Published in final edited form as:
Addict Biol. 2010 April ; 15(2): 103–108. doi:10.1111/j.1369-1600.2009.00188.x.

Consilience of Rodent and Human Phenotypes Relevant for Alcohol Dependence

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A diagnosis of the substance abuse disorder alcohol dependence (AD) based on the DSM-IVR is categorical, and presentation of any 3 of 7 symptoms with persistence of at least one year is required. This means that any group of individuals with a diagnosis reflects substantial clinical heterogeneity, which likely reflects heterogeneity at the etiological, biological, and genetic levels (Hasin *et al.* 2006;Kendler 2006). Yet, most clinical genetic research has been directed toward diagnostic groups. Throughout biological psychiatry, the modest success in identifying genes associated with diagnoses has fueled a trend toward a focus on endophenoypes or intermediate phenotypes (Gottesman, Gould 2003), but such studies are still in the minority. An array of endophenotypes is under investigation, including but not limited to low response (LR) to alcoholism and electrophysiological responses such as low voltage fast power or P300 of the event related potential. In addition to intermediate phenotypes, there are numerous risk factors under investigation in human studies, ranging from personality traits such as behavioral under-control to comorbid diagnoses such as antisocial personality disorder, anxiety disorders, and depression (Kendler *et al.* 2008;Pihl 2007)..

On the laboratory animal side, numerous lines of rats and mice have been selectively bred for a genetic predisposition to drink alcohol when it is offered as a choice versus tap water [see multiple recent reviews: (Colombo *et al.* 2006;Ciccocioppo *et al.* 2006;Quintanilla *et al.* 2006;Bell *et al.* 2006;Sommer *et al.* 2006;Murphy *et al.* 2002;Le *et al.* 2001;Green, Grahame 2008)). Many candidate genes have been targeted for studies in mice and most affect alcohol drinking, either to increase or decrease it (Crabbe *et al.* 2006). While we have learned a great deal about the neurobiology of alcohol and its pathological sequelae from such genetic animal models, most believe that no single model offers a completely convincing analogue of the human diagnosis (Crabbe 2008;McClearn 1979;Vengeliene *et al.* 2008). Even if there is such a model, the complexity of alcoholism argues strongly that additional value could be realized from studying animal surrogates of crucial risk or protective traits, and intermediate phenotypes.

Over the years, many of us in the field of alcohol research have experienced frustration at the limited resemblance between the phenotypes studied in humans and the laboratory animal phenotypes devised ostensibly to model the human targets. There have been conference workshops devoted to this topic, but the results have thus far been limited. The recent expansion in both the power and the extent of genetic studies in human and non-human animals offers a focused window for viewing this problem. Although the problem of the dissimilarity between human and rodent phenotypes is certainly not limited to genetic studies, the cost of failure to achieve parallel results in genetics is high. Association and linkage studies, coupled with much lower costs for genotyping and high throughput

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sequencing, have proposed numerous specific genomic locations and candidate genes for AD-related phenotypes in humans (Agrawal *et al.* 2008;Johnson *et al.* 2006). Progress has been similarly rapid using genetic animal models (Tabakoff *et al.* 2008;Carr *et al.* 2007). Because of the 85% syntenic conservation (i.e., the retention of specific genes in the same order across species on chromosomal segments) of the genomes of humans vs mice due to shared ancestry, there is every reason to expect that rodent genetic studies and human genetic studies should offer opportunities for mutual potentiation. Rodent studies offer particularly strong opportunities for mechanistic exploration of the effects of single genes or groups of genes, as well as systematic evaluation of gene-environment interaction. However, these opportunities are not being maximally exploited.

Rodent studies with the intent of modeling AD-related traits typically focus on very few phenotypes. The most common is two-bottle preference drinking. Although there are many procedural variants, in the usual version of this test, animals are offered a bottle of (usually 10%) unflavored alcohol vs a bottle of tap water *ad libitum* and the amount consumed is measured daily. Genetically predisposed mice will drink as much as 20 g/kg ethanol/day, while similarly high-preference rats will self-administer 5-10 g/kg/day. However, one of the limits of alcohol preference drinking studies has been that rodents, unlike humans, rarely drink enough alcohol to reach blood alcohol levels that are consistent with behavioral intoxication. Rodents seem to self-limit their rates of drinking such that they can efficiently metabolize ethanol (Dole *et al.* 1985;Murphy *et al.* 1986). Humans struggling with AD and related drinking disorders often report being unable to control their drinking. Lines that have been selectively bred for high ethanol preference also generally limit their drinking to amounts and rates yielding blood alcohol levels of about 50 to 70 mg% (Murphy *et al.* 1986). These levels roughly correspond to the legal driving limit in the USA.

Under very specific conditions, some of the genetically-predisposed rat lines will drink significant amounts of alcohol (Murphy *et al.* 2002). Some P rats can become physically dependent on freely self-administered alcohol if a research protocol involving many weeks of access to alcohol or one involving gastric intubation is employed, and restricting the period of access to alcohol drives blood alcohol levels higher [(Murphy *et al.* 1986) (Kampov-Polevoy *et al.* 2000) (Waller, McBride, Lumeng, and Li 1982)) (Waller *et al.* 1984) - for discussion, see (Crabbe *et al.* 2009)]. Another method for inducing rats or mice to increase their drinking is the Alcohol Deprivation Effect (Sinclair, Senter 1968). The ADE describes a relatively short-lived increase in drinking seen in animals first offered alcohol for a long time to establish preference, and then withdrawn for a period. Reintroduction of alcohol availability leads to a spike in intake, and repeated cycles of the ADE show more prolonged enhancement (Rodd-Henricks *et al.* 2000;Rodd *et al.* 2009). There are a number of other protocols that lead to the elevation of drinking in rats and mice, but to achieve this behavior involves either many weeks of testing, scheduling and/or operant procedures, technically challenging procedures such as gastric intubation or exposure to ethanol vapor by inhalation, and/or restriction of food or water [for discussion see (Rhodes *et al.* 2005)].

In addition to excessive drinking, another key feature of human AD is the development of dependence itself. Dependence criteria used in humans such as problems with family and friends, legal problems, drinking when not intending to, etc., are not easily studied in rodents. The concept of physiological dependence was operationally defined as the state that manifests itself upon withdrawal of EtOH (Friedman 1980;Kalant *et al.* 1971); but see (Cappell, LeBlanc 1979). EtOH and other central nervous system depressants are now well-known to produce signs and symptoms during withdrawal that are opposite in direction to those induced by intoxication (Victor, Adams 1953;Friedman 1980;Kalant *et al.* 1971). Dependence putatively occurs as the result of adaptation of the system in the presence of

EtOH such that EtOH is required for quasi-normal function. Removal of EtOH through metabolism following cessation of intake or treatment leads to a rebound hyperexcitability during withdrawal that is opposite in direction to that of the sedative effect (Koob, Le Moal 2001) (Solomon, Corbit 1974). Cicero (Cicero 1980) and others [e.g., (Kalant *et al.* 1971)] have argued that measurement of physiological dependence is problematic without a clear definition and that it is preferable to define and quantify withdrawal.

In humans, anxiety is lessened by EtOH consumption and is increased during the withdrawal episode (Isbell *et al.* 1955). Besides anxiety, the human EtOH withdrawal syndrome includes irritability, nausea, vomiting, insomnia, tremor, hyperthermia, hyperventilation, tachycardia, and neural hyperexcitation, manifestations of which include (albeit rarely) hallucinations, delusions, and *grand mal* seizures; these symnptoms develop at different times during withdrawal (Isbell *et al.* 1955;Victor, Adams 1953).

Physiological dependence on EtOH can be induced in rodents by multiple injections or intubations, by chronic feeding with a liquid diet containing ethanol, or by vapor inhalation. Multiple withdrawal signs have been described in many mammalian species, all of which, like the human, have been shown to display tremor and in severe cases potentially fatal convulsions following withdrawal from EtOH (Friedman 1980;Kalant 1977). Goldstein introduced the handling-induced convulsion (HIC) as a method of quantifying withdrawal in mice after chronic administration of EtOH in a vapor inhalation chamber, and subsequently demonstrated that the severity of withdrawal HICs was dose-dependent, heritable, and could be modified by a wide variety of drugs (Goldstein 1975). Nearly all studies employing mice to study alcohol withdrawal use the severity of the HIC as the dependent variable. Rats, however, do not display this sign, and withdrawal studies in rats employ other behavioral indices.

Rodent models of EtOH withdrawal-induced anxiety are thought to more closely model the more common physiological aspects of withdrawal seen in humans, and drugs that reduce anxiety in humans also reduce withdrawal-induced “anxious” behaviors in rodents (Emmett-Oglesby *et al.* 1990;Pandey *et al.* 2003). Both rats and mice display increases in anxiety-like behavior during withdrawal (Pandey *et al.* 2008;Finn *et al.* 2007), although interpretation of these studies can be difficult as motor activity is also often depressed during withdrawal, at least in mice (Kliethermes 2005).

The specific genes or gene networks influential in one species would only be expected to be similar to those in another if the same phenotypes were under investigation (and/or if different phenotypes were under similar genetic influence). Specific genomic regions have been proposed to be associated with risk for withdrawal HIC in mice (Hitzemann *et al.* 2009;Shirley *et al.* 2004;Fehr *et al.* 2002), and similar studies have implicated genomic regions associated with AD in humans (Mayfield *et al.* 2008). Given the somewhat orthogonal definitions of dependence across species, it is difficult to predict how well the genomic regions thus implicated should correspond across species. Of course a mouse will never be a human, but all of us believe that we could do a better job of realizing consilience of the targeted phenotypes across species. Specifically, it is not clear which risk or protective factors or intermediate phenotypes are crucial to understanding the etiology or treatment of alcoholism.

Thus, it has been difficult to determine what additional models in animals would be useful. We recognized that the lack of real progress toward this goal during the years of the genomics revolution to date indicated strongly that progress was not likely to happen unless it was adopted as the intentional goal of some individuals. Therefore, in partnership with Andrew Heath, we convened a group of researchers in Portland, Oregon in October 2007 for

a one and a half day meeting. For lack of a better term, we referred to the goal of the meeting as a search for better consilience from rodent and human phenotypes. Here, we followed the spirit of Edward O. Wilson (1998), who described consilience as “a jumping together of knowledge by the linking of facts and fact-based theory across disciplines to create a common groundwork for explanation.” In our thinking, the chasm we were trying to bridge was not so much based in disparate disciplines but in disparate phenotypes that claimed to represent the same underlying constructs across species. The meeting’s participants (John Crabbe, Chris Cunningham, Danielle Dick, Andrew Heath, Michela Gallagher, Markus Heilig, Stephanie O’Malley, and Kenneth Sher) represented a range of interests and experience with phenotypes relevant for understanding alcohol use disorders. Experience with humans, mice and rats was at the table with disciplines including psychiatry, psychology, behavioral and molecular neuroscience, and genetics. The meeting was co-sponsored by 4 NIAAA Alcohol Research Centers (Oregon, Missouri, New Haven, Scripps) and by the Oregon Clinical and Translational Research Institute. The meeting was attended informally by several Portland students, postdoctoral trainees, and investigators; some of the latter became more involved as the project developed.

There was broad consensus that better articulation of phenotypes was needed at both the human and the rodent level (the importance of other animal models such as non-human primates and invertebrate species was recognized, but deferred for the time being). We also agreed that this would most productively be accomplished if discussion of phenotypes was conducted in coordinated fashion, simultaneously considering the human traits and the realities of animal modeling. We considered a wide range of risk and protective factors and intermediate phenotypes. We recognized that many of the questions we were discussing were applicable to the modeling of any personality trait or psychiatric disorder, and that given the extensive comorbidity of alcohol use disorders with other psychiatric diagnoses, the outcomes would likely have applicability beyond the field of alcoholism research. However, we concluded that the problems were so complex that there was benefit to limiting the initial efforts to alcoholism.

We concluded that there were at least seven broadly-defined areas where we felt further specification of phenotypes would be useful. We decided that an initial step toward solving the problems would require deeper discussion of each of these domains, involving others with specific expertise, and some delving into the extensive literatures on these topics. To begin the process, we assigned subgroups to develop short white papers on each topic -- it is these that follow in the special issue. Each subgroup recruited additional co-authors as the papers were developed.

Four of the domains are reasonably specific to alcohol-related diagnoses. The initially targeted domains are:

1. Low level of response to alcohol. In the early 1980’s, Marc Schuckit at UCSD embarked on a prospective study comparing two cohorts of young men, one Family History Positive (FHP) for alcoholism, and the other Family History Negative (FHN). He found that FHP were less responsive to alcohol than FHN (Schuckit 1985). Low level of response is measured as subjective “high,” static body sway, and prolonged cortisol and prolactin release. Which of these endophenotypes is crucial to the eventual risk for alcoholism? Each of these could be modeled in rodents, but further specification of the human phenotype was needed before that can occur.
2. Acute withdrawal and protracted abstinence. Withdrawal symptoms are understood to be an important stimulus for relapse, whether the hangover after a single night of drinking, or the more pervasive sequelae of chronic drinking. Which symptoms are

of most importance to human relapse, and at what points during abstinence? Animal data have established that dependence leads to subtle neuroadaptations that increase both drinking and sensitivity to stress. The “self-medication” concept postulates that emotional changes are induced by a history of alcohol use which persist into abstinence and maintain alcohol dependence.

3. Quantity, frequency and patterns of drinking. There was general agreement that patterning of intake was extremely important to defining alcohol addiction (or, in more neutral language, alcohol use disorders). Yet, given that current diagnostic criteria do not utilize this information, which patterns and quantities important for humans should be examined closely in animal models is not known. Although an increasing pattern of alcohol use is an acknowledged hallmark of alcoholism, there is no consensus about the quantity/frequency patterns that are most important. Moreover, there is only modest overlap in the most common drinking phenotypes measured in animal studies (e.g., two bottle preference) and those typically studied in humans (e.g. maximum drinks at one time).

4. Comparison of human and rodent candidate genes and Quantitative Trait Loci (QTL). There are substantial data from both humans and rodents on the genomic locations of specific genes of potential importance (i.e., QTL). Human genetic data have also often targeted particular candidate genes (e.g., dopamine receptors) seeking polymorphisms associated with alcohol dependence. Yet, these data had barely been examined systematically for their agreement.

Three other areas of phenotypic importance appeared to us to be more general than specific to alcohol.

5. Behavioral undercontrol impulsivity - executive function - novelty seeking - risk taking. Impulsivity may be a risk factor contributing to the development of alcohol problems and other psychopathology. Recent studies have parsed impulsivity in humans into several coherent dimensions (urgency, lack of premeditation, lack of perseverance, and sensation-seeking). Similarly, a number of different measures of impulsivity exist in the animal literature (e.g., Go/No-go task, delay discounting). We saw the need to determine which aspects of this complex personality domain were most important for human risk, and which behavioral assays in rodents might best be used to model them.

6. Reward dysregulation. Biopsychological theories assume that individual differences in sensitivity to alcohol’s motivational effects play a critical role in the etiology and maintenance of alcoholism. Animal model researchers have devoted substantial effort to refining techniques that reflect the presumed rewarding/reinforcing effects of alcohol (e.g., operant self-administration, place preference) and their modulation by factors such as stress, anxiety, tolerance/dependence and genotype. Reward dysregulation in alcoholism and in animal models are approached quite differently. Almost by definition, someone whose life is hostage to alcohol drinking displays dysregulation of the usual patterns of reward. Personal relationships are sought because they are rewarding, but may be relatively devalued by alcoholics. How can the relevant reward-related behaviors be modeled effectively across species?

7. Role of environmental context (including GXE interactions). Genes and environments appear to contribute about equally to risk for alcoholism. What are the crucial environmental risk factors, and how do they interact with risk-promoting genotypes? Environments are thought to influence alcohol-related behavior in two distinct ways: influencing the development or degree of dispositional risk factors; and influencing the manifestation of predisposing

dispositions situationally. Drinking behavior can be disaggregated into trait and state components. Gene-environment interplay occurs with both distal and proximal environmental variables, but the meaning of the GXE interactions and G-E correlations is very different for treatment and prevention for distal versus proximal environmental influences.

Although not specifically targeted in any paper, we also recognized that alcoholism is at its core a developmental disorder. Risk of harmful drinking changes over the life span, and so do the consequences. The assessment, or even the meaning of the data, on an important phenotype may differ in adolescents and adults, or in early-stage and late-stage drinking. All papers sought to feature attention to this developmental perspective.

At the end of our meeting, we felt that we had made some progress in recognizing the complexity facing the issue. We agreed that we would continue to work on the problem of achieving great phenotypic consilience, but that the next step would best be taken after further thought. We then adjourned to the Oregon pinot noir (no more than 5 drinks for men, or 4 drinks for women). Some members of the group have met briefly since, at the 2007 and 2008 Annual Meetings of the RSA, and a Workshop on this topic was presented at the 2008 meeting.

I agreed to serve as guest editor of the Special Issue devoted to these white papers. In that role, I oversaw peer review of each submitted paper adhering to the review standards of the journal. I thank the reviewers, particularly those from outside of the group effort, who took the time to read these pieces and offer comments.

As is evident from the list of authors and co-authors on the papers, the process has been enough of a success to recruit interest from several others in the field. We hope that the papers achieve their intended effect, that of stimulating argument, comment, and possibly even contributing to the needed further development of better phenotypes for both human and rodent studies. We hope to find ways to realize some practical advances in phenotype assessment for both human and rodent future studies as well. I want to take this opportunity to thank all the participants for their extended and quite voluntary efforts.

Acknowledgments

Preparation of this introduction was supported by a grant from the US Department of Veterans Affairs, and by NIAAA Grants AA10760 and AA13519.

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