Candidate Statement

Research

My research program is focused on better understanding the ways in which genetic variation is associated with individual differences in behavior. My earliest work utilized fruit flies (*Drosophila melanogaster*) as research subjects and was aimed at characterizing the genetic basis of a relatively simple behavior (i.e. geotaxis—orientation and movement with respect to gravity). Three publications resulted from this work (Stoltenberg, Hirsch & Berlocher, 1995; Stoltenberg & Hirsch 1996; Stoltenberg & Hirsch 1997; **see "Publications (1995-2008) and Publications (2009-present)" folders in Appendix for copies of all of my publications**). Recently, the Stoltenberg & Hirsch, (1997) paper has been cited several times because it is one of the few studies providing empirical evidence for genes on the Y-chromosome in *D. melanogaster* being associated with individual differences in behavior. My transition from fruit fly behavior genetics to human alcoholism genetics meant that this line of research was essentially for me a dead end.

The remainder of my work falls into two areas that have a clear intersection. The first area has to do with better understanding the genetic influence on propensity to engage in health-risk behaviors. The second area is an effort to understand the joint influences of multiple genes on behaviors using a system dynamics, or control system modeling approach. It remains to be seen which of these areas is more significant. The former has resulted in more peer-reviewed publications and citations, but the latter may eventually prove to be a greater contribution to theory and to knowledge. Both have contributed to grant funding and continue to comprise my research program.

It is of critical importance to better understand how genetic variation is associated with individual differences in propensity to engage in risky behaviors such as alcohol use. My research focus has been increasingly directed toward the more basic behavioral level of decision making and behavioral control. My work has documented the influence of genetic variants in the serotonin neurotransmitter system on both decision making (Stoltenberg & Vandever, 2010; Stoltenberg et al., 2011) and behavioral control (i.e. impulsivity; Stoltenberg, et al., 2006; Stoltenberg, et al., 2012). Such basic findings are critical in the ongoing efforts to characterize the genetic architecture of key behaviors.

It might be useful here to discuss the current thinking on how genes influence behaviors. The age old Nature versus Nurture debate has died a slow but natural death. Decades of solid convergent empirical evidence has demonstrated beyond a doubt that both genes and environments have important influences on behaviors. Now the difficult work begins. It is necessary to identify which genes and environments influence behaviors and to characterize the pathways through which these effects are manifest. Developments in biotechnology and bioinformatics (i.e. computational science) have made it possible to begin to ask questions about the relations between specific genetic variants and individual differences in behavior. Identifying single genes that influence major genetic diseases like Huntington Disease was

relatively straightforward. In such cases, inheriting a certain form of a gene results in the development of a disease. For mental illnesses or other complex behavioral traits, however, such one-to-one relationships do not exist. The relationships between genes and behaviors is even more complex and likely involves many genes, each having a small effect, and includes interplay between those genes and myriad environmental inputs. Understanding how genes and environments influence the function of brain systems and ultimately an individual's risk for developing a mental illness will require a substantial effort across disciplines and levels of analysis. Such is the work in which we are engaged in my research program.

The second area of interest of my research program is the application of complex system modeling approaches to better understand how overall genetic variation in neurotransmitter systems affects the function of the system. In other words, I am applying well known approaches such as control system modeling in order to examine the effects of various combinations of genetic variation at multiple components in a neurotransmitter system (e.g. receptors and enzymes). This approach is one type of systems biology application that attempts to go beyond the examination of one variable at a time. Biological systems, such as neurons and neural circuits, are comprised of many component parts, each of which can vary genetically. Such genetic variation can have significant impacts on the function of a given component. Such work requires the use of computer models that enable the examination of many variables and their interactions. While I was at the University of Michigan I took courses at the Center for the Study of Complex Systems as part of my K01 award, which led to the development of my first models and my first modeling publication (Stoltenberg, 2003). I have since published other work building on this initial model alone (Stoltenberg, 2005 and 2011) and in collaboration with a mathematician (Stoltenberg & Nag, 2007 and 2010). It seems to me that without using computational models we will not be able to understand the genetic architecture of complex traits such as behaviors.

I have been successful in obtaining external funding. At both the University of Michigan and at Black Hills State University, as principal investigator, I obtained grants from the NIH totaling over $739,000. I have also sought and obtained internal research funds and foundation funding. Recently, a grant application to the National Institute of Alcohol Abuse and Alcoholism on which I am a co-investigator, was awarded nearly $1.7 million to conduct a 4-year project to study the role of traumatic stress and genotype on alcohol problems (PI, Jeff Simons, University of South Dakota). I plan to continue aggressively seeking external funding for my research program.

I've been actively collaborating or planning collaborations with several UNL faculty and investigators from other institutions. My lab has extracted DNA and done some genotyping for a project with John Hibbing and Kevin Smith in Political Science. This work has resulted in a manuscript that is currently under review (Smith, et al., under review). Mike Dodd and I regularly have discussions regarding projects and have collected some pilot data that includes antisaccade measurements with his eye tracker and cheek cells from which we've extracted DNA and done some genotyping. We have also applied for and received seed funding for a pilot project from the UNL Substance Abuse and Violence Initiative to study the role of genetic variation and attentional control in individual differences in substance use and intimate partner violence. Sarah Gervais and I have also received seed funding from SAVI to study the potiential

influence of 5-HTTLPR genotype on response to sexual objectification. We will examine the influence of early life trauma and genotype on coping drinking. David DiLillo and I have also received SAVI seed funding to study the potential influence of particular genotypes on propensity to engage in aggressive behavior while intoxicated. These data will be collected in the context of Laura Watkins' dissertation study. Dennis McChargue and I have collaborated on a paper (Herschl, et al., 2012) and on an NIH grant application that was declined. We have overlapping interests and will surely collaborate in the future. Gustavo Carlo (former UNL faculty, now at the University of Missouri) and I are in the process of analyzing some data that will lead to multiple publications about specific genes and prosocial behaviors. I'm involved with the Substance Abuse Research Cluster and the Substance Abuse and Violence Initiative and those efforts have resulted in a publication (Grant, et al., 2011) and an NIH R01 application (declined). Jukka Savoleinen (UNO, Criminology), Lorine Hughes (UNO, Criminology) and I have applied for and received $35,000 of internal (UNO) funding to collect saliva samples from incoming UNL freshman for genotyping candidate genes for association studies with longitudinal data on substance use. I've also recently had discussions with several UNL Psychology faculty (Lisa Crockett, Jeff Stevens and Dennis Molfese) about future collaborations. Additional current collaborators are located at the University of Michigan (Frederic Blow, Maureen Walton, Kirk Brower) and Idaho State University (Maria Wong). Copies of my funded grant applications can be found in folders labeled "Funded Grants (1998-2009)" and "Funded Grants (2009-present)".

Areas of Interest

Serotonin System Genes

One of my primary interests is to understand how genetic variation in serotonin system genes is related to behaviors that are influenced by serotonin function. There are several components of the serotonin system that vary genetically including: receptors, the transporter and various enzymes. The potential number of genetically different combinations of components is quite large; especially when one considers that there are at least 14 different types of serotonin receptors, enzymes that synthesize and degrade serotonin and transmembrane proteins all of which vary genetically. This focus of my research program began when I was at the University of Michigan and has provided empirical support for associations between serotonin system genes and antisocial alcoholism severity (Hill, et al., 1999), impulsivity (Twitchell, et al., 2001; Stoltenberg, et al., 2006; Stoltenberg et al., 2012), indices of serotonin function (Stoltenberg, et al., 2002), neuroticism (Sen, et al., 2004), eating problems (Stoltenberg, et al., 2012) and risky decision-making (Stoltenberg & Vandever, 2010; Stoltenberg, et al., 2011a).

Given this complexity, I use control system modeling to enable me to examine different genotype combinations and their potential effect on indices of serotonin function. Control system modeling is a well-established approach that utilizes systems of differential equations to mathematically represent multi-component, interactive, systems (Stoltenberg & Nag, 2007; 2010). These efforts have been important in the development of my thinking about the role of genes in behaviors and may prove useful in understanding the basics of gene-gene interaction (Stoltenberg, 2005) and in predicting the outcome of pharmacological treatment for alcoholism (Stoltenberg, 2003 and 2011).

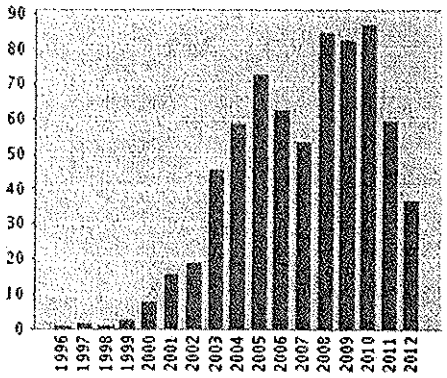
Impulsivity

Impulsivity is a risk factor for a variety of health-risk behaviors, such as gambling, substance use and risky driving. There appear to be a variety of types of impulsivity such as motor, attentional and non-planning, too quick responding, reduced response inhibition, etc. It also appears that these aspects of impulsivity vary quantitatively and are to some extent, independent of each other. I am interested in how the serotonin system might influence impulsivity and, by extension, propensity for engaging in health-risk behaviors. Because diagnoses for mental illnesses have not proven to be very useful phenotypes for genetic analyses, my research program has been focusing on impulsivity as a phenotype because it is a risk factor for a variety of health risk behaviors including substance use, gambling and eating problems. Thus far, we have shown that the association between types of impulsivity and alcohol problems may differ for men and women (Stoltenberg, et al., 2008), that a genetic variant of a serotonin system gene is associated with individual differences in behavioral inhibition (Stoltenberg, et al., 2006) and we've extended our control system model of the serotonin system to include impulsivity (Stoltenberg & Nag, 2010). We have also recently identified epistatic (gene x gene) and gene x environment interplay in serotonin system genes on associations with specific facets of impulsivity (Stoltenberg, et al., 2012). We also recently reported evidence that genetic variation in a particular gene involved in neural function (neurexin 3) was associated with increased risk for alcohol problems and impulsivity in men (Stoltenberg, et al., 2011b). Impulsivity will remain a core construct in the future directions of this research program.

Alcoholism

Much of the work that I did while at the University of Michigan addressed issues surrounding alcoholism, especially the influence of Family History of alcoholism on risk and the influence of the serotonin system on a specific subtype of alcoholism called antisocial alcoholism. There is a tremendous amount of evidence that alcoholism runs in families, so individuals with a family history of alcoholism are at increased risk for developing alcohol related problems. In my first alcohol paper, I showed that using a measure of family history of alcoholism that utilized information from parents and grandparents (those first degree relatives that pass on genes to the next generation) did a better job at predicting alcohol problems than did simple dichotomous measures of family history (Stoltenberg, et al., 1998). The effects of family history may be moderated by gender and socioeconomic status (Curran, et al., 1999). The risk for developing antisocial alcoholism for women has risen in recent years (Stoltenberg, et al., 1999), which is consistent with changes in gender roles and is evidence against the notion that antisocial alcoholism is "male-limited". My work with alcoholism has been an important part of my career and continues to be a focus of my research program. The two recent NIH grant applications on which I'm a co-investigator focus on risk for alcohol problems in veterans with PTSD (Simons; funded); and on relations among sleep and alcohol problems (Wong; declined).

Impact



To date my research program has been focused on better understanding gene-behavior with a focus on impulsivity, alcoholism and genes in the serotonin system, but also including eating behaviors, decision making, control system modeling and fruit fly geotaxis. Since 1996 my 30 peer-reviewed articles have been cited 627 times (excluding self cites; see figure) for an average of 20.9 times per article and an h index = 12 (according to a Web of Knowledge Citation Analysis on 9/19/2012). My work has been cited in 59 different research areas including (Psychiatry, Neuroscience, Substance Abuse, Psychology, Genetics, Pharmacology, Behavioral Sciences, Public Environmental Occupational Health, Zoology, Cardiovascular System Cardiology, Cell Biology, Pediatrics, Biophysics, Evolutionary Biology, Family Studies, and Nutrition Dietetics). My work has been cited in high profile journals such as Science (twice), Proceedings of the National Academy of Sciences (thrice), Psychological Bulletin (4 times), and specialty journals such as Alcoholism: Clinical and Experimental Research (41 times), American Journal of Medical Genetics Part B: Neuropsychiatric Genetics (31 times) and Biological Psychiatry (24 times).

There is good reason to believe that my research program is poised to make an even larger contribution to knowledge in the future. The quality and quantity of my research during the probationary period suggests a clear promise of continuation. By coming to UNL I have increased my pool of collaborators, improved my resource base, increased my access to graduate students and increased my research apportionment. I have a relatively large database in hand that was collected with the support of an NIMH grant at BHSU that has resulted in four publications and three manuscripts that are either under review or in preparation. I am co-investigator on two recent NIH grant applications and I am planning collaborations with several colleagues at UNL and at other institutions. I am grateful for the generous support of the Psychology Department since my arrival in 2009. I also acknowledge the hard work and dedication of the students in my lab. Clearly, this work is the product of many individuals. We moved into our new lab space at the start of December 2011, which should further aid productivity. I fully expect to contribute significantly to knowledge about gene-behavior relations for the remainder of my tenure at UNL.