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MIDWEST ALCOHOLISM RESEARCH CENTER: AN OVERVIEW

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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 two 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

- Four 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
  - 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 four research projects directly funded through the NIAAA Center grant. Five research areas/approaches are represented:

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

A. <u>Methodologic Research Projects</u>

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. <u>Gene-Mapping Projects</u>

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. The second is using both diagnostic and quantitative indices of alcohol dependence and consumption patterns, and is now conducting genomewide association study analyses.

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

C. Conventional Prospective Epidemiologic & Genetic Epidemiologic Projects

There are two major projects focused on adolescents or young adults and their parents. These are (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; and also (ii) a prospective study of young adult twin pairs who have been followed since their mid-teens.

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

D. <u>Human Experimental Projects</u>

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 of students followed through the college years, with assessment prior to entry to college, and planned follow-up through the same age range.

E. <u>Human Micro-Assessment Studies</u>

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.

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.

- **Scientific Resource Core** (PI Bucholz)

  Development of an integrated database to handle phenotypic, genotypic & environmental exposure data; coordination of assessment protocols across projects; and management of databases for research subject selection.

- **Pilot Project Core** (PI Madden)

  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 *(con't.)*

Project 5: Molecular Epidemiology of Alcoholism & Comorbid Disorders (PIs Lynskey)

This project builds upon gene-discovery projects which are studying treatment-ascertained alcoholics and their relatives, and the MARC-affiliated Alcohol-QTL IRPG consortium (PIs Heath, Martin, Madden), 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, Anokhin, 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 Trull, Sher)

This study extends ongoing research on both drinking and smoking using ecological momentary assessment (EMA) to examine the use of alcohol with and without conjoint smoking to regulate emotions, and the effects of these regulation strategies on subsequent mood. We add a comparison group of Borderline Personality Disorder (BPD) patients. BPD exhibits high comorbidity with alcohol use disorders (AUDs) in both clinical and population-based samples. Cardinal symptoms of BPD, impulsivity and affective instability, are central constructs in theories of AUD etiology, so BPD represents a type of "model system" for studying the role of emotion regulation and disordered self-control in the genesis of AUD. We will collect EMA data from both random and event-based (e.g., drinking, smoking) assessments to address our aims..

This study examines:

i. drinking episodes in BPD patients will be presaged by both positive and negative moods; drinking in non-affected controls (CON) will be presaged by positive but not negative moods; impulsivity will moderate these mood-substance use relations;

ii. BPD patients' drinking episodes will be associated with heavier consumption (sex and body weight adjusted) than CON; group differences will be moderated by both affective instability and by impulsivity. Drinks consumed will be moderated by number of cigarettes in both groups ;

iii. Alcohol consumption's effect on mood will be characterized by both positive and negative reinforcement; smoking will attenuate the degree of reinforcement due to acute cross-tolerance effects in both groups. In BPD patients, underlying affective instability will attenuate the duration of alcohol-related, salutary effects on mood ;

iv. Negative post-drinking effects of alcohol on mood will be larger in BPD patients than controls because of additive effects of hedonic rebound effects of alcohol and negative affectivity in BPD patients; smoking will increase these effects in both groups. This study will provide important information about the role mood dysregulation plays in the etiology and maintenance of AUD, and how impulsivity and smoking may interact with mood dysregulation to lead to increased drinking. These results will have implications for both prevention and treatment of alcohol problems.

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

Project 7: Examining genotype x environment interaction in the context of a GWAS (PIs Nelson, Martin)

This is a follow-up of a sample for a funded Genome-wide Association Study (GWAS) of alcohol dependence (1799 alcohol dependent cases and 1808 controls). This cohort, which has a demonstrated commitment to research participation of more than a decade, is unique in that is comprised of individuals who were ascertained from prior community-based (rather than clinical) assessment and who grew up during a period of very restrictive Australian divorce laws so that 85% of those reporting a history of parental alcoholism were raised by both biological parents through age 16. This project draws on data from the project director's recently-completed Trauma Study (AA13446) which comprehensively assessed severe childhood stressors in a partially-overlapping sample of twins and siblings. We present data demonstrating the feasibility of the assessment (on which the current proposal's assessment is based) including strong evidence for its utility in collecting retrospective history of childhood events (i.e excellent within-pair agreement for same-sex twins), and the ability to derive factors from its use that have excellent psychometric properties, display a dose-response relationship with report of parental alcohol problems), and which contribute significantly to the proposal's primary dependent measure, a quantitative alcohol consumption factor. We believe that the proposed design is uniquely well-suited to uncover G x E interactions contributing to the liability for alcohol consumption and has adequate power for this purpose.

This study will:

i. Assess lifetime history of severe childhood and adult environmental stressors, DSM-IV lifetime diagnoses of PTSD and illicit drug dependence, and updated histories of alcohol consumption measures and DSM-IV alcohol dependence in this sample of Australians for whom whole genome SNP genotyping is in progress

ii. Using a quantitative heaviness of drinking factor score, test for moderation of SNP genotype effects by history of severe childhood stressors

iii. Test for moderation of SNP genotype effects on alcohol dependence symptoms by history of severe childhood stressors

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

Project 8: Executive Cognitive Functioning (ECF) in Alcohol Use and Problems

(PI Bartholow, McCarthy)

Alcohol consumption leads to a number of behavioral problems, including increased risk of accidents, interpersonal conflict, and risky decision-making, which account for significant health care costs in the U.S. annually. Recent research indicates that alcohol causes impairment of so-called "executive cognitive functions" (ECFs), and suggests that this impairment is the driving force behind alcohol-related changes in behavior. However, alcohol's effects on ECF, including whether particular aspects of ECF are more susceptible to alcohol-induced impairment than others, are not fully understood. In addition, there are wide individual differences in executive ability, but very little is known about how these baseline differences may moderate the acute effects of alcohol on ECF. Therefore, the long-term objective of this proposal is to increase understanding of alcohol's effects on ECF, including which aspects of ECF are most impaired by alcohol, how separable aspects of ECF relate to one another, and how these effects differ between individuals. To achieve this goal, a series of specific aims will be addressed using 3 experiments. These aims include determining alcohol's effects on three specific components of ECF (shifting, updating, and inhibition), testing whether alcohol-induced impairment of ECF differs on the ascending and descending limbs of the blood alcohol concentration curve, and the extent to which baseline differences in ECFs moderate the acute effects of alcohol. Finally, the three experiments are designed so as to permit an over-arching meta-analytic integration using data from all of them, in order to test how the three components of ECF relate to one another and to performance on complex executive tasks. A design like this has never been used in any published study on the effects of alcohol. The outcome of this project will have important implications for understanding the cognitive impairment resulting from alcohol intoxication.

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, and the Prevention Research Center at Arizona State University. 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
B. Bartholow, PhD	Psychology, University of Missouri-Columbia	Electrophysiology, challenge studies
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
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
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
D. McCarthy, PhD	Psychology, University of Missouri –Columbia	Pharmacogenetics of Behavior
M Lynskey, PhD	Psychiatry, Washington University	Drug Abuse, Genetic Epidemiology
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
V. McCutcheon, PhD	Psychiatry, Washington University	Childhood trauma, female alcoholism
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
C. Sartor, PhD	Psychiatry, Washington University	Childhood trauma, drinking trajectories
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
A. Todorov, PhD	Psychiatry, Washington University	Biometrics, statistical 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	Psychology, Indiana University	Clinical psychology, family studies