Genes, Cognition, and Social Behavior:
Next Steps for Foundations and Researchers

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Final Version: January 2011

Funded by the National Science Foundation's Political Science Program (SBE -1037831)

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Executive Summary

Social behavioral research has improved the quality of life for millions of people. It influences and makes more efficient actions ranging from the treatment of individual ailments to the development complex human institutions. As this research evolves, it is increasingly apparent that a greater understanding of social behavior can come from dynamic new inquiries that integrate leading-edge social science with practices and content from research on genes and brain cells. There is a growing belief that our ability to address many critical social challenges can be transformed by greater knowledge of social behavior's biological foundations.

At present, few biologists are aware of best practices and relevant concepts in social behavioral research. Moreover, few social scientists have more than a passing familiarity with biological concepts and practices. As a result, the existing knowledge base of how to conduct biologically-informed social behavioral research is minimal.

Such tendencies will not quickly self-correct. In addition to career pressures that dissuade innovative younger scholars from interdisciplinary research, there are material barriers to entry for scholars who otherwise would advance biologically-informed social behavioral research. Even in our Internet age, data is scarce. While there are interesting social behavioral datasets and innovative data being collected on genes and cognition, there are relatively few datasets where both kinds of data are collected simultaneously. Hence, even basic biologically-informed social behavioral hypotheses are difficult or impossible for researchers to evaluate.

The issue before us is whether and how to entities such as NSF should support social scientific research that builds from increasingly credible biological foundations.

This report seeks to inform funding decisions about next steps in scientific research on genes, cognition, and social behavior. Its conclusions are derived from a workshop and associated white papers that were developed in the spring and summer of 2010 and presented to NSF in June of that year.

The workshop's main objective was *to specify how fundable research on genetics, cognition and social behavior will generate transformative scientific practices, scholarly infrastructure, and widely relevant findings of high social value*. It and the white papers described in this report provide rigorous and broad expertise about the current state and near-future of research agendas associated with genes, brains, and social behavior.

The report pays particular attention *relative investment returns*. The key question is not whether new investments in research on genes, cognition, and social behavior can generate positive scientific and social impacts, but whether the likely returns on these investments are greater or less than those that could be earned were individual scholars, research institutions, and the federal government to invest their funds elsewhere.

This report's main conclusion is that *there exist exciting opportunities to support transformative biologically-informed social science research*. While this conclusion has a positive-valence, it makes no attempt to sugar-coat the challenges. There are multiple inferential, intellectual, and cultural challenges inherent in such pursuits. Chief amongst these challenges is an appetite amongst some in the media and the public for dramatic claims about genetic determinants of particular behaviors. This appetite can skew researcher incentives away from credible research agendas and fuel public misunderstanding of genetics, cognition, and science in general. With such challenges in

mind, this report identifies a number of fundable activities that can provide substantial investment returns in the next five to seven years.

One emphasis is on education-oriented strategies for advancing biologically-informed social behavioral research. Workshop participants argued that a transformative and effective *biologically-informed social behavioral research community cannot exist without clusters of researchers who have knowledge of both biological and social scientific research*. In this light, workshop participants expressed support for *educational programs that would expand the number of social scientists who have expertise in relevant biological areas*. While the participants also discussed providing social science training to natural scientists, we believed that there would be greater demand for such training from social scientists and that the value added to providing such opportunities to social scientists was substantially higher than other alternatives.

Data availability was another point of emphasis. Participants agreed that there are very few data sets upon which a credible and broadly-effective biologically-informed social science can currently be built. Workshop participants argued that *exploring the social behavior of participants in existing health studies (by adding a questionnaire) would be most effective and efficient* -- compared to genotyping respondents in extant social science databases or creating entirely new datasets. Participants also concluded that greater emphasis on animal studies would generate higher investment returns than attempting to tack biological content on to existing social behavioral data collections. We saw potential value in getting social and natural scientists to work together to identify common genomic and/or neural substrates for social behavior across species.

At the same time, participants concluded that the value of new datasets depends on the inferential abilities of scholarly communities. In other words, robust discoveries come not just from having researchers who can propagate new findings, but also from having sufficiently distributed expertise in relevant research methods to ensure that robust findings can be distinguished from more speculative fare in peer review processes.

Given the minimal existing overlap between social behavioral, genetic, and cognitive research traditions, it appeared to all participants that *a necessary step in developing a credible, legitimate, and effective biologically-informed social behavioral research community is to provide opportunities for sustained interaction amongst social and natural scientists*. Workshop participants agreed that lack of a common language and the absence of social networks amongst social and natural scientists is an impediment to the development of biologically-informed social behavioral research.

Another point of emphasis was to voice support for mechanisms that will allow individual social behavioral researchers to immerse in relevant biological science environments and for programs that would allow groups of social and natural scientists to convene in rigorous and sustained ways. Such endeavors can take many forms: post-docs, multi-year training arrangements, or calls for problem-oriented grant proposals that would require detailed and credible plans for teamwork amongst social and natural scientists.

Our main conclusion is that *there exist exciting opportunities to support transformative biologically-informed social science research*. Throughout this report, we identify a number of areas where greater communication and collaboration amongst social and natural scientists is very likely to produce important new discoveries about

social behavior in the near-future. Because there are multiple opportunities of this kind, we also attempt to shed light on near-future opportunities where the greatest investment returns are possible.

While many people offer opinions about the causes of human social behavior, it is critical that *scientific inquiries* into such matters be supported. Societies that have the ability to confront important social hypotheses with credible evidence and rigorous evaluative procedures gain the ability to develop and maintain increasingly complex social institutions. Compared to societies where such inquiries are not permitted or supported, societies that commit to rigorous evaluation of critical hypotheses are better able to defend themselves against many threats and can provide their citizens with opportunities to participate in, and benefit from, many valuable forms of social coordination. The effective and efficient functioning of numerous aspects of modern social infrastructure depends on the insights that science can offer. It is with such goals in mind that we present this report to you. We appreciate the opportunity that NSF, and its Political Science program, have given us to explore how next steps in the study of genes, cognition, and social behavior can provide new scientific insights of significant social value.

I. Introduction[1]

Scientific research on how people feel, think, and act fuels human progress. Discoveries from the social sciences inform, and often change, how well countries, businesses, communities and individuals perform. In many ways, research on social behavior has improved the quality of life for millions of people.

For decades, NSF has taken a lead in supporting social behavioral research. As these kinds of inquiries progress and become more influential, there is increasing interest in learning more about biological foundations of social behaviors. For some researchers, this interest has led them to ask questions about how social behaviors are linked to the functioning of the mind and brain. For other scholars, it has prompted questions about how social behavior relates to the functioning of genes and genomes.

The existing knowledge base of how to conduct biologically-informed social behavioral research is minimal. Depending on the social behavioral subject area, there is little to no interaction between social scientists and the natural scientists who could help them better explain how humans think, feel, and act. As a result, few social scientists are very knowledgeable about potentially helpful biological concepts. At the same time, few

[1] We are grateful for assistance and advice received during the preparation of this report and the organization of the associated workshop. We thank Carol Mershon, Brian Humes, and Frank Scioli of NSF and Jim Granato of the University of Houston for advice offered at the initial stages of this project. We thank David Howell, Barbara Opal, Laurie Winslow, and Monique Willis of the University of Michigan's Center for Political Studies and Alison Smith of NSF for assistance in organizing the workshop. We thank Christina Farhart for helping us to document the workshop proceedings. We thank the many NSF program directors and staff who attended the workshop for their many questions and contributions. We offer particular thanks to NSF Assistant Director, Directorate for Social, Behavioral & Economic Sciences Myron Gutmann for his support and participation in the workshop. We thank Logan Casey, John Hibbing, Rose McDermott, Spencer Piston, and Timothy J. Ryan, Allan Stam for commenting on initial drafts of the report. In acknowledging this assistance, please note that the principal investigator remains responsible for the content of this report.

biologists have more than a passing familiarity with social scientific concepts to which their work could be relevant.

Today, many ambitious researchers, many of whom are just starting their research careers, are willing to commit substantial effort to examining the extent to which people are: biologically predisposed to have certain socially relevant feelings, process social information in particular ways, or take certain socially relevant actions. Such research has the potential to change our nation's understanding of how to improve many aspects of the human condition. At present, however, the opportunities available to ambitious researchers for pursuing such work in a serious manner are few.

Barriers to entry for scholars who want to pursue biologically-informed social behavioral research are often prohibitive. Consider, for example, the paucity of relevant data. There are few efforts to collect data that biologically-informed social behavioral researchers can leverage for potentially transformative insights. While new and exciting datasets on genetic, cognitive, and social behavioral phenomena are emerging, datasets that allow simultaneous analysis of social and biological phenomena remain rare. Moreover, of the few "integrated" datasets that do exist, many are behind firewalls or subject to proprietary arrangements that make them inaccessible to the broader scientific community. Other such datasets are, from a social behavioral perspective, too limited to allow credible evaluations of even the most rudimentary behavioral hypotheses.

Hence, we stand at a crossroads. The issue before us is whether and how to support social scientific research that builds from increasingly credible biological foundations. One option is to hope that such research evolves organically through the continuation of existing scholarly norms and practices. Another option is to actively

intervene by creating new opportunities. This report focuses on the wisdom of such interventions.

Our focal question is:

> *When are studies of social behavior that are informed by biological research on topics such as genetics and brain function of greater social and scientific value than studies of the same topics that ignore such factors?*

With this question in mind, we seek to inform funding decisions about next steps in scientific research on genes, cognition, and social behavior. We discuss not only the extent to which existing practices in research on genes, cognition, and social behavior provide scientific and social benefit, but also seek specific circumstances in which new investments of labor and capital are a necessary condition for enhancing scientific merit and allowing our nation to realize more tangible research-related benefits.

Our primary source for this report is a workshop that was held at the National Science Foundation on June 28, 2010. The workshop's main objective was *to specify how fundable research on genetics, cognition and social behavior will generate transformative scientific practices, scholarly infrastructure, and widely relevant findings of high social value*.

The workshop produced many ideas about how the nation's scientists and research institutions can use new inquiries into relationships amongst genes, cognition, and social behavior as a means for producing robust scientific findings that are of great value to the nation.

Our main conclusion is that *there exist exciting opportunities to support transformative biologically-informed social science research*. We identify a number of areas where greater communication and collaboration amongst social and natural

scientists is very likely to produce important new discoveries about social behavior in the near-future.

The report continues as follows.

In Section 2, we present the framework that we used in organizing the workshop, and in writing this report, to evaluate various proposals for how best to achieve the objectives listed above. Because there are multiple potential ways to move forward, and limited resources, an important element of our approach is our focus on *relative investment returns*. Hence, the key question is not whether new investments in research on genes, cognition, and social behavior can generate positive scientific and social impacts, but whether the likely returns on these investments are greater or less than those that could be earned were individual scholars, research institutions, and the federal government to invest their funds elsewhere.

In Section 3, we convey the workshop's main findings. With relative returns in mind, we describe promising opportunities in three areas: *new collaborative opportunities*, *new data collections*, and *new educational programs*.

Following the main body of this report (Sections 1-3) are materials that were critical to its development: *a series of white papers*. Scholars from nine different universities, and almost as many academic disciplines, contributed white papers. The disciplines included: genetics, cognitive and neurosciences, decision making and risk analysis, economics, political science, and sociology. These contributors include senior scholars in genetic, cognitive, or social behavioral fields as well as younger scholars who are conducting innovative work that is pertinent to the workshop themes and that cross traditional disciplinary boundaries. As individuals, these contributors have developed

successful research agendas. Collectively, their reports provide rigorous and broad expertise about the current state and near-future of research agendas associated with genes, brains, and social behavior.

A concluding section provides closing remarks and additional details about the workshop. Whether your main interest is in funding biologically-informed social behavioral research, supporting it in other ways, or conducting it yourself, we hope that you find this report helps you to make more effective decisions about the future of social behavioral research.

2. Our Approach

It is easy to imagine the potential benefits of a biologically-enriched social science. Many biological phenomena are sufficiently well defined and suitable for observation. Some of these phenomena have the potential to generate both more precise and more general inferences about how humans feel, think and act. Such knowledge can give us greater insight into the human condition. It also has the potential to inform public policy. It can help us understand the conditions under which certain types of medical, economic, or other social interventions can have desired effects.

At the same time, such work presents important challenges. People and institutions that are considering investing in biologically-informed social behavioral research will benefit by keeping these challenges in mind.

A common challenge entails maintaining the legitimacy and credibility of the science despite strong social pressures to do otherwise. For example, people who seek fame can find it by claiming to identify a neuron or gene that determines a socially-relevant behavior. We have all seen and heard many such claims. In a quest for attention, certain elements of the news media find such claims very appealing and can broadcast them broadly, loudly, and quickly.

The problem with many widely-publicized claims about biological origins of social behaviors is that they are difficult or impossible to replicate – and often reflect poor research practices. The processes linking neurons and genes to observable behaviors are more complex than the typical news release suggests. Hence, a challenge for foundations, individuals, and institutions that are considering next steps in research on

genes, cognition, and social behavior is to make investments that can provide socially valuable insights while also being legitimate and credible from a scientific perspective.

Procedural transparency and rigor are means for managing such challenges. Research that is procedurally transparent facilitates replication. Replication, in turn, confers legitimacy when it clarifies how findings were uncovered.

Similarly, research that is procedurally rigorous can clarify the extent to which findings are – or are not – dependent on specific assumptions. Such clarity, in turn, confers credibility when it gives audiences reasons to believe that the finding is not spurious. Given our emphasis on helping potential investors in research on genes, cognition, and social behavior evaluate returns from various investments, and our belief that producing such returns requires science that is seen as legitimate and credible, we want to privilege ideas that promote procedural transparency and rigor.

In that spirit, we developed a framework for evaluating the many proposals that people might bring forward to advance social science through greater interaction with natural scientists and relevant biological phenomena. The framework begins with some basic definitions.

- By *genes*, we mean genetic materials, their essential properties, and their relationships to human and environmental phenomena.

- By *cognition*, we mean the relationship between brain, body, and world with a special interest in how those relationships affect socially-relevant perceptions and actions. "Cognition" is meant to cover activities studied in the domains of cognitive science, the neurosciences and in various subfields of psychology. It is not meant to exclude studies of emotional response, which we treat here as products of cognitive processes.

- By *social behavior*, we refer to a range of activities that affect and reflect how individuals react to their environments, with a specific emphasis on reactions to other people and to human institutions.

We now turn to a few basic assumptions that informed the workshop and that inform this report.

First, as NSF is a plausible funding source for social behavioral research that incorporates biological phenomena, we define investment returns with respect to NSF's mission. This mission, as determined at the time of the foundation's creation, is "to promote the progress of science; to advance the national health, prosperity, and welfare; to secure the national defense…" Since that time, NSF has sought to achieve this mission by soliciting, evaluating, and funding proposals for scientific activity in a wide range of research domains. To this end, NSF selects from amongst the many types of scientific inquiry it can fund, and from amongst the many proposals that it receives, by evaluating both a proposal's intellectual merit (e.g., the extent to which it advances science) as well as its broader impacts (e.g., how well do activities advance education and enhance social welfare)**.** While various individual and institutional investors in scientific research have diverse objectives, we proceed on the assumption that for many readers of this report, the NSF criteria are highly relevant, if not critical.

Second, a key question is not simply whether investments in genes, cognition, and social behavior can generate positive scientific and social impacts, but whether the likely returns on investments in such research are *greater or less than those that could be earned were individual scholars, research institutions, and the federal government to invest their funds elsewhere*. NSF, as well as other individuals or entities who have the opportunity to invest intellectual resources or capital into new scientific ventures, will always have a wide range of potential uses for extraordinarily scarce resources.

Hence, with these definitions and assumptions in mind, this report focuses on providing information that can help potential investors in research on genes, cognition, and social behavior evaluate returns with respect to NSF's criteria.

To this end, NSF's stated "outcome goal for discovery" is as follows:

- foster research that will advance the frontier of knowledge,
- emphasizing areas of greatest opportunity and potential benefit and
- establishing the nation as a global leader in fundamental and transformational science and engineering.

For individuals and entities that have analogous objectives, it would not be sufficient for this report to produce an unfocused conversation on the possible returns on investments in vaguely stated notions of what genetics, cognition, and politics research could be. Our objective is to *specify how fundable research on genes, cognition and social behavior will generate transformative scientific practices, infrastructure, and findings of extraordinarily high social value*.

While many people would agree that transformative practices and high value outcomes are worth pursuing, a broad interdisciplinary conversation about such matters may yield disagreements about which practices are "transformative" and findings "valuable." In the remainder of this section, we propose a procedural means for managing such conflicts. Our proposal is based on two propositions. The first proposition is that for the purpose of this report, the optimal time horizon for evaluating returns is the "near future" -- as it is the time horizon on which NSF can have the greatest and most credible impact today. The second proposition is that success in the domain of biologically-informed social behavioral research requires a kind of communication that is currently uncommon. Successful interdisciplinary collaboration requires vigorous and sustained interaction amongst social and natural scientists who commit to non-trivial

understandings of one another's epistemologies and to making shared progress towards concrete research objectives. After we make this argument, we conclude this section with a summarizing comment about our approach.

2.A. The Time Horizon is the Near-Future

As is the case with any new inferential method that has multidisciplinary roots (with at least some roots being unfamiliar to most of the discipline to which the work is speaking), interdisciplinary implications, and a requirement of specialized skills not possessed by most of the extant research community, there are substantial debates about the credibility and value of the new approach.

What can we learn from these debates? In asking this question, it is important to separate aspects of the debate that represent little more than self-interest from substantive questions about the validity, reliability, and added value of new findings. Self-interest in such contexts often manifests as broad statements about the general inapplicability or irrelevance of the methods being discussed. Self-interest leads debate participants to convince themselves of the superiority of new methods despite a lack of concrete contributions to broader inquiries. Self interest also manifests as broad statements about the inapplicability or irrelevance of the old method. While statements of each kind may contain some truth, they are often too broad to evaluate rigorously. Constructive conversations, on the other hand, identify specific conditions under which increased attention to genetic and cognitive phenomena are (and are not) likely to produce concrete scientific advances of high social value.

We proceed on the assumption that constructive conversations can be accomplished by focusing on specific research accomplishments that are achievable in

the near-future (i.e., funded and executed in the next five to ten years) rather than attending to less reliable speculations about distant futures. The near-future focus leads us to privilege present experience as a credible evidentiary basis for evaluating the kinds of "next steps" that are not only plausible to accomplish within the next five years but also very likely to provide high-value outcomes.

One might ask why not take a longer view and ask grander questions? One answer is that we did not seek to silence such suggestions in the course of this report's development. However, given that the main motivation of this workshop entails providing actionable suggestions, we directed our efforts towards clarifying what is possible to achieve in the near-future. We are interested in learning about new and innovative approaches that are plausible given existing knowledge and that leverage the diverse (but not yet integrated) insights and research practices of geneticists, cognitive scientists of all stripes, and social scientists who are interested in developing rigorous and reliable explanations of human social behavior. In other words, we are most interested in transforming science and society by clarifying new paths from present activities to concrete outcomes, rather than imagining paths from future efforts to unknowable results.

2.B. Success Requires Communication

While striving for interdisciplinary and biologically-informed social behavioral research may seem uncontroversial, maintaining procedural transparency and rigor in such circumstances can be difficult. Scientific findings emerge from paradigms – distinct ways of knowing – that vary from discipline to discipline. Because these paradigms imply diverse evidentiary and inferential rules, findings made by scientists in one discipline are not always directly portable to another discipline. A neuroscientist's

conclusions, for example, are derived from assumptions (some of which are explicit and others of which are implicit in normal neuroscientific practices). When a social scientist seeks to import a neuroscientist's conclusions into their work, the validity of the import attempt depends on the extent to which the neuroscientist's assumptions are valid in the social scientist's domain of study.

Since a biologically-informed social science requires the cooperation, or active participation, of participants from multiple scientific disciplines, such endeavors' legitimacy depends on the extent to which they are informed by multiple scientific knowledge bases. If, for example, a program at NSF were to fund research on politics and genetics that built from inferential or procedural foundations that have already been rigorously evaluated and rejected in other fields, then that program would likely find it difficult or impossible to build supportive coalitions with other programs.

Hence, researchers or organizations that seek to convince others of the likely positive returns on new investments in research on genes, cognition, and social behavior, must be able to:

- articulate distinct attributes of social contexts that make biologically-informed procedures potential sources of new inferential value, and/or
- argue that procedures or ideas that have been rejected elsewhere are, in fact, appropriate for new areas of study because of the domain's distinct attributes.

Such considerations can also be particularly helpful in developing criteria and objectives for "co-review" procedures. In other words, specifying the kinds of research practices that are, and are not, capable of rendering valid and reliable findings about genes, cognition, and social behavior, as well as the subset of those activities that are capable of producing high-value outcomes, can form the basis by which potential

investors from currently distinct scientific disciplines can formulate credible proposals for new investments.

2.C. Concluding Remarks about Our Objectives

Given our desire to help individuals and institutions that are considering investing labor and capital into genetic and/or cognitive-based inquiries into social behavior, we devote substantial attention to questions of relative investment returns. Specifically, under what conditions is it likely that investments in research on genes, cognition, and social behavior will contribute more to helping individuals or institutions achieve high-value scientific goals than other investments they could make…

In political science?

In the social and behavioral sciences generally?

In research on genetics generally?

In research on cognition generally?

The strongest arguments for funding will rigorously answer these questions with respect to the near-future (so that extant evidence is relevant) and with respect to a broad knowledge base (so that natural science and social science participants see the venture as legitimate and worthy of support).

In recognition of this report's funding source, we will pay special attention to scientific endeavors whose implications speak directly to the Political Science program's areas of interest. But such attention does not preclude broader inquiries. Many of the most important ideas from the natural sciences, for example, can impact human life only if public sector actors react in certain ways. As noted science historian Charles C. Gillispie (1998) pointed out:

> Science is anything but apolitical in its application, practice and very possibility. What else but politics decided the fate of the Superconducting Supercollider, which might have fortified the laws of physics?

In sum, this report is designed to spark and guide near-future decisions about whether and how to support research on the genetic and/or cognitive bases of social behaviors. To this end, we asked workshop participants to discuss how to reconcile current theoretical, methodological, and empirical controversies about the interplay of genetic, cognitive, and environmental influences on these behaviors. With greater clarity on such issues, we hope that the report will help potential investors identify the most fruitful projects to support.

3. Findings

We now report on specific proposals and evaluations that emerged from the workshop. We began the proceedings with a reference to advances in science and technology that are dramatically changing the costs of observing biological phenomena such as brain activity and genomes. The decreasing cost of such data and the prospect of increasing opportunity for social scientists to collect or use such data would seem to be boons to the development of a biologically-informed social science. These advances, however, may come with costs other than monetary. Hence procedural transparency and rigor is useful. For biologically informed social behavioral research to advance and be viewed as legitimate, attention must be paid to the methods by which such data are being produced. To see why such attention is needed consider three examples.

For the first example, consider some implications of dramatic changes in the costs of sequencing a human genome. The genome originally sequenced by the International Human Genome Sequencing Consortium took 13 years to complete and cost $3 billion. *The Economist* ("Biology 2.0", June 19, 2010) reports that a company, Illumina, of San Diego, uses the latest sequencers to read a human genome in eight days at a cost of about $10,000. *The Economist* also reports that a firm called Pacific Biosciences, of Menlo Park, has a technology that can read genomes from single DNA molecules. The firm's researchers project that in three years' time their technology will map a human genome in 15 minutes and for a cost of less than $1,000.

On many levels, these are momentous advances. But at what cost do they come? It is important to know that the technologies and algorithms used to reduce the time and money required for genome sequencing are based on assumptions about underlying

biological phenomena. Some of these assumptions are controversial. Others are just wrong. These attributes of genomes sequenced quickly and on-the-cheap can be consequential for scientific work. The "price" paid for increasing speed and decreasing cost is a loss of information about properties of the genome that could prove very important. For example, genetic material that even a decade ago was derisively labeled "junk DNA" has subsequently been discovered to be critically important to genetic functioning. At present, it is far from obvious that the simplifications inherent in any given firm's sequencing technology are not treating as "junk" biological phenomena that may prove critical to other scholarly endeavors as our understanding evolves.

This situation provides an initial example of a circumstance where social and natural scientists working together can generate new research findings that all involved can view as legitimate. Foundations, and other people who can influence researcher decisions, can encourage (or even require) social scientists who integrate sequenced data into their research to include on their research teams geneticists, statisticians, or programmers who can clarify the kinds of inferences that are – and are not -- valid to draw from such data.

For the second example, consider a set of recent findings about genes that may not be as well known to social scientists. The findings pertain to the causal link between genes and behaviors. Specifically, the findings show that causation can go in more than one direction. Genes can not only affect behavior, they can be affected by it.

An increasing number of studies show that genes can be turned on and off by environmental stimuli. Consider for example that maternal licking has been shown to correlate with the activation and deactivation of genes in rats (Weaver et al. 2004).

Similar effects are observed in monkeys that were peer raised as opposed to having been raised maternally (Suomi 2003). Hence, attempts to draw claims about how genes influence behavior must find a way to manage the fact that behaviors can affect the activation of genes. Foundations and other people who can influence researcher decisions can encourage (or even require) social scientists who want to explain social behaviors as a function of genes to include on their research teams geneticists, statisticians, or programmers who can clarify the kinds of inferences that are – and are not -- valid to draw given the best available information about genes.

Our third example pertains to attempts to advance social behavioral research with the use of fMRI data. Workshop participants expressed dismay at many fMRI-based behavioral inferences that have found their way into the popular press. Debates about such claims now circulate broadly. Many such debates focus on lapses in procedural transparency and rigor that often accompany such claims (see, e.g., Abbott (2009) "Brain Imaging Studies Under Fire: Social Neuroscientists Criticized for Exaggerating Links between Brain Activity and Emotions." *Nature* 457: 245). Social scientists who are interested in using such data to explain higher order behaviors have a substantial incentive to become informed about, or to collaborate with, scholars who understand what properties such brain-based data do (and do not) have. Such collaborations can help scholars who want to advance social behavioral research better understand the kinds of inferences that are – and are not – valid to draw.

Biologically-informed social behavioral research holds great promise and also entails important challenges. With such promises and challenges in mind, our question becomes, *when are studies of social behavior that are informed by biological research on*

topics such as genetics and brain function of greater social and scientific value than studies of the same topics that ignore such factors? To answer this question in a way that is actionable for NSF and other interest parties, we used the workshop to *specify how fundable research on genes, cognition and politics will generate transformative scientific practices, effective infrastructure, and robust findings of extraordinarily high social value*.

Our findings fall into three topical categories.

a. Biologically-Informed Social Science Requires Greater Education About Biological Concepts and the Potential Relevance to Social Behavior

b. Biologically-Informed Social Behavioral Research Needs More Data and Better Inferential Standards

c. Biologically Informed Social Behavioral Research Needs Serious and Sustained Collaborations Between Social Scientists and Natural Scientists

Each type of endeavor shares the property that they provide a means for managing the kinds of challenges that we have articulated in previous sections and in the three examples just described. These endeavors also share the property that they are unlikely to happen without significant external support. In the remainder of this section, we will evaluate specific ideas that were presented in each of the three categories. We will use the workshop's deliberations to comment on the extent to which each of these ideas is capable of generating transformative scientific practices, infrastructure, and findings of extraordinarily high social value in the near-future.

3.A. A Biologically-Informed Social Science Requires Greater Education About Biological Concepts and the Potential Relevance to Social Behavior

Our discussion of education-oriented strategies for advancing biologically-informed social behavioral research focused on two distinct audiences.

The first audience was scientists themselves. Some workshop participants argued that *biologically-informed social behavioral research cannot exist without researchers who have knowledge of both biological and social scientific research*. From the genetics perspective, for example, few social scientists have the background necessary to conduct research that geneticists would find legitimate. Workshop participants also opined that there are even fewer geneticists with the background necessary to conduct credible social behavioral research.

The second audience was the general public, including policymakers. Workshop participants cited multiple instances where the public's understanding of social behavior's biological foundations was incorrect or, at best, outdated. They also saw how such misunderstandings could lead governments to adopt suboptimal programs.

This section conveys the workshop's views about how NSF and other interested parties could most effectively achieve desired educational outcomes with these respective audiences.

3.A.1. Educating Scientists

On several occasions during the workshop, participants argued that biologically-informed social-behavioral research is viable only to the extent that participating natural and social scientists understand enough about one another's knowledge bases and epistemologies. A common belief amongst workshop participants is that few social scientists are fluent in such matters as they pertain to the topic of genetics. While a greater number of social scientists, particularly in psychology and related subfields of the other social sciences, have some fluency in the domain of cognition, the distribution of such knowledge remains quite thin. Workshop participants expressed support for

educational programs that would expand the number of social scientists who have expertise in relevant biological areas.

Currently, there are few social scientists with the necessary background to work in genetics and even fewer geneticists with the necessary background to do work in the social sciences. Most of the participants agreed that this would likely continue to be the case without encouragement from NSF or analogous sources.

All participants agreed that the barriers for any scholar to seek such expertise were considerable. Participants with experience in biology and genetics said that it would be extremely difficult for a scientist to leave the field for very long to learn another discipline. Participants with social scientific backgrounds also noted career risks inherent in attempting to gain expertise in another field. While research communities in fields such as neuroeconomics and neuropolitics have emerged, there have not been parallel movements on the genetics side. Without incentives to pursue such expertise and support for those who choose to do so, participants thought that a sizeable community of genetically-informed social behavioral researchers was unlikely to emerge.

Workshop participants also expressed the opinion that social scientists would be more interested in learning genetics than the other way around. Participants argued that the questions geneticists tend to study do not require information about social behavior to be seen as legitimate. Geneticists to whom we spoke had a hard time seeing direct applicability of social scientific concepts to "hot" topics in their field. On the other hand, social scientists who want to provide transformative and robust accounts of the causes of important social, economic, or political behaviors may have an easier time seeing the potential benefits of learning more about genes or cognition.

Reinforcing this asymmetry is that the amount of funding available to conduct biological research is far greater than the amount of funding available for social science. So where an enterprising social scientist may gain access to deeper and broader revenue streams by integrating biological phenomena into her research, the same would not likely be true for a biologist who was considering branching out into the social sciences. Hence, participants agreed that the near-term investment returns from *efforts to educate scientists would likely be higher from educating social scientists about biological phenomena* rather than the other way around.

While there was broad consensus that the training efforts ought to focus on social scientists, the participants do not agree on the level of expertise that social scientists need to gain. Some participants argued that no expertise is strictly necessary. Instead, social scientists can collaborate with geneticists to work on biology-influenced social science and neither needs to know the science of the other. Others argued that a few weeks of training would allow a social scientist to communicate with sufficient effectiveness that they could begin to do some rudimentary work with geneticists.

The majority view was that legitimate biologically-informed social behavioral research will require a network of researchers who have a strong working knowledge of both fields. Such researchers ought to be able to speak the language of both disciplines and do the lab work required in both.

Workshop participants discussed three types of audiences to which such programs could be aimed: graduate students, post docs, and experienced scholars.

Funding for graduate students can create a new crop of interdisciplinary scholars. In the current academic environment, it is both difficult and costly for social science

graduate students to obtain any training in genetics. While there are more opportunities for training in cognition, particularly in disciplines such as psychology and subfields such as behavioral economics and political psychology, they are still quite limited in number. Workshop participants believe that many social science graduate students are interested in pursuing such opportunities.

A potential drawback of funding programs that support graduate students has to do with timing and risk. Funding this type of program is unlikely to have a measurable near-future impact. Creating a group of biologically-informed social behavioral graduate students could have significant impact five or ten years in the future as these scholars learn how to cultivate effective research agendas. But many graduate students who are now interested in learning more about genes and cognition may, for professional or personal reasons, choose to pursue more conventional research agendas (i.e., without genes or cognition).

Workshop participants also debated how much exposure would be sufficient for programs aimed at graduate students. A two-week workshop in genetics, for example, is no substitute for years of dedicated graduate training. That said, a number of workshop participants who had also participated in such endeavors when they were younger reported that even these limited exposures provide important insights into questions and problems being researched in by other scientists. Such exposure can pique graduate students' interests and inform their research agendas for decades. Several participants argued that similar workshops helped launch the field of cognitive neuroscience by sparking early interest in graduate students who became part of the rising generation of cognitive neuroscientists. Aside from influencing research agendas, summer workshops

devoted to graduate student education can also help the students establish a common frame of reference with their peers who study genes or cognition and enable them to focus on the kinds of questions that make sense to ask from a biological perspective.

Funding for post docs was also discussed. Several workshop participants argued that a summer workshop or several weeks of classes were not sufficient to enable researchers to perform independent lab work in genetics. Participants then debated the type and length of exposure that would allow a social scientist to do this kind of work. Some participants argued that two years attached to a research lab were necessary to gain the depth of experience such work would require. Others argued that one year would be enough to get the students started and that funding students for one year would allow NSF or analogous funding sources to fund twice as many. Participants argued that funding greater numbers of post docs for shorter periods would allow the NSF to "diversify its portfolio and spread its risk," and would increase the odds of a positive average investment return. Others argued that NSF need not decide between the two methods, but instead choose a hybrid of the two, providing funding for one year post docs and extending them to two years based on need and demonstrated results.

Workshop participants also discussed educational endeavors that were aimed at scholars regardless of age. Several workshop participants suggested that it would be most helpful to provide funding that allowed students and scholars at different stages in their careers access to the resources that would help them gain the necessary skills to perform this work. Several options were discussed, with some participants advocating for split funding wherein the NSF would fund a graduate student to train in genetics research and subsequently fund the same individual as a post doc attached to a research lab. Others felt

that it would be best to focus funding on post-doctoral scholars with attachments to a research lab as they could start researching more rapidly, without the distractions of finishing a degree, while simultaneously forming lasting professional relationships and a long-term research agenda. By and large, most participants argued that graduate students, post-docs, and junior faculty provided the best potential investment returns since, if properly screened, they are most likely to have the time and incentive required to augment conventional discipline-based training with sustained attention to methods from other fields.

3.A.2. Educating the Public and Policymakers

Participants also discussed other ways that social science and biology could usefully interact. For example, several of the social sciences cultivate expertise on topics such as teaching and persuasion. With the educational part of NSF's mission in mind, participants discussed ways to *apply and extend existing social science knowledge on topics such as persuasion and human learning to improving how researchers and scientific organizations communicate critical biological facts to scholarly and lay audiences*. In addition to improving educational effectiveness and efficiency, such collaborations can also help policy makers. Such assistance could come from applying social scientific insights about persuasion and strategic communication to scientific organizations so that they can learn how to more accurately and accessibly convey important biological and biologically-informed social scientific insights to media organizations, policy makers, and other interested members of the public.

Participants agreed that such education is necessary because of the often-wide gap between popular ideas about genetics and cognition and the best scientific understanding

of these topics. In the last ten years, for example, researchers have made several discoveries that have led them to revise their understanding of the genome, including discoveries mentioned at the beginning of Section 3. Many members of the public and many policymakers seem unaware of these advances and are willing to base important social explanations on outdated or falsified biological views.

Workshop participants expressed support for programs that would enhance the public's understanding of the relevant science. At the same time, participants recognized a special challenge in the domain of genetics. Many people are aware that there have been horrible public acts committed in the name of genetics, including forced sterilization and mass murder. Such knowledge can make people resistant to gene-oriented behavioral explanations and overly-reliant on environmental explanations.

When we combine public resistance to gene-oriented behavioral explanations with the fact that the correspondence between behavior and genetics is more complex than many members of the public appreciate, the table is set for important public misunderstandings of biologically-informed social behavioral explanations. As a result, educational programs that do not anticipate such resistance are likely to be less effective than the scientific community desires. Fortunately, several existing avenues of social scientific research speak to such problems. Social scientific literatures on persuasion and strategic communication, which have been applied successfully in conveying climate science (see, e.g., Abbasi 2006), can also be used to more effectively and efficiently convey important facts about genes, cognition, and social behavior to important public audiences.

3.A.3. Final Remarks about Educational Strategies

In all such cases, participants agreed that *any such educational effort needs to identify a target audience and commit to measurable outcomes*. In particular, if we cannot identify what tasks a particular target audience cannot accomplish today as a result of their lack of information, and if we cannot identify how a specific educational intervention would improve their competence at these tasks, then we will not be well suited to credibly distinguish our successes from our failures. Without clear objectives and associated measures, the resulting educational endeavors are likely to be less effective and efficient.

In sum, workshop participants agreed that the knowledge base for advancing a biologically-informed social science is quite limited, particularly from the genetics perspective. In many cases, these limitations do not appear to be self-correcting. As potentially valuable as biologically-informed social behavioral research appears to be, pursuing such research involves career risks for individual investigators and confronts a public that has been scarred by previous misuses of genetics. NSF is well positioned to make a difference by providing opportunities for scholars and the public to learn more about genes, cognition, and social behavior. Not only can it fund mechanisms for providing important facts to new audiences, it can also leverage social science's knowledge base about persuasion and learning to convey these facts more effectively.

3.B. Biologically-Informed Social Behavioral Research Needs More Data and Better Inferential Standards

A frequent topic of discussion during the workshop was the quantity and quality of available data. Participants agreed that there are very few data sets upon which a biologically-informed social science can currently be built. Another point of consensus pertained to barriers to effective statistical inference. Participants pointed out that many

of the available datasets available to scholars have too few cases or too little variance to evaluate even rudimentary social behavioral hypotheses.

Participants discussed a wide range of possible responses to this problem. They discussed adding social behavioral content to existing biological datasets, adding biological data to existing social science datasets, and creating entirely new datasets. Amongst the ideas for entirely new datasets, animal studies were vigorously discussed.

Participants also discussed problems with inference. Today, we observe many examples of claims about gene-behavior or brain-behavior relations that are not replicable. Many of these findings are due to poor research practices. In many areas of research activity, there appears to be no critical mass of scholars who hold one another accountable for the validity of their claims in peer review process. Participants were in favor of programs that would more widely distribute such training – programs that could be included in the educational endeavors described in Section 3.A. of this report or the collaboration-inducing endeavors that will be described in this report's Section 3.C.

Participants also raised concerns about data access. Access to datasets that could be of interest to scholars interested in biologically informed social behavioral research, and be the lynchpin of transformative discoveries, is limited for many reasons.

Some limitations are the result of proprietary claims. These datasets are either owned by private entities or by scientific researchers whose funding arrangements with various agencies do not require them to share their data with other researchers.

Other limitations are the result of important respondent privacy concerns. We are conscious of the risks inherent in making available data that contains both biological and survey interview information about individuals. At the same time, restricting researchers'

access to such data is also consequential. Tight control inhibits replication studies, which can be critical to establishing the legitimacy or credibility of a claim.

Hence, participants discussed not just proposals for new kinds of data, but also means of increasing the availability of such data to researchers – including *support for statistical masking or analogous technologies that allow researchers to share individual level data while reducing, and perhaps even eliminating, privacy risks*.

In what follows, we convey the workshop's findings on problems of data availability (Section 3.B.1), inference quality (3.B.2), and data sharing (3.B.3). In each case, the report will focus primarily on constructive ways that NSF and other interested parties can respond.

3.B.1. We Need More Data

Hypothesis testing is a primary means by which science advances. Hypothesis testing allows ideas from various theories to be sorted by how well they survive confrontations with what we can observe. For many hypothesis tests, multiple observations are necessary to draw reliable inferences. The necessity comes from a desire to separate the effects in which we are interested from the effects of potentially confounding variables.

Workshop participants agreed that data availability inhibits evaluations of even rudimentary biologically-informed social behavioral hypotheses. Throughout the day, participants commented on how the data currently available on genes and cognition was insufficient for many of the tasks that would be most important to social scientists. Frequent references were made to statistical power, or more accurately the lack thereof.

Individuals differ in many ways. So do their environments. Many of these variations can affect gene-behavior relations or relationships between specific brain functions and behaviors. To derive credible inferences about such relations in the context of potentially confounding variations requires a larger number of observations than are typically seen, say, in organic chemistry.

The contribution to this report by Daniel Benjamin provides a vivid example of the problem.

"To get a sense for the magnitude of the problem, consider a researcher studying a particular candidate genetic marker. To simplify, suppose there are only two alleles for the marker, with carriers of the High variant, as opposed to carriers of the Low variant, hypothesized to have a higher value for the phenotype of interest. To further simplify, suppose there are only two possibilities: either there is a true association, or there is not. Imagine the phenotype of interest is distributed normally. Suppose it is known that, if there is an association, then the genotype of interest explains $R^2 = 0.1\%$---a rather large effect size for a single marker. For illustrative purposes, suppose any given sample has an equal number of High and Low carriers; in the usual case of asymmetric frequencies, the same amount of statistical power may require a much larger sample size. Finally, suppose that in a sample of size *N*, a researcher observes a statistically significant association at the standard .05 significance level. How large does *N* have to be in order for this result to constitute substantial evidence about whether there is an association? Table 1 shows how a researcher's posterior belief (after having seen the data) that there is a true association depends on the researcher's prior belief and on *N*.

Table 1. Posterior probability of a true association as a function of prior probability and sample size.

		Sample size				
		N = 100 (power = .06)	*N* = 1,000 (power = .17)	*N* = 5,000 (power = .61)	*N* = 10,000 (power = .89)	*N* = 30,000 (power = .99)
Prior prob. of true assoc.	.01%	.01%	.03%	.12%	.18%	.20%
	1%	1%	3%	11%	15%	17%
	10%	12%	27%	58%	66%	69%

Notes: Entries calculated by the author as described in the text. Power is calculated using Purcell, Cherny, and Sham's (2003) online tool: http://pngu.mgh.harvard.edu/~purcell/gpc/qtlassoc.html. Posterior probabilities are then calculated by Bayes' Rule:
Pr(true|significant) = (power × prior) / ((power × prior) + (.05 × (1-prior))).

Of course, it is difficult to know what an appropriate prior belief is, but for a typical candidate marker, it is probably much less than 10%. In any event, the clear message from these calculations is that a researcher should conclude almost nothing about a genotype-behavior relationship from a sample size in the hundreds, and sample sizes must number in the several thousands before non-negligible inferences are appropriate.

Relative to complex behavioral phenotypes, the power challenge is less daunting for intermediate phenotypes, such as functional Magnetic Resonance Imaging (fMRI) data, but adequately-powered research still requires sample sizes much larger than is currently typical. For instance, suppose it is known that, if there is an association, then the genotype of interest explains $R^2 = 3\%$. Under the same optimistic assumptions as above, for the conventional 80% power level, a sample size of $N = 258$ is required. In contrast, due to the cost of using the fMRI scanner, a typical large fMRI study currently has a sample size of $N = 100$."

Some workshop participants expressed the view that *if investors continue to pour resources into studies with low numbers of observations, they are likely wasting resources on studies that are too small to significant inferential value or to provide substantial investment returns*. Increasing the availability of existing data and making new data available to broader research populations was seen by many workshop participants as activities that can contribute to transformative research innovation in the near future and should be given priority by foundations and related entities.

In addition to limited numbers of cases, workshop participants also argued that most behavioral genetics studies have been conducted on very narrow groups of people. Calls were made to move on from typical convenience samples (e.g., undergraduates at research institutions or people who live near universities) and try to get more diversity in available datasets.

Augmenting the problems caused by smaller datasets is the fact that as research on the functioning of neurons or genes has progressed, a common kind of finding emerges – neither entity tends to have a simple relationship to higher-level behaviors. Genes, for example, are laborious to define with precision and a gene's relationship to

many behaviors typically depends on other genetic or environmental triggers. Such attributes of genes can complicate attempts to identify causal relations. One implication, as Benjamin's white paper explains, is that genotype-behavior associations typically have tiny effect sizes and are likely confounded with many other variables.

The lack of available data not only inhibits future researchers, it reduces the legitimacy of existing research. Consider, for example, the legitimating role that replicability plays in scientific research. Scholars who make their data available and their procedures transparent provide other researchers with an opportunity to evaluate the truth value of extant claims and the extent to which particular claims are robust to interesting procedural variations. In many fields, the scholarly community discounts or ignores claims made by researchers whose findings cannot be replicated.

Data problems of the kind described above inhibit replicability and threaten legitimacy. In some areas of medical genetics, for example, it is widely accepted that most published associations are not reproducible.

Workshop participants spent considerable time discussing whether investments in new or augmented data collections could fundamentally advance scientific attempts to understand genetic foundations -- or at least genetic correlates -- of important social behaviors. Since genetic effects on complex behaviors are likely very small, large-scale data sets directly address the problem of underpowered research by enabling greater statistical power and more accurate conclusions. Workshop participants focused on two methods for creating larger datasets: augmenting existing human studies and creating new datasets using animal studies. Both methods were seen as more cost-effective than

creating entirely new human-based datasets. We convey insights from each discussion below.

3.B.1.a. Augmenting Existing Human Studies

In our discussion of how to create larger datasets, the workshop covered three ways of proceeding. First, researchers could add a social science questionnaire to existing biological or medical studies. Second, researchers could request genetic information (likely in the form of a swab) from participants in existing social science studies. Third, researchers could assemble an entirely new opt-in panel to participate in research on genes, cognition, and social behavior. While participants would be interested in a new panel, they saw it as less cost effective than the first two alternatives. Hence, they focused their discussion on the first two alternatives.

Workshop participants argued that *exploring the social behavior of participants in existing health studies (by adding a questionnaire) would be most effective and efficient* -- compared to genotyping respondents in extant social science databases or creating entirely new datasets. They also discussed a number of challenges associated with such endeavors.

One such challenge pertains to the content of social science questionnaires that are added to biological datasets. If we randomly selected geneticists, neuroscientists, and social scientists from various disciplines to design a questionnaire, it is unlikely that they would agree on which behaviors are most important to study or what to ask about any behaviors on whose importance they might agree. With such situations in mind, workshop participants argued that NSF's investment returns would likely be higher if participants in such collaborative endeavors knew more about one another. The kinds of

educational endeavors described in Section 3.A. of this report and the mechanisms for increasing collaboration described in Section 3.C. of this report can help these relationships to develop. We think that such endeavors are necessary to increase the pool of researchers who are capable of achieving a common understanding of the types of questionnaires that are most likely to generate meaningful and legitimate insights. Moreover, if such endeavors entail administering questionnaires to subjects, then the legitimacy of the endeavor would greatly benefit from the *participation of social scientists with expertise in survey design and in the psychology of survey response* (i.e., researchers who know how to word questions and response categories that generate valid measures of the topics of interest).

Workshop participants also discussed challenges associated with adding biological content to existing social science datasets. A common way that this can be, and has been done, is to bring a swab to a survey interview and use it to collect saliva – a substance from which genetic information can be retrieved.

Workshop participants who had experience designing credible surveys expressed concerns about how such exercises would affect data quality. When researchers attempt to collect biological materials (e.g., saliva) from participants in longitudinal social science data collections (e.g., survey respondents) there is a possibility that the request for these materials will cause people who otherwise would complete the survey to refuse participation. To date, there is little known about how such attempts affect participation and hence the extent to which we can recruit sufficiently diverse and representative participant samples. Moreover, we know of no research on the best ways to approach potential survey participants about providing biological materials. If people, institutions,

or foundations are interested in supporting biologically-informed social science through funding of simultaneous social science and biological data, they should consider *investing in experimental research that clarifies the conditions under which such appeals are consistent with the acquisition of sufficiently diverse and representative samples.*

Several workshop participants have had positive experiences in this domain and point to existing protocol. For example, the Health and Retirement Study (HRS) began collecting genetic data in 2006 to supplement its social behavioral information. The Panel Study of Income Dynamics (PSID) is considering a similar strategy. To date, the social behavioral questions asked in these studies have not been those of principal interest to political scientists. The National Annenberg Election Study also collected saliva, but the makers of this survey have chosen not to make these data available to researchers outside of their project.

To facilitate provision of social-biological data that can advance political science and other fields, NSF may find it beneficial to give researchers opportunities to make specific arguments for specific topics for which an integrated social-genetic dataset can be transformative. This can be done through *a special call for proposals that coordinates with an existing biological (including health related) data collection endeavor*. As stated elsewhere in this report, if such a call were made in the context of the kinds of educational endeavors described in Section 3.A. of this report or the collaboration-inducing activities of Section 3.C. of this report, it is more likely that the responses would be sufficiently well informed about relevant social and biological sciences to generate robust scientific findings and greater investment returns. Of course, a parallel exercise

could also be developed for proposals for collecting biological materials from social science datasets.

3.B.1.b. Increasing Data Availability Through Animal Studies

One idea that generated substantial enthusiasm at the workshop was *using animal studies to make progress in developing a biologically-informed social science*. The principal benefit of using animal research is that scientists can obtain data that would be difficult or impossible to obtain in human studies. Animal researchers, for example, have observed the effects of turning off the functionality of a gene. They also selectively breed animals to observe the way that traits are inherited. These types of studies, which are impossible to conduct using human subjects, yield invaluable data about the functionality of genes. While most studies using data from humans can only show correlation, the ability to alter the animals' genes and control the animals' environments can help researchers to demonstrate causation.

Animal studies also tend to cost less than studies involving humans. They can yield data more quickly. There are fewer complications from privacy concerns. Workshop participants viewed animal studies as a potentially beneficial venue for making progress.

Against the potential benefits, however, are important questions. In addition to questions about how animals in such research are treated, participants also raised a question that is directly related to the purpose of this report. Why should studies using animals have any relevance to human behaviors?

In the course of the workshop, participants cited research that indicates the correspondence between certain genes and higher-level behaviorally-relevant phenomena

are similar or even identical in large classes of animals (e.g., all mammals). One example of scholarly evolution from animal to human models lies in research on the neural systems underlying emotion. Over the past several decades, animal models have drawn attention to the amygdala for its relationship with emotion; particularly fear. This research helped to stimulate interest in the human amygdala and its relationship with fear and emotion. Subsequent research has identified parallel relationships in humans. These findings cover topics ranging from emotional learning and its effects on memory to emotion's role in social behavior (for a review, see Phelps & LeDoux, 2005). To the extent that such similarities exist and affect social behaviors, there is potential value in getting social and natural scientists to work together to identify common genomic and/or neural substrates for social behavior across species.

One of the areas in which animal studies can be most helpful in the near-future is in *illuminating the mechanics of gene-by-environment interactions*. For example, Stephen J. Suomi and other scholars have demonstrated that a genetic mutation is Rhesus monkeys can cause them to exhibit increased aggression in adulthood. However, early childhood bonding with their mothers can negate these genetic effects (see for example Champoux et al. 2002 "Serotonin transporter gene polymorphism, differential early rearing, and behavior in rhesus monkey neonates" *Molecular Psychiatry* 7:10).

Continuing work in this area has begun to clarify the mechanism behind the environmental effects. This research also suggests connections to human behavior. In another example, Weaver et al (2004) shows that maternal licking can alter gene expression in rats. Genes are "turned on" or "turned off" depending on how an individual

rat's mother licks it in the first few weeks of its life and these genetic changes can persist into adulthood.

Given the potential effectiveness and cost efficiencies of animal studies, some workshop participants argued that higher near-term returns will come when behaviors can be studied in animals whose neural or genetic materials are sufficiently similar to humans. So, for example, if NSF were to *fund large consortia based on behaviors such as aggression, cooperation, child-rearing – where evidence of inter-species similarity has emerged* -- experts in many fields including social science, cognitive neuroscience, psychology and genetics could be brought together to productive ends relatively quickly.

3.B.2. Legitimacy Requires Attention to Methodological Concerns

Recall, from Section 3.B.1, that in some areas of medical genetics it is widely accepted that most published associations are not reproducible. While low sample size can hinder attempts to reproduce a statistically-defended claim, sample size is not the sole hindrance. Many causal claims linking gene or neural-level phenomena to specific behaviors are the consequence of broader deficits in methodological training that allow scholars to believe that they can make such claims and not have them challenged at seminars or in the peer review process. As Conley (2009) recently argued in a *Biodemography and Social Biology* article, "social science and genomics can be integrated; however, the way this marriage is currently occurring rests on spurious methods and assumptions and, as a result, will yield few lasting insights…."

For a biologically-informed social science to generate robust scientific findings in the face of pressures to make dramatic causal claims, investors have an interest in developing clusters of scholars who have the skills required to evaluate the claims'

legitimacy and credibility. In this light, many workshop participants *voiced support for activities that would help social scientists deal responsibly and legitimately to these analytic challenges*. In particular, participants voiced support for interventions that *would broaden training in relevant methods of inference for a broad range of participants who had the potential to develop transformative and biologically-informed social behavioral research* agendas

There is a special reason to consider methodological challenges in conversations about the creation of new data. In short, if the new data is irresponsibly analyzed then its value to science and society is reduced. Hence, if we want to enhance the scientific merit of such activities, we should pay for it only if the scholarly community has ability to draw credible and legitimate inferences from it.

The methodological challenges that will confront a biologically-informed social science are neither abstract nor remote. Consider, for example, assumptions inherent in new genome sequencing technologies. Technological advances are dramatically reducing the time and money required to sequence a genome. By lowering the costs, these technologies have the potential to change the way genetic research is done.

But these advances may include hidden costs. Researchers who want to draw inferences about behavior from sequenced data need to understand genetic assumptions that are implicit in sequencing technologies. The most prominent technologies, for example, use single-nucleotide polymorphism (SNPs) and linkage disequilibria to explore genes that are passed on together based on their proximity. Less broadly understood is the fact that SNPs are but a small portion of the genetic variation that exists between individuals.

In addition to paying greater attention to spatially proximate materials, current technologies also generate sequencing speed by eliminating materials that do not fit certain assumptions. In particular, many current technologies sequence genes by chopping DNA into smaller pieces. They then use these smaller parts to generate larger sequences. Such mapping, however, often involves decisions to ignore many observed and observable genetic properties.

These attributes of sequencing technologies increase speed and decrease monetary costs. But at what price for science? Historically, a common assumption about DNA was that if it is not conserved, then it is not important. Scientists have since come to realize that the materials once derisively referred to as "junk DNA" are actually much more important. What will today's scholars come to realize about the assumptions inherent in their current decisions to ignore genetic properties in the service of faster and cheaper sequencing technologies?

Until such matters are better understood, biologically-informed social behavioral research can generate robust scientific findings while enhancing scientific merit by *adhering to inferential practices that rigorously and transparently account for the assumptions underlying available data*. Without such adherence, data that appears exciting at first glance may have limited value in advancing our understanding of social behavior. As Liz Hammock's contribution to this report explains: "In the next 5 to 10 years, we should see more examples of gene variation linked to social behavioral variation, especially with the kinds of genomic variation that are currently understudied." With such adherence, by contrast, the foundations for significant research transformations are established.

Workshop participants expressed similar concerns about the use of fMRI technology in social behavioral research. In recent years, fMRI-based social behavior studies have gained substantial attention. For example, researchers in neuroeconomics have used the technology to explore brain activity under immediate or delayed reward situations (McClure et al. 2004) and they have highlighted the role of emotion in Ultimatum games – an informative bargaining environment (Sanfey et al. 2003). Such efforts have clear potential to provide new insight into human behavior.

The increasing availability of FMRI data also introduces inferential challenges that parallel those described for sequenced genome data. For example, similar to genome-wide association studies, fMRI research is often characterized by datasets that have too few cases or too little variation to provide the statistical power needed to evaluate even basic behavioral hypotheses. The typical fMRI study involves fewer than twenty-five people.

Workshop participants discussed a number of constructive ideas for improving this situation. One idea involved *standardizing the protocol for fMRI studies* (e.g., what is measured, at what level of precision, etc.). With greater standardization, researchers can more efficiently make sense of one another's data and data sharing will be more productive. By merging standardized datasets, moreover, greater observational variation will result. Indeed, with greater standardization, the scale economies and likely scholarly impact of an fMRI brain scan database improve tremendously. Some participants argued, however, that such solutions are feasible only for structural fMRI research, as functional studies vary too much to standardize. That said, we standardization where possible as a

means for increasing potential investment returns that can be accomplished at a very low cost (i.e., by changing existing practices).

A second idea involves developing improved interpretative norms. With fMRI research, several workshop participants voiced the need for researchers to have a specific paradigm and mechanism in mind before starting the study. Clearly-stated brain-behavior models that build from recognizable biological foundations, they suggested, are more informative. With a coherent theoretical foundation, even studies with small sample size have the potential to generate robust results.

A view that emerged from these conversations is that *funding for fMRI data and standardization should be a lower priority* than many of the other data collection ideas that were discussed during the day. Participants viewed this method as very expensive relative to other types of data collection and as having limited ability to produce high near-future returns in social behavioral contexts. Participants pointed, in particular, to a "new phrenology" that fMRI studies have fueled – a practice where researchers base a causal claim about behavior on correlations between behaviors and theoretically-underdeveloped color patterns in fMRI images. Participants voiced the view that neuroimaging is more effective in allowing researchers to evaluate hypotheses that compare a limited number of discrete models. For example, if Brain-Behavior Model A implies activity in a particular brain region and Brain-Behavior Model B implies no such activity, then fMRI studies can provide a critical test of which model accurately characterizes the specified behavioral domain. Contrast this practice to many extant fMRI studies whose conclusions are difficult to validate because they are difficult to link to any well-specified brain-behavior model.

Workshop participants exchanged ideas about other ways that NSF and similarly interested entities could assist in improving the legitimacy and reliability of biologically-informed social behavioral research. This discussion included the following ideas:

- A number of participants proposed *requiring power calculations from researchers* who were asking for funds to collect new data. In other words, foundations that seek to maximize expected investment returns should encourage applicants to offer a precise and rigorous explanation of why a dataset of a certain size is necessary and/or sufficient to accomplish a concretely-stated analytic goal. It has been our experience that grant applicants who do not think through such matters make ineffective (they do not ask for far fewer cases than they need) or inefficient (they ask for far more cases that they need) for resources.
- Participants hoped that NSF and other interested entities would *encourage replication studies*. Participants agreed that without replication, or at least the prospect of replication, the legitimacy of scientific endeavors is imperiled.
- Participants expressed a similar view about "non-findings" and "negative" findings. Participants were concerned about the effects that publication bias (publishing "positive" results that show a relationship between factors X and Y, while simultaneously not publishing results that show no such relations) could have on the development of biologically-informed social behavioral research. Given the headline-grabbing potential that "positive" studies have, the practice of only publicizing the results of studies that have statistically significant effects could lead the scientific community and the public to develop a skewed view of important relationships. While all workshop participants expressed doubt that

journals would become more interested in publishing non-findings and negative findings, NSF and other entities could *fund endeavors (e.g., online databases, meta-analyses) that make "non-findings" easier to learn about*. Sharing such information quickens scientific progress by limiting the extent to which researchers seek to discover that which has already been found.

3.B.3. Final Remarks about Data Strategies

Should foundations, researchers, or other interested persons seek to advance behaviorally-informed social behavioral research by creating new human data that can be used by many scholars, they will face important challenges associated with releasing such information. Social behavioral research can inquire about matters that are sensitive, such as religiosity, political beliefs, and sexual orientation. Biological research can also delve into matters that individuals would not want released. Public releases of datasets that combine both types of information have the potential to provoke considerable anxiety.

Given the many reasons articulated for producing more human data, participants spent time discussing how to manage the tension between respondent privacy and scientific advancement. In the process, they described a number of ways that such endeavors can be effectively managed.

Consider, for example, the practices of leading social behavioral surveys that the NSF already funds. One such project is the American National Election Studies (ANES) – the nation's benchmark academic election study. The ANES collects data not only on respondents' voting behavior and opinions about social issues, it also collects socioeconomic variables, religiosity, sexual orientation, neighborhood, and so on. Its challenge is to provide high-quality election-oriented data to tens of thousands of

researchers and other interested persons around the world while protecting the identity of individual respondents.

ANES responds to this challenge in innovative ways. For example, they will release data on a respondent's age and the state or congressional district in which a respondent lives, but they do not publicly release the respondent's county or date of birth. Scholars who want access to more detailed information than their public dataset provides must fill out "restricted data" requests which are legally-binding contracts across universities that specify how and when such data can be used.

Workshop participants described additional ways to make potentially sensitive data available while managing privacy concerns. One set of suggestions referred to algorithms that investigators could use to mask individual identities while preserving population averages and even first and second-order relationships between key variables.

Another set of suggestions focused on secure servers. In one version, researchers could sign up for access, agree to limits on how they would use the data, and then run their own analyses. In another version, researchers would send instructions to qualified research staff employed by the server's overseers. The dedicated staff would be sufficiently well trained to run the analyses and then return the results to the requesting scholar. Such procedures could increase the range and number of scholars who could conduct analyses of integrated social-biological data while minimizing the number of people who have direct access to potentially sensitive data. Workshop participants see such methods as a cost effective way for NSF and related entities to expand access to uniquely-valuable and scientifically-important existing and emerging datasets.

Another barrier to data availability is proprietary claims. In some cases, potentially relevant social-biological datasets are owned by private corporations (e.g., drug companies). In other cases, scholars who have "integrated" data share them only with members of their labs. Workshop participants wanted foundations and similar entities to be more consistent and persistent in *making data-sharing a requirement for funding*. We believe that this move alone would make a number of the data-availability problems articulated throughout this section less severe. Broader availability of integrated data can provide researchers with opportunities to produce near-future returns on existing and new data investments.

To this end, workshop participants also advocated for the creation of consortiums of data providers that are willing to contribute to large-scale shared data resources. Examples in the medical field of such consortia have increased the size of available data on topics ranging from breast cancer to stem cells. Further success in this domain may require finding a specific topic of interest that would benefit from a multidisciplinary approach, such as those behaviors that can be modeled in both humans and animals, such as aggression.

In sum, there are many researchers who want to make scientific and socially valuable contributions by conducting transformative and rigorous social behavioral research. But when it comes to conducting such research in a biologically informed way, the data does not exist or the people who have such data will not share it. The lack of data availability is a significant impediment to scientific advance. At the same time, there are concerns about what scholars do with the data that is available. In many cases, these problems do not appear to be self-correcting. NSF is well positioned to make a difference.

It can provide leadership and resources that support new data sources and induce larger groups of scholars to improve inferential methods. Such support is particularly important in the domain of research on genes, cognition, and social behavior due to the public's and media's fascination with the subject and their tendencies to be influenced by methodologically irresponsible, but headline grabbing claims. For an energetic and effective biologically-informed social behavioral research community to generate robust scientific findings, enhance scientific merit, and transform contemporary understandings and approaches, it is essential that able foundations and institutions support efforts to expand available data and improved inferential standards.

3.C. Biologically Informed Social Behavioral Research Needs Serious and Sustained Collaborations Between Social Scientists and Natural Scientists

Of all the types of recommendations for advancing biologically-informed social behavioral research that we discussed at the workshop, the type that generated the deepest and most sustained enthusiasm was attempts to build rigorous and lasting social networks of potential scholarly collaborators (e.g., interdisciplinary post doc programs and summer training institutes). The main premise underlying these recommendations is that there are many social scientists who want to rigorously engage biological reasoning and evidence, but most lack real opportunities to do so. Participants believe that the gulf currently dividing social and natural scientists is too broad to be bridged by fleeting and uncoordinated interactions. This gulf is widened by institutional tendencies that reinforce existing disciplinary boundaries rather than making measurable progress on the nation's most serious economic, health, military, and social challenges. Bold and public initiatives that are problem-oriented are required to counter common career pressures to speak only

to a narrow disciplinary audience and to signal to younger scholars that the nation benefits from dynamic, new, and multidisciplinary approaches to critical social problems.

Summer institutes in which social and biological scientists come to better understand one another's areas of expertise and develop common frames of reference were raised as an example of how to generate more collaborative opportunities. In general, workshop participants argued that opportunities to engage in deep and long-lasting collaborations were critical to establishing basic foundations of procedural knowledge and substantive knowledge that biologically-informed social behavioral researchers will need to generate legitimate, credible, and transformative research outcomes.

The main premise supporting arguments for intense and sustained collaborative opportunities is as follows: To conduct credible and legitimate biologically-informed social behavioral research requires mastery of multiple technical fields, access to brain scanners and/or to molecular biology labs and expert personnel. All workshop participants agreed that these requirements are significant.

Every workshop participant, however, had an experience – often early in their careers – in which they were given an opportunity to interact in a sustained and intense manner with scholars from other disciplines. Workshop participants referred to those experiences are formative and as "necessary to even speak the same language." For some participants, these experiences took the form of a multi-week summer institute. For others, these experiences took the form of multi-year post docs. In both cases, the sustained nature of the opportunity gave individual participants the opportunity to build conceptual

bridges between the jargon and practices of their own discipline and parallel elements of other disciplines.

Given the minimal existing overlap between social behavioral, genetic, and cognitive research traditions, it appeared to all participants that a necessary step in developing a credible, legitimate, and effective biologically-informed social behavioral research community is to provide opportunities for sustained interaction amongst social and natural scientists. Without such opportunities, participants surmised that the centripetal force of discipline-based work, and the tendency for disciplines not to reward scholars who pursue interdisciplinary research agendas would prevent a credible research community of the kind described above from evolving organically.

To provide a foundation for transformative work on genes, cognition, and social behavior, many workshop participants argued that *funding for sustained and rigorous interaction amongst scholars from these diverse traditions should be a top priority*.

For many researchers interested in biologically informed social science, access to facilities capable of conducting such research, as well as expertise to operate and interpret the technology is a barrier. For scholars interested in genes, cognition, and social behavior, a built-in bottleneck often stops researchers with no background from ever exploring their research interests. In this sense, the need for infrastructure is a major problem to advancing the field. Two recommendations were proposed to circumvent these barriers.

First, *a time-sharing program for equipment* could be created amongst interested scholars and institutions. TESS (Time-shared Experiments for the Social Sciences) was raised as an exemplar of such possibilities. Problematic in this solution however, is that it

alone does not address the expertise required to operate equipment and interpret results. In the long run, it is better if social scientists not only have the ability to collaborate via time-sharing but also have the kind of broader and deeper knowledge base of what biologists that can transform their research agendas. Nonetheless, time-sharing arrangements would constitute substantial progress from the current state of affairs.

Second, NSF could invest in the *creation of core facilities that cater to non-specialists in the social sciences* by providing not only access to equipment and but also expertise in designing and analyzing studies. Here too, the success of any such venture would be improved by the simultaneous emergence of social scientists with a broader biological knowledge base. Researchers still need to be highly trained at all levels in order to grasp not only the technological output and statistical analysis, but also the key question and theory that motivated the research.

In general, there are not very many people with the time and ability to become genetic experts, neuroimaging experts, and social experts at the level needed to conduct this type of research with legitimacy. As a result, a number of participants preferred to focus on a truly collaborative model (i.e., more sustained involvement in stable laboratories) in tandem with the creation of facilities or a network of interested PIs that could share facilities.

Several participants recommended the creation of a *collaborative grant or dual-PI granting mechanism*. Here, teams of social and natural scientists would submit grant proposals. A key part of proposal evaluation would be the credibility of team members in each area as well as the extent to which the proposed activities leveraged both kinds of expertise. A concern raised with such ideas is that the cultural and professional gap

between social and natural scientists is so large, that such groups would not naturally form. Other participants argued that researchers will "follow the money." In other words, if NSF or another entity were to put enough money on the table for dual-PI projects that could advance the study of genes, cognition, and social behavior, qualified teams would emerge.

Much of the conversation on this point turned to the topic of summer institutes and/or post docs. These activities were seen as being good ways to build the scholarly networks that are needed to seed a broader set of new collaborative research teams that have the expertise and motivation necessary to develop a more biologically informed social science.

An issue to be addressed with the creation of these facilities, networks or programs is how to establish their objectives. One view is that more concrete objectives will help researchers and staff work more efficiently (towards the objectives). Proponents of this view argued that such objectives provide foci to which natural and social scientists can direct their expertise and against which progress can be measured. A number of participants argued that focusing the research agenda on a topic of interest and providing funding for specific purposes often proves to be one of the most inventive ways to break down the barriers associated with collaborative work.

An alternate model seeks to induce collaboration in broader topical domains. An example of this approach is the Department of Defense's Minerva Research Initiative. Minerva is a "university-based social science research initiative launched by the Secretary of Defense focusing on areas of strategic importance to U.S. national security

policy"[2]. A similar approach is pursued by NSF's Science and Technology Centers, such as the Center for Behavioral Neuroscience (CBN), and by the Research Coordination Network (RCN) competition (in the Biological Sciences), which brings people together to develop infrastructure such as meetings or monthly teleconferences around one topic of interest. Some workshop participants, moreover, argued that collaborative endeavors of the kind just described could speed effective solutions to data limitation problems described in Section 3.B. The underlying premise of these arguments is that effective data sharing requires agreement on principles of conceptualization and measurement. Participants argued that having social and natural scientists who can speak the same language was necessary to produce transformative data that would be of broad scholarly relevance.

Workshop participants also argued for collaborative endeavors that would generate more rigorous and useful models. A common view is that extant social science models are not well-prepared to integrate biological content. Participants also argued that more rigorous and transparent theorizing about biological-social behavioral relationships could help scholars more effectively manage some of the data problems described in Section 3.B. Better models would not only give researchers the ability to refine data collection strategies with respect to relationships of interest. They could also reduce the number of observations required for sufficiently-powerful statistical analysis (i.e., by identifying observational domains where certain potentially confounding relationships are impossible). In other words, participants argued that better hypotheses can guide empirical research designs in ways that make larger effect sizes derivable from smaller numbers of cases.

[2] See http://minerva.dtic.mil/ <Accessed August 2, 2010>.

While discussing templates for possible collaborative endeavors, NSF personnel in attendance at the workshop raised the Integrative Graduate Education and Research Traineeship program (IGERTs) as a template. Many workshop participants were receptive to this idea, though it was also agreed that since proposals that integrate biological and social behavioral content are so rare at present, and so at odds with how many disciplines currently view social behavioral research, NSF leadership or their analogues at other institutions would need to send a strong signal of their interest in funding such work to have an IGERT program draw large numbers of high-quality proposals.

Another obstacle for researchers in this field is simply finding and pairing up with collaborators that have the necessary skills and interests to contribute to a common research agenda. Workshop participants argued for *the creation of an online clearinghouse (or "match-making" site)* for PIs to share both substantive interests and complementary skill sets.

In sum, workshop participants agreed that lack of a common language and the absence of social networks amongst social and natural scientists is an impediment to the development of biologically-informed social behavioral research. The communicative and conceptual chasms separating these researchers would likely not disappear on their own. Participants voiced support for mechanisms that would allow individual social behavioral researchers to immerse in relevant biological science environments and for programs that would allow groups of social and natural scientists to convene in rigorous and sustained ways. NSF is well positioned to make a difference in providing new opportunities for collaboration and the development of social research networks that are

essential to making significant progress in understanding relations amongst genes, cognition, and social behavior.

4. Conclusion

For decades, NSF has taken a lead in supporting basic and applied social behavioral research. As the kinds of inquiries that NSF and other public and private institutions have progressed and become more influential, there has been increasing interest in tying explanations of high-level social behaviors to more basic biological phenomena. Two focal classes of such phenomena are genes and cognition.

It is possible that our understanding of human behavior, and our ability to develop new and existing and human institutions, can come from such inquiries as they currently exist. But such a conclusion should be drawn only after we compare existing practices to feasible alternatives. With that objective in mind, this report inquires about specific circumstances in which new investments of labor and capital from individual researchers and science-oriented institutions are a necessary condition for innovative and new research-related benefits to be realized.

Our main conclusion is that *there exist exciting opportunities to support transformative biologically-informed social science research*. Throughout this report, we identify a number of areas where greater communication and collaboration amongst social and natural scientists is very likely to produce important new discoveries about social behavior in the near-future. Because there are multiple opportunities of this kind, we also attempt to shed light on near-future opportunities where the greatest investment returns are possible.

While a scientific approach to understanding social behavior can have great legitimacy and credibility, such efforts depend on its practitioners adhering to certain rules of conduct. The most important rules pertain to procedural transparency and method

of inference. Researchers who derive social behavioral claims from transparent, rigorous, and replicable procedures of discovery and inference can have great influence in both educating populations about important attributes of social behavior and in informing society about effective and efficient ways to deal with behavior-related problems.

While many people offer opinions about the causes of human social behavior, it is critical that *scientific inquiries* into such matters be supported. Societies that have the ability to confront important social hypotheses with credible evidence and rigorous evaluative procedures gain the ability to develop and maintain increasingly complex social institutions. Compared to societies where such inquiries are not permitted or supported, societies that commit to rigorous evaluation of critical hypotheses are better able to defend themselves against many threats and can provide their citizens with opportunities to participate in, and benefit from, many valuable forms of social coordination. The effective and efficient functioning of numerous aspects of modern social infrastructure depends on the insights that science can offer. It is with such goals in mind that we present this report to you. We appreciate the opportunity that NSF, and its Political Science program, have given us to explore how next steps in the study of genes, cognition, and social behavior can provide new scientific insights of significant social value.

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5. Workshop and Contributors

The workshop was held on June 28, 2010 from 8:30 am to 4:00 pm at the National Science Foundation in Arlington, Virginia. The agenda was as follows:

8:30 **Welcome**: Myron Gutmann, NSF Assistant Director, Directorate for Social, Behavioral & Economic Sciences

8:40 **Welcome,** Frank Scioli, NSF Division Director, Social & Economic Sciences

8:50 **Introductory Remarks:** Arthur Lupia, Workshop PI, Carol Mershon, NSF Program Director, Political Science

9:00 **Session 1**: What is the scientific and social value of current and near-future research on genes and social behavior?

10:30 *Break*

10:45 **Session 2:** What is the scientific and social value of current and near-future research on cognition and social behavior?

12:15 *Lunch*

1:00 **Session 3**: What is the scientific and social value of research on social behavior that simultaneously leverages genetic and cognitive content?

2:30 *Break*

2:45 **Concluding Session:** On what kinds of social behavioral inquiries are near-future investment returns likely to be greatest?

4:00 *Adjourn*

Many NSF Program Officers and related staff attended the workshop throughout the day. The main participants in the workshop were invited from outside of NSF.

Participants were sought from multiple research areas including: genetics, cognitive and neurosciences, decision making and risk analysis, economics, political science, sociology. Our goal was to assemble a group of scholars who as individuals have developed distinct successful research agendas and who, collectively, can provide

rigorous and broad expertise about the current state and near-future of research agendas associated with genes, brains, and social behavior. Invitees were selected based on recommendations of, and consultations with, NSF program officers and related personnel. This list includes senior scholars in genetic, cognitive, or social behavioral fields as well as younger scholars who are conducting innovative work that is pertinent to the workshop themes and that crosses traditional disciplinary boundaries.

The faculty participants were: Arthur Lupia (Principal Investigator), Professor of Political Science, University of Michigan; Daniel Benjamin, Assistant Professor of Economics, Cornell University; Turhan Canli, Associate Professor of Psychology, Stony Brook University; Susan Courtney, Professor of Psychological and Brain Sciences, Johns Hopkins University; Russell Fernald, Professor of Biology, Stanford University; Jeremy Freese, Professor of Sociology, Northwestern University; Elizabeth Hammock, Instructor of Pediatrics, Vanderbilt University; Peter Hatemi, Assistant Professor of Political Science, University of Iowa; Rose McDermott, Professor of Political Science, Brown University; and Aldo Rustichini, Professor of Economics, University of Minnesota.

Graduate student participants also attended the meeting and kept records of the proceedings. These students were: Christina Farhart, Science Assistant, National Science Foundation; Jedediah Madsen, Department of Political Science, University of Michigan, and Kristyn Miller, Department of Political Science, University of Michigan.

To facilitate effective and rigorous interaction at the outset of the workshop, we asked each invited participant to submit a short "white paper" in advance of attending the workshop. Our guidance regarding the content of these contributions entailed writing “a short essay on what their knowledge of current trends and recent advances in studies of

genes, cognition, and social behavior implies for near-term NSF research investment strategies that are likely to have the highest payoff in terms of intellectual merit and broader impact." After the workshop, participants were given an opportunity to revise their contributions. What follows are the revised versions of those white papers. They are included in this report with the express permission of the authors.

6. A White Paper by Daniel Benjamin, Department of Economics, Cornell University[3]

Due to time and space constraints, I will restrict my discussion to molecular genetics in the social sciences, an enterprise which I am optimistic will eventually be transformative.

Broadly speaking, I believe that molecular genetics will ultimately contribute to social science research in three main ways. First, genetic information could eventually be useful for targeting social-scientific interventions, much like it is beginning to be useful for targeting medical interventions. For example, if dyslexia can eventually be predicted sufficiently well by genetic screening, children with dyslexia-susceptibility genes could be taught differently how to read from a very young age.[4]

Second, social scientists could use genotypic data to learn about the biological mechanisms that lead to behaviors of interest. One possibility is that the genetic data bear on existing hypotheses. For example, experiments in which humans were exposed to the neuropeptide oxytocin suggest that oxytocin causes trusting behavior.[5] This suggests the hypothesis that variation in the gene *OXTR*, which encodes the receptor for oxytocin, may be related to variation in trust-related behaviors.[6] Even more intriguingly, the genetic data might suggest new hypotheses. If a genetic marker is unexpectedly found to associate with some behavior, then the marker's biological pathway is implicated in that behavior.

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[3] I take sole responsibility for the opinions expressed here, but many of my views and most of my knowledge is the result of countless conversations with friends and collaborators, including Jonathan Beauchamp, David Cesarini, Christopher Chabris, Ed Glaeser, Ben Hebert, and David Laibson.
[4] See Schumacher et al (2007) for a recent review of genetic predictors of dyslexia.
[5] Kosfeld et al (2005).
[6] Indeed, Israel et al (2009) report an association between OXTR and dictator game giving---but Apicella et al (forthcoming) fail to replicate it in a much larger sample.

Third, social scientists might be able to use genotypic data to more effectively address social science questions---questions that, in themselves, may have nothing to do with genetics. Rather mundanely, genotype data can be used simply as control variables to increase power in otherwise-standard statistical analyses. Most intriguingly---and most speculatively for reasons explained below---social scientists may be able to use genetic markers as "instrumental variables (IVs)" to infer the causal effect of (non-genetic) factor *X* on (non-genetic) factor *Y* using observational data. Among the several economics papers that already attempt to use this strategy, Fletcher and Lehrer (2009) study the effect of mental health (*X*) on academic achievement (*Y*).[7] In effect, the idea is to use the fact that genotypes affecting mental health are randomly assigned among siblings within a family as a natural experiment. Under the assumption that the genetic marker IVs affect academic achievement only via their effect on mental health, the estimated causal effect of the genetic markers on academic achievement can be rescaled appropriately to infer the magnitude of the causal effect of mental health on academic achievement.

Despite the recent explosion in the number of papers reporting genotype-behavior associations, I am pessimistic that any of these potentially transformative contributions can be convincingly realized within the next 10 years. The most urgent problem---discussed below---is that genotype-behavior associations have tiny effect sizes, so current research designs in the social sciences are woefully underpowered. However, even once this problem has been solved, there are further obstacles that must be overcome before the contributions can commence.

[7] The other papers are Ding, Lehrer, Rosenquist, and Audrain-McGovern (2009); Norton and Han (2009); and von Hinke Kessler Scholder, Smith, Lawlor, Propper, and Windmeijer (2010).

For one thing, the biological-mechanisms and genes-as-IVs contributions require uncovering the causal effect of particular genetic markers on behavior, but most existing research designs focus on detecting correlations. There are myriad confounds to a causal interpretation, e.g.: genotypes are correlated with ethnicity which is correlated with behavior; an individual's genotype is correlated with his parent's genotype which is correlated with his family environment; and each genotype is highly correlated with many nearby genotypes that are in "linkage disequilibrium" with it. Ultimately, convergent evidence for a causal relationship will come from large family samples, where behavioral differences across siblings can be attributed to Mendelian random assignment of genotypes; modeling, measurement, and estimation of environmental factors and gene-environment interactions; experimental evidence from animal models where genes are selectively "knocked out"; and biological evidence on the function of protein products of the gene.

There is a further obstacle to using the IV strategy credibly. For IV estimation to be valid, not only must the genetic markers have sufficient predictive power for the *X* variable, but the causal effects of the genes must be understood well enough to rule out alternative pathways (besides *X*) by which the genes could affect outcome *Y*. Since the proteins produced by genes generally appear to have multiple effects, most of which we have barely begun to understand, it seems unlikely that we can be confident about all of the consequences of any particular genotype in the foreseeable future.

Targeting interventions is probably the potential contribution closest at hand because the genetic markers can be merely predictive, rather than established to be causal, and because an index composed of many markers can be used, which may in the

aggregate have sizeable predictive power even if any constituent marker in the index has little. However, while I expect eventual successes, it will likely be slow and challenging to find sufficient predictive power even from an index. In medical genetics, with the exception of a few rare single-gene disorders, there has been a general failure to find sizeable aggregate predictive power---a problem now called the "missing heritability" puzzle.[8] Consider height, a highly-studied physical trait that is both measured with much less error than most behavioral traits and is more heritable, with behavioral genetics studies on twins and other relatives indicating that about 80% of the variability in height is due to genetic factors. Yet the aggregate predictive power from known genotypes is only about 5%, with 0.3% being the largest R^2 that has been found out of the 44 genotypes so far found to be associated.[9] Given the failure to find sizeable predictable power in physical traits, the challenge is likely to be at least as large for behavioral traits where the causal mechanisms are arguably more complex.

The most urgent problem, however, is that most efforts in the social sciences to discover genetic associations are underpowered. Fundamentally, there are two reasons. First, with the exception of rare mutations, almost every true genotype-behavior correlation is probably very small. To take a social science example that seems fairly typical, a meta-analysis of 46 studies concluded that variation in the *COMT* gene explains 0.1% of variance in cognitive ability.[10] Second, while my collaborators and I were initially encouraged by the large number of associations reported regularly, we have now come to the view that the usual concerns about publication bias---the tendency for findings, as opposed to non-findings, to be selectively reported by researchers and

[8] See, e.g., Sklar, Purcell, et al (2009).
[9] Wheedon and Frayling (2008).
[10] Barnett, Scoriels, and Munafò (2008).

selectively published by journals---are magnified in genetic association work because the typical dataset has many behavioral measures and many genetic markers. In order to account for publication bias and multiple hypothesis testing, it is important to adopt stricter statistical significance thresholds than usual, further reducing the power of a study with any given sample size to detect a true association.

If studies are underpowered, then the rate of false positives will be high. In the medical genetics community, it is now widely accepted that most published associations are not reproducible.[11] In my own social science work and the work of my close collaborators, we have been disappointed by our failure to replicate initially promising associations between genetic polymorphisms and economic phenotypes, despite samples of several thousand individuals.[12] Consequently, we have begun to systematically test existing candidate genes. In ongoing work using the Wisconsin Longitudinal Study (WLS), my collaborators and I attempted to replicate previously-reported associations of 13 genetic markers with cognitive ability. We can reject the hypothesis that the mean effect of those markers is larger than a tiny R^2 = .05%---and given our sample size of 5,413 individuals, we have essentially 100% power to detect effects of that size.[13] Also using the WLS, Freese et al (2010) attempt to replicate associations reported in the literature between *Taq*1a and educational attainment, voting, partisanship, organization memberships, socializing, tobacco use, and alcohol use, and conclude that none of the associations replicate.

To get a sense for the magnitude of the problem, consider a researcher studying a particular candidate genetic marker. To simplify, suppose there are only two alleles for

[11] See Ioannidis et al (2001) and Hirschhorn et al (2002).
[12] Beauchamp et al (2010) and Benjamin et al (2009).
[13] Chabris et al (2010).

the marker, with carriers of the High variant, as opposed to carriers of the Low variant, hypothesized to have a higher value for the phenotype of interest. To further simplify, suppose there are only two possibilities: either there is a true association, or there is not. Imagine the phenotype of interest is distributed normally. Suppose it is known that, if there is an association, then the genotype of interest explains $R^2 = 0.1\%$---a rather large effect size for a single marker. For illustrative purposes, suppose any given sample has an equal number of High and Low carriers; in the usual case of asymmetric frequencies, the same amount of statistical power may require a much larger sample size. Finally, suppose that in a sample of size N, a researcher observes a statistically significant association at the standard .05 significance level. How large does N have to be in order for this result to constitute substantial evidence about whether there is an association? Table 1 shows how a researcher's posterior belief (after having seen the data) that there is a true association depends on the researcher's prior belief and on N.

Table 1. Posterior probability of a true association as a function of prior probability and sample size.

		Sample size				
		$N = 100$ (power = .06)	$N = 1{,}000$ (power = .17)	$N = 5{,}000$ (power = .61)	$N = 10{,}000$ (power = .89)	$N = 30{,}000$ (power = .99)
Prior probability of true association	.01%	.01%	.03%	.12%	.18%	.20%
	1%	1%	3%	11%	15%	17%
	10%	12%	27%	58%	66%	69%

Notes: Entries calculated by the author as described in the text. Power is calculated using Purcell, Cherny, and Sham's (2003) online tool: http://pngu.mgh.harvard.edu/~purcell/gpc/qtlassoc.html. Posterior probabilities are then calculated by Bayes' Rule:
Pr(true|significant) = (power × prior) / ((power × prior) + (.05 × (1-prior))).

Of course, it is difficult to know what an appropriate prior belief is, but for a typical candidate marker, it is probably much less than 10%. In any event, the clear message from these calculations is that a researcher should conclude almost nothing about a genotype-behavior relationship from a sample size in the hundreds, and sample sizes must number in the several thousands before non-negligible inferences are appropriate.

Relative to complex behavioral phenotypes, the power challenge is less daunting for intermediate phenotypes, such as functional Magnetic Resonance Imaging (fMRI) data, but adequately-powered research still requires sample sizes much larger than is currently typical. For instance, suppose it is known that, if there is an association, then the genotype of interest explains $R^2 = 3\%$. Under the same optimistic assumptions as above, for the conventional 80% power level, a sample size of $N = 258$ is required. In contrast, due to the cost of using the fMRI scanner, a typical large fMRI study currently has a sample size of $N = 100$.

Over the next few years, due to the plummeting cost of genome-wide scans, virtually all association studies will move from being candidate gene studies to being Whole-Genome Association Studies (GWAS). This switch is scientifically appropriate: Existing candidate genes were initially studied primarily because those genetic markers were technologically feasible to genotype. There is every reason to believe that markers elsewhere on the genome will be more strongly associated with behavioral phenotypes than the tiny fraction of all markers that happened to be available to researchers first. However, concerns about power are many times more severe in GWAS. Current GWAS platforms genotype about 2 million markers, and future platforms will genotype far more,

so the prior probability on any particular marker must be miniscule, probably much smaller than .01%.

In my view, if a funding agency were to fund genetics research in the social sciences, the clear top priority is to put together datasets that are large enough to have adequate power to detect genotype-phenotype relationships in GWAS. Over the past several years, the medical genetics community has paved the way, forming large consortia of data providers, the most famous example being the Wellcome Trust Case Control Consortium. The resulting samples on the order of N = 20,000-30,000 are sufficiently large to detect alleles with modest effect sizes. These studies also tend to be very stringent in their hypothesis testing, thereby reducing the risk of false positives. Indeed, the findings that have emerged from these cooperative studies appear to be more likely to survive the challenges of replication.

I am optimistic that social scientists can follow suit within the next few years. For one thing, although existing medical consortia mainly study disease phenotypes, most of these datasets contain basic markers for socioeconomic outcomes as well. Furthermore, there are a number of large-scale social science datasets that have begun genotyping participants or plan to do so in the near future. The cost and ease of genotyping is plummeting: A commercial whole-genome scan of an individual (which measures about 2 million markers) currently costs less than $500, and since 1990, the price has been falling by half every 1-2 years.[14] Consequently, it seems likely to become standard for large-scale social science data providers from all over the world to genotype their participants, with an aggregate sample size of several hundred thousand.

[14] http://singularityhub.com/2008/12/30/whole-genome-sequencing-to-cost-only-1000-by-end-of-2009/ as accessed on June 9, 2010.

Should a funding agency put money behind genetics research in the social sciences? I believe the answer is yes *if* (1) the research will have adequate power, and (2) the researchers are held to an unusually high standard of accurately communicating their results. More insistently than for other research, funding agencies should *require* grant proposals to include power calculations. Unfortunately, underpowered research has negative value-added because it generates false positives; some researchers will squander resources pursuing a dead end, and others will spend resources undoing the damage by publishing non-replications. Moreover, due to the media attention any gene-behavior association work will surely attract, even adequately-powered research runs the risk of exposing the general public to a rollercoaster ride of frequently-reported genetic associations with important social behaviors that subsequently turn out to be false positives. Funding agencies should pay attention not only to whether researchers are capable of carrying out the scientific work, but also whether the researchers are committed to highlighting the limitations of the work, such as the possibility of a false positive, and the appropriate interpretation of the work, namely tiny predictive power from any given genetic marker and inevitability of gene-environment interaction. In addition, funding agencies should encourage grant proposals that aim to replicate previously-obtained results and encourage publication, even/especially if the attempted replications fail.

If these conditions are met, then I think funding agencies should view molecular genetics research as having an attractive risk-return profile. It is high risk because it is possible that the enterprise as a whole may fail; there may be too many genetic markers with effects that are too small and too complex, and hence researchers may never be able

to pin down causal relationships that have non-tiny predictive power in the aggregate. Even if the research is successful, it will be slow-going over many years, literally with the character of trying to find needles in a haystack, one at a time. However, the ultimate contributions to social science are potentially quite large, and molecular genetics research is rapidly becoming remarkably inexpensive.

Another funding priority of at least equal importance---about which I write less only because I know less---is research on the economics, politics, and ethics of using genetic information by both public agents (like governments) and private agents (like therapists and insurance companies). The cheap and plentiful availability of genetic data outside the scientific community in the near future will raise enormous social challenges. Research that studies these challenges may anticipate and offer policy suggestions to reduce potential risks.

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7. A White Paper by Turhan Canli, Department of Psychology, Stony Brook University

Executive Summary

The area of *Genes, Cognition and Social Behavior* (GCSB) lies at the intersection of the social sciences, psychology, neuroscience, and molecular biology. To date, most of this work has sought to link behavioral phenotypes, such as self-reported personality traits, with common variations in the DNA sequence, known as polymorphisms. In the last decade, there has been an increasing use of neuroimaging to detect endo-phenotypes (such as brain activation associated with particular cognitive-affective processes) in the hope of elucidating the underlying biological processes that link genes and behavior. Yet, many investigators are excluded from these exciting developments because the barriers to entry are considerable: mastery of multiple highly technical fields, access to brain scanners, access to molecular biology labs and expert personnel, access to potential collaborators. I suggest that the highest impact investment that NSF can make is to build an educational and technological infrastructure to enable a larger number of researchers to enter the field of GCSB and foster collaborations between scholars in the social and biological sciences. These activities can start with covering tuition for social scientists to enroll in (already existing) summer courses for non-experts for immediate impact at low cost. A next step could be the establishment of networks of PIs in the social and biological sciences through workshops, conferences, and retreats, whose collaborative interests would be funded through a seed grant mechanism. Finally, a truly transformative initiative would be the establishment of GCSB-dedicated Core Facilities around the United States, that cater technical services to researchers with great ideas but

no access to the proper facilities. Such Core facilities would not need to be created from scratch. Rather, funds could be made available to existing facilities (NSF-funded MRI or Genetics Centers) to support the purchase of additional equipment and the hiring of additional staff (technicians, biostatisticians etc.) whose primary duty is to serve a user base of non-experts. This would be an initiative with immediate impact, creating high-quality technical jobs and opening access to a large group of scholars that are currently excluded from contributing their intellectual visions to the development of GCSB.

Genes, Cognition and Social Behavior

In this White Paper, I will review an illustrative example of how research on Genes, Cognition and Social Behavior is conducted. I will focus on a common variation (polymorphism) within the gene that encodes the serotonin transporter, known as the *5-HTT*-linked polymorphic region (5-HTTLPR)l, describing both initial promising findings and subsequent complications. I conclude that rigorous research in GCSB requires scholarship in both the social and biological sciences, and will give very specific examples of such high-impact investments.

Polymorphisms linking genes and behavior

Initial results

Efforts to understand the biological basis of individual differences in complex traits have been catalyzed in the past fifteen years by advances in molecular biology and in neuroimaging. Molecular biologists have uncovered the basic nucleotide sequence of the human genome's DNA, begun to identify common variations within this sequence, and identified common gene variations that are associated with individual differences in personality traits. This is perhaps best illustrated in the case of the personality trait of

neuroticism, which is associated with heightened negative affect that figures prominently in a number of influential models of personality, such as Eysenck's [1] or the Big Five personality models [2].

Like all personality traits, neuroticism has a high degree of heritability: twin and adoption studies using a quantitative genetic approach estimate that about 40-60% of the variance for personality traits like neuroticism is accounted for by genetic factors [3]. In 1996, Lesch and colleagues reported a significant association between self-reported neuroticism and a common variation (polymorphism) within the gene that encodes the serotonin transporter, known as the *5-HTT*-linked polymorphic region (5-HTTLPR), [4]. This transporter regulates the reuptake of serotonin following its release into the synaptic cleft between two neurons. The polymorphism is located within the regulatory region of the gene, which determines how much serotonin transporter is produced, and it comes in a short (s) and a long (l) variant. Because each individual carries two copies of the gene (one from each parent), the possible combinations are: s/s, s/l, and l/l. Lesch and colleagues discovered that those who are either s/s or s/l reported significantly higher levels of neuroticism than those who are l/l.

Complications

The effect size of the influence of this polymorphism is small, however. Presence of the s variant only accounted for 7-9% of the genetic variance in measured neuroticism, suggesting that at least another 10-13 genes of similar effect size (or many more of smaller effect size) influence this trait. Moreover, replication studies have produced conflicting results. Even meta-analytic analyses of the literature have produced conflicting results: Two meta-analyses [5-6] found that 5-HTTLPR genotype is

associated with neuroticism but not with harm-avoidance, whereas another group reported the opposite pattern [7]. To some extent, these discrepancies may reflect the selection of different study samples, based on differing inclusion/exclusion criteria, or choice of genotype comparisons. The largest contributor to these varying findings may, however, be differences in the approach to statistical analysis: when the third meta-analysis was re-analyzed [8] using the approaches of the others, 5-HTTLPR was significantly associated with neuroticism.

Another complicating factor is the presence of an A-to-G single nucleotide polymorphism (SNP) associated with the long allele, which may render the long allele to be functionally similar to the short allele [9].

Neural endophenotypes

Initial results

In part, inconsistent associations between 5-HTTLPR genotype and personality traits may be attributed to small effect sizes. Thus, for phenotypes such as self-reported behavioral traits, the results are consistent with the view that the influence of a single, common polymorphism on continuously distributed traits is likely to be modest, if not minimal [10].

A promising approach in bridging the gap between gene variants with small effects and complex behavior is the use of endophenotypes [11], such as measures of neural activation or structure. A seminal publication by Hariri and colleagues [12] showed that individuals who carry one or two copies of the 5-HTTLPR short allele (from now on referred to as *S* subjects) had significantly greater activation in the amygdala (a brain region well known for its role in affective processes) than did individuals who only

carried the 5-HTTLPR long allele (from now on referred to as *L* subjects). Subsequent studies have used a wide range of task paradigms and different subject populations, with remarkably similar findings and confirmed by a recent meta-analysis [13].

Complications

Although there is no disagreement over the basic phenomenon (i.e., greater amygdala activation to negative compared to neutral stimuli as a function of the 5-HTTLPR short variant), there is considerable debate about the interpretation of this observation [14]. The intuitive interpretation, which I refer to as the "standard" or "phasic activation" model, states that presence of the short variant enhances amygdala reactivity to briefly presented negative emotional stimuli. The alternative "tonic activation" model states that presence of the short variant enhances baseline resting activation of the amygdala in the absence of cognitive processes. In support of this model, we have presented data from fMRI studies suggesting elevated amygdala activation in S subjects when participants are not engaged in emotional perception and attention tasks [15-16], and also shown that blood flow at rest is elevated as function of the short variant [16], an observation that was independently confirmed [17]. However, an alternative interpretation of this data is that participants are reacting to the uncertainty of being placed in a brain scanner with no specific task [18], so that the elevated activation still reflects a response to external stimuli rather than an internal level of elevated baseline activity. And so the debate continues.

Gene-environment interactions

Initial results

The seminal work of Caspi and colleagues showed that the influence of life stress on depression is moderated by 5-HTTLPR genotype [19]: *S* subjects were found to be up to two-fold more likely to become depressed after stressful events such as bereavement, romantic disasters, illness, or job loss, and childhood maltreatment significantly increased this probability.

Complications

Later partial replications suggest further moderation by gender [20-21] or social support [22]. Two studies [23-24] failed to replicate this GxE effect altogether, but also used older subject populations than the other studies, suggesting that age may also be an important variable. As was suggested for earlier association studies, partial or inconsistent replications may also be attributable to a small effect size, which may be addressed with endophenotype measures, such as those obtained through neuroimaging. The authors of a recent meta-analysis concluded that adding the 5-HTTLPR genotype does not improve the prediction of depression in relation with exposure to negative life events [25]. However, this meta-analysis did not take into account many of the potentially important methodological differences across studies that may have affected study outcomes [26], such as subject characteristics (age, gender) and lifetime stress assessment (self-report versus interview).

Toward molecular mechanisms

Initial results

An attractive candidate set of molecular mechanisms of GxE interactions is *epigenetic programming*, in which environmental factors may be able to cause changes in gene activity (turning on or off genes, altering their expression levels). One such epigenetic

mechanism involves DNA methylation, in which methyl groups are added to the cytosine bases on CpG islands (repeated sequences of CG in the DNA sequence), with the functional consequence of commonly reducing or silencing gene expression. Indeed, there is now preliminary evidence for methylation differences as a function of 5-HTTLPR genotype [27-28]. However, the most striking evidence for a GxE interaction involving life experience as an environmental factor comes from rodent studies that have shown that early maternal experience alters methylation of the glucocorticoid receptor gene in a manner that affects later stress reactivity and that is reversible through cross-fostering or through chemical agents that reverse gene methylation [29].

Complications

Gene expression, unlike an individual's DNA sequence, is tissue-specific, meaning that some genes may be activated in some tissue but not in other. This poses a problem for social scientists who wish to relate gene expression to behavioral phenotypes, because access to brain tissue is limited. Thus, work has either relied on animal brain tissue [29], or used *postmortem* human brain tissue, as in studies comparing brain tissue from suicide and accident victims [30-34]. Future technologies based on imaging ligands that are sensitive to epigenetic molecules may widen access to the living human brain, but it is unknown if and when such technologies will become available.

There is some evidence that peripheral tissue may contain useful epigenetic clues. For example, social stress such as loneliness or care-giving has been associated with differential genome-wide transcriptional activity in peripheral blood leukocytes (which are regulated by cortisol, a stress hormone) [35-36]. Such data illustrate that gene expression can be differentially regulated in the periphery as a function of psychological environmental factors, presumably as a downstream consequence of other processes taking place in the brain.

A role for social scientists

There are several reasons to increase the number of social scientists in GCSB. First, the phenotypes of interest are behaviorally defined, requiring expertise in the conceptual tools of behavioral analysis. Second, given that gene expression can be regulated by life experience, genetically informed behavioral interventions may be useful avenues for future research. Third, the abundance of genetic data, as obtained from genome-wide expression studies, may benefit from a behavioral analysis that prioritizes the study of specific genes that may be particularly relevant for behavioral phenotypes of big social relevance (e.g., addiction, aggression, risk-taking).

Overcoming barriers of entry: High impact investments in GCSB

The barriers of to entry to social scientists are considerable: mastery of multiple highly technical fields, access to brain scanners, access to molecular biology labs and expert personnel, access to potential collaborators. I suggest that the highest impact investment that NSF can make is to build an educational and technological infrastructure to enable a larger number of researchers to enter the field of GCSB and foster collaborations between scholars in the social and biological sciences.

Immediate impact at minimal cost: Tuition coverage for summer courses for non-biologists

There are *existing* summer courses in molecular biology that are designed for non-experts, and even non-biologists. NSF could cover the tuition (usually at most a few thousand Dollars) of individuals who seek to attend such courses. For example, my own foray into molecular biology was launched in a two-week summer workshop at Smith College in Massachusetts, called the "New England Biolabs Molecular Biology Summer Workshop"

(http://www.science.smith.edu/neb/). This workshop is accessible even to non-biologists, with no prerequisite knowledge required. Students spend 10-12 hours a day for two weeks in lectures and in the lab, and gain hands-on experience from Day 1. The course has been taught for 23 years, is offered three times each summer, and its contents are continuously updated to teach the latest techniques. This course is so efficiently designed and run that after two weeks students will have the knowledge and hands-on experience comparable to about one year of graduate-level molecular biology.

In addition to the Smith College workshop, Cold Spring Harbor Laboratory offers a large number of workshops and courses throughout the year (http://meetings.cshl.edu/). The offerings vary from year to year, but always feature leading scientists as organizers and speakers. In a similar vein, Woods Hole Marine Biology Laboratory also has a fantastic reputation for its summer courses (http://www.mbl.edu/education/courses/summer/index.html). I am sure this is not an exhaustive list, but a useful starting point for researching training and educational opportunities.

Longer-term impact at medium cost: Building a network of collaborating PIs supported by seed grants

NSF could fund workshops, conferences, and retreats designed to bring together experts in the biological and social sciences for the purpose of exploring collaborative interests. In order for these collaborations to take off, it would be critical to offer a funding mechanism for dual-PI (one social, one biological) seed grant applications.

Transformative impact: Core Facilities

A truly transformative initiative would be the establishment of GCSB-dedicated Core Facilities around the United States that cater technical services to researchers with great ideas but no access to the proper facilities. Such Core facilities would not need to be created from scratch. Rather, funds could be made available to existing facilities (NSF-funded MRI or Genetics Centers) to support the purchase of additional equipment and the hiring of additional staff (technicians, biostatisticians etc.) whose primary duty is to serve a user base of non-experts. This would be an initiative with immediate impact, creating high-quality technical jobs and opening access to a large group of scholars that are currently excluded from contributing their intellectual visions to the development of GCSB.

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8. A White Paper by Susan Courtney, Johns Hopkins University, Department of Psychological and Brain Sciences

The Cognitive Neural Subsystems of Self-Control:A starting point for understanding of the effects of genes and experience on social behavior

INTRODUCTION

While often studied in experimentally imposed isolation, genes, cognition, and social behavior are inextricably intertwined, and their effects on each other evolve with development and experience. Genetic variation affects the production of proteins necessary for the development and function of all neural circuits and systems, including those involved in cognition and social behavior. Social behavior depends on the encoding, maintenance and manipulation of goal-relevant information in cognitive systems. The goal-relevant information maintained and used by the cognitive system is in part gained through social interactions. Cognition is also affected by social behavior and socially-relevant stimulus feedback through the influence of expected reward on selective attention and other cognitive information processing systems. Finally, cognitive and social stimuli and behaviors affect gene expression and change these systems both in the short and the long term. Understanding how the interactions among genes, cognition, and social behavior affect individuals and society throughout the lifespan is a tremendous challenge, but one which the interdisciplinary scientific community is ready to tackle. What we need is a tractable framework regarding the hubs in this system. Making progress on understanding each of these hubs will have a large impact on our understanding of the entire system.

In this paper I will focus on one potential hub, a set of cognitive neural systems involved in a key aspect of social behavior, self-control. Optimal behavior of an

individual in an ever-changing social environment requires the integration of multiple types of information and the processing of complex relationships. Cognitive neural systems must engage in reasoning in order to develop a prediction of what will be the most productive strategy and translate that strategy into a series of concrete behaviors. Information about the current goals and the means to achieve those goals must be maintained or updated over time as events unfold. Explicit self-control involves using these maintained representations of what is most important for the current context to guide behavior. The neural mechanisms of this "self-control" process compete with those governing potential pre-potent and habitual responses. An example of self-control regarding social behavior would be the ability to suppress an angry response to a conflict and instead choose to engage in more productive, problem-solving dialogue. Another example of self-control would be the ability to use one's limited grocery budget this week to buy healthy food instead of the habitual or emotionally appealing junk food. Thus, understanding the genetic and environmental factors underlying individual differences in the ability to exercise self-control, would have broad impacts on fields as diverse as individual health, public safety, and national defense.

The stronger the representation of a pre-potent or habitual response, the more difficult it will be for the cognitive reasoning systems to achieve control over one's behavior. The relative strengths of the cognitive, emotional, and habitual neural systems (and thus the likelihood that one or the other will win the competition) are influenced by attention, by genes and by experience. They are also subject to the effects of damage, disease, and stress. In this paper I highlight a few of the recent findings regarding the

neural systems of self-control that suggest potentially transformative research directions regarding social behavior.

NEURAL MECHANISMS OF SELF-CONTROL

Working memory: Encoding and Maintenance of Goal-Relevant Information

A fundamental cognitive ability underlying self-control is working memory. Working memory is the ability to maintain a limited amount of currently relevant information in an active state in order to use that information to guide behavior. Baddeley and Hitch (1974) developed a classic model of working memory, which involved two "slave systems" for representing the stored information, and the "central executive" for selecting, manipulating, and using that information. They proposed two separate slave systems: the phonological loop for maintaining verbal information (such as words or digits) and the visuospatial sketch pad, for maintaining visual and spatial information (such as spatial locations or images of objects and faces). Recent research suggests that more abstract types of information, such as rules and relationships, may also be maintained in working memory through similar neural mechanisms (e.g. Montojo and Courtney, 2008). The prefrontal cortex, which plays a critical role in maintaining information in working memory appears to have multiple, interacting parallel pathways, each of which may be hierarchically organized from posterior to anterior prefrontal cortex (Kochelin et al., 2003; Christof et al., 2009; Badre & D'Esposito, 2009) with more abstract or relational information processed and represented in more anterior areas. The most ventral, medial, and anterior parts of prefrontal cortex appear to be particularly important for remembering and using social information.

The prefrontal cortex does not work alone to maintain or use these various types of currently relevant information. Recent theories posit that at least some kinds of information are maintained in working memory through reverberating circuits between prefrontal cortex and secondary sensory areas (Fuster, 2001), perhaps resulting in the reinstatement of information in sensory areas (Woloszyn & Sheinberg, 2009), and affecting the processing of future expected stimuli. Accordingly, recent evidence suggests that working memory performance is dependent on the long-range white matter pathways that connect these areas. Individual differences in performance on a working memory task for faces was found to be specifically correlated with individual differences in the microstructure of one of these pathways, suggesting a role for genetics and/or experience in face memory ability (Walsh et al., under review). Similar results might be expected regarding the structure and function of neural systems that maintain more complex and abstract information in working memory, such as rules or relationships.

Neural mechanisms of responses based on stimulus salience or habit

In the absence of biasing signals from prefrontal cortex, behavior is driven primarily by stimulus salience and by the behavior performed on previous occasions with a similar stimulus context, either recently or habitually. Behavior that may have been initially dependent on the prefrontal cortex becomes with repeated performance "automatic", proceding without cognitive control (Raichle et al., 1994). The more established an "automatic", habitual behavior is, the greater the input needed from prefrontal cortex to override that behavior. Injury, disease or lack of full development can all weaken prefrontal cortex, making it more difficult for an individual to change maladaptive behavior habits. Prefrontal cortex can also be strengthened or weakened by

transient changes in the levels of neurotransmitters, such as dopamine and noradrenaline during states of high emotional stress (Arnsten, 2009) or due tonic individual differences from genetic variants (e.g. Bertolino et al., 2006).

Stimulus salience is usually discussed in terms of physical stimulus properties such as color contrast or sound intensity. Sensory neurons have a larger change in activity for stimuli that are more different from stimuli that are nearby in space or time. In addition, reward expectation (and perhaps also reward history in the absence of current reward expectation) can change the effective salience of a particular stimulus for an individual. It might also change the pre-potency of a particular response associated with a stimulus. Normal genetic variation influences the responsivity of brain areas involved in coding the expected reward and response to reward receipt (Dreher et al., 2009). Thus, the brain response to a stimulus associated with an expected reward may be inherently stronger or weaker in some individuals than in others (e.g. Beaver et al., 2006). Reward-related tuning of prefrontal cortex is also likely to be different across individuals.

Thus, multiple lines of research are beginning to establish a framework for understanding the cognitive neural systems that are necessary for self-control, and some of the many factors, including genes and experience, that predict whether an individual will be successful at over-riding salient or habitual responses and exerting self-control.

Neural basis of "Free will" a.k.a. "Voluntary decisions"

As complex as these cognitive neural systems and the factors that influence them are, there is another more elusive element to "self-control." What happens when there is no clear winner among the stimulus driven, habitual, or cognitively reasoned behavioral options? We say that we "choose" one option over the other. What are the neural

mechanisms behind this "free" behavioral choice? Most research on the neural mechanisms of voluntary actions has used instructional cues that tell the subject when to respond and/or what the correct (or rewarded) action is. This situation is seen as a voluntary action because the subject can choose whether to comply with the instructions and the instruction cue for one behavior is not more physically salient than the cue for a different behavior. The behavior is still externally influenced, however. Experimentally it is difficult to separate the decision process from the stimuli leading to the decision or the motor response indicating the outcome of the decision. Researchers have begun to develop methods with functional brain imaging to monitor the attentional state of the subject without any explicit instructional cues or overt motor acts (Gmeindl, et al., in prep). By doing so, one can deduce when a subject chose to shift from one attentional state to another and then look backward in time to examine the neural processes that lead to that choice. In these experiments, subjects have no expectations of reward for choosing to pay attention to one thing versus another at any particular time. The results of these experiments suggest a gradual build up of activation within prefrontal cortex prior to a shift of attention, which apparently eventually triggers a transient shift signal within the same brain areas as those that govern instruction cue-driven shifts of attention.

These types of purely voluntary shifts of attention are likely large ultimate contributors to purely voluntary behavioral choices. The relative strength of the neural representation of a stimulus-driven, habitual, or cognitively reasoned course of action can be influenced by attention. Furthermore, the relative strength of representation of various factors contributing to a cognitive reasoning process can also be strengthened by attention, affecting the outcome of that reasoning process. With a deep understanding of this system,

we may find the same genetic and environmental factors discussed earlier as being involved in stimulus-salience driven, habitual, or cognitively reasoned decisions, may also affect the outcome of these "free" decisions. Alternatively, there may be different or additional factors, such as an individual's preferences (which may in turn have their own genetic and environmental/experience-related influences).

OPPORTUNITIES

Below I list some example research areas with the potential for near-term high-impact discovery regarding the interactions among genes, cognition and social behavior, focusing on components of the cognitive neural systems of self-control.

1) Attention:

Attention dynamically shifts the competitive bias and thus the enhanced processing of information from, for example, different sensory stimuli, social interactions with different individuals, different emotional states, or different pieces of evidence relevant to a decision. We pay attention to things that we want to acquire, things we want to avoid, and things that provide information about what actions are likely to result in acquiring what we want and avoiding what we don't want. Many factors influence what an individual will pay attention to at any given moment. Here are a few of those factors that are amenable to research with further development of existing methodologies

a. Genetically and developmentally influenced individual differences in reward sensitivity.

b. Individual differences in reward history

c. Genetically and developmentally influenced individual differences in the ability to focus and to shift attention

d. Individual differences in brain structure and function related to these factors.

2) Working memory:

The neural systems underlying working memory have been studied primarily in the context of remembering concrete information, usually information directly tied to specific sensory stimuli. Perhaps more relevant to social behavior research is the ability to maintain in working memory more abstract information, such as rules and relationships. A few research directions that could have a high impact on understanding social behavior are:

a. Are the neural systems that maintain concrete stimulus information in working memory the same as those that maintain more abstract (rule, relational, or social) information in working memory?

b. Are the genetic, developmental, and environmental factors that are related to individual differences in working memory capacity for concrete information, and the associated aspects of brain structure and function, the same as those that influence working memory capacity for abstract information?

3) Control over actions

While we would like to believe that our behavior is under our conscious control and that we can act according to our cognitively reasoned evaluation of the action most likely to result in our desired outcome, there are clearly instances in which this is not the case. There are additional steps and additional neural systems that translate cognitively derived and maintained information into actions. These systems enable us to inhibit undesired actions and initiate desired actions.

a. What are the neural systems underlying voluntary (internally driven) behavioral choices and how are these systems influenced by genes, development, and environmental factors?

b. What are the neural mechanisms that stop a planned or ongoing behavior pattern and initiate a new course of action, and how are these systems influenced by genetic, developmental, and environmental factors?

4) General aspects of brain structure, function, and organization that are influenced by genes and environment.

In addition to the potential selective effects of genes on subcomponents of cognitive neural systems and the effects of cognitive abilities on social behavior, there are likely genetic and environmental factors that result in broader individual differences in brain structure, function, and organization that influence both cognition and social behavior.

a. What are the factors affecting individual differences in the functional balance between and interactions of the dorsal (spatial and cognitive control) and ventral (stimulus recognition and reward responsive) brain systems?

b. What are the factors affecting the relative strength of long-range interactions among brain areas (that might be more related to attention, working memory and action control) versus those affecting short-range interactions, such as bottom-up stimulus processing and subcortical mechanisms of emotion and motivation.

c. What effects do chronic stress and current stress states have on the relative strengths of different brain systems?

Much research is already being done in these areas, but it is generally isolated from questions of the impact of such systems on social behavior, in part because of the difficulty in establishing socially relevant variables that are well defined and controlled. This barrier is not insurmountable, however. In addition, current research suggests that neuroimaging measures of cognitive neural systems may provide a very sensitive bridge between genetic and environmental factors and cognitive/social abilities and behaviors. In some cases too many uncontrollable variables preclude finding a relationship between a genetic or environmental factor and a social behavior directly. However, one may be able to identify a link between the function or structure of a neural system and a social behavior, and, independently, a link between genetic or environmental factors and individual variation in the function or structure of that same system. Similar results have been found recently for cognitive (Walsh et al., submitted) and emotional (Kim &

Whalen, 2009) neural systems. A similar approach applied to the neural systems of self-control may prove highly fruitful for social behavioral research.

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9. A White Paper by Russell Fernald, Department of Biology, Stanford University

What fundable research on genetics, cognition and social behavior will generate transformative scientific practices, scholarly infrastructure, and widely relevant findings of high social value?

1. Educational programs about genes, genomic function and use of genomic information

1.A. NSF could develop and promote genomic teaching and learning across the age spectrum.

The sequencing of the human genome was announced with great (and justified) fanfare: "So never fear -- the human genome is nothing like the bland medical textbook that those who decoded it are intent on describing. When fully translated, it will prove the ultimate thriller -- the indisputable guide to the graces and horrors of human nature, the creations and cruelties of the human mind, the unbearable light and darkness of being."(N. Wade, NYT, 2/18/2001). Yet, ten years later we know: "But the primary goal of the $3 billion Human Genome Project — to ferret out the genetic roots of common diseases like cancer and Alzheimer's and then generate treatments — remains largely elusive. Indeed, after 10 years of effort, geneticists are almost back to square one in knowing where to look for the roots of common diseases. (N. Wade, NYT 6/12/2010).

There are several issues here that reflect a widespread, essential ignorance in the general public about the new "science" of human genetics. I propose that a useful and relevant goal for NSF could be broadly conceived as 'genomics education'. Since genomic information will continue to dominate parts of the national conversation from health care (including genetically based choices during pregnancy), social welfare, the

judicial system and many other domains including education itself, we need to have informed citizens who know what genomic information is, how to think about it and specifically what to do with this new class of information.

A sequenced genome is simply a 'parts list,' not a blueprint that might be used to assemble an organism. Scientists who advocated sequencing the human genome clearly knew this but the hubris surrounding the sequencing effort was interpreted by a public without reasonable knowledge about what exactly to expect from a genome sequence. Among other things, the sequenced genome has not proven particularly useful for predicting disease. For example, 101 genetic variants, statistically linked to heart disease in various genome-scanning studies had no value in forecasting disease among 19,000 women who had been followed for 12 years. Rather, a family history was a better guide (cited in Wade, NYT 6/12/20100).

Why is this? Once an organism is born, its genes are not passive but active participants in the life of an organism, being turned on and off as needed. Moreover, since the early days of genetic sequencing, when large expanses of the human genome were described as "junk DNA", newly discovered genes controlled by this 'junk DNA' (RNAi, microRNAs, eRNAs etc.) have been identified and provide a glimmer of their complex roles in regulating gene expression in functioning organisms.

Who needs to know about this and what kind of information do they need? In pregnancy, women at University hospitals are now confronted with over 100 kinds of risk associated with particular genes. But most have little idea about how to assess probabilities of risk in making important life and death suggestions. In the new "genetic medicine" there are now drugs whose efficacy is understood to depend on particular

genes in the patient. Can the patient understand that she will not receive a drug because of the prediction *a priori* that it will not work? These are just the tip of the iceberg of issues already upon us that hint at the importance of an educated public.

1.B. NSF could promote genomic teaching and learning for the next generation of social scientists.

As genomic information becomes more readily available, there needs to be social scientists that are conversant with the power and limits of genetic tools applied to social questions. There are now conferences directed at the role of genomics in social questions (e.g., http://www.colorado.edu/ibs/CUPC/conferences/IGSS_2010/) but very few explicit training programs. One relatively simple solution to this problem is to develop a summer institute for graduate students and postdoctoral fellows that will provide instruction for a new generation of scholars. One very effective example of this is the Summer Institute in Cognitive Neuroscience founded and directed by Michael Gazzaniga (U.C. Santa Barbara). This program has provided important teaching and learning for neuroscientists who are beginning to develop research programs about cognition. While some other organizations exist that work on similar issues (e.g., http://www.nchpeg.org/index.php?option=com_content&view=article&id=56:morbi-dolor&catid=35:todays-highlights), it seems clear that the Summer Institute has had a major impact on the development of the field of cognitive neuroscience. A similar program that was directed to social scientists learning about the value and limits of genetic information could be transformative.

2) Social Information Processing, Genomic Programs and Psychopathology

To survive, social species must collect, process and respond to social signals from

conspecifics. Suitable and appropriate responses are necessary not only for reproductive success but also for functioning in complex social groups. These skills are most evident in human societies but are equally important in other animals living socially. Understanding the biological bases of behavioral responses and corresponding social signal processing is important not only to address biological questions, but also for human health issues. For example, nearly every psychiatric illness listed in DSM-IV includes aspects of competence in social capability as a core component of real-life impairments. For example, mood disorders, schizophrenia, personality disorders, drug addiction, and anorexia nervosa seriously impact social functioning. Neurodegenerative disorders such as Parkinson's, Huntington's, and Alzheimer's disease also have a strong impact on social functioning. What could genetics bring to these problems?

Developmental biology benefited tremendously from the discovery that specific gene networks, the HOX gene families, are responsible for body plan development and are highly conserved across all species. One key question is whether there is a comparable conserved gene network for vertebrate social cognition and behavior? Evidence for such conservation of function for molecules and systems involved in regulating social behavior can be glimpsed in the peptides oxytocin, vasopressin and their ancestral homologues (Donaldson and Young 2008). Extensive research implicates these peptides in regulating social behavior from sexual behavior to parental and social bonding in all vertebrate taxa. Recent work even implicates oxytocin, for example, in altruistic group behavior and punishing members of a competing group (De Dru et al, 2010). Ancestral homologues of these peptides regulate sexual behavior and egg laying behavior in earthworms and snails. Recent studies demonstrate that oxytocin treatment

enhances social cognitive function in autistic individuals (Hollander, Bartz et al. 2007; Guastella, Einfeld et al. 2009; Andari, Duhamel et al. 2010). This observation provides a proof of principle that 1) evolutionarily conserved molecules and systems very likely regulate social behavior at some level, and 2) that discoveries made in animal models regarding social behavior can have direct translation implications for treating human psychiatric condition.

NSF could lead the way in funding groups of scientists who collaborate in finding genomic substrates for social behavior.

3) Gene by Environment Interactions Influencing Social Behavior

It is widely accepted that social behavior depends on both environmental and genetic variation, but our knowledge of environmental interactions with genes at the molecular level (GXE) are not well understood. Recently, there have been numerous reports describing moderating effects of particular genetic associations with social environment on particular behaviors or psychiatric conditions (Gillespie, Phifer et al. 2009). These arise because in human populations, epidemiologists observe interactions between two groups within a population, typically testing a behavioral effect relative to the presence or absence of a specific genetic polymorphism. Yet despite many reports of this type of interaction, recent studies suggest that there are limited cases in which clear relationships can be demonstrated due to insufficient statistical power (Munafo et al. 2008). However, it is essential that such connections between environmental and genomic influences be understood. We know, for example, that social inequalities have profound effects on the physical and mental health of children and that these effects can be traced to the electrical activity in the brain (e.g., Kishiyama et al., 2009). Understanding how genetic differences

amongst individuals contribute to these effects is critical for designing remediation programs.

NSF could initiate programs to discover how genetic and environmental differences among individuals produce the consequences for physical and mental health.

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10. A White Paper by Jeremy Freese, Department of Sociology Northwestern University

Why should social scientists be interested in using molecular genetic data?

First, given evidence from twin- and other family-based designed studies of the causal importance of genetic differences on a wide range of outcomes of social scientific interest, integrating genetic causes into social science theories is a necessary task toward understanding and explaining variation in these outcomes.

Second, abundant evidence points to the potential for genetic causation confounding estimates of social or other environmental causes on outcomes, and thus failure to account for confounding by genetic differences can lead to large biases throughout social science studies of individual-level outcomes.

Third, the *strict intrageneration exogeneity of DNA* – that baseline DNA assays do not change as a result of external events or internal development – suggests genetic data potentially being leveraged using "natural experiments" methods in order to better estimate effects of particular environmental causes on outcomes in situations that might otherwise appear intractable because of pervasive endogeneity.

Fourth, genetic measurement provides an entirely new and more powerful set of tools for studying migration and mating patterns.

Finally, given the usual failure of conventional social science models of individual outcomes to explain much of the existing variation in those outcomes, gene-environment interactions might be an important reason why individuals with similar environmental measures often still have very different outcomes.

To date, of course, research using molecular genetic data has been dominated by the pursuit of medical knowledge. As social scientists become interested in using genetics

in the study of a broader range of individual outcomes, an important question is whether social scientists can use lessons from the history of medical genetics research to minimize the extent to which social scientists repeat the same problems. Most prominent here is that, for studying the association between genetic variants and outcomes: *discovery is the easy part; separating true discoveries from false ones is much harder.* Medical genetics literature has a very large number of published associations that has subsequently failed to be replicable, including some that have received considerable media attention. The "candidate gene" approach of genetic research looks, from afar, like the proper method for science, with articulated hypotheses applied to data.

However, candidate gene studies are regarded with much suspicion in many areas of medical genetics, because *post hoc* explanations are relatively easy to recast as a priori hypotheses and because even findings from purely *a priori* hypotheses can result in a distorted literature due to publication biases of investigators, reviewers, and editors.

Candidate gene studies that have been published so far in major sociology, demography, and political science journals have various features that, taken together, could be read almost as a catalog of indicators of unlikely-to-reliably-replicate results: *ad hoc* model specification, *ad hoc* subgroup restrictions, *ad hoc* genetic models, and *ad hoc* selections of environmental variables for analyses of gene-environment interactions.

Analyses have tended to eschew power analyses and have reported effect sizes far larger than any reasonable expectation about the possible effect size. To take one example, a study of educational attainment published in the *American Journal of Sociology* reported an effect size for a genetic variant (*Taq*1a) on going to college that is as large as the total black- white difference in going to college. Indeed, nothing as yet

exists to contradict the gloomy hypothesis that the aforementioned social sciences have yet to publish a single genetic main effect or gene-environment interaction that is "real" in the sense of an established, replicable causal relationship still appears reasonable. In other words, it is quite reasonable to suppose that *none* of the few dozen studies that have been published to date will withstand future empirical study on independent data.

The primary source of this problem is plain enough: *presently there are enough data to discover associations, but not enough data to discern true associations from false ones*. Most of the candidate gene studies in social science have relied on genetic data available in a single data source, the National Longitudinal Study of Adolescent Health (Add Health). Add Health deserves considerable credit for being pioneering in obtaining molecular genetic assays and in making its data securely available to a broad number of investigators without onerous co-authorship agreements. But, medical genetics makes plain that single- dataset discoveries of gene-outcome associations (and, worse, gene×environment-outcome associations) are prone to very high rates of replication failure. Accordingly, any literature for which “discoveries” of gene or gene×environment associations from single datasets and with ad hoc specifications are publishable is a literature that will be replete with false positive findings. Opinions vary about the pragmatic virtues of weeding out false positive findings before or after publication, but, one way or another, their weeding is an absolute necessity in order to have any firm basis toward realizing any of the potential benefits of genetic data to social science presented above. This can only be done with more data that are available to more investigators.

Happily, much more data is on the way, including assays in other large population datasets with long established track records, like the Wisconsin Longitudinal Study and

the Health and Retirement Study. Funding for these initiatives is driven almost entirely by the prospective contributions of these datasets to health research, although fortunately in the aforementioned cases a broader substantive range of outcomes of interest to social scientists happen to be included, along with a range of psychosocial measures that can be used toward possibly identifying mediating psychological mechanisms of genes and social science phenotypes. (Add Health, WLS, and HRS all have significant cognitive assessments, for instance.) Given the complexity and cost of assaying -- even as the latter rapidly declines -- social science funding sources may receive a better return from attempting to extend social science measures for which assays are available or underway, rather than supporting assaying of respondents for other datasets unless the latter offer particular advantages and wide availability to social scientists. (Importantly, a condition of investing in social science measures needs to be that these measures will be available to the broad community of investigators for analysis without onerous co-authorship agreements.)

In medical science there has been increasing movements toward consortia that allow for inference from combined datasets. Regardless of how cheap genotyping becomes, such consortia seem a necessity for various types of social science studies with genetic data to be conducted with any appreciable statistical power, barring some substantial revision in the variance accounted for by individual SNPs or sites of copy number variation.

Consortia in medicine are logistically complicated in ways that are consistent with the high expense and broad distribution of specialized methodological expertise in health research. Even under bullish scenarios, the integration of genetics into social science will

be carried forward by fewer people doing projects for less money, and consortia need to be organized in ways that are nimble, efficient in terms of staffing required to access data, and working to share expertise as well as data. For this, *outreach projects focused on improving data accessibility and methodological training may be particularly valuable for social science*, especially insofar as they help toward building ties across institutions to compensate for the more diffuse affiliations of investigators.

Much of the social science interest in genetics has focused on possible gene × environment interplay, and often in terms of "contextual" environmental variables. An example would be recent work on how heritability of smoking varies as cigarette taxes vary.

Consortia seem essential to the extension of work to molecular genetic data, given power considerations are even more acute for estimating systematic moderation of causal effects than for estimating average causal effects. Beyond this, however, such studies may benefit particularly from ongoing work that is attempting to extend inference for sparse data by combining information across datasets (an example of this would be using census data to strengthen state-level inferences in a public opinion poll that would be otherwise too sparsely distributed). In other words, as statistical power appears likely to be a vital issue for any applications of molecular genetic data in social science, *the continued development of methods to increase power of studies by combining data sources* will be among those most beneficial to the enterprise.

Because health research has so far provided the major resource for molecular genetic data collection and analysis, much of the methodological apparatus has developed with health outcomes foremost in mind. As interest in genetics has broadened to

substantive domains that are unrelated to health, the possibility increases of methodological problems due to disanalogies between prototypic health outcomes and other outcomes social scientists study. Many social attainments, for example, are of interest to social scientists in no small part because of their intergenerational reproduction--that is, socioeconomic attainment in one generation provides an advantage toward socioeconomic attainment in the next. Moreover, ancestry itself is a source of social categorization and action by others upon that categorization. For those reasons, what genetic research calls the problem of "population stratification" glosses a series of a fairly foundational social dynamics, whose implications for the study of genetics and attainments are at present essentially unexplicated. That marks a key area for theoretical development, but it also has the direct consequence that population stratification likely provides a much more significant problem for estimation than many social scientists presently appreciate. This is especially so for approaches to population stratification other than the simplest and most assured: the analysis of sibling data. *When evaluating different candidate data sources for investment, the special value of data with siblings -- and, even better, combinations of siblings and parents -- needs to be emphasized.*

Large-scale assaying has yielded some applications of inferences based on deviations from .5 inheritance by descent among full siblings. This has been suggested as a general technique by which sibling data could be used to make inferences similar to what twin data are used for presently, which would have the nice consequence of alleviating concerns about particularities of twinning and twin-based sampling. In other words, this could make sibling data even more valuable to genetics studies. At the same time, homogamy and other nonrandom mechanisms exist that can yield different

estimates of inheritance by descent, and the implications for inference are, to my knowledge, not well- specified, especially in terms of outcomes like attainments and for how homogamy affect the potential use of this technique for studying environmental moderators of heritability.

Another area in which seemingly strong methodological promise is tempered by practical ambiguity is the use of genetic variants to conduct instrumental variable estimation (sometimes called "Mendelian randomization" techniques). A medical example is using a known genetic marker of variation in C-reactive protein to estimate the relationship between C-reactive protein levels and cardiovascular disease, which reported that this apparent relationship might be spurious. An attempted social application has been to use genetic variants associated with obesity to estimate the relationship between obesity and socioeconomic attainments. On the one hand, the techniques seem very promising for addressing problems that otherwise might be intractable because of pervasive reverse causality, given the natural intragenerational exogeneity of genes. On the other hand, given that genes typically have very small and multiple effects, the exclusion criterion of IV estimators are almost certainly going to be often violated, but the consequences of this violation might be mitigated by the ability to use a number of different variants as instruments. Again, though, it seems like basic methodological work is going to be central to figuring out whether substantive breakthroughs for the social science can be achieved using this technique or whether problems associated with it are effectively insurmountable.

Taking stock, for genetics research to realize its promise in the social sciences, we need more data and more development of methods with specific challenges of social

science analysis at the fore. Additionally, genetics work in the social sciences remains relatively underdeveloped in terms of the integration of actual social science theory. For instance, basic sociological or economics theory expects people to specialize in areas in which they evince aptitude and that specialization will lead to further gaps in proficiency between the specialist and others. If aptitudes in various domains are ubiquitiously influenced by genes, as behavioral genetics would lead us to expect, then gene-environment correlations should be an ubiquitous and essential feature of the social world (i.e., at least regarding social attainments, genetic predictors of skills and attainments should be pervasively positively correlated with conditions promoting those same skills and attainments).

As another instance, a staple of epidemiological sociology is that social differences (especially in education) influence the extent to which individuals can act upon knowledge to achieve better health outcomes. We would therefore expect take-up of knowledge gained from genetic to differ by social groups in ways that are presently underexamined. More than this, differences in action on the indirect information about inheritance and disease that already exist may be an important systematic moderator of the relationship between genes and health outcomes. The strength of social science is its dynamic vision of actors with beliefs and preferences interacting with one another and with larger institutions. The implication of causally relevant genetic differences need to be fully integrated into that vision.

In the long run, molecular genetics work will almost certainly transform our understanding of basic human behavior and the conduct of the social science study of individual-level outcomes. Evidence of the importance of genetic causes of social science

outcomes is abundant, as is their potential for revision and elaboration of our understanding of social causes, and data that will allow increased understanding of these causal relationships is increasing rapidly and inexorably. At the same time, we are at the point where pitfalls of inferences from genetic data are apparent and a key part of investment is figuring out the most efficient way of navigating these pitfalls, with a minimum of accumulated distrust from premature claims. Achieving this efficiency is going to require basic work on data availability, the dissemination of expertise, the creation of collaborative relationships across institutions, the development of methods, and the improved conceptual integration of genetics with social science theory.

11. White Paper by Elizabeth Hammock, Department of Pediatrics, Vanderbilt University

Purpose: To define gene variance and describe the advances in the genetics and neuroscience of social behavior of the past decade and to propose suggestions for efficient resource use for research in the near term.

Bottom-up perspective on Social behavior

From a biologist's perspective, social behavior includes any behavior that involves at least two actors. By this definition, social behavior can include aggregation in slime molds, the colony structure of the eusocial insects or the coordinated efforts of humans across vast distances to successfully land on the moon. The diversity of this range of behavior shares one driving force: natural selection. While natural selection acts at the level of phenotype (e.g. morphology, metabolism, behavior) the ultimate unit of natural selection is the gene contained in DNA -the object of inheritance. The relationship between DNA and social behavior is uncovered in the field of *sociogenomics* defined as the mechanistic study of genes, gene products and gene x gene interaction networks supporting emergent social behaviors [1-3].

From a neuroscientist's perspective, the brain is an experience-expectant organ that serves to maintain homeostatic balance. The main behavioral tasks that the brain has been selected to perform are the "four Fs": feeding, fleeing, fighting and mating. Mammalian brains have added layers and layers of control to these behaviors. Extra layers of control correlate with larger brains requiring longer postnatal development before reaching full maturity. The extra experience-expectant developmental time allows us to gain skills to manage and manipulate our environment, including our social environment. There is significant variation in this ability across individuals as well as

across time within a given individual. This variability must come from individual differences in brain structure/function, which in turn derives from genes, environment and their interaction throughout development and into maturity.

Really, what is a gene?

Historically, text books defined a gene as a linear sequence of DNA that is translated into protein by specialized cell machinery. Proteins were awarded the status of the intermediary between DNA and phenotype. In recent decades, however, this view has been clarified. It turns out that "genes" are really laborious to define with precision and are of somewhat indeterminate size and proteins are not the only product of DNA with functional properties. The hardest part of defining a gene is determining which parts of the genome carry instructions for when and where a gene product should be made. Should a protein be present only in neurons that produce glutamate or neurons that produce some other neurotransmitter? Should it be present throughout the lifespan of the individual or only during development or only after mating or in a fight-or-flight moment? Some gene control regions occur in the linear DNA sequence immediately before the protein coding region starts, some control regions occur immediately after the coding sequence has ended, and there are even control regions for a given gene that may exist thousands of base pairs away from the protein-coding region of the gene, and are sometimes intermingled with other protein coding regions for separate genes. Gone are the days of the simple notion of a "gene". A protein or other product of a DNA sequence is nothing without the instructions for where and when it should be expressed. As an illustration, there are very few differences in protein coding regions between

chimpanzees and humans, the majority of the genomic differences reside in the non-coding gene-control sequences.

How do individual genomes differ?

Gene variation among individuals contributes to variation in brain structure and function which contributes to differences in social behavior. There are several kinds of individual variation in genomes. There are single nucleotide polymorphisms (SNPs), short tandem repeats (STRs), inversions, insertions/deletions (INDELs) and copy number variation (CNV). These changes in the sequence of DNA can occur within coding regions of genes and can alter protein activity or they may occur in non-coding regions of DNA where they do not alter the transcribed portion of a gene but instead alter the quantity and location of a protein or other gene product.

How do we assess genome differences? Long sequence reads allowed us to piece together the draft genome. These long reads employ labor intensive methods and are cost-prohibitive. Brand new techniques involving sequencing by synthesis are high throughput allowing for very short sequence reads, but force the genome into a single size mold and are not technically capable of discovering certain kinds of gene variation, including STRs and inversions. There are several new technologies emerging on the horizon that can make up for the gaps in methodology. One such method involves threading single DNA molecules through a nanopore detector that immediately reads the sequence [4]. When applied in parallel, multiple long DNA molecules can be read simultaneously. Theoretically, this permits determination of all kinds of gene variation. The newest arrival on the horizon of whole genome analysis involves high throughput ascertainment of the significant inter-individual structural variation in the human genome

[5], with promised structural analysis of individual genomes for less than $1000 in under an hour.

Why is genetic methodology so important? Not all technologies are capable of recognizing all kinds of gene variation. There is growing frustration in medical and psychiatric genetics for the disappointing strength of findings in gene association studies as researchers continue to look for "the missing heritability" [6]. The causal gene in single-gene disorders such as Huntington's disease, Rett syndrome and Fragile X, has been identified. In contrast, we are still searching for gene variation that will robustly explain risk for disorders with high heritability, including autism and schizophrenia. Until recently, SNPs have been the main target for investigation. This approach has yielded some insights into risk alleles that may contribute to these disorders (e.g. [7, 8]). Both common alleles and rare mutants have been studied and both offer some explanation. Promising new insights have come from focusing not on SNPs but on other kinds of genomic variation, including structural variation in the genome [9-12] . To make steady progress in understanding how genetic variation leads to behavioral variation in health and disease, ALL kinds of genomic variation should be considered.

What do we know about gene variation and social behavior?

Let us look at a few examples from the literature that relate each kind of genetic variation to individual or species differences in social behavior. First, we will look at SNPs, then STRs and finally CNVs and structural variation. The examples included are chosen because of the strong correlation between a given gene variant and behavior, but also because they demonstrate mechanistic evidence at the level of the nervous system.

Such evidence adds weight to the gene:behavior relationship. Because of this, these examples are limited to animal studies and gene studies in human disease.

Single Nucleotide Polymorphism and social behavior: The roundworm *C.elegans* is a well-known tractable model system in biology. While the social behavior of the roundworm is severely limited compared to that of humans, or vertebrates in general, we have been able to learn about mechanisms of genetic variation related to social behavior variation. Roundworms are a diverse species. Some strains of roundworms feed in social groups while others are solitary feeders. Variation in a single nucleotide in the coding region for a g-protein coupled receptor that looks like a mammalian neuropeptide y receptor (*npr-1*) can create this behavioral tendency [13, 14]. Roundworms feed on bacteria which can contain noxious stimuli. Noxious stimuli can cause worms to aggregate, perhaps to cooperate to secrete enzymes to inactivate bacterial toxins, for example. One version of the *npr-1* strongly inhibits aggregation in response to signals from bacteria. The other version of *npr-1* does not inhibit aggregation. Further, the probability of social aggregation is directly related to population density and the food satiety of the animals. The molecular and cellular players in detecting population density and satiety create an added layer of control. This example is not only informative in the details of gene and social behavioral variation but it also illustrates the molecular mechanisms of cooperation and competition that subserve social behavior (e.g. whether or not the worm should aggregate and cooperate to feed or remain in isolation).

Short Tandem Repeat and social behavior: Repeats have long been overlooked in association studies. They are more difficult to measure than SNPs and they incur statistical costs because of the high levels of polymorphism. There are multiple examples

of STR variation playing a role in social behavior phenotypes. The vasopressin 1a receptor (*Avpr1a*) promoter region in voles has become a popular example. A long history of behavioral neuroscience research on this receptor and its ligand, vasopressin, implicated this system in mediating pro-social attachment related behaviors in adult voles. In a series of comparative genetic studies, the *Avpr1a* upstream regulatory region was compared across four closely related species of voles. The length of a STR appeared to correlate with the species social structure. This simple finding led to a testable hypothesis that intraspecific variation in repeat length might be associated with intra-specific variation in social behavior. A breeding scheme that selected for longer STR length resulted in offspring that had a higher probability of forming a mate preference, increased social approach behavior and altered brain expression of the *Avpr1a* gene product [15]. This one example represents a minute portion of the possibility of the thousands of potentially functional STR sites in the human genome. Bioinformatic metanalysis of the genome indicates that many genes involved in neurodevelopment are enriched for STRs. This is an understudied area that deserves more attention. Developmental biologists will need to determine the developmental impact of relevant STRs and they would do well to accept the aid of statisticians who can help solve problems related to statistical power when there are so many allele possibilities.

Copy Number Variation and Structural Variation and social behavior: There are several disorders of brain development where structural variation and CNVs are caused or implicated. These include autism and schizophrenia, Williams syndrome, Prader-Willi/ Angelman syndrome. There are no examples yet of CNV or structural variation within the range of typical behavior in humans. In humans, mice and rats, there is evidence that

normal copy number variation across strains contributes to variation in gene expression [16-18]. It is not a stretch to consider a similar mechanism for individual differences in genes in the brain contributing to normal variation in behavioral traits. This is a promising area of future research.

What should we know about genes and social behavior? What is knowable in the near future with the right investment strategies? What is not knowable?

As we look at the near term (2010-2020) for research areas in which to invest precious research dollars, there are transformative ideas and curiosity-driven research questions that come to mind.

Near term research needs in new or understudied areas:

1) *Genome variation and behavioral variation in infancy and childhood*. In an effort to understand the strength of gene:behavior variation, it is reasonable to hypothesize that the earliest social orienting behaviors might have robust genomic correlates and that such gene effects are diluted over time due to environmental variance.

2) *Better understanding of sequence and structural variation in the human genome in healthy individuals.* This is a pressing topic in the face of the "missing heritability" question. Research is needed in coding and non-coding variation.

3) *Assessment of CNV/structural genome variation and typical social behavior variation*. This includes advances in statistical and computational approaches to determine significant relationships.

4) *Gene association studies are best understood in functional biological contexts* (i.e. what does a particular associated gene do in the biological system and when and where is it expressed.) This is a critical need in human development. We have very little knowledge of gene expression patterns in the developing and maturing human brain. To illustrate this point, oxytocin has been proposed as an adjunct treatment in the context of behavioral intervention for autism. We have no data regarding where these receptors are located in the human brain during childhood.

5) Epigenetic modifications by experience and parental inheritance.

Curiosity driven questions:

1) The neurobiology of in groups and out groups.
    a. Social phobia
    b. Political unrest
    c. Population genomics of jingoistic policies?
2) Social matching (genetic and behavioral typing)
    a. Mate finding
    b. Job matching
    c. Parent-child/ caregiver-child matching in domestic foster care?
    d. More efficient rehabilitation methods in criminal justice system?
3) Social ontogeny
    a. Post-natal social programming by experience-dependent epigenetics
    b. Are there other experience-dependent changes to the genome?
    c. What are the developmental sensitive periods
    d. What are neurobiological effector molecules?
    e. Is it possible to re-open sensitive period plasticity for retraining?
4) Trans-generational effects of social programming
5) Comparative genetics among social and non-social congeners
    a. voles
    b. primates
    c. domestic dogs
6) How do social and stress systems in the brain interact?
7) What potential impact can economic and/or social policy have on human genetics?
    a. With cultural bias for males, is there genetic selection in China after 1 child rule? This could serve as a bellwether for the impact of policies on population genetics.
    b. After The Pill and Roe V. Wade, is there genetic selection in the US against traits associated with reproductive choice (whatever those might be)?
8) Feasibility of Personal Genomics as a diplomacy tool (e.g. 23andme "ancestry finder")?

In the next 5 to 10 years, we should see more examples of gene variation linked to social behavioral variation, especially with the kinds of genomic variation that are currently understudied. We will not likely be able to predict with meaningful accuracy an individual's behavior based on an individual's genome or life history. However, at

group levels we will have increasing power to assess the probability of given traits and social behaviors. This can have important societal and economic consequences as personal genomics may help optimize matching for mates, pets, jobs and living environments. As we approach an era of personalized genomics, we will be forced to confront new questions in individual rights and responsibilities. Fortunately, as a social species, our large brains have evolved to manage the balance of the relationship between self and others.

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12. A White Paper by Peter Hatemi, Department of Political Science, University of Iowa

Over the last half century, theoretical and methodological advances in neurobiological approaches have led us to this current opportunity, which has the potential to permanently alter the pathways in which social scientists can approach the study of human behavior. A rapidly growing body of scholarship has found that individual differences in political, social and economic behaviors are in part due to differences in genetic structure, neurological function, hormones, and physiological response to stimuli.[15] Individuals are dispositionally different from one another and such differences, in combination with what people experience in life, are reflected in different social preferences and behaviors. The complex interaction of neurobiology and social forces is largely viewed as the preferred model to achieve a more complete understanding of cognition, perception, preferences, and ultimately similarities and differences in behaviors in changing environments. However, the vast majority of social scientists do not have the funding means and research opportunities to take part in such research, thus creating a situation in which only those in the life sciences, with the methods and samples, but less knowledge of the phenotypic properties of many social traits, are producing the majority of the research.[16] As a result, the National Science Foundation organized a Workshop on Genes, Cognition and Social Behavior, directed by Arthur Lupia. This white paper was developed as part of the workshop and provides: 1) a brief summary of the rapidly growing research on political and social behaviors which utilizes genetic and neurobiological approaches 2) the import of this research to the study of social and

[15] For a review see Fowler, Schreiber. 2008. *Science* 322(5903):912-914.
[16] See special issue of *Science*. 2008: From Genes to Social Behavior 322: 5903

medical traits 3) the unsustainability of current research strategies undertaken by social scientists who have embraced these interdisciplinary approaches and 4) specific recommendations for investment strategies to promote wider disciplinary access and sustainable research programs focused on neurobiological approaches.

There has long been a division between the life and social sciences. This division was nurtured by the very nature of the traits studied. For example, the study of medical traits such as birth defects, logically lend themselves to medical examination, testing for genetic abnormalities, drawing blood, physiological examination, and so forth. Social traits appeared to have little place in these designs and in many ways the methods and research topics of the life sciences are fused into a single approach. The social sciences, on other hand, have focused primarily on expressed traits in the social environment, and in the past there appeared to be little need to explore individual differences in anatomy or physiology. Indeed, the idea that our attitudes or social preferences were in part some result of evolutionary adaptation and individual difference was inconceivable. Such a division of course is now no longer plausible as the scientific community has become aware of the importance of the combination of both our genetic and physiological disposition in conjunction with the environments we live in, for every trait we study, social or clinical. Even those traits that are highly heritable (e.g., breast cancer), or those brain injuries that appear unmanageable, the environments people live in and how they were raised are a critical part of prevention, liability, and recovery. As such, more integrative approaches have been born (epidemiology for example), in which the social environment and individual disposition are mutually incorporated into understanding a trait, to include strategies for prevention and treatment in the case of clinical traits. This

integrative view has now moved into the domains of and topics of interest to, the social sciences.

Recent neurobiological explorations of social traits include: genetic sources of individual differences for cooperative behavior[17], empathy, trust, altruism, social hierarchy, bargaining, risk, affiliation, leadership, punishment, social organization, ideology, attitudes[18], voter behavior,[19] gene by environment interactions of life events and attitudes[20], multivariate genetic models of personality and attitudes[21], genome wide explorations of ideology[22], differences in testosterone levels and political competition[23] and aggression, different physiological reactions to threat between those with liberal and conservative orientations[24], different neural activations patterns across different political orientations, among many others.[25] *These are just a few examples recently undertaken by social scientists, and does not include the majority of explorations published in the general science, neuroscience, psychological, genetic, and physiological literatures which were undertaken by scholars outside of the social science disciplines.*

This is of critical importance because the question is no longer whether this research should be taking place, or if social scientists are interested in taking part in this

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research. The paradigm shift toward a combined social and neurobiological approach has already occurred, and there is enormous growth in cross-disciplinary research focusing on social traits using neurobiological methods and approaches. Indeed the NIH recently opened a new funding mechanism, the Basic Behavioral and Social Science Opportunity Network (OppNet), to expand the funding of basic behavioral and social sciences research related to health traits. The question is should a funding mechanism be developed to support *social scientists* doing this type of research?

This is of critical importance because only recently have neurobiological approaches become part of the discourse of the social and political sciences, and only a handful of the most entrepreneurial social scientists have truly engaged in this area, largely due to the difficulty and time investment required for training, analysis and data collection. This leaves the social science community at a disadvantage. The traits social scientists most care about, voting for politics, rationality for economics, social movements for sociology, and so forth, have been explored using genome wide association, fMRI, hormone levels, and physiological response by those who are not political scientists, sociologists, or economists. That is, if social scientists are unable to engage in their own area of research using these tools, then an explicit choice is made to cede a good part of the future and most novel research in their fields to those not in the social science disciplines, or at the very least to only a small handful of social scientists who have a foot in both worlds. That is, those with the most knowledge of the social traits, context, and history, will be selected out of the study of, design, and eventual scholarship on these traits. Some may argue that is rightly so, as neurologists are much more adept at neuroimaging than political scientists. However, this view wrongly

associates method with the phenotype, and leaves those most adept at the methods, but more deficient at the context, studying the traits of interest to the social sciences. For example, at a recent conference a paper was presented in which party identification and vote choice was used synonymously with liberalism and ideology in a neuroimaging study. Such an approach is not empirically justified based on decades of social science research, which have long found critical differences between vote choice and ideology.

Critical importance to Foster this Research

A great amount of time and attention in the social sciences has been paid to rational action versus social upbringing and emotion versus reason. Though these dichotomies are false, in scholarship they are oft construed as reality. However their limitations are well known; rational choice lacks sources of preferences, sociological explorations lack individual difference, etc. None are complete, but none are "wrong". Recent neurobiological approaches have proved critical at bridging some of these gaps. Glimcher and Rustichini's (2004) summation of Platt and Glimcher's[26] experiments is a foundational discovery for how neurobiology can provide sources of rationality. Monkeys were trained to recognize that by looking certain directions when prompted with a light, they would receive a juice reward at varying percentages during multiple rounds of play. Examining brain activity during the decision process revealed that certain neurons encoded the value and likelihood of reward during the lottery phase of each round. In other words, the brains of the monkeys explicitly encoded something very much like expected value of each light in the lottery task. But after the learning period the monkeys exhibited no activity in the brain outside of the neurons in the eye when faced

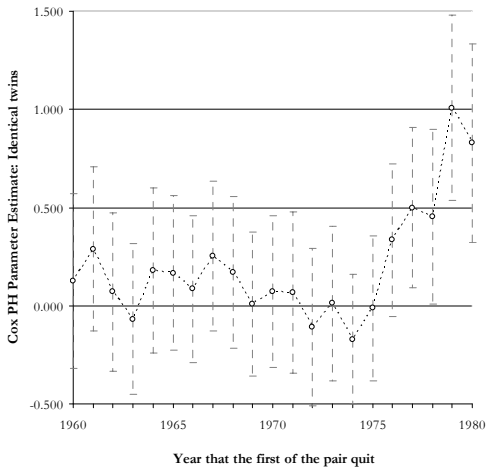
[26] Glimcher, Rustichini. 2004. *Science* 306:447-452; Platt, M.L. and Glimcher, P.W. (1999). Nature. 400: 233-238

with the decision task. In short, the monkey's optical neuron encoded a defined expected utility and in turn reacted in anticipation of a preferred outcome without ever accessing the brain after training. After environmental "training" the single neuron is rational (unbeknownst to the individual), even if the brain and person in their entirety is not. So, in this way, socialization (training to look a certain way) and genetic disposition (preference for juice) set the preference structure, while the encoded rationality and utility function in the neuron set the behavior. Rationality exists, but it is not the rational choice that scholars in the social sciences use. Socialization exists, but socializing a neuron to act is not what one typically considers. The sources of our preferences are some combination of biology and environment. One can only imagine how such a study, which merges social and neurobiological designs for a common phenotype, could vastly alter theoretical and empirical models in the social sciences. If social scientists were given the research opportunities to explore studies using similar approaches, it may very well lead to a transformation of the disciplinary approaches to behavior across disciplines and subfields.

Mutual Benefits to Social and Medical Sciences

While clinical and social traits are more often explored within their respective disciplines, some traits explicitly cross into both areas, though seldom do the medical and social sciences work together. Smoking cessation is one such trait. The medical community has long explored genetic sources of addiction, and the associated array of negative health impacts. Policy analysts have focused on the financial costs of smoking, prevention or tobacco regulation programs, as well as the impact of laws and insurance regulation. However, when disciplines converge, important new discoveries which affect

prevention and treatment, as well as public policy, can arise. For example, it is well understood that genetic diversity and environment contributes to differences in the risk for substance use disorders. Most often models include the social and the physical environment, and the interaction between parent and child, peers, and role models.



However, in a recent study political scientists and sociologists included the macro environment, the change in public policy, and found that it strongly shaped the genetic influence on quitting.[27] Looking at the figure below, genetic factors for smoking desistance increase in importance following the surgeon general's warning and restrictive legislation on smoking that occurred in the early and mid 1970s. The implications are profound. First, the policy initiative certainly worked as smoking decreased, but it did not work for all. It appears that those most genetically susceptible to smoking are affected to a much lesser degree by the current successful prevention and regulation programs. These individuals likely require different reinforcement or treatment mechanisms than the others. Only using a combined genetic and social model is this clear. Practitioners and medical researchers can gain traction using macro environmental models to target treatment. Policy analysts and makers can benefit by developing targeting regulation and prevention programs for this specific portion of the public that is the most genetically susceptible to

[27] Boardman, Blalock, Pampel, Hatemi, et al. "Period differences in the genetics of smoking desistence." Forthcoming, *Demography*.

smoking and less likely to quit. Extensions of this approach can be applied to a wide array of traits of interest to the social and medical sciences.

Integration for the Public Good

Words like determinism are oft used to cue the public that combing social and neurobiological approaches lead to negative outcomes. However, it turns out that it may very well be the other way around. For instance, as sexuality has been shown to be in part "biological", the public has become more accepting of homosexuality and gay marriage. However, combining social and biological approaches to better inform the public has only scarcely been introduced into the social science literature. A recent paper by Hatemi, McDermott, and Martin[28] found that gender (femininity-masculinity, not to be confused with sex) is largely a function of genetic and unique environmental influence (to include in-utero environment), while socialization has no significant role whatsoever. This view runs completely counter to the current gender literature in the social sciences, but is entirely consistent with the life sciences. However life science studies tend to focus on gender from a clinical perspective, and do not explore the social implications of gender being biologically influenced. The implications for reducing discrimination, and making better public policy can only be realized when health researchers, policy analysts and policy makers speak the same language. An important means for this to occur is through social science research which speaks directly to the public and policy makers.

How do we Fund Social Science Research using Neurobiological Methods?

The number of social science scholars who have invested in neurobiological methods can be seated at a single table. Most only gained the ability to do primary research through the "kindness of strangers". The time needed to learn new methods, the

[28] Hatemi, McDermott, Martin *Pol Res Quart*, in revision

ability to fund training, collect new data, and conduct primary research is prohibitive and very few travel the high risk entrepreneurial road which is the only current avenue. For instance, the NSF recently funded 20 political scientists to attend a behavior genetics workshop (NSF 0921008: PI Hatemi), but twice as many applied. The interest is great, but the ability is lacking. I receive scores of emails asking for access to data and training, and special conferences on neurobiological approaches are being held consistently in political science[29], sociology[30] and social science in general[31]. Yet as mentioned, most primary research in this area has relied on goodwill, access to data at others expense, or free training. My own path began this way. With no knowledge of where to turn, I contacted all the authors I could find in genetics, neuroscience, and endocrinology that had at some point worked on social traits. None responded kindly, save one, Nick Martin, who invited me to his genetic epidemiology lab at the Queensland Institute of Medical Research (QIMR). At his expense, I become a formal member of the lab as a pre-doctorate, and was trained in the lab; the pre-doc led to a post-doc in human and psychiatric genetics at the Virginia Institute for Psychiatric and Behavioral Genetics (VIPBG), under Lindon Eaves. There I began primary data collection, and was further trained in statistical genetics, endocrinology, developmental psychology, and neuroscience (off-site). In order to stay abreast and continue primary research, I return to QIMR every winter and summer. The investment is substantial, but being part of QIMR and VIPBG allows me access to data, ability to conduct new data collection, training, collaboration, and a network of like minded scholars. While the path was incredibly rewarding, and forever changed my academic and personal life in positive ways, such a

[29] Political Ecology Conference, UCSB, Feb 2009, Organizers McDermott, Hatemi.
[30] http://www.colorado.edu/ibs/CUPC/conferences/IGSS_2010/
[31] http://www-app.igb.uiuc.edu/biopolitics/

path is simply not plausible for all scholars. Therefore I believe it is time to create a formal mechanism for interested scholars, rather than force them to radically alter their career path, to take part in this important research. Based on my experiences, and conversations with others who run NIH training grant programs, direct interdisciplinary institutes, labs, and integrated departments, I have developed a short list of potential funding mechanisms. None are mutually exclusive, and it is likely a multi faceted approach is best.

1. *K award system (K01R01)* - this would mimic an NIH kangaroo award, which allows researchers to invest in new methodologies and tackle questions of import to the discipline. The K01R01 funds several years of training at institutes of choice, then funds a primary research component for data collection for a single PI. The intention is to provide the skills and necessary data to allow a scholar to move into a new area. It funds salary and benefits, along with training and research money for primary collection up to 5 years. The benefits are that it allows scholars to gain all the skills, networks and support to take part in this research, while not penalizing them for being outside the discipline, or relying on fortune to gain access to needed training and data. This will be tailored toward neurobiological approaches and is unlike the Career award, which has a teaching focus and is open to all research areas.
2. *Post doc transfer* – fund and develop a post doctorate transfer program. Post doctorates create a bridge between labs, departments and research programs. A transfer program can house a post-doc with a specific skill (e.g., neuroimaging, genetics, endocrinology, etc) in a social science department under the supervision

of the PI to help train the PI and PI's students while conducting their own research. There are many ways this can be done:

a. Train social sciences PhD's in a specific research area then return them to their home departments for 1 year to teach PhD's and assist faculty in primary research in this area. As test of viability, I have received approval in principle from three locations which are adept at training, Queensland Institute of Medical Research, Virginia Institute for Psychiatric and Behavioral Genetics, and the Institute of Behavior Genetics (to train social scientists if funded). This will build a sustainable research program and develop pre and post-docs and faculty.
b. Recruit life science post-docs to do a year in behavior work, and vice versa (send social scientists to assist in phenotype collection and contextual processes)

3. *Consortium /Economies of Scale* – The significant cost of genotyping, imaging, or taking hormonal assays is prohibitive. The cost of a questionnaire or experiment is a pittance in comparison. Adding a simple 2 page questionnaire on existing health studies could create data for hundreds of scholars. In a recent venture (NSF 0721707) we paid for a political battery to be given to a population of twins, in which DNA and familial data were already collected. The costs of the project ran under $150,000, though it would normally cost ~$500,000. This of course is a single study, but the NSF could fund a consortium mechanism. There are many ways this can be achieved.

a. Interested health science scholars can open their projects to add on a limited number of phenotypes for a cost. This will reduce the cost to the NIH PI's while allowing access to the social science PI's at an affordable rate. Similar mechanism can be developed to share equipment (magnet, psycho physiological equipment, lab space, etc). An official program, which rewards people who buy-in, will be a mechanism that will both create connections between life and social scientists, foster post-doc transfer and collaboration, as well as provide public data on a wide array of traits and covariates. Certain set up and infrastructure will need to be developed.

b. Develop an ongoing population data set for global use. Similar mechanisms exist for TESS and there are some preliminary versions of this such as the University of Michigan Health and Retirement Study (HRS) (NIA U01AG009740).

4. *Traditional mechanism* (SBE subdivision) - Creating a new subdivision or similar to fund research that utilizes neurobiological approaches has the specific benefit of a proven system in place. This mechanism would be no different from other mechanisms save the need for specific approaches. The benefit is clear in that no new investment be made in building the infrastructure. The drawback is that this area of research differs greatly and has specific needs such as longer project times (it takes years for some types of collection), need for salary support, need for post-doctorates, and need to combine training and data collection projects, etc; all of these do not necessarily fit within traditional funding mechanisms.

Conclusion

By funding social scientists to take part in neurobiological approaches, and developing a funding mechanism to specifically address this new and quite different need, the NSF has a real opportunity to truly integrate the social sciences with the life sciences in a very positive and mutually beneficial way. Thank you.

13. A White Paper by Rose McDermott, Department of Political Science, Brown University

The current research climate provides an auspicious opportunity to undertake foundational investigations at the intersection of the natural and social sciences to produce transformative work with broad import for society. A great deal of relevant work examining the genetic, neurobiological and neuropsychological bases of social and political behavior has already taken place. But much of this work has been conducted simultaneously in a variety of different fields and disciplines. In addition to needlessly duplicating some research paradigms, thus wasting time and resources, such efforts have often also lacked a coherent core of *social* and *political* models and theories to guide such inquiry. With proper coordination and leverage, such efforts can achieve tremendous gains in terms of harnessing the skills, methods and models of the natural sciences in service of addressing some of the most destructive and endemic social and political problems which plague our planet.

The intersection between genes, cognition, culture and behavior remain myriad, complex, largely unknown, but increasingly susceptible to systematic investigation. This commentary begins with a brief comment on the multiple approaches, offering the greatest prospects for intellectual merit. These examinations, particularly in the areas of hormones and neuropsychology, can be used to interrogate the social phenomena in which we are interested. Some of the most pressing and promising areas of application, offering great purchase on the kinds of broad societal impact we both need and expect, include attempts to understand various facets of violence, aggression and threat detection.

The various implications of this area appear vast. Potential plans of action for possible avenues of support can achieve a lasting scientific and social impact in this area.

Multiple Approaches

Clearly, multiple approaches exist to examine the same neural pathways of interest. Scholars can use a wide variety of techniques and methods to examine similar pathways of action from genes to brains to behavior (Hatemi, 2010). Investigations can concentrate on the various neural pathways, and the connections between them, using functional magnetic resonance imaging, genetic studies, and other techniques.

In the past, scholars who examined problems in the social sciences tended to dismiss or ignore the import to biological factors such as genes, in their analyses. Similarly, scholars working in the hard sciences often restrict their inquiries to their own areas, and do not necessarily venture afield to apply their methods or findings to problems in the large scale social world. And yet there is no a priori reason why such disciplinary boundaries should remain. In combination, researchers working in both areas could combine their skills to investigate the nature and dynamics of large scale social processes using methods and models based on individual biology, cognition and genetics.

Evolutionary psychologists such as Steven Pinker have discussed the importance of the deep mechanisms which undergird the innate and universal aspects of human psychology. But often the exact nature of those mechanisms *in social context* has remained largely unexplored. And yet human experience is patterned by culture, and the human mind is likely shaped by various cultural variables to a greater extent than ever imagined. These culturally patterned behaviors and experiences can, in turn, influence the very connectivity of the brain itself, as demonstrated in the famous study showing that

cab drivers in London have larger hypothalamuses than controls with less need of spatial orientation ability. Indeed, the brain is likely the primary site for cultural information to accumulate over the relatively long span of a lifetime. Such cultural values contain meaning and encompass several elements, including values, practices and psychological tendencies. This process does not exist in isolation, but rather produces a reciprocal loop which itself contributes to the production and change of cultural practices and identity formation and enculturation. This interaction results in neuroplastic changes in the brain itself throughout the course of the lifespan in response to experience, offering both affirmation of self-identity and well-being, as well as resulting in other biological changes.

This reality highlights the importance of social science approaches to the examination of medical traits as well. Most scientific methods have been developed for the study of clinical traits which exist at the extremes, and not for the greater percentage of traits which exist in a normal distribution within a population. The empirical traditions of the life sciences were largely designed to examine rare variance, which by definition encompasses relatively few people. Yet the traits typically explored by social scientists affect everyone, often in a normally distributed fashion. This inherent distinction can be bridged to create a common ground for mutual communication around the large scale investigation of social traits using techniques and methods perfected in the clinical realm. We can thus use the knowledge developed for the investigation of medical conditions for the mutual benefit of both fields of inquiry. Historically, social science has ignored many of these methods, just as clinical science had often neglected the consideration of social processes, including policy choices, in potentiating the development of medical

conditions, which can affect everyone in a given society. Social science and medicine can and should engage, and speak directly to, one another to the reciprocal insight and benefit of each discipline. In short, the valuable research traditions inherent in the history of social science investigation can improve medical and clinical science, just as the perspective of the hard sciences can inform the nature of social science inquiry.

Many social scientists ask: What is the point of studying the brain if we already know all about behavior? The response given by say, a psychologist, is that understanding the brain can indicate those more proximate mechanisms which reveal how cultural information becomes processed, constructed and stored in the mind. This remains important because the brain serves as a physical repository of cultural and social information and it provides an absolutely critical basis upon which to dissect the interaction between the individual and the society in which she lives.

A plurality of approaches exists for exploring this intersection from a genetic standpoint. Genes create proteins which spur neural activity which can result in behavior. Dispositionally influenced neural activity, in interaction with the environment, can create different kinds of behavior, and we cannot afford to ignore these influence. Rather, we can profit from its deeper and fuller investigation. Higher level stuff can worm its way down to the genetic level. Genes alone do not cause behavior, but culture can affect genetic processes and structures. Clearly, a certain level of understanding would be hard to get from behavior alone. However, we can make predictions about what motivates behavior, or what it means, by exploring what different brain regions can tell us about the interconnectivity of the brain with behavior. We can use our knowledge of these regions as a kind of signature which we can then use to try to examine other related behavioral

processes like cooperation or aggression. In this way, connectivity and location can help illuminate the basis for behavior, by signaling a particular kind of brain process.

What do we learn by adding brain phenotype into the equation? Are we likely to garner better information than we could by employing simple behavioral measures alone? Distributions of particular genetic polymorphisms across populations may or may not be socially meaningful. Common variance may be adaptive, for example by supporting immunity to particular pathogens, or they might prove useful in one context, moot in a second and maladaptive in a third, as may be the case with cystic fibrosis.

Oftentimes, however, there is not a simple mapping across levels of analysis. Complex behaviors can be produced by different mechanisms, and multiple systems can exist across several different levels of psychological organization. The brain's level of complexity is geometric. The brain may represent an intervening step between the genetic structures we examine and the behavior we seek to explicate. We need to examine genes and cognition in order to get to slightly simpler mapping of biology to behavior. It is not always possible to simply map across different levels of analysis with direct or even linear causal pathways from genes to behavior, but one has to understand each to gain traction on the other. This provides all the more reason to explore these processes from the perspective of social science; we simply cannot take the brain outside of its interaction with the social world in which it evolved to function.

It is easy to remain reductionistic about other people's areas because we each understand the complexity within our own fields so much better than the nuance that exists in someone else's area of expertise. But if we genuinely want to learn about behavior and the biological substrates of behavior, we need to mix levels of analysis and

disciplinary fields precisely because of the limitations in vision inherent in each. The real quandary is how to go about this without getting too reductionistic in the new area of inquiry.

Any comprehensive model designed to estimate and examine this process must incorporate the reciprocal interaction between neural and cultural processes, accepting that the central dynamics involved remain behavioral as well as cognitive in nature. This recognition ignites the intersection of genetic and cognitive processes with the social behavior they inspire and inflame.

Promising Areas of Application

One of the behavioral problems that appear endemic to all societies over time and space relates to understanding and controlling the sources and forces of violence. This phenomenon has many aspects, both positive and negative. We all want powerful and effective leaders, but ones who don't exploit those that support them. We all want to be protected from threat, but we don't want to have to live with the societal consequences that befall many who go to war. Because of the universal nature of many of these processes, it seems logical to examine the extent to which some of these behaviors find their roots in genetic and cognitive processes which result in behaviors we both desire and admonish.

As a result, it seems that one of the most important areas in which the natural and social sciences might converge for effective collaboration surrounds the neurobiological and neuropsychological bases of aggression and violence. This fundamental area of inquiry offers a great deal of potential for both avenues of important intellectual work, as well as massive positive societal impact.

Specifically, genetic differences may exist in such characteristics as power seeking, impulsivity or reaction to provocation which can influence the extent to which individual strive for leadership positions, or attempt to overthrow those who might try to dominate them. These differences may manifest in different hormonal or endocrine reactions, including testosterone, in the face of challenge, threat or provocation. There appear to be differences in population prevalence of COMT and MAOA among other genetic structures. Perhaps these differences emerge within particular ecological contexts to produce effective leaders in one situation and disastrous dictators in others. Studies which strive to examine the genetic and hormonal substrates of personality and leadership could go far toward illuminating the nature of both its effective and destructive forms.

To take the societal consequence of violence I know best, more extensive investigation into the intersection between genetic and environmental risk factors for post traumatic stress disorder (PTSD) in the face of extreme violence could go far to both alleviate vast amounts of suffering as well as potentially saving society enormous sums of money, wasted time and productivity. This is one critical area in which the social and medical aspects of vulnerability, treatment and recovery remain profoundly, intrinsically intertwined. Treating the medical or social aspects of this process as distinct does a deep disservice to all those affected, as well as those who research and treat the condition.

PTSD has an 8% lifetime prevalence; the only mental illness with higher incidence is depression, which affects about 15-20% of people over the course of a lifetime. It involves the intrusive re-experiencing of past traumatic events, avoidance of related stimuli, emotional numbing and increased autonomic arousal. The traditional model assumed that PTSD emerged out of a basic fear conditioning, in the wake of some kind of

indelible experience (Pitman, 1989; LeDoux, 1996; McCaugh, 2003). This notion was based largely on an animal model of fear conditioning, where, it might be noted, the animal was not allowed to do what it might normally do when scared, which is run away.

So the question became: is it reasonable for this basic model of fear conditioning to serve as an appropriate model for the emergence of PTSD? Based on behavioral models of enhanced fear conditioning for twenty-five years, this model held sway. However, once it was possible to examine brain activation with fMRI techniques, it became possible to disaggregate the hyperactivity in the amygdala expected with fear conditioning. Specifically, the medial prefrontal cortex appears to have separate modules capable of increasing or decreasing fear expression after extinction. Interestingly, the problem with PTSD was not the increasing susceptibility to acquiring fear conditioning, but rather the failure to extinguish fear remains the problem (Quirk, 2005).

Behavioral data alone never highlighted this distinction, which emerges critical for both assessing initial susceptibility, but also in developing more effective treatment protocols. In seeking to understand susceptibility, it was always assumed that the severity of the exposure to trauma was the best predictor of vulnerability; this outcome remains obvious is fear conditioning is the problem. However, the behavioral data did not support this. Indeed, there were all kinds of problems with appraisal and prediction of who would prove vulnerable prior to the actual event; in particular, there were early problems with the predictors typically favored by social scientists related to IQ, SES, and other factors which supposedly should mediate the risk factors which predisposed individuals to PTSD. Rather, various characteristics of the stimulus prove critically

important in predicting the probability of PTSD. In particular, interpersonal trauma, such as rape, can be more likely to instigate PTSD than other horrific events which result from so-called acts of God, for precisely this reason. So, for example, although from the perspective of a standard model there is no reason this should work, there is some evidence that tight unit cohesion provides one of the few reliable protectors against PTSD independent of the severity of exposure to trauma. This factor relates directly to the arguments involving the role of the medial prefrontal cortex in integrating social relatedness into self-concept outlined below, which clearly preserves the contextualization which ruptures in the face of trauma.

Similarly, in attempts to develop effective treatment, clinicians were puzzled by the fact that the relationship between a given trauma and the stimulus that provokes symptoms can be vague and difficult to define. In addition, patients do not seem to have problems with fear conditioning outside their traumatic events. Moreover, cognitive treatments such as exposure seem to be effective. And yet none of this should be true if the basis for developing PTSD is fear conditioning (Casteli, 2000; Greene, 2001; Ochsner, 2002; Taylor, 2003; Britton, 2006)

But all of these findings make sense and cohere once genetic and hormonal elements are introduced, along with the environmental assault, into painting the background to the picture of PTSD. Social emotions and self relatedness become key in this vision, where the assessment of one's social milieu becomes the source of social relatedness and social salience. Such a foundation provides the perception of social landscape which allows you to define yourself, as well as those associated with yourself, those like yourself but not yourself, and those who are completely not associated with the self. These images

define the map of social distance and critically affect stress regulation through hormonal mechanism. For example, cortisol levels rise precipitously fifteen minutes before an individual's 1st parachute drop precisely because expectation signals those social processes which are most important for each organism. And the medial prefrontal cortex seems to be at least partly responsible for establishing this contextualization, by putting different stimuli into proper context of cognitive expectation and social environment.

In this way, PTSD can be re-interpreted as a failure to contextualize the emotion responses and traumatic memories triggered by contextual cues, especially those that involved difficult social interactions which violated expectations. In this case, as in others, culture shapes our perception of ourselves and elicits the specific cognitive appraisal processes we use or don't use to respond to a given situation. A given event activates a particular contextual meaning of an experience which, in turn, feeds back into the amygdala to recontextualize it as a traumatic experience. The person then tries to link that trauma to a cultural experience in order to process it. This attempt to integrate can involve a wide variety of psychological and cognitive processes including cognitive appraisal, self perception, stress perception, physiology and brain physiology.

From this perspective, exposure therapy does not represent simple extinction as it would in a straightforward fear conditioning model. Rather, the goal is to help the person recontextualize their experience within their own parameter of cognitive expectation and social connectedness. In addition to trying to find a way to tell the person that the world is safe now for them (if it is), it remains critical to provide a safe interpersonal context to allow the traumatized individual to individually and idiosyncratically recontextualize their own interpersonal context. Therefore, a model which examines the interaction

between biology and behavior allows a different assessment of the factors that place individuals at risk for PTSD but also provides novel opportunities for the development of more effective treatment protocols.

Moving Forward

Rather than institutionalizing a new division at NSF to integrate the social and natural sciences for an integrated study of social behaviors of import, it seems that NSF could serve a potential matching function to encourage, through structured funding opportunities which require both social and natural scientists to participate, a more synthetic approach to the study of these important phenomena. Perhaps such funding opportunities could follow the K award model to support scholars who wish to obtain additional training outside their original area of study to allow for more productive interdisciplinary collaboration. Perhaps it might involve supplemental grants for RO3 funded eligible grants. Or perhaps some work might involve a time sharing model, such as that developed for Experiments, to share expensive equipment, such as fMRIs, or to leverage large genetic data sets obtained with prior funding. The most important element, it seems, is to harness the institutional reputation of the NSF to signal support for such research. Clearly, we stand at a watershed moment in the application of genetic, biological and psychological models and information to address critical problems which beset our social and political lives. With internecine religious conflict erupting all across the globe, political battles becoming ever more polarized, and social challenges appearing more intractable, working to understand the basic ways in which our fundamental human nature interacts with others in the context of an inextricably social world appears the most critical task we can undertake.

14. A White Paper by Aldo Rustichini, Department of Economics, University of Minnesota

Genetic Analysis of Economic and Strategic Behavior: A Discussion of the Method

I. Introduction

The analysis of the genetic factors affecting economic behavior presents specific challenges, and as study in the field progresses an analysis of the methods used may be necessary for a sound research. We consider here all research that takes as observable traits any variable describing economic behavior, assumes that it may be influenced by a genotype, and tries to determine the degree and manner of this influence. This field of study we may call for convenience *neurogenetic economics*, to emphasize (as we are going to discuss later) how the most profitable method for this field of research will consist of the integration of methods in genetics and neuroeconomics. We use economic behavior in a wide sense, to include behavior of individuals in strategic situations, where the outcome of actions taken by an individual depends not only on the anonymous working of markets, but on the purposeful actions of others.

II. Specific problems in neurogenetic economics

1. First problem: Phenotype in economic analysis

The first fundamental problem to be solved is a precise definition of the phenotype to be studied. Consider for example the variables that are classically object of economic analysis: these may include data that are collected empirically, like an individual's occupation, income, consumption or asset portfolio, as well as data that can be generated in experimental conditions, like behavior in a choice of lottery under

uncertainty, or behavior in a game in the laboratory. Since these variables are typically precisely measurable they may be the object of statistical analysis of genotype influence.

Although a direct study of variables like these may give some useful insight, this empirically oriented approach is unlikely to be a good guidance for future research. There is a need for a careful definition of phenotypes that are general enough and theoretically stable so that the associations found are not fragile, and are not too sensitive to slightly different definitions of the variable. For example, it is reasonable to assume that the trusting behavior of an individual in an experimental trust game depends on several details of the specific form of the game. Hence, even if we accept that we try to determine the genotype of such an elusive concept as trust, we should not take as phenotype the behavior in one of these specific forms. Similarly, the income of an individual is a derived variable, which is product of several characteristics, such as attitude to risk, subjective discount, but also intelligence, motivation, positive emotionality and so on. The research strategy should be to focus on these intermediate characteristics, rather than on their final outcome. In this case the parallel research in the field of cognitive neuroscience will provide extremely useful guidance. We will discuss this in the methodological section III.

2. Second problem: Polygenic traits

The second fundamental problem is that any of the phenotypes that have been considered so far in the genetic analysis of economic behavior are likely to be highly polygenic: that is net effect of a large number of genes, each contributing in a small measure to the phenotype. All significant behavior, as well as underlying traits, that are of interest are continuous rather than binary, and are almost by definition common. So

they all fall under the hypothesis of common disease-common variant rather than the opposite Mendelian case, where a single variant can determine a disease: two defective variants of the gene CFTR induce cystic fibrosis in the individual with those variants. All the variants involved are likely to contribute little (between a 1.1 and 1.5 Genetic Risk).

A measure of the difficulties that researchers may encounter, and ideas on possible solutions, may be provided by recent studies of two traits that share many characteristics with economic variables: adult height and schizophrenia. A brief survey of the findings, the puzzles, and the new methods of research suggested in these two lines of research may suggest much of what is in waiting for neurogenetic economics.

Adult height shares many of the qualities of variables in economic analysis. Like, say, life-time income, or asset portfolio composition, it is easily observable and measurable, and is a continuous variable. We also know that it is highly heritable: up to 90 % of the variation in adult height within a population is explained by genetic variation (Carmichael et al. (1995), Macgregor et al. (2006), Perola (2007), Preece et al. (1996), Silventoinen et al.(2000), Silventoinen et al., (2003)). It is also known that mutations in certain well known genes can produce extremely high or extremely low height. These are however rare mutations and explain very little of the variability observed in common population.

Hence height in normal adults is the ideal object for a study that postulates the potential effect of genotype on individual characteristics. Since it is also readily available and typically collected in virtually all genetic studies, it has been recently the subject of systematic studies, in particular genome-wide associations studies (GWAS). (Lettre et al. (2008), Gudbjartsson et al. (2008), Weedon et al. (2008); for a survey see Visscher

(2008)). All the studies followed a multistage procedure of first identifying the most promising single nucleotide polymorphisms (SNP's) and then in later stages validating the results conjectured in the earlier stage.

The conclusion common to the three studies cited is that 54 loci (surviving out of the 95 initially identified in first stage) in the total of the three studies have been finally identified that contribute significantly to explain the variance in height. Two of the previously identified genes (*HMGA2* and *GDF5-UQCC*) have been confirmed in the cited studies.

However, all these variants together explain about 5 % of the variance, in spite of the very large samples used in the studies (~63,000 individuals in total). The average effect size is ~ 0.4 centimeters. There is also an overlap, although modest, between the genes identified in the three different studies cited above. The stringent conditions imposed by the need to control for multiple comparisons in the GWA studies may explain the small size of the overlap (Visscher (2008)). Some of the genes (for example, the *ZBTB38* have also been found to be associated with effects on blood and adipose tissue, while others had been found to influence mesoderm development and skeletal development, suggesting possible biological pathways of the genetic effect.

An important practical lesson that can be derived from the GWAS studies of height is the extreme importance of sample size even for qualitative conclusions. The QQ-plot reported in Figure 1 of Weedon et al. (2008), as well as Figure 1 of Lettre et al., (2008), shows that significant associations detected in the pooled data set (with a total sample size of ~19,000 individuals) from six different studies (each with sample size between ~2,000 and ~13,000 individuals) were substantially larger than those determined

in the separate studies. Obviously, if effects sizes are small, large sample sizes are going to be needed to detect associations in a reliable way. And just as in studies of common diseases, where single laboratories integrate into consortia to reach the necessary size of the study, a similar conclusion will probably have to be drawn for studies of economic behavior.

The second characteristic that has been recently extensively studied is schizophrenia and bipolar disorder (Stefansson. H. et al., (ISC), (2009), Purcell, S. M. et al., (ISC), (2009)). Schizophrenia is a mental disorder with an incidence of about 1%, and has an heritability estimate of about 80 % (Cardno et al. (2000), Sullivan et al. (2003)). A polygenic theory of schizophrenia was formulated at the early stage of behavioral genetics (Gottesman et al. (1967)).

The research tested for association ~1 million SNP's on a sample of ~3,300 European individuals with schizophrenia and ~3,500 controls. Two groups of SNP's were found to have strong and significant association, the second having a large number (450) on the chromosome 6p spanning the major histo-compatibility complex. In addition the authors tested whether common variants have an important role in the etiology of schizophrenia, relying on the thousand of potential sources of very small effects. The *score allele* methodology used may be interesting for economic applications: a score allele is a combination of a large number (~74,000) autosomal SNP's, computed for each individual by weighting the set of alleles by the log odds ratio. The common polygenic variation is estimated (as a lower bound) to explain one-third of the total variation in schizophrenia. The estimated component also contributes in a significant measure to the

risk of bipolar disorder, but does not contribute to several non-psychiatric diseases that have been used as test.

The results of the study point to a disease that is very highly polygenic disease, and suggest that genetically influenced individual differences are derived through different, possibly numerous pathways. It is conceivable that individual characteristics, which are relevant for economic behavior, like, for example, the attitude to risk aversion, have a similar multiple causation, both for the genetic loci involved and for the biological pathways through which they operate.

The existence of a large number of common variants, each contributing in very small measure to the risk of schizophrenia is particularly important if one considers the selection operated by reproductive fitness: the very small effects sizes will operate a very small selective pressure, and this may explain the persistence of the disease. A similar mechanism operating on variants that influence economic and social behavior would probably put the idea that selective pressure operates as a consequence of economic success and social behavior in a different prospective.

3. Missing heritability

The two cases we have considered in detail of normal adult human height and schizophrenia are typical of a much broader class of traits and diseases. Most common diseases exhibit a similar pattern, and the results of the early GWA studies have been considered puzzling, since there is a large fraction of phenotypic variance that is considered to be heritable and that is not explained by the SNP's that have been determined in association studies (Wellcome Trust, (2007), Maher (2008), Manolio, T. et al., (2009)). The explanation of this ``missing heritability'' is one of the challenges for

future genetic research, and it is quite likely that researchers in neurogenetic economics will face it as well.

4. Lessons for neurogenetic economics

We summarize now what can be useful for future research of the findings we have briefly reviewed.

4.1. Organization of the research

We have already seen some of the implications that these studies suggest and are potentially useful for neurogenetic economics: first among them the possibility that the most important characteristics of economic behavior have a genetic explanation but provided by a large number of common variants, each with small effects. They should probably be used to organize the research in the field, to avoid mistakes that have already been made.

4.2. Explanation of behavior

An implication that the studies we have reviewed is directly on the usefulness of the neurogenetic economics research program. It seems very unlikely that specific genes for risk loving, or patient behavior in inter-temporal choices, are ever going to be determined. It is even less likely that the genes for altruism, or egalitarianism, or cooperative behavior are going to be determined. If the findings for height or schizophrenia foreshadow what researchers are likely to find, we are probably facing a small number of genotypes having a large effect. This will also make the interpretation from the point of view of the biological pathways that explain how the effect is produced relatively harder.

4.3. Predictions

Are these findings going to be useful for prediction of individual behavior on the basis of individual genetic testing? This answer to this question is particularly important in clinical applications for obvious reasons: diagnosis, treatment, prognosis and prevention. But it is also important in various other fields, as agriculture: for example it might be important to determine SNP's that affect milk production of the offspring of a bull, in which milk production cannot be observed directly. This information is valuable to determine the economic value of individuals. It is easy to see that the same applies to some of the important characteristics and economic preferences. For example, insurance companies might find useful to risk propensity of individuals they insure; banks might want to know the saving propensity of borrowers, or investment institutions the potential income earnings of applicants.

An analysis of the correct prediction that can be made on the basis of GWAS findings is in Wray et al., (2007), Goddard et al., (2009), in particular to correct for the bias introduced (known as the Beavis effect in agricultural genetics, or winner's curse) that makes the predicted effect larger than the real. But again, if the case of neurogenetic economics turns out to be similar to the one of height or schizophrenia, or the many common diseases, it is likely that the large number of variants would make this prediction hard. Some of the more sophisticated techniques are also difficult to apply. For example, the authors of the score allele estimates state clearly (Purcell et al, (2009), page 750) that ``*the scores derived here have little value for individual risk prediction, meaning that application to clinical genetic testing for schizophrenia would be unwarranted*.''

III. Methodological prescriptions

1. Intermediate levels of analysis

In research fields that share some of the methodological difficulties of neurogenetic economics (most notably, cognitive neuroscience, and personality theory) a productive use has been made of the intermediate phenotype strategy. In the case of cognitive and psychiatric neurogenetic, this research strategy (Caspi et al., (2006); Meyer-Lindenberg & Weinberger, (2006), Green et al., (2008)) proceeds from the assumption that variations in *genotype* can produce variation of *cognitive and psychological functions*, but there is an intermediate level between the two, the *brain-based intermediate phenotype*. The role of the intermediate phenotype is to provide the model for a mechanistic reconstruction of the chain from genes to proteins to brain to psychological functions and behavior.

For example, consider performance of individual subjects in the Attention-Network Test (ANT) a measure of executive control (Posner et al., (2007), orienting and alerting components of attention. The executive control measure has a high degree of heritability (89 %; Fan et al., (2001)) so it is a good candidate for the study of genetic analysis of a psychological function. Brain imaging studies (fMRI) of subjects performing the task have identified a network of brain regions involved in the performance of ANT; in particular including the anterior cingulate cortex (ACC). GWA studies have shown correlation of the differences in activation in ACC during performance in the ANT and individual variation in the monoamine oxidase-A (MAOA) gene. Other examples of cognitive-psychological functions include emotional regulation (Hariri et al. (2006), Neumeister et al., (2006)); inhibitory control (Passamonti et al.,

(2006)); impulsivity and violence (Meyer-Lindenberg et al., (2006)); working and long term memory (Hariri, A. R. et al., (2003), Pezawas, L. et al., (2004), Bertolino, A. et al., (2006), Szeszko, P. R. et al., (2005), Bueller, J. A. et al. (2006), Bath, K. G. & Lee, F. S., (2006)), negative affects and anxiety related traits (Hariri, A. R. *et al.* , (2002), Sen, S., Burmeister, M. & Ghosh, D., (2004), Schinka, J. A., Busch, R. M. & Robichaux-Keene, N., (2004), Munafo, M. R., Clark, T. & Flint, J., (2005), Hariri, A. R. *et al.* , (2005), Munafo, M. R., Clark, T. & Flint, J., (2005), Munafo, M. R., Brown, S. A. & Hariri, A. R., (2008)).

The relationship between genotype and psychological functions is the field of investigation of behavioral genetics; the one between psychological functions and brain-based structure is the domain of cognitive neuroscience. Cognitive neurogenetic investigation is the study of the link between genes and psychological functions mediated by the understanding of the effects of genes on brain structures. Behavioral genetic studies, which shortcut the mediation of the neural characteristics, would be useful in testing whether psychological functions vary with some specified genetic variation.

2. Intermediate phenotypes, economic theory and personality theory

Consider now the natural extension of this research strategy to analysis of genetic influence on economic behavior. As in the case of cognitive neurogenetic, we consider the effects of a genotype thought the mediation of a brain-based phenotype. What replaces the cognitive-psychological functions?

Economic theory suggests a very short list of relevant factors. In the most extreme version, two parameters completely describe the decision maker: the degree of risk aversion and the degree of patience in inter-temporal choices. We suggest a different

approach, based on the integration of classical decision theory and personality theory. We have developed this approach in detail in a different paper (Rustichini, (2009)), so we refer the interested reader to that.

IV. Conclusions

We have examined the future prospects of research in what we called neurogenetic economics. The name that wants to emphasize the need to provide the analysis of the effect of genotype on individual social behavior on the foundation of a good understanding of the intermediate phenotype, the brain functions affecting this behavior.

Here are our main prescriptions for a productive research in this area:

1. There is a need for a theory of economic and strategic behavior that extends the classical economic theory based on choice under uncertainty and time discount. We believe that an integration of classical economic theory and personality theory is a good starting point.

2. Recent progress in neuroeconomics are a good foundation for the understanding of the intermediate phenotype; there is now the need for an integration of the two lines of research. This integration will require an adjustment of the research in neuroeconomics. For example this will require the use of larger samples of subjects (from the 12-30 typically used in fMRI analysis to a sample size of 100-150, all subjects genotyped for a large enough number of SNP's, between 600,000 to 1 million).

3. The research will have to anticipate the likelihood that in neurogenetic research we are probably in the case already encountered in genetic analysis of common traits (like height) or common diseases. In the map described by Manolio et al., (page Manolio, T. et

al., (2009); see also McCarthy, M. I. et al., (2008)) neurogenetic economics is likely to be in the bottom right corner: common allele frequency and low effect size. This recognition will require an adjustment of the organization of research. For example, in GWA studies the sample size required for effective research is likely to be larger than the potential of single laboratory. The institution of consortia for the study of specific questions (like any of the two economic theory parameters, risk attitude or time preferences, of any of the Big Five personality traits) should be fostered. *The International Schizophrenia Consortium* is a good example to keep in mind.

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15. Slides Used During the Course of the Workshop

The following slides were used to guide discussion during the course of the workshop.

NSF WORKSHOP ON GENES, COGNITION, AND SOCIAL BEHAVIOR

June 28, 2010/Arlington, VA

Gratitude

- Myron Guttman & Frank Scioli
- Carol Mershon & Brian Humes
- Allison Smith & Barb Opal
- Kristyn Miller & Jed Madsen
- NSF program directors

Participants

- **Dan Benjamin** – Cornell, Economics
- **Turhan Canli** – Psychology, Stony Brook
- **Susan Courtney** – Psychological and Brain Science, Johns Hopkins
- **Russell Fernald** – Biology, Stanford
- **Jeremy Freese** – Sociology, Northwestern

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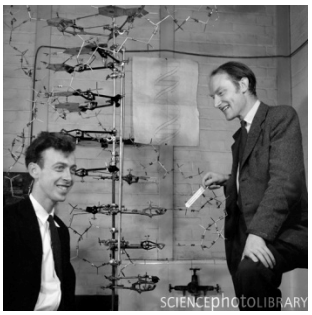
- **Russell Fernald** – Biology, Stanford
- **Jeremy Freese** – Sociology, Northwestern
- **Elizabeth Hammock** –Pediatrics, Vanderbilt
- **Peter Hatemi** -- Political Science, Iowa
- **Rose McDermott** -- Political Science, Brown
- **Aldo Rustichini** – Economics, Minnesota

Main Objective

- *Specify how fundable research on genes, cognition and social behavior will generate*
  - *transformative scientific practices,*
  - *scholarly infrastructure,*
  - *and widely relevant findings of high social value.*

Is Change Possible?

Watson and Crick, 1953



Is Change Possible?

- **The genome sequenced by the International Human Genome Sequencing Consortium**
  - **took 13 years and cost $3 billion**
- **Today, Illumina of San Diego, reads a human genome in**
  - **eight days for ~$10,000**
- **Pacific Biosciences tries to read genomes from single DNA molecules.**
  - **In three years' time it expects to map a human genome in**
  - **15 minutes**
  - **for less than $1,000.**

—The Economist June 19, 2010



INTERDISCIPLINARITY

June 28, 2010/Arlington, VA

Opportunity

- Social behavior research that builds from gene & cognition discoveries
- may be of greater social and scientific value
- than studies that ignore such factors

Challenge

- Disciplines derive knowledge from diverse paradigms.
- A paradigm establishes
  - a context for discovery
  - a way of "knowing"
- A finding's meaning can be context-dependent.
  - Which meanings are portable?

Challenge

- Which meanings are portable?

Challenge

- Which meanings are legitimate?

Challenge

- Which meanings are credible?

Challenge – Competing Levels of Analysis

- There are many possible levels of analysis.
  - Genes
  - Parts of genes,
  - Groups of genes,
  - Neurons
  - Groups of neurons,
  - parts of neurons,
  - Phenotypes,
  - Groups of phenotypes
  - parts of phenotypes….

Challenge – Competing Levels of Analysis

- There are many possible levels of analysis.
  - Genes
  - Parts of genes,
  - Groups of genes,
  - Neurons
  - Groups of neurons,
  - parts of neurons,
  - Phenotypes,
  - Groups of phenotypes
  - parts of phenotypes….
- When does "Level X" more efficiently/effectively produce intellectual merit and broader impact than "Level Y"?

Key Question

- Are the likely scientific and social returns on investments in [YOUR IDEA HERE] are greater or less than NSF & others can earn elsewhere?

Agenda

- What is the value of current & near-future research …
  - **S1:** on **genes** and social behavior?
  - **S2:** on **cognition** and social behavior?
  - **S3**: that leverages **S1 & S2 simultaneously**
- **S4:** On what kinds of social behavioral inquiries are investment **returns** likely to be **greatest**?

WHAT IS THE VALUE OF RESEARCH ON GENES AND SOCIAL BEHAVIOR?

Session 1/ 900-1030

Key Question

- Are the likely scientific and social returns on investments in this research are greater or less than NSF & others can earn elsewhere?

WHAT IS THE VALUE OF RESEARCH ON COGNITION AND SOCIAL BEHAVIOR?

Session 2/ 1045-1215

Key Question

- Are the likely scientific and social returns on investments in this research are greater or less than NSF & others can earn elsewhere?



WHAT IS THE VALUE OF SOCIAL BEHAVIOR RESEARCH THAT SIMULTANEOUSLY LEVERAGES GENES AND COGNITION?

Session 3/ 1300-1430

Re-set

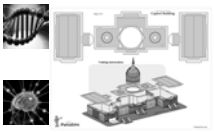
- Opportunities
  - "We simply cannot take the brain outside of its interaction with the social world in which it evolved to function" - R. McDermott.
  - "The sources of our preferences are some combination of biology and environment. One can only imagine how such a study, which merges social and neurobiological designs for a common phenotype, could vastly alter theoretical and empirical models in the social sciences." – P. Hatemi

Re-set

- Challenges
  - "social science and genomics can be integrated; however, the way this marriage is currently occurring rests on spurious methods and assumptions and will yield few lasting insights…."
    - D. Conley. Biodemography and Social Biology. 2009.

Key Question

- Are the likely scientific and social returns on investments in such research are greater or less than NSF & others can earn elsewhere?



ON WHAT KINDS OF SOCIAL BEHAVIORAL INQUIRIES ARE NEAR-FUTURE INVESTMENT RETURNS LIKELY TO BE GREATEST?

Session 4/ 1445-1600

Key Question

- Are the likely scientific and social returns on investments in such research are greater or less than NSF & others can earn elsewhere?

Education

- K Award System
- Tuition for Summer Courses
- Post-Doc Transfer Program
- Integrated research and training program (IGERT)

Data

- Add Questionnaire to Existing Health Studies
- Genotype Participants in Existing Social Science Studies
- Develop an Ongoing Population Data Set
- Create a Consortia of Data Providers
- Standardized fMRI practices and shared data

Collaboration

- Core Facilities
- Time Sharing of Equipment
- Seed Grants for Collaborative PI Network
- K Award System
- Clearinghouse for pairing PIs with common substantive interests
- Collaborative groups focused on specific topic areas: aggression, cooperation, maternal behavior

Next Steps…

Produce a report

- Draft: end of summer
- Final: fall 2010

- Contents
  - Executive summary
  - Recommendations and findings
  - Documentation of procedures including edited versions of all white papers.



THANK YOU!