Behav Genet (2006) 36:473–482
DOI 10.1007/s10519-006-9072-9

ORGINAL PAPER

Challenges in Genetic Studies of the Etiology of Substance Use and Substance Use Disorders: Introduction to the Special Issue

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Received: 10 March 2006 / Accepted: 14 March 2006 / Published online: 19 May 2006

Abstract Misuse of psychoactive substances is associated with substantial costs to users and to society. A growing literature suggests individual differences in vulnerability to develop substance related problems are influenced to a large degree by genetic factors. We review the evidence from genetic epidemiologic and molecular genetic studies of problematic use of alcohol, tobacco, and other drugs, then discuss the challenges for the next generation of studies of genetic influences on substance use. These challenges are addressed in the remaining papers of this special issue. The papers cover a variety of approaches, substances, and non-human as well as human studies, but are united by their focus on going beyond heritability estimates to address the mechanisms and processes underlying the development of substance use and substance related problems, including measurement, precursors of substance abuse, stages of substance involvement, and specificity of genetic influences.

Keywords Substance use · Substance abuse · Review · Genetic epidemiology · Molecular genetics

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Introduction

Psychoactive substance use and abuse is associated with enormous costs. In addition to the medical and psychological consequences experienced by those who are addicted, there are enormous costs to society arising from crime, accidents, lost earnings and disrupted families and social relations (Room et al. 2005). The annual economic impact of alcohol and illicit drug abuse in the U.S. exceeds hundreds of billions of dollars (e.g., Rice 1999). Cigarette smoking remains the leading behavioral risk factor for premature morbidity and mortality in both industrialized and developing countries (Shafey et al. 2003). In the U.S., cigarette smoking accounts for approximately one-quarter of all deaths (Peto et al. as cited in Shafey et al. 2003).

Offsetting these negative outcomes are the positive consequences of moderate consumption of psychoactive substances. Psychological benefits associated with consumption of psychoactive substances include relaxation, anxiety reduction, social enhancement, and enhanced alertness. Medical benefits of moderate drinking include reduced risk of cardiovascular and pulmonary disease (Klatsky 1999; Sisson et al. 2005). Use of cannabis reduces nausea, and has been found helpful for management of symptoms of glaucoma and multiple sclerosis (Corey 2005). Nicotine and stimulants are used widely to enhance concentration and promote weight loss (Gehricke et al. 2006; Gurwitz 1999; Gardner et al. 2006). Furthermore, some charge that the costs and consequences of the criminalization of drug use and the age restrictions applied to alcohol and tobacco are not justified by the positive effects of these measures (e.g., Benson et al. 1992; Wolfson and Hourigan 1997).

Understanding the sources of variation in predisposition to use and abuse of substances is thus a worthwhile goal.

In this article we briefly review the results from genetic epidemiological studies and molecular genetic studies of alcohol, tobacco, and illicit substances. We then consider some of the aspects of substance use research that make this field more complex than studies of other behaviors and describe how these challenges are being addressed by the next generation of studies, including the research featured in this special issue.

Genetic and environmental influences on substance use and substance use disorders

A large number of review papers have been published on genetic influences on substance use disorders in humans. Indeed, for genetic epidemiological research the number of review papers and chapters probably exceeds the original studies. We thus provide only a brief summary here. Details can be found in recent reviews by Ball and Collier (2002), Dick and Foroud (2003), and Li (2003). In our review of the literature on alcohol, we describe problematic use in adults; for nicotine and other drugs (for which the literature is more limited) we also summarize studies of regular use in adults and relevant literature in adolescents. It should be noted that the genetic epidemiologic literature on substance use and abuse comes predominantly from studies based in Northern Europe, the U.S. and Australia. Thus, it is unclear how well these estimates will generalize to individuals from other cultures.

By focusing our review on the human literature we do not mean to minimize the important contributions of animal studies to the understanding of the etiology of substance use and dependence. Animal models exist for assessing genetic influences on many aspects of substance-related behavior, including sensitivity, acute and chronic tolerance, physiological dependence and withdrawal. The literature encompasses a wide range of species (from invertebrates to primates) and methodologies (from in vitro genetic expression studies to naturalistic studies of the impact of social contexts on substance use). A review of this work is beyond the scope of this introduction (and the expertise of the authors). We refer readers to recent reviews by Balogh et al. (2002), Lovinger and Crabbe (2005), Phillips (2002) and Thibault et al. (2005).

Alcohol

Risk to develop alcoholism has been consistently shown to run in families (e.g., Cotton 1979). Results from adoption studies indicate significantly increased rates of alcoholism (e.g., 1.6–3.6 fold) among males adopted away from their biological alcoholic parents (Cadoret et al. 1985, 1987; Cloninger et al. 1981; Goodwin et al. 1973; Sigvardsson et al. 1996). Studies of female adoptees have been less consistent, but these were limited by small sample sizes (Bohman et al. 1981; Cadoret et al. 1985; Goodwin et al. 1977; Sigvardsson et al. 1996). Results from adult twin studies of alcoholism are remarkably consistent for males, with most finding heritability estimates of 50% or greater (Heath et al. 1997; Kaij 1960; Kendler et al. 1997; McGue et al. 1992; Prescott et al. 1999, 2005; Romanov et al. 1991; True et al. 1996) and little evidence for shared environmental influences. Studies of female twins identified through treatment settings suggest some of the familiality of alcoholism among women may be due to shared environments rather than to genetic factors (McGue et al. 1992; Prescott et al. 2005), whereas studies using population-based twin registries have found genetic influences on alcoholism to be of similar magnitude in males and females (Heath et al. 1997; Kendler et al. 1992). It seems likely these differences may be due to methodological differences between studies, but it is also possible that the sexes have only partially overlapping etiology (e.g., Prescott et al. 1999).

Several linkage studies of alcoholism have been conducted and have generated a number of promising findings, including replicated evidence for susceptibility loci on chromosomes 1 (Hill et al. 2004; Lappalainen et al. 2004; Reich et al. 1998) and 4 (Ehlers et al. 2004; Long et al. 1998; Prescott et al. 2006; Reich et al. 1998). The region on chromosome 4 is near the ADH cluster, one of the two sets of genes primarily responsible for ethanol metabolism. A large number of candidate gene studies have been conducted, but with mixed results, other than for ethanol metabolism genes (ADH and ALDH). Replications exist for a number of variants in neurotransmitter systems including dopamine, serotonin, and GABA. However, for all these candidates there are negative as well as positive reports of association with alcoholism, so this field must be considered in an early phase.

Tobacco

Unlike for alcohol use, where exposure (in Western populations) is nearly universal, many individuals never try tobacco or illicit drugs. Thus, genetic and environmental influences on substance use are in part dependent on whether individuals initiate use. (We consider the implications of stages of alcohol involvement later). Family studies of regular smoking suggest that genetic factors influence cigarette smoking; rates of tobacco use and dependence are elevated in the relatives of regular smokers. For example, Chinese individuals with a nicotine dependent sibling were 2.1–3.5 times more likely to be nicotine dependent (defined by Fagerstrom-based questionnaires) than those without a nicotine dependent sibling

(Niu et al. 2000). Estimates of the heritability of smoking based on adult twin samples are generally high, with most values falling between 40 and 70% (see Li 2003). One of the most striking aspects of this literature is the consistency of heritability estimates across a wide range of ages, countries and gender (Madden et al. 2004), and in adolescents (Boomsma et al. 1994; Kaprio et al. 1995; Han et al. 1999; Maes et al. 1999b; Rhee et al. 2003). Reared-apart twin (Kendler et al. 2000) and adoption (Eaves and Eysenck 1980; Osler et al. 2001) studies find significant similarity among biological but not adoptive family members, confirming the hypothesis of strong genetic influences on smoking behaviors.

Several twin studies have investigated nicotine dependence including DSM-based (Lessov et al. 2004; Prescott and Kendler 1995; Kendler et al. 1999b; True et al. 1999; Maes et al. 2004), and Fagerstrom-based measures of nicotine dependence (Kendler et al. 1999b; Maes et al. 2004; Lessov et al. 2004), nicotine withdrawal (Xian et al. 2005; Pergadia et al. in press) and dependence proxies (such as smoking persistence: Heath et al. 1995; Madden et al. 1999). Twin studies have provided equally consistent evidence for genetic effects on heaviness of smoking (usually assessed by typical number of cigarettes smoked per day; Carmelli et al. 1992; Koopmans et al. 1999a; Lessov et al. 2004). In aggregate, these studies support moderate heritability (50–60%) and a small role for family environment (perhaps 10–15%). It is perhaps noteworthy that higher heritability estimates were obtained in studies using direct measures of nicotine dependence.

Candidate gene studies of smoking have tended to focus on genes related to nicotine metabolism (e.g., CYP genes), nicotinic receptors (e.g., CHRNB2) and genes involved in brain reward pathways (DA and 5HT). Thus far a consistent picture has not emerged from these studies. This may be in part because most candidate gene studies have used small samples and have not examined nicotine dependence directly but used current smoking status as the outcome. Several linkage studies of smoking-related behaviors have been conducted and implicated a number of regions that may contain susceptibility genes. However, thus far the regions are largely non-overlapping across studies. For much of the published literature, analysis has been based on samples where the characterization of smoking history was not the primary focus, and has consequently been very limited (e.g., the alcoholism-focused COGA study (Duggirala et al. 1999; Bergen et al. 1999; Bierut et al. 2004) included only measures of quantity smoked and years smoked, did not assess nicotine dependence, and did not clearly discriminate non-regular smokers from never smokers). As a consequence, we see a literature on linkage studies of smoking that is focused on quite diverse aspects of cigarette smoking, and with positive findings reported for most chromosomes. To our knowledge, only one published linkage study has specifically targeted nicotine dependence, using data from the Christchurch sample (Straub et al. 1999; Sullivan et al. 2004), although we are aware of other as yet unpublished linkage studies that specifically target nicotine dependence as an outcome.

Other substances

Family, twin and adoption studies specifically investigating the familial aggregation of *illicit* substance abuse and dependence also support genetic and familial contributions to illicit substance use disorders (Annis 1974; Gfroerer 1987; Kosten et al. 1991; Luthar and Rounsaville 1993; Maddux and Desmond 1989; Maes et al. 1999b; McGue et al. 2000; Merikangas and Avenevolvi 2000; Newlin et al. 2000; Rounsaville et al. 1991; Tsuang 1998). Results from studies of illicit substance use disorders (SUD) have been less consistent than for tobacco and alcohol (Anthenelli and Schuckit 1992; Kumpfer and Marsh 1985; Tarter and Edwards 1987). However, because there are likely to be stronger age/cohort differences in substance availability and preferences than for tobacco and alcohol, very little family data appropriate for examining the familial aggregation of illicit substance abuse has been available until recently. For example, not until the 1960s and 1970s were a variety of drugs, such as marijuana and cocaine, readily accessible. Thus, it is only recently that it has become feasible to acquire family data where both parents and children have gone through the ages of highest risk for drug abuse, and where the risk in both generations is comparable. Earlier family and adoption studies tended to study the association of drug use in offspring with alcoholism in their parents and the results suggests familial transmission of liability to substance use disorders (e.g., Merikangas et al. 1998; Langbehn et al. 2003).

Estimated heritabilities from the handful of available adult twin studies of substance abuse and dependence range from 25–80%, with most being in the 50–70% range (Kendler et al. 1999a; Tsuang et al. 1996; van den Bree et al. 1998). Although there is diversity of estimates across sexes and substances, in most cases these are not significantly different, in part due to the relatively low prevalences for abuse/dependence on most substances. Twin studies in adolescent samples have focused on illicit substance use (rather than abuse or dependence), but also suggest significant genetic influences (e.g., Han et al. 1999; Iacono et al. 1999; Maes et al. 1999b; McGue et al. 2000; Miles et al. 2001; Rhee et al. 2003; for a recent review, see Hopfer et al. 2003). Like the adult data, heritability estimates have ranged widely (9–83%), but in general, have been more modest than those obtained from adult samples. Most studies of adolescents also indicate substantial shared

environmental influences, but there is also evidence to suggest that estimates of the magnitude, or importance of genetic and environmental influences are likely to be moderated by assessment differences, age, sex, substance type, patterns of comorbidity, specific contexts, and socio-regional influences. Further, censoring of individuals that have not passed through the age of greatest risk for developing problem use is an added complication in studies of adolescents that has not been adequately addressed.

Data collection for several linkage studies for illicit drugs is underway, but as of this writing few results are available. Stallings et al. (2003) used sibling-based linkage methods in an adolescent sibling sample to study dependence symptoms for both licit and illicit substances. They found promising regions on chromosomes 3 and 9. The strongest support for linkage was to the 9q34 region using a composite index of substance dependence and conduct disorder symptoms (Stallings et al. 2005).

The candidate genes tested for illicit drugs are similar to those described for alcohol and nicotine, including genes involved in the reward system, as well as receptors for specific drug classes. Many studies are underway, but thus far, few findings have been replicated and most of the genes involved are not known to have functions related to the actions of the drug class studied (e.g., Kreek et al. 2004).

Challenges for genetic research on substance use

Several challenges confront researchers studying genetic influences on substance related behavior. First, there is substantial variation across cultures and historical periods in the prevalences and types of substance use. Societal interventions, such as prohibition of alcohol sales in the U.S. in the early 20th century or, more recently, the opening of borders in eastern Europe and economic development in Asia, have dramatic effects on the availability of psychoactive substances. Changing social norms about the acceptability of drug use influences consumption patterns and also affects individuals' willingness to participate in research. Studies of family members from different generations are thus complicated by the varying availability of drugs during the periods when individuals were at greatest risk to initiate substance use. The issue of whether genetic factors measured in some contexts pertain in different environments is thus a key issue for substance use research. In this issue, Crabbe and colleagues extend their prior findings (e.g., Crabbe et al. 1999) by studying the evidence for genetic effects across different mouse strains and experimental procedures.

Most behavior is assumed to be multifactorial in origin, arising from a combination of genetic and environmental factors. Usually, none of these factors is assumed to be necessary or sufficient. But for substance use, a necessary environmental factor is availability of the substance. Exposure to substances is not universal and is to some degree self-initiated and thus probably does not occur randomly with respect to genetic risk. Individuals who have a family history of substance abuse (and thus presumably have higher genetic risk) are likely also to have increased environmental risk from increased access to substances used in their households. On the other hand, there is also evidence that some individuals with a positive family history have decreased phenotypic risk (e.g., Orford and Velleman 1991), perhaps arising from their determination to avoid substance use after witnessing its effects in their relatives. Thus, the common assumption in genetic epidemiologic studies of independence of genetic and environmental risk may not hold for substance-related behavior. The implications of this are examined by several papers in this issue. Agrawal and colleagues (*this issue*) consider the implications of different mechanisms of assortative mating (the tendency for individuals to have spouses with similar behaviors) on the conclusions obtained from family and twin studies of substance involvement. Another methodological challenge in substance abuse research in twin samples is potential violations of the equal environment assumption (that the environments of DZ twin pairs are as similar as those of MZ pairs). This assumption has been tested previously for alcohol consumption, but with mixed conclusions (e.g., Kendler and Gardner 1998; Rose et al. 1990). In their article, Pergadia and colleagues (*this issue*) studied the effects of substance use of one's twin as a social influence on substance use and as a potential methodological bias in twin study results.

The genetic and environmental factors that influence initiation of substance use are likely to differ from those that affect development of regular use once drug exposure has occurred and these in turn may differ from those underlying the development of addiction. Several papers in this issue address genetic and environmental influences on the stages of substance involvement. Pagan and colleagues (*this issue*) studied whether environmental and genetic influences were stage-specific or extend across stages of alcohol use in adolescent and young-adult twins. Vargas-Irwin and colleagues (*this issue*) describe a method for analyzing dimensions in acquisition of drug use for genetic studies using animal models. Neale and colleagues (*this issue*) have further developed their model for use contingent upon initiation (e.g., Kendler et al. 1999a, b) and report its application to stages of tobacco and cannabis involvement among adult twins.

Another complication for substance abuse research is the diversity of the behaviors which may precede problematic substance involvement. Two widely studied risk factors are early substance use (e.g., Grant and Dawson

1997; Prescott and Kendler 1999) and use of gateway substances (e.g., Kandel 2003). Lessem and colleagues (*this issue*) report on the role of environmental and genetic factors in the transition from marijuana use in adolescence to illicit drug use in adulthood. Other risk factors may be in domains other than substance use. In this issue, McGue and colleagues extend their work on shared liability to substance use and externalizing in adolescence (e.g., McGue et al. 2001) to examine the genetic and environmental overlap between problem behaviors in adolescence and risk for adult substance abuse. Dick and colleagues (*this issue*) describe how variation at a specific genetic locus (GABRA2) may influence conduct disorder in adolescence but alcohol and drug dependence in adulthood.

Other prominent themes in substance abuse research are heterogeneity and comorbidity. There is substantial variation in clinical presentation and course of substance use disorders and many speculate there is also heterogeneity in etiology. In U.S. epidemiological studies more than 50% of individuals who meet diagnostic criteria for an addictive disorder have at least one other disorder (Kessler et al. 1997). For many individuals, problematic use may arise as a consequence of using substances to manage symptoms of other disorders, including depression, mania, anxiety and psychosis. Chronic substance use may precipitate or exacerbate mood, anxiety and psychotic symptoms (Schuckit et al. 1997; Pencer et al. 2005), further complicating the etiological picture. A large literature based on family, twin and adoption studies exists for the overlap of alcoholism with other disorders, but less evidence exists concerning the basis for the overlap of nicotine dependence and drug abuse with other (non-substance) disorders. The literature which does exists is far from cohesive, with some studies suggesting comorbidity arises from common genetic vulnerability (Kendler et al. 1993), whereas others conclude the overlap is due to phenotypic association (e.g., depression causing alcoholism or alcoholism causing depression; e.g., Merikangas et al. 1985). It seems likely that all these processes may exist and this heterogeneity in etiology has impeded this line of research. This may be one question that cannot be resolved with genetic epidemiological approaches given the available samples and likely effect sizes. Identification of susceptibility loci should help to clarify this issue. Some evidence from linkage (e.g., Nurnberger et al. 2001; Stallings et al. 2005) and association studies (e.g., Namkung et al. 2005) suggests the existence of loci that contribute to risk for both psychiatric and substance use disorders.

A related issue is whether genetic factors affecting substance use are substance-specific or confer a more general predisposition to multiple substances. Specific effects might occur at the level of receptors that differentially bind to particular classes (e.g., opiates, nicotine, benzodiazepines). General effects could occur through genetic influences on variation in the reward system. Adult twin studies of the overlap across drug categories suggest there are overlapping genetic factors for smoking with alcoholism or heavy drinking (e.g., Swan et al. 1996; True et al. 1999) and across classes of illicit drugs (e.g., Tsuang et al. 1998; Kendler et al. 2003), with some evidence for additional specific factors. In a review of linkage studies of alcoholism, nicotine dependence and illicit drugs Uhl (2004) identified several regions which evidence for linkage to multiple substance classes. Several papers in the current issue report results bearing on this issue. In particular, Young and colleagues (*this issue*) studied the genetic and environmental overlap for drug use and abuse in a sample of adolescent twins and adoptees.

This special issue includes only a sampling of the approaches and designs being applied to the study of substance use disorders in genetically informative samples. Also noteworthy are studies using extended twin-family designs (Maes et al. 1999a), adoption designs (Langbehn et al. 2003), twins reared apart (Heath et al. 2002), and children of twins (Silberg and Eaves 2004) to address the role and transmission of environmental influences. A number of investigators have reported on the moderation of genetic influences on substance use and abuse by environmental factors, such as marital status (Heath et al. 1989), religiosity (Koopmans et al. 1999b), geographic region (Rose et al. 2001), and family functioning (Kendler et al. 2004; Miles et al. 2005). Still other factors may mediate genetic influences on substance use disorders, including drug sensitivity (Wilhelmsen et al. 2003) and cognitions about expected drug effects (Slutske et al. 2002; Prescott et al. 2004). Another promising approach is the identification of endophenotypes, genetically influenced characteristics that precede and index risk for substance abuse. Possible endophenotypes include psychophysiological and electrophysiological response (Carlson et al. 2002; Enoch et al. 2002) and response to drug challenge (Heath et al. 1999; Viken et al. 2003). Developments in animal models include studying the effects of inactive forms of genes (knockouts), evaluating the effects of specific genes placed in new genetic backgrounds (transgenics), and assessing changes in gene expression following exposure of tissue to substances (see Phillips 2002; Thibault et al. 2005 for reviews).

Overview of the special issue

This special issue of *Behavior Genetics* contains papers examining the role of genetic factors in the etiology of substance use and substance use disorders. These papers were selected by the editors from nearly 30 responses to a

call for abstracts distributed to the BGA membership and other listservs. Selection was on the basis of the relevance of the papers to various aspects of the development of substance involvement and related problems. We also attempted to include papers that would cover a variety of approaches, substances, and non-human as well as human studies.

Our primary goal was to feature studies that go beyond heritability estimates to address mechanisms and processes in the development of substance use and substance related problems. The papers reflect several themes, including genetic influences on stages of substance involvement (Pagan et al. 2006; Lessem et al. 2006; Neale et al. 2006; Vargas-Irwin et al. 2006), factors which predict adult substance related problems (Dick et al. 2006; McGue et al. 2006; Lessem et al. 2006), and measurement and other methodological issues in substance abuse genetics (Crabbe et al. 2006; Agrawal et al. 2006; Pergadia et al. 2006; Neale et al. 2006). Five of the papers examine risk factors that extend across classes of substances (Lessem et al. 2006; McGue et al. 2006; Young et al. 2006; Neale et al. 2006; Dick et al. 2006), whereas the others focus on a specific substance class, including alcohol (Pagan et al. 2006; Crabbe et al. 2006), tobacco (Agrawal et al. 2006; Pergadia et al. 2006), and cocaine (Vargas-Irwin et al. 2006).

A second goal for this special issue was to communicate to readers outside behavior genetics how genetically informative approaches can address broader questions about the measurement and etiology of substance use and related problems. Toward this end, we invited Zucker (2006) to provide a commentary. His paper concludes the issue with a summary of the other articles, placing their findings in the context of the literature of developmental psychopathology and offering his perspective on the field's successes and future challenges.

In this era of increasing emphasis on molecular approaches, it is noteworthy that the majority of the papers used inferential methods (comparing genetic strains or MZ and DZ twin pair similarity) for examining genetic influences. The content of this issue underscores the point that much that can be learned about the development, assessment and complexity of substance related behavior from all types of genetically informative studies.

Acknowledgments The editors thank Rebecca Ortiz of VCU for managing the abstract submission. Naimah Weinberg provided helpful advice during the development of the issue and John Hewitt and Christina Hewitt guided us throughout the process. We are grateful to our colleagues who provided excellent reviews of the papers appearing in this issue. We thank our universities and funding sources for supporting this effort, including the Department of Psychiatry at Virginia Commonwealth University, NIAAA and NIMH (for CAP), and NIDA (for PAFM and MCS).

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