



MIDWEST ALCOHOLISM RESEARCH CENTER: AN OVERVIEW

Andrew C. Heath, D. Phil.
Director, Midwest Alcoholism Research Center
Spencer T. Olin Professor of Psychiatry
Department of Psychiatry
Washington University School of Medicine



GOAL

- ♦ To conduct a collaborative program of community-based research on the etiology and course of alcohol problems and associated comorbidity, with an emphasis on prospective high-risk, behavioral and molecular genetic, genetic epidemiologic and experimental perspectives, and with a particular focus on adolescents and youth, to address three etiologic models and five major research questions.
- ♦ **Etiologic Models for Alcohol Dependence**
 - **Behavioral undercontrol** – what is the role of impulsive traits, attentional problems, and adolescent conduct problems (or problem behaviors) in the etiology of alcohol dependence?
 - **Negative affect regulation** – what is the role of negative affect, depression and anxiety disorders and early onset suicidality in the etiology of alcohol dependence?
 - **Pharmacologic vulnerability** – what is the role of innate differences in metabolic, subjective, psychomotor and physiologic responses to alcohol, and to nicotine, in the etiology of alcohol dependence?



Major Research Questions

- ♦ **Gene discovery**
Can we use genetic linkage or association approaches to identify novel genetic risk factors for alcohol dependence or associated substance use disorders (e.g., tobacco dependence)?
- ♦ **Developmental course/natural history**
Can we identify stage-specific risk factors (genetic or environmental), e.g., different risk or protective factors for initiation of adolescent drinking versus transition to problem drinking versus remission of alcohol problems?
- ♦ **Risk Modifiers**
What modifiers/vulnerability factors, genetic or environmental, interact with known risk factors to exacerbate or diminish risk (e.g., under what environmental conditions is the effect of genetic risk increased or diminished – genotype x environment interaction)?
- ♦ **Human experimental paradigms**
What sociodemographic, personality, psychiatric, or other individual difference variables account for genetic (or environmental) influences on risk of alcohol dependence?
- ♦ **Micro-level (ecological) analysis of human behavior**
How do real-time recording method, (e.g. Palm-Pilot-based methods) confirm or disconfirm findings based on more global self-ratings of behavior.



Approach

- ♦ Bring together expertise in diverse areas of alcohol research, represented principally at the three major research universities of the state of Missouri:
 - Washington University School of Medicine—expertise in biological psychiatry, genetic and epidemiologic aspects of alcoholism
 - University of Missouri–Columbia—expertise in psychosocial, psychobiological approaches to understanding alcoholism etiology and consequences
 - Saint Louis University School of Public Health—expertise in public health, epidemiologic aspects of alcoholism research
- ♦ Five other institutions collaborate in our research program:
 - Queensland Institute of Medical Research, Brisbane, Australia—provides access to a large number of families with adult twins (>10,000 families), permitting cross-cultural comparisons with a heavy drinking society
 - Palo Alto Veterans Administration, Palo Alto, California—expertise concerning psychosocial and family study approaches in alcoholism research
 - Brown University, Providence, Rhode Island—expertise in behavior genetics, and quantitative psychology and longitudinal methods
 - University of Iowa, Iowa City, Iowa—expertise in psychological disorders and psychosocial research pertaining to adult and adolescent alcoholism
 - Arizona State University, Tempe, Arizona—expertise in the development of substance abuse/dependence in adolescents and adults and associated mental health disorders



Center-Affiliated Research Projects, Science Cores, and Training Programs

- ♦ The Center's alcoholism research program is much broader than the scientific cores and three research projects directly funded through the NIAAA Center grant.
- ♦ Table 1 (later panel) summarizes (most of) the Center's relevant research and training portfolio that is supported through other research mechanisms. Five research areas/approaches are represented:



Center-Affiliated Research Projects, Science Cores, and Training Programs (*con't.*)

A. **Methodologic Research Projects**

Methodological projects involving original theoretical work, computer simulation, and secondary data analysis, that are designed to develop improved methods of collecting and analyzing data on genetic influences on risk of alcoholism and related phenotypes, and their interactions with environmental risk factors.

B. **Gene-Mapping Projects**

The emphasis here is on projects using community-based rather than clinic-based sampling schemes, and using a Quantitative Trait Locus approach. One funded project is focused on smoking and nicotine dependence, but is included here because it is also assessing alcohol-related phenotypes, to take advantage of the overlap of genetic risk factors for alcohol and nicotine dependence. Three are using both diagnostic and quantitative indices of alcohol dependence and consumption patterns. Another project is using a mutation screening approach to identify genes that contribute to risk of co-occurring alcohol and nicotine dependence.



Center-Affiliated Research Projects, Science Cores, and Training Programs (*con't.*)

C. Conventional Prospective Epidemiologic & Genetic Epidemiologic Projects

Because of the relative maturity of the field of genetic epidemiologic research on alcoholism, these are primarily focused on comorbid phenotypes such as gambling where mediators and modifiers of genetic influence are less well understood, as well as other laboratory-based molecular genetic studies (e.g. mutation screening, candidate gene studies). There are several projects focused on children, adolescents or young adults and their parents. These include (i) an African-American family study, focused on adolescent siblings and their parents, with oversampling of high-risk families where there is paternal history of alcohol dependence and/or recurrent drunk-driving convictions; (ii) twin-family studies of childhood Attention Deficit Hyperactivity Disorder (ADHD), a disorder of particular interest because it is observed much more commonly in the children with an alcoholic biologic parent; (iii) a prospective adolescent male twin study of adolescent smoking and nicotine dependence which is coordinated with the MARC adolescent twin project; (iv) a mentored clinician scientist award focused on parental alcoholism and adolescent suicidality; (v) a longitudinal study of drinking and high-risk sexual behavior which is following a panel of subjects first assessed as young adults; (vi) and an adolescent twin project focused on adolescent and young adult alcohol problems and dependence, with follow-up assessments at ages 17-25 of participants first assessed at ages 13-19.



Center-Affiliated Research Projects, Science Cores, and Training Programs (*con't.*)

D. Human Experimental Projects

One project collects data on the children of a comparison group of drug-dependent twins and their cotwins, and will be especially powerful for detecting the environmental influences of parental alcoholism, including those whose effects may depend upon offspring genotype (genotype x environment interaction). A 20-year project has completed repeat assessments of student drinking and alcohol dependence, and comorbid problems, through the college years, with follow-up in adulthood. A new cohort is now being recruited, with assessment prior to entry to college, and planned follow-up through the same age range. Another project is using electrophysiological approach using nicotine challenge to define heritable dimensions of response to nicotine and/or alcohol, which may be associated with differences in alcohol dependence risk.

E. Human Micro-Assessment Studies

A new direction of the MARC, these studies use moment-to-moment assessment of behavior (via electronic diary [ED, i.e. Palm Pilot] assessment) with the goal of bridging the gap between association found in genetic epidemiology (including molecular genetic) studies, and findings from studies investigating these associations in the human experimental laboratory.

Table 1: Research projects and training programs (including grants pending funding or pending review) of MARC personnel.

PI	Funding Agency	Mechanism	Title	Project Period
A. Methodologic Research Projects				
1. Cooper, M.	NIH/NIH	K02	Functional Perspectives on Health and Risk Behaviors	05/04-04/09
2. Fu, Q. J.	NIH/NCI	K07	The Genetics of Smoking: The Trans-theoretical Model	09/05-08/10
3. Heath, A.	NIH/IAAA	R37	Genetic Epidemiologic Models of Alcohol Abuse	07/89-06/08
4. Jackson, K.	NIH/IAAA	K01	Longitudinal Methodology and Alcohol Use	08/03-07/08
5. Lessov-Schlaggar, C.	NIH/IDA	U01	Core--Statistics	09/05-06/10
6. Trull, T.	NIH/NIH	R21	Characterizing Affective Instability Using EMA	09/04-08/07
B. Gene-Mapping Projects				
7. Heath, A.	NIH/IAAA	R01	Molecular Epidemiology of Alcoholism 3--EDAC Families	09/01-08/07
8. Madden, P.	NIH/IDA, NCI	R01	Genetics of Vulnerability to Nicotine Addiction	05/00-04/07
9. Price, R.	NIH/IDA	R01	Disentangling Substance Use & Psychiatric Disorder Comorbidity for Future HuGE	09/05-08/10
10. Todd, R.	NIH/IAAA	R01	Molecular Epidemiology of Alcoholism 2--Big Sibships	04/03-03/08
11. Todd, R.	NIH/NIH	R01	Molecular Genetics of Inattention in Australia	09/05-06/10
12. Todd, R.	NIH/IAAA	R01	Mutation Screening of Nicotine and Alcohol Dependence	08/02-07/07
C. Conventional Prospective Epidemiologic & Genetic Epidemiologic Projects				
13. Anokhin, A.	NIH/IAAA	R01	College Drinking: A Twin Study	09/02-08/07
14. Bucholz, K.	NIH/IAAA	R01	Alcoholism: Epidemiologic High Risk Family Study	07/01-06/09
15. Dick, D.	NIH/IAAA	R01	Gene-Environment Interplay in Adolescent Alcohol Use	09/05-08/10
16. Glowinski, A.	NIH/NIH	K08	Familial Transmission of Youth Suicidal Behavior	05/02-04/07
17. Heath, A.	NIH/NIH	R01	GxE in Early Childhood: Twin Mothers	01/05-12/09
18. Heath, A.	NIH/IAAA	R01	Parental Alcoholism & Child Environmental Risk	09/04-08/09
19. Jacob, T.	NIH/IAAA	R01	Offspring of Twins: G, E and GxE Risks for Alcoholism	03/98-01/10
20. Jacob, T.	NIH/IAAA	R01	Alcoholism Course Throughout Midlife	09/06-08/10
21. Knopik, V.	NIH/IDA	K01	Externalizing Behavior: Genetics x Prenatal Nicotine	07/04-06/09
22. Lynskey, M.	NIH/IDA	R01	Cannabis and Other Illicit Drug Use: A Twin Study	09/05-08/10
23. Lynskey, M.	NIH/IDA	R01	Cannabis Use, Abuse and Dependence: Exploring Phenotypes	09/04-06/09
24. Nelson, E.	NIH/IAAA, NIH, NICHD	R01	Childhood Trauma, Parental Alcoholism, and Comorbidity	09/02-08/07
25. Nelson, E.	NIH/IDA	R01	Opioid Dependence: Candidate Genes and GxE Effects	09/03-08/08

Table 1 (cont.): Research projects and training programs (including grants pending funding or pending review) of MARC personnel.

PI	Funding Agency	Mechanism	Title	Project Period
C. Conventional Prospective Epidemiologic & Genetic Epidemiologic Projects (cont.)				
26. Pergadia, M.	NIH/IDA	K08	Refining Phenotypic Measures of Nicotine Withdrawal	08/05-07/10
27. Philibert, R.	NIH/IDA	R01	Genetic Studies of Substance Abuse in Iowa Adoptees	07/04-06/09
28. Price, R.	NIH/NIH, NIDA	R01	Follow-Up of Vietnam Veterans at Risk for Suicide	09/01-08/07
29. Slutske, W.	NIH/NIH	R01	Genetic Epidemiology of Pathological Gambling	04/03-03/08
30. Todd, R.	NIH/NIH	R01	Molecular Epidemiology of Inattentive ADHD	01/04-11/08
31. Todd, R.	NIH/INDS	R01	Mutation Screening of ADHD	06/02-05/07
32. Todorov, A.	NIH/IDA	R01	Genetic Epidemiology of Opioid Dependence in Bulgaria	08/06-04/11
D. Human Experimental Projects & Human Micro-Assessment Projects				
33. Anokhin, A.	NIH/IDA	K01	Biobehavioral Markers of Risk for Nicotine Addiction	07/01-06/07
34. Anokhin, A.	NIH/IDA	R01	Neurocognition, Genetics, and Adolescent Substance Abuse	09/04-07/09
35. Bucholz, K.	NIH/IDA	R01	Gene-Environment in Outcomes of PSuD Twins' Offspring	06/01-05/07
36. Chassin, L.	NIH/IDA	R01	Substance Use Among Children of Alcoholics	09/87-06/11
37. Constantino, J.	NIH/NIH	R01	Autistic Traits: Life Course and Genetic Structure	04/02-03/08
38. Sher, K.	NIH/IAAA	R37	A Prospective Study of College Students	06/87-06/07
39. Sher, K.	NIH/IAAA	R01	Long Term Consequences of Collegiate Alcohol Involvement	09/02-08/07
40. Sirevaag, E.	NIH/IDA	R01	Behavioral Genetics of Nicotine Dependence	08/01-05/07
41. Bucholz, K.	NIH/IAAA	U13	A New Annual Alcohol Research Forum: Guze Symposium	05/02-04/07
42. Chassin, L.	NIH/NIH	T32	Research Training--Child Mental Health/Primary Prevention	07/87-06/10
43. Cicero, T.	NIH/IDA	T32	Biomedical Research Training in Drug Abuse	09/91-06/06
44. Heath, A.	NIH/IAAA	T32	Biomedical Training in Alcoholism Research	07/00-06/10
45. Sher, K.	NIH/IAAA	T32	Psychology of Alcohol Use and Dependence Training	07/02-06/07
G. Midwest Alcoholism Research Center				
46. Heath, A.	NIH/IAAA	P50	MARC: Genetic Epidemiology of Alcoholism & Comorbidity	06/04-05/09
47. Piasecki, T. and Sher, K.	NIH/IAAA	P50	Conjoint Alcohol and Tobacco Use: An Ecological Study	06/04-05/09
48. Slutske, W.	NIH/IAAA	P50	Australian Children of Alcoholic Female Twins	06/04-05/09
49. Todd, R.	NIH/IAAA	P50	Molecular Epidemiology of Alcoholism/Comorbid Disorders	06/04/05/09



Organization:

1. Scientific Cores

- ♦ **Administrative Core (PI Heath)**

Responsible for coordinating the MARC research program, facilitating communications among the eight participating sites, monitoring project productivity and human subjects protections, and arranging oversight by the External Scientific Advisory Board and Community Advisory Committee.
- ♦ **Pilot Project Core (PI Bucholz)**

Provides pilot project support for junior investigators and others who are trying to develop new directions in alcoholism research.



Organization:

2. Center-Based Research Projects

Project 4: Australian Children of Alcoholic Female Twins (PIs Slutske, Treloar)

This ongoing project examines the role of genetic and family environmental influences, and their interaction, in the development and course of alcohol use disorders (AUD) by studying Australian women who are mothers and twins and their offspring as young as 7 years old.

Our research will enable us to confirm or disconfirm our emerging data based on retrospective reports of twin mothers about their adolescent and young adult offspring on disorders with early childhood onset (ADHD, Oppositional Defiant Disorder [ODD], conduct disorder [CD]). And by the end of the renewal period, samples will be sufficiently large so that complex cross-sectional and longitudinal analyses will be firmly based.

The research strategy incorporates:

- use of the children of twins (COT) design involving twins who are concordant or discordant for AUD as well as control pairs
- assessment of children of alcoholic mothers
- use of a prospective design which allows for description of offspring development from preadolescence through the late twenties

This prospective study is coordinated with two R01 projects focused on U.S. national samples of alcoholic and control Vietnam-era veteran male twins and their cotwins, spouses, and offspring.



Organization: 2. Center-Based Research Projects *(con't.)*

Project 5: Molecular Epidemiology of Alcoholism & Comorbid Disorders (PIs Todd, Trull)

This project builds upon gene-discovery projects such as COGA (Collaborative Study on the Genetics of Alcoholism: PI Begleiter) and similar projects which are studying treatment-ascertained alcoholics and their relatives, and the MARC-affiliated Alcohol-QTL IRPG consortium (PIs Heath, Martin, Madden, Todd), which is studying community-ascertained alcoholics and heavy smokers and their adult relatives, by incorporating a molecular genetic component into 4 mature, prospective longitudinal studies (PIs Chassin, Cooper, Heath, Sher) spanning the age-range from early adolescence into young adulthood, with 3-7 waves of prospective assessment. In addition to collecting DNA from the target samples (years 1-3), this project combines secondary data-analysis and genotyping, proceeding in 4 stages:

- i. behavioral genetic analyses using existing twin data sets (MOAFTS, the former MARC Project 1, or other US and Australian data-sets to which we have access through the MARC) to confirm heritability of phenotypes defined at stage (i), determining whether that phenotypic operationalization is optimal for understanding genetic effects (years 1-3);
- ii. longitudinal and other phenotypic analyses to establish consistent phenotype definition across informative data-sets (years 1-3);
- iii. Genotyping for a limited number of candidate genes (years 3-5); and
- iv. genetic association analysis (years 4-5).



Organization: 2. Center-Based Research Projects *(con't.)*

Project 6: Conjoint Alcohol & Tobacco Use: An Ecological Study (PIs Piasecki, Sher)

This study uses the Ecological Momentary Assessment (EMA; Stone & Shiffman, 1994) to investigate hypothesized mechanisms that may motivate joint use of alcohol and cigarettes, assessing alcohol use and smoking, their subjective antecedents and sequelae, and environmental contexts allowing comparisons to be made between (i) drinker-smokers, (ii) only drinkers, (iii) only smokers, and (iv) neither drinkers or smokers.

- Via handheld electronic diary (ED, i.e. Palm Pilot), subjects enter ED recordings, including morning assessments, drinking episode assessments, and smoking episode assessments, as well as random prompts, over a 3-week period.

This study examines:

- i. the unique effects of conjoint alcohol-smoking, relative to smoking alone and drinking alone, on both positive and negative affective states;
- ii. the relation between individual differences in conjoint alcohol-smoking and substance-specific changes in positive/negative affect and subsequent drinking and smoking behavior;
- iii. the extent to which individual difference variables condition the magnitude of conjoint and substance-specific effects on alcohol and/or tobacco seeking behavior;
- iv. the association between smoking level and acute and delayed aversive (punishing) effects of alcohol; and
- v. the extent to which individual differences in these aversive consequences predict subsequent drinking behavior



Investigators

- ♦ A multi-disciplinary team of faculty investigators is taking part in this research program, many with primary appointments in the Department of Psychiatry at Washington University, which has a long history of trans-disciplinary research on alcohol, tobacco, and other drug dependence; but with other investigators drawn from departments as diverse as Neurology and Otolaryngology at Washington University, the Department of Psychological Sciences at University of Missouri–Columbia, the Department of Psychiatry at the University of Iowa, the Family Study Center at the Palo Alto VA, the Center for Alcohol & Addiction Studies at Brown University, the Prevention Research Center at Arizona State University, and the Department of Community Health at Saint Louis University School of Public Health. Eight post-doctoral fellows also participate in this research program. Fourteen faculty investigators are also former graduates from our training program.
- ♦ Because foreign populations may offer particular advantages for genetic research, foreign collaborators from Australia are included in our team of investigators, with other collaborations with investigators in Japan, China, Finland, and the Netherlands under active development.



Table 2. Faculty Investigators

Investigator	Department, Institution	Expertise
A. Agrawal, PhD	Psychiatry, Washington University	Psychiatric disorders, statistical genetics
A. Anokhin, PhD	Psychiatry, Washington University	Psychology, behavioral genetics
K. Bucholz, PhD	Psychiatry, Washington University	Epidemiology, genetic epidemiology, adult assessment
L. Chassin, PhD	Psychology, Arizona State University-Tempe	High-risk longitudinal research
J. Constantino, MD	Psychiatry, Washington University	Child psychiatry, epidemiology
L. Cooper, PhD	Psychological Sciences, University of Missouri-Columbia	Social and developmental psychology
N. Cowan, PhD	Psychological Sciences, University of Missouri-Columbia	Memory and attention in human cognition
D. Dick, PhD	Psychiatry, Washington University	Behavioral and psychiatric genetics
Q. Fu, MD	Community Health, Saint Louis University	Health psychology
A. Glowinski, MD	Psychiatry, Washington University	Child psychiatry, child assessment
J. Goebel, MD	Otolaryngology, Wash University	Dynamic posturography
J. Grant, PhD	Psychiatry, Washington University	Developmental psychology, behavioral genetics
R. Haber, PhD	Family Study Center, Palo Alto Veterans Administration	Clinical psychology, family studies
A. Heath, DPhil	Psychiatry, Washington University	Behavioral genetics, genetic epidemiology
K. Jackson, PhD	Community Health, Brown University	Quantitative psychology, longitudinal methods
T. Jacob, PhD	Family Study Center, Palo Alto Veterans Administration	Clinical psychology, family studies
V. Knopik, PhD	Community Health, Brown University	Psychology, behavioral genetics
C. Lessov-Schlaggar, PhD	Psychiatry, Washington University	Genetic epidemiology, twin methodology
C. Lewis, MD	Psychiatry, Washington University	Addiction psychiatry
P. Madden, PhD	Psychiatry, Washington University	Behavioral genetics, genetic epidemiology



Table 2. Faculty Investigators (con't.)

Investigator	Department, Institution	Expertise
N. Martin, PhD	Genetic Epidemiology, Queensland Institute of Medical Research	Genetics, longitudinal studies
E. Nelson, MD	Psychiatry, Washington University	Psychiatry genetics, alcohol and anxiety
R. Neuman, PhD	Psychiatry, Washington University	Mathematics, statistical genetics
M. Pergadia, PhD	Psychiatry, Washington University	Behavioral genetics
R. Philibert, MD, PhD	Psychiatry, University of Iowa	Psychiatric genetics
T. Piasecki, PhD	Psychological Sciences, University of Missouri-Columbia	Psychology of addiction
R. Price, PhD	Psychiatry, Washington University	Sociology, psychiatric epidemiology
J. Rohrbaugh, PhD	Psychiatry, Washington University	Psychophysiology, challenge studies
J. Romeis, PhD	Community Health, Saint Louis University	Public health, behavioral genetics
J. Scherrer, PhD	Psychiatry, Washington University	Behavioral genetics, epidemiology, longitudinal research
K. Sher, PhD	Psychological Sciences, University of Missouri-Columbia	Clinical psychology, high-risk longitudinal research
E. Sirevaag, PhD	Psychiatry, Washington University	Psychophysiology, nicotine challenge
W. Slutske, PhD	Psychological Sciences, University of Missouri-Columbia	Behavioral genetics
R. Todd, PhD, MD	Psychiatry, Washington University	Child psychiatry, molecular neurobiology
A. Todorov, PhD	Psychiatry, Washington University	Biometrics, statistical genetics
S. Treloar, PhD	Genetic Epidemiology, Queensland Institute of Medical Research	Population studies, human genetics
W. True, PhD	Community Health, Saint Louis University	Public health, behavioral genetics
T. Trull, PhD	Psychological Sciences, University of Missouri-Columbia	Clinical psychology, personality & personality disorder
P. Wood, PhD	Psychological Sciences, University of Missouri-Columbia	Quantitative psychology
M. Waldron, PhD	Psychiatry, Washington University	Clinical psychology, family studies