OPPNET Basic Behavioral & Social Science Opportunity Network

Improving Animal Models of Human Behavioral and Social Processes

July 23-24, 2012

Workshop Summary

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DEPARTMENT OF HEALTH & HUMAN SERVICES · USA ·

National Institutes of Health (NIH)
Basic Behavioral & Social Science Opportunity Network (OppNet) Workshop
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Improving Animal Models of Human Behavioral and Social Processes

Overview
On July 23-24, 2012, the National Institutes of Health (NIH) Basic Behavioral & Social Science Opportunity Network (OppNet) hosted a workshop, *Improving Animal Models of Human Behavioral and Social Processes*. OppNet is a trans-NIH initiative supported and managed by 24 Institutes and Centers (ICs) and four program coordination Offices within the Office of the Director. Its mission is to pursue opportunities for strengthening basic behavioral and social science research (b-BSSR) at the NIH while innovating beyond existing investments. OppNet advances b-BSSR through activities focusing on basic mechanisms of behavioral and social processes that are relevant to the missions and public health challenges of multiple NIH ICs and Offices, and that complement and build upon existing NIH investments. By fostering basic research on behavioral and social processes throughout the lifespan, OppNet supports the NIH mission to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce the burdens of illness and disability. Additional information about OppNet can be found at http://oppnet.nih.gov/index.

Workshop Objective
To develop a set of recommendations for NIH action to foster the identification and development of powerful animal models for human behavioral and social processes, particularly those that have traditionally been difficult to model.

Workshop Summary
The OppNet Workshop brought together experts from the scientific community and the NIH to discuss strategies for improving animal models of human behavioral and social processes. Two main goals were accomplished:

- Animal models of human behaviors and social processes that have been particularly successful or generative were identified so that participants could learn from those successes to guide future activities. This was accomplished through presentations of research methodologies and findings by participants with diverse expertise within the scientific community.

- Best approaches to modeling human processes in animals were discussed. Through moderated discussions and subsequent recommendations from workshop participants, divided into groups for breakout sessions, specific recommendations for NIH actions were generated. Groups also suggested strategies for implementation.

Day 1: Research Presentations

Welcome and Introductions, Deborah Olster, PhD, Office of Behavioral and Social Sciences Research (OBSSR), NIH

Dr. Deborah Olster, co-chair of the Workshop Planning Group, welcomed participants, and thanked members of the Workshop Planning Group and Lewis-Williams Conference & Logistics Management, LLC, for logistical support. Dr. Olster reviewed two previous NIH activities that informed the planning of this Workshop. The first was a series of NIH Behavioral and Social Sciences Research Coordinating Committee discussions about translational research, particularly "Translation Zero" research, defined as bidirectional exchange between basic research in animal models and basic research in humans. The second activity was an October, 2010 public meeting, *OppNet: Expanding Opportunities in Basic Behavioral and Social Science Research*. At a breakout session on *Animal Models, Human Applications* attendees brainstormed on this topic and produced a number of recommendations, including the following:

- Stimulate collaborative basic behavioral sciences research between investigators working on animal models and those conducting research with human subjects; and
- Host a meeting of investigators who have succeeded in doing this, to help identify barriers and opportunities.

This OppNet Workshop provided an opportunity for following through on these two recommendations.

Dr. Olster reiterated the one overarching question for the participants in the Workshop: "What can NIH do to identify appropriate model animals and enhance the development of powerful animal models for human behavioral and social processes, particularly those that have been traditionally difficult to model?" Following Dr. Olster's comments, each participant introduced himself/herself by name and affiliation.

NIH OppNet Overview, William Elwood, PhD, OBSSR, NIH

Dr. Elwood began by presenting OppNet's mission and goals:

- To foster research initiatives on basic social processes and behavioral mechanisms across public health challenges;
- To develop the body of knowledge on the nature of behavior and social systems;
- To support b-BSSR that is relevant across the missions of the NIH Institutes, Centers, and Offices (ICOs); and
- To expand NIH's funding of b-BBSR with additional investments that complement the agency's entire extramural research portfolio.

Dr. Elwood explained that the NIH Director Dr. Francis Collins launched OppNet in November 2009. The initiative was created in recognition of that fact that basic research in the behavioral and social sciences spans the missions of individual NIH ICs, each of which has a specific disease, life course, or somatic focus. In 2010, OppNet's first year, it received more than 250 responses from the scientific community in response to a Request for Information (RFI) soliciting input on priorities for OppNet. Frequently occurring responses included:

- Capacity Building
- Cognition and Emotion
- Cultural Aspects of Health
- Decision Making
- Development (Time, Exposure and Change)
- Gene Environment Interactions
- Health Behaviors
- Stress
- Social Environment

- Sleep and Circadian Rhythms
- Social and Personality Psychology
- Social Gradients/ Stratification
- Health Inequities

Respondents also articulated the utility and importance of animal models to improve our understanding of the basic behavioral and social processes listed above.

An analysis of RFI responses, internal NIH portfolio analyses, and recent published literature informed the development of 18 funding opportunity announcements (FOAs) during 2010, 2011 and 2012. OppNet is currently engaged in a self-study to evaluate the outcomes of its activities to date, to inform discussions about the potential extension of the initiative beyond its original targeted end date of 2014.

Dr. Elwood explained NIH's definition of b-BSSR -- that it furthers understanding of fundamental mechanisms and patterns of behavioral and social functioning relevant to the nation's health and well-being, as they interact with each other, with biology, and with the environment. Dr. Elwood discussed the three components of b-BSSR:

- Behavioral and social processes (such as attention, learning, and memory, emotion, motivation, and language development)
- Biopsychosocial research (such as behavioral genetics, biosocial surveys, and psychophysiology
- Methodology and measurement (such as data collection and analysis, modeling, and research design)

Dr. Elwood noted that OppNet members created a set of answers to frequently asked questions (FAQs), such as, "What is the difference between *basic* and *applied* research based on the NIH definition?" Further, Dr. Elwood described OppNet's Steering Committee of ICO directors or their designees as enthusiastically involved in OppNet's processes and sincerely dedicated to OppNet's success.
One of their ideas was to host a Symposium Series that linked human and animal models research in the behavioral and social sciences. Drs. Jeanne Altmann (Princeton University) and Steve Cole (University of California, Los Angeles) participated in the most recent Seminar in March 2012, *Big man on campus: Social regulation of gene and endocrine expression in human and nonhuman primates*. There have been five symposia to date and OppNet makes the Symposium Series available for public viewing on its website (http://oppnet.nih.gov/news-symposium.asp).

Dr. Elwood listed examples of OppNet animal models grants funded over the past two fiscal years. He emphasized that the ICO Directors continuously encourage of the inclusion of animal models research in all of OppNet FOAs. He provided his contact information and instructions to find OppNet representatives from each NIH ICO, as well as links to the OppNet Twitter and Facebook feeds. On behalf of all of NIH, he thanked and welcomed all participants to the Workshop.

Workshop Goals, Minda Lynch, PhD, National Institute on Drug Abuse (NIDA), NIH
"Call the Movers! Moving Animal Research Findings to Human Application"

Next, Dr. Minda Lynch, co-chair of the Workshop Planning Group, welcomed Workshop participants and shared the vision that guided development of this Workshop. She thanked her NIH colleagues for their input and for identifying experts in the NIH b-BSSR community for participation in this "think tank". Dr. Lynch offered the following provocative questions to guide discussion:

- Of all the animal model research in behavior that NIH supports, how much of this research has been used to inform human laboratory investigation?
- How much has ever seen the light of day in human application?

There are really exciting findings and results that are never brought to human laboratory or field-based studies, which is a logical next step in the translational process. This is a major concern at the "Translation Zero" level. The hope is that research using animal models will eventually inform and improve human health. She then asked the audience, "What are the obstacles that impede moving animal research findings to the 'next step' in a translational process?" The charge to the Workshop participants is to identify barriers and obstacles in that movement and to determine if Workshop participants have found successful and creative strategies to optimize that movement.

Dr. Lynch suggested that one possible barrier to translation is the problem of validation of animal models. She cited an example where NIDA convened a meeting of nicotine and smoking (animal model and human) experts to discuss an appropriate behavioral test composite for screening putative cessation compounds. This was a great opportunity because there are good animal behavioral models that mimic essential features of human abuse and addiction. However, participants expressed concern that cross-validation in humans must be completed first, begging the questions, "Do manipulations induce the same effects in human smokers? For example, are the anxiety and anhedonia inferred from rodent behavior equivalent to that reported by human smokers in withdrawal?"

With these issues in mind, she posed challenging questions to the Workshop participants, including: "What needs to be done to 'move' animal findings?" She suggested that participants start with a basic question by asking, "What *is* translational science at the intersection of animal behavioral models and human research?" (This would be a focus of Day 1 discussion and a topic in the next day's breakout sessions). Dr. Lynch urged participants to identify what was needed, specifically, for a bi-directional interaction between animal modelers and those engaged in human research programs, and to suggest what could be done by NIH to facilitate this interaction. She asserted that many research questions are being addressed in isolation, where, "Animal modelers are working completely separately from investigators studying the same processes in human subject research, at various levels and in different settings."

In the discussion that followed this presentation, one participant commented on the more common use of the phrase *translational science* to refer to applying findings from an animal model to a human disease, rather than to basic biological or behavioral processes. Dr. Lynch affirmed this observation, noting that this comment raised a couple of important points: In OppNet, the focus is basic behavioral and social processes, therefore understanding human health in normal processes; but if one can study them in the context of disease or disorders to understand normal processes that become dysregulated, OppNet can support research in that context. Also, the neurobiological substrates, processes, and mechanisms of behavior are very appropriate for OppNet, but not neurobiology in isolation because there is existing research support for basic neurobiological research at NIH. She further explained that when discussing disease models, if the research can inform basic social and behavioral processes, both the modeling of these processes and better understanding in humans, then we are on the right topic; "it's kind of a fine line that we walk." Dr. Lynch remarked, in response to a question from the audience about the definition of translation for this purpose being not translation to the clinic, but crossing the animal-human border.

Lastly, in summarizing the charge to participants she asked them to "bring all of your creative energies and expertise to interact with colleagues, especially about especially difficult behaviors to model".

1. Session 1: Opening Addresses

a) Dario Maestripieri, PhD, University of Chicago

Animal Models of Human Behavioral and Social Processes: What is a Good Animal Model?

Dr. Maestripieri described three criteria for assessing the validity of animal models of human behavior as face validity (qualitative), predictive validity (empirical), and construct validity (theoretical). He then

discussed the construct validity criterion in greater detail and argued that research with animal models of human behavior should be theoretically grounded in evolutionary biology. Evolutionary processes that produce phenotypic similarities in humans and animals fall into two categories: Convergent evolution and phylogenetic inheritance. In convergent evolution, similar morphological, physiological, behavioral, and psychological traits that evolve independently by natural selection in response to similar environmental pressures produce analogous traits. In phylogenetic inheritance, similar morphological, physiological, behavioral, and psychological traits can occur in closely-related species because these species have inherited these traits from a common ancestor. These traits are homologous; therefore, homologous traits have, by definition, a common phylogenetic history and are produced by similar developmental processes.

Dr. Maestripieri discussed how evolutionary principles can guide the development of animal models and how knowledge of a species' behavior and ecology can guide the selection of a particular process as an animal model. Dr. Maestripieri discussed three examples of social-behavioral processes for which the rhesus monkey would be an ideal model: the effects of early psychosocial stress on offspring's behavioral and physiological development; the effects of chronic social subordination on behavior and physiology; and the effects of social variables on gene expression.

Dr. Maestripieri identified a number of constraints on the use of particular animal models including availability of the animal itself; housing and maintenance requirements; breeding; welfare issues; cost; time; training; limited opportunities to do invasive and/or manipulative research; previous knowledge of the species; number of researchers already using the model; and the probability of funding. Regarding the reliability of an animal model, Dr. Maestripieri quoted from a Geyer and Markou (2000) publication, stating that "Having a reliable and reproducible experimental system is essential to scientific study… and it should be emphasized that there are cases in which the study of the variability of the model system could lead to a better understanding of the phenomenon. Variability cannot always be considered as error." Dr. Maestripieri stressed that this is the case for models of human behavioral and social processes and noted that, traditionally, decisions about the development and use of animal models for behavioral and biomedical research have been driven by constraints rather than by theoretical principles or knowledge of the behavior and ecology of a species.

Dr. Maestripieri suggested that developing animal models on the basis of sound theoretical principles instead of constraints is a key strategy to advancing b-BSSR. Further, he stated that, "Researchers should be encouraged to develop theoretically relevant, original, and interesting new models of human behavioral processes. This can be done by the researchers themselves through the peer review process; research institutions through the support of appropriate facilities; and the funding agencies through encouragement of exploratory high-risk, high-payoff approaches to the use of animal models."

Dr. Maestripieri discussed the need to conduct more population-based research studies on behavioral and social processes to answer questions surrounding such phenomena as effects of group size and socio-demographic structure on social and cognitive development in early life; the effects of social support provided by large kin networks on health in mid-life; and environmental maternal effects mediating the intergenerational transmission of maladaptive social behavior. Dr. Maestripieri also suggested that nonhuman primates such as macaques and baboons are excellent animal models for population-based research on behavioral and social processes due to their similarities to humans (for example, in their genetic, anatomical, and physiological characteristics), availability in large numbers, ability to survive and breed well in a wide range of environments, relative ease of handling, shorter than human lifespans, and in some cases, complete mapping of their genomes.

Dr. Maestripieri concluded with a brief discussion of the challenges and rewards of population-based bio-behavioral research with rhesus monkeys. Challenges included funding, logistic difficulties, investment of time, training and skills needed for the research, and publication of research findings. The rewards were

ecological validity of findings, "extrapolability" to humans, and opportunities to understand biology-environment interactions and the effects of social environment on behavior, physiology and health. In addition, the lifespan approach provides an opportunity to study phenomena in the population in terms of distribution, maintenance, and intergenerational transmission of phenotypes and genotypes.

b) C. Sue Carter, PhD, Research Triangle Institute International

Animal Models: Themes and Examples

Dr. Carter asserted that animal models come from many forms and may have many purposes, and researchers need novel ideas, good techniques, and resources to model human behaviors in animals. Concerning the future of animal models, there will be comparative approaches grounded in ethology, ecology, evolution, and development; new perspectives and theories; new paradigms and technologies; multidisciplinary and integrative approaches; collaborations and recognition that no one person can do everything; a search for patterns but recognition of individual differences and the mechanisms that may underlie them, e.g., epigenetics; and the critical need for support for new scientists and new energies.

Dr. Carter described her personal perspective on the various factors that influence the selection of animal models for behavioral research and the sources of knowledge and approaches to behavioral sciences, as these, too, have impacted the selection of animal models. These include hypothesis-driven and curiosity-based research; disease or problem-driven versus funding-based investigations; empirical or descriptive studies; domain- or scientific discipline-based work; interest in social organizations and mating systems; and, processes or mechanisms.

In examining domain- or scientific discipline-based research, Dr. Carter noted that knowledge of natural history and the presumed "normal environment" of a species may be necessary to interpret the expression of behavior. Evolution searches for the origin of species, origin of behavioral systems, and origins of processes that regulate behavior. Comparing fish, reptile, and human nervous systems, Dr. Carter pointed out that the human nervous system is a consequence of evolution, with a massive increase in size of the cerebral cortex as compared to the other classes. However, the old parts of the nervous system are still present and can influence the actions of more modern components. Thus, comparative approaches have much to teach about basic processes, such as emotion. She also described how the new technologies and methodologies allow investigation of variations across and within species. Individual differences have become more apparent and dominant in our understanding of behavior. The genomic and epigenomic revolutions are especially important to the study of individual differences.

The choice of animal models is also driven by considerations of accessibility, availability, and suitability for laboratory work, i.e., the animal should display "normal" behaviors and physiology under laboratory conditions. Ideally, the animals would reproduce easily and rapidly under laboratory conditions, although this may truncate the natural processes that affect animal development and behavior. We humans, with our anthropomorphic thinking, desire animals that model human traits and behaviors and also prefer them to be genetically and neurobiologically similar to us. The availability human and financial resources also influence the selection of animal models for research. Purchasing animals from a commercial vendor is often less labor-intensive and less expensive than catching them in the wild. It's easier and cheaper to keep small animals whose dietary needs are easily met. Finally, Dr. Carter discussed how many mammalian species now used as animal models have been commensal with or have co-evolved with humans. We have domesticated them and used them for food or work or as companions, as well as for scientific research.

Dr. Carter concluded by discussing her own research using prairie voles (categorized as socially monogamous rodents). This work has been particularly helpful to understanding social behavior and the social nervous system. Prairie voles can be studied in nature as well as in the laboratory and exhibit

selective (and in nature), life-long social bonds. At least some of the behavioral differences between monogamous and non-monogamous vole species may be based on genetic differences, e.g., in the vasopressin receptor, as shown by Thomas Insel, Larry Young and their colleagues. Research also indicates that early experiences -- some as simple as how animals are handled or manipulated during weekly cage cleaning -- can have life-long epigenetic consequences for social behaviors, including behaviors such as alloparenting and social-bond formation, both considered defining features of social monogamy.

2. Session 2: Success Stories (Chaired and moderated by Jeanne Altmann, PhD, Princeton University)

a) Tim Bussey, PhD, University of Cambridge

What do we want out of our ideal behavioral method?

Dr. Bussey studies cognition in animals, particularly mice and rats. He stated that he is aware of the pessimism regarding the translation from mice and rats to humans and back again in the area of cognition, especially in neuropsychiatric disease or degenerative disease. He asked, "What can we do to improve it? One way is to start from scratch and ask if none of these other behavioral methods involving animals existed, what would one fantasize to be ideal behavioral methods for rats and mice, if anything goes?"

Dr. Bussey offered his wish list for the characteristics of a good animal cognition testing paradigm. First, it should be automated so that tasks can be done in parallel, rather than in series. Advantages to automation are that the computer runs the task; there is no human interference with the animal (such as picking it repeatedly); measures of delay and reaction times are accurate to the millisecond; data are saved automatically; and there is potential for standardization. It should be non-aversive and not stressful (unless, e.g., one is interested in modeling Post-Traumatic Stress Disorder). But if interested in cognition, ideally one would use a method that didn't involve a lot of stress, since stress can affect cognition. The paradigm should be multi-dimensional and useful to test and compare results across completely different testing situations, using a single piece of apparatus that uses the same stimuli, measures the same responses, delivers the same reinforcers, etc. Dr. Bussey's approach was to bring the human and mouse/rat testing as similar as possible in order to validate the task for translational work between the human and animal species.

Dr. Bussey's cognitive testing method involves computer-automated stimuli presented on a computer screen to rats and mice, a method often used in human studies. This method has the advantages of contiguity of stimulus and response, facilitation of learning, replicability, and removal of confounds associated with divided attention. In one of Dr. Bussey's studies, nonverbal stimuli shapes were presented to rats and mice with the animals responding by touching the screen to receive associated rewards. In a visual-discrimination learning task, the rat appeared to be contemplating prior to making its selection. In studies exploring the role of genetics in cognition, mice with a particular gene variant displayed cognitive impairments on multiple tests, as did humans with that variant. That particular gene variant has been linked with schizophrenia, although not everyone with the variant has been diagnosed with schizophrenia. Currently, Dr. Bussey is attempting to take this method to clinicians in order to bring together the testing of humans, mice, and rats in an effort to facilitate translation as across species. Dr. Bussey concluded that, "There is an enormous amount of work still left to do."

b) John Capitanio, PhD, University of California, Davis

Psychosocial Stress and Immunodeficiency Virus Disease in Rhesus Macaques

Dr. Capitanio related a quote from 1984 that proposed that, "Emotional and personality factors might have direct influences on the onset and course of [AIDS]." He studies simian immunodeficiency virus (SIV) infection of rhesus monkeys and a model of psychosocial influences on SIV disease, comparing

well-socialized adult males in stable social groups and those in unstable social groups. Currently, research is underway to determine whether beta-blockers can impact disease progression and whether artificial stimulation of the sympathetic nervous system (via methamphetamine) amplifies these effects. The success of the model can be attributed to the broader model (rhesus/SIV) recapitulating the pattern of the disease in an accelerated fashion, as compared to human HIV. This model species shows important similarities with humans such as phylogenetic proximity and a high degree of sociality. The models also provided for tight experimental control, which was impossible to achieve in human studies. The studies modeled important aspects of "stress" experienced by humans, i.e., unpredictability in one's social opportunities and the need to re-adjust social relationships.

Dr. Capitanio attributed the success of the model to "being in the right place at the right time," insomuch as (a) the idea of psychosocial factors affecting immunity was "in the air" -- a variety of studies were being done in humans examining psychosocial stress such as bereavements and felt stigma in AIDS and in other human diseases, and (b) there was an excellent animal model of AIDS available and being used for studies of basic pathogenesis. And lastly, the success of the model was due to the availability of a set of ready resources (in terms of expertise and infrastructure) in support of the studies, and researchers were able to leverage the model to explore mechanisms beyond the original team's expertise through collaborations.

c) Martha McClintock, PhD, University of Chicago

Rodent Models of Sociality, Health and Life Histories: Social Isolation, Stress, and the Biological Mechanisms of Breast Cancer

Dr. McClintock pointed out that humans are animals, too, and that we evolve by the same principles. The goal is to discover common principles about behavior and its relation to various environments and to physiology. The first principle was the profitability of thinking about the function of behavior. She asked, "What is behavior?" and argued that, "It is the interface, the surface between the internal (the physiology, genes, systems) that allow reproduction and survival and the external world. Behavior allows an organism to carve its niche out of a continuous blended, physical world and focus on specific resources and face specific risks within that." Dr. McClintock likened behavior to the placenta, which determines the dynamic interaction between (internal) fetus and (external) mother.

The second principle she emphasized was that minds are not unique to humans. Dr. McClintock has chosen vigilance in response to stress as a mental state to study in non-human animals, one that also serves an organism's particular role in a social group. Vigilance in rats can be altered by social housing condition, i.e., housing the rats in isolation versus in groups. She also pointed out that traditional, biomedical laboratory conditions are often un-natural for the species and therefore limit the validity of research findings. It would be preferable to control housing conditions, photoperiod, etc. to align more closely with the natural environment of the species under study.

A proponent of transdisciplinary research, Dr. McClintock collaborates with pathologists to study the role of social stressors (and the biological responses they trigger) in mammary tumor development in rodents. Her transdisciplinary research with Dr. Conzen, supported by the National Cancer Institute, focuses on the interaction between social behavior and disease, working with animals and performing parallel and clinical studies in humans. In both rat and transgenic mouse models, it was discovered that social isolation dysregulates the adrenal axis and stress reactivity, disrupts the inflammatory response, increases the risk of developing malignant mammary tumors, accelerates aging and shortens lifespan. Taken together, these observations demonstrate that social isolation regulates the molecular mechanisms of disease progression and aging. By focusing on social and behavioral regulation of physiological systems, gene expression, disease, and mortality through transdisciplinary research, this successful model was created.

The studies in humans are geared toward trying to understand why African American women have a much higher mortality rate from breast cancer than white women. Dr. McClintock asked, "How can we go a step further in the transdisciplinary process?" answering that, "We go back and forth between the animal and human research." In an attempt to understand the behavioral implications of stressors to tumors, Dr. McClintock participates in an NIH study where researchers go to women's homes to gather social, psychological, and biological information to test hypotheses about dynamics and reciprocal relationships between the social world, physical world, mental states, cognition, the aging process and health and disease. Dr. McClintock concluded that behavior is the interface with biological and environmental processes.

d) Suzanne Mitchell, PhD, Oregon Health & Science University

Delay Discounting (Intertemporal Choice or Impulsive Choice) in Mice and Rats

Dr. Mitchell described a popular model, called *Delay Discounting*, which examines choices between rewards that are small and available immediately or after a short delay versus larger rewards delivered after a longer delay. Deciding the better alternative is an ubiquitous problem that humans and animals face. Interestingly, drug use is associated with a higher likelihood of selecting the smaller, more immediate reward. She asked, "What's the mechanism underlying this associative relationship?" Possibly, discounting decisions are somehow associated with subsequent initiation of drug use. Another possibility is that drug use causes neurophysiological changes, which cause steeper discounting and devaluing delayed rewards. Dr. Mitchell explained that evidence suggests that it's a little bit of both, but animal models are essential to answering this question. (No one is volunteering their child to be introduced to cocaine to see whether discounting changes). Also, to understand the genetic relationships, between responses to drug and discounting, animal models are necessary and findings from such models have implications for prevention and treatment of drug abuse in humans.

In the basic model, during an experimental session, Dr. Mitchell first offered food-restricted mice a choice of an immediate receipt of sucrose solution or a two-second delayed amount that was twice as large. The amount of immediate reward was titrated according to the mice's choices: preference for the delayed reward caused the size of the reward to be increased, while preference for the immediate reward caused its size to decrease. Different delays were associated with different titrated amounts of sucrose solution. When performance data became stable, Dr. Mitchell was able to plot them as function and determine one number that quantified the extent to which *discounting* happened over a range of delays. Dr. Mitchell also mentioned that there are other models where delay is adjusted instead of the amount of reward, and that percent choice of rewards differing in size and delay could also be measured. It is also possible to correlate discounting under one procedure to another. These and other models could be used for translational comparisons of the effects of similar manipulations, for example, between species.

Dr. Mitchell found that, "Convergent results force us to consider that at least some of the neurobiology and some of the genetic underpinnings are shared by the animal and human model, but the correspondence is not perfect. This may be because of procedural distinctions between human and animal models. For example, rewards in human studies are commonly hypothetical and not experiential, as opposed to food rewards for animals. Delay lengths are also very different. Thus, in humans, if we were to change the size of the delayed reward, there is a systematically lower rate of discounting. This is not seen in the rats. Also, drug administration affects discounting in rats, but not in humans. These raise concerns about the model."

Dr. Mitchell provided some suggestions to reconcile these differences in the animal model, which included creating rodent methods that do not use food restriction; utilizing procedures that yield reliable

data more rapidly; delineating the component processes and how they influence discount decisions; setting the limits of task sensitivity; and performing studies that assess divergence directly.

e) Larry Squire, PhD, University of California, San Diego

Animal Models of Human Memory and Human Memory Impairment

In 1957, when the noted patient HM was first described, efforts began immediately to create an animal model of human memory impairment. One can say this took 21 years, until an animal model was described by Mishkin in 1978. It took a long time because it wasn't understood which structures within the medial temporal lobe were important to HM's memory impairment. In addition, it was not initially understood that there are multiple types of memory. Many of the tasks that early on were given to monkeys in the name of understanding human memory impairment were really non-declarative memory tasks that could be supported by other brain systems outside of the province of the medial temporal lobe. For example, Dr. Squire's research showed that after medial temporal lobe lesions the same monkeys that could not remember the identity of an object after a 10-minute delay were able to remember a motor skill task for a month.

Dr. Squire posed this question: "With tasks like these and with an animal model in place it became possible to ask over time, what are the structures within HM's large lesion that are important to understanding his memory impairment?" The answer proved to be the hippocampus and adjacent structures in the parahippocampal gyrus. Comparisons of the brains of humans, monkeys, and rats were shown to illustrate the location of these structures in each species. After the animal model was first described, it took 13 more years to identify the structures of the medial temporal lobe memory system.

Animals with medial temporal lobe lesions exhibit many characteristics of human memory impairment. Examples of these characteristics were shared with the audience. Dr. Squire stated that this research can be considered a success story but that challenges were also found, which complicate efforts to move from findings with the animal model to principles of human memory. Dr. Squire stated, "One challenge is that tasks can be learned with alternative strategies. Some tasks are acquired declaratively by humans through conscious memorization, but in experimental animals the same tasks tend to be learned nondeclaratively. A second complication arises from differences in cognitive capacity between humans and animals. These differences can lead to salient non-parallels in task performance that can be difficult to interpret (such as path integration and spatial cognition)." Thus, a different study showed that rats were impaired at path integration after hippocampal lesions, even when the path was simple and direct. In contrast, patients with hippocampal lesions performed the same task well when the path was simple and direct.

Dr. Squire proposed that, unlike humans (who have a rich capacity for working memory), rats with hippocampal lesions may not be able to construct an effective working memory using the distributed cues needed to represent spatial environments. The rats' difficulty may not be with spatial functions that were lost after their hippocampal lesions, but with limitations in how well the medial prefrontal cortex can support memory in the presence of a hippocampal lesion. There are many tasks that test memory in a hippocampus-dependent way and where parallel findings are obtained in monkeys, rats, and humans. However, one needs to be attentive to the fact that alternative strategies are available for many tasks, and this can make it challenging to bridge from animal findings to human applications. Dr. Squire concluded that, "We should also be aware of the capacities that animals bring to tasks and the ways in which these different capacities can impact performance."

f) Mort Mishkin, PhD, National Institute of Mental Health

Less Successful Animal Models

Dr. Mishkin felt it was important to include discussion of some failures of animal models to understand human processes involved in memory, by considering differences in sensory modality and underlying neurobiological substrates. He presented results from a number of studies designed to explore the neural pathways underlying long-term memory in monkeys. Removal of the rhinal cortex (or the inferior temporal cortex that innervates this region) impairs performance on a delayed, non-matching to sample task that relies on vision. This is truly a memory, rather than a sensory, deficit in lesioned animals, as they perform quite well when required to respond to a single stimulus or after a very brief delay. Yet despite similar organization of neural pathways for other sensory modalities, i.e., audition and somatosensation, the effects of lesions on memory based on these modalities can be quite different from those observed on vision-based memory tasks. For example, rhinal lesions had no demonstrable effect on the animals' performance on tasks relying on auditory memory. There are differences in short-term memory for different sensory modalities as well. Studies involving short-term memory tasks indicate that monkeys can remember a visual stimulus quite well even with many distracters inserted between the original stimulus presentation and the matched stimulus. In contrast, they do quite poorly on a similar task involving auditory stimuli. Dr. Mishkin explained that, "What happens in vision and touch is not the same as what happens in audition. Why this is so, is an important question."

Dr. Mishkin suggested a theoretical explanation that humans have excellent auditory memory because of speech and language, which monkeys and other non-human primates do not possess. Dr. Mishkin concluded that, "The animal model we may have to use to understand this process in audition (and in order to serve us in the animal model for humans), may be songbirds or sea mammals who are vocal learners like we humans."

g) General Discussion (Moderated by Jeanne Altmann, PhD, Princeton University)

Dr. Altmann asked the participants to consider a series of questions, including, "What are our goals in doing any of the research? Where are we headed ultimately? What kinds of models, experiments, and studies do we start with? What are the steps? To what extent does a research group plan for the next generation? Can we make laboratory-based studies more ecological? What are the pros and cons? Why is it so difficult to model psychiatric disorders?"

One participant stated that psychiatric disorders are emotional disorders and that although the latter have been well accepted as biological disorders, the scientific community does not take animal emotions seriously. Another participant countered this argument, stating that he had studied cognitive impairments in schizophrenia, which is an emotional disorder. He proposed that sub-components of the disorder can be modeled in animals. The difficulty, he claimed, lies in defining disorders in the context of behavioral processes.

Another participant suggested that the key is finding the right unit of analysis for behavior. She claimed that humans are so focused on what humans think that they don't focus on how behavior functions simultaneously with the social and physical environment. The goal is to shift the lens a little; that is the challenge.

Someone asked, "How can we make progress on psychiatric disorders until we get an understanding of the instinctual nature of mammalian creatures? Nature provided some tools for living and we haven't had a disciplined conversation at that level within the neurosciences." Dr. Lynch commented that the Workshop discussions showed fabulous research being supported by NIH ICs with disease-focused missions, but explained that OppNet was created to build research in the basic behavioral and social sciences. The Workshop was designed to inform OppNet on how to improve the back and forth

translation of research on basic behavioral and social processes between animal models and humans, not necessarily to relate animal models to disease in humans. One participant noted a huge gap in model development and translation, but that disease comes into the processes and cannot be avoided.

Regarding sociology, one participant stated that over the last 10-15 years, a lot of talented people who did basic research never thought about diseases and they went out of business and stopped training graduate students. He continued, "Part of the challenge for OppNet is to revive this tradition where people are working across species and on fundamental issues like learning, memory, and emotion. This will take time because they don't have labs or grants, and we have stopped hiring them." This raised the issue and a discussion of taking the historical approach to solving these problems.

3. Session 3: Particularly Challenging Human Behavioral and Social Processes

a) Introduction to Session 3 "Conversations"

Dr. Olster explained that the "Conversations" were designed to start a dialogue between a pair of investigators: one who works with human subjects and the other, with a model organism, on a human behavioral or social process that is difficult to model in animals. Each investigator delivered a brief presentation and then participated in a discussion moderated by NIH staff.

b) Conversation 1 - Social Interactions: Cooperative and Competitive Behavior, moderated by Janine Simmons, MD, PhD, National Institute of Mental Health

I. Bill Harbaugh, PhD, University of Oregon

Animal Models of Human Social Behavior

Dr. Harbaugh believes the biological basis of human social behavior is interesting and important and that animal models are useful for understanding this. Dr. Harbaugh's study with Mayr and Burghar in 2007, *Neural responses to taxation and voluntary giving reveal motives for charitable donations*, indicated that there are neural correlates of taxation and charity. Mandatory taxation to pay for a public good activated the same neural reward circuitry as does the money itself and the degree of activation predicts giving. Ultimately, the study showed that altruists give nearly twice as often as egoists.

However, limitations existed and were demonstrated in the following study: In a game with 10 players, five had a good they would be willing to give up at a cost. Five wanted a good that they valued at a certain amount. Five exchanges, therefore, should produce a total of five units of net benefit. In this scenario, this should happen, but did not happen. Using children in the experiment, playing cards are dealt out: five red for sellers and five black for buyers. The children were given a simple set of rules regarding transferable property rights and prices. They got nine units of benefit instead of just five, where the price is equal to 3.5.

Dr. Harbaugh's findings revealed that self-interest leads to maximum total net benefit. However, additional experimentation showed that an external cost scenario of self-interest did not lead to maximum total net benefit. Dr. Harbaugh determined that the most important forms of human social behavior are politics and market exchanges. Animals compete and maybe even exchange, but they don't establish or manipulate the rules of exchange. They also do not use politics to set rules that can harness one motive for another person. Dr. Harbaugh left the participants with the question, "Can animal models tell us much about how and when human markets and politics succeed and fail?"

II. Jeffrey Stevens, PhD, University of Nebraska-Lincoln

Cognitive Building Blocks of Cooperation

Dr. Stevens posed the research question, "What cognitive building blocks are needed to implement cooperative strategies?" In particular, he focused on cognitive building blocks that result in reciprocal cooperation via tit-for-tat (TFT). Possible cognitive building blocks include individual recognition, inhibitory control, quantification, patience, and memory. In a study of discounted reciprocity (high vs. low patience), results showed that Blue jays with high patience cooperated more than those with low patience. More patient humans were also more cooperative than less patient individuals. Other results suggest that human memory does not work like computer memory, but more like an internet search engine. Errors associated with this type of memory may make it difficult to use reciprocal cooperative strategies such as TFT. Dr. Stevens concluded with the following take-home message: "We ignore cognition at our peril. Animal models provide insights into cognitive building blocks, and animal models force us to reconsider assumptions about cognitive mechanisms underlying human social interactions."

c) Conversation 2 - Emotion, moderated by Ellen Witt, PhD, National Institute on Alcohol Abuse and Alcoholism (NIAAA)

I. Jaak Panksepp, PhD, Washington State University

How Neuroscience Can Illuminate the Nature of the Human Emotional Feelings: To Understand Key Psychiatric Issues We Need a Cross-Species Neuroscientific Understanding of Neglected Topics such as Sadness and Joy

Dr. Panksepp conducts research on the primary processes of emotional understanding across mammalian species and other creatures. He discussed "an area where we have been in the dark" and provided a brief description of joy and sadness studies. He strongly believes that in order to understand animal emotions, one must take the evolutionary approach. He reasoned that for the very same reasons human emotional feelings are studied (curiosity, origins, and implications for certain behaviors), so should humans study them in animals.

Dr. Panksepp proposed that most scientists believe that animal feelings cannot be studied, but that he disagreed and argued that feelings are common to all animals. This is the gateway to understanding animal emotions. If one can understand their feelings of respect, one will begin a science for humans. However, because humans are skeptics by nature, they rely on the weight of evidence and abide by the rules of evidence. Dr. Panksepp recommended that investigators study the brain from an evolutionary perspective, both bottom up and top down in order to understand unconditioned stimuli and unconditioned responses in the study of emotion.

Dr. Panksepp asserts, "That which came first controls what comes second" and that, "Animal thoughts are harder to understand than emotions." He concluded that, "We talk past each other because we don't have a language that we agree upon at the evolutionary levels of the mind and the brain."

II. Robert Levenson, PhD, University of California, Berkley

What Happens to Our Emotions in Normal Aging?

Dr. Levenson's research program focuses on human emotion. He studies organization of physiological, behavioral, and subjective systems; the ways that these systems are impacted by neuropathology, normal aging and culture, and the role that emotions play in the maintenance and disruption of committed relationships. Dr. Levenson discussed levels of cognitive and physical functioning, and presented classic and newer views of emotion. The classic view is that old age is a time of dampened, rigid, and flat emotionality, while the newer view sees old age as a time of emotional vibrancy, refinement, and well-being when close relationships become increasingly important. Dr. Levenson concluded that the correct

view is more “new” than “old” but with some additional complexities for specific aspects of emotional reactivity, regulation, and empathy.

Regarding what makes marriage last, Dr. Levenson’s research revealed that it depends on healthy emotions, empathy between partners, physiological arousal (soothing), genes, and “some good breaks” such as staying healthy and emptying the nest. Dr. Levenson discussed what happens to emotions in abnormal aging and contrasted anatomical differences in frontotemporal dementia and Alzheimer’s disease. The presentation ended with a brief discussion of what emotions ”look” and ”feel” like.

d) Conversation 3 - Communication (Voice, Speech, and Language), moderated by Lana Shekim, PhD, National Institute on Deafness and other Communication Disorders

I. Kristina Simonyan, MD, PhD, Mount Sinai School of Medicine

Communication (Voice, Speech, and Language)

Dr. Simonyan started by defining *voice, speech, singing,* and *language* and delineated the similarities and differences between these behaviors. The term *voice* usually refers to any sound (i.e., innate or learned) that is produced during vocal fold vibration. When using the term *speech*, we usually consider human learned voice production with semantic content, while *language* is used to describe human learned spoken, written, gestural communication with semantic and affective content. While speech and language are unique human behaviors, another vocal behavior, singing, may be found in both humans and animals, especially birds. There are, however, some critical differences between singing in humans and singing in birds. While human song is a learned voice production with or without semantic content and usually with affective meaning, bird singing may be both learned and/or innate with affective content only.

With these different behavioral constraints on voice production in humans and animals, improving the animal models of human communication is a challenging task. Innate voice production is controlled mostly by subcortical structures and is present throughout the animal kingdom. It is thus feasible and possible to develop different animal models for the understanding of basic mechanisms of innate voice control. On the other hand, due to the unique complexity of human speech and language behaviors, these may not be possible to model in their full extent in any animal species. However, animals that are capable of learning and producing vocal expressions but have somewhat different (from human) brain anatomy (i.e., bats, songbirds), and animals that have limited ability to learn and produce vocal expressions but have closer brain anatomy to that of humans (i.e., non-human primates, rodents), may successfully be used for probing molecular, chemical and anatomical pathways of human speech and language behaviors using an approach of forward-and-back translations. An illustration of such translational approach is the mapping of representation of the larynx in the cortex. While the first reports on the ability to elicit the laryngeal muscle response due to electrical stimulation of the primary motor cortex in humans appeared in 1930’s, follow-up studies to map the location of laryngeal muscles, structural connections and functional importance of this region for learned voice control were not conducted until early 2000’s. Meanwhile, continuous studies in non-human primates conducted between the 1950’s and 2000’s, have determined the exact anatomical representation of different laryngeal muscles in the primary motor cortex and defined the connectivity of this region with other brain structures involved in voice control. With the recently renewed interest in understanding the central mechanisms of human speech and voice production, the results of these animal studies have been instrumental as starting points in human investigation, and have demonstrated both similarities and differences in the organization of the laryngeal motor cortex between species. The combined knowledge from both animal and human studies has been critical in deriving conclusions about why the ability to produce voice depends on certain connections of the laryngeal motor cortex and why these connections may be indispensible for our ability to speak but may not be important in our closest relatives, non-human primates. However, despite this recent progress in understanding the brain mechanisms of learned voice control, several questions still remain. Research studies, which are taking a translational approach between humans and various animal species for more

complete understanding of such "challenging-to-model" human behaviors as speech and language, should be further encouraged.

II. Erich Jarvis, PhD, Duke University

Communication (Voice, Speech, Song, Language)

Dr. Jarvis discussed the differences between vocal learning (production learning) and auditory learning (comprehension and usage learning). Dr. Jarvis suggested that auditory learning, where dogs can understand the sound *sit* (English), *sientese* (Spanish), and *osuwari* (Japanese) is clearly distinguished from vocal learning, where dogs cannot learn to say these sounds; however, vocal learners can learn to say these sounds. Vocal learning is a critical behavior for spoken language. Dr. Jarvis discussed findings of song pitch convergence in mice, caused by competitive social experience (adult males singing at different pitches in the presence of females).

After discussing the spectrum of vocal-learning complexity and sequence-learning complexity in humans, parrots, finches, mice, monkeys, and chickens, Dr. Jarvis suggested a "continuum hypothesis" which posits that vocal learning is not dichotomous, but a continuous trait. He claimed that mice are limited vocal learners. Mice may serve as genetic models for some properties thought to be unique to humans for speech-language disorders. Given the convergent behavior, neural networks, and genes for vocal learning, it is theoretically possible to enhance the circuit. Learned vocal communication, Dr. Jarvis argued, can be modeled in animals on a continuum of traits depending on species. Auditory processing, including complex communication, can be more easily modeled in many non-human animals than vocal learning. Dr. Jarvis' research results revealed that, "Not all features of human spoken-language can be modeled in animals, but then again, not all features of other animals can be modeled in humans."

e) Conversation 4 - Population Dynamics, moderated by Michael Spittel, PhD, OBSSR

I. James Holland Jones, PhD, Stanford University

Humans, Nonhumans and General Principles of Disease Ecology

Dr. Jones explained that he does not work on animal models *per se*, but is interested in general principles about complex systems, specifically, the dynamics and control of emerging infectious disease. Broadly comparative perspectives (cross-cultural or cross-specific) give one the ability to make broad principle statements about systems. Dr. Jones cautioned the audience to not fall into the trap of essentializing about categories of organisms (e.g., "the monkey" or "the rodent") but to consider carefully the natural history of the specific animal in question (including humans). He discussed two case studies of long-term observational studies that relied on a fundamental understanding of the ecological context -- especially social behavior, and the natural history of the species involved.

Dr. Jones described a coupled infectious disease model that includes social, ecological, and disease-transmission interactions, characterized by chaotic dynamics. He noted that prediction about the future state of the system is hard, and control of the system is even harder. Models of infectious disease emergence naturally focus on the transmission dynamics and increasingly, incorporate ecological information (e.g., species interactions). However, such models rarely specifically address social interactions among the spillover host. Dr. Jones surmised that there is no way to predict or control the state of the system if one blinds oneself to entire subsystems within the larger system. These three subsystems are: epidemic, social, and ecological. Unfortunately, in disease ecology, the social is often ignored.

Research findings in a study of free-ranging chimpanzees in the Gombe National Park, Tanzania, showed that SIV-infected chimpanzees die of AIDS-like illness at a rate 10-16 times greater than non-infected chimps. Observed sexual networks show that the population is highly connected, with an average

minimum distance connecting any two chimps in the community of less than two. This suggests that transmission of SIV must be limited somehow, perhaps only occurring during primary infection. The high virulence of SIV in wild chimpanzees also explains the puzzling landscape-level pattern of whole communities in similar regions as SIV-endemic communities being SIV-free. Detailed individual-based simulations reveal that the virulence of SIV in chimpanzees causes the virus to frequently go extinct in local populations before it can be exported to the broader metapopulation through dispersal. This work highlights some key conditions for the emergence of HIV-1.

Studies of black-tailed prairie dogs in the western United States also show the importance of social structure and interspecific interactions in the generation of disease dynamics. This work helps address a fundamental question of disease ecology, specifically, how does a highly virulent pathogen persist in a landscape when it wipes out an entire host population? Prairie dogs are subject to intermittent epizootics of plague, cause by the bacterium *Yersinia pestis*, which often decimate entire towns of up to tens of thousands of individuals. Detailed individual-based simulations coupled with extensive, long-term ecological research suggest that plague is, in fact, enzootic in prairie dog towns, simmering at low prevalence for long time periods. Transmission in these large aggregations of prairie dogs is ultimately limited by the strong territoriality of prairie dog coteries within the town, meaning that each coterie is connected to only four or so other coteries. Epizootics are triggered by the presence of grasshopper mice, which can connect more distant coteries within the town through their movement of infected fleas across prairie dog territories.

These results highlight the importance of incorporating information on social behavior and ecology in models that try to understand transmission dynamics of emerging infectious diseases of potential public health significance.

II. James Carey, PhD, University of California, Davis

Evolution of Sociality in Wasps: Implications for Comparative Studies of Social and Behavioral Processes

Dr. Carey studies the biology and demography of aging and lifespan using insect model systems such as fruit flies and social insects. Dr. Carey described a theory of social evolution in wasps from the ancestral solitary form (parasitoid wasps) through eusociality (the most advanced stages of sociality in insects). A key concept in this evolutionary process was the emergence of a mother-daughter kinship group. Because the lifespans of two generations overlap, a division of labor and basic social behaviors began to emerge. This incipient sociality reduced mortality of the group which, in turn, allowed members to live longer and evolve more complex social behavior. Thus the processes of longevity extension and social evolution became self reinforcing.

Dr. Carey described a technology developed by his team for the high resolution monitoring (five records/second) of behavior and movement in insects. Dr. Carey's technicians monitored fruit flies throughout their lifetimes using this *Lifetime Recording System*, thus generating informatics-level data on behavior in individual flies. Viewing behavior as a sequence of events captured in micro-time intervals allowed them to use genomics-inspired software for automating the analysis of behavior over entire lifetimes. Dr. Carey and his colleagues referred to this new area as 'behavioral informatics' — the data intensive analysis of high resolution, long-term behavioral databases using event history data.

f) Conversation 5- Lifespan/Development Perspective, moderated by Erica Spotts, PhD, National Institute on Aging

I. Gabriella Conti, PhD, University of Chicago

Health Effects of Early Life Adversity: Evidence from Non-human Primates

Dr. Conti conducts research to understand the biological mechanisms underlying the relationship of social environment to health by examining interactions from the cell to the lifecycle. Dr. Conti suggested separating biological mechanisms by experimentally manipulating investments/environments. In one experiment with monkeys, early life experiences changed the way genes expressed themselves. She posed the question, "Can the effects of adverse early conditions be reversed by a normal social environment later in life?" In a second (post-experimental) phase, it was found that long-lasting effects are not compensated by a normal social environment later in life. Given these findings, still many questions remain unanswered, such as: How quantitatively important are epigenetic effects? Are epigenetic changes on the causal pathway between early conditions and adult outcomes? Is it possible to compensate for changes in gene expression?

In order to attempt to answer these questions, Dr. Conti is taking repeated measures of gene expression, health, and development over three years in humans. She then proposes conducting an investigation across species with the same experimentally-induced exposure and the same measurements of phenotypes, to improve our understanding of the common biological pathways that are conserved across species.

II. Mar Sanchez, PhD, Emory University

Nonhuman Primate Models of Developmental Effects of Early Life Stress: Brain, Behavior, and Stress Physiology

Dr. Sanchez showed that the strengths of her non-human primate (rhesus monkey) early life stress model are its reproducibility and validity for the human condition, reverse translation (via critical collaborations with human researchers) and newly developed experimental designs that address the question of experience versus heritability (cross-fostering at birth with random assignments to the experimental group). Challenges of using the rhesus monkey model include understanding the core phenotype in humans to define the phenotype in the animal model, identifying critical development periods, and experience titration. There is a basic need to use animal models with ecological validity in terms of early experience, testing paradigms, and behavioral outcomes. In addition, there is a critical need for close collaboration between researchers working with humans and those using animal models, to foster back-and-forth translation and advance our understanding of normative brain and behavioral development to interpret the effects of early experiences (partially a funding issue for animal models).

Studies in rhesus monkeys have shown that that infant maltreatment impacts the development of socioemotional behavior, stress responses, and the neural circuits underlying these functions. Non-human primates provide a unique research opportunity to understand neurobiological mechanisms underlying behavioral outcomes of early adverse experiences.

Contributions of Dr. Sanchez's animal model for the human condition include the study of critical periods. One such critical period requires proper maternal care during the first three months of rhesus infant life (roughly equivalent to the first year in humans). This is crucial for normal brain and behavioral development. Adolescence is another critical period due to brain reorganization. Some effects of early experiences are persistent, whereas others are transient. Factors that increase vulnerability (or resilience) to early adverse experience are genetics, individual temperament and coping skills, and social support. Aspects of maternal care are critical for proper primate infant development. Dr. Sanchez's research showed that rejection is a stronger predictor of poor developmental outcomes than physical abuse.

Day 2: Breakout Sessions

1. Orientation/Charge for Breakout Sessions and Pre-session Discussion, Minda Lynch, PhD, NIDA

The charge to all Breakout Groups was to suggest realistic goals and strategies for the next three years to improve the development of animal models for human behavioral and social processes. A second question was also to be considered : "What are the arguments most persuasive to building a case for sustaining NIH investments in b-BSSR?" Dr. Lynch encouraged each participant to look at the breakout session as a "fantasy world" and to let all flowers bloom.

2. Reports & Recommendations from Breakout Sessions

a) Group 1: Science of Behavioral Animal Models Translation

Moderated and scribed by Lisa Freund, PhD, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

This group was tasked with addressing the following questions:

- How can we develop a "Science of Translation", specific for animal behavioral models, which includes best practices and procedures for optimizing translation of findings from animal behavioral models to the next logical step in a translational sequence to human application?
- Who should be involved in building this science?
- What would the best practices be? Paradigms? Design? Measurement Systems? Methods of Validation?
- What would that next logical step be (e.g., to human laboratory- or field-based studies, therefore, addressing questions of clinical validity and cross-validation)?
- What are the barriers to this translation? Lack of homology/conservation? Different underlying neurobiological processes/substrates? Different methods of behavioral assessment between animal and human subjects? Data harmonization/standardization? Differing environments (i.e., natural vs. artificial)?
- Can trainees be better educated in this science and these practices?
- What can NIH do to foster the creation of a science of translation for animal behavioral models?

Participants identified the following most critical challenges associated with their breakout session topic:

- Difficulty with human subject researchers accepting the value of animal research;
- Issues of standardization across animal model labs, methods, tasks, and interpretation of behavioral data;
- Insufficient facilitation of bi-directional (between human subjects and animal models) research approaches;
- Lack of appropriate expertise on grant review committees; and
- High cost of animal model translational research.

The most promising opportunities associated with the science of behavioral animal models translation include the following:

- Initiatives for specifically testing a hypothesis in humans based on research in an animal behavioral model;
- Interdisciplinary training in working with animal models and human subjects for researchers and reviewers;
- Commentary in major journal(s) advocating value of animal model behavioral research; and
- The establishment of more than one NIH study section to review all animal behavior model research.

This group identified potential outcome indicators and metrics as publications with human/animal subjects in translational studies; an increase in animal/human translational research grants; discoveries

leading to improvements the understanding of the origins and the treatment of human diseases or disorders; and, indicators associated with training and graduate student education on this topic.

a) Group 2: Human Capacity Building and Training

Moderated and scribed by Deborah Olster, PhD, OBSSR

This breakout group addressed the following questions:

- What skills are needed to develop animal models that are more "translatable" to the human condition?
    - Training to study the same behavioral/social process in animal models and humans?
    - Training in measurement of behavioral/social processes (that is bi-directionally translatable between humans and animal models)?
    - Training in the validation of animal models for human behavioral/social phenomena?
    - Training to study animals (and humans) in natural environments?
- Should we train individuals in all of these skills or would it be more fruitful to train sets of people with complementary skills that could work in teams? (Or both?)
- Are there unique capacity building/training needs for the five "difficult-to-model" behavioral and social processes discussed on Day 1 of the Workshop?
- What can NIH do to facilitate this? Provide specific recommendations for NIH actions that would foster the creation and maintenance of an appropriately-trained, scientific workforce to develop improved animal models for basic human behavioral and social processes.

Participants identified the most critical challenges associated with human capacity building and training as follows:

- Inadequate opportunities for investigators to engage in thoughtful discussions about translational research between animal models and humans;
- A lack of training in certain aspects of psychology in animal models (e.g., emotion/affect/stress) and disease models;
- Entrenched "camps" of thinking that are barriers to collaborative work and knowledge sharing;
- Insufficient understanding/appreciation of the social environment and how behaviors change in different social contexts; and
- Insufficient long-term funding.

Specifically, participants in this group recommended breaking down "camps" of thinking and building new models as well as providing long-term, sustained funding, as the investigation of more complex behavioral and social processes require this level of financial commitment. They also recommended that NIH require training programs to build in research rotations for graduate students or perhaps support "summer schools" of 3-4 months duration on particular topics.

This group identified the most promising opportunities associated with capacity building and training as:

- Utilizing interdisciplinary research training in animals and humans to explore different methods and disciplines;
- Building expertise in human behaviors (lab-based and field-based); recruiting more established investigators across disciplines, models, and methods; building expertise in animal psychology (e.g., affect); and
- Cross-training people in animal/human research. This cross-training might target junior faculty, more established investigators, and post-docs and provide opportunities to test whether the behavioral/social processes they model are valid.

Group 2 also identified outcome indicators and metrics that could be used to measure such success as: publications demonstrating the training focus; Institutional Review Board or Institutional Animal Care and Use Committee protocols demonstrating more collaborative work; presentations at conferences outside of one's field; and tracking careers of individuals working at the interface of animal models and humans.

b) Group 3: Measuring Behavioral and Social Processes

Moderated and scribed by Minda Lynch, PhD, NIDA

The measurement group grappled with the following questions:

- What are the most profound measurement challenges your field faces? How do you overcome those challenges in your current work?
- How do we know we are measuring similar behavioral, cognitive, emotional, or social processes in human and non-human species? What data support the concordance?
- What approaches, resources, or methodologies are on the horizon that hold promise greater concordance between animal models of basic behavioral and social processes and human experience?
- What can NIH do to strengthen measurement of basic behavioral and social processes in animals to improve the "translatability" of findings between animal models and humans?
- How does one measure implicit processes in animal behavioral models?
- How can you identify the most salient environments in humans and replicate them in animal models?
- What are the constraints/confines of different environmental milieus? For example, simple, limited and constrained or social and complex?
- How can we measure across multiple scales in animal behavioral models, as well as in analogous human studies; and across temporal dynamics?
- If standardization of measurement (for a given behavioral/social process in humans and non-human models) is desirable, how is it best achieved?

Participants identified the most critical challenges associated with their measurement session as:

- A lack of prioritization of social and behavioral processes to improve translation;
- A lack of support for methodological studies;
- Validation measures and methodological development; and
- Understanding conserved behaviors across species.

This group recommended that NIH develop a culture of respect for social/behavioral research; promote comparative, evolutionary studies (public/private mechanisms); include methodology in FOAs; fund longitudinal research; fund working groups (such as the MacArthur Networks); and share methodologies.

This group identified the most promising opportunities associated with measurement of behavioral and social processes as:

- Providing the appropriate technology for measurement, analysis, and dissemination;
- fostering collaboration; and
- Encouraging National Science Foundation (NSF) and NIH collaboration.

This group identified outcome indicators and metrics as better predictions to inform human health; the establishment of research networks; and the sharing of methodological details and findings.

c) Group 4: Fostering Collaboration Among Scientists Who Work on Animals and Those Who Work on Humans

Moderated and scribed by Ivana Grakalic, PhD, NIAAA

This group addressed the notion that collaborations between human and animal researchers require the formation of interdisciplinary research teams, and addressed the following issues involved therein:

- Educational efforts to train researchers in the language, culture, and knowledge of their collaborators;
- Human factors in building research teams (e.g., personality, conflict resolution, communicating about science);
- Providing opportunities for students and postdoctoral fellows to get training in interdisciplinary research;
- The development of innovative policies and infrastructure at academic institutions to foster interdisciplinary research;
- Facilitation of team leadership skills; and
- The ability of funding organizations to provide creative mechanisms to broaden training opportunities and link interdisciplinary researchers.

The overarching question posed to this group was the following: Can specific recommendations be made regarding these issues, problems and opportunities, which will provide the NIH with strategies to promote interdisciplinary collaborations between human and animal researchers?

Participants identified the most critical challenges associated with their breakout session as:

- Limited availability and access to appropriate resources for studying behavior in animals that can translate to human work (e.g., R24 mechanism to be able to develop core facilities that can support such work);
- Poor communications between human and animal modelers; and
- Barriers that impede the use of alternative and non-traditional animal species (e.g., birds) as model organisms.

This group recommended that NIH

- Initiate and facilitate workshops like this one or that are organized by investigators themselves;
- Foster transdisciplinary discussions (between human and animal researchers);
- Provide opportunities for peer-to-peer and principal-to-student training; and
- Encourage the use of non-traditional, ecologically valid species in by inserting specific language in FOAs.

Group 4 identified the most promising opportunities to foster collaboration as:

- Short term investments to support transdisciplinary training at the principal investigator level with supplements to the existing R01awards;
- Long term investments in programs to train students (e.g., administrative supplements, modified T32 mechanisms and multi-institutional training programs);
- Support for initiatives that require multidisciplinary teams; and
- Requirement for equal recognition for all team members on group projects.

This group identified outcome indicators and metrics of collaboration as: publications/journals outside of one's discipline, and the training of pre- and post- doctoral students, with an emphasis on meeting presentations as well as publications.

3. Presentation: *Reflections on Translation from Animal Models to the Human Condition*, Rajita Sinha, PhD, Yale University School of Medicine

Dr. Sinha explained that in modeling social and behavioral processes, there are numerous animal models available for a number of social and behavioral processes (e.g., learning, short term memory, fear conditioning; drug seeking, intake, and relapse; and different types of stress exposures). In determining the usefulness of a model, Dr. Sinha stated, "There are no good or bad animal models - just those that are useful and those that are not."

Dr. Sinha identified challenging processes to model. First, early life stress is an area where researchers are unsure of the components or stimuli that trigger the negative effects, as stressors are not consistent across studies. Secondly, although individual differences are important, it is questionable whether successful models of a specific behavior can capture variation in a meaningful way. Thirdly, a researcher may capture a behavior or process in a model but it is unknown whether the model is truly predictive of a process that mirrors the human condition.

Dr. Sinha discussed the paucity of human laboratory and experimental studies of the relevant processes. There is a basic need to go from animal models development to the human condition (back and forth) in model development, thereby determining utility and predictive validity. This can be done rapidly and efficiently in collaborative teams through interdisciplinary and transdisciplinary approaches, which aid in breaking silos and institutional barriers. These teams need clear goals with a time line of outcomes, products and deliverables. There is a training gap in interdisciplinary approaches and an urgent need to specifically train the next generation of scientists in collaborative science. Challenges to collaborative team science are a lack of strong leadership cores with scientific vision and a lack of essential team-based leadership skills that deliver products and outcomes.

Additionally, Dr. Sinha found it critical that leaders identify the "right" type of collaborators/team scientists and invite only these individuals to join the team. Participants should operate under a clear outline of team structure and organization. Programs and initiatives must have institutional and stakeholder priority with resource allocation and support, with stakeholders as partners in the process. Dr. Sinha concluded her presentation by acknowledging that such commitments command a high demand on time and energy but yield high potential for payoff, as well.

4. General Discussion

The following topics were touched upon in the general discussion session: investigating whether animal behavior is habitual or in response to stimuli; declarative versus non-declarative memory; interdisciplinary teams and their contributions to b-BSSR; ways to enhance institutional support; funding limitations for research on animal modeling of human behaviors; ways in which NIH may improve publication records and giving proper credit to researchers; assistance and mentoring to junior investigators; cross-pollination of disciplines for new discoveries; partnering with non-governmental organizations to achieve research goals; short-term and long-term OppNet goals; administrative supplements for students; relatively small investments in grassroots efforts; training individuals at the translational intersect; the challenges of getting one's research finding published and distributed to the wider scientific community; and the possibility of producing a publication of the Workshop, if participants expressed interest.

A number of participants described specific research initiatives and projects they would like to conduct in advancing b-BSSR. Dr. Lynch explained that anything is possible, pending the availability of resources. NIH has many mechanisms at its disposal, and could consider initiatives for translational bi-directional training between animal modelers and individuals who use human subjects in laboratory or field settings; sabbaticals; FOAs that target investments in methods in technology development in the behavioral

sciences; and other efforts. Dr. Lynch assured the participants that all advice would be taken into consideration for future OppNet initiatives.

One participant mentioned that often, professional institutions don't have resources to support much-needed research areas and suggested that NIH partner with other organizations (such as the Association for Psychological Science and American Psychological Association) for travel awards that would allow investigator's to attend meetings or trainings outside of their fields. She found it useful and was sure others would, as well. Another invitee suggested that NSF Synthesis Centers could be a resource/opportunity for researchers. These Centers focus on synthesis, not the collection of new data, and also Centers offer sabbaticals and support postdocs and working groups. While leveraging existing funds, she suggested, researchers may be able to accomplish some of the goals of the Workshop through this type of partnership. Another participant suggested that NIH provide administrative supplements to existing grants to support (ideally) two years of cross-training at the PhD or postdoctoral level. This mechanism could be accomplished at a relatively low cost and would be enormously helpful to students when institutional support ends.

5. Next Steps

In response to the question of what NIH planned to do in terms of concrete action items, as a result of the Workshop, Dr. Olster answered that lots of ideas were on the table and that a report on the Workshop would be drafted and posted on the OppNet website, along with other material, including the agenda, speaker presentations (with permission), list of attendees, etc. The Workshop planning group would review the Workshop report and ongoing and planned NIH activities on the topic of improving animal models of human behavioral and social processes. The group would then explore acting on the recommendations to develop new initiatives as appropriate. Dr. Olster emphasized that she cannot make any guarantees, but that even if recommendations are not taken up by OppNet, good ideas could be pursued by individual or groups of NIH Institutes and Centers, pending the availability of resources.

6. Adjourning of Meeting

Drs. Olster and Lynch thanked the participants for attending, wished everyone "happy travels" and adjourned the Workshop.

National Institutes of Health Basic Behavioral & Social Science Opportunity Network Workshop:
Improving Animal Models of Human Behavioral and Social Processes
July 23-24, 2012
Room C2F, Executive Plaza North
6130 Executive Blvd.
Rockville, MD 20852

Agenda

Day 1 (July 23, 2012)

8:30 am - 8:40 am	Welcome and introductions *Deborah Olster, PhD, NIH Office of Behavioral and Social Sciences Research*
8:40 am - 8:55 am	The NIH Basic Behavioral & Social Science Opportunity Network *William Elwood, PhD, OppNet Facilitator* *NIH Office of Behavioral and Social Sciences Research*
8:55 am - 9:05 am	Setting the stage and goals of the workshop *Minda Lynch, PhD, National Institute on Drug Abuse*

Session 1: Opening Addresses

9:05 am - 9:35 am	*Dario Maestripieri, PhD, University of Chicago*
9:35 am - 10:05 am	*C. Sue Carter, PhD, Research Triangle Institute International*
10:05 am - 10:20 am	Break

Session 2: Success stories *Chaired and moderated by Jeanne Altmann, PhD, Princeton University*

In this session, researchers who work on a behavioral process in both humans and animal models (either themselves or by collaboration) will discuss the principles and processes of successful development of an animal model for a human behavioral or social process.

10:20 am - 10:40 am	*Tim Bussey, PhD, University of Cambridge*
10:40 am - 11:00 am	*John Capitanio, PhD, University of California, Davis*
11:00 am - 11:20 am	*Martha McClintock, PhD, University of Chicago*
11:20 am - 11:40 am	*Suzanne Mitchell, PhD, Oregon Health and Sciences University*
11:40 am - 12:00 pm	*Larry Squire, PhD, University of California, San Diego*
12:00 pm - 12:05 pm	Lessons learned from the less successful efforts *Mort Mishkin, PhD, National Institute of Mental Health*
12:05 pm - 12:40 pm	General Discussion
12:40 pm - 1:40 pm	Lunch (on your own)

Session 3: Particularly challenging human behavioral and social processes

1:40 pm - 1:45 pm Introduction to Session 3 "Conversations"
Deborah Olster, PhD, NIH Office of Behavioral and Social Sciences Research

1:45 pm - 2:20 pm Social interactions: Cooperative and Competitive Behavior
Janine Simmons, MD, PhD, National Institute of Mental Health, Moderator

- *Bill Harbaugh, PhD, University of Oregon*
- *Jeffrey Stevens, PhD, University of Nebraska-Lincoln*

2:20 pm - 2:55 pm Emotion
Ellen Witt, PhD, National Institute on Alcohol Abuse and Alcoholism, Moderator

- *Jaak Panksepp, PhD, Washington State University*
- *Robert Levenson, PhD, University of California, Berkeley*

2:55 pm - 3:30 pm Communication (Voice, Speech and Language)
Lana Shekim, PhD, National Institute on Deafness and other Communication Disorders, Moderator

- *Erich Jarvis, PhD, Duke University*
- *Kristina Simonyan, MD, PhD, Mount Sinai School of Medicine*

3:30 pm - 3:45 pm Break

3:45 pm - 4:20 pm Population dynamics
Michael Spittel, PhD, NIH Office of Behavioral and Social Sciences Research, Moderator

- *James Holland Jones, PhD, Stanford University*
- *James Carey, PhD, University of California, Davis*

4:20 pm - 4:55 pm Lifespan/developmental perspective
Erica Spotts, PhD, National Institute on Aging, Moderator

- *Gabriella Conti, PhD, University of Chicago*
- *Mar Sanchez, PhD, Emory University*

4:55pm - 5:30 pm General Discussion & Wrap-up for the Day

<u>Day 2 (July 24, 2012)</u>

8:30 am – 8:45 am Orientation/charge for breakout sessions
Minda Lynch, PhD, National Institute on Drug Abuse

8:45 am -10:15 am Breakout sessions
In these sessions, participants discuss potential next steps toward solutions in a number of domains, including specific recommendations for NIH actions.

- Science of behavioral animal models translation
  Lisa Freund, PhD, Eunice Kennedy Shriver National Institute of Child Health and Human Development, Moderator/Scribe

- Human capacity building and training

Deborah Olster, PhD, Office of Behavioral and Social Sciences Research, Moderator/Scribe

- Measuring behavioral and social processes
  Minda Lynch, PhD, NIDA
  Moderator/Scribe

- Fostering collaboration among scientists who work on animals and those who work on humans
  Ivana Grakalic, PhD, National Institute on Alcohol Abuse and Alcoholism, Moderator/Scribe

10:15 am – 10:30 am Break

10:30 am – 11:10 pm Reports from breakout sessions

11:10 am – 11:30 am Reflections on translation from animal models to the human condition
Rajita Sinha, PhD, Yale University

11:30 am – 12:00 pm General Discussion
Next steps

12:00 pm Adjourn

Workshop Planning Group

Minda Lynch, PhD, National Institute on Drug Abuse (co-Chair)

Deborah Olster, PhD, Office of Behavioral and Social Sciences Research (co-Chair)

Lisa Freund, PhD, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

John Glowa, PhD, National Center for Complementary and Alternative Medicine

Ivana Grakalic, PhD, National Institute on Alcohol Abuse and Alcoholism

Peter Kaufmann, PhD, National Heart, Lung and Blood Institute

Stephen Marcus, PhD, National Institute of General Medical Sciences

Paige McDonald, PhD, MPH, National Cancer Institute

Lisbeth Nielsen, PhD, National Institute on Aging

Lana Shekim, PhD, National Institute on Deafness and other Communication Disorders

Janine Simmons, MD, PhD, National Institute of Mental Health

Michael Spittel, PhD, Office of Behavioral and Social Sciences Research

Erica Spotts, PhD, National Institute on Aging

Catherine Stoney, PhD, National Heart, Lung and Blood Institute

Ljubisa Vitkovic, PhD, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

Ellen Witt, PhD, National Institute on Alcohol Abuse and Alcoholism

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