitudes to these loaded issues to be a result of familial socialization (Legge, 1983) or psychological/societal factors (Herek & Capitanio, 1996). In an intriguing study, Eaves and Hatemi (2008) modeled not only the social transmission of attitudes toward abortion and gay rights, but also, notably, the biological basis for these beliefs in a large sample of adult twins, siblings, and their parents (nuclear family). Their results showed a surprisingly low nongenetic effect of parental attitudes ("vertical cultural inheritance") on the development of adult values in their children, whereas there was a substantial role of genes (50–70 percent) overall in the transmission of attitudes toward both abortion and gay rights. Overall, social learning from the parental attitude accounted for less than 5 percent of the total variance.

Notably, it is the choice of mate (apparently assortative mating and not spousal interaction) that has an important impact on polarization of social values, consistent with research in the social sciences, and that attests to primary phenotypic assortment (spousal correlations) for attitudes on many salient social issues. Indeed, it is the social structures involving mate selection that may represent the mechanism by which parents impact their children's long-term attitudes toward social issues such as gay rights or abortion. The choice of mate is an example of gene–environment correlation (rGE). If genes are important in determining the traits (viz., attitudes toward abortion and gay rights) on which assortment occurs, then the choice of mate is a form of rGE in which parental genes impact the social behavior and preferences of their offspring. Remarkably, by this scenario, a social act (choosing a mate) increases the genetic impact of parents on their children.

C. Hard and Soft Social Issues

Interestingly, in the social sciences, certain political issues are "hard" (e.g., educational reform) and most often require evaluation and reflection, whereas other attitudes, including abortion and gay rights, are "soft" or "easy" and evoke an instant "gut feeling" in eliciting particularly strong opinions. Tesser (1993) provides evidence that attitudes with stronger genetic influences are manifested more quickly, are more stable, and are more likely to lead to assortative mating. Attitudes toward abortion and gay rights appear to fall into this category, suggesting that they are inherently more difficult to change and likely resonate more strongly with holders of more polarized opinions. This being said, it is worth noting that attitudes toward these issues are not written in stone, and there have been marked changes in public opinion toward gay rights and abortion in the past half-century. These considerations underscore an important feature of heritability of complex traits: the influence of time, culture, and

specific contexts. Heritability is a dynamic concept, shifting slowly and reflecting often-unknown tides of change. Examples illustrating this somewhat counterintuitive aspect of heritability are, on the one hand, the significant gene contributions to height (Yang et al., 2010) and IQ (Flynn, 2000). Although measurements of these two phenotypes indicate significant recent changes, they clearly do not evidence evolutionary selection. The realization that peoples' attitudes on social and political issues are formed and maintained to some degree by "hardwiring" and are encoded in our DNA has important implications for understanding current political trends, especially in countries such as the United States where these issues often influence elections at a national level. The subject of same-sex marriage is one of the most volatile political issues in the United States (Sherkat, Powell-Williams, Maddox, & de Vries, 2011), and it is even more remarkable that attitudes toward this issue are, to a not inconsiderable extent, heritable. As stated in a recent article on this subject "there is substantial, entrenched, opposition to same-sex marriage, and opposition to same-sex-marriage in the younger cohorts is rooted strongly in religious and political identifications. Values are changing, but conflicts over same-sex-marriage are not going away any time soon." (p. 177). We suggest the notion that one key concept needed toward understanding future changes in attitudes toward gay rights is the realization that some of the variance in such opinions is genetically determined and hence perhaps resistant to easy modification.

D. What Twins Tell Us About the Epigenome

The current wave of intense study of the epigenome and its implications for understanding complex behaviors has presented a unique opportunity to use twin studies, particularly of MZ twins (see Bell & Spector, 2011, for a current review). Epigenetic studies in twins can answer some important questions. First, is there epigenetic heritability across the genome? Second, to what extent do epigenetic patterns truly contribute to complex traits? Simply put, any phenotypic differences within MZ twin pairs presumably are a result of different environmental exposure between twins. Epigenetic study of traits that are discordant in MZ twins is a powerful research strategy for understanding disease- or trait-specific epigenetic changes. Moreover, it has been suggested that epigenetics is perhaps the key to understanding the heritability of complex traits (Petronis, 2010).

An epigenetic MZ/DZ twin study (Kaminsky et al., 2009) suggests that MZ methylation patterns are more similar in DZ twins across tissues. Interestingly, the most heritable CpG sites were correlated with functional regions and promoters, suggesting that functionally relevant methylation patterns are under strong genetic control. In an intriguing study by Fraga et al. (2005), it was observed that twins are epigenetically indistinguishable during the early years of life but, as they age and their lifestyles diverge, MZ twins exhibit differences in their epigenetic signatures that affect their gene expression portrait. A recent *Science* article (Freund et al., 2013) underscores the role of environment in shaping behavior. By studying inbred mice in an enriched environment, the authors showed that factors unfolding or emerging during development contribute to individual differences in structural brain plasticity and behavior, including exploratory behavior and hippocampal neurogenesis.

II. Association Studies

A. Candidate Gene Approach

Human behavioral genetics studies have, in the past two or more decades, employed several strategies in an effort to identify genes associated with human traits. The most obvious strategy is the so-called *candidate gene approach* that tests polymorphic genes hypothesized to contribute vulnerability to particular diseases or traits. A good example are genes that encode dopamine receptors that, based on the dopamine hypothesis of schizophrenia (Snyder, 1976), were hypothesized to be likely candidates for conferring vulnerability to schizophrenia. Treatment of schizophrenia depends on blocking the DRD_2 receptor, making this gene a prime target for association studies. Yet, genetic studies only weakly support such a contention. Indeed, a recent functional genomics study did not flag DRD_2 as a likely candidate contributing to schizophrenia, albeit other top candidates did emerge using this innovative design (Ayalew et al., 2012).

The failure to replicate many candidate gene studies has been extensively commented on (Ioannidis, Ntzani, Trikalinos, & Contopoulos-Ioannidis, 2001; Ioannidis, Trikalinos, Ntzani, & Contopoulos-Ioannidis, 2003). Many reasons explain the difficulty in replicating those first studies. Complex traits reflect a large number of genetic and environmental factors and their interactions. Common alleles contributing to such traits are probabilistic and not

deterministic in comparison to rare Mendelian disease alleles. Hence, such alleles only slightly contribute to the traits they are associated with. Moreover, to identify specific genes associated with complex traits, a phenotype with at least moderate heritability is a prerequisite.

Perhaps the most important reason for poor replication of candidate gene studies is limited sample size, which increases the chance of false-positive results. Small studies overestimate the true effect of gene variants. As Ioannidis et al. have observed (2003), the magnitude of the genetic effect differed significantly in large versus smaller studies, and the largest studies generally yielded more conservative results. Only in nine (16 percent) meta-analyses was the genetic association significant and replicated without hints of heterogeneity or bias. Lest we think that these problems of replication are somehow unique to candidate gene studies, the reader is referred to an intriguing discussion suggesting that most findings across biomedicine are likely false (Ioannidis, 2005), and similar issues have been recently raised in social psychology (Carpenter, 2012; Simmons, Nelson, & Simonsohn, 2011).

Other reasons for failure to replicate (see Li & Meyre, 2012, among many reviews) include lack of correction for multiple testing; population stratification; genotype misclassification; inappropriate statistical analyses; gene × gene (G×G) and G×E interactions; genetic, phenotypic, and ascertainment heterogeneity; inheritance models; and subjective interpretation of data (the Proteus phenomenon; Ioannidis & Trikalinos, 2005; Pfeiffer, Bertram, & Ioannidis, 2011).

Despite the bad reputation now attached to candidate gene studies, we suggest that there is a danger of throwing out the baby with the bath water because there have been some important success stories using the candidate gene approach. A good example is the role of the dopamine D_4 receptor (DRD4) variable number tandem repeat (VNTR) in contributing vulnerability to attention deficit hyperactivity disorder (ADHD; Smalley et al., 1998). In the first study of *DRD4* and ADHD, the number of subjects examined was less than 100. Nevertheless, despite the odds of this finding being a false positive, it has been subsequently replicated, and meta-analyses attest to its robust association with ADHD (Faraone, Doyle, Mick, & Biederman, 2001; Gizer, Ficks, & Waldman, 2009; Ptacek, Kuzelova, & Stefano, 2011).

Another good example of a successful candidate gene strategy is the association between *SORL1* and Alzheimer's disease (Lee et al., 2007; Reitz et al., 2011; Rogaeva et al., 2007). The generation of the Aβ toxic neuropeptide derived from the amyloid precursor protein (APP) via the endocytic pathway is a main cause of late-onset Alzheimer's disease (AD). This concept is supported by prior reports that the expression of several candidate proteins within these pathways (such as SORL1 and VPS35) is reduced in brain tissue from individuals with AD, and reductions in the expression of some of these proteins are associated with increased Aβ production. However, it was unclear whether these changes were causal or simply reactive to AD. Based on these considerations, *SORL1* association with AD was tested (Rogaeva et al., 2007). The samples from six datasets were divided into a "discovery cohort" composed of families with late-onset familial AD (FAD) and a "replication cohort" composed of discordant sibships and collections of individuals with AD and normal controls matched for age, gender, and ethnic origin. Association was demonstrated between *SORL1* single-nucleotide polymorphisms (SNPs) and haplotypes with AD; importantly, this finding was subsequently confirmed in a later meta-analysis (Reitz et al., 2011). The *SORL1* story underscores the usefulness and value of a well-designed candidate gene approach in two ways. First, the *SORL1* success story is based on robust evidence regarding the molecular basis of the disease itself and, second, on expression studies that considerably strengthened the hypothesized role for the candidate gene in the pathology of AD.

B. Imaging Genomics

So-called *imaging genomics* (Hariri & Weinberger, 2003; see also the chapter by Hyde, Bogdan and Hariri in this Handbook) is making an important contribution to understanding the action of common polymorphisms at the neural level and the molecular mechanisms underlying variance in complex behaviors. Many of these functional polymorphisms will impact information processing in the brain. Functional neuroimaging, including positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and electroencephalography/magnetoencephalography (EEG/MEG), because of its ability to individually evaluate information processing in distinct brain regions, is uniquely placed as a strategy for explaining aspects of functional genomics in the brain. One of the first demonstrations of the power of this approach was a seminal study by Egan et al. (2003) who showed that a common *BDNF* polymorphism, which predicts secretion of this hormone,

mediates aspects of human memory and hippocampal function.

There are many other examples of how a neurogenetics approach coupled with brain imaging can explain the neural basis of complex traits and the underlying molecular architecture. One focus of the current review is social decision making, and two peptide hormones—oxytocin (OT) and arginine vasopressin (AVP)—play key roles in social information processing, not only in voles but also in humans (Insel, 2010; Young, Lim, Gingrich, & Insel, 2001). Indeed, a number of candidate gene studies suggest provisional association between the oxytocin receptor (*OXTR*) gene and facets of the social brain (Ebstein, Knafo, Mankuta, Chew, & Lai, 2012). Among the *OXTR* SNPs tentatively identified with social traits, one of these, rs2254298 (G>A), has also been associated with differences in amygdala volume (Furman, Chen, & Gotlib, 2011). Similarly, the arginine vasopressin 1A receptor (AVPR1a) promoter-region polymorphism, also associated with normal and abnormal human social behavior, predicts amygdala activation (Meyer-Lindenberg et al., 2009; for a detailed discussion of OXTR and AVPR1a in voles, see the chapter by Barrett and Young, and in humans, by Westberg and Walum, elsewhere in this Handbook).

Overall, a number of imaging genetics studies have demonstrated how amygdala activation is modulated by different genes that agree with their neurochemical relationship with the amygdala (Blasi et al., 2009; Canli & Lesch, 2007; Drabant et al., 2006; Fakra et al., 2009; Hariri & Whalen, 2011; Manuck et al., 2010; Rasch et al., 2009; Roiser et al., 2009; Smolka et al., 2005).

The imaging genomics strategy can be especially important in confirming gene associations and is a great aid in strengthening the robustness of provisional findings. A good example is the story of *ANK3*, which has been implicated in genome-wide association studies (GWAS) of bipolar disorder (Chen et al., 2011) and schizophrenia (Ripke et al., 2011). *ANK3* belongs to a family of proteins (Ankyrins) that are involved in cellular functions such as motility, activation, proliferation, and the maintenance of specialized membrane domains. In an innovative study, Roussos et al. (2012) found that mRNA expression of multiple nodes of Ranvier-expressed genes was decreased in schizophrenia. Specifically, the *ANK3* rs9804190 C allele was associated with lower *ANK3* mRNA expression levels and with higher risk for schizophrenia in the case–control cohort. It was also associated with cognitive impairments with respect to working memory and executive function, as well as with increased prefrontal activation during a working memory task in healthy individuals. Altogether, such a combined strategy goes beyond “mere” GWAS and offers a path to confirming promising gene associations with complex disorders.

III. Genome-Wide Association Studies

A. Discovery Through Sample Size

The advent of GWAS in the past 5 or more years has led to an enormous acceleration in the discovery of genes contributing to complex traits, and more than 1,000 loci have been convincingly associated. Importantly, the establishment of international consortiums generating large combined cohorts enables the identification of variants with modest effect sizes (odds ratio [OR] <2). For example, it is remarkable that it has also been possible to carry out a GWAS of hippocampal volume on approximately 9,000 dementia-free subjects, and at least two SNPs clocked in at p values of 10^{-11} (Stein et al., 2012). This study was leveraged by combining the resources and findings from ten independent groups across three continents.

In schizophrenia research, the recent meta-analysis carried out by the Schizophrenia Psychiatric GWAS Consortium (Ripke et al., 2011) is a mega-study looking at approximately 22,000 European schizophrenic subjects in the discovery sample (17 separate studies) and a stage-two replication sample of close to 30,000 patients—a remarkable achievement. The combined analysis showed GWAS significance levels for seven loci. It is important to emphasize that the individual cohorts collected in many countries were relatively modest in scope, and it was only the combined sample that reached such mega proportions.

B. Missing Heritability

One of the mysteries of the GWAS revolution is that, for most traits that have so far been studied, the associated SNPs from GWAS only appeared to explain a very small fraction of the heritability—the enigma of the so-called *missing heritability* (Maher, 2008; Manolio et al., 2009). A number of possibilities have been suggested to explain

the missing heritability. Among these suggestions, the most likely is that complex traits like height are characterized by a large number of common polymorphisms, each only explaining a very small percent of the variance. Other explanations include a few rare variants with large effects and copy number variations. In a recent study, Yang and his colleagues (Yang et al., 2010; Yang, Lee, Goddard, & Visscher, 2011) implemented a method for estimating the total amount of phenotypic variance due to variance of all SNPs on the chip array and found that, for height, almost 45 percent of the variance could be explained by all these common variants, in comparison to 90 percent heritability in twin studies and only a few percent heritability when only individual SNPs producing significant GWAS levels were considered (the difference between the heritability estimates from twin studies and the heritability explained by these "hit" SNPs is the so-called missing heritability). As the authors noted, most of the missing heritability is, in fact, there but "hiding." A similar observation has been reported for IQ (Davies et al., 2011). It should be noted that, as discussed earlier, the classical estimation of heredity by twin studies is about the influence of all the SNPs, whereas the method used by Yang et al. focuses on the influence of all the SNPs covered in the GWAS chip array, which offers an alternative and complementary approach to measuring the contribution of genes to complex traits. Emerging technologies such as next-generation sequencing (NGS) are also offering unprecedented opportunities to detect an entire spectrum of genetic variants in individuals at the whole-genome level (Altshuler et al., 2010; Shendure & Ji, 2008; The 1000 Genomes Project Consortium 2010, 2012). Most rare SNP associations with medium to large effects may be missed by current GWAS methods, and multiple rare SNPs (frequency of less than 1 percent), together with thousands of common small-effect variants, may play a bigger role than previously thought in accounting for this "missing heritability" in complex traits (Dai, Jiang, & Dong, 2012; Siu, Zhu, Jin, & Xiong, 2011).

In a recent review, Marian (2012) noted further important sources that could account for missing heritability, including G×G and G×E interactions. Moreover, since SNPs identified in GWAS are often not the actual functional alleles but merely in linkage disequilibrium (LD) with the risk alleles, such "hits" tend to underestimate the true heritability (Spencer, Hechter, Vukcevic, & Donnelly, 2011). This is because LD is very rarely 100 percent. Some of the missing heritability may be due to such epistatic effects. Lander and his colleagues have termed this "phantom heritability" (Zuk, Hechter, Sunyaev, & Lander, 2012).

Unfortunately, G×G interactions (epistasis) are difficult to estimate from GWAS. Modeling gene–gene interaction is very complex. Even for the simplest case, where gene–gene interaction is restricted to SNP–SNP interaction (or two-locus interaction), the number of interaction models is huge. Second, whole-genome screening is very time-consuming. For example, exhaustive investigation of SNP–SNP interaction leads to $1.25 \times 1{,}011$ statistical tests for datasets from 500 k chips. Nevertheless, new statistical treatments are being developed to overcome these difficulties (see, e.g., Emily, 2012).

One strategy in examining the role of epistasis in human social behavior can be implemented in studies of lower mammals. A good example of this approach is demonstrated in a quantitative trait locus (QTL) genetic analysis of nest building in mice (Sauce, de Brito, & Peripato, 2012). Nest building is a complex social trait in mice important for fitness and survival of pups. Altogether, 15 direct-effect QTLs were found, explaining from 4 to 13 percent of the phenotypic variation, mostly with nonadditive effect. Notably, 71 significant epistatic interactions were discovered, accounting for 28.4 to 75.5 percent of the variation. Thus, the genetic contributions to nest-building behavior appear to reflect primarily epistatic processes. Indeed, the authors suggest that fitness-related phenotypes like nest-building reflect a genetic architecture with small direct effects and a larger number of epistatic interactions.

Considerable insight about the molecular architecture of complex traits is gained from these mouse studies. Apparently, traits that are directly related to fitness (i.e., survival and reproduction) differ from traits that are not directly related to fitness (Peripato et al., 2004): compared to the latter, the former may have less relative (per gene) additive genetic variation, have more dominance and epistatic genetic variation (Lynch & Walsh, 1998; Merila & Sheldon, 1999). Intriguingly, by studying non–fitness-related traits such as morphology (growth of long bones) and body composition, more direct-effect locus QTLs of small additive effect and more epistatic QTLs were found than compared to those for fitness-related traits (Norgard et al., 2008).

We believe that there is an important message here. Many arguments about the nature of complex human traits are based on traits not directly related to "fitness" (e.g., height, blood pressure, and even IQ). The possibility needs to be considered, based on some of these studies from mouse genetics, that not all human complex traits are going to have the same molecular genetic architecture as, for example, height. Indeed, is there any reason to believe that

risk behavior and height have the exact same architecture? If risk behavior is a "fitness" trait and height is not, then we might expect that fewer additive genes and more epistatic interactions would characterize risk behavior, compared to height.

C. Pathway Analysis

Genome-wide association studies seek to identify polymorphisms that are causal in disease or contribute to behavioral traits in a hypothesis-free manner, in contrast to the candidate gene association approach, which is hypothesis-based. However, so far, the identified loci typically explain only a small proportion of the heritable variation. One likely explanation is that the genetic contribution is distributed over many functionally related loci and genes with large collective impact but with only modest individual effects that do not reach genome-wide significance in single SNP tests. To capture this molecular genetic architecture, pathway-based approaches have been recently used to examine whether a group of related genes, based on prior biological knowledge, have consistent deviation from chance. It is well known that genes do not work in isolation, and, indeed, complex molecular networks and pathways are often involved in disease susceptibility and progression. Therefore, by taking into account prior biological knowledge about genes and pathways, pathway analysis might provide a better road to identifying those genes and mechanisms that are involved in disease pathogenesis (see reviews by Ideker, Dutkowski, & Hood, 2011; Wang, Li, & Hakonarson, 2010). Indeed, pathway analysis may be one way to overcome the harsh multiple testing burden imposed by genome-wide SNP studies.

O'Dushlaine and colleagues recently applied a pathway-based approach to GWAS results to data-mine for genetic signals in schizophrenia and bipolar disorder (O'Dushlaine et al., 2011). Their study illustrates a successful application of this approach in the field of psychiatry, with clear implications for other research areas. They compared the ratio of nominally significant to nonsignificant SNPs in a given pathway (trhe SNP ratio test) and applied this approach to the International Schizophrenia Consortium (n = 6,909) as a discovery sample and the Genetic Association Information Network (n = 2,729) for validation. They investigated 212 experimentally validated pathways described in the Kyoto Encyclopaedia of Genes and Genomes in the discovery sample, of which five pathways were found to be significant. Furthermore, the CAM pathway, which is important for neuronal cell adhesion and thus affects cell signaling, was also significant in an independent GWAS dataset (the Wellcome Trust Case Control Consortium [WTCCC]) for bipolar disorder. Their results suggest that mechanisms involved in neuronal cell adhesion may contribute broadly to neurodevelopmental psychiatric phenotypes.

The pathway analysis strategy could be of particular usefulness for studying human social behavior. In the social sciences, using pathways is likely to be more informative than examination of individual SNPs, which only contribute small effects. For example, research in neuroeconomics has consistently shown the important role of dopamine in reward and reward learning, and much of this evidence is drawn from monkey research using single-neuron recording. When applying these findings to human decision making, researchers rely on imaging studies and infer the role of dopamine indirectly as indexed by striatal activation. Pathway analysis based on GWAS data is a complementary approach that could test multiple dopamine pathway genes for association with decision-making tasks rather than solely relying on an individual SNP approach.

In summary, following Basson et al. (2012, p. 54), we suggest the notion that "focused studies investigating epistasis, gene-environment interactions, and rare variants in systematic and biologically plausible ways (such as through emphasis on genes in pathways) constitute novel alternative approaches. Although exhaustive epistasis examination in GWLS [genome-wide linkage study] and GWAS involves an unacceptable multiple testing burden, a focused investigation of gene-environment interactions (e.g., gene- age, gene-sex, and gene-race) seems desirable and feasible." Importantly, pathway analysis allocates resources toward understanding how existing signals influence complex traits rather than simply accumulating more independent data (Harrap, 2009), which may yield diminishing returns or may be difficult to analyze.

D. Is There a Place for Candidate Gene Studies in the Age of GWAS?

We discuss in the next section the major advances made in understanding the genetic architecture of complex traits and diseases following the advent of the GWAS era based on high-throughput genotyping of hundreds of thousands or even millions of SNPs on microarrays. Considering the remarkable success of this endeavor, it is fair to ask whether smaller scale candidate gene studies still have a place in the strategy of understanding human

complex traits and especially behavioral genetics. We suggest that the answer is affirmative and that even small-scale studies using a neurogenetic component are informative and advance our understanding of complex behaviors.

First, many behavioral phenotypes are not logistically implemented in large-scale GWAS, as are now being carried out for complex diseases such as diabetes, cardiovascular disorders, and cancer. A good example is laboratory-based experimental-economic paradigms that are the mainstay of the field of behavioral economics. Such games are carried out in controlled conditions prevailing in a classroom setting and are moreover incentivized with real money. Such tests cannot feasibly be carried out for tens of thousands of subjects. Later in this review, we discuss the tradeoff between employing such sharply defined phenotypes compared to the use of very general survey questions. We argue that survey questions, by their very nature, are very distant from the underlying biological substrate of traits, targeting perhaps the same economic attitudes as games, but likely (we suggest) to generate a much noisier phenotype.

In a hypothetical scenario, an investigator interested in economic behaviors might initially carry out a study with a relatively small group of several hundred subjects and test association between his laboratory-based phenotype (a game) and a candidate gene that biologically makes sense in its possibly contributing to the trait in question. In a second stage of this research, the first pilot study can serve as the basis for a larger scale study of several thousand individuals, thus allowing the implementation of a GWAS strategy. The relative cost of carrying out the first pilot study is quite low, especially if saliva samples are used for DNA extraction and a limited number of candidate genes are examined. Moreover, such pilot studies are important to testing the experimental paradigms in one's own population and gaining practice in the mechanics of carrying out a study involving DNA collection on hundreds of students. The downside of the pilot study is the likelihood that these first genetic findings are false positives. To play devil's advocate, we suggest that the publication of a potentially false-positive result is not so bad. After all, many groups are in a position to quickly replicate or refute such first findings at a minimum cost, and, within a short period, meta-analysis can be carried out to ascertain the robustness of the first exploratory study.

It is difficult to actually estimate what percentage of serious candidate gene studies are really false positives. From the widely cited studies of Ioannidis and his colleagues, it appears that approximately 16 percent of candidate genes initially identified (and that are of sufficient interest to catalyze attempts at replication) might turn out to be true findings without evidence of bias or heterogeneity (Ioannidis et al., 2003). Some distinction also needs to be made between well-conducted and plausible candidate gene studies and poorly designed experiments that are likely to be more or less ignored by the scientific community. The 16 percent of candidate gene studies robustly replicated by meta-analysis presumably fall into the first category of carefully initiated exploratory studies. We suggest that a one in six success rate for such studies may be an acceptable statistic. At the end of the day, the powerful tool of meta-analysis will, in due course, determine the robustness of candidate gene findings that are of significant interest to the research community. Moreover, the research community is sufficiently sophisticated in its evaluation of first findings, and investigators are well aware of the provisional nature of these initial publications. Independent investigators are usually well positioned to replicate candidate gene studies in a cost-effective manner because cohorts are already available and replication usually involves simply genotyping an existing DNA library for a limited number of SNPs.

IV. Social Cognition

By social cognition we mean the set of skills and abilities that enables us to successfully interact with other human beings. It includes several sequential brain activities, including the encoding, storage, retrieval, and processing of critical information relating to conspecifics. This *receptive* process leads to the next phase of social interaction—the *expressive* or decision-making phase, when action based on the accrued information is acted on (Insel, 2010).

Such expressive actions encompass communication, reproductive behavior and parenting, agonistic actions (aggression and predation), and affiliative behaviors. In lower mammals, as well as in humans, gonadal sex hormones acting primarily as transcription factors play a key role in orchestrating this variety of social interactions (McEwen, Davis, Parsons, & Pfaff, 1979). Insel has called the "neural space" between receptive and expressive social cognition the "dark matter" of social neuroscience (Insel, 2010). In humans, there are, perforce, higher levels of processing of social information and decision making not easily identifiable in our more distant

evolutionary cousins, including even chimpanzees (Silk et al., 2005). These higher domains include such unique human abilities such as mind reading, empathy, and taking another person's perspective.

Many of the advances in understanding the molecular mechanisms underlying human social behavior are based on translational studies. Even the "lowly" worm *Caenorhabditis elegans* has been studied for feeding and social avoidance behavior. For example, at the cellular level of analysis of social behavior, affiliative behavior is regulated by a set of cells that are organized in a hub-and-spoke model to process social information (Macosko et al., 2009). Another example occurs at the molecular level of analysis of social behavior, where social feeding in *C. elegans* largely depends on a neuropeptide receptor, encoded by the *npr* gene (de Bono & Bargmann, 1998). As noted by Insel (2010), these studies in the worm suggest that complex social behaviors may rely on surprisingly simple molecular mechanisms and that neuropeptides and their receptors appear to be important mediators of social behaviors. Finally, comparative studies have often proven to be a powerful approach for social neuroscience.

Other translational studies have focused on affiliative behavior. For example, the role of AVP and OT as paramount social hormones across the animal kingdom has been extensively studies, as reviewed elsewhere (Donaldson & Young, 2008; Goodson, 2005) and in this handbook (see chapters by Barret and Young, and by Westberg and Walum, for a detailed discussion of OXTR and AVPR1a on affiliative behavior in voles and humans, respectively). In mammals, these two nonapeptides play a key role in modulating the social brain (Insel, 2010), and there is compelling evidence for a parallel role in human social behavior. Human research with these two neuropeptides has employed pharmacological (Churchland & Winkielman, 2012), imaging (Furman et al., 2011; Meyer-Lindenberg, Domes, Kirsch, & Heinrichs, 2011; Sauer, Montag, Worner, Kirsch, & Reuter, 2012; Shamay-Tsoory, 2011), and genetic studies (Ebstein et al., 2010; 2012) to demonstrate that OT and AVP are indeed social hormones in people. The rest of this review focuses on how best to study individual and social decision making in humans, with particular emphasis on studies carried out under the controlled conditions of laboratory-based science.

V. Economics and Decision Making

A. System 1 and System 2 Decision Making

Kahneman, in his article on bounded rationality (2003) following his receiving the Nobel prize in economics, draws critical attention to the widespread biases in human decision making that distinguish real people from the virtual-reality rational agent model favored by neoclassical economics. Their model of choice under risk—*prospect theory* (PT)—has an apparent world record of more than 23,000 citations based on Google Scholar. Prospect theory as a descriptive model for choice under risk is represented in a set of lottery paradigms. The choice of the lottery paradigm is foreign to psychological thinking and yet, in using this apparently simple approach to determining people's choices, fundamental insights are obtained about human decision making and risk attitude. Indeed, we argue that these simple paradigms involving real money—"putting your money where your mouth is"—are near ideal phenotypes for molecular genetic studies.

The preferences revealed in the studies of Kahneman and Tversky, among others, show that people's responses often deviate from the normative theories on many decision-making tasks. For example, people assess probabilities incorrectly, they display confirmation bias, they test hypotheses inefficiently, they violate the axioms of utility theory, they do not properly calibrate degrees of belief, they overproject their own opinions on others, they allow prior knowledge to become implicated in deductive reasoning, and they display numerous other information-processing biases (Stanovich & West, 2000). As Kahneman notes, these biases reflect thinking processes wherein most judgments and choices are made intuitively. Intuitive thinking is done spontaneously and comes to mind easily, whereas reasoning is done deliberately and effortfully. Curiously, most thoughts are intuitive, the monitoring of these intuitions is lax, and hence many expressed thoughts are erroneous (Kahneman & Frederick, 2002).

Behavioral economics is devoted to revealing preferences in human decision making, and often these preferences appear to be deviations from rational, reasoned thinking. However, that being said, such "deviations" once understood are actually rational and follow reasoned thinking. Even more revealing is that such thinking drives a good deal of our cognitive behavior. Somewhat oddly, it appears that *H. sapiens* (the "wise man") is less "wise" at

least on a day-to-day basis than we perhaps like to admit, and cognitive biases are the common denominator of much of human thought. Moreover, the "intuitive" mode of reasoning may have a more ancient evolutionary origin based on the need for easily accessible heuristics in making decisions affecting survival in our hunter-gatherer days.

These considerations have led to the concept of a dual model of human reasoning, system 1 and system 2 (see discussion in Kahneman, 2003). System 1 is fast, automatic, and effortless, associative and often emotionally charged. The operations of system 2 are slower, serial, effortful, and deliberately controlled. It would appear that most behavioral economics paradigms tap into the interplay between system 1 and system 2; hence, perhaps the distance from gene to the behaviors arising from system 1 may be shorter than the one from system 2.

B. Experimental and Behavioral Economics

> *Science is measurement.*
>
> – Henry Stacy Marks

Economics is a field studying decision making under limited resources, and it builds on formal mathematical models of rational economic agents developed since the 1950s. In the 1970s, Kahneman and Tversky (1979), among others, cast doubt on these assumptions and pioneered the introduction of psychological considerations such as anxiety and fairness into economic thinking. This effort broadened the scope of economics and made economics more able to address issues in social sciences in general. In the meantime, laboratory experiments were also introduced into economics that allowed researchers to examine economic models in controlled settings (Smith, 1962). Experimental and behavioral economics are highly related overall in their approaches to studying economic attitudes but are nevertheless characterized by some differences (Loewenstein, 1999). Both disciplines draw heavily from psychology and derive much of their insights from that science. Although many behavioral economists use paradigms derived from experimental economics, they are, however, more eclectic in their approach and not as rigid in the methodologies they employ. Conversely, experimental economists have developed a consensus and endorsement on the use of experimentation as their sole research tool. Notably, experimental economists have developed a significant number of novel methods for addressing economic issues and, importantly, share a number of methodological principles in their discipline. Experimental economists generally adhere to the following methodological guidelines:

- Do not use deception.
- Incentivize subjects with real monetary payoffs.
- Publish full experimental instructions.
- Avoid using specific or concrete contexts.
- Maintain some degree of anonymity if possible.

Although Loewenstein (1999) has some cogent criticism of some of the conventions employed by experimental economists, we believe that such rigid adherence to very exacting experimental protocols has decided advantages in characterizing phenotypes suitable for molecular genetic studies. Most importantly, behavioral and experimental economics have developed a compelling body of decision-making tasks geared toward measuring diverse aspects of human social preferences in the laboratory, including the dictator (Hoffman, McCabe, & Smith, 1996), trust (Berg, Dickhaut, & McCabe, 1995), ultimatum (Guth, Schmittberger, & Schwarze, 1982), prisoner's dilemma (Axelrod & Hamilton, 1981; Chammah & Rapoport, 1965), and public goods games (Fehr & Gachter, 2002; Ledyard, 1994).

C. Neuroeconomics

In the 1990s, behavioral economics embraced neuroscience, and the nascent field of neuroeconomics was born (Loewenstein, Rick, & Cohen, 2008). The contribution of this nascent field is twofold: on the one hand, behavioral and experimental economics provide a large set of decision-making phenomena for the neuroscientists to investigate, which eventually will lead to a better understanding of how the brain works. One the other hand, neuroscience expands the scope of observations for economics beyond observable choices, which develops new

challenges for economic theories. In addition, the understanding of how the brain makes decisions also contributes to the understanding of the cognitive process of decision making. Three domains of behavior are of particular interest to both behavioral economics and psychology: decision making under risk and uncertainty (De Martino, Kumaran, Seymour, & Dolan, 2006; Dreher, 2007; Hsu, Bhatt, Adolphs, Tranel, & Camerer, 2005; Huettel, Stowe, Gordon, Warner, & Platt, 2006; Kahneman & Frederick, 2007; Knutson & Cooper, 2005; McClure, York, & Montague, 2004; Montague, King-Casas, & Cohen, 2006; Rangel, Camerer, & Montague, 2008; Tom, Fox, Trepel, & Poldrack, 2007), intertemporal choice/delay discounting (Hariri et al., 2006; Kable & Glimcher, 2007; Luhmann, 2009; Marco-Pallares, Mohammadi, Samii, & Munte, 2010; McClure, Laibson, Loewenstein, & Cohen, 2004; Peters & Buchel, 2010; Prevost, Pessiglione, Metereau, Clery-Melin, & Dreher, 2010; Wittmann, Lovero, Lane, & Paulus, 2010; Xu, Liang, Wang, Li, & Jiang, 2009), and social decision making (de Quervain et al., 2004; Moll et al., 2006; Rilling et al., 2002; Rilling, Sanfey, Aronson, Nystrom, & Cohen, 2004*b*). Neuroeconomics has made significant contributions to our understanding of these three central domains. The first fruits of the neuroeconomics strategy grew from an innovative combination of functional brain imaging and behavioral economic paradigms that allowed the mapping of social and individual decision making to brain regions and pathways.

Although, as underscored in many reviews (Kahneman, 2003), economics has been more influenced by psychology than psychology has been influenced by economics, we suggest that cognitive science and psychology are being enriched by the new field of neuroeconomics. Neuroeconomics is the “hot” interface among economics, neuroscience, and psychology, and this boundary appears almost seamless. Indeed, many of the topics that are the focus of neuroeconomics cannot be distinguished from economics on the one hand and psychology on the other. For example, altruism is an “anomaly” not only in economics but also in evolutionary theory and was commented on by Darwin and Adam Smith. Any understanding of human altruism must take an evolutionary perspective (Sigmund & Hauert, 2002) and a microeconomic view (Hoffman et al., 1996) and wield a psychological disposition (de Waal, 2008; Warneken & Tomasello, 2009*a*). Indeed, altruism can be investigated by survey information on charitable giving (Bekkers & Wiepking, 2011; Wilhelm, 2006) in the behavioral economics laboratory (Andreoni & Miller, 2002), as an object of Darwinian selection, and profitably studied in other mammals ranging from voles (Carter, 1998), chimpanzees (Warneken & Tomasello, 2009*b*), and birds (Olendorf, Getty, & Scribner, 2004), to insects (Gadagkar, 2011). The experimental strategies employed for understanding altruism run the gamut across the life and social sciences. One might well ask where neuroscience begins and economics ends in explaining human altruism. Social preferences similar to intertemporal discounting, risk attitude, and strategic thinking cannot easily be assigned to only one of the sciences, and we suggest that these are best studied using multidisciplinary approaches that aim to capture the full scope of these domains.

Neurogenetics (“genoeconomics”) is one particular strategy in neuroeconomics that has recently begun to gain some traction (see Benjamin et al., 2007; 2012; Navarro, 2009), and it is discussed in the next section.

D. Genoeconomics

A neurogenetics strategy in social cognition research attempts to explain the genetic variance underlying individual differences. Moreover, the neurogenetic approach is a powerful tool to identify the salient neurochemical pathways underlying economic decision making. For example, identification of a dopamine receptor in a genetic association study with risk behavior ipso facto implicates the dopamine neuropathway in mediating risk attitude (see Zhong, Israel, Xue, Sham, et al., 2009, for an innovative implementation of this idea). Hence, one of the challenges in social cognition is to discover phenotypes that are most addressable by molecular genetics. The potential promise of genoeconomics, as with neuroeconomics, is twofold. First, several decades of research in experimental and behavioral economics, reviewed earlier, have generated a conceptual framework for characterizing phenotypes that we believe are critical for advancing our knowledge of the molecular genetic architecture of the human social brain. Second, the advancement of genetic architecture would contribute to the understanding of economic decision making and eventually improve economic modeling and prediction. Benjamin et al. (2007) suggest three ways in which genetic information can be incorporated into economics. We suggest that, on the contrary, economics methodology, particularly experimental and behavioral economic analytical tools embodied in so-called behavioral games, can provide a useful tool for measurement and inform human behavioral genetics research. Indeed, we put forth the notion that controlled laboratory games are a unique research tool for defining phenotypes that are particularly well-suited to molecular genetic studies of human behavior. Hence, ask not what economics can learn from genetics but what behavioral geneticists can learn from experimental

economics.

D.1 Phenotypes

Somewhat surprisingly, the definition of the phenotype is the focus of a recent review (Wojczynski & Tiwari, 2008). We use "surprisingly" since it seems obvious that genetic studies would target phenotypes most likely to match the underlying genetic architecture of the traits being studied. But this is not always, and perhaps even rarely, the case. Thus, although genotypes affect proteins, cells, and biological pathways, phenotypes are most readily observed as appearances, signs, and characteristics of a trait or, if a disease, the symptoms of that disease. The problem of phenotype definition becomes acute when the phenotype is a complex trait bearing no obvious relationship to any underlying biology. Some phenotypes are particularly slippery and not easily pinned down, especially phenotypes related to mental illness for which no biomarkers or laboratory tests are currently available (Ecker, 2011; Le-Niculescu et al., 2009). To start with, the phenotype is the expression of the individual's genotype but, clearly, as organisms grow more complex, the phenotype is increasingly distant from the biochemical pathways contributing to the trait. Moreover, the phenotype is a dynamic concept impacted by both the environment and genes.

Thus, the definition, measurement, and validity of phenotyping need to be standardized in genetic studies to increase the quality of research and the reproducibility of linkage and association studies (Schulze & McMahon, 2004). Finding genes for complex traits is the goal of neurogenetics, and to accomplish this aim, an accurate phenotype definition (i.e., one that has high specificity) is necessary to minimize the number of genes that may affect risk of disease and thus increase the odds of finding these genes (Winawer, 2006). Additionally, because the phenotype is the expression of the underlying biology, a precise (highly specific) definition is necessary to further understand the neurochemical mechanisms involved with the expression of the trait (Bel, 2004). Much consideration should therefore be put into the underlying biology of a phenotype when attempting to define it for a study (Winawer, 2006).

We suggest that in undertaking a study designed to explore the molecular genetic architecture of individual and social decision making, we need to consider the following points (see Wojczynski & Tiwari, 2008) in phenotype measurement: (1) dichotomous versus continuous traits, (2) study base, (3) composite phenotypes, and (4) narrow versus broad phenotype. Disregard of these issues can lead to major confounds in interpreting first findings in genoeconomics.

D.2 Dichotomous Versus Continuous Traits

Examples of dichotomous traits—those that are either present or absent—in many medical GWAS are diseases such as cancer, arthritis, and heart disease. Behavioral disorders including the major mental illnesses and childhood disorders such as ADHD are categorical traits defined by the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) and investigated using GWAS. On the other hand, a continuous trait has a range of possible values, and QTLs can often be extracted from categorical traits. Quantitative traits refer to phenotypes that vary in degree and can be attributed to multiple genes as well as to the environment. Quantitative trait loci are regions of DNA containing or linked to the genes that underlie a quantitative trait. Examples of continuous traits include height, body mass index (BMI), blood pressure, blood lipid levels, and IQ. We suggest that QTLs are perhaps more amenable to genetic association studies for complex behavioral traits and more easily reflect the underlying biology because the continuous measurement is more precise and hence probably gives us more statistical power.

D.3 Study Base

Study base refers not only to ethnicity of the studied group but also to the method of subject recruitment (sampling scheme). Both of these can influence the outcome of the genetic analysis, leading to heterogeneity and confounds in replication. A unique perspective on the confounding effect of ethnicity is an older but still relevant article on the "chopsticks gene" (Hamer & Sirota, 2000). The article discusses the conundrum of population stratification as a potential source of error in psychiatric genetics by using as a fictitious example an association study attempting to identify the gene that contributes to use of chopsticks. From the statistical point of view, the ideal situation is to have a random sample. However, there are many sources of unobserved heterogeneity, such as ethnicity, and even within "homogenous" ethnic groups variables such as age, health status, and education, are pertinent. All

these variables may have positive and negative impacts on a study. It should be noted, however, that it is likely difficult to compare the results across such studies when the study bases are heterogeneous, and the heterogeneity likely influences the study results. Clearly, minimizing heterogeneity should be an overarching aim in choosing a study base.

D.4 Why Study Students?

We suggest that the study base, especially for first GWAS of decision-making traits, should be limited to homogenous groups of subjects across age, ethnicity, socioeconomic status (SES), and cognitive ability to control unobserved heterogeneity. Hence, we suggest that student populations targeting one ethnic group maximize chances of finding true associations. Several common-sense reasons support this contention. First, student groups are characterized by a narrower IQ and socioeconomic range than the general population; hence, focusing on students should reduce experimental noise—the same reason that, since 1828, white rats are the animal of choice in many biomedical and psychological experiments. Although eventually extending gene findings across ethnic groups is clearly an important goal, first studies should focus on maximizing the chances of replication, and including a replication sample using identical experimental techniques and subjects with identical ethnicity would ipso facto improve the chances of finding true GWAS associations.

A good example of how genetic studies can be confounded by mixed demographics is suggested in a recent review of intelligence and heredity by Nisbett et al. (2012). An intriguing confound emerges regarding the heritability of IQ, which in some but not all twin studies appears to be dependent on SES. Somewhat remarkably, heritability of IQ is greater in higher SES groups compared to lower SES groups—an observation that so far is unexplained. If these results with IQ extend to genoeconomic phenotypes such as risk attitude and other-regarding behaviors, then using groups of mixed backgrounds may likely generate many false-negative results and result in a failure to find true associations.

D.5 Composite Phenotypes

Wojczynski and Tiwari (2008) discuss in some detail the use of composite phenotypes. They propose a potential selection strategy using all correlated phenotypes and incorporating the correlation structure in the analysis. For example, in seeking genes for a trait, Y_i, the aim is to derive a composite score (phenotype), Z, for an individual when multiple measurements are available on that individual. This method should reduce measurement errors, and thus composite phenotype may be worth exploring in large studies when multiple and often correlated phenotypes are ascertained.

In an interesting behavioral twin study by Wood et al. (Wood, Rijsdijk, Saudino, Asherson, & Kuntsi, 2008), the genetic and environmental etiology across three measures of activity level were studied: parent and teacher ratings of hyperactivity-impulsivity and actigraph measurements. Notably, along the lines of generating a "composite phenotype," they tried combining the three measures with an eye to eventual neurogenetic studies. Indeed, a common underlying phenotypic factor was highly heritable (92 percent), even more so than the sum of all three measurements (77 percent). The authors suggest "that distilling what is common to all three measures may be a good method for generating a quantitative trait suitable for molecular studies of activity level in children" (p. 266).

D.6 Narrow Versus Broad Phenotype Definition

Narrowing the phenotype can have advantages in identifying traits with greater genetic loading. The tradeoff is the loss of power in selecting a smaller group of subjects to analyze. Such an approach has been used in a GWAS of epilepsy (Leu et al., 2012), as well as in a twin study of substance abuse with hopes of defining a phenotype in genetic association studies (Hicks, Schalet, Malone, Iacono, & McGue, 2011). Similarly for major depressive disorder, several of the best GWAS results were supported primarily by evidence from narrow cases or from either males or females (Shyn et al., 2011). Examples of this approach are abundant.

D.7 Measurement Error

Measurement error is an additional serious issue in genetic studies. The measurement error with phenotype, as a dependent variable in the regression analysis, could be problematic; hence, the use of variable methods to assess

and measure phenotypes contributes nontrivial sources of variability to any genetic study (Bearden & Freimer, 2006). Thus, to confirm a phenotype and reduce its potential misclassification, it is important to use standard phenotype definitions, as well as secondary data sources. Validity is the concept of knowing what is being measured and how accurately it is being measured (Schulze & McMahon, 2004). Furthermore, most phenotypes can be defined by more than one instrument, with each instrument using slightly different measures for the same phenotype that adds variability in phenotype definition and makes cross-study comparisons difficult. Therefore, standardized, structured instruments for collecting clinical data used to define phenotypes should be employed. In addition to validity, the reliability (Schulze & McMahon, 2004) of these instruments should be assessed.

As an example of the crucial importance of measurement error, we cite the study of Wong et al. (Wong, Day, Luan, & Wareham, 2004) who investigated the effect of measurement error on the power of the G×E interaction for continuous traits. They used the classical measurement error model to describe the uncertainty in measurements in the outcome and the exposure. They found that the magnitude of the impact of measurement precision on the power to detect G×E interaction on continuous traits would suggest that smaller studies with better measurements may be preferable to very large studies with less precise measurement. *The greater impact on power came not from the genotyping errors but from the precision with which the exposure and outcome were estimated.*

We argue that measurement error is minimized in laboratory-based measurements of decision-making phenotypes as practiced in behavioral economics.

We illustrate the guidelines we believe should be followed in studying individual and social decision making with the phenotype of "altruism." Altruism has a narrow definition in the literature of evolution and also in behavioral economics. In the broader view, altruism can mean prosociality with one's peers, giving to charity, joining voluntary organizations, and a host of other actions. We could simply ask people if they are "altruistic," thus generating a dichotomous definition, or we could rate subjects using a pencil-and-paper approach. Continuous measures of altruism (QTLs) can be generated by quantitatively measuring an individual's donations to charities or time spent working in voluntary organizations. Alternatively, we can use a very narrow definition of altruism, following in the footsteps of behavioral economics, and use the dictator game. We could also attempt a composite measure combining various phenotypes using one or another statistical technique like factor or principal component's analysis. Another important decision is what study base to use. We could use a homogenous student population from a specific ethnic group or enlarge our net of prospective subjects and leverage survey data from a cross-section of the public, with little screening for homogeneity. We should, of course, minimize our measurement error, which demands the use of standardized, structured instruments.

D.8 Some Issues Raised by Recent GWAS in Genoeconomics

Despite great potential, genoeconomic studies require the same kind of critical review that pertains to any other phenotypic studies. In survey studies, there is a tradeoff between those that are based on laboratory-based phenotypes, which we suggest are closer to the underlying biology, and those that are based on paper-and-pencil responses, which are more practical to administer, but which may not be ideal phenotypes to capture in a GWAS approach. Although the large number of participants found in national surveys and panel studies is attractive and certainly cost-effective for genoeconomics, there are downsides such as heterogeneity and phenotype definition that need also to be considered.

One example for problematic phenotype selection may be "educational attainment," which was the focus of a recent GWAS (Beauchamp, Cesarini, Rosenquist, Fowler, & Christakis, 2009), one that generated some interesting findings in the discovery sample (Framingham Heart Study), with some SNPs clocking in at 5×10^{-7}, but failed to replicate in the replication sample (Rotterdam Study). We suggest that the choice of "educational attainment" is not an efficient phenotype for matching to molecular genetics. Educational attainment refers to years of schooling, which appears to be an extraordinarily complex "phenotype." After all, it likely depends on IQ, motivation, opportunity, SES, cultural trends, and a host of other factors whose connection to the underlying biology is tenuous at best. Some factors are totally exogenous; for example, tuition and the state of the economy. Moreover, the interpretation of educational achievement may be quite different in Holland and the United States.

Another example for a problematic phenotype selection is a study on economic and political preferences by Benjamin and colleagues (Benjamin et al., 2012). This was a large-scale study, based on a total of 9,836 Swedish twins who were genotyped using the Illumina Human OmniExpress BeadChip genotyping platform. Collected

phenotype data included a total of 3,233 observations for a number of economic and political preferences, in addition to education. The economic preferences include risk aversion, patience, trust, and fair-mindedness, and the political preferences consist of immigration/crime, economic policy, environmentalism, feminism/equality, and foreign policy. The study found no single SNP that attained a P-value lower than 10^{-7} for any of the ten traits, although the study was well-powered to detect individual markers that explained at least 1.25 percent of trait variation at a nominal significance level of 10^{-7}. They further conducted genomic-relatedness-matrix restricted maximum likelihood (GREML) analysis to estimate the proportion of variance in these traits that can be jointly explained by all the genotyped SNPs. For economic preferences, common SNPs explained phenotypic variation that ranged between 0 percent (fairness) to a maximum of 20 percent (trust), and for political preferences from almost 0 (0.20 percent; immigration/crime) to a maximum 35 percent (foreign policy). They attributed these findings of unreliably low "narrow heritability" to poor retest reliability (viz., 57 percent). The reader should note that twin studies of economic preferences and political attitudes show much greater heritability, suggesting that some caution is warranted in interpreting the data they present. Why this gap between twin studies and the global SNP estimates in this study? Notably for height (Yang et al., 2010), intelligence (Davies et al., 2011), and schizophrenia (Lee et al., 2012), much higher heritability estimates are observed from global SNP genotyping approaches. We suggest that there are several reasons for both the failure to identify any GWAS level of significant SNPs, as well as the discrepancy between many twin studies and this report (Benjamin et al., 2012). Note that all the preference measurements were assessed using a questionnaire without monetary incentive and, as we have repeatedly underscored in this review, pencil-and-paper phenotypes may not be the ideal medium for GWAS of preference in the social sciences. Additionally, panel studies generally target heterogenous populations differing across many demographic characteristics. We suggest that despite these two recent negative GWAS findings in the nascent field of genoeconomics (Beauchamp et al., 2009; Benjamin et al., 2012), there is still room for considerable optimism in the value of GWAS in genoeconomics, especially for well-designed investigations that use uniform student populations and laboratory-based behavioral economic games. We bring the reader's attention to the most recent study of this group. Rietveld et al. (2013) carried out a GWAS study of approximately 125,000 subjects and identified SNPs contributing to educational attainment at GWAS-level significance. Estimated effects sizes were small ($R2 \approx 0.02\%$), which we (but not the authors) suggest are likely due to a poorly defined phenotype.

To illustrate our reasons for optimism, we note a recent GWAS of visual cortical surface area that examined a discover sample of "only" 421 subjects and two replication samples (482 and 278 subjects) and nonetheless identified a gene contributing to this phenotype (Bakken et al., 2012). What is the secret to this apparently successful investigation? Most importantly, the phenotype (an MRI measure) in the Bakken et al. study (2012) was close to the biological substrate, and a successful matching to the underlying genetic architecture was therefore more likely. Second, the ascertainment of the phenotype was exact and used state-of-the-art brain imaging procedures. Remarkably, despite a very small sample size, a provisional association was discovered that appears to be robust, thus strengthening the notion that imaging genomics (Hariri & Weinberger, 2003; Thompson, Martin, & Wright, 2010) is a powerful strategy for gene discovery of brain-expressed genes (Bis et al., 2012). A second recent publication with a considerably larger discovery sample size (approximately 9,000 subjects) was successful in discovering two genes for hippocampal volume and several likely candidates (Bis et al., 2012). This consortium study again used a well-defined neural phenotype and pooled data from a number of ongoing studies that had brain imaging data.

D.9 Summary Guidelines for Modeling Individual and Social Decision Making in the Laboratory

To summarize, we suggest that the following guidelines be followed in neurogenetic studies of individual and social decision making:

- Use continuous measures.
- Use the narrow phenotype defined by the behavioral economic paradigms.
- Use an ethnically homogenous student group.
- Reduce measurement error by carrying out classroom experiments.
- If multiple phenotype measures are used and show moderate correlations, we suggest that factor analysis or a similar statistical technique be used to extract a composite phenotype (viz., combined dictator, trust, and ultimatum games) that can be tested for association.

VI. Phenome

Although most investigations of human behavior are usually sharply focused on a particular phenotype, as in our example of altruism, there is growing interest in a more comprehensive approach that envisions capturing the entire sum of human phenotypes—the phenome. Indeed, it has been suggested that phenomic-level studies (Houle, Govindaraju, & Omholt, 2010) are required to intelligently interpret GWAS results, especially in light of the pleiotropic nature of most gene variants. Phenomics potentially enables relating genotypes and myriad environmental factors and phenotypes. Houle et al. (2010), in their review of phenomics, make an important distinction between *extensive* and *intensive* phenotyping. Extensive phenotyping aims at accumulating information for a wide variety of phenotypes (e.g., educational attainment, SES, and health), whereas intensive phenotyping characterizes a particular phenotype (prosociality) in great detail (e.g., fairness, altruism, trust). Current phenomic efforts largely adopt extensive sampling by choosing a wide range of conventional, *low-dimensional* measurements. However, we suggest that such low-dimensional measurements are often found lacking, and high-dimensional quantitative measurements are more valuable and informative. Human phenotype data often represent qualitative judgments, for example, those relating to disease states, environmental exposures, and many behavioral economic phenotypes that are natural QTLs. Although some phenotypes are sometimes simply binary—such as college-educated or not—in most cases, the underlying more "biological" state most proximal to genes is likely quantitative (e.g., standardized measurements of intelligence or "g," brain volume, functional connectivity, etc.). The continuous and multivariate nature of most decision-making phenotypes suggests that categorical phenotyping (e.g., do you trust other people?) may lose critical information compared to more quantitative measures (e.g., the trust game—a QTL of how much you really do trust other people), especially when looking for genetic correlates of phenotypic traits.

For some phenotypes, especially those extracted by laboratory-based paradigms, the phenotype may best be thought of as a function-valued trait, rather than as discrete measurements that can be used to capture the shape of the function (see Kingsolver, Gomulkiewicz, & Carter, 2001, for discussion of the evolution and selection of function-valued trait). We note that behavioral economics often generate QTL function-based traits that are potentially much more informative than categorical one-dimensional phenotypes, especially those based on pencil-and-paper questionnaires. It is interesting to speculate that function-based phenotypes from such games are potential targets for evolutionary selection. Did evolution select for "educational attainment" or some basic fundamental cognitive system contributing to "g," such as brain connectivity or reaction time? Hence, in looking for genes, "g" or a related endophenotype (Gottesman & Gould, 2003) seems a better target than simply attending college or not.

Of particular interest for the current review are the activities of the Consortium for Neuropsychiatric Phenomics (CNP) that has a truly phenomics vision and is supported by the National Institutes of Health (NIH) Roadmap initiative (Bilder et al., 2009). The purpose of the consortium is to illustrate the principles of phenomics research to help investigators assemble, visualize, and ultimately test multidimensional phenomics hypotheses. It is important to realize that phenotyping has become the key rate- and cost-limiting factor in human genetics. Importantly, phenotypes need to be assessed in a well-operationalized fashion. Moreover, wherever possible, phenotypes should be defined from the perspective of a relevant biological context. It is also notable that many phenotypes used in the social as well as the medical sciences do not align readily with genetic determinants because such phenotypes were not conceptualized with genetics in mind. This would certainly include many survey questions in the social sciences that are very distant from any underlying biology and, hence, we suggest, are particularly difficult to match to genes. On the other hand, the phenomics strategy explicitly calls for efforts to redefine phenotypes as multilevel combinations of measures that may offer more realistic constraints on the mechanistic paths leading from genome to syndrome. For phenotypes of individual and social decision making, one suggestion that is worth examining is to extract, for example, a combined "prosociality" or "risk attitude" index based on multiple game assessments.

In considering the desiderata of a good phenotype, measurement properties are of paramount importance (Bilder et al., 2009). Phenotypes need to show not only high internal consistency (e.g., Cronbach's α) but also ensure that a meaningful and coherent construct is being measured to begin with. Phenotypes should be stable over time and organismic states. Moreover, the sensitivity of the phenotype measurements should be strong across widely varying levels of phenotype expression. Another consideration is how well the phenotype is suitable to high-throughput phenotyping because highly informative, intensive phenotyping now exceeds the cost and time of

genotyping. For example, a "comprehensive" examination of cognitive abilities may require 10–20 hours, and briefer assessments routinely fail to provide broad phenotypic coverage, fail to specify adequately the phenotypes of interest, or both. Whether more cost-effective phenotyping procedures (e.g., internet-based) can preserve the needed information for genetic analysis remains to be seen.

VII. Schizophrenia Consortium

The work of the International Schizophrenia Consortium illustrates what we believe is the road to take in identifying genes contributing to the molecular genetic architecture of complex traits characterizing individual and other-regarding decision making. First, it is crucial that a meticulous definition of the phenotype be employed, with no shortcuts. Otherwise, there is a danger of a garbage-in garbage-out GWAS based on poorly constructed and biologically distant and implausible phenotypes that are badly matched at the molecular level. Such a phenotype-weak study is likely to lead to false-negative findings and an overly pessimistic view that impedes future progress. Second, it is crucial to assemble individual groups of investigators willing to contribute to the larger consortium, yet with each one/group toiling in their own "backyard" with well-documented phenotypic definitions and ascertainment procedures in place. Moreover, such individual groups provide a cultural and ethnic diversity to the ultimate GWAS meta-analysis so that results can be generalized across populations. Finally, these individual studies are pooled to attain the power needed for finding genes of moderate to small effect sizes characteristic of complex traits. Notably, in the psychiatric genetics field, potential candidate genes flagged in GWAS are often further authenticated by drawing on results from imaging genomics, expression studies, and pathway analyses, as was carried out so elegantly by Ayalew et al. (2012) and is discussed in the next paragraph.

A beautiful example of a novel approach in the field of complex behavioral phenotypes is the recent article by Ayalew and his colleagues (2012). They used a so-called *translational convergent functional genomics* (CFG) design to identify and prioritize genes involved in schizophrenia by gene-level integration of GWAS data with other genetic and gene expression studies in humans and animal models. Notably, they showed how the top candidate genes identified by their approach can be used to generate a genetic risk prediction score (GRPS) to assist in schizophrenia diagnosis. The first step in their analysis was to comprehensively identify candidate genes, pathways, and mechanisms for schizophrenia, integrating all available evidence. They used data from GWAS investigations and integrated those data with gene expression studies from relevant animal model brain and blood gene expression data. The second step was to integrate, as part of this comprehensive approach, other genetic data—human genetic data (linkage, copy number variant [CNV], or association), as well as relevant mouse model genetic evidence.

VIII. Decision Making

A. Individual Decision Making: Risk Attitude

Recently, genoeconomics (Navarro, 2009) has gained traction with the publication of a number of candidate gene studies using behavioral economic paradigms as QTLs (Apicella et al., 2010; Avinun et al., 2011; Chew, Ebstein, & Zhong, 2012; Dreber & Apicella, 2009; Eisenegger et al., 2010; Israel et al., 2009; Kuhnen & Chiao, 2009; McDermott, Tingley, Cowden, Frazzetto, & Johnson, 2009; Roe et al., 2009; Zhong, Chark, Ebstein, & Chew, 2012; Zhong, Israel, Xue, Ebstein, & Chew, 2009; Zhong, Israel, Xue, Sham, et al., 2009). The first such molecular genetic investigation employing a classical behavioral economic phenotype, the dictator game, was carried out by us and is discussed in the next section (Knafo, Israel, et al., 2008).

The studies to date of economic risk employed only a small number of subjects and must be considered exploratory and provisional. Nevertheless, they do add, albeit incrementally, to our knowledge of the neurochemical substrate underlying economic risk attitude. One of the first studies was by Dreber et al. (Dreber & Apicella, 2009; Dreber et al., 2010). The study was quite small and included only 94 Harvard undergraduates who were administered an investment game with real monetary payoffs (Gneezy & Potters, 1997). However, the choice of a candidate gene was hypothesis-driven, based on more than a decade of evidence showing in some (but not all) studies a relationship between the dopamine D_4 receptor exon 3 VNTR and novelty seeking, risky behavior, and impulsivity (Ebstein, 2006; Ebstein et al., 1996; Munafo, Yalcin, Willis-Owen, & Flint, 2008). Inter alia, it is worth

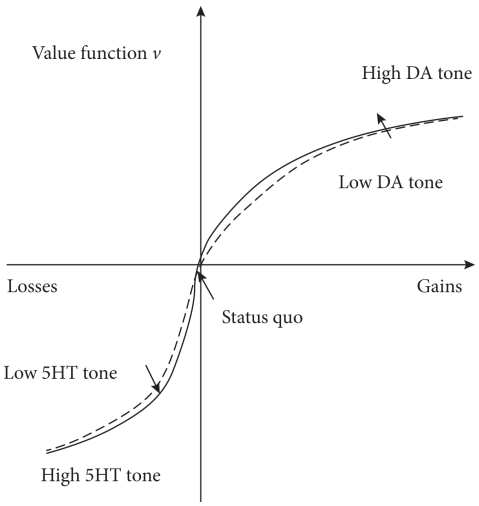
noting that although the evidence for a role of this gene in the personality trait of novelty seeking is mixed, some imaging studies support the involvement of DRD4 in novelty-related brain events (Marco-Pallares, Nager, et al., 2010; Strobel et al., 2004). Additionally, dopamine pathways are central to brain reward mechanisms, and the DRD4 gene has been implicated in magnitude-related reward effects in the anterior insula and cingulate cortex (Camara et al., 2010). As predicted, Dreber et al. found that carriers of the 7 repeat invest more money in a financial risk game relative to noncarriers; in contrast, there was no association as a function of allelic genotype in the DRD2 gene. Kuhnen and Chiao (2009) reported similar results for 65 subjects when they reported that DRD4 7-repeat carriers took 25 percent more risk than did noncarriers. They also observed that subjects who carried the serotonin transporter promoter-region (5-HTTLPR) short allele were less risk-taking, which is consistent with a large literature suggesting a role of this polymorphism in anxiety-related personality traits (Canli & Lesch, 2007). However, two studies failed to replicate the association between DRD4 and risk taking (Carpenter, Garcia, & Lum, 2011; Frydman, Camerer, Bossaerts, & Rangel, 2011). Although the Carpenter et al. study seems contrary to the conclusions about risk reported in Kuhnen and Chiao (2009), Dreber et al. (Dreber & Apicella, 2009), and Frydman et al. (2011), the risk tasks used in those studies were all somewhat different, perhaps explaining the inconsistent results obtained. In the Kuhnen and Chiao (2009) and Dreber et al. (Dreber & Apicella, 2009) studies, the tasks were actually more similar to the loss task in the Carpenter et al. (2011) study, and, for loss, a marginally significant effect was observed for DRD4 7R. Whether there is a true association between DRD4 and risk taking will become clearer as more evidence accumulates for meta-analysis. The next study implemented a pharmacogenetic approach toward evaluating the role of the DRD4 gene in risky behavior. Eisenegger et al. (2010) used a gambling task and demonstrated an interaction between L-DOPA administration (that increases dopamine [DA] release in the brain) and the DRD4 7-repeat. They observed increased gambling in subjects who carried the 4/7 genotype and who received L-DOPA, but not in those who received L-DOPA and who carry the 4/4 genotype. In this study, introducing a pharmacological arm helped sharpen the distinction between 4/4 and 4/7 carriers, thus underscoring the power of pharmacogenomics as a strategy in association studies.

Another well-characterized, widely studied, and functional polymorphism that has been associated with financial risk is the monoamine oxidase-A (MAOA) promoter region repeat polymorphism (Frydman et al., 2011; Zhong, Israel, Xue, Ebstein, et al., 2009). Our group (Zhong, Israel, Xue, Ebstein, et al., 2009) observed subjects' incentivized choices in a controlled laboratory setting and investigated their task performance in association with MAOA. We found that subjects with the high MAOA activity (4-repeat) allele were characterized by a preference for riskier choices (i.e., in favor of the long-shot lottery and also less insurance purchasing) compared to subjects with the low MAOA activity (3-repeat) allele. Our study was the first to link attitude toward long-shot risks to a specific gene. It complements recent findings on the neurobiological basis of economic risk taking discussed earlier. In a second study, the authors (Frydman et al., 2011) followed the strategy first developed by our group (Avinun et al., 2011; Israel et al., 2009; Knafo, Israel, et al., 2008; Zhong, Israel, Xue, Ebstein, et al., 2009) and combined methods from neuroeconomics and behavioral genetics to investigate the impact that the genes encoding for MAOA, 5-HTTLPR, and DRD4 have on these two computations. Consistent with previous literature, and specifically our own study, they found that carriers of the MAOA 4-repeat polymorphism were more likely to take financial risks. The computational choice model, rooted in established decision theory, showed that 4-repeat carriers exhibited such behavior because they are able to make better financial decisions under risk and not because they are more impulsive. In contrast, and as mentioned earlier, they found no behavioral or computational differences among the 5-HTTLPR and DRD4 polymorphisms.

The study by Roe et al. (2009) found association between two SNPs in the *VMAT2* gene and risk attitude using a behavioral economic paradigm but failed to find association with the *MAOA* VNTR. However, the study included only 67 subjects of mixed ethnicity and some nonstudents.

It is of interest to note that some of the VNTRs (MAOA, DRD4, DAT1, and 5-HTTLPR) just discussed are not genotyped in the usual GWAS that rely on mass SNP arrays. Hence, it behooves the careful investigator, especially in the nascent field of genoeconomics, to examine these polymorphisms using more "custom" genotyping.

B. A Neurochemical Model of Risk



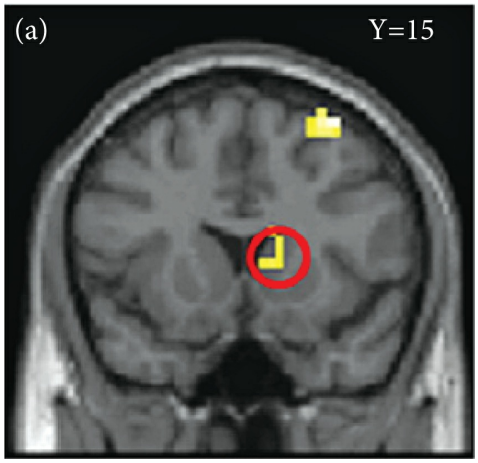
Click to view larger

Figure 1 . Figure from Zhong, S., Israel, S., Xue, H., Ebstein, R. P., & Chew, S. H. (2009). Loss–gain differentiation. Prospect theory assumes a loss-averse value function that is concave over gains, convex over losses, and vanishes at the status quo, represented by 0. Our hypothesis is that DA (5-HT) tone modulates sensitivity toward incremental gain (loss) and the higher the DA (5-HT) tone, the lower (higher) the sensitivity toward incremental gain (loss).

Prospect theory proposes that people have diminishing sensitivity in valuing increases in the size of monetary outcomes for both gains and losses. For decision making under risk, this implies a tendency to be risk tolerant over losses while being generally risk averse over gains. In a first study of its kind, our group suggested a neurochemistry-based framework for understanding an economic model for PT—specifically, the diminishing valuation sensitivity hypothesis. We propose that DA tone modulates the sensitivity toward valuation of gains, whereas serotonin (5-HT) tone modulates the sensitivity toward valuation of losses. Consequently, higher DA tone would yield a more concave valuation function over gains, whereas higher 5-HT tone would yield a more convex valuation function over losses. Using a neurogenetics strategy to test our neurochemical model (Zhong, Israel, Xue, Sham, et al., 2009), we found that subjects with the 9-repeat allele of DAT1 (lower DA tone; van Dyck et al., 2005) dopamine transporter polymorphism are more risk-tolerant over gains than are subjects with the 10-repeat allele, and that subjects with the 10-repeat allele of STin2 (higher 5-HT tone; Hranilovic et al., 2004) are more risk tolerant over losses than are subjects with the 12-repeat allele. Overall, our results support the implications of our model and provide the first neurogenetics evidence that risk attitudes are partially hardwired in differentiating between gain- and loss-oriented risks (see Figure 1).

C. Imaging Genomics of the Neurochemical Model of Risk

Our group was one of the first to use a neurogenetic strategy/behavioral economic paradigm combined with functional imaging to reveal the underlying neurochemical pathways of risk attitude (Zhong, Chark, et al., 2012) to test the neurochemical model just described. We found enhanced striatal activation responding to increases in the magnitude of utility for risks over gains and to increases in the magnitude of disutility for risks over losses, whereas increased amygdala activation correlates only with the disutility for risks over losses. Stratifying brain activation by genotype, we found that DAT1 contributes to individual differences in striatal response for gain-oriented risks, whereas a polymorphism in the 5-HT transporter (STin2) partially accounts for individual differences in amygdala responses for loss-oriented risks. No association was observed for COMT and 5-HTTLPR in either region.



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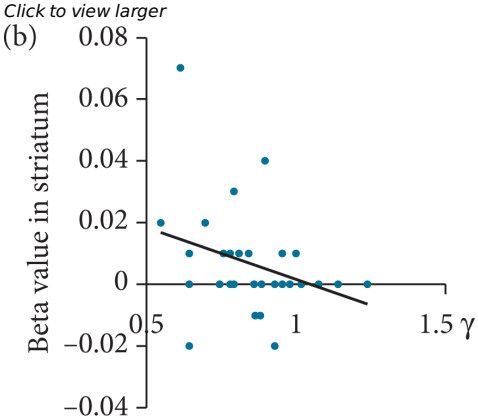

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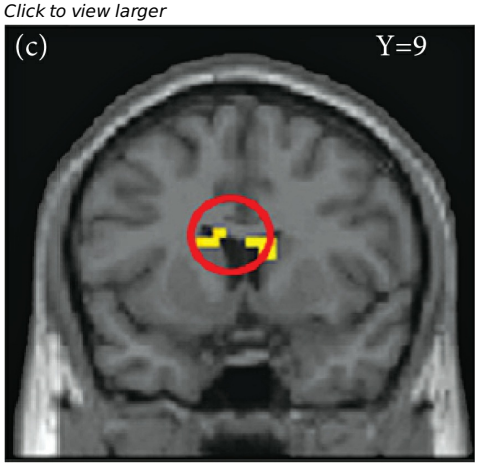

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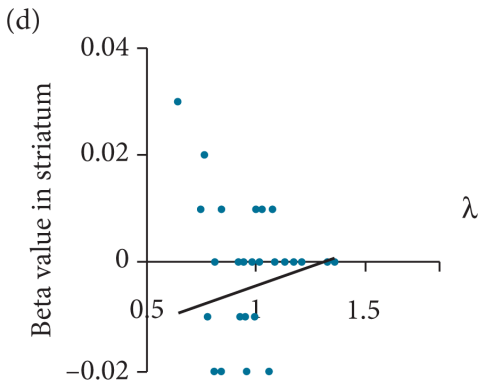

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Figure 2 . Striatal activation correlates with utility for prospects. Figure from Zhong et al. (2012). (A) Coronal section showing the striatum whose activation correlates significantly with increases in the magnitude of the utility for prospects. (B) The β value of striatum activation is significantly negatively correlated with the index γ of the utility function over gains, γ, in which lower values of γ represent greater degrees of risk aversion. (C) Coronal section of striatum whose activation correlates significantly with increased magnitude of utility for hazards. (D) The β value of striatum activation is not significantly positively correlated with the index λ of the utility function over losses, in which higher values of λ represent greater degrees of risk aversion.

Together, our results suggest the role of the amygdala and corresponding serotonergic pathway in evaluating losses. This further corroborates the hypothesis of 5-HT being linked to DA in an "opponent partnership" (Daw, Kakade, & Dayan, 2002) (see Figure 2).

IX. Other-Regarding or Social Decision Making

Other-regarding preferences can be measured in the laboratory using "classical" behavioral economic paradigms. The reader is referred to the excellent article by Fehr and Camerer (2007) for a detailed discussion of behavioral economic paradigms widely used in measuring social norms. These "classic" games include the prisoner's dilemma, public goods, ultimatum, dictator, third-party punishment, trust, and gift exchange games. Of course, such preferences can also be examined using survey information, and the relationship between survey results and laboratory-based studies are of considerable interest (Dohmen et al., 2006; E. Fehr, 2009).

Some social behaviors, such as parenting, can also be studied in the laboratory. Behaviors such as pair bonding and mate preferences can feasibly be studied only in field experiments and surveys. In the next section, we discuss in detail the trust game and some of the important applications of this game in neuroeconomics and as an important laboratory-based paradigm in genetic analyses.

A. Trust Game

The trust game is a singular success of neuroeconomics strategy in understanding the molecular architecture of human decision making. It is based on a seminal article by Kosfeld et al. (2005) in which intranasally administered OT was demonstrated to enhance trust but not trustworthiness. Importantly, this experiment wove together two important research strategies in revealing human preferences—behavioral economics and pharmacology. Moreover, the choice of OT as a neuropeptide likely to enhance trusting behavior is based on a large body of animal (aka "translational") evidence showing the importance of this nonapeptide as a paramount social hormone in mammals (Insel, 2010).

In the trust game, the first player is endowed with a certain amount of money, say $20, while the second player is endowed with nothing. In the first stage, the first player decides how much to send (S) to an anonymous and randomly matched second player ($20 – S). For every dollar the first player sends, the second player receives three times (3S) as much. In the second stage, the second player decides how much (B) out of 3S to send back to the first player. At the end, the first player receives ($20 – S + B), being the amount he or she keeps plus the amount the second player sends back, whereas the second player receives three times the amount sent deducting

the amount sent back (3S – B). This is the design employed by Kosfeld et al. in their seminal article (Kosfeld et al., 2005). A modification of the trust game is the strategic method (Camerer, 2003; Camerer & Fehr, 2004), in which the second player states his or her response to each of several multiple possible choices from the first player. Every participant plays both roles of first and second players without any feedback. At the payment stage with real money, there is a random determination of the specific role—first or second mover—for each pair of subjects. The amount sent by the first player is used as a measure of trust, whereas the average return amount from the second player is a measure of trustworthiness. The strategic method allows more observations to be generated, whereas the standard method is more likely to induce positive or negative emotion when responding to actual choice. Experimental evidence shows no significant difference in behavior between the two approaches (Camerer, 2003; Camerer & Fehr, 2004).

An important application of the trust game has been published by the Montague group, who examined play in an iterated trust game in a group of subjects with borderline personality disorder (BPD) (King-Casas et al., 2008). Nonclinical subjects were characterized by a linear relation between anterior insula response and both magnitude of monetary offer received from their partner and the amount of money repaid to their partner. Intriguingly, activity in the anterior insula of BPD participants was related only to the magnitude of repayment sent back to their partner. Importantly, these results suggest that subjects with BPD are not sensitive to social norms. Importantly, this game-theoretic strategy toward understanding psychopathology may provide a new window into characterizing and studying other psychiatric disorders.

Trust game play has been examined with interesting results via MRI in a number of other studies of nonclinical subjects. For example, Koscik and Tranel (2011) found that the amygdala is required in the development of normal interpersonal trust. The study of van den Bos and colleagues (2009) examined the neural basis of reciprocity using a trust game and imaging. Krueger et al. (2007) examined the underlying brain mechanisms of conditional and unconditional trust in social reciprocal exchange. They used a hyperscanning approach in which two strangers interacted online with one another in a sequential reciprocal trust game while their brains were simultaneously scanned. Delgado and colleagues (2005) investigated whether prior social and moral information about potential trading partners affects the neural circuitry of trust. The trust game has also been used to reveal prejudices, as in the study carried out by Stanley and his collaborators (2012). Their results suggest that the amygdala may represent emotionally relevant social group information as a subset of the general detection function it serves, whereas the striatum is involved in representing race-based reputations that shape trust decisions.

Taken together, these studies ingeniously use a behavioral economic paradigm to measure trust, which, coupled with cutting-edge tools from the neurosciences, provides a powerful insight into human decision making.

B. Dictator Game

The dictator game is a one-shot game with two players. Player 1 is given a fixed sum of money and has to decide how to split it between himself and an anonymous Player 2 endowed with no money. Player 2 simply receives the money from Player 1 and does not have an active role in the game. Because the recipient is completely powerless, “dictators” are unconstrained by fear of reprisal or other strategic considerations, and their allotment can be seen as a measure of altruism (Forsythe, Horowitz, Savin, & Sefton, 1994; Kahneman, Knetsch, & Thaler, 1986). In short, the dictator game offers a simple, straightforward measure of altruism and generosity, a laboratory-based distillation of the essence of prosocial behavior.

Similar to other behavioral economic paradigms, the dictator game lends itself exquisitely to imaging and psychophysiological studies (Gunther Moor et al., 2011; Meshulam, Winter, Ben-Shakhar, & Aharon, 2012; Moor et al., 2012; Weiland, Hewig, Hecht, Mussel, & Miltner, 2012). Combining imaging and the dictator game helps identify neural pathways underlying altruism and sense of fairness. Fewer studies have combined neurogenetics × imaging × games, but such approaches have the potential to shine a spotlight with greater certainty on the neurotransmitter pathways and elements of synaptic transmission in decision making (see, e.g., Zhong, Chark, et al., 2012; Zhong, Israel, Xue, Sham, et al., 2009).

Weiland et al. (2012) examined subjects via MRI while playing the ultimatum and dictator games. Their study supports the idea that altruistic motives primarily drive fair offers in the dictator game, denoted in that report as altruistic fairness. In an interesting study, the dictator game was used to examine how individuals can regulate their

emotions, indexed by skin conductance and post-game self-report questionnaires, in response to fair and unfair offers (Meshulam et al., 2012). The authors were able to demonstrate that people could choose their own mental state when incentivized to do so. Angry but not happy emotions could be manipulated. In a study combining an imaging protocol and pharmacological manipulation, albeit not the standard dictator game paradigm, van Ijzendoorn and his colleagues examined charitable giving to UNICEF in a laboratory setting and found that asymmetric frontal brain activity significantly predicted donating (van Ijzendoorn, Huffmeijer, Alink, Bakermans-Kranenburg, & Tops, 2011). Additionally, frontal α asymmetry moderated the interactive effect of OT and parental love withdrawal on charitable giving.

Games lend themselves to precise, reproducible, and objective cross-cultural studies in the laboratory, allowing the focused evaluation of human social behavior among various ethnic and population groups (Henrich et al., 2005; Herrmann, Thoni, & Gachter, 2008; Norenzayan & Shariff, 2008). One of the most interesting of such studies (Henrich et al., 2005) is a cross-cultural study of behavior in three representative games measuring other-regarding behavior: the ultimatum, public goods, and dictator games. Moreover, the study was carried out in no less than 15 small-scale societies characterized by a diverse set of economic and cultural variables. Notably, the neoclassical economic model of purely selfish behavior toward maximizing profit cannot explain the behavior in the societies studied. Second, a larger than expected amount of behavioral variability is observed. Third, the greater the market integration and the higher the monetary reward to cooperation in everyday life, the greater the level of prosociality displayed in experimental games. Fourth, and surprisingly, individual-level economic and demographic variables do not explain the variance in game behavior, either within or across groups. Fifth, in many cases, experimental play appears to resonate with the social exchanges occurring in day-to-day living.

One of the more intriguing applications of economic games is arriving at an understanding of the evolution of human cooperation (Gintis, Henrich, Bowles, Boyd, & Fehr, 2008; Hagen & Hammerstein, 2006; Price, 2008). A recent article in this debate by Marlowe and his collaborators (2011) shows that strong reciprocity, including generous offers and third-party punishment (3PP; see Fehr & Fischbacher, 2004), takes place mainly in complex societies characterized by dilemmas involving collective action. Hence, they argue that “spiteful” second-party punishment (2PP; as modeled by the ultimatum game), motivated by the basic emotion of anger, is more universal than 3PP and that it is sufficient to explain the origins of human cooperation.

Economic games can also be used to trace the ontogeny of human fairness from childhood through adolescence (Almas, Cappelen, Sorensen, & Tungodden, 2010). Using modified versions of the dictator game, these authors demonstrated that children’s level of self-interest was stable across adolescence, whereas their concept of fairness markedly shifted in the same period. In particular, they observed an enhanced focus on the value of meritocratic fairness in evaluating the allocation of funds, a view that requires the player to make a distinction between various origins of inequality. Such studies of the development of fairness would lend themselves to both a neurogenetic and imaging strategies but, to our knowledge, have yet to be reported.

A final word on the use of the dictator game involves the exploration of psychopathology and the potential value of economic games in understanding decision making in mental illness. For example, one study examined decision making in the ultimatum and dictator games as a function of subjects’ level of schizotypy across the full schizotypal continuum (van ‘t Wout & Sanfey, 2011). The results showed that higher levels of schizotypal symptoms, particularly positive and disorganized schizotypy, were related to proposing higher offers to both human and nonhuman computer partners. Additionally, the number of interpersonal schizotypal symptoms was associated with an increased acceptance rate of very unfair offers from human partners, possibly reflecting a blunted emotional response to such offers.

Another study using the ultimatum and dictator games compared performance of schizophrenic patients to nonpatient controls (Wischniewski & Brune, 2011). The study found that even though both groups increasingly rejected unfair offers as the level of unfairness increased, patients accepted significantly more unfair offers than did controls.

Ebstein and colleagues carried out the first molecular genetic study examining individual differences in dictator game allocations (Knafo, Israel, et al., 2008). This study showed a significant association between the length of the RS3 AVPR1a promoter region repeat and allocations in the dictator game. The long repeats were associated with greater allocations. They also showed a relationship between RS length and transcription of AVPR1a in postmortem

hippocampal specimens, and the long repeat predicted greater AVPR1a mRNA levels. The decreased expression of the RS3 short repeat has been replicated in an in vitro expression system (Tansey et al., 2011). A partial replication of this finding was then demonstrated in children using a somewhat different classification scheme for the RS3 repeat (Avinun et al., 2011). In the "dictator kids" publication, Avinun et al. classified the RS3 repeat by comparing the second most common allele versus all others (327 or 334 base pair [bp] vs. all others). The second most common allele has been associated with autism (Kim et al., 2002) and poor pair bonding in humans (Walum et al., 2008); for a detailed discussion of the AVPR1a gene and social behavior, see Westberg and Walum, elsewhere in this handbook. Interestingly, Meyer-Lindenberg and colleagues have shown that the RS3 repeat predicts amygdala activation using both classification schemes (Meyer-Lindenberg et al., 2009). Further evidence for functionality of the AVPR1a RS3 repeat was obtained from a study of prepulse inhibition (Levin et al., 2009).

Identification of an association between AVPR1a and dictator game allocations immediately suggested the possible involvement of OT as well, since both nonapeptide hormones contribute to social and affiliative behaviors in animals and people. Hence, we examined the role of the oxytocin receptor gene, OXTR, in dictator game giving (Israel et al., 2009). Three tagging SNPs across the gene region showed significant association with both the dictator and the social values orientation games (Van Lange, 1999). However, in a study of Swedish twins, no association was observed between OXTR and either the dictator or the trust games (Apicella et al., 2010). More recently, it was shown in healthy male students participating in a trust game that a commonly occurring genetic variation (rs53576) in the OXTR gene is reliably associated with trust behavior rather than a general increase in trustworthy or risk behaviors (Krueger et al., 2012). Individuals homozygous for the G allele (GG) showed higher trust behavior than did individuals who were A allele carriers (AA/AG).

Evidence for involvement of both the OXTR and AVPR1a genes in real-world prosocial activity was reported by Poulin and his colleagues (Poulin, Holman, & Buffone, 2012). They examined OXTR rs53576, as well as AVPR1a polymorphisms rs1 and rs3 in a national sample of US residents (n = 348). These polymorphisms interacted with perceived threat to predict engagement in volunteer work or charitable activities and commitment to civic duty. Perceived threat was assessed at all waves of the life-events study with a reverse-coded, six-item version of Janoff-Bulman's World Assumptions Scale (Janoff-Bulman, 1989). Items on the scale included "There is more good in the world than bad" and "Human nature is basically good"; participants responded to each item using a scale from 1, *strongly disagree*, to 5, *strongly agree*. Specifically, greater perceived threat predicted engagement in fewer charitable activities for individuals with A/A and A/G genotypes of OXTR rs53576, but not for G/G individuals. Similarly, greater perceived threat predicted lower commitment to civic duty for individuals with one or two short alleles for AVPR1a rs1, but not for individuals with only long alleles.

The rs53576 SNP is of interest because it has been associated with a variety of social behaviors and cognition such as parenting (Bakermans-Kranenburg & van Ijzendoorn, 2008), empathy (Rodrigues, Saslow, Garcia, John, & Keltner, 2009; Wu, Li, & Su, 2012), loneliness (Lucht et al., 2009), emotional support seeking (Kim et al., 2010), social auditory processing (Tops, van Ijzendoorn, Riem, Boksem, & Bakermans-Kranenburg, 2011), psychological resources (Saphire-Bernstein, Way, Kim, Sherman, & Taylor, 2011), social support (F. S. Chen et al., 2011), and neurocardiac reactivity to social stress (Norman et al., 2012). On the clinical side, this SNP has been associated with facets of disorders of social cognition including autism (Wu et al., 2005; but also see Jacob et al., 2007), depression (Costa et al., 2009), and ADHD (Park et al., 2010).

C. Ultimatum Game

In the ultimatum game, two players are offered a chance to divide a certain sum of money. The proposer proposes how to split the sum. The responder can accept or reject the deal. If the proposal is accepted, there is a deal. If the proposal is rejected, neither player gets anything. The rational solution, suggested by game theory, is for the proposer to offer the smallest possible share and for the responder to accept it. However, when humans play the game, the most frequent outcome is a fair share. Overall, considerable evidence shows that, in the ultimatum game, substantial offers are often made and sometimes rejected (C. Camerer & Thaler, 1995). Offers average 30–40 percent of the total and even splits are generally the mode. Offers of less than 20 percent are generally rejected.

A study by Zhong and colleagues examined the role of the dopamine D_4 receptor VNTR in contributing to ultimatum game behavior (Zhong et al., 2010). The DRD4 exon3 VNTR is a well-characterized functional polymorphism

known to be associated with ADHD and personality traits including novelty seeking and self-report altruism. Applying a neurogenetic approach, these investigators found that DRD4 is significantly associated with fairness preference. Additionally, the interaction among this gene, season of birth, and gender is highly significant. This is the first result to link preference for reciprocal fairness to a specific gene and suggests that G×E interactions contribute to economic decision making.

Other biological markers have also been associated with ultimatum game behavior. Low serum levels of omega-3 polyunsaturated fatty acids have been linked to impulse control and hostility. Emanuele et al. (2009) examined the serum omega-3 and omega-6 fractions in relation to ultimatum bargaining behavior. Participants were 60 economy students, and the results of this study suggest that a depletion of the serum omega-3 fatty acids is associated with rejections of unfair ultimatum offers in an experimental neuroeconomic setting.

The neurotransmitter 5-HT has also been shown to partially mediate ultimatum game behavior (Crockett, 2009; Crockett, Clark, Tabibnia, Lieberman, & Robbins, 2008). Participants with depleted 5-HT levels rejected a greater proportion of unfair offers, but not fair offers, without showing changes in mood, fairness judgment, basic reward processing, or response inhibition. These results suggest that 5-HT may play a critical role in regulating emotion during social decision making. Interestingly, low platelet 5-HT may serve as a reliable biomarker to identify people who are more likely to reject unfair ultimatum offers in the ultimatum game (Emanuele, Brondino, Bertona, Re, & Geroldi, 2008). These data point to a role for the serotonergic system in human sense of fairness modeled in the ultimatum game.

In an innovative study by Takahashi and colleagues (2012), it was shown that individuals who were characterized as “peaceful” (characterized by high levels of straightforwardness and trust) rejected unfair offers more often than did individuals who were characterized as “aggressive” (characterized by high levels of impulsivity or hostility) (Takahashi et al., 2012). Moreover, PET scanning associated reduced 5-HT transporter levels in the dorsal raphe nucleus with honesty and trustfulness, the traits associated with retaliatory behavior in the ultimatum game. As the authors note “higher central serotonin transmission might allow us to behave adroitly and opportunistically, being good at playing games while pursuing self-interest” (p. 4281).

Weiland and colleagues examined neural correlates of preferences modeled in the dictator and ultimatum games (Weiland et al., 2012). Functional MRI analysis revealed that almost a third of fair offers in the ultimatum game were correlated with greater activity in prefrontal areas, especially in regions presumed to be involved in reward and theory of mind. A limitation of the study is that the number of fair and unfair offers differed among participants and conditions. Because participants could choose freely among the six alternative offers, there was no way to prevent such a bias without risking the free-choice condition. As a result, some participants had to be excluded from analysis, and therefore only 28 percent of the fair offers were included. This observation suggests that egoistic motives are mainly responsible for fair offers, which the authors call *strategic fairness*. Fair offers in the ultimatum game hence are suggested to be related to strategic processing and are mainly motivated by egoistic motives to emphasize reward. This result was corroborated by the significant activity in the striatum in comparing the ultimatum game with the dictator game. Fair offers in the dictator game, however, were related to greater activity in the dorsal anterior cingulate cortex and the posterior cingulate cortex. This lends support to the idea that altruistic motives are driving fair offers in the dictator game, which the authors designate *altruistic fairness*. In another investigation of the neural substrate underlying fairness, responder behavior was examined to unfair offers in the ultimatum game with conditions that differed in their intentionality constraints (Guroglu, van den Bos, Rombouts, & Crone, 2010). Intentionality is the perceptions of fairness that are influenced by the intentions of the interaction partner. It is context-dependent information that highly influences fairness judgments. Brain activity underlying rejection versus acceptance of unfair offers appeared highly dependent on intentionality. These results highlight the significance of intentionality considerations in fairness-related social decision-making processes. In another study of patients with brain lesions, it was shown that the ventromedial prefrontal cortex (vmPFC) encodes the expected value of abstract, future goals in a common neural currency that takes into account both reward and social signals in order to optimize economic decision making in the ultimatum game (Moretti, Dragone, & di Pellegrino, 2009).

D. Prisoner’s Dilemma

The prisoner’s dilemma is an exemplary game that has been intensively studied in game theory and has

considerable importance in economics, psychology, and evolutionary studies. In the game, two players choose to either cooperate or defect and receive a payoff that depends on the interaction of their respective choices. It creates a situation in which cooperation is in the best interest of the group but defection is in the best interest of the individual. The iterated version of the prisoner's dilemma game is a model for relationships based on reciprocal altruism.

A series of interesting studies examining the neural basis of social cooperation using the prisoner's dilemma paradigm have been carried out by Rilling and his colleagues (Rilling et al., 2002; Rilling et al., 2011; Rilling et al., 2007; Rilling et al., 2008; Rilling, Sanfey, Aronson, Nystrom, & Cohen, 2004*a*; Rilling et al., 2004*b*; Wood, Rilling, Sanfey, Bhagwagar, & Rogers, 2006). A sequential-choice prisoner's dilemma game was employed in which player 1 chooses and player 2 is then able to view player 1's choice before making his own choice. Each of the four outcomes is associated with a different payoff. In one of the first studies of its kind, Rilling and colleagues showed that mutual cooperation was associated with consistent activation in brain areas that have been linked with reward processing: nucleus accumbens, the caudate nucleus, ventromedial frontal/orbitofrontal cortex, and rostral anterior cingulate cortex. Based on these observations, the authors propose that activation of this neural network positively reinforces reciprocal altruism, thereby motivating subjects to resist the temptation to selfishly accept but not reciprocate favors. In an attempt to identify the neural substrate of cooperation, Rilling and colleagues used a tryptophan-depletion paradigm. Tryptophan depletion produced significant reductions in the level of cooperation shown by participants when playing prisoner's dilemma (Wood et al., 2006). This effect was accompanied by a significantly diminished probability of cooperative responding given previous mutually cooperative behavior. These data further strengthen the notion that 5-HT plays a significant role in the acquisition of socially cooperative behavior.

In a more recent study, researchers manipulated brain neurochemistry in subjects by administering intranasally either AVP or OT (Rilling et al., 2011). Imaging results showed that, compared to both AVP and placebo, OT enhanced the caudate nucleus reaction to reciprocated cooperation. Oxytocin also increased left amygdala activation following reciprocated cooperation (the reader is referred to the article by Baas et al., 2004, regarding the significance of amygdala lateralization). At the level of behavior, intranasal OT led to increased rates of cooperation following unreciprocated cooperation in the previous round compared with AVP. AVP strongly enhanced cooperation following a cooperative gesture by the partner compared with both placebo and OT. In response to reciprocated cooperation, AVP enhanced activation in an area including vasopressin circuitry implicated in affiliative behaviors in nonhuman species. Finally, both OT and AVP increased amygdala functional connectivity with the anterior insula. It was suggested that increased connectivity between these two regions may increase the amygdala's ability to evoke visceral somatic responses that modulate decision making. As the authors noted, these findings extend our knowledge of the neural and behavioral effects of OT and AVP to the context of genuine social interactions.

E. Ingroup Versus Outgroup Paradigm

A recent meta-analysis investigating the effects of OT on intergroup trust concluded that OT administration enhances ingroup trust but does not decrease outgroup trust (Van IJzendoorn & Bakermans-Kranenburg, 2012). The studies reviewed in the meta-analysis, most notably those by De Dreu et al. (2010; 2011), were set in contexts of intergroup competition. Although consistent with this finding, results from the study of Israel et al. (Israel, Weisel, Ebstein, & Bornstein, 2012) demonstrate that when set in a context of intergroup cooperation, OT not only improves contributions to the ingroup but also increases contribution rates to the collective interest of all groups. These results suggest that group-oriented prosocial effects of OT may be sensitive to contextual cues, which may differ depending on the inherent structure of the social dilemma. Importantly, these prosocial effects do not extend to AVP, suggesting an OT-specific neuropeptide influence on cooperative intergroup behavior.

Additionally, within the framework of the nested social dilemma, participants receiving OT in the Israel et al. study were not only more willing to give to others, but they also expected that others would reciprocate their cooperative behavior. This effect is supported by the positive effect of OT on the expectation that others would contribute to both local and global interests and by the closer pairing of expectations to behavior in the OT condition only.

In today's increasingly interconnected world, deciding with whom and at what level to cooperate is a matter of increasing importance because large-scale cooperation often comes at the expense of cooperating at the local

level and vice versa (Dietz, Ostrom, & Stern, 2003). Studies employing the nested social dilemma paradigm help to delineate the behavioral effects of OT and AVP in these types of social dilemmas and provide additional evidence for the positive effects of OT in facilitating cooperative behavior, both within and across groups.

We are aware of three additional investigations that bear on the role of OT in ingroup–outgroup altruism (Declerck, Boone, & Kiyonari, 2013; Declerck, Boone, & Kiyonari, 2010; Radke & de Bruijn, 2012). However, none of these three studies actually implements a true ingroup–outgroup game paradigm, although they draw inferences from single-player games including the dictator, ultimatum, and prisoner's dilemma games. We therefore believe their conclusions need to be interpreted cautiously when their results are compared to the nested social dilemma game. In the Radke and de Bruijn study (2012) subjects played a one-shot dictator game and a modified ultimatum game. The results suggest that OT decreases the adherence to fairness norms in social settings where others are likely to be *perceived* (herein lies the rub) as not belonging to one's ingroup. The authors interpret their results as not supporting the prosocial conception of OT, and they corroborate recent ideas that the effects of OT are more nuanced than assumed in the past. In the first Declerck et al. study (2010), participants received OT or a placebo and played two economic games: a coordination game (with strong incentives to cooperate) and a prisoner's dilemma (with weak cooperative incentives). Oxytocin enhanced cooperation only when social information was present, and this effect was significantly more pronounced in the coordination game. When social information was lacking, OT surprisingly decreased cooperation. In the second Declerck et al. study (2013), a one-shot prisoner's dilemma game design was used. The outcome of these mixed-motive games are known to be highly dependent on values and on social information that might reveal the partner's intent. Oxytocin and social information interact significantly to affect the behavior of individuals with a pro-self value orientation: following prior contact with the game partner, OT enhances cooperative behavior, whereas in anonymous conditions it exacerbates their intrinsic self-interested behavior. These effects of OT do not hold for individuals with a prosocial value orientation, whose cooperation levels appear to be more influenced by prior contact with the game partner.

F. Competitiveness

The gender gap in wages is an interesting observation in the labor market (Goldin, 1990). One behavioral interpretation has to do with gender difference in competitiveness. In an experimental setting (Gneezy, Leonard, & List, 2009; Niederle & Vesterlund, 2007), subjects were asked to perform simple arithmetic calculations with real monetary incentive. When asked to choose either a tournaments payment scheme or a piece-rate payment scheme, the majority of male subjects choose the tournaments scheme, whereas the majority of female subjects choose the piece-rate scheme.

The role of socialization in competitiveness has been recently examined by Gneezy and colleagues (Gneezy et al., 2009). They investigated gender-specific competitiveness in a patriarchal society, the Maasai in Tanzania, and a matrilineal society, the Khasi in India. Notably, among the Khasi, women chose the competitive environment more often than did men. As with findings in contemporary Western societies, Maasai men opt to compete at roughly twice the rate as do Maasai women. These findings underpin socialization as an important determinant of the observed gender difference in behavior, suggest that culture can trump genetic and hormonal influences, and highlight how culture may contribute to observed gender differences.

However, not all differences in ultimatum game behavior or other examples of revealed preferences are due to socialization. As shown in the papers by Chen et al. (Chen, Katuscak, & Ozdenoren, 2013) and by Pearson and Schipper (2013), hormonal factors indexed by menstrual cycle phase play a role in women's preferences. Regarding men, those who reject low offers ($5 out of $40) have significantly higher testosterone levels than those who accept low offers (Burnham, 2007). A within-subject repeated measures study found that men were 27 percent less generous toward strangers with money they controlled when their testosterone levels were artificially raised, compared to when they were on placebo (Zak et al., 2009).

Despite the growing literature documenting a significant role for sex hormones in decision making related to our sense of fairness, little is known about the underlying genetic mechanisms mediating these effects. Using a genetic association approach, we examined in a first study (Chew, Ebstein, & Zhong, 2011) the neurogenetic basis for gender difference in ultimatum game behavior. Using a Chinese and an Israeli sample, we genotyped participants for three well-characterized repeat polymorphisms of sex-hormone receptor genes: androgen receptor gene (AR), estrogen receptor alpha gene (ERα), and estrogen receptor beta gene (ERβ). Our findings were twofold. For the

Chinese sample, males who carried the AR short CAG repeat allele (which encodes a polyglutamine stretch, the length of which correlates inversely with androgen activity) stated higher minimal acceptable offers than did males who only carried the long repeat allele. On the other hand, females who carried the CA long repeat allele of ERβ (which is associated with less estrogen activity) stated higher minimal acceptable offers than did females who only carried the short repeat allele. Our findings for the Israeli sample replicated the role of ERβ among female subjects but not the role of AR for male subjects.

X. Parenting

In the past several years, significant insights have been gained regarding the neuroendocrinological and neurogenetic mechanisms underlying human parenting. In particular, the role of the OT–vasopressin and the dopaminergic neural pathways in these processes has been revealed. Studies mostly used a neurogenetic approach and genotyped subjects for the DRD4 receptor and OXTR and AVPR1a genes. Relevant to the current review are studies of parenting in a controlled laboratory setting or experimental sessions during home visits (Avinun, Ebstein, & Knafo, 2012; Avinun et al., 2011; Bakermans-Kranenburg, H., Pijlman, Mesman, & Juffer, 2008; Bakermans-Kranenburg & van Ijzendoorn, 2006; 2008; 2011; Bakermans-Kranenburg, Van, Caspers, & Philibert, 2011; Feldman, Gordon, & Zagoory-Sharon, 2011; Gervai, 2009; Kaitz et al., 2010; Knafo, Israel, & Ebstein, 2011; Lee et al., 2010; Luijk et al., 2011; Naber, van Ijzendoorn, Deschamps, van Engeland, & Bakermans-Kranenburg, 2010; Propper, Willoughby, Halpern, Carbone, & Cox, 2007; Sheese, Voelker, Rothbart, & Posner, 2007; Van Ijzendoorn & Bakermans-Kranenburg, 2006; van IJzendoorn, Bakermans-Kranenburg, & Mesman, 2008).

Additional evidence for a role of OT in parenting comes from the studies by Feldman and her colleagues (Feldman, Gordon, Schneiderman, Weisman, & Zagoory-Sharon, 2010; Gordon, Zagoory-Sharon, Leckman, & Feldman, 2010) who measured plasma OT levels in new fathers and mothers across the transition to parenthood in relation to maternal and paternal typical parenting behaviors. More recently, this group has added a neurogenetic perspective to their studies of parenting (Feldman et al., 2012).

Another notable study examined the role of OXTR and the influence of depressive symptoms in explaining differences in physiological reactivity to infant crying (Riem, Pieper, Out, Bakermans-Kranenburg, & van Ijzendoorn, 2011). Heart rate responses of healthy females without children were measured during the presentation of three episodes of infant cry sounds. Participants with the presumably more efficient variant of the oxytonergic system gene (OXTR GG) had more pronounced physiological reactivity to repeated cry sounds, except when they showed more symptoms of depression. This is the first study to suggest effects of OXTR genotype on physiological reactivity to infant crying. Depressive symptoms may, however, suppress the effect of the OXTR GG genotype. (For a general review of the role of OT in mother–infant relations, the reader is referred to a recent review by Galbally, Lewis, Ijzendoorn, and Permezel [2011].)

To summarize, laboratory-based studies of parenting, similar to laboratory-based studies of decision making, have gained considerable traction and are paving the way for a deeper understanding of the biological and especially genetic underpinnings of human parenting. Most of these studies are relatively small-scale, reflecting the constraining logistics of laboratory measures of parent–child interactions. Such studies are labor intensive and not easily scaled up to the numbers currently needed for a GWAS approach. Nevertheless, it might be considered that grants covering many participating investigators could generate the numbers required for high-throughput genotyping approaches.

XI. Political Arena

> Liberalism is trust of the people tempered by prudence; Conservatism is distrust of the people tempered by fear.
>
> – William E. Gladstone

There is considerable family resemblance in political attitudes (Alwin, Cohen, & Newcomb, 1991), which has generally been attributed to social transmission within families. However, considerable evidence also points to a genetic contribution to political attitudes (Eaves, Eysenck, & Martin, 1989), More recently, longitudinal and

extended pedigree studies further underscore the important role of genes in shaping political attitudes (Eaves & Hatemi, 2008; Hatemi et al., 2010). Family, twin, and adoption studies set the stage for searching for specific genes that contribute to political attitudes (Fowler, Baker, & Dawes, 2008*b*). To our knowledge, the first report identifying a specific gene with a political phenotype is by Fowler and colleagues (Dawes & Fowler, 2009; Fowler, Baker, & Dawes, 2008*a*; Fowler et al., 2008*b*; Fowler & Dawes, 2008; Settle, Dawes, Christakis, & Fowler, 2010). Using the National Longitudinal Study of Adolescent Health, Fowler et al. (Dawes & Fowler, 2009) showed that individuals with the A2 allele of the D_2 dopamine receptor gene were significantly more likely to identify themselves as a partisan (one holding party identification) than were those with the A1 allele. The baseline model shows that the A2 allele is significant, and the odds of an individual with one A2 allele being a partisan are 1.2 times greater than for someone with no A2 alleles, and the odds of an individual with two A2 alleles being partisan are 1.4 times greater than for someone with no A2 alleles. The A2 allele remains significant in the model even when SES measures and ORs are nearly identical. Furthermore, they find that this gene's association with partisanship also mediates an indirect association between the A2 allele and voter turnout. These results were the first to identify a specific gene that may be partly responsible for the tendency to join political groups, and they may help to explain correlations in parent and child partisanship and the persistence of partisan behavior over time.

Toward understanding how DRD2 may influence partisanship, the authors hypothesized that improved ability to form social attachments and/or improved cognitive function, both of which have been shown to be associated with the A2 allele, may increase the likelihood that an individual with the A2 allele will form and/or maintain an attachment with a political party.

In a second study, these authors examined a second DA receptor, DRD4 (Settle et al., 2010). They showed that among those who carry the 7R allele of the DRD4 gene, the number of friends a person had in adolescence was positively associated with liberal self- identification in early adulthood. Among those who did not carry the 7R allele, there was no relationship between number of friends and ideology. Moreover, the 7R allele was not directly associated with the reported number of friends, nor was it directly associated with ideology. Instead, it was the combination of this specific gene variant with a specific social environment that may have contributed to the development of a liberal political ideology.

Hatemi and colleagues carried out the first genome-wide study of political attitudes (Hatemi et al., 2011). This "linkage" study was carried out using microsatellite markers, which, it should be noted, provide a less dense coverage of the map than the usual GWAS SNP-based studies. Hence, their power to detect regions of small effect sizes was limited despite the large number of subjects (approximately 13,000 from about 2,700 families) examined. Subjects were of Caucasian ancestry and inventoried for political attitudes using a 50-item scale. Their results revealed three peaks with LOD scores of greater than 3.0, indicating genome-wide level linkage and one peak at "suggestive" linkage (greater than 2.5; Lander & Kruglyak, 1995). The four most significant QTLs accounted for between 9 and 12.9 percent of the total phenotypic variation on the Conservatism–Liberalism attitude factor scale.

These provisional linkage sites from the Hatemi et al. study explain a surprisingly relatively high percentage of the variance for this trait. Moreover, three regions reached genome-level significance, and a fourth region clocked in as "suggestive." At first glance, this phenotype might appear to be distant from the underlying biology. However, a closer look at political attitudes reveals something quite interesting. It is intriguing that ideology is impacted by fear, threat, and anxiety (Lupia & Menning, 2009). Oxley et al. (2008) found physiological differences in threat reaction in those individuals who held more conservative attitudes toward outgroup members, and Hatemi and colleagues (Hatemi, McDermott, Eaves, Kendler & Neale, 2013) found that individual differences in fear disposition were a significant predictor of political attitudes. Interestingly, the relationship between social fear and outgroup attitudes was largely a function of shared genes (Jost et al., 2007). Moreover, certain serotonergic markers are associated with political participation (Fowler & Dawes, 2008) and power seeking (Madsen, 1986), further strengthening the link between political attitudes and anxiety/neuroticism based on the role of 5-HT as a paramount neurotransmitter associated with withdrawal as opposed to approach behavior.

Taken together, these considerations suggest the notion that some political attitudes are driven by "motivated reasoning" (Westen, Blagov, Harenski, Kilts, & Hamann, 2006), with "hard" social issues perhaps reflecting "gut feelings" and largely conforming to Kahneman's system 1 reasoning. These kinds of attitudes are apparently closer to genes than are soft social issues and system 2 reasoning. Interestingly, some political science investigations are using imaging studies to advance a deeper understanding of the underlying cognitive and emotional processes

involved in political attitudes (Tingley, 2006).

We note that although the Hatemi study (Hatemi et al., 2011) observed several chromosomal regions that reached genome-wide significance levels (LOD score of more than 3.0) for political attitude, no such success was reported by the Benjamin study (Benjamin et al., 2012), which also examined political attitudes using a high-throughput SNP approach. The reasons for this discrepancy are at present unclear, but the relative success of the Hatemi study detracts somewhat from the argument put forward by Benjamin et al. that social phenotypes such as political or economic attitudes need tens of thousands of subjects to find genes contributing to these traits. It would be exciting if Hatemi could genotype his sample using a SNP platform.

XII. Conclusion

The take-home message from this review is that it is not only possible, but indeed eminently desirable, to measure individual and social decision making in the laboratory, especially when the goal of the research has a primarily genetic perspective. Laboratory-based decision-making paradigms are, we believe, the best phenotypes for molecular genetic association studies of social behavior. The choice of phenotype is critical to the success of GWAS, and identifying phenotypes that are closest to the underlying neurobiological structure is crucial. We suggest that employing phenotypes that are distant from any supporting biology are less likely to generate significant findings regardless of the number of subjects inventoried. Indeed, the recent failure of a GWAS of "educational attainment" and economic/political preferences is a case in point (Benjamin et al., 2012).

Often, the tradeoff in GWAS design is between pencil-and-paper questionnaire phenotypes that are relatively cheap to ascertain and laboratory-based paradigms from behavioral economics that are more costly both in time and money but that, we suggest, minimize measurement error and are reproducible across studies. Few, if any, GWAS have been reported for behavioral phenotypes, especially for nonclinical subjects, to judge which approach is more likely to capture significant associations between genes and decision making.

Indeed, we venture to suggest a litmus test of what constitutes a good nonclinical behavioral phenotype that is likely to generate significant GWAS results. We would simply ask whether the phenotype lends itself to fMRI studies. If so, then the phenotype is likely matching up with more basic neurobiology, and hence we suggest it is likely to successfully capture GWAS at a 5×10^{-8} level of significance. For example, risk attitude and social decision making have been modeled by behavioral economic paradigms in many imaging studies, suggesting that these games are indeed closely tapping into the underlying neural pathways. Moreover, imaging studies using behavioral economic paradigms are well suited to the addition of a genetic component, further tightening the link between biology and phenotype. Altogether, what we call "gutsy" phenotypes and "hard" social issues are more likely to have a narrower genetic base than more reflective system 2 reasoning and soft social issues.

A final word regarding the study base of GWAS of individual and social decision making is that we understand the convenience of leveraging existing survey studies that may have been ongoing for decades and have been genotyped for public health issues to extract information for GWAS of political and economic attitudes. Yet such studies are heterogeneous across a wide variety of demographic, socioeconomic, and cognitive variables. We believe that such heterogeneity, often unobserved, generates so much noise that the genetic signals are difficult if not impossible to detect. The alternative is to focus on study groups of homogenous student populations with a narrow age and ethnic background, which we suggest are much more promising to identify genes for social and individual decision making. Student populations of similar ethnic background should be characterized by a minimum signal-to-noise ratio compared to population samples and hence are the desirable target for first GWAS of decision making.

XIII. Future Directions

For future directions, we thought it would be informative to present some of our work-in-progress. We are located in the National University of Singapore, giving us potential access to a Singapore population of Chinese, Malay, Indian, and Caucasian. The overarching aim of our research is the molecular genetic architecture and biological basis of individual and social decision making. In our research, we chose behavioral economic paradigms implemented using a laboratory-based, incentivized design. We recruited only Han Chinese university students to

minimize population stratification in genetic studies. We have carried out initially three waves of subject recruitment. The first wave of subjects was done in Singapore, and we recruited approximately 1,150 Han Chinese students. We further recruited a replication sample of 660 Han Chinese students from Beijing University who have a similar genetic background to our core sample of Singaporean Han but who are characterized by somewhat different cultural/environmental exposures. We have recruited additional groups from Singapore and Beijing and now have approximately 3,400 subjects for GWAS.

Blood samples have been obtained from the first two waves of students and saliva samples for the second Singapore replication sample. For the first Singapore wave, the blood samples were taken so that DNA, RNA, and hormone levels could be ascertained. All subjects are genotyped using Illumina OmniExpress Bead Chips at the Genome Institute of Singapore in collaboration with Dr. C. C. Khor. Genome-wide genotyping data from 731,442 SNPs genome-wide were available. In addition to SNPs, we also undertook genotyping of a number of microsatellite and VNTR markers that are of considerable interest in behavioral genetics such as the DRD4 exon3 VNTR, DAT1, 5-HTTLPR, AVPR1a RS3, and MAOA.

Furthermore, we positioned ourselves to examine hormone levels (plasma OT, cortisol, and others) and RNA expression in 1,150 of these subjects. Additionally, we are undertaking epigenetic studies of peripheral DNA by examining methylation patterns for candidate genes, as well as overall methylation levels.

The first results from our ongoing study are encouraging. From the core decision-making tasks (risk and social), we observed several promising "hits" at p values from 10^{-7} to 10^{-10} including one finding, which we are now preparing for submission (on altruistic giving measured by the modified dictator game of Andreoni and Miller [2002], with our top SNP reaching significance levels of 6.87×10^{-10} and located in a biologically plausible gene). We are also testing our top hit candidate SNP in an imaging paradigm designed to further validate the role of this SNP in altruistic giving under MRI.

We also have two papers (one accepted, one under review) related to plasma OT levels. The accepted publication describes a significant U-shaped relationship between plasma OT levels and behavior in the trust game, such that the extremes of plasma OT levels are associated with trust behavior (Zhong, Monakhov, et al., 2012). In the second paper, which is in preparation (Zhang et al., in preparation), we observe a relationship between plasma OT levels and an impulse-purchasing scale (Zhang et al., in preparation). Our results indicate a significant interaction between plasma OT levels, OXTR genotype, and gender in predicting scores on the impulse-purchasing scale. Significant findings between OXTR SNPs and plasma OT levels with a social phenotype (mother–infant interactions) have been recently reported (Feldman et al., 2012). Finally, we have a work in progress in which we observe a relationship between the DRD4 gene and altruism measured in the dictator game, but the association is contingent on religious affiliation. This study is the first to examine the interaction effect of gene and culture using incentivized economic games, suggesting that both situational factors and cultural factors could be interacting with a gene to shape human behavior.

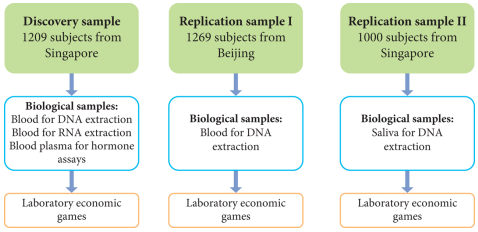

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Figure 3 . Work flow of B^{2}ESS (http://b2ess.nus.edu.sg/) GWAS study of human financial decision making.

This description of our group's activities needs to be taken with caution since our results have yet to be vetted by peer review; they should be considered provisional at best. Nevertheless, we bring them to the attention of the reader to underscore how we have built our study to maximize the information we can gain from our study population. We have both positioned ourselves to carry out one of the first GWAS on approximately 3,400 student subjects from a homogenous ethnic group but also to use a candidate gene and biomarker approach. We have yet to begin analyzing our epigenetic and expression studies. We are optimistic that a study in depth of a few thousand subjects is a more productive strategy than studying tens of thousands of subjects superficially (see

Figure 3).

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