Research conducted in the Department of Psychiatry and Behavioral Neuroscience is broad and multidisciplinary, spanning molecular biological and genetic approaches in animal models through to patient based clinical investigations. Strong research programs are in place aimed at deciphering and developing treatments for a number of psychiatric conditions including aggression, anxiety and depression, bipolar illness and schizophrenia, eating disorders, and substance abuse. Others focus on understanding developmental influences as well as cultural variables that impact mental health. Research faculty in the Department of Psychiatry and Behavioral Neuroscience continue to be among the best funded in the Division of Biological Sciences at The University of Chicago with strong support from the National Institutes of Health as well as a number of private foundations. These diverse research programs and the funding that supports them are described on the following pages.

Paul Vezina, PhD
Research Section Chief and Mission Director

Kai Jackson, BS, MS
Research Section Manager

Jessica Chen, BA, MBA
Grants and Contracts Specialist

Janet Nelson
Grants and Contracts Specialist
Judith A Badner, M.D./Ph.D. (Psychiatry & Behavioral Neuroscience). Dr. Badner is an associate professor in the Department of Psychiatry at The University of Chicago. She is both a clinical psychiatrist and statistical geneticist. Her research has focused on identifying genes for traits and disorders that do not have a simple mode of inheritance. She has worked with a number of groups both within the Department of Psychiatry and the Medical Center as well as outside the University. Her work has involved bipolar disorder, autism, schizophrenia, obsessive-compulsive disorder, attention deficit disorder, pharmacogenetics of cancer chemotherapy, and the identification of genes involved in DNA methylation and gene expression. She is currently working on large scale genetic linkage and association projects in adult and pediatric psychiatric disorders.

Training.

B.S., Biology, Massachusetts Institute of Technology, Cambridge, MA, 1982

M.S. Hyg, Human Genetics, University of Pittsburgh, Pittsburgh, PA, 1985

Ph.D., Human Genetics, University of Pittsburgh, Pittsburgh, PA, 1988

M.D., University of Pittsburgh, Pittsburgh, PA, 1990

Psychiatry Residency, McLean Hospital, Harvard University, Belmont, MA, 1990-1994

Fellowship, Psychiatric Genetics, National Institute of Health, 1994-1998

Research Program.

Dr. Badner started her research in 1983 while working on her Master’s degree at the University of Pittsburgh. The focus of her research was to develop new methodologies for genetic linkage analysis (identifying a region of the genome where a gene for a trait or disorder may be located). After completing her Master’s degree, she enrolled in the M.D./Ph.D. program at the University of Pittsburgh. The focus of her Ph.D. was to identify the pattern of inheritance of Hirschsprung disease, a deficiency of nerve cells in the colon. Dr. Badner then completed medical school and started a psychiatric residency. During her last year of residency, she collaborated on a project studying the inheritance of schizophrenia and eye tracking dysfunction within the same families.
Figure 1. Multipoint nonparametric analysis of a genome scan on chromosomes 13, 1, 4, 7, 12, 14, 18, 21, and 22 for bipolar disorder. ASM I=SA-BP, BPI, BPII. ASM II=ASM I+MDD. From Detera-Wadleigh et al. (1999).

Dr. Badner moved to the NIMH to focus more intensively on psychiatric genetics. She was involved in the genetic analysis of schizophrenia and bipolar disorder, using both genetic linkage analysis and association analysis (determining if a particular gene is involved in the expression of a trait or disorder). A major project involved a whole genome linkage scan for bipolar disorder. In this analysis, evidence was found for genes located on the long arm of chromosome 13, the long arm of chromosome 1, and the short arm of chromosome 18. Once at The University of Chicago, Dr. Badner continued to study the linkage to chromosome 13. This linkage was supported by genotyping more genetic markers in the same region. Then association studies were performed to identify the gene in the region that was involved in the development of bipolar disorder. After several candidate genes were investigated, evidence of association of the D-amino acid oxidase activator gene/G72 was found in two different datasets. This gene had previously been found to be associated with schizophrenia.
Figure 2. 95% confidence interval for location of bipolar susceptibility gene as estimated by haplotype sharing. From Hattori et al (2003).

Dr. Badner has worked on developing new methodologies for identifying genes for complex genetic traits and disorders while at the NIMH and The University of Chicago. She performed simulations to demonstrate that linkage to common genes may be more easily identified in smaller, less densely affected pedigrees, in contrast to rare genes which are more easily identified in large, densely affected pedigrees.

Meta-analysis of genetic linkage studies has been a particular interest of Dr. Badner. She first started thinking about this when looking at simulated data as part of the Genetic Analysis Workshop. She developed a new method, Multiple Scan Probability, and applied it to autism to identify a region on chromosome 7. Similarly, she applied this
method to bipolar disorder and schizophrenia to identify regions on chromosomes 13 and 22 for both disorders and a region on chromosome 8 for schizophrenia.

Other psychiatric disorders that Dr. Badner has worked on include autism and attention-deficit disorder. She has also been involved in studies of pharmacogenetics.

Dr. Badner’s most recent work involves whole genome association scans of quantitative measures of DNA methylation and gene expression. This work has shown that variants that regulate methylation and expression are most likely to be within or very close to the genes being methylated/expressed (cis-regulation). However, there is evidence that genes on different chromosomes regulate methylation itself. For some genes, the same variants are involved in decreased methylation and increased expression.

Dr. Badner performed the analysis for a multicenter whole-genome linkage study of almost 1000 bipolar pedigrees. She found strong evidence of linkage to 6q21 and 9q21, and in families with early age of onset, 2q12. She also found individual pedigrees that show evidence of segregation of a rare locus. The information from this study will be used for future sequencing studies. She has also found evidence for linkage to 1p in a set of European-American OCD families and 15q in a set of Costa Rican OCD families.

**Figure 5.** Distribution of methylation and expression of IRF6 by rs2235375 genotype. From Zhang et al. (2010).

**Figure 6.** Parametric and non-parametric linkage results for bipolar disorder. From Badner et al. (2011)
Funding.

- NIH/NIMH R01MH080425: The Genetic and Genomic Study of MicroRNA in Bipolar and Schizophrenia
  - PI: Liu 07/01/2007-06/30/2011
  - PI: Sweeney 09/29/2007-05/31/2011

Selected Publications of Note.


Emil F. Coccaro, M.D. (Psychiatry & Behavioral Neuroscience). Dr. Coccaro is Ellen C. Manning Professor and Chair of the Department of Psychiatry and Behavioral Neuroscience at The University of Chicago. Dr. Coccaro has broadly been involved in the study of the biology, genetics, neuroscience, and treatment of impulsive aggression in human subjects. Currently, he is most involved in the behavioral genetics and neuroscience study of social and emotional information processing (SEIP). His newest work relates to the development of assessments of SEIP and to the neuroscience of SEIP in aggressive and non-aggressive subjects. One project involves the exploration of the genetic and environmental architecture of SEIP in the context of an fMRI study of twins. Another study involves the nature of SEIP in distributed networks in the brain in aggressive and non-aggressive subjects. In yet another study, Dr. Coccaro is studying the role of serotonin in the activity of distributed networks of the cortico-limbic system underlying SEIP. In addition, Dr. Coccaro continues to process data from his recently completed NIMH grants and other projects related to: a) family study of aggression, b) twin study of aggression, c) anti-aggressive treatment response study comparing fluoxetine vs. divalproex vs. placebo, d) fMRI and DTI studies of aggressive and non-aggressive subjects.

Training.

B.S., In Cursu Honorum, Fordham University, Bronx, NY, 1975
M.D., New York University School of Medicine, New York, NY, 1979
Internship in Internal Medicine, U. Cincinnati Medical Center, Cincinnati, OH, 1980
Residency in General Psychiatry, Mt. Sinai Medical Center, New York, NY, 1983

Research Program.

Dr. Coccaro began his research career while still a Resident in Psychiatry at the Mt. Sinai School of Medicine from 1980-1983. His first work involved studies with the Dexamethasone Suppression Test (DST) in mood disordered patients. The DST was a simple laboratory test of plasma cortisol in which non-suppression but dexamethasone indicated the presence of hyperactivity of the Hypothalamic-Pituitary Axis (HPA). His first original research paper in Psychiatry, published in the American Journal of Psychiatry (Coccaro et al., 1984a), was the first to describe the effect of hospitalization on the DST in psychiatric patients. This paper reported that the DST was more likely to show non-suppression in depressed patients on the first day after admission than at any other time after that. This suggested that the HPA axis of depressed patients was more sensitive to environmental events/stress and that the sensitivity of the DST might be
enhanced by performing it as soon as possible after hospital admission. Dr. Coccaro published two additional papers related to the DST soon after that (Coccaro et al., 1984b, 1985).

After completing his Psychiatry Residency, Dr. Coccaro was appointed Instructor of Psychiatry at the Mt. Sinai School of Medicine. He was assigned to the Psychiatry Service at the Bronx VA Medical Center and was mentored in psychobiological research by Larry J. Siever, M.D. Dr. Siever had joined the Department of Psychiatry at the Mt. Sinai School of Medicine in 1982 after a four year research staff appointment at the NIMH in the Laboratory of Neuropsychopharmacology of Dennis L. Murphy, M.D. This laboratory focused on neurotransmitter correlates of mood disorders and was a leader in a novel methodology involving pharmaco-challenge studies in which small doses of neurotransmitter specific agents are given to human subjects so that physiological responses to these agents can be measured as an index of the responsivity to stimulation of specific neurotransmitter receptors.

Dr. Coccaro’s initial research was in the neuropsychopharmacology of depression. This work involved both noradrenergic (NE) and serotonergic (5-HT) studies of mood disorder in both the acute and remitted state. At about the same time, Dr. Coccaro began a series of studies examining the 5-HT correlates of impulsive aggression in personality disordered patients. These studies led him to his first extramurally funded grant which, in turn, led him down the path of studying the biology and treatment of impulsive aggression in humans.

In 1989, Dr. Coccaro published the first study to demonstrate physiological correlates of central 5-HT function in mood and personality disordered (PD) patients (Coccaro et al., 1989). This study reported reduced 5-HT function in both mood and PD patients compared with controls. It also reported an association between reduced 5-HT function and history of suicidal behavior. Lastly, it reported an inverse correlation between central 5-HT function and measures of aggression and impulsivity in PD, but not mood disordered, patients. Further analysis discovered that the dimensional relationship between central 5-HT function and impulsive aggression was the core finding and underlies any other group difference observed among the patients (e.g., history of suicidal behavior was explained by the inverse correlation between central 5-HT and the dimension of impulsive aggression). This work was replicated by a number of investigators and was replicated by Dr. Coccaro in much larger studies in a community sample of subjects (Figures 1-2: Coccaro et al.,
Other work by Dr. Coccaro determined that the components of the 5-HT synapse underlying these findings included the synthesis and release of 5-HT from the pre-synaptic terminal (Coccaro et al., 1998) and post-synaptic 5-HT1a (Almeida et al., in press) as well as 5-HT-2c receptors (Coccaro et al., 1997, 1998). Other studies by Dr. Coccaro and colleagues revealed a role for GABA (Lee et al., 2008, Vasopressin (Coccaro et al., 1998) and oxytocin (Lee et al., 2009). GABA and vasopressin appear to be facilitatory to aggression while oxytocin appears to be inhibitory.

The finding of an inverse relationship between central 5-HT function and aggression in PD individuals led to the development of a psychopharmacologic treatment study involving the 5-HT selective uptake inhibitor, fluoxetine. Prior to this study, outcome measures for assessing current levels of aggression were developed leading to the Overt Aggression Scale-Modified for Outpatient Use (OAS-M). The OAS-M has excellent psychometric properties and is the leading assessment for outpatient clinical trials of aggression. The first study testing the efficacy of fluoxetine in the treatment of aggression in impulsively aggressive PD subjects reported a clinically significant reduction in OAS-M Aggression and OAS-M Irritability scores (Coccaro et al., 1997; Coccaro et al., 2009; Figures 3-4). This effect appeared early in the trial but was most evident during the third month of the trial. The anti-aggressive effect of fluoxetine was not accompanied by any antidepressant effect indicating that enhancement of central 5-HT activity can lead to a specific anti-aggressive effect in impulsively aggressive PD subjects. Curiously, pre-treatment studies of central 5-HT function revealed a direct relationship between central 5-HT function and improvement on fluoxetine (Coccaro et al., 1997). This finding suggested that the less functionally intact 5-HT neurons are the less well an SSRI will work to reduce impulsively aggressive behavior. Extrapolating from this, it is possible that the more aggressive one is, the less likely an SSRI will work to treat one’s aggression.
The finding of an inverse relationship between central 5-HT measures and aggression and the finding that 5-HT specific agents can reduce aggression in impulsively aggressive individuals, led to a phenomenological analysis to describe these kinds of individuals. This work led to a refinement of the DSM-IV Criteria Set for Intermittent Explosive Disorder (IED; Coccaro et al., 1998) and then to epidemiological (Coccaro et al., 2004, Kessler et al., 2006; Figure 5), family (Coccaro 2003), and further neurobiological studies of IED (Coccaro et al., 2010, Coccaro, in press). Epidemiologic studies suggest a lifetime rate of IED in the US of about 5% [for DSM-IV IED: Kessler et al., 2006; for Research Criteria (IED-IR): Coccaro et al., 2004], a rate that has been replicated in other studies in other countries such as South Africa and the Ukraine. Reanalysis of the Kessler et al. data set suggests that the lifetime rate of IED is closer to 2.5-3.0%.

Family studies suggest that IED is about three times as high in first-degree relatives of individuals with IED and is not related to comorbidity in the IED probands or their first degree relatives (Coccaro, in press). This strongly suggests that IED is a signal that runs in families and is not simply an epiphenomenon of other psychopathology that may be associated with impulsive aggressive behavior (Figure 6). This is consistent with twin studies that demonstrate that both the trait of aggression (Coccaro et al., 1997; Yeh et al., in press) and the trait of impulsivity are under genetic influence (Serozynski et al., 1999). For the trait of aggression, genetic influence increases as one goes from verbal aggression to physical aggression against objects to physical aggression against people, suggesting that as one goes from less severe forms of aggression to more severe forms aggression, the influence of genes increases as well (Coccaro et al., 1997).

Biomarker studies using PRL[d-FEN] responses as a measure of central 5-HT function strongly suggest that 5-HT abnormalities are best associated with the new Research Criteria for IED (IED-IR) than are other definitions of IED (e.g., DSM-IV or IED-R; see Coccaro et al., 2010, Figure 7). The same is true when considering Platelet 5-HT Transporter Binding Sites. This suggests that the new Research Criteria for IED, which allow for low intensity, but high frequency, impulsive aggressive outbursts represent a significant addition to the power of this diagnostic set to identify individuals with recurrent, problematic, impulsive aggressive behavior.
Other studies, using the new Research Criteria for IED-IR, suggest abnormalities in social and emotional information processing in individuals with IED (Best et al., 2002), specifically an increase in hostile attribution and negative emotional response compared with controls (Coccaro et al., 2009, Figure 8). These data show very clearly that individuals with IED are more likely than others to perceive ambiguous social-emotional cues [e.g., in a vignette, someone does something “hurtful” to another person but the intent behind the action is not clear; it could be “Hostile” (HA), “Instrumental” (IA), or “Benign” (BA)] from other individuals as “hostile” and that they are more likely than others to feel “angry” or “upset” (“NER”) in those situations. Further analysis revealed that the more hostility individuals with IED attribute to the other person in socially ambiguous situations, the more “angry” or “upset” they expect they would become. Under this model, a reduction in brain 5-HT function would lower the threshold to act impulsively aggressive but the trigger for the aggressive action would be the misperception of “hostility” on the “other person’s” part directed at the individual with IED.

This work is consistent with results from clinical trials using a form of cognitive behavioral therapy, “CRCST” (Cognitive Restructuring, Relaxation Training, and Coping Skills Training), that show a reduction in OAS-M Aggression and in Automatic “Hostile Thoughts” (McCloskey et al., 2008, Figure 9). CRCST involves 12 sessions that focus in sequence on Relaxation Training, then Cognitive Restructuring, and then Coping Skills Training with several practice sessions to help guide the individual to deal with his/her aggressive outbursts. CRCST can take place individually or in a group setting. Efficacy is similar in both versions but individual CRCST offers more flexibility in clinical practice.
More recent studies demonstrate that the amygdala of individuals with IED is hyper-responsive to specific types of “threat”, namely exposure to anger faces in the fMRI environment (Coccaro et al., 2007; Figure 10). At the same time, it appears that the orbitofrontal areas of the brain are less active in response to anger faces in individuals with IED compared with healthy controls (Figure 11). In addition, there appears to be good functional connectivity between the orbitofrontal cortex and the amygdala in healthy individuals but not in individuals with IED. This suggests a “disconnect” between the higher centers of the brain and lower centers of the limbic system that detect “threat” and then fire to trigger the organism to act. This may be associated with pathology of white matter tracks in social emotional information processing circuits. There is low fractional anisotropy (FA) in areas next to the amygdala (Figure 12A) and in U-fibers connecting the left and right frontal lobes (Figure 12B). Low FA is an index of white matter (fiber tract) integrity.

In preliminary treatment studies, we have found that the fMRI BOLD amygdala response to anger faces is suppressed by 12-weeks of treatment with anti-aggressive agents (fluoxetine or divalproex; Figure 13). Moreover, the degree of suppression of the fMRI BOLD amygdala response to anger faces appears to be related to the degree of anti-aggressive response to these agents.
At this time Dr. Coccaro is following up on these findings with new studies designed to examine the role of genetics and environment in social emotional processing circuits as well as the role of 5-HT in social emotional information processing. A new, developing, fMRI BOLD study will examine the nature of distributed networks underlying hostile attributional bias and negative emotional responses to ambiguous social situations in human subjects (Figure 14).

**Figure 14. Schema for fMRI BOLD Study of Socio-Emotional Response To Ambiguous Social Stimuli.**

**fMRI SEIP Trial Design**

**Funding.**

- NIH/NIMH RO1 MH80108: Understanding the pathways to aggression
  PI: Coccaro 03/01/2008-02/28/2013
- NIH/NIMH R21 MH083198: Development of pharmaco-fMRI challenge in healthy control & aggressive subjects
  PI: Coccaro 01/01/2009-12/31/2011
- American Foundation for Suicide Prevention: Diffusion tensor imaging (DTI) studies of suicidal behavior
  PI: Coccaro 07/01/2009-06/30/2012
Selected Publications of Note.


Coccaro EF, Kavoussi RJ, Sheline YI, Lish JD, Csernansky JG. Impulsive aggression in personality disorder: Correlates with \(^3\)H-Paroxetine binding in the platelet. Archives of General Psychiatry 53:531-536, 1996.


Harriet de Wit, Ph.D. (Psychiatry and Behavioral Neuroscience). Harriet de Wit is Professor in the Department of Psychiatry and Behavioral Neuroscience at The University of Chicago. The main focus of her research is to identify determinants and consequences of drug use and abuse, by studying the acute effects of psychoactive substances in healthy volunteers. In controlled laboratory-based studies, she has investigated a range of biological, psychological and contextual variables that are either risk factors for drug use, or consequences of drug administration. These controlled studies form a critical bridge between findings from studies with laboratory animals and clinical problems encountered with drug abusers. The following are examples of some of the important findings from her laboratory.

Training.

B.A., Psychology and Philosophy, University of Calgary, Calgary, Canada, 1970.

M.A., Experimental Psychology, Concordia University, Montreal, Canada, 1976.

Ph.D., Experimental Psychology, Concordia University, Montreal, Canada, 1981.

Research Program.

Genetic variations in acute responses to drugs. Dr. de Wit has pioneered studies of genetic factors that influence individual differences in acute subjective and behavioral responses to drugs. In these studies, she examined polymorphisms in the neurotransmitter-related genes in relation to variations in responses to acute responses to caffeine and d-amphetamine in healthy volunteers. In the first study in this series, she collaborated with Dr. Jurgen Deckert at the University of Munster, to investigate genetic determinants of responses to acute doses of caffeine. They found that individuals who had a certain polymorphism in the adenosine receptor gene experienced greater anxiety after a single, low dose of caffeine, compared to individuals without this polymorphism (Alsene, Sand, Deckert and de Wit, 2004). Notably, this same polymorphism is associated with Panic Disorder, a psychiatric condition characterized by acute anxiety and sensitivity to caffeine. It suggests that genetic variations in function of a particular neurotransmitter receptor may influence both a psychiatric disorder and inter-subject variations to a commonly-used recreational drug. Subsequently, in studies conducted in collaboration with Dr. Edwin Cook and Dr. Abraham Palmer at The University of Chicago, Dr. de Wit used a similar approach to study variations in responses to amphetamine. In an early study, they found that polymorphisms in the dopamine transporter gene were related to the mood changes subjects experienced after a single dose of d-amphetamine (Lott, Kim, Cook and de Wit, 2005). Subjects who were homozygous for the 9 repeat allele of the VNTR
polymorphism experienced less pronounced mood effects from a low acute dose of amphetamine than individuals with either the 9,10 or 10,10 alleles. Notably, this finding coincided with another study showing that ADHD children who had this same polymorphism benefited less from treatment with methylphenidate than children with more common genotypes. Since that early study, they have now examined variations in 7 other genes to study associations with different effects of amphetamine in human volunteers (Hohoff et al, 2005; Veenstra-Vander Weele et al, 2006; Flanagan et al, 2006; Lott et al, 2006; Dlugos et al, 2007; 2009a; 2009b; Hamidovic et al 2009; 2010a; 2010b).

This line of research has potential for understanding variations in both therapeutic and recreational effects of drugs. It also has potential for studying the role of different receptor mechanisms in normal brain function and pathophysiology of psychiatric disorders, including drug abuse. The research was conducted in collaboration with Dr. Abraham Palmer, of the Department of Human Genetics.

**Interactions between acute stress and drugs.** The de Wit laboratory has also investigated interactions between stress and psychoactive drugs. Stress is known to play an important role in drug abuse. Behavioral studies with laboratory animals suggest that acute stress increases the propensity to self-administer drugs, and clinical reports of human drug users indicate that both acute and chronic stress are risk factors for drug use. Dr. de Wit has completed a series of studies investigating interactions between stress and amphetamine.
acute stress and responses to drugs using a public speaking model of acute stress in healthy volunteers (Soderpalm and de Wit, 2002; de Wit, Nikolayev and Soderpalm, 2003). She has examined the effects of acute stress on responses to acute administration of nicotine, amphetamine and alcohol. She is also studying individual differences in stress reactivity, including comparisons of stress reactions in smokers and non-smokers, men and women, and in women at different phases of the menstrual cycle (Childs and de Wit, 2009; 2010).

Finally, Dr. de Wit is also studying whether stress reactivity in occasional, light smokers predicts the progression to regular daily smoking. These studies were funded by an NIH grant and by the Cancer Research Center of the University of Chicago.

**Impulsivity and drugs of abuse.** In a third line of research, Dr. de Wit is investigating the role of impulsivity in the propensity to use drugs. Impulsivity is closely linked to drug abuse, both as a risk factor predisposing certain individuals to use drugs, and as an adverse behavioral consequence of using drugs (de Wit and Richards, 2004). She has studied the effects of acute drugs on different subtypes of impulsive behavior, including behavioral inhibition and cognitive decision-making tasks. In collaboration with Dr. Jerry Richards, she conducted parallel studies in humans and nonhumans, and found a remarkable concordance in the results using rats, mice and humans using two distinct behavioral measures of impulsive behavior (Richards et al, 1999; Feola et al, 2000; Enggasser and de Wit, 2001; de Wit et al, 2002; MacDonald et al, 2003; de Wit and Richards, 2004). Since then, they have examined the effects of several classes of drugs on impulsive behavior, and examined relationships between other variables, such as IQ (Hariri et al, 2006), genotypic variability related to dopamine D2 receptors (Hamidovic et al, 2009) and ratings of amphetamine-induced liking (McCloskey et al, 2010). These translational studies help to validate procedures and findings across species, and provide a rich body of knowledge on the acute effects of drugs on impulsive behavior in humans.

![Figure 2. Changes in cigarette craving and the total number of smoking choices after control and stressful tasks. Data indicate mean ± SEM. Asterisks indicate a significant difference between the tasks (Student's paired t test, p < .01). TSST = Trier Social Stress Test.](image)
**MDMA.** Dr. de Wit has initiated a series of studies to investigate the effects of MDMA, or Ecstasy, on emotional responses. Ecstasy is a widely used drug that reportedly has unique effects, distinct from other stimulants; most notably it is said to increase feelings of empathy and closeness to others. These so-called ‘empathogenic’ effects on social and emotional processing appear to contribute to the widespread recreational use of the drug, as well as its purported utility as an aid in psychotherapy. The main psychoactive constituent of ecstasy is ±3,4-methylenedioxymethamphetamine (MDMA), which acts on serotonin and dopamine, two neurotransmitter systems integrally involved in modulation of affect and reward. In one project (Bedi et al, 2009), Dr. de Wit showed that MDMA altered brain responses to social threat, using fMRI.

**MDMA (1.5 mg/kg) decreased reactivity in the left amygdala with angry vs neutral faces.**

**Figure 3.** This figure illustrates the relatively greater amphetamine-induced ratings of drug liking in subjects with high or low numbers of lapses of attention in a reaction time task (McCloskey et al, 2010).

**Figure 4.** This figure illustrates the relative decrease in amygdala activity after administration of MDMA (Bedi et al, 2009).
In an ongoing study, she is investigating dimensions of social and emotional processing that may contribute to the putative ‘empathogenic’ effects of MDMA. She is studying the effects of MDMA (0, 1.0 and 1.5mg/kg) on emotional recognition and emotional responsivity, both central aspects of social and emotional processing, and on sociability. She will compare the effects of MDMA to the effects of oxytocin, a hormone which is thought to produce similar behavioral effects of increased empathy and feelings of social connectedness. The study applies state-of-art techniques from social neuroscience to the study of processes involved in the rewarding effects of drugs. This project has the potential to broaden our perspective on how drugs interact with the social and emotional context in which they are used, and how these interactions influence vulnerability to repeated or compulsive use of these drugs.

**Incubation of craving.** In another project, Dr. de Wit explored the time course of cue-induced craving in abstinent cigarette smokers. Abstinent drug users remain at risk for relapse for long periods of time, well after their withdrawal symptoms subside. In laboratory animals responses to drug-related cues not only persist, but actually increase with abstinence duration. Dr. de Wit investigated whether cue-elicited craving increases with duration of abstinence in cigarette smokers. Smokers were randomized to four groups paid to abstain for 7 (Group 1), 14 (Group 2), or 35 (Groups 3, 4) days. Abstinence was biochemically verified daily. Groups 1, 2, and 3 underwent a cue exposure session to measure cue-elicited craving on the last day of abstinence (days 7, 14, or 35), whereas Group 4 underwent three repeated cue sessions (days 7, 14, and 35). Dr. de Wit measured self-reported craving and negative affect after exposure to smoking and neutral cues. In both between- and within-groups analyses, she found that cue-induced craving increased as a function of abstinence duration. Participants in Group 3 (35-day abstinence) reported significantly greater smoking-cue-elicited craving than did Group 1 participants (7-day abstinence). Participants in Group 4 (repeated cues) reported greater cue-elicited craving at 35 days than at 14 days.

This is the first evidence of incubation of craving in human drug users. The finding that craving elicited by cues may increase with abstinence even as daily cravings and nicotine withdrawal symptoms subside, has significant implications for treatment.
Funding.

Principal Investigator:
NIDA RO1 DA032015: Genetic basis of impulsivity in humans  
2011-2016
NIDA R01 DA02812-25: Determinants of drug preference in humans  
1987-2013
NIDA R21 DA031796: Memory effects of stimulant drugs in humans  
2012-2014
NIDA R21 DA026570: Is Ecstasy an empathogen? Effects of MDMA on social and emotional processing  
2009-2011

Co-investigator or sponsor:
NIAAA RO1 AA013746: Alcohol stimulation and sedation in binge drinkers  
PI: Andrea King  
2003-2013
NIAAA R21 AA017502: Acute brain response to alcohol: an fMRI study  
PI: Childs  
2009-2012
NIDA R01 DA030386: Gender differences in responses to caffeine in children and adolescents  
PI: Temple  
2011-2016
NIDA F31 DA030863-01: The effect of amphetamine on the different stages of emotional memory  
PI: Ballard  
2011-2013
Alcoholic Beverages Medical Research Foundation: Contextual conditioning of alcohol effects in humans  
PI: Childs  
2012-2014
NIDA F32 DA033756-01: Impulsivity and stimulant drug reward  
PI: Weafer  
2012-2014
NIAA R21 AA020964-01: The role of environmental conditioning in responses to alcohol and cognitive behavior  
PI: Childs  
2012-2014

Recent Publications (2010-2012).

Childs, E., N.T. Van Dam, H. de Wit (2010) Effects of acute progesterone administration upon responses to acute psychosocial stress in men. Experimental Clinical Psychopharmacology, 18, 78-86. PMID: 20158297


**Books.**

Stephanie C. Dulawa, Ph.D. (Psychiatry & Behavioral Neuroscience). Stephanie Dulawa is Associate Professor in the Department of Psychiatry and Behavioral Neuroscience at The University of Chicago. Dr. Dulawa studies the neural mechanisms of mood and anxiety using mouse models. Recently, she developed several mouse models that can be used to study the neural substrates of these psychiatric disorders and to develop novel treatments. In her models of chronic antidepressant action, mice respond behaviorally to chronic, but not short term, antidepressant treatments. These models are being used to study the mechanisms underlying the therapeutic effects of antidepressant treatments, and to identify faster-acting antidepressants. Another major focus of Dr. Dulawa’s laboratory has been the development of a novel mouse model for aspects of Obsessive Compulsive Disorder (OCD). In this model, activation of 5-HT1B receptors induces OCD-like behaviors in mice that can be prevented by chronic treatment with selective serotonin reuptake inhibitors (SSRIs), but not ineffective treatments for OCD. Her recent work suggests that desensitization of 5-HT1B receptors in the orbitofrontal cortex by SSRIs may contribute to their therapeutic effects in OCD. She is also using the activity-based anorexia model in mice to study the neural mechanisms underlying the hyperactivity and self-starvation that characterizes Anorexia Nervosa. She recently found that the atypical antipsychotic olanzapine, but not antidepressant drugs, attenuates hyperactivity and self-starvation at doses that do not alter bodyweight or produce sedation. Dr. Dulawa’s group is currently investigating the effects of more selective pharmacological agents, and how changes in neuroplasticity induced by olanzapine may contribute to its therapeutic effects. Her laboratory has also recently begun investigating epigenetic mechanisms that modulate depression-like behavior. The primary approaches used to dissect the neural mechanisms of anxiety- and depression-like behaviors in these experiments are pharmacological, biochemical and molecular genetic and include the generation of genetically modified mice and microarrays.

Training.

B.A., Psychobiology, Occidental College, Los Angeles, California, 1993.

Ph.D., Neuroscience, University of California at San Diego, California, 2000.

Postdoctoral Scholarship in Mouse Genetics, Columbia University, New York, New York

Research Program.

Mouse models of chronic antidepressant action.

All classes of antidepressants currently in use, including SSRIs, require 2-4 weeks of treatment for their therapeutic effects to emerge. This delay in therapeutic onset places
depressed patients at increased risk of suicide. Furthermore, all current antidepressants utilize monoaminergic-based approaches, to which 30-40% of depressed patients do not respond adequately. Thus, antidepressants with a faster onset and with a novel mechanism of action are greatly needed.

A major obstacle to identifying faster-acting antidepressants has been a lack of animal behavioral models that exhibit sensitivity to chronic, but not short term, antidepressant treatment while maintaining high predictive validity and ease of use. Dr. Dulawa recently developed mouse behavioral models in which chronic, but not subchronic, treatment with SSRIs and tricyclic antidepressants reduce anxiety- and depression-like behavior in the open field, novelty-induced hypophagia, and forced swim tests in BALB/cJ mice (Dulawa and Hen 2005; Dulawa et al. 2004; Holick et al. 2007; Jiao et al. 2010). Using one of these mouse models (Figure 1), she recently identified novel selective ligands as putative faster-acting antidepressants (5 days) compared to SSRIs (12 days). She is currently examining the potential antidepressant properties of these ligands using behavioral, biochemical and molecular approaches.

Using her models of chronic antidepressant action, Dr. Dulawa recently implicated genetic variability in tryptophan hydroxylase-2 (Tph2) in the therapeutic response to antidepressants. Tph2 is the rate-limiting enzyme for the biosynthesis of brain serotonin. In the mouse, substitution of C by G at position 1473 changes a proline to an arginine at position 447 in Tph2 protein. The 1473C allele is highly conserved across species, while the 1473G form is found in several inbred mouse strains and confers a 50% reduction in Tph2 enzymatic activity. Thus, mouse strains possessing the 1473G allele exhibit marked reductions in brain serotonin synthesis and tissue content. However, the role of Tph2 polymorphisms in the antidepressant response in humans remains unclear.

**Figure 1.** Ligands RS and SB reduced immobility and increased swimming behavior after 5 days of treatment, while 12 days of treatment with citalopram was required for these effects. Day 5 and day 12 data were collected from separate groups of animals. Values are means ± SEM. *, P<0.05 vs control group, with ANOVA.
Dr. Dulawa assessed eight strains of mice (BALB/cJ, BALB/cByJ, SEA/GnJ, A/J, C57BL/6J, C57BL/10J, CAST/EiJ and SM/J) for C1473G genotype and characterized their behavioral response to 4 weeks of treatment with the SSRI citalopram in the chronic forced swim test (FST). She found that the BALB/cJ, BALB/cByJ, SEA/GnJ, and A/J strains all carried the 1473G allele and showed an antidepressant-like response to chronic citalopram treatment in the FST (Figure 2). C57BL/6J, C57BL/10J, CAST/EiJ and SM/J all carried the 1473C allele and did not respond to chronic citalopram. These findings suggest that the 1473G allele in Tph2 is correlated with antidepressant response to chronic SSRI treatment. Dr. Dulawa is currently generating a knockin mouse line in which the 1473C allele will be expressed on the BALB/cJ background. This mouse line will allow her to determine whether the C1473G allele plays a causal role in the response to chronic antidepressant treatment.

Figure 2. Effects of 4 weeks of treatment with citalopram on FST behavior. **Top.** Total immobility is shown for BALB/cJ (C), BALB/cByJ (CBy), A/J (A), SEA/GnJ (SEA), C57BL/6J (B6), C57BL/10J (B10), CAST/EiJ (CAST), and SM/J (SM) mice. **Bottom.** Total climbing is shown. Citalopram-treated C, A, and SEA mice showed significant decreases in immobility, and CBy mice showed significant increases in climbing. Values are means ± SEM.

**Epigenetic control of depression-related behavior.**

Dr. Dulawa’s group is also examining the contributions of genetic vs. epigenetic influences on depression-like behavior and the response to chronic SSRI treatment. Dr. Dulawa previously identified the BALB/cJ mouse strain as behaviorally sensitive to
chronic, but not short-term, SSRI treatment, unlike many other strains including C57BL/6J (Dulawa et al. 2004; Jiao et al. 2010; Velez et al. 2009). She is therefore investigating whether sensitivity of the BALB/cJ mouse strain to chronic SSRI treatment is determined genetically or by environmental factors, including the in utero environment or early life experience (maternal behavior). Environmental factors alter gene expression through epigenetic mechanisms, including DNA methylation.

Dr. Dulawa evaluated the influence of genetics vs. environment on two measures: 1) baseline depression-like behavior, and 2) the behavioral response to chronic SSRI treatment. C57BL/6J mice show higher immobility than BALB/cJ mice in the FST (Dulawa et al. 2004; Jiao et al. 2010), a test of depression-related behavior in which more immobility indicates more depression-like behavior. Additionally, BALB/cJ mice respond to chronic SSRI treatment in the FST, while C57BL/6J mice do not. To determine the relative contributions of genetic vs environmental factors to these behaviors, she performed a reciprocal intercross between C57BL/6J and BALB/cJ mice. F1 females (offspring from reciprocal intercrossing of these strains) provide a model to study the interplay of genetic and environmental factors on phenotypes of interest. Female mice from these strains are nearly genetically identical. Thus, genetic variation is held constant, and the influence of differential environmental influences, such as in utero factors or early rearing can be evaluated.

Dr. Dulawa recently found that genetic factors determine the response to chronic fluoxetine treatment in BALB/cJ mice. F1 mice born to either BALB/cJ or C57BL/6J dams showed a robust antidepressant response to chronic fluoxetine treatment as evidenced by reduced immobility. Thus, a dominant genetic factor is likely responsible for the behavioral response of BALB/cJ mice to chronic SSRI treatment. In contrast, Dr. Dulawa found that F1 females born to C57BL/6J dams displayed higher immobility, and thus more depression-like behavior, than F1 females born to BALB/cJ dams (Figure 3). This result suggests that epigenetic factors account for the differences in baseline depression-like behavioral traits. Possible epigenetic factors include imprinting, in utero environment, and early life experience.

Dr. Dulawa’s group then investigated whether the differences in baseline depression-like behavior observed between the two F1 groups resulted from intra uterine factors, or from rearing effects. They performed reciprocal intercross between BALB/cJ and
C57BL/6J strains. Additionally, F1 offspring from both groups were cross-fostered either within strain or between strains at postnatal day 1. As above, the FST was performed in adulthood. F1 offspring born from C57BL/6J dams showed more depression-like behavior regardless of which strain reared them. Likewise, F1 offspring born from BALB/cJ dams showed less depression-like behavior, regardless of whether they were reared by C57BL/6J dams or by BALB/cJ dams (Figure 3). These results suggest that the depression-like behavior in this model is determined either by intra uterine factors or maternal imprinting.

Microarray analysis of hippocampal tissue and follow-up qPCR studies have identified expression differences in candidate genes between these F1 offspring. One candidate gene with the largest expression differences has been previously implicated in depression in humans and is located in a region rich in imprinted genes. Dr. Dulawa is currently examining allelic variation in expression of this candidate gene and assessing the role of this gene in depression-like behavior in mice.

5-HT1B-induced mouse model of OCD-like behavior.

Obsessive-compulsive disorder (OCD) is characterized by intrusive thoughts, images, or impulses and/or repetitive behavior. OCD patients exhibit reduced prepulse inhibition (PPI) and symptom exacerbation following challenge with 5-HT1B receptor agonists. These represent potential biomarkers in OCD. Dr. Dulawa has shown that in mice, 5-HT1B agonists induce PPI deficits (Dulawa and Geyer 2000; Dulawa et al. 2000;

![Figure 4](image.png)

Figure 4. Total locomotor activity is shown for BALB/cJ mice pretreated with 0 or 15 mg/kg/day fluoxetine for 1 (A) or 4 weeks (B). All mice received saline, RU24969 (5-HT1B\1A agonist) and 8-OH-DPAT (5-HT1A agonist) treatment. Chronic, but not subchronic, 15 mg/kg/day Flx blocked the locomotor hyperactivity induced by 10 mg/kg RU24969. 8-OH-DPAT reduced locomotion across all pretreatments. Values are means+SEM. *Significant difference from saline-treated animals within the same pretreatment group. #Significant difference from fluoxetine-pretreated animals within the same treatment group.
Dulawa et al. 1997; 1998) and perseverative hyperlocomotion (Shanahan et al. 2009). Long-term treatment with SSRIs provides the only pharmacological monotherapy for OCD. Thus, SSRIs such as fluoxetine and clomipramine are effective in OCD, but the noradrenaline reuptake inhibitor desipramine is not. Dr. Dulawa tested the specificity and time-course for SSRI antidepressants to block 5-HT1B-induced OCD-like behavior in mice. Mice were treated chronically with clomipramine, fluoxetine, or desipramine. Mice then received acute 5-HT1B agonist challenge and were assessed for PPI and perseverative hyperlocomotion. Additionally, separate groups of mice were treated with fluoxetine for 4, 14, 21, 28, or 56 days and assessed for OCD-like behavior or depression-like behavior for comparison. She found that only chronic treatment with SSRIs attenuated 5-HT1B-induced OCD-like behavior. Specifically, SSRI reversal of 5-HT1B-induced PPI deficits and perseverative hyperlocomotion required 3-4 weeks to emerge. Reversal of depression-like behavior required only 2 weeks. These findings regarding effective treatments and time-course parallel what is observed clinically in OCD patients (Wang et al. 2009).

To better understand how chronic SSRI treatment reduces OCD symptoms, Dr. Dulawa is currently attempting to localize the brain region in which 5-HT1B receptor activation produces OCD-like behaviors in mice. She hypothesizes that chronic SSRI treatment should reduce 5-HT1B receptor sensitivity in this brain region. Thus, she assessed 5-HT1B receptor expression and G-protein coupling in brain regions implicated in OCD including the orbitofrontal cortex (OFC), caudate/putamen and nucleus accumbens following chronic antidepressant treatment. Recently, she found that chronic SSRI treatment reduces 5-HT1B receptor expression in the OFC suggesting that downregulation of 5-HT1B receptors in this region may underlie the therapeutic effects of SSRIs in OCD. This novel mouse model provides a tool for identifying the neural substrates underlying aspects of OCD and the therapeutic mechanisms of SSRIs in this disorder.

Dr. Dulawa is currently generating genetically modified mice that will contain uncommon mutations identified in humans with OCD. These humanized mice will then be assessed for OCD-like behaviors.

**Mechanisms of activity-based anorexia.**

Anorexia Nervosa (AN) is a serious psychiatric disorder that occurs in an estimated 0.5 to 3.7% of women. Mortality rates associated with AN are higher than those for any other psychiatric disorder. Both etiology and treatment of AN are poorly understood. AN typically onsets in mid adolescence and therefore early treatment is critical to promote good outcome and prevent chronicity. However, no effective pharmacological treatments exist for AN. A better understanding of the neurobiology underlying AN will be critical for developing novel treatments in this domain.

Activity-based anorexia (ABA) provides an animal model of AN. In this paradigm, rodents are provided free access to running wheels and have restricted access to food
(2-4 hours daily). Under these conditions, rodents exhibit increased wheel-running, show a paradoxical reduction in food intake, and develop progressive weight loss which results in death. This effect is more pronounced in female than male rodents. The ABA phenomenon mimics several core features of AN, including hyperactivity, extreme weight loss, and female preponderance.

In an attempt to identify effective treatments for AN, Dr. Dulawa recently examined the effects of antidepressants and atypical antipsychotics on ABA. Her recent findings suggest that olanzapine prevents the development of activity-based anorexia, while antidepressants have no effect (Figure 5). Importantly, olanzapine reduced ABA at doses that did not induce sedation, as assessed by wheel running. Although the weight gain induced by olanzapine may provide a helpful side effect in treating AN patients, olanzapine reduced ABA at doses that did not alter bodyweight in control mice. Dr. Dulawa is now investigating the mechanisms by which olanzapine reduces activity-based anorexia (ABA) in adolescent mice. She aims to determine the receptor types responsible for the attenuation of ABA by olanzapine.

Figure 5. Effects of drugs on activity-based anorexia in mice. A. 4 weeks of fluoxetine treatment did not alter survival time. B. Treatment with 20 or 40 mg/kg/day olanzapine significantly increased survival time.

Atypical antipsychotics including olanzapine have been shown to enhance synaptic plasticity and cellular resistance, and this property may contribute to their therapeutic effects. For example, preclinical studies in rodents have reported that extended olanzapine treatment (≥1 week) increases expression of the neurotrophins brain-derived neurotrophic factor (BDNF) and B cell lymphoma protein-2 (Bcl-2) as well as the dendritic marker microtubule-associated protein (MAP-2), and prevents the downregulation of these factors by stress. Dr. Dulawa hypothesizes that enhancing synaptic plasticity and cellular resistance may contribute to therapeutic effects in AN. For example, cerebral grey matter volumes are reduced in AN and does not completely normalize with recovery.
Funding.

- NIH/NIMH R01 MH079424: Mechanisms for 5-HTT control of PPI and perseverative behavior using mouse models
  PI: Dulawa  03/22/2007-02/29/2012
- NIH/NIMH R24MH080022: Building translational research in obsessive-compulsive disorder

Selected Recent Publications of Note.

Holick KA, Lee DC, Hen R, Dulawa SC (2007) Effects of chronic fluoxetine in BALB/cJ mice do not require adult hippocampal neurogenesis or the serotonin 1A receptor Neuropsychopharmacology 33: 406-417
Elliot S. Gershon, M.D., is a research psychiatrist who has been Professor of Psychiatry & Behavioral Neuroscience and Human Genetics at the University of Chicago since 1998. Dr. Gershon spent his scientific career in biologic, epidemiologic, and genetic studies of major psychiatric disorders, particularly bipolar manic-depressive illness. His laboratory currently focuses on clinical and molecular genetics of Bipolar disorder and Schizophrenia, genomics of gene expression in brain, and transgenic mouse models (the last two items in collaboration with Assistant Professor Chunyu Liu, Ph.D.). He has received multiple awards for his research, including an international award for research in depression, the German Anna-Monika Foundation prize, in 1979 and again in 2005, and the Lifetime Achievement Award of the International Society for Psychiatric Genetics in 2006. Since 2003, Dr. Gershon has been listed by the Institute for Scientific Information on its Highly Cited Authors list. He was Chief of the Clinical Neurogenetics Branch of the NIMH Intramural Program from 1984 until moving to the University of Chicago in 1998. Although he is better known for his research findings than for his training activities, he has had at least one postdoctoral fellow each year, and in the course of time trained a considerable number of now-prominent researchers in psychiatric genetics and in clinical psychiatry. From among his former trainees, the following persons are now full professors (or NIH equivalent) doing well-regarded research in genetics and related fields in psychiatry and psychobiology: Miron Baron (Columbia University), James F. Leckman (Yale University), Lynn R. Goldin (National Cancer Institute), John I. Nurnberger, Jr. (Indiana University), Wade H. Berrettini (University of Pennsylvania), Lynn E. DeLisi (SUNY Stony Brook), Pablo V. Gejman (University of Chicago), Joel Gelernter (Yale University). Additional trainees who are now faculty members include Chunyu Liu and Judith A. Badner, both at the University of Chicago. In addition to research and training, Dr. Gershon served as Officer of Science of the Alcohol, Drug Abuse and Mental Health Administration (1986-87) and as President of the American Psychopathological Association in 1991-92. More recently, he was the Chair of the Department of Psychiatry at University of Chicago (1998 to 2004) after which he stepped down to return to a main focus on research and teaching.

Training.


M.D., Harvard University School of Medicine, Cambridge, MA, 1965.

Internship, Mt. Sinai Medical Center, NY, NY, 1965-66.

Residency, General Psychiatry, Massachusetts Mental Health Ctr, Boston, MA, 1966-69.

Dr. Gershon has worked on elucidation of the genetics of major mental illnesses for almost four decades. He started in Genetic Epidemiology, which began with development of methods for family study. The diagnostic spectra of bipolar disease (BP) and schizophrenia (SZ) became better understood through family studies by many investigators. Bipolar II as a related diagnostic entity was defined by Dr. Gershon and his colleagues in 1976 (4), and cyclothymic personality was defined and identified in relatives in his two family studies in 1975 and 1982 (5;6). His 1982 family study publication has been considered a landmark study, and has been cited 503 times to date. Chromosomal linkage markers. Several lessons were learned from failures of replication of 1987 reports of linkages on the X-chromosome and chromosome 11. The most important is that the genetic model of illness (single-gene dominant inheritance) could not have been correct. Development of appropriate statistical models and analysis methods for linkage and association in complex inheritance disease was, in retrospect, greatly stimulated as a result. With Dr. Badner, Dr. Gershon developed a method for meta-analysis of multiple genome linkage scans based on reported scores and probabilities at each region on the genome (1). As applied to BP and SZ, their meta-analysis revealed two regions, on chromosome 13q and 22q, that were significantly positive regions for each disorder (2). No other region was significantly positive for BP, although there was an additional region on chromosome 8p that was positive for SZ. This led them to the speculation that the same genes, on chromosomes 13 and 22, could be contributing to susceptibility to both disorders. Since they raised this possibility, susceptibility genes for both disorders were discovered on the chromosomal regions they predicted, most strikingly on chromosome 13q32-33.

The strongest single linkage result on BP on chromosome 13q32-33 had been reported by Dr. Gershon’s results. He thus decided to attempt positional cloning of a BP susceptibility gene in that region. A French biotechnology corporation, Genset, had meanwhile discovered and patented a previously undiscovered gene complex (G72/G30) in the same region of chromosome 13, and in 2002 reported association of this gene with SZ. G72 and G30 are on overlapping sense and antisense strands of DNA. This complex was one of the genes Dr. Gershon tested for association with BP and it proved to be associated in both the pedigrees he had collected in Bethesda, and in an independent set of pedigrees from the NIMH Genetics Initiative, using TDT analysis (7). Multiple published replications have been published of this gene’s association with BP and SZ. In his own meta-analysis, there was significant support for association of a particular risk allele in Asians (9). Dr. Gershon and his colleague, Dr. Chunyu Liu, are currently working on a mouse transgenic model of G72, where the genetic region is derived from an Asian family with that susceptibility allele.

Dr. Gershon’s current work is focused on rare chromosomal microdeletions and microduplications (Copy Number Variants; CNVs) that are associated with psychiatric disorders. Dr. Gershon and his group recently published the first association evidence associating genome-wide microdeletions with Bipolar disorder, particularly early-onset Bipolar disorder (11), and have also been involved in similar findings in autism (3). He is
a member of the CNV group of the worldwide Psychiatric Genetics Consortium, and in that group he is pursuing further replication of these findings. Based on the findings of genome-wide association studies in Bipolar disorder and Schizophrenia, Dr. Gerhson argues that there is a relative paucity of common genetic variants causing these disorders, and that rare variants with potent effects on risk, such as CNVs, will make up a substantial proportion of the inherited susceptibility to these disorders.

Functional Genomics. Recently, as a collaborator with Dr. Chunyu Liu, Dr. Gershon has moved into a new research area: genetical genomics of specific gene expression and methylation in human and rodent brain (8;10).

### Singleton Deletions Throughout the Genome Increase Risk of Bipolar Disorder

<table>
<thead>
<tr>
<th>test</th>
<th>cases</th>
<th>controls</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bipolar vs. Controls all RATE</td>
<td>0.411</td>
<td>0.380</td>
<td>0.156</td>
</tr>
<tr>
<td>PROP</td>
<td>0.324</td>
<td>0.290</td>
<td>0.054</td>
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<tr>
<td>deletion RATE</td>
<td>0.176</td>
<td>0.134</td>
<td>0.010</td>
</tr>
<tr>
<td>PROP</td>
<td>0.162</td>
<td>0.123</td>
<td>0.007</td>
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<tr>
<td>duplication RATE</td>
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<td>0.246</td>
<td>0.706</td>
</tr>
<tr>
<td>PROP</td>
<td>0.197</td>
<td>0.191</td>
<td>0.378</td>
</tr>
</tbody>
</table>

Problem of demonstrating a biological or statistical effect of any one of these 310 deletions is very challenging.


### Rare but Recurrent CNVs Associated with More Than One Psychiatric Disorder

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>1q21</th>
<th>2p16</th>
<th>15q11-15q13</th>
<th>16p11</th>
<th>22q11</th>
<th>Genome-wide rare CNV burden</th>
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<tr>
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<td>SZ, ASD, AUT</td>
<td>SZ, BD, ASD, AUT</td>
<td>AUT, SZ, BD</td>
<td>SZ, AUT, ASD, ?BD</td>
<td>SZ, BD, ASD</td>
</tr>
<tr>
<td>Susceptibility genes</td>
<td>?</td>
<td>Neurexin1</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>
More about rare recurrent CNVs

- High Odds Ratios (OR)
  - OR is ratio of CNV frequency in patients vs. controls.
  - ORs of SZ associated CNVs: 7 to 24
  - In comparison, the associated common SNPs had ORs ~ 1.1 to 1.2
- CNV frequencies quite rare.
  - Example: 16p11 duplication found in 0.03% of controls and 0.46% of SZ patients.
- CNVs detected by GWAS platforms are generally 100 kb or greater in size
- Many genes included
  - Which gene(s) causes the elevated risk?

Funding.
- NIH/NIMH T32 MH200065: Multidisciplinary psychiatric genetics training program.
  PI: Gershon  07/01/02-06/30/12
- NIH/NIMH R01 MH61613-05: Genetic Linkage Studies in Bipolar Disorders.
  PI: Gershon  03/04/05-03/30/2010
  PI: Liu  07/01/2007-06/30/2011
- NIH/NIMH R01MH081804: Analysis of Whole Genome Association Data for Bipolar Disorder.
  PI: Kelsoe  09/20/2007-09/29/2010 (subcontract)
- NIH/NIMH R01 MH077862: Bipolar & Schizophrenia Consortium for Parsing Endophenotypes.
  PI: Sweeney  09/2007-05/2011 (subcontract)

Selected Recent Publications of Note.
Andrea Goldschmidt, Ph.D. (Psychiatry and Behavioral Neuroscience). Andrea Goldschmidt is an Assistant Professor in the Department of Psychiatry and Behavioral Neuroscience at The University of Chicago. Her research interests concern the etiology, psychosocial correlates, and treatment of pediatric binge eating and obesity. This work includes the application of novel methodologies to study proximal triggers to aberrant eating in children. The ultimate goal of Dr. Goldschmidt’s research is to develop interventions for problematic eating in overweight and obese youth. Dr. Goldschmidt’s clinical interests include evidence-based treatments for eating disorders and obesity across the age spectrum. She is particularly interested in family-based and group psychotherapy. Dr. Goldschmidt joined the Eating and Weight Disorders Program at University of Chicago in 2010 as a post-doctoral fellow. In addition to seeing families and young adults in the Eating and Weight Disorders Clinic, she currently serves as a study therapist on an NIMH-funded treatment trial for adolescent bulimia nervosa and helps oversee the psychology team at the University’s Center for Surgical Treatment of Obesity.

Training.

B.A., Psychology and English, Rutgers the State University of New Jersey, New Brunswick, NJ, 2002

M.A., Clinical Psychology, Washington University in St. Louis, St. Louis, MO, 2006

Ph.D., Clinical Psychology, Washington University in St. Louis, St. Louis, MO, 2010

Clinical Psychology Internship, University of Missouri Counseling Center, Columbia, MO, 2010

Postdoctoral Fellowship, The University of Chicago, Chicago, IL, 2011

Research Program.

Dr. Goldschmidt’s research program broadly focuses on the classification, etiology, and psychosocial correlates of pediatric binge eating, and its intersection with obesity. She is especially interested in the phenomenology of binge eating (defined as the consumption of unambiguously large amounts of food accompanied by a sense of loss of control while eating), particularly its hallmark feature, loss of control (the sense that one cannot control what or how much one is eating). Loss of control is strongly associated with obesity and with elevated levels of eating disorder and general psychopathology, yet it is poorly understood and difficult to measure due to its complex nature and to qualitative differences in its presentation. This dearth of research is especially pronounced in youth, despite this population being optimal targets for early intervention.

Dr. Goldschmidt’s research in this area extends back to her undergraduate training, during which she worked with Dr. G. Terence Wilson, a noted expert in the eating disorders and obesity fields. She earned her doctoral degree in clinical psychology from Washington University in St. Louis in 2010, under the mentorship of Dr. Denise Wilfley.
She has been involved with several empirical projects demonstrating the clinical significance of loss of control eating among youth (Goldschmidt, Jones et al., 2008; Goldschmidt, Tanofsky-Kraff et al., 2008), and her work has helped highlight the importance of early identification and treatment of such behavior (Goldschmidt, Aspen, Sinton, Tanofsky-Kraff, & Wilfley, 2008). In particular, Dr. Goldschmidt’s research has shown that the experience of loss of control while eating appears to be a strong marker for psychopathology and distress among individuals with binge eating problems, regardless of eating episode size (Goldschmidt, Engel et al., 2012; Goldschmidt, Jones et al., 2008; see figure 1). These findings have important implications for the current system of diagnosing disorders involving binge eating.

Throughout her training, Dr. Goldschmidt developed a particular interest in studying affective triggers of loss of control eating episodes. To this end, she collaborated on one of the first studies to link loss of control directly to the experience of negative affect in youth (Tanofsky-Kraff et al., 2007). Her dissertation study followed up on these findings by using a novel feeding laboratory paradigm to investigate the role of negative emotions in triggering loss of control eating

Figure 1. The three-way interaction among binge eating disorder status, loss of control, and kilocalorie consumption with respect to post-meal negative affect. Note: BED=binge eating disorder. Higher scores on the y-axis indicate greater negative affect. From Goldschmidt, Engel et al., in press.

Figure 2. Mean overall energy intake during sad and neutral mood conditions among participants with and without binge eating problems. Note: BE=at least one episode of loss of control eating in the past 3 months; CON=no history of loss of control eating. From Goldschmidt, Tanofsky-Kraff, & Wilfley, 2011
episodes among children. This study, funded in part by an Academy for Eating Disorders Student Research Grant, provided support for a relation between mood state and the subjective experience of loss of control while eating in children (Goldschmidt, Tanofsky-Kraff, & Wilfley, 2011): although a negative mood induction did not elicit overeating relative to a neutral mood induction among children with loss of control eating problems (see figure 2), baseline low mood among these children predicted their likelihood of reporting loss of control during a later test meal. More recently, she has also become involved in research using ecological momentary assessment to study “real time” antecedents and consequences of binge eating and other problematic eating-related behaviors in the natural environment (Goldschmidt, Engel, et al., 2012; Goldschmidt, Peterson, et al., in press). She continues to pursue research in this area with the ultimate goal of understanding precipitants to eating disorder behaviors that may one day inform intervention efforts. Current related projects involve examining daily mood and eating patterns in obese adults with and without comorbid depression symptoms (Goldschmidt, Crosby, et al., under review) and identifying event-related antecedents to momentary negative affect among individuals with bulimia nervosa (Goldschmidt, Wonderlich, et al., in preparation).

Dr. Goldschmidt joined the Eating and Weight Disorders Program at the University of Chicago in 2010 under the auspices of an NIH-funded training grant in eating disorders research. During her fellowship, she continued to build her research program in pediatric binge eating and obesity (Goldschmidt, Wall, Loth, Le Grange, & Neumark-Sztainer, 2012; Goldschmidt, Wilfley, Paluch, Roemmich, & Epstein, in press; Goldschmidt, Wilfley et al., 2011), while also pursuing other related research questions in different populations. For example, Dr. Goldschmidt recently published the first study to examine binge eating disorder in normal weight adults. Her findings suggest that psychopathology in binge eating disorder appears to be independent of weight status (Goldschmidt, Le Grange et al., 2011), refuting some investigators’ beliefs that distress and impairment among those with the disorder are simply due to comorbid obesity.

Dr. Goldschmidt joined the faculty at the University of Chicago in 2011 and plans to develop a paradigm for eliciting loss of control in the laboratory, which she hopes will eventually help elucidate neural mechanisms underlying the construct. Her long-term career goals include developing effective treatments targeting both loss of control eating and obesity in children and adolescents.

**Funding.**

NHLBI T32-HL007456: Nutrition-behavioral cardiovascular disease prevention  
PI: Samuel Klein  
2005-2009

Academy for Eating Disorders Graduate Student Research Grant: A laboratory-based study of mood and eating behavior in overweight children  
PI: Andrea Goldschmidt  
2008-2009

NIMH T32-MH082761: Regional postdoctoral training grant in eating disorders research  
PI: Scott Crow  
2010-2011
Selected Publications of Note.


**Jon E. Grant, M.D. (Psychiatry & Behavioral Neuroscience).**  
Dr. Grant is a Professor in the Department of Psychiatry and Behavioral Neuroscience at The University of Chicago. Dr. Grant has been involved in the study of the biology and treatment of impulsive-compulsive behaviors in humans. Currently, he is involved in the use of cognitive neuroscience and neuroimaging to target pharmacological treatment for these behaviors. His newest work relates to the use of novel pharmacological agents – cannabinoid agonists, COMT inhibitors, and glutamatergic agents for gambling disorders, cocaine dependence, skin picking and trichotillomania. In addition, Dr. Grant is examining neurocognitive antecedents for the development of impulsive-compulsive behaviors and early cognitive interventions in young adults at high risk of developing these behaviors.

**Training.**

B.A., University of Michigan, Ann Arbor, MI 1986  
M.A., University of Chicago, Chicago, IL 1987  
J.D., Cornell University, Ithaca, NY 1992  
M.D., Brown University, Providence, RI 1999  
M.P.H., Harvard University, Cambridge, MA 1999  
Residency in General Psychiatry, University of Minnesota, Minneapolis, MN 2003

**Research Program.**

Dr. Grant began his research career while a medical student at Brown University involving phenomenological studies of body dysmorphic disorder. Using these early research skills, Dr. Grant then turned his attention to the field of impulse control disorders during his residency at the University of Minnesota, focusing largely on behaviors such as gambling, sex and stealing. His early original research in this area led to the publication of some of the first articles examining the complex clinical presentation of these behaviors and the recognition that these behaviors shared overlapping clinical phenomenology with substance addiction. Dr. Grant also undertook the first pharmacological studies of these behaviors using medication options that had previously been used to reduce urges in substance addictions. This led to a major paradigm shift with these behaviors being conceptualized as behavioral addictions.

As a junior faculty member at Brown University, Dr. Grant began using neuroimaging techniques, such as diffusion tensor imaging, to better understand the complex biology of these behaviors. In addition, he began to compile massive databases of the clinical features of these behaviors. This work has led in turn to the continued examination of various subtypes within impulsive-compulsive behaviors to explain why certain people benefit from treatment while others do not. At Brown University, Dr. Grant also developed manualized behavioral
treatments for these impulsive behaviors using techniques such as imaginal desensitization. This behavioral treatment has since been used in two NIH-funded research studies and has become the treatment for gambling problems used by the government of South Africa (with whom Dr. Grant collaborates).

Returning to the University of Minnesota as a professor of psychiatry, Dr. Grant began exploring treatments for behaviors that bridged the gap between impulsive and compulsive and this led to a large research program focusing on grooming behaviors such as hair pulling and skin picking. Dr. Grant published the first successful treatment for trichotillomania using N-acetyl cysteine and began using neurocognitive measures to fractionate aspects of impulsivity and compulsivity in these behaviors. This has led to a long-standing international collaboration with Cambridge University.

Since taking a position at the University of Chicago, Dr. Grant has continued his research in the novel pharmacological treatment of impulsive behaviors. He has examined COMT inhibitors and the concomitant use of genetics and neuroimaging to understand the biological basis for treatment response and ultimately the appropriate selection for patients for particular treatments. He has published the first imaging study of skin picking behavior, the first study using genetics and neuroimaging in combination with pharmacotherapy for gambling disorders, and studies of neurocognition underlying a range of compulsive behaviors.

Dr. Grant currently directs a Center of Excellence in Gambling Research at the University of Chicago. This Center allows for the longitudinal, prospective cognitive examination of young adults and their possible development of impulsive behaviors. In addition, the Center examines genetic associations with cognitive measures and is developing novel cognitive, brief interventions to thwart the development of or reduce impulsive behaviors. In addition, Dr. Grant continues to research neuroimaging and neurocognitive correlates of and treatments for a range of impulsive and compulsive behaviors, including deep brain stimulation for obsessive compulsive disorder.

**Funding.**

NIH/NIDA RC1DA028279-02: N-acetyl cysteine plus behavior therapy for nicotine dependent pathological gamblers
   PI: Grant       08/02/2009 – 10/01/2012

NCRG: Center of Excellence in Gambling Research: Susceptibility to Pathological Gambling
   PI: Grant       08/02/2009 – 01/01/2016
Selected Publications of Note (from over 250 peer-reviewed publications).


Hodgins DC, Stea JN, Grant JE. Gambling disorders. Lancet 2011;378(9806):1874-84


Kristen C. Jacobson, Ph.D. (Department of Psychiatry & Behavioral Neuroscience). Kristen Jacobson is Associate Professor in the Department of Psychiatry and Behavioral Neuroscience at The University of Chicago. Through a combination of collaborative and independent studies Dr. Jacobson has developed a program of research that sheds light on the underlying biological pathways through which social and environmental experiences “get under the skin” to affect behavior, which in turn can help to better understand the underlying causes of mental health. Likewise, her research investigating how individual differences, including individual differences in biological and genetic characteristics, moderate the effects of environmental and social factors on behavior can help to inform and design more targeted intervention and prevention programs. Dr. Jacobson is a behavioral geneticist by training, and is currently Co-Associate Director of Twin Projects at the University of Chicago. Her behavioral genetic work has focused primarily on identifying gene X environment (gXe) interactions and on using genetically informative designs to better understand the development and structure of problem behavior. In addition, Dr. Jacobson’s current research uses interdisciplinary approaches to examine the joint interplay of environmental, social, psychological, and biological influences on adolescent development. Newer research interests concern the underlying neurobiology of socioemotional development, the role of oxytocin and vasopressin in sensitivity to social environments, and the influence of human-animal interaction on biology and behavior. As a behavioral scientist, Dr. Jacobson bridges the gap between biological and social sciences. Her research program is unique in that it is highly interdisciplinary, spanning fields of developmental psychology and psychiatry, behavioral genetics, sociology, anthrozoology, neuroscience, and endocrinology.

Training.

A.B., Psychology (cum laude) and English, Cornell University, Ithaca, NY, 1990

M.S., Human Development & Family Studies, Pennsylvania State University, State College, PA, 1994

Ph.D., Human Development & Family Studies, Pennsylvania State University, State College, PA, 1999

Post Doctoral Fellow, Virginia Institute for Psychiatric & Behavioral Genetics, Virginia Commonwealth University, Richmond, VA, 1999-2000

Research Programs.

Behavioral Genetics

Traditionally, behavioral genetics designs rely on studies of identical (monozygotic, MZ) and fraternal (dizygotic, DZ) twins to determine the extent to which genes and
behaviors or traits. Figure 1 shows the standard behavioral genetic model for a single trait. Because identical twins share 100% of their segregating genes and fraternal twins share approximately 50% of their segregating genes, behavioral genetic models can be used to decompose the variation in any given phenotype into three sources: additive genetic factors (A), common shared environmental factors (C), and nonshared environmental factors (E). The proportion of individual differences in a given trait that is due to genetic factors is referred to as the heritability of a trait. Shared environmental factors include those environmental factors that serve to make individuals in a family similar to one another. Common shared environmental influences include socioeconomic status, family structure, and shared peer influences. To be considered a shared environmental influence, the environmental influence must be experienced by both individuals. Thus, shared environmental factors (C) are correlated 1.0 across twins, regardless of whether they are identical or fraternal twins. In addition, the shared environmental influence must have the same influence on behavior for both individuals. For example, the experience of parental divorce is an environmental factor that is shared by two siblings in the same family. However, if one sibling responds to the parental divorce by throwing himself into his studies, and the other sibling responds by acting out and skipping school, then parental divorce is not likely to be a shared environmental influence for the cognitive development of these two siblings. If divorce typically had dissimilar effects on siblings, it would count mostly as a nonshared environmental influence. Nonshared environmental influences are any environmental influences that serve to make individuals dissimilar. Nonshared environmental influences can occur if exposure to the environment is not shared by siblings. For example, birth order, accidents, and different peer groups are nonshared environmental influences. Likewise, as stated above, “shared” environmental factors that have different influences on behavior for individuals are considered nonshared environmental factors, as are measurement errors, which are assumed to be random and uncorrelated across twins. By definition, nonshared environmental factors do not correlate across twins.

*Behavioral genetics within an ecological framework*

While the importance of genetic influence on individual differences in personality, behavior, and mental and physical health is now widely accepted, Dr. Jacobson’s early behavioral genetic studies challenged the notion that heritabilities are the same for
For example, she discovered that the importance of genetic factors on adolescent body mass index varied as a function of both gender and race/ethnicity (Jacobson & Rowe, 1999). Likewise, her collaborative research was the first to show that the heritability of cognitive ability varies among individuals in different socioeconomic contexts (Rowe, Jacobson, & van den Oord, 1999). As seen in Figure 2, the heritability of verbal IQ is greater among adolescents whose parents are more highly educated. Among highly educated families, the heritability of verbal IQ was .76, and shared environmental effects were negligible. In contrast, among less well-educated families, shared environmental factors accounted for a significant proportion of variance (23%), and genetic factors accounted for only 26% of the variance. Results from this paper have been widely replicated in other samples of children and adolescents, and the socioeconomic moderation of genetic factors on cognition is considered one of the best examples of gene X environment (gXe) interactions in twin studies.

Interestingly, follow-up work examining whether the heritability of cognitive ability varies across socioeconomic context in studies of older adults has not found evidence for gXe interactions. In a study of word recognition in middle-aged male twins from the Vietnam Era Twin Registry (VETR), Dr. Jacobson found that while the importance of shared environmental factors was higher among adults from less well-educated families, there was no difference in the importance of genetic factors (Kremen, Jacobson, et al., 2003). A more recent study using the VETR sample also failed to find any evidence for moderated genetic or environmental influences on general cognitive ability in early adulthood (Grant, et al., 2010). The discrepancy in results among studies of children and adolescents versus studies of adults suggests the intriguing possibility that there may be a critical period of development during which early environmental experiences can alter genetic programming of cognition. Recently, Dr. Jacobson tested this hypothesis directly using longitudinal data from the twin/sibling sample of the National Longitudinal Study of Adolescent Health (Jacobson &
Vasilopoulos, under review). This study, which was a replication and extension of results reported in Rowe et al. (1999), found that, as predicted, parental education moderated additive genetic influences (A) on Peabody Picture Vocabulary (PPV) in adolescence (Wave 1) but not in young adulthood (Wave 3) (see Figure 3). In addition, the effects of shared environmental factors (C) were markedly weaker in young adulthood, consistent with other longitudinal research.

These results suggest that the importance of childhood environmental factors on individual differences in cognitive ability decreases over time, and also that childhood environmental factors “lose” their ability to modify genetic influences on adult phenotypes. However, recent work from Dr. Jacobson’s laboratory indicates that untreated hypertension suppresses genetic influence on cognitive ability among middle aged male twins (Vasilopoulos, et al., 2012b), indicating that the types of environmental factors that can disrupt genetic programming of cognition may vary across the lifespan.

Behavioral genetics and the development and structure of problem behavior

Dr. Jacobson also uses multivariate behavioral genetic models to better understand the development and structure of problem behavior. One of her early papers was the first to report that the heritability of conduct disordered behavior has decreased over time, due primarily to an increase in the importance of shared environmental factors among twins born in more recent cohorts (Jacobson et al., 2000).

Another paper showed that the importance of genetic factors on antisocial behavior varies as a function of both gender and age. As can be seen in Figure 4, genetic influence on antisocial behavior increases from childhood to adolescence and adulthood, and the increase in heritability occurs earlier among females than males (Jacobson et al., 2002). These findings suggest that physiological and/or social factors associated with puberty may “turn on” genes related to antisocial behavior, a hypothesis Dr. Jacobson is currently testing in other samples.

Dr. Jacobson has further combined multiple measures of problem behaviors into single multivariate behavioral genetic models to better understand the structure of problem behavior. In a paper published in the American Journal of Psychiatry, she found that common genetic factors accounted for most of the comorbidity between different types of substance use and misuse among adult male twins in the Virginia Twin Registry (Kendler, Jacobson, Prescott, & Neale, 2005). With Laura Baker at the University of Southern California, she discovered that combing reports of childhood problem
behaviors from parents, children, and teachers results in higher heritabilities than analyses based on only a single reporter, supporting strong genetic influence on shared views of problem behavior (Baker, Jacobson, et al., 2007). Recent work with the Pennsylvania Twin Cohort sample has revealed that different aggressive behaviors are underpinned by two distinct etiological factors with different genetic and nonshared environmental influences (Yeh, Coccaro, & Jacobson, 2010).

Relatedly, multivariate behavioral genetic models including both psychosocial variables and behavioral outcomes have begun to shed light on processes of gene-environment interplay in the development of problem behaviors. For example, Jacobson & Rowe (1999) found that the relationship between attachment to family, attachment to school, and adolescent depressed mood is explained in large part by common genetic factors. Work done with colleagues at VCU has implicated a complex pattern of genetic and environmental influences on longitudinal relationships between peer group deviance and conduct disordered behavior (Kendler, Jacobson, Meyer, & Eaves, 2008) and peer group deviance and cannabis use (Gillespie et al., 2009).

In 2003, Dr. Jacobson received a Mentored Scientist Training Award (K01) from the National Institutes of Mental Health to examine the role of genetic and environmental influences on biological measures that may serve as endophenotypes for antisocial and related problem behaviors. She has been involved in projects investigating the underlying genetic and environmental architecture of physiological measures (e.g., Crider et al., 2004; Tuvblad et al., 2010) and cortisol response (e.g., Franz et al., 2010), and she has been a long-time collaborator on the Vietnam Era Twin Study of Aging (VETSA), which includes analysis of genetic and environmental influences on brain structure related to cognitive aging (e.g., Kremen et al., 2010; Panizzon et al., 2009, 2012). One of her recent postdoctoral trainees has used the VETSA sample to better understand relationships among physical health and cognitive function in older adults (Vasilopoulos et al., 2012a, 2013). Finally, Dr. Jacobson is a Co-Investigator on Dr. Emil Coccaro’s NIMH-funded study, Pathways to Aggression, which is collecting functional magnetic resonance imaging (fMRI) data from over 200 pairs of twins from the Pennsylvania Twin Cohort to better understand how genetic factors influence socioemotional processing related to aggressive behavior.

Example Publications:


Multiple Levels of Influence on Adolescent Problem Behaviors

Dr. Jacobson’s work is greatly influenced by the Bioecological Model developed by Dr. Urie Bronfenbrenner, whom she was privileged to work with after college. This model has guided her research examining influences on youth problem behaviors at different ecological levels, including neighborhood, school, peer, family, and individual psychosocial, biological, and genetic factors. Bronfenbrenner’s multi-layered model highlights not only the importance of measuring environmental, biological, social, and genetic factors at multiple levels of analysis, but also the importance of unique person and environmental characteristics as potential moderators of the relationship between family processes and adjustment.

As part of her graduate work at Penn State, Dr. Jacobson applied Bronfenbrenner’s Ecological Model to examine person and context moderators of the relationship between family processes and adolescent adjustment. Part of this research focused on gender, age, and maternal work status as moderators of the relationship between parental monitoring and adolescent delinquency. She found that effective parental monitoring had a greater impact on adolescent delinquency among older adolescents compared to younger adolescents among males, but that the reverse was true for females (Jacobson & Crockett, 2000). She also found that parental monitoring had a stronger association with adolescent delinquency and sexual behaviors when adolescents had mothers who were employed full- or part-time, suggesting that effective parental monitoring might compensate for a lack of direct supervision (Figure 5).
Dr. Jacobson’s interest in applying ecological models to understand individual differences in development has continued throughout her career. Recently, her lab published a paper showing that children high on psychopathy are less responsive to parental affect than children with low levels of psychopathic traits (Yeh, et al., 2011). As shown in Figure 6, 9-10 year old children with high levels of psychopathy are less responsive to variations in both positive and negative parental affect than children lower on psychopathology. This novel finding suggests that psychopathy is related to overall deficits in processing of emotional stimuli, and not just to deficits in the processing of negative (aversive) stimuli. Another of her postdoctoral fellows has conducted a series of projects looking at interactions between individual and environmental characteristics on adult aggression, and found that the relationship between hostile attribution bias and aggression in adults is moderated by levels of impulsivity (Chen et al., 2012a) and that exposure to childhood trauma alters the relationships between measures of social information processing and aggression (Chen et al., 2012b).

Figure 6. Interactions between Child Psychopathic Traits (CPS) and Parental Positive and Negative Affect

From Neighborhoods to Neurons and Beyond

In 2007, Dr. Jacobson received an NIH Director’s New Innovator Award to conduct a multi-phase study investigating how community- and school-level factors moderate biological and psychosocial influences on individual differences in adolescent behavior. This project generated the “Neighborhoods to Neurons and Beyond” (NNB) cohort.

In Phase I, Dr. Jacobson obtained in-school survey data from N=3,350 6th-8th graders across 14 public schools in the Chicago area. Individual schools were selected to maximize racial/ethnic and socioeconomic variation. 40.4% of NNB youth were in schools with high racial/ethnic variation, 34.2% in minority schools, including predominantly African American (15.0%) and predominantly Hispanic schools (19.2%), with the remaining 25.5% in predominantly Caucasian schools. Schools differed in the % of students eligible for free meal programs (a marker for SES), ranging from 7-80% (M=44.0%). Importantly, there was variation in SES among African American (34-80%) and mixed race/ethnicity (21-62%) schools, with less variation among Hispanic (65-70%) and Caucasian (7-17%) schools. Phase I also include data from an additional
N=232 youth who were enrolled in private/Catholic schools. **Phase II** was an in-lab, follow-up, family study of N=241 youth quasi-randomly selected from the NNB cohort. Phase II obtained detailed self-report and interview data on youth behavior and individual and contextual factors, as well as biological and behavioral measures described below. Data were collected from N=241 Phase I youth, their primary caregivers (77.1% biological mothers), and N=137 siblings aged 10-18.

Data collected during Phases I and II include self-report measures on risk/protective factors and youth problem behaviors. Phase II included caregiver reports of family history of psychopathology, demographic characteristics, and youth behavioral problems, and expanded the self-report measures in youth. In addition, youth in Phase II participated in a series of objective, behavioral tasks assessing decision-making (i.e., the Delay Discounting task), impulsivity (e.g., the Go/No-Go task and Balloon Analog Task), stress response (e.g., the Countdown task), and socioemotional processing (e.g., recognition of emotional FACES and affective pictures from the IAPS paradigm). Dr. Jacobson also added measures of empathy and prosocial behavior to the NNB Phase II cohort to look at both positive and negative youth outcomes, and collected plasma to use for baseline measures of oxytocin from N=265 youth and N=59 biological mothers. These samples were assayed by Dr. Sue Carter, one of the world’s leading experts in the study of neuropeptides. At present, NNB is the largest sample of baseline oxytocin data in youth. In addition, a subset of N=40 NNB youth participated in an fMRI study of emotion recognition and empathy (**Phase III**) through collaboration with Dr. Jean Decety, and blood was collected from all NNB youth and their parents for use in later genetic and epigenetic analyses.

**Associations between exposure to community violence and youth outcomes**

Exposure to community violence is one of the strongest predictors of youth outcomes in the NNB sample. During Phase I, NNB youth indicated if they had been exposed to 3 violent events (seen someone shot/stabbed, had someone pull a weapon on them, been jumped) and the frequency at which they heard gunshots during the past month, combined into a single yes/no index of community violence exposure (CVE). 34% of the NNB cohort reported exposure to one or more of these events; percentages of youth within a given school who reported CVE ranged from 15.2-74.2%. The CVE measure was also used in the Phase II study. In both studies, exposed youth showed poorer outcomes (effect sizes range from $d = 0.25$ to $d = 0.96$), including higher rates of delinquency, aggression, depressed mood, and illegal substance use, and lower levels of prosocial behavior and empathy, even after controlling for age, gender, race/ethnicity, and socioeconomic factors. Exposed youth reported significantly ($p < .001$) higher levels of parent-child conflict ($d = 0.75$), providing support for correlations of exposure to violence across both community and family levels. In a manuscript under review (**Jacobson & Chen, under review**), youth reporting CVE ($b = -0.08$, $p<.05$) showed smaller area-under-the-curve (AUC) during the Delay Discounting task, indicating that they were more likely to devalue future rewards relative to immediate rewards. Moreover, the relationship between CVE and AUC was stronger for youth aged 14 and older (**Figure 7**), consistent with current theories on relationships between
developmental changes in brain structure and function, decision-making, and youth risky behavior. The fact that CVE may alter youth’s cognitive and emotional capabilities that underpin risky behavior is the basis for a follow-up R01 grant application submitted to NIDA (currently under review), where new longitudinal data would be collected from the NNB Phase II cohort to determine the extent to which CVE (and other risk factors) alter both behavioral and neurobiological indicators of decision-making that predict trajectories of youth sexual risk and substance use behaviors.

Given the significant negative effect of CVE on youth outcomes, a recent manuscript (Chen, Voisin, and Jacobson, in press) examined whether promotive factors across different ecological levels (i.e., future hopefulness, family warmth, school attachment, and neighborhood cohesion) moderated relationships between CVE and youth delinquency in N=2,980 youth from the Phase I NNB study (M_{age}=12.5; 41.1% males). After controlling for demographic factors, delinquency was positively associated with CVE and inversely associated with each of the promotive factors. When interaction effects between all promotive factors and CVE were examined simultaneously, only future hopefulness moderated the relationship between CVE and delinquency. Specifically, CVE had a weaker association with delinquency for youth reporting high levels of future hopefulness in comparison to those with low levels of future hopefulness (Figure 8). At the same time, promotive factors from other domains are also important. For example, a second paper from the NNB study found that family factors were especially important in reducing delinquency among impulsive youth (Chen & Jacobson, in press). Specifically, parental knowledge had a stronger association with decreased levels of delinquency for adolescents reporting higher levels of impulsivity, compared with youth reporting lower levels of

![Figure 7. Effects of Exposure to Violence on Objective Measures of Decision Making: Moderating Effects of Age](image)

![Figure 8. Future Hopefulness & Youth Exposure to Violence: Joint Effects on Adolescent Delinquency](image)
impulsivity. In addition, the inverse relationship between family warmth and delinquency was significant for adolescents with high levels of, but not for those with average or below-average levels of impulsivity.

**Oxytocin as a potential biological marker of youth sensitivity to social environments**

Dr. Jacobson is currently testing the novel hypothesis that the neuropeptide oxytocin (OT) may serve as a biological marker of youth sensitivity to social environments. Prior research in other labs has shown that OT administration enhances affiliative behaviors, suppresses production of cortisol during physical or psychological challenges, and reduces psychological distress. OT is also implicated in social and affective disorders. Clinical studies have shown decreased levels of OT in adult patients with depression and studies have found that trauma predicts lower levels of basal OT in adults. However, emerging evidence suggests that, under certain conditions, oxytocin may increase *maladaptive* social behaviors (e.g., aggression), indicating that the effects of oxytocin may be sensitive to environmental and social conditions. Analysis of the first N=179 baseline OT samples from Phase II NNB youth revealed that OT is unrelated to CVE or youth behavioral or emotional problems. However, OT correlates with youth reports of attachment to mothers ($r = 0.23$, $p < .05$), validating this measure of OT as a potential biological indicator of social affiliation. In addition, OT interacted with peer deviance to predict youth reports of aggression, attention problems, and anxious/depressed symptoms from the CBCL, but did not interact with peer deviance to predict delinquency. Specifically, youth with higher levels of OT and higher reports of peer deviance show the greatest levels of problem behavior (*Figure 9*), and the relationship between peer deviance and negative outcomes was stronger for youth with higher levels of OT.

*Figure 9. Oxytocin (OT) as Modulator of Associations between Peer Group Deviance (PGD) and Youth Problem Behaviors*

**Example Publications:**


Research on Human-Animal Interactions

Dr. Jacobson’s lab is also investigating the effects of human-animal interaction (HAI) on youth biology and behavior, funded by the NICHD. In one study, detailed measures of pet ownership, attitudes towards pets, and attachment to family dogs were added to the Phase II NNB study. In this project, attitudes towards pets and attachment to family dogs are correlated with youth empathy and prosocial behavior, and that these associations with youth socioemotional development are as strong (or stronger) than the effects of positive family, school, and neighborhood characteristics (Jacobson, forthcoming). At the same time, the causal effects of HAI have yet to be determined. For example, a recent publication by Dr. Jacobson showed that individual differences in the frequency of playing with pets in middle aged male twins was due, in part, to genetic factors, and that the impact of shared environmental factors, which would include childhood exposure to pets, was negligible (Jacobson et al., 2012). Likewise, characteristics of both human and the animal are likely to influence attachment to family pets and the potential positive impact of HAI. A forthcoming publication by one of Dr. Jacobson’s postdoctoral trainees found that attachment to family dogs varied systematically as a function of specific canine behavioral characteristics, including trainability, separation problems, excitability, and attention-seeking behaviors (Hoffman et al., in press).

Currently Dr. Jacobson is conducting a study of the effects of HAI on prosocial behavior and stress reactivity in N=120 young adults aged 18-25. Subjects are brought into Dr. Jacobson’s lab for two separate visits. During the second visit, subjects participate in a brief interaction with a trained therapy dog. Subjects also complete several prosocial behavior paradigms, and participate in the Trier Social Stress Test, with the order of tasks counterbalanced across subjects. Plasma samples are taken before and after the HAI to determine whether interacting with a therapy dog increases oxytocin levels. The primary research hypotheses are that HAI will increase prosocial behavior and decrease
biological markers of stress responsivity (i.e., physiological measures and cortisol response), and that the positive effects of HAI will be increased among subjects with a history of positive childhood exposure to dogs.

Example Publications:


**Funding.**

**Current Projects:**

- NIH/NICHD R03 HD070679: *Long-term benefits of child dog ownership: Effects on stress and social behavior*
  PI: Jacobson  01/01/12-12/31/13
- NIH/NICHD R03 HD066598: *They Call it Puppy Love: Epidemiology and biology of the child-dog bond*
  PI: Jacobson  07/01/10-06/30/13
- NIH/NIA R01 AG018386: *VETSA 2: A longitudinal twin study of cognitive aging*
  PI (subcontract): Jacobson  09/15/08-08/31/13
- NIH/NIMH R01 MH080109: *Understanding the pathways to aggression*
  PI: Coccaro  04/16/08-03/31/13
- University of Chicago CTSA-ITM: *Core Subsidy Award*
  PI: Jacobson  09/01/12-05/31/13

**Selected Past Projects:**

- NIH/OD DP2 OD003021: *From Neighborhoods to Neurons and Beyond*
  PI: Jacobson  09/30/07-08/31/12
- BRF Seed Grant: *A Pilot Study of genetic and environmental influences on amygdala and dorsal anterior cingulate cortex activation: A Twin Study of fMRI*
  PI: Jacobson  06/01/07-05/31/08
- NIH/NIA R01 AG022982: *VETSA longitudinal twin study of cortisol and aging*
  PI (subcontract): Jacobson  09/30/06-06/30/09
- NIH/NIMH R01 MH058354: *Development of conduct problems: Genetic and environmental interface*
  PI (subcontract): Jacobson  01/05/06-06/30/11
- NIH/NIMH K01 MH068484: *Genetics of vulnerability to antisocial behavior*
  PI: Jacobson  09/15/03-08/31/07
Sarah K. Keedy, Ph.D. (Psychiatry & Behavioral Neuroscience). Dr. Keedy is Assistant Professor and Associate Director of the Cognition and Emotion Neuroscience Laboratory in the Department of Psychiatry and Behavioral Neuroscience. She is a licensed clinical psychologist with specialization in neuropsychology, and the majority of her work is to conduct research on neurocognitive processes in psychotic disorders. In addition to trying to uncover functional neuropathology underlying psychotic illnesses such as schizophrenia and bipolar disorder, Dr. Keedy also tracks effects of antipsychotic medication on neural systems to help enhance our understanding of its efficacy as well as its limitations. Currently antipsychotic treatment is only effective for positive symptoms such as hallucinations, whereas other symptoms, particularly cognitive impairments, remain some of the more debilitating aspects of the illness. Gaining a clearer understanding of how antipsychotics affect brain function is key in the process of determining how best to improve treatment approaches. Dr. Keedy’s general approach to addressing these overarching aims is to examine cognitive task performance along with *in vivo* measures of brain function – namely functional magnetic resonance imaging (fMRI) and high density electroencephalograms (EEG). The basic study design is to track psychosis patients from acute illness phases and to post-acute phases where antipsychotic treatment is initiated or altered.

Training
B.S. with Honors, Psychology, Oklahoma State University, Stillwater, OK, 1996

Ph.D., Clinical Psychology, Rosalind Franklin University of Medicine and Science, North Chicago, IL, 2004

Clinical Psychology Internship, Jesse Brown Veterans Administration Medical Center, Chicago, IL, 2004

Postdoctoral Research Associate/Clinical Neuropsychology Fellow, University of Illinois at Chicago; Chicago, IL, 2006

Research Program

Much of Dr. Keedy’s work has specifically addressed attention and sensory processing in schizophrenia, which has been of interest for decades due to perceptual symptoms in the illness such as hallucinations. Dr. Keedy includes both bottom-up and top-down assessments of sensory processing in her research program, as even a brain function as seemingly straightforward as sensory information processing is subject to
both the complexities of regulation from local circuit features (bottom-up) and more distant connections with executive control systems (top down). As evidence suggests each of these mechanisms may be aberrant in psychosis, Dr. Keedy aims to determine relationships between these two general processes, and to relate them specifically to hallucination severity. Another aim of Dr. Keedy’s work is to assess these neurocognitive processes in both affective and nonaffective psychotic disorders. While the classic psychotic disorder is schizophrenia, bipolar disorder with psychosis and schizoaffective disorder patients are also part of the research studies, to determine whether similar pathophysiology underlies similar symptoms, e.g., do patients along this psychosis spectrum (schizophrenia-schizoaffective-bipolar) with hallucinations exhibit similar pathophysiology? Is it a matter of symptom severity?

A significant portion of Dr. Keedy’s prior work has been conducted in the context of first episode schizophrenia studies. Such work is advantageous for answering questions about illness pathology without the confounds of prior medication exposure or other chronic illness concerns such as substance abuse. In first episode studies, patients presenting for clinical care early in the course of their illness, often for the first time, are recruited and assessed with a variety of neurocognitive measures before they begin medication. They are then re-tested about 4 weeks after initiating antipsychotic treatment. One major aspect of these studies is to have such acutely ill patients participate in (fMRI) studies. In addition to accumulating technological and clinical expertise over her years running these imaging studies with patients, in 2006, Keedy and colleagues published the first paper examining unmedicated first episode schizophrenia patients while they performed a variety of eye movement tasks during scanning. Indeed, this paper was among the first to report task-based functional imaging of any kind in first episode schizophrenia patients, though technologically at the time, scan coverage was limited to only the dorsal cortex. Significant neocortical activation deficits were found in the untreated schizophrenia patients for all eye movement tasks. Underactivation was found specifically in the frontal and supplemental eye fields and superior parietal cortex. They were particularly pronounced for a visually guided saccade task examining basic attention and sensorimotor responding (following a dot on a screen; Fig 1). Dorsolateral prefrontal cortex activation was also significantly underactivated during the oculomotor delayed response task (Fig 2), a spatial working memory task where patients traditionally show performance impairments. Dr. Keedy and her colleagues have written about the advantages of these eye movement paradigms for clinical patient studies, emphasizing that their translational nature assists with clearer

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**Fig. 1.** Differences in activation between unmedicated schizophrenia patients and matched healthy controls (t values) performing a visually-guided saccade task ($t = 47$), overlaid on the overall group average anatomical image. Colored voxels were those surviving the contiguity threshold that preserved a type I error rate at $p < .025$. Healthy controls display greater activation in frontal and supplementary eye fields (FEF, SEF), the precuneus gyrus, and in the intraparietal sulcus (IPS). From Keedy et al., 2006.
interpretation of the data, as knowledge is well established regarding the neural circuitry supporting these tasks, via prior work in animals and human lesion reports (Sweeney et al., 2007; Reilly et al., 2008). These deficits in brain activation across tasks imply reduced attentional/top down regulation from neocortex in saccade control.

Dr. Keedy replicated the finding of underactivation during the visually guided saccade task in unmedicated first episode schizophrenia patients, and extended the work to full brain scans and a longitudinal design, where patients were re-scanned after 4 weeks of second generation antipsychotic treatment (Keedy et al., 2009; Fig. 3). After treatment, schizophrenia patients had improved activation in those neocortical regions associated with attentional control of saccades (frontal eye fields and parietal cortex), but there was continued abnormality in primary and secondary sensory cortex not seen in the first study due to limited coverage of the brain. There were also new activation deficits seen in the caudate, dorsomedial thalamus, and dorsolateral prefrontal cortex. These latter structures together comprise a circuit crucial for higher cognitive operations, and the dorsal caudate is of particular interest as it is the direct target of antipsychotic medication given its concentration of D2 dopaminergic receptors. Affinity for D2 is the best correlate of antipsychotic efficacy, but the mechanisms beyond that remain poorly understood. The observations from this longitudinal study provide insight into both beneficial and potentially adverse effects of antipsychotic treatment on functional neural systems. The pretreatment deficits – reduced frontal and supplementary eye field activation – were no longer observed posttreatment, consistent with improved top down attentional control, as also suggested by laboratory studies of visually guided saccades where patients are abnormally fast prior to treatment but after treatment, slow down (e.g., are more controlled; Reilly et al., 2006). The post-treatment dorsal prefrontal cortex and associated circuitry activation deficit suggests effects of antipsychotic treatment on neural systems supporting behavior
may not only lack efficacy for cognitive enhancement, but may also work against some aspects of improved cognitive function. By contrast, antipsychotic treatment had no such apparent impact on brain function supporting smooth pursuit eye movements in first episode schizophrenia patients (Lencer, Keedy et al., 2011). For this latter task, prefrontal activation was actually abnormally increased before treatment, a possible compensatory activation pattern, but an altogether different pattern of findings. The reliance on prefrontal cortex by patients for smooth pursuit, alongside a lack of such compensation for visually guided saccades, suggests this may be a key difference in whether antipsychotic treatment will have an appreciable impact on functional neural systems. The sensitivity of visually guided saccades during fMRI studies of patients...
before and after antipsychotic treatment may be an important biomarker and requires further study.

The continued heightened activation in sensory cortex noted even after treatment in the visually guided saccade task (Fig 3, bottom row blue) spurred Dr. Keedy’s interest in aberrant sensory processing in acute psychosis and the potential to assess it in fMRI studies. Currently she is conducting studies investigating how well psychosis patients show modulation of task-irrelevant sensory system responding when their attention is focused on something else, such as an eye movement task as described previously or a more conventional sustained attention paradigm such as a continuous performance task. This is a novel, testable model of top down regulation of sensory processing emphasizing peripheral sensory information regulation, and is a novel use of fMRI for such a question, as traditionally EEG methodologies have dominated similar lines of inquiry. In addition to testing unmedicated first episode patients with this paradigm (in collaboration with Dr. John Sweeney at the University of Texas Southwestern Medical Center), acutely psychotic patients with poor treatment response who are switching medications or increasing doses and other such treatment change scenarios will also be followed to better assess the neurophysiology of acute psychosis itself. Parallel EEG studies and additional cognitive batteries are administered to capture a complete picture of relevant neurocognitive functioning.

A final component of Dr. Keedy’s research program is her development of a detailed interview for hallucination severity. With this, the sensitive neurocognitive measures (fMRI, EEG) may be more clearly associated with the clinical presentation of hallucinations. Particular aspects may be more strongly associated with neurophysiological abnormalities than others (frequency, distress, negative content, etc.). Hallucination severity is a poorly-fleshed out concept, and the full picture of the phenomenology of hallucinations with respect to patients’ experiences of different sensory modalities may be informative in understanding not only their illness presentation but the relationship between the symptom and underlying neuropathology.

**Funding**

NIH/NIMH K23MH092702: Antipsychotic Effects on Top Down Attentional Control of Sensory Processing in Schizophrenia

PI-Keedy 01/01/11-12/31/15

NARSAD Young Investigator Award: Attention-Modulated Sensory Processing in First Episode Psychosis

PI-Keedy 01/01/10-12/31/11 (NCE)
Selected Publications of Note


Kathryn Keenan, Ph.D. (Psychiatry & Behavioral Neuroscience). Dr. Keenan is a Professor of Psychiatry and Behavioral Neuroscience at the University of Chicago. Dr. Keenan's program of research in developmental psychopathology spans several developmental periods and types of disorders. The integrative thread running through each study is the aim of identifying the earliest appearing individual differences that connote risk for psychopathology, and the environmental factors that are associated with the transition from risk to the expression of a disorder. The work is designed to be relevant to the understanding of etiological mechanisms and to the development of clinical assessment strategies and early intervention, and prevention.

**Training.**


M.S. Clinical Psychology, University of Pittsburgh, Pittsburgh, PA, 1993.

Ph.D., Clinical Psychology, University of Pittsburgh, Pittsburgh, PA, 1995.

**Research Program.**

Dr. Keenan's developmental psychopathology research program spans several developmental periods and types of disorders.

**Early Life Stress and Mental Health.**

The aims of this program are to determine the earliest point at which patterns of stress reactivity early in development, as measured by neuroendocrine and behavioral response to stimuli, are predictive of psychopathology. This is being tested in a sample of 100 healthy African American neonates whose families were living in low-income environments. Although children living in low-income environments are at higher risk for developing psychopathology, the vast majority of such children do not. Thus, poverty is a non-specific risk factor. We are interested in determining for which children does living in poverty connote risk.

Our work has focused on testing operational definitions of atypical stress reactivity (Keenan, Grace, & Gunthorpe, 2003), and identifying early factors associated with individual differences in stress modulation in the first hours of life. As shown in Figures 1-2, above average levels of behavioral distress to a social stimulus and below average levels of behavioral distress to a painful stimulus was associated with very different patterns of cortisol response. These are the first data to provide empirical support for context specific-definitions of atypical stress reactivity in the human.
Figure 1. Average changes in cortisol in response to the NBAS as a function of level of high behavioral distress. Quadratic effect for high distress group by repeated measures ANOVA ($F(1.37, 30.23)=6.14$, $p=.01$, $\eta^2=.46$), no significant change for average to low distress group.

Figure 2. Average changes in cortisol in response to the heel stick as a function of level of low behavioral distress. Interaction effect tested by repeated measures ANOVA: $F(1.2, 72.8)=4.88$, $p=.024$, $\eta^2=.27$.

From 2003-2006, Dr. Keenan participated in an NIMH sponsored Level I Translational Science Network to study perinatal experience and children’s mental health. The network included scientists using a variety of models to study the effects of prenatal stress on the development of the hypothalamic-pituitary-adrenal axis in the offspring. The network continues to work together via several conceptually linked R21 applications. In one, we are testing whether DHA supplementation during pregnancy among women living in poverty who report low fish consumption improves regulation of stress during pregnancy and infant outcomes. As shown in the model depicted below (figure 3), we will conduct a preliminary test of whether maternal psychosocial stress during pregnancy (1) and an increase in maternal cortisol response to stress (2) is associated with poor infant modulation of cortisol in response to stress (5). The hypothesized increase in fetal cortisol (3) and alterations in fetal stress architecture (4) are not directly tested in this exploratory study. Establishing an association between maternal psychosocial stress and modulation of cortisol response to stress and infant outcomes, and, more importantly determining if DHA supplementation moderates that association is a necessary first step. If the data support the model, then we will embark on a larger study aimed at testing whether a reduction in exposure to maternal glucocorticoids, an increase in availability of maternal DHA, or both, account for variance in infant outcomes.
In the second, we are testing the impact of suboptimal nutrition during pregnancy on neurodevelopmental outcomes in the baboon. This project is headed by colleagues at The University of Texas at San Antonio and the University of Texas Health Science Center. The goal is to generate data to determine whether there is the potential to use nutritional intervention to moderate the association between prenatal stress and the mental health of children.

**Publications on Early Life Stress and Mental Health.**


Figure 4. Average rating of functional impairment over time as a function of CD diagnostic status. Significant effect of time by diagnostic status on impairment ($F(4,181)=6.47, p<.001, \eta^2=.35$).

Preschool Disruptive Behavior Disorders.

A second area of research is testing the validity of diagnostic constructs in early childhood, specifically oppositional defiant and conduct disorders (ODD and CD). These are prevalent disorders of childhood and are the most common reason for referral for services. Although field trials were conducted in preparation for the most recent version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), children under 6 years were not well represented, raising important questions about the validity of the diagnoses of ODD and CD in younger children. Because a substantial number of preschool age children present for mental health services it is necessary to know the age at which one can validly diagnose ODD and CD. The preschool period is an important developmental period in which to test diagnostic validity because many of the behaviors comprising the symptoms of ODD and CD, such as aggression and noncompliance, are common and not pathognomonic in and of themselves. Therefore, whether we can differentiate typical from atypical manifestations of these behaviors is
an important empirical question. If we can validly apply these diagnostic constructs to preschoolers, then it is likely that the etiologic underpinnings of ODD and CD exist much earlier in development than has been thought. Our findings to date support the concurrent and predictive validity of DSM-IV ODD and CD in preschool children. For example, we tracked the level of impairment among preschoolers who did and did not meet criteria for CD at baseline. As shown in Figure 4, preschoolers who met criteria for CD were more impaired over time. Moreover, preschoolers who would go on to have a chronic course of CD were the most impaired, even at the baseline assessment.

**Publications on Preschool Disruptive Behavior Disorders.**


**Funding for Preschool Disruptive Behavior Disorders.**

- NIH/NIMH R01 MH62437: Validity of preschool disruptive behavior disorders
  PI: Kate Keenan  Funded: 04/01/2002-03/31/2007
- NIH/NIMH R01 MH68455: Observational measurement of preschool behavior problems
  PI: Lauren Wakschlag  Funded: 04/01/2004-01/31/2009
- CIHR 222306: The origins of gender differences in disruptive behavior problems
  PI: Raymond Baillargeon  Funded: 07/01/2008-06/30/2011

**Developmental Psychopathology in Girls.**

In collaboration with faculty at the Western Psychiatric Institute and Clinic at the University of Pittsburgh, the NIMH-funded Pittsburgh Girls Study is designed to identify precursors to conduct disorder in girls by conducting annual assessments of girls who at the start of the study ranged in age from 5-8 years. Additionally, we aim to test hypotheses regarding the validity of diagnostic nosology of CD for girls.

In preparation for the DSM-V, we have provided the first prospective assessment of the prevalence and age of onset of CD in girls in a community sample. In the present sample, DSM-IV CD symptoms were assessed in girls from ages 7-15 years by parents and youth. It was found that the lifetime, weighted prevalence of CD was 21.2%, the prevalence across age ranged from 4.9-8.9%, and the most common age of onset was prior to the age of 10 years. Approximately half of the more than 500 girls who met criteria for CD in at least 1 year during the period of assessment were reported to have manifested the first symptom at 7 years of age, and close to 90% who met DSM-IV criteria for CD had an onset before age 10.
A more common outcome for girls than antisocial behavior, however, is depression. In order to take advantage of this representative sample of girls in Pittsburgh, funding was obtained from NIMH to conduct a study on preadolescent precursors to depression in girls. A predominant view is that increases in rates of depression in girls during adolescence result from newly encountered risk factors that are primarily specific to adolescence such as the physical and psychological changes associated with pubertal development and emerging autonomy. The fact that most of these experiences are common to all females (e.g., pubertal development), however, argues for a broadening of the current developmental models to include characteristics that can be identified earlier in development (i.e., preadolescence) that may lead to the development of depression during the transition to adolescence.

Results from this study demonstrate that depressive disorders during adolescence likely have an insidious onset that is measurable in the preadolescent period. For example, the odds of meeting criteria for depressive disorders and for demonstrating impairment at ages 10 or 11 increased by 1.9 and 1.7, respectively, for every increase in the number of depression symptoms reported at age 9. These data are evidence of significant morbidity associated with preadolescent depressive symptoms and disorders in girls.

In addition, we are probing the unfolding of the relations between depression and pain in girls with the goal of revealing a developmental link between early individual differences in pain sensitivity and later risk for depression. Individual differences in pain tolerance and threshold are measured using a cold pressor task. Results thus far demonstrate that low threshold and tolerance for pain at age 10 is associated with depressive symptoms at ages 10 and 11, even after controlling for earlier depression symptoms. Interestingly, race and pubertal stage moderate the association. For example, as shown in Figure 5, pain tolerance and depression symptoms were more strongly associated among European American girls compared to African American girls.

**Figure 5.** Interaction between race and pain tolerance on youth reported symptoms of depression at age 10 (n=224): $B = .007$, Wald $\chi^2 = 4.91$, $p < .05$), model fit measured by the likelihood ratio chi-square ($\chi^2 [9] = 59.10$, $p < .001$). Difference in depression symptoms between African American girls with low (mean = 1.7) and average to high (mean = 1.4) pain tolerance. Difference in depression symptoms for European American girls with low (mean = 1.4) and average to high (mean = 0.6) pain tolerance.
Publications on Developmental Psychopathology in Girls.


**Funding for Developmental Psychopathology in Girls.**

- NIH/NIMH R01 MH56630: Development of Conduct Disorder in Girls
  
  PI: Rolf Loeber
  Funded: 09/30/1998-09/30/2013

- NIH/NIMH R01 MH66167: Preadolescent precursors to depression in girls
  
  PI: Kate Keenan
  Funded: 12/01/2003-12/31/2010

- NIH/NICHD R03 MH084073: Developmental comorbidity of pain and depression in preadolescent girls
  
  PI: Kate Keenan
  Funded: 05/01/2009-04/30/2012

- NIH/NIMH R34 MH092467: An innovative approach to preventing depression in African American girls
  
  MPI: Kate Keenan/Kathy Grant
  Funded: 08/02/2011-04/30/2014

- NIH/NIMH R01 MH093605: Changes in brain function during adolescence and risk for depression in girls
  
  MPI: Kate Keenan/Erika Forbes/Amanda Guyer
  Funded: 08/02/2011-04/30/2014
Dr. King is a Professor of Psychiatry & Behavioral Neuroscience. Dr. King’s primary goal is to examine the mechanisms of vulnerability to substance use disorders and to identify efficacious behavioral and pharmacological interventions for treatment of addiction. The main focus of her research has concentrated on the etiology and treatment of alcohol and nicotine dependences. While use of alcohol and drugs is widespread, only a portion of individuals exposed will develop chronic heavy, maladaptive use. Therefore, it is imperative to elucidate psychobiological risk factors that predispose some persons to substance dependence. In addition, most treatments for addictive disorders only reach a small percentage of those afflicted and only improve outcomes for the minority of persons treated. Combinations of behavioral and pharmacological approaches have shown the most promise, and newer studies are examining such integrated treatments among a wide variety of patients, including racial/ethnic minorities and women. Dr. King examines factors involved in differential outcomes with the ultimate goal to ameliorate such disparities. The research program in Dr. King’s Clinical Addictions Research Laboratory includes integrated human laboratory and clinical trials research methodology to bear a psychobiological perspective on addiction. These research endeavors are summarized in this document into two main areas: human laboratory research and clinical treatment trials.

Training.

B.S., University of Illinois, Urbana-Champaign, IL, 1987.

Ph.D., University of Oklahoma Health Sciences Center, Oklahoma City, OK 1992.


Research Program.

I. Laboratory Studies

Human laboratory studies in Dr. King’s laboratory have been two-fold: a) to examine subjective, objective, and performance effects of alcohol and placebo in high- and low-risk drinkers; b) to examine alcohol’s effects on smoking, urge, behavior, and neurobiological functioning in heavy drinker social smokers.

a. Program of Research on Alcohol Response in High-Risk Drinkers

The basic research aspect in Dr. King’s lab utilizes pre-clinical human laboratory studies to examine the consequences, mechanisms, and biobehavioral risk factors underlying alcohol use disorders. Results from these placebo-controlled investigations have established that persons at risk for alcohol use disorders by virtue of a heavy drinking
phenotype at a young age, exhibit differential responses to alcohol compared to their low-risk counterparts. The most recent of these studies is summarized in the next section.

The prevailing theory for vulnerability to alcohol use disorders has been the low-level response model, which posits that persons at risk for alcoholism are less affected by alcohol and they need to drink more in order to achieve intoxication. Conversely, newer models purport that at-risk drinkers may show differential alcohol response (greater stimulation and less sedation) based on the phase of the blood alcohol curve (BAC). Other theories expound on incentive-salience of drugs of abuse, including alcohol, such that motivation to use (“wanting”) sensitizes over time but hedonic effects (“liking”) do not. Dr. King is the first human laboratory researcher to specifically test these models in well-controlled laboratory studies with longitudinal follow-up. The main findings from these studies include:

- High-risk, heavy drinkers exhibit significantly greater increases in subjective alcohol stimulation and less sedation than light drinkers; the effects are most notable during the early phase of the drinking episode, i.e., when blood alcohol levels are rising
- Responses to alcohol in light drinkers (primarily subjective sedative effects and increased cortisol) suggest important “protective” mechanisms potentially garnering them at low risk for future alcohol problems
- Heavy and light drinkers show comparable alcohol-induced psychomotor performance and select eye movement impairment, suggesting that the former group may be at heightened risk for consequences and harmful effects of episodic heavy drinking

Dr. King is in her second award phase of NIAAA funding for the “Chicago Social Drinking Project” (CSDP; R01-AA013746 2003-2013). In CSDP, several hundred young adult social drinkers have participated in individual laboratory sessions where they consume, under double-blind conditions, a low and high dose of alcohol (0.4g/kg and 0.8 g/kg, respectively) and a placebo beverage (1% alcohol as a taste mask) given in random order. Participants met criteria for one of two distinct groups: heavy drinkers (HDs), who consumed 10 or more standard drinks weekly and engaged in binge drinking at least once but no more than five times weekly for at least the last two years, or light social drinkers (LDs), who consumed five or fewer drinks weekly with no or rare binge occasions. After completing the laboratory portion, all participants take part in extensive follow-up of alcohol drinking and other behaviors over the next several years. Retention in CSDP has been extremely high, with no subjects lost to follow-up and an overall follow-up rate as of October 2011 of 99.1% (1,872 out of a possible 1,890 interviews conducted thus far). Also impressive is the rate of 87.6% (156 out of 178 eligible participants) of participants who returned from all regions of the city, state, country and even internationally, in some cases, to complete two additional re-examination sessions during their fifth year of follow-up.
Results have shown that HDs were more sensitive to positive-like alcohol effects (see Figure 1 depicting stimulation and alcohol wanting), and less sensitive to sedative-like effects than LDs. The HDs also showed less cortisol increases to alcohol. Performance deficits were similar in the two groups. However, HDs perceived they were less intoxicated than the LDs, which may render them at higher risk for alcohol-related injury and harm. These results were evident even after controlling for several psychosocial and demographic risk factors known to relate to heavy drinking, such as male sex, White race, disinhibited personality and family history of alcohol use disorders.

Over the subsequent two years, there were four drinking trajectory groups that best fit the HDs, and two groups in the LDs. Among HDs, 6.7% were categorized as exacerbating their binge drinking behavior, while 25.0% were categorized as high-frequency binge drinkers, 59.6% as moderate-frequency binge drinkers and 8.7% gradually matured away from binge drinking. Our prospective analysis of alcohol response factors that may predict drinking over time showed that greater sensitivity to positive-like effects and less...
negative-like effects were associated with heightened binge drinking frequency among HDs (Figure 2). There were no factors in LDs that predicted drinking over time, and their drinking remained largely low-risk and infrequent (King et al. 2011).

During the period from Spring 2009 to Autumn 2011 an additional 104 heavy drinkers were recruited in order to double the original cohort sample size. In the midst of enrolling the second cohort, follow-up interviews and re-examination sessions with the original cohort were also conducted. As mentioned above nearly 85% of the original cohort returned to complete a second round of alcohol challenge sessions, thanks in no small part to the efforts of the laboratory staff and project coordinator. Initial analyses of both the re-examination sessions as well as the new cohort sessions have largely replicated the original findings and bolster confidence in the results.

b. Program of Research on Alcohol-Smoking Interactions

Concurrent heavy drinking and smoking are major contributors to disease, such as cancer, cardiovascular and pulmonary disease, and early mortality. Several biobehavioral mechanisms have been suggested for the co-occurrence of alcohol drinking and cigarette smoking, including negative reinforcement, positive reinforcement, cross-tolerance, and paired-associate learning. However, comprehensive testing of these theories is lacking. A research program examining alcohol’s elicitation of smoking behaviors began surreptitiously about a decade ago. At that time, Dr. King and colleagues were recruiting heavy drinkers for an alcohol study but required them to be nonsmokers. Recruitment was challenging and generalizability to the larger population was hampered, given how commonly these substances are used conjointly. Therefore, Dr. King embarked on studies to examine how alcohol affects various aspects of nicotine use.

The first of these studies was a dose-response study showing that the greater the consumption of alcohol the greater the subjective urge to smoke (Figure 3). This investigation was the first to establish that episodic heavy drinker-smokers exhibit significant increases in smoking urge as a function of alcohol dose and BAC phase. Cigarette craving increased substantially with greater alcohol consumption and was particularly evident during rising BACs, i.e., the phase when heightened stimulant-like effects predominate, which is counter to the notion that smoking occurs during alcohol drinking episodes to offset alcohol’s sedative effects. Rather, the data suggest that smoking occurs to augment positive, stimulant-like effects, however further studies are needed (King & Epstein 2005).

These data have fostered several lines of additional funding by NIH and the Brain Research Foundation for more in-depth behavioral and neurobiological studies of alcohol-nicotine...
interactions. In the behavioral study, participants’ acute responses to alcohol or a placebo control beverage on smoking topography were examined for nicotinized and de-nicotinized cigarettes in heavy drinkers who often smoke during intoxication. Results from this study showed that alcohol increased smoking behaviors, but only in men and not in women. Among women, smoking levels increased after consumption of either alcohol or placebo beverage, but in men, smoking only increased in the context of alcohol drinking. The results support the body of work showing more complex factors involved in women’s smoking behaviors and extend the work to alcohol-smoking comorbid use (King et al. 2009). (Figure 4).

Figure 4

![Figure 4](image1.png)

In a separate study in Dr. King’s laboratory, functional magnetic resonance imaging (fMRI) was utilized to discern brain activity underlying cigarette craving induced by alcohol. Specifically, we examined how brain processes are altered under the influence of alcohol to salient smoking versus non-smoking visual cues (Figure 5).

Figure 5

![Figure 5](image2.png)

In this study, reactivity in the ventral striatum and other brain regions was probed during exposure to visual smoking versus nonsmoking control cues. Results showed that alcohol enhanced self-reported ratings of desire to smoke, and in this context, significantly increased ventral striatum responses to smoking.
compared with control cues (Figure 6). In exploratory analyses, we observed that alcohol dampened orbitofrontal activity across both cue types, whereas dorsolateral, prefrontal and anterior cingulated cortex activation to smoking cues was not affected by alcohol. This study bridged a pharmacological challenge approach to the study of brain reactivity to smoking cues, extends prior cigarette cue imaging studies to nondependent smokers, and elucidates a potential neurobiological mechanism to explain the co-consumption of alcohol and cigarettes in nondependent users (King et al. 2010).

Additionally, separate analyses were performed on a emotional recognition task. The amygdala was observed via fMRI after consuming a placebo and an alcohol beverage in separate sessions. Alcohol was found to significantly reduce reactivity to the threatening images over placebo, indicating that alcohol may lead to decreased perception of risks and dangerous situations (Sripada et al. 2011).

II. Treatment Studies

Dr. King is a licensed clinical psychologist who is interested in developing clinical applications of laboratory-based findings, discovering new efficacious treatments for nicotine and alcohol use disorders, and examining underserved subgroups based on sex, ethnic/racial and low-income backgrounds. Dr. King has successfully built on two foundations for these intervention studies by extracting her pre-clinical laboratory findings showing acute effects of naltrexone decreasing smoking urge and behavior in an ongoing second clinical trial with naltrexone in men and women smokers (R01-DA016834) and expanding outreach to underserved smokers and apply scientific skills to examine differential outcomes and/or effects of targeted treatments to reduce health disparities. The latter has been largely developed through Dr. King’s work as a Co-Program Leader in the Cancer Risk and Prevention program at the University of Chicago Comprehensive Cancer Center (UCCCC). In addition to these aforementioned studies, Dr. King also currently has two pilot projects underway to examine smoking behaviors among cancer patients (n=65 as of December 2011), and to develop a targeted smoking program for African American HIV+ men; as of December 2011, this project has completed its pilot enrollment and will publish its results in 2012.

a. Program of Research on Naltrexone Efficacy for Smoking Cessation

Translational work in Dr. King’s laboratory is highlighted by the series of studies she has conducted with colleagues on responses to naltrexone, a primary mu opioid receptor antagonist. These studies began with pre-clinical human psychopharmacology paradigms examining subjective, behavioral, and neuroendocrine responses after acute naltrexone
administration in men and women smokers. The acute findings from the laboratory suggested that naltrexone may be efficacious in treating nicotine dependence. Subsequently, Dr. King embarked on a randomized, placebo-controlled clinical trial to test the efficacy of naltrexone, along with nicotine patch and counseling, for smokers desiring to quit.

**Main discoveries from these studies**

Naltrexone reduced smoking behavior and smoking subjective responses, confirmed by objective carbon monoxide readings and plasma nicotine levels (Epstein & King, 2004), and naltrexone acutely increased levels of stress hormones to a larger extent in women smokers versus men (Roche & King, 2010).

In Dr. King's clinical trial (King et al., 2006), placebo-treated women had lower quit rates than men, but the sexes showed similar quit rates with naltrexone. Adjunct treatment with naltrexone may therefore close the “gender gap” in outcome. A larger trial is currently underway (#R01-DA016834) to extend findings. In smoking cessation, naltrexone also significantly reduced weight gain (King et al., 2006), and heavy drinking rates (King et al., 2009); both of these are important secondary outcomes as weight gain may deter women especially from quitting smoking, and alcohol consumption is a risk factor for smoking relapse.

More recently, these effects were further elucidated. In a recent paper (King et al., 2012 under review), naltrexone increased quit rates during treatment (versus placebo), especially in men. Women, however, had a significant reduction in weight gain compared to men. Furthermore, this effect extended beyond treatment for up to six months. Weight gain is a commonly cited concern for women entering into a smoking cessation program, so while naltrexone did not acutely affect quit rates in women, the observed reduction in weight gain may be highly clinically relevant.

In keeping with examining sex differences in naltrexone’s efficacy, Dr. King has a small trial underway (#F31DA030073) that seeks to determine whether if naltrexone affects the hypothalamic-pituitary-adrenal (HPA) axis differently in women than it does in men, as well as whether menstrual cycle phase plays a significant role in women’s response to naltrexone. Some evidence suggests that the HPA axis may react differently to stress in smokers versus non-smokers, so a deeper understanding of naltrexone-HPA interactions among non-smoking men and women may be important to determine if effects are specific to nicotine exposure and history, or are more pervasive.

**b. Program of Treatment Research in Underserved Minorities**

Given Dr. King’s successful recruitment of African Americans, and her role at the UCCCC, her interests in studying underserved subgroups has been honed and refined. Dr. King’s studies often include oversampling for racial/ethnic minorities, including African Americans to discern if differential recruitment, retention, and outcomes are observed. In addition, she and colleagues have embarked on a series of studies examining African American smokers’ receptivity to community-delivered evidence-based treatment, response to culturally appropriate targeted materials, and enrollment barriers in a
mainstream pharmacotherapy trial. These studies have shown that underserved African American smokers have shown good acceptability and feasibility with a community-delivered behavioral and pharmacological intervention (King et al., 2008), and outcomes in terms of program completion and quit rates are even better in a group receiving a culturally-targeted version of the cognitive-behavioral treatment (Matthews et al., 2009). A 2011 paper (Sánchez-Johnsen et al., 2011) found that African American and Caucasian female smokers have different concerns about weight when enrolled in a smoking cessation program, adding further credence to the notion of culturally-targeted smoking cessation treatments. Finally, within Dr. King’s randomized, placebo-controlled smoking cessation trial with naltrexone, significant racial disparities were observed in eligibility determination and enrollment among African Americans versus Whites, and directions for amelioration in future studies were outlined (King et al., 2011).

**Funding.**

- NIAAA R01-AA013746: Alcohol Stimulation and Sedation in Binge Drinkers.
  Pl: King   01/01/2009-12/31/2013
- NIAAA R01-AA013746-S1: Research Supplement to Promote Diversity in Health-Related Research.
  Co-I: King   08/15/2010-07/31/2013
- NIH/NIDA R01-DA016834: Efficacy of Naltrexone in Women’s Smoking Cessation.
  Pl: King   09/01/2005-05/31/2012 (NCE)
- NIH/NIDA R01-DA023935: Culturally Targeted and Individually Tailored Smoking Cessation Study.
  Co-I: King   09/30/2010-07/31/2015
  Pl: King   11/01/2009-10/31/2012

**Selected Publications of Note.**


Daniel Le Grange, Ph.D. (Psychiatry and Behavioral Neuroscience). Dr. Le Grange is Professor of Psychiatry and Behavioral Neuroscience in the Department of Psychiatry, and Director of the Eating Disorders Program at The University of Chicago. He received his doctoral education at the Institute of Psychiatry, University of London, and trained in family-based treatment for adolescent anorexia nervosa at the Maudsley Hospital in London. At the Maudsley Hospital he was a member of the team who developed the “Maudsley Approach” as a treatment for early onset anorexia nervosa. He completed a postdoctoral training at the Maudsley Hospital and University of London and introduced the Maudsley Approach to his colleagues when he moved to the United States to do a postdoctoral fellowship at Stanford University School of Medicine. Dr. Le Grange has been devoting most of his career to the development and testing of treatments for adolescents with eating disorders utilizing randomized controlled trials. His work expands across the eating disorder diagnostic spectrum (i.e., anorexia nervosa, bulimia nervosa and eating disorders not otherwise specified).

Training:
B.A. (Hons) (Psychology), University of Johannesburg, South Africa, 1981
MA (Clinical Psychology), University of Johannesburg, South Africa, 1983
PhD (Psychology), University of London, UK, 1989

Research Program History:
Dr. Le Grange is a clinical psychologist specializing in treatment outcome research of eating disorders. He received his education in South Africa and the United Kingdom before relocating to the United States to do postdoctoral training at Stanford University in 1994-1995. After completing this postdoctoral fellowship, he was research assistant professor at the State University of New York at Stony Brook for two years. He joined The University of Chicago as assistant professor in July 1998 and was promoted to Professor with tenure on January 1, 2009. His primary research and clinical interests are treatment outcomes studies for adolescent anorexia nervosa (AN) and bulimia nervosa (BN) as well as cross-cultural issues in eating disorders.

Most of Dr. Le Grange’s training prior to coming to The University of Chicago occurred at the University of London (Institute of Psychiatry/The Maudsley Hospital) focusing on treatment studies for adolescent eating disorders. It was at London that he was a member of the team that pioneered family-based treatment for adolescent AN (FBT-AN) (also known as the “Maudsley Approach”), regarded by many as the gold-standard therapy for this patient population. While at London he conducted the first RCT that compared two forms of outpatient FBTs for adolescent AN (International Journal of Eating Disorders, 1992). Since then, he has devoted most of his career to the development and dissemination of FBT, as well the expansion of its applicability to related clinical populations.

Treatment of Adolescent Bulimia Nervosa: Since joining Chicago, Dr. Le Grange has collaborated with colleagues from London and Stanford and developed a manual for the
only evidenced-based therapy for anorexia nervosa (AN): *Treatment manual for anorexia nervosa: A family-based approach* (Guilford Press, 2001). This manual represents the only evidenced-based treatment for this patient population and this treatment is now utilized quite extensively in the US, Canada, and Australia. This work was expanded for adolescents with bulimia nervosa (BN), and we published a comparative study of adolescents with AN and BN addressing the ‘evolving’ nature of BN in this age group (*Arch Ped Adol Med*, 2004) (see Table 1). This study demonstrated that there are relatively few clinical differences between patients who present with full syndrome BN as opposed to those who present with partial syndrome.

**Table 1: Eating Disorder Examination (EDE) Symptomatology (M, SD):**

<table>
<thead>
<tr>
<th></th>
<th>BN (n=36)</th>
<th>PBN (n=36)</th>
<th>AN (n=27)</th>
<th>F</th>
<th>Sign</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDE Obs frequency</td>
<td>31.4 (23.6)</td>
<td>3.6 (5.1)</td>
<td>0.7 (3.5)</td>
<td>49.485</td>
<td>.000</td>
</tr>
<tr>
<td>EDE SBE frequency</td>
<td>11.1 (18.7)</td>
<td>21.1 (20.1)</td>
<td>1.7 (4.5)</td>
<td>6.974</td>
<td>.002</td>
</tr>
<tr>
<td>EDE Vomit frequency</td>
<td>45.5 (30.4)</td>
<td>17.8 (25.1)</td>
<td>0.8 (2.3)</td>
<td>24.177</td>
<td>.000</td>
</tr>
<tr>
<td>EDE Restraint</td>
<td>3.87 (1.1)</td>
<td>3.91 (1.6)</td>
<td>2.02 (1.7)</td>
<td>16.115</td>
<td>.000</td>
</tr>
<tr>
<td>EDE Weight Concern</td>
<td>4.24 (1.4)</td>
<td>3.48 (1.9)</td>
<td>1.81 (1.7)</td>
<td>15.853</td>
<td>.000</td>
</tr>
<tr>
<td>EDE Shape Concern</td>
<td>4.46 (1.3)</td>
<td>3.76 (1.8)</td>
<td>1.84 (1.8)</td>
<td>18.888</td>
<td>.000</td>
</tr>
<tr>
<td>EDE Eating Concern</td>
<td>3.23 (1.2)</td>
<td>2.55 (1.4)</td>
<td>1.38 (1.3)</td>
<td>16.320</td>
<td>.000</td>
</tr>
</tbody>
</table>

Key: OBE = Objective Bulimic Episodes (DSM-IV binge, i.e., the consumption of an objectively large amount of food accompanied by a sense of loss of control); SBE = Subjective Bulimic Episodes (the consumption of a normal to small amount of food accompanied by a sense of loss of control).

Note: For the EDE, higher scores imply greater psychopathology.

At the same time, and in a Career Development Award from the National Institute of Mental Health (NIMH) (2001-2006), Dr. Le Grange evaluated the relative efficacy of two kinds of psychological treatments in the management of adolescent BN, i.e., manualized family-based treatment (FBT-BN) vs. manualized individual supportive psychotherapy. This RCT was the first for adolescent BN to be conducted in North America and, in short, our findings showed that FBT-BN is more efficacious than individual supportive psychotherapy for adolescent BN (*Arch Gen Psychiatry*, 2007) (see Figure 1 to the left).

Predictor and moderator analyses, demonstrated that that lower eating concerns are the best predictor of remission, and that FBT-BN might be most effective for cases with low levels of eating disorder psychopathology (*J Am Acad Child Adol Psychiatry*, 2008). Based on this work, Dr. Le Grange recently completed the first treatment manual for adolescents with BN, entitled: *Treating bulimia in adolescents: A family-based approach* (Guilford Press, 2007). In addition to this clinician manual (as well as the one for AN – *Treatment manual for anorexia nervosa, second edition*, Guilford Press, 2012), he has also co-authored two parent handbooks that are to be used in conjunction with the clinician manuals: *Help your teenager beat an eating disorder* (Guilford Press, 2005), and *My kid is back* (Routledge, 2009). In addition, Dr. Le Grange co-edited a clinician handbook
Early Treatment Response: Separately, we were interested in the early response to treatment in adolescent BN. The purpose of this study was to determine if early response predicted remission at the end of this RCT. Response to treatment was assessed via self-report of bingeing and purging. Remission was defined as abstinence from bingeing and purging for the last 28 days and measured by investigator-based interview, i.e., the Eating Disorder Examination. Receiver operating characteristic analyses showed that, regardless of treatment, symptom reduction at session 6 predicted remission at post-treatment (AUC = .814 (p<.001)) and 6-month follow-up (AUC = .811 (p<.001)). Results suggest that adolescents with BN who do not show early reductions in bulimic symptoms are unlikely to remit at post-treatment or follow-up (Int J Eat Disord, 2008) (See Figure 2 below).

Figure 2: ROC Curves for Session 6 at End-of-Treatment and Six-Month Follow-up

Similarly, we looked at early response to family-based treatment for adolescent AN. The purpose of this study was to determine if early weight gain predicted remission at the end of treatment in a clinic sample. 65 adolescents with AN (mean age = 14.9 years, SD = 2.1), from two sites (Chicago n=45; Columbia n=20) received a course of manualized Family-based Treatment (FBT). Response to treatment was assessed using percent ideal body weight (IBW) with remission defined as having achieved >95% IBW at end of treatment (session 20). Receiver operating characteristic analyses showed that a gain of at least 2.88% in ideal body weight by session 4 best predicted remission at end of treatment (AUC = .674; p=.024). Results suggest that adolescents with AN, receiving FBT, who do not show early weight gain are unlikely to remit at end of treatment.

Treatment of Adolescent Anorexia Nervosa: In a recently completed multi-site RCT (Chicago and Stanford), funded by NIMH, Dr. Le Grange and colleagues compared
manualized FBT-AN with a manualized individual treatment. This is the first adequately powered treatment trial of FBT for adolescents with AN (Figure 3). Based on mixed effects analysis estimates, full remission rates between treatments did not differ statistically at EOT (FBT=42%; AFT=23%, p=.055, Number Needed to Treat (NNT) =5); however, at 6 month follow-up (FBT=40%, AFT=18%, p=.029, NNT = 5) and 12 month follow-up (FBT=49%, AFT=23%, p = .024, NNT = 4), FBT was statistically superior to AFT. Rates of partial remission were greater in FBT than AFT at post-treatment (FBT = 89%, AFT = 67%, p= .023, NNT= 5), but did not differ at follow-up.

Treatment effects on age and gender adjusted BMI percentile were greater in FBT than AFT (mean difference=8.0, CI=-0.1,15.9, p=.048, NNT=5) at EOT, but not at follow-up. Treatment effects on EDE were greater in FBT than AFT (mean difference=-0.49, CI= -0.93,-0.06, p=.030, NNT=4) at EOT, but not at follow-up. Of the 29 (10 AFT, 19 FBT) subjects who were in full remission at EOT, 6 had relapsed at 12-month follow-up 2: (10%) from FBT and 4 (40%) from AFT. Of the 71(31 AFT, 40 FBT) who achieved partial remission, 9 relapsed by the 12-month follow-up: 7(18%) from FBT and 2 (6%) from AFT. Relapse rates cannot be detected on Figure 3 as the percentage reported at follow-up time points are totals that include newly remitted subjects as well as those that remained remitted from EOT (Arch Gen Psychiatry, 2010). For moderators and mediators, see Beh Res Therapy, 2011).

**Figure 3: Partial and Full Remission for FBT vs AFT**

![Graph showing remission rates for FBT and AFT](image)

**Current Work:** The next step in the treatment development for adolescents with AN, given the findings from our most recent RCT, is to augment FBT-AN and develop a more intensive form of treatment that may help improve the current remit rate of 50%. To this end, Dr. Le Grange and his colleagues at Stanford University have just started a 3-year treatment development study funded by the NIMH (2011-2014). In this study, we are testing a more adaptive/intensive form of FBT for adolescents with AN. In another new, yet related effort, colleagues at Stanford and Dr. Le Grange’s team, have been awarded...
a five year grant to optimizing FBT for adolescent with AN. The main goals of this study is to refine an existing fidelity assessment for FBT, to examine the relationship between FBT fidelity and its components to patient outcome, to explore predictors of fidelity in FBT, and to develop a focused training and supervision program for FBT.

For adolescents with BN, and to follow-on our own initial RCT for adolescent BN, Dr. Le Grange and his colleagues are comparing FBT-BN with cognitive-behavior therapy (CBT) in another NIMH funded multi-site study (Chicago and Stanford). This five-year investigation (2008-2013) is now in its fifth year and more than 125 participants have been randomized across the two sites. The goals of this study are to test the relative efficacy of these two active treatments for this patient population and to explore possible moderators and mediators of treatment outcome. We hope to complete this study soon, and present our findings in the very near future.

Classification of Eating Disorders in Adolescents
Since the inception of the Eating Disorders research Program at Chicago, Dr. Le Grange and his lab have consistently collected assessment and treatment data from all adolescent AN and BN patients. Some of these data examined clinical outcome in our service delivery and were published in two papers with the Journal of the American Academy for Child and Adolescent Psychiatry (2005 and 2006). In addition, and in preparation for DSM-V and evaluating the diagnostic criteria for eating disorders especially for adolescents, we have published several papers from my lab (Int J Eat Disord, in press; J Am Acad Child Adolesc Psychiatry, 2008; 2010; J Nervous Mental Disease, 2009). In these studies we have shown that, as in adults with eating disorders, EDNOS predominates and is heterogeneous with regard to eating disorder pathology and associated features in an adolescent clinical sample. Lack of differences between AN and SAN suggests that the strict criteria for AN could be relaxed; differences between BN and EDNOS bulimic variants do not support their combination (See Table 2 below).

Table 2: Eating Disorder Not Otherwise Specified (EDNOS) Types
Specifically with an eye toward DSM, and the classification of eating disorders in
children and adolescents, Dr. Le Grange is part of the Workgroup for Classification of Eating Disorders in Children and Adolescents, or WCEDCA, and we have now published two position papers arguing for specific ways in which the diagnostic criteria for eating disorders in children and adolescents should be adjusted (Int J Eat Disord, 2007; Eur Eat Disord Rev, 2010). For adults, Dr. Le Grange and his collaborators have recently published at least two papers that shed more light on the diverse EDNOS diagnosis (Int J Eat Disord, 2012; Eur Eat Disord Rev, 2013).

**Research Collaborations outside Chicago**

In addition to the many projects that Dr. Le Grange collaborates on (colleagues at Stanford University, University of Minnesota, and the Neuropsychiatric Research Institute), he also has significant collaborative relationships with colleagues in New York and in Australia.

With colleagues at Mt. Sinai in New York (Katharine Loeb, PhD), Dr. Le Grange and his team are in the follow-up phase of a treatment development study which is testing an adaptation of FBT to a pediatric overweight population (FBT-PO). This study is now nearing completion with almost 80 participants assigned two one of the two study treatments. Our plan is to submit a collaborative RO1 to investigate the efficacy of FPT-PO and treatment as usual.

Colleagues at the University of Sydney (Stephen Touyz, PhD) and I were awarded two three-year grants from the National Health & Medical Research Council (NHMRC) to conduct RCTs in Sydney (both these grants have multiple PIs). The first study builds on our experience with FBT-AN and investigates the question of whether inpatient weight restoration prior to outpatient FBT improves outcomes in adolescent AN. The second focuses on the treatment of chronic presentations of AN and compares two manualized treatments, CBT and standard clinical care for adults with AN. Both studies have recently been completed and both main outcome papers have been or will shortly be submitted for review. Long-term outcome studies for both patient cohorts are currently underway.

With colleagues at the University of Melbourne, and through a grant from the Baker Foundation (Australia) (2009-2015), Dr. Le Grange has helped to establish a research infrastructure to their clinical program, and started an RCT comparing FBT-AN with Parent-Focused Treatment for teens with AN. We have now randomized more than 60 participants since June 2010 and are in the process of submitting to the NHMRC a multi-site RCT with Westmead Children’s Hospital in Sydney.

**Cross-Cultural Issues in Eating Disorders**

Beyond treatment outcome research, Dr. Le Grange has continued a research interest in cross-cultural issues in eating disorders. Prior to joining The University of Chicago, he has conducted several studies investigating the prevalence and nature of pathological eating habits and eating disorders among students (white, black and mixed-race) in South Africa, as well as Caucasians, African Americans, Hispanics, Asians and Latinos here in the United States. He is the author of the first comprehensive survey of eating pathology among South Africans of all ethnic groups (American Journal of Psychiatry, 1998). This study has shown that eating disorder pathology was as prevalent among black South Africans as it was among white South Africans, challenging the assumption that eating disorders are confined to Western societies. Dr. Le Grange and his colleagues replicated these early findings in a separate South African investigation.
(European Eating Disorders Review, 2000), and since coming to Chicago, he completed a large two-stage epidemiological survey of eating psychopathology among South African students. In this study, Dr. Le Grange and colleagues in South Africa surveyed a study group of ~1,000 students between the ages 16-24 years for eating psychopathology. This survey was followed by clinical interviews in a subset of the study group to establish eating disorder diagnosis and the meaning of their questionnaire responses given the non-western context within which the study was conducted. This was the first investigation of its kind in Southern Africa and two manuscripts, one in Culture, Medicine and Psychiatry (2005) and another in Transcultural Psychiatry (2006), will go some way toward commenting on the important methodological concerns for future cross-cultural studies as well as confirming that white and black females in South Africa seem to be at equal risk for the development of eating disorder psychopathology.

**Education in Eating Disorders**

Dr. Le Grange maintains a strong commitment to educating the next generation of eating disorders clinicians and researchers. He has mentored several pre-doctoral psychology interns and postdoctoral fellows as well as child and adolescent psychiatry fellows over the past 14 years. In addition to directing the Eating Disorders Track for pre-doctoral psychology interns, Dr. Le Grange is the site director at Chicago (Scott Crow, M.D., Site Director at the University of Minnesota and PI, and Stephen Wonderlich, Ph.D., Site Director at the Neuropsychiatric Research Institute) for a recently awarded five-year NRSA T32 Regional Postdoctoral Training Grant in Eating Disorders Research (for PhD and MD Fellows). The first fellows were enrolled in July 2010 and Kristen Culbert, Ph.D. will be the fourth Chicago fellow to graduate from this program in June 2013.

**Currently Funded Projects (Selected)**

- **NIMH R01 MH079979: Treatment of adolescent bulimics**
  PI: Le Grange 07/01/2008–06/30/2013
- **NIMH R01 MH079979 (Administrative Supplement): Treatment of adolescent bulimics**
  PI: Le Grange 06/01/2009-02/28/2013
- **Baker Foundation: FBT for adolescent anorexia nervosa**
  MI: Sawyer, Le Grange 06/01/2009-05/31/2015
- **NRSA T32 MH 08276: Regional postdoctoral training grant in eating disorders research**
  PI: Crow, Site Director: Le Grange 07/01/2009-06/30/2014
- **NIMH R34-MH093768: Adaptive family treatment for adolescent anorexia nervosa**
  PI: Le Grange 09/01/2011-08/31/2014
- **NIMH R21-MH096779-01: Optimizing fidelity to family-based treatment for adolescent anorexia nervosa**
  PI: Lock, Subcontract PI: Le Grange 07/01/2012-6/30/2017
- **Insight Behavioral Health: Refining family-based treatment for adolescent anorexia nervosa**
  PI: Le Grange 01/01/2013-12/31/2015

**Selected Publications of Note**


Royce Lee, M.D.  (Psychiatry & Behavioral Neuroscience).

Royce Lee is an Associate Professor in the Department of Psychiatry and Behavioral Neuroscience at The University of Chicago. Dr. Lee’s research is focused on the effects of neuropeptides on brain function relevant to emotion and stress-related psychiatric disorders. Neuropeptides are administered intranasally to the olfactory epithelium. Cortical effects are measured using EEG. Behavioral effects are measured using laboratory paradigms that simulate aggression and self-aggression. The neuropeptides currently being studied in human volunteers and patients include corticotropin releasing hormone, vasopressin, oxytocin, and insulin. The clinical population of interest is severe personality disorder. Dr. Lee is also interested in developing reliable measures of brain function that reflect either neuropeptide related neural mechanisms or correlates of psychopathological states that could be used for diagnostic or prognostic purposes.

**Training.**

B.A., English, Honors, Northwestern University, Chicago, IL, 1992

M.D., Northwestern University Feinberg School of Medicine, Chicago, IL, 1996

Adult Residency in Psychiatry, Rush Medical Center, Chicago, IL, 2000

**Research Program.**

Corticotropin-releasing hormone (CRH) was first discovered by Wylie Vale (Science 1981; 213: 1394-7). CRH is a 41-amino acid peptide that mediates the central and peripheral stress response. CRH and its primitive isoforms are phylogenetically ancient
and ubiquitous in animals. Its receptors are expressed in the periphery, where they mediate the classic hypothalamic-pituitary adrenal stress response. Importantly, its receptors are also expressed in brain circuits mediating emotional behavior, and their activation is associated with increased intensity of stress-reactive behaviors.

Corticotropin-releasing hormone acts as a neuromodulator in the brain. An enormous body of basic science has demonstrated the importance of this neuropeptide in stress-reactivity and emotional functions mediated by the brain. This large body of work has yet to impact the clinical approach to stress-related psychiatric disorders. The relative impermeability of the blood brain barrier to neuropeptides has created a literal “bubble” of scientific knowledge regarding central CRH function that has not yet been translated into new clinical approaches. The goal of this program of translational research is to pop this bubble using innovative science in order to improve the clinical approach to stress related psychiatric disorders.

The long-term objective is to improve the treatment of stress-related psychiatric disorder by accessing, measuring, and/or altering central corticotropin-releasing hormone (CRH) function. Dr. Lee has specifically focused on personality disorder and difficult-to-treat major depression. Although the last half century of research on monoamine neurotransmitters has led to considerable improvement in the treatment of these disorders, a large portion of those treated remain very symptomatic. Evidence suggests that optimizing currently available treatments that are focused on modification of monoamine neurotransmitter function by rearranging the order or combination in which they are administered does not result in significant improvement of treatment outcome. *This phenomenon is well known and quickly recognized by patients and their families.*

To attain this long-term objective, Dr. Lee’s research has been focused on: 1) Risk factors for increased central CRH drive (childhood trauma); 2) Understanding the biological and psychological consequences of increased CRH drive (altered adrenal function and paranoid anxiety); 3) Developing novel approaches to probe and alter central CRH function in humans (intranasal probes of CRH function and intranasal anti-CRH therapeutics).

**Childhood Trauma is a Risk Factor for Increased Central CRH Drive in Adults with Personality Disorder**

Dr. Lee and his colleagues were the first to report a positive correlation between central CRH peptide hormone levels (measured in the lumbar cerebrospinal fluid) and severity of childhood trauma history in adults with personality disorder, as measured by the Childhood Trauma Questionnaire (Lee et al., 2004). In this study, the Emotional Neglect subscale of the Childhood Trauma Questionnaire was specifically negatively correlated with CRH peptide hormone levels. This finding was replicated with an enlarged sample, using the Parental Bonding Inventory (Lee et al., 2007). In the second study, a significant negative correlation was found between cerebrospinal fluid CRH
concentration and total score on the Parental Care/Involvement subscale (which is itself negatively correlated with the Emotional Neglect subscale of the Childhood Trauma Questionnaire).

These findings have been replicated yet again by Dr. Lee’s group in the context of an NIMH funded study. In a sample of 22 adult subjects (with and without personality disorder) free of psychotropic medications or drugs of abuse, they found once again that cerebrospinal fluid corticotropin releasing was significantly and positively correlated with the Emotional Neglect subscale of the Childhood Trauma Questionnaire ($r = .406, p = .03$). That is, the more Emotional Neglect reported, the higher the level of central corticotropin releasing hormone. Interestingly, in this third study, they found that score on the Validity subscale of the Childhood Trauma Questionnaire was negatively correlated with CRH level ($r = -.527, r = .006$). This subscale score does not provide information regarding the truthfulness of remembered childhood trauma, but does reflect a tendency to view events positively (higher score) or negatively (lower score). This finding emphasizes the need to view the correlational findings as reflecting a complex interrelationship between the variables, rather than simple causation.

**Figure 1.** Group differences in cerebrospinal fluid CRH concentration. Personality disordered subjects reporting low levels of parental care in childhood (Low PBI) had significantly higher cerebrospinal fluid CRH concentration in comparison to normal controls and personality disordered subjects reporting high levels of parental care (High PBI).

**Figure 2.** Group differences in cerebrospinal fluid CRH concentration. Personality disordered subjects reporting low levels of parental care in childhood had significantly higher cerebrospinal fluid CRH concentration in comparison to normal controls and personality disordered subjects reporting high levels of parental care.

These findings have been replicated yet again by Dr. Lee’s group in the context of an NIMH funded study. In a sample of 22 adult subjects (with and without personality disorder) free of psychotropic medications or drugs of abuse, they found once again that cerebrospinal fluid corticotropin releasing was significantly and positively correlated with the Emotional Neglect subscale of the Childhood Trauma Questionnaire ($r = .406, p = .03$). That is, the more Emotional Neglect reported, the higher the level of central corticotropin releasing hormone. Interestingly, in this third study, they found that score on the Validity subscale of the Childhood Trauma Questionnaire was negatively correlated with CRH level ($r = -.527, r = .006$). This subscale score does not provide information regarding the truthfulness of remembered childhood trauma, but does reflect a tendency to view events positively (higher score) or negatively (lower score). This finding emphasizes the need to view the correlational findings as reflecting a complex interrelationship between the variables, rather than simple causation.

**Childhood Trauma is Related to Down Regulation of Pituitary Adrenal Sensitivity to Exogenous CRH**

A large clinical literature has examined responsiveness of the hypothalamic-pituitary adrenal axis in response to exogenously administered stress hormone (dexamethasone + CRH). An important prediction from the basic science literature is that higher baseline
CRH concentration should predict decreased pituitary-adrenal reactivity via blunted pituitary CRH receptor sensitivity. Dr. Lee conducted an NIMH funded study to examine pituitary-adrenal reactivity to exogenous dexamethasone and CRH in a sample of adults with and without personality disorder who had experienced high and low levels of childhood trauma. As predicted, high levels of childhood trauma were associated with blunted cortisol and adrenocorticotropin hormone response to exogenous dexamethasone/CRH (Figure 3). These data have been submitted for publication and contribute to an ongoing debate regarding hypothalamic-pituitary adrenal axis function following trauma and stress-related psychiatric disorder. Although our subjects did not have post-traumatic stress disorder, the direction of findings is similar to that seen in clinical groups diagnosed with this disorder.

**Figure 3.** High levels of childhood trauma (High CTQ) as measured by the Childhood Trauma Questionnaire is associated with blunted cortisol response (left) to standardized doses of dexamethasone and CRH as well as blunted adrenocorticotropic (ACTH, right), presumably reflecting down-regulated pituitary CRH receptor sensitivity in the face of chronic CRH overdrive.

In the subset of subjects that underwent both lumbar puncture for cerebrospinal fluid sampling and dexamethasone/CRH challenge, it was found that delta cortisol (cortisol level at 120 minutes post CRH challenge – baseline cortisol) was significantly inversely correlated with CSF CRH (r = -.589, p = .016). This finding provides confirmation regarding an inverse relationship between cortisol responsiveness to exogenous CRH and resting central CRH level. Dr. Lee’s finding that both childhood trauma and central CRH concentration are related to blunted cortisol response to exogenous CRH provides novel information regarding the possible adulthood consequence of childhood trauma + enhanced CRH drive. An unanswered question regards the behavioral consequences of increased central CRH drive on central CRH receptors in emotion-related brain networks. Other research has established that high central CRH levels may increase
the risk for anxiety and depressive disorder, but this work has not specified a behavioral or psychological correlate of increased CRH drive. Dr. Lee found that Paranoid Personality Disorder, characterized by longstanding, abnormal suspiciousness of others is associated with increased central CRH level (Lee et al., 2007) and as described above, with decreased “Validity” score on the Childhood Trauma Questionnaire, reflecting a tendency towards negative interpretations of childhood. These findings suggest that one consequence of increased central CRH may be increased suspiciousness, or paranoid anxiety. While these are important leads to follow, it was important for Dr. Lee’s laboratory to enable more rigorous testing of hypotheses regarding central CRH function. In order to do this, developmental work was completed to create a novel probe of central CRH function using the transnasal route of drug administration.

**Novel Methodology to Access Central CRH Receptors for Research and Therapeutic Purposes**

**Central Stress Neuropeptide Signaling as a Target of Novel Treatments.** A large body of basic science research has confirmed that corticotrophin-releasing hormone plays an important neuromodulator role in neural circuits mediating emotional behaviors. This body of knowledge has not yet translated into a new treatment option for the clinician optimizing treatment of a depressed patient. There are two main reasons for this. The first is that the blood brain barrier constrains the molecular properties of neuropeptide receptor agonists and antagonists, delaying the deployability of non-peptide small-molecules in clinical populations. The second is that biomarkers of central neuropeptide function remain unavailable to the clinician or researcher. Dr. Lee’s laboratory has worked to address the two aforementioned obstacles by optimizing intranasal application of neuropeptides to the olfactory epithelium (Figure 4). Intranasal administration of neuropeptides results in low but biologically and behaviorally meaningful absorption into the forebrain. In order to investigate stress-system related neuropeptides, Dr. Lee’s laboratory has conducted experiments measuring the neuropharmacological effect of neuropeptides such as corticotrophin-releasing hormone, oxytocin, and insulin. Additionally, his laboratory has been conducting work to identify biomarkers of depression-relevant neuropeptide function. Specifically, his laboratory has demonstrated that intranasal corticotrophin releasing hormone is
associated with blunting of the P300 wave to novel visual stimuli in humans, and in those with a history of major depression, enhancement of the emotion-modulated acoustic startle reflex. Blunted P300 and enhanced acoustic startle reflex have been previously linked to both depressive disorder and corticotrophin-releasing hormone, and thus represent biomarkers that reflect the underlying pathophysiology of depressive disorder.

Effect of Intranasal CRH on Emotion Modulated Startle Reflex. Potentiation of startle reflex with CRH has been found in preclinical models of fear and anxiety, but this has not yet been applied to humans due to the limited ability of intravenous or orally administered CRH to cross the blood brain barrier. With the support of NARSAD, Dr. Lee sought to test the hypothesis that intranasal CRH administration, which may allow for absorption into the forebrain, would be associated with augmentation of the acoustic startle reflex in humans. It was additionally hypothesized that neurotics (non-depressed individuals with a history of at least one episode of major depression) would show greater sensitivity to CRH effects. 16 consenting adults (9 normal controls and 7 with history of depression) underwent a double-blinded, placebo-crossover study of the acute effects of 100 micrograms of CRH. Drug order was randomized and counterbalanced. CRH was administered in divided doses between the left and right nares using an intranasal device engineered to generate 50 μm droplets (MAD-device, by Wolfe-Torrey Pharmaceuticals). 45 minutes after drug administration, subjects were administered the acoustic Startle-Blink paradigm. During passive viewing of negatively valenced images from the International Affective Picture Series (IAPS), noisebursts of broad frequency noise were administered through headphones, jittered randomly at 120, 4000 and 5000 milliseconds after picture onset. Startle stimuli were also administered during passive viewing of a fixation cross as a control condition. Startle amplitude data were examined for eye-blink and movement artifact. Intranasal CRH was well tolerated. During viewing of a fixation cross, a statistical trend was found for a Drug x Group interaction, with CRH tending to increase startle amplitude relative to placebo in the neurotic group. During viewing of negative IAPS images, a significant interaction of Drug x Group was found. In the history of depression group, mean startle amplitude was higher following intranasal CRH. No significant difference was seen in the normal control group. Thus, in neurotics, intranasal CRH was associated with increased startle amplitude during viewing of negatively valenced IAPS stimuli. No such effect was found in the normal controls. CRH increased startle in neurotics during viewing of fixation cross at a trend level of significance. This is the first demonstration in humans of CRH potentiation of startle reflex magnitude and of group differences in sensitivity to CRH.

Development of an EEG Measure of Emotion Processing. With support from the American Psychiatric Association and NIMH, Dr. Lee obtained training in the area of clinical electrophysiology, focusing on the development of an EEG measure of emotion processing suitable for neuropharmacological research. Although several well validated paradigms have been developed for the study of attention and working memory (novelty related auditory evoked potential), no validated task has been developed for research in emotion-related processing. Towards this end, Dr. Lee adopted the novelty related auditory P300 paradigm for this purposes by substituting validated visual emotional
stimuli (Ekman faces). In the Threat Related EEG task, a series of happy emotional faces is presented, interspersed in an unpredictable schedule with infrequent “angry” faces. In a separate block, infrequent “neutral” faces are presented (Figure 5). This design allows for analysis of brain activity in response to novel emotional stimuli that is able to account for novelty and emotion-specific effects.

In order to validate signal-averaged scalp EEG signals as a valid measure of brain function related to processing of the emotional stimuli, work was conducted using fMRI and intracranial EEG with the assistance of Dr. Vernon Leo Towle (Figure 6). fMRI data provide spatially accurate but temporally “smeared” information regarding brain hemodynamic function (which is turn correlated with at least some forms of neural activity). fMRI imaging during the Threat Related EEG task revealed frontal and temporal-parietal regional brain activation, consistent with distribution of neural circuits previously identified as being involved in the processing of emotional faces, and plausibly related to scalp EEG data collected in Dr. Lee’s laboratory. 3-dimensional

Figure 5. Emotional face presentation. Left: Frequent Happy faces jittered with infrequent Neutral faces. Right: Frequent Happy faces littered with rare Angry faces.

Figure 6. The Threat Related EEG task was repeated using intracranial EEG recording, high density EEG, and fMRI. A-B. ERP to Rare Angry Faces recorded on intracranial electrode array (n=1) directly on the right anterior temporal lobe (A) compared to simultaneously recorded scalp ERP (B) reveals overlap of the face related N200 and provides argument against eye or face muscle artifact as a generator. C. Source density analysis (LORETA) of High density EEG recorded ERP to Rare Angry face stimuli (n=12) reveals sources in parietal and frontal lobes at 200 msec post stimulus onset. D-E. fMRI whole-brain analysis with a conservative statistical threshold (p<.001; >8 contiguous voxels) reveals frontal (D) and parietal (E) regions of BOLD activation in contrasts of Angry face vs. fixation point.
source density analysis of scalp EEG data collected with multi-electrode array confirmed frontal and parietal sources of activity. Intracranial EEG data provide electrophysiological data directly from the surface of the brain. Because these data are much less affected by eye and facial muscle activity, they are invaluable in confirming that the signal recorded from scalp EEG does in fact reflect brain activity. When compared with scalp EEG data, the intracranial EEG data confirmed that the N200 signal detected by scalp EEG in Dr. Lee’s laboratory is of brain origin.

**Intranasal CRH is Associated with Increased N200 and Decreased P300 to Emotional Faces.** Major depression has previously been associated with altered neural processing of salient stimuli. It is not clear if CRH mediates altered processing of salient stimuli relevant in major depressive disorder. It was hypothesized that intranasal CRH would alter neural processing of threatening information, in this case emotional Ekman face stimuli. 100μg CRH was administered in a double-blinded placebo crossover experiment. EEG was recorded continuously during viewing of a series of Ekman face stimuli presented on a CRT screen. Happy Ekman faces were presented jittered randomly with Angry Ekman faces in a 4:1 ratio. Subjects were instructed to press the left or right mouse button depending on whether the facial expression was the “frequent” or “rare” stimulus. Two blocks of this series were presented, along with two blocks in which the rare stimulus was a Neutral Ekman face, holding constant the Ekman model. A Neuroscan Stim and Acquire workstation was utilized for this task; EEGs were recorded with 5 electrodes (EOG, Fz, Cz, Pz, Oz). Analysis of P300 amplitude revealed a significant effect of Condition, with P300 amplitude greater during viewing of rare Angry vs. rare Neutral faces. An overall effect of Drug was found, with CRH associated with reduced P300 amplitude (Figure 7. Analysis of N200 amplitude revealed a main effect for Drug, with CRH associated with greater N200 amplitude. These findings represent the first demonstration of altered central neurophysiologic reactivity to threatening stimuli with exogenous CRH in humans. A significant effect of CRH was found across both conditions (Neutral and Angry faces) and across both diagnostic groups (normal control and history of depression). The primary finding of interest is that CRH is associated with blunting of P300 amplitude. The direction of this change is the same as found in comparisons of P300 amplitude in depressed versus normal control groups, raising the possibility that CRH related P300 change is a biomarker reflecting underlying biological risk for depression.

**Figure 7.** Average ERP (n=18; each subject with >25 analyzable epochs) recorded during rare Angry stimuli. CRH relative to placebo was associated with increased N200 amplitude and decreased P300 amplitude. ERP to Neutral stimuli not shown.
Preliminary Work Regarding the “Anti-CRH” Neuropeptides Oxytocin and Insulin

Intranasal Oxytocin is Associated with Decreased N200 to Emotional Faces. Given the effects of intranasal CRH on threat processing, and preclinical and clinical data indicating possible “anti-stress” effects of oxytocin, the ability of intranasally administered oxytocin to counter a central measure of threat processing is of interest. Therefore, it was hypothesized that intranasal oxytocin would be associated with changes to threat-related ERP opposite to those seen with intranasal CRH. Intranasal oxytocin (20 IU), dap (20 IU) or placebo was administered in double-blinded fashion over three study sessions at least 5 days apart to adult males and females, followed 45 minutes later by EEG recording during viewing of emotion Ekman faces. The ERP paradigm was identical to that described above with intranasal CRH. For N200 amplitude, a significant interaction of Drug x Electrode was detected. Focusing on placebo – oxytocin differences, follow up analyses revealed that oxytocin was associated with lower N200 amplitude at the Fz electrode at a trend level (Figure 8). For P300 amplitude, a strong effect for Condition was found, again with angry faces associated with larger amplitude P300. Thus, when compared to placebo, intranasal oxytocin is associated with reduced amplitude of N200 during viewing of emotional Ekman faces. This contrasts with the effects described above for intranasal CRH.

Intranasal Insulin ASPART Does Not Affect Plasma Glucose. To establish feasibility and safety of administering intranasal insulin, pilot work was conducted to test the metabolic and behavioral effects of two doses of intranasally administered Insulin Aspart. Insulin Aspart was chosen because it is optimized for subcutaneous absorption. Placebo, 20, or 40 IU of Insulin Aspart were administered in double-blinded, randomized and counter-balanced order in two subjects. No clear dose dependent change in plasma glucose was detected. Both subjects noted reduction of hunger on insulin days (20 and 40 IU) relative to placebo, which was remarkable given that both subjects were fasting during the study procedures (Figure 9). Subject 2 passed the medical screening, but later admitted to previous work up for Type II diabetes with borderline results, and a strong family history of Type II diabetes. Thus, feasibility was demonstrated for the safe administration of intranasal Insulin Aspart. Dr. Lee’s preliminary results resemble those of other investigators administering intranasal insulin, demonstrating a lack of hypoglycemia that would otherwise be expected if system absorption were occurring.
In summary, Dr. Lee’s laboratory has been conducting systematic research regarding central CRH signaling in order to discover novel targets for the treatment of depression and stress-related psychopathology. This work has conceptualized depressive disorder and trauma-related personality disorder broadly as disorders of central CRH overdrive. Further work is needed to better understand the behavioral and psychological aspects of central CRH hyperfunction. The overall objective of the work is to improve the clinical treatment of difficult-to-treat stress-related psychopathology. Towards this end, Dr. Lee has been conducting innovative work using a novel central probe of CRH function. Exciting preliminary findings include the first-ever demonstration in humans of the effect of exogenous CRH on brain function in response to emotionally relevant stimuli (acoustic noisebursts and emotional face stimuli). The direction of findings is consistent with preclinical data regarding the anxiogenic effects of increased central CRH. Dr. Lee is currently obtaining replication data regarding the effects of intranasal CRH. In parallel with this work, his laboratory has begun collecting data regarding an approach to antidepressant treatment that is not based on modifying monoamine function, but rather targets the now well-recognized hyperfunction of central CRH in depressive disorder. Thus, Dr. Lee has begun exploring intranasally administered insulin, oxytocin, and adrenocorticotropic as candidate antidepressant therapies.

**Funding.**

- Azevan Pharmaceuticals: Vasopressinergic modulation of emotion: An fMRI study
  PI: Lee  
  12/01/2010-12/01/2011
- NIH/NIMH R21 MH083309: Effects of intranasal CRH on cortical and subcortical measures of arousal in major depressive disorder
  PI: Lee  
  07/01/2009-06/30/2011
- NARSAD: A pilot study of the effect of intranasal corticotropin-releasing hormone on emotion processing in remitted depression
  PI: Lee  
  07/01/2006-06/30/2008
- Clinical and Translational Science Award: Effects of intranasal insulin on EEG correlates of working memory
  PI: Lee  
  01/01/2008-01/01/2009

**Figure 9.** Within-subjects comparison of plasma glucose levels following double-blinded administration of two doses of Insulin Aspart versus placebo. No clear dose-related effect on plasma glucose level was detected.
Selected Recent Publications of Note.


Paul Vezina, Ph.D. (Psychiatry & Behavioral Neuroscience). Paul Vezina is Professor as well as Research Section Chief and Mission Director of the Department of Psychiatry and Behavioral Neuroscience at The University of Chicago. The overarching goal of his research is to understand the environmental and neurobiological determinants of motivated behaviors. Whether manifested as the initiation of sexual activity or the seeking out and ingestion of a food substance, the generation of such behaviors is critical to the survival and healthy development of all animal life forms. When impaired, as in the production of behaviors inappropriate to the environmental context or the exaggerated pursuit of substances such as food or drugs, the consequences for the individual and society can be devastating. Characterization of the neurobiological events that give rise to these behaviors is necessary to better understand the circumstances surrounding their expression and to develop successful interventions when necessary.

Training.

B.A., Psychology, Honors with Distinction, Concordia University, Montreal, Canada, 1981

M.A., Behavioral Neurobiology, Concordia University, Montreal, Canada, 1983

Ph.D., Behavioral Neurobiology, Concordia University, Montreal, Canada, 1987


Research Program.

Dr. Vezina’s research focuses on the ascending dopamine systems of the midbrain. These groups of neurons project to a large number of forebrain sites and are known to profoundly influence motor and affective behaviors directed at biologically significant stimuli in the organism’s environment. Importantly, they have been linked to several disease processes such as schizophrenia and substance abuse. Dr. Vezina’s strategy is to conduct basic research in rodents to understand how changes in the reactivity of these midbrain dopamine systems can contribute to such disorders. Of particular interest is a type of plasticity exhibited by these neurotransmitter systems whereby their response to a pharmacological or environmental stimulus becomes exaggerated (sensitized) and the behavior associated with this response is enhanced. As outlined below, his laboratory has made significant advances, first, in understanding how such
changes can impact the expression of motivated behavior particularly as it relates to the pursuit and abuse of drugs, and, second, in determining how neurotransmission in these systems becomes sensitized and how this plasticity impacts activity in other mid- and forebrain neurotransmitter systems.

This research is of vital importance. The constellation of disorders directly linked to the impaired expression of motivated behavior constitutes a major public health concern. Of these, the problems associated with substance abuse are particularly troubling and continue to require substantial and necessary allocations of resources by this country’s Public Health Service and judicial system.

One of the most notable accomplishments achieved by Dr. Vezina’s laboratory has been to demonstrate a clear relationship between sensitized neuronal activity and the enhanced generation of motivated behavior. Using drug-taking as a model, his laboratory demonstrated that, although all animals will intravenously self-administer psychostimulant drugs, animals exposed to a drug regimen known to sensitize the reactivity of midbrain dopamine neurons will subsequently work considerably more than non-sensitized animals to do so.

![Figure 1](image1.png)

**Figure 1. Sensitized animals show a greater brain dopamine response and work more to obtain intravenous amphetamine.** A. Results of an in vivo microdialysis experiment showing extracellular levels in the nucleus accumbens before and after an injection of amphetamine (arrow). Sensitized rats show a greater response to this injection than control rats that are not sensitized. B. Sensitized rats tested over 6 days work more (emit more presses) and as a result self-administer more amphetamine than non-sensitized controls.

These findings are important because they clearly indicate that sensitization within these dopamine systems impacts individuals’ motivation to engage in this behavior (Vezina et al., 2002). This enhanced motivation for drug self-administration requires the
activation of D1 dopamine, NMDA, AMPA and metabotropic glutamate receptors and is accompanied by elevated levels of extracellular dopamine in subcortical dopamine neuron terminal regions (summarized in Vezina, 2004). These findings represent an important step towards our understanding of the neuronal events that underlie the escalation of drug seeking associated with substance abuse and they continue to motivate behavioral, electrophysiology and molecular biology based experiments in Dr. Vezina’s group as well as other laboratories working in the area. The enhancements observed in behavioral and dopaminergic responding that are characteristic of sensitization are enduring and it is conceivable that they may play an important role in the reinstatement of drug taking in individuals that have been drug free for some time.

Figure 2. Working model underlying ongoing multidisciplinary experiments assessing the effects of nicotine exposure on midbrain nicotinic acetylcholine receptors, neuronal excitability, biochemistry and behavior.

Dr. Vezina’s laboratory also continues to make important advances in the characterization of the neuronal events that underlie sensitization. Earlier, his group showed that the process of sensitization is reducible to at least two events - induction and expression - and that these are temporally, neuroanatomically and mechanistically distinct. These findings continue to guide experimentation in the field at multiple levels of analysis. Dr. Vezina and his colleagues were recently awarded a Program Project Grant to characterize the neuronal events by which nicotine promotes self-administration behaviors. Using a multidisciplinary approach, these experiments are examining the effects of exposure to nicotine on midbrain nicotinic acetylcholine receptors, neuronal excitability, biochemistry and behavior. The working model underlying this work is outlined above, where nicotine exposure is hypothesized to produce upregulation of nicotinic receptor function, leading to enhanced excitation of midbrain dopamine neurons and the induction of Long Term Potentiation. These steps lead ultimately to sensitization of midbrain dopamine neuron reactivity and to behavioral manifestations of sensitized responding to the drug.

More recently, Dr. Vezina has begun studying the post-receptor signalling pathways in medium spiny neurons in forebrain that underlie the expression and long-lasting maintenance of sensitization. These neurons express a number of receptor types including those binding dopamine and glutamate that are supplied by converging dopamine and glutamate inputs. Currently, experiments are underway delineating the pathways involving

Figure 3. Schema of a medium spiny neuron segment illustrating dopamine and glutamate receptor initiated signalling pathways.
two protein kinases: calcium/calmodulin dependent protein kinase II (CaMKII) and casein kinase 1ε (Csnk1ε). Dr. Vezina’s group recently used viral-mediated gene transfer to transiently overexpress CaMKII in forebrain medium spiny neurons. They found that this led to functional upregulation of ionotropic AMPA receptors in these cells and the long-lasting expression of sensitized behavioral responding to amphetamine (Loweth et al., 2010). Remarkably, enhanced responding to amphetamine was observed not only when CaMKII was overexpressed but long after levels of this protein had returned to baseline. Among the behaviors affected was the amount of work output rats emitted to obtain intravenous amphetamine. Interestingly, exposure to amphetamine also leads to transient increases in CaMKII in forebrain. These findings are important because they reveal how genetically (using viral-mediated gene transfer) or experientially induced neuronal adaptations in a specific population of neurons (in individuals previously exposed to a drug) can lead to enhanced drug intake. Dr. Vezina’s group is continuing these experiments to delineate the post-receptor pathways

Figure 4. Transiently increasing αCaMKII in neurons of the forebrain (arrows) leads to long-lasting increases in the work rats will emit to obtain amphetamine. Data are shown as mean (±SEM) number of infusions obtained on each day. Filled circles: infected. Open circles: control.

Figure 5. Amphetamine can produce two types of changes in dendritic morphology in the rat forebrain: one corresponding to nonassociative drug sensitization (top) and one corresponding to associative conditioning (bottom). The first is produced by exposure to amphetamine in the midbrain (VTA); the second by exposure to amphetamine systemically. While both types of exposure produce sensitization, only the second produces conditioned locomotion (more locomotion in animals previously administered the drug Paired with the testing environment; left). The drawings of medium spiny neurons to the right (each with a highlighted dendritic length) illustrate the effects of exposure to amphetamine on the different morphological measures quantified in the bar graphs.
that lead to the enhanced generation of drug seeking. A major component of these experiments is to understand how these neurons integrate information that is provided by the dopamine and glutamate inputs they receive. Clearly, glutamate-dopamine interactions are important mediators of drug effects and signalling pathways using CaMKII and Csnk1ε are involved.

In a separate group of experiments, Dr. Vezina is examining the effects of exposure to psychostimulants like amphetamine on the morphology of medium spiny neurons in forebrain. Recently, his group demonstrated that these drugs produce a number of long-lasting effects on the morphology of these neurons (Singer et al., 2009). They found that the opportunity to form conditioned associations between a drug and an environmental context leads to increases in spine density as well as dendritic length and branching. On the other hand, nonassociative neuronal plasticity like that underlying drug sensitization was accompanied by decreases in these morphological measures, a finding most likely related to the fact that the procedures used to produce sensitization in these experiments (application of amphetamine directly to the midbrain) fail to produce any kind of conditioning. Learned associations between contexts and the presence or absence of drugs are important determinants of drug taking and relapse (Vezina and Leyton, 2009). These results are beginning to elucidate how such effects can be mediated. The communication between cells that occurs at synapses located on the spine heads of medium spiny neurons is most certainly affected when drugs like amphetamine affect the physical properties of these cells. Dr. Vezina’s group is pursuing these findings to more clearly understand these drug-induced morphological changes and how they impact behavior. Current experiments are using different dyes to study drug-induced changes in immunohistochemically identified groups of cells in the forebrain.

**Figure 6.** Example of a dye-filled dendritic segment of an identified medium spiny neuron in the forebrain showing different types of spines (left) and a sample tracing of the dendrite and its spines using Imaris® 3-D reconstruction software (right).
Vezina Laboratory Website.

http://vezinalab.bsd.uchicago.edu/index.html

Funding.

- NIH/NIDA R01 DA09397: Sensitization and stimulant self-administration
  PI: Vezina  07/01/1995-06/30/2012 (NCE)
- NIH/NIDA P01 DA019695: Nicotine exposure: Molecular to behavioral consequences
  PI: Vezina  05/01/2007-03/31/2013 (NCE)
- NIH/NIDA T32 DA07255: Neuropsychopharmacology training for drug abuse research
  PI: Vezina  09/30/1991-06/30/2013
- NIH/NIDA R01 DA025088: Extinction of cue-elicited cocaine seeking
  PI: Xu   04/15/2009-03/31/2014
- National Research Foundation of Korea: CART peptide signalling in the nucleus accumbens: Interactions with psychostimulants and other appetite-related peptides
  PI: Kim/Vezina   09/01/2011-08/31/2014

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