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Consilient Research Approaches in Studying Gene x Environment Interactions in Alcohol Research

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Abstract

This review article discusses the importance of identifying gene-environment interactions for understanding the etiology and course of alcohol use disorders and related conditions. A number of critical challenges are discussed including the fact that there is no organizing typology for classifying different types of environmental exposures, many key human environmental risk factors for alcohol dependence have no clear equivalents in other species, much of the genetic variance of alcohol dependence in human is not “alcohol specific”, and the potential range of gene-environment interactions that could be considered is so vast that maintaining statistical control of Type 1 errors is a daunting task. Despite these and other challenges, there appears to be a number of promising approaches that could be taken in order to achieve consilience and ecologically valid translation between human alcohol dependence and animal models. Foremost among these is to distinguish environmental exposures that are thought to have enduring effects on alcohol use motivation (and self-regulation) from situational environmental exposures that facilitate the expression of such motivations but do not, by themselves, have enduring effects. In order to enhance consilience, various domains of human approach motivation should be considered so that relevant environmental exposures can be sampled as well as the appropriate species to study them in (i.e., where such motivations are ecologically relevant). Foremost among these are social environments which are central to the initiation and escalation of human alcohol consumption. The value of twin studies, human laboratory studies, and pharmacogenetic studies is also highlighted.

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The Institute of Medicine (2006) report's chapter, “The Role of Animal Models,” notes (p.132) that “the commissioned paper submitted by Steve W. Cole was used in the preparation of [the] report.”

Keywords

alcohol; animal models; environmental effects; genetics; gene-environment interaction

Hopes for identifying single genes that explain more than a small proportion of liability for common mental and physical disorders have diminished greatly in recent years as most replicable genetic effects provide, at best, very modest effects, with odds ratios in the 1.1-1.5 range (Kendler, 2005; Kraft & Hunter, 2009). This may reflect, in part, the “efficiency of natural selection in prohibiting increases in disease-associated variants in the population” (Goldstein, 2009, p. 1698). Although proponents of genome-wide association studies (GWAS) are confident that many new loci important for common diseases will be discovered in the next few years (e.g., Hirschhorn, 2009), as noted by Moffitt et al. (2005), the “main-effects approach” embodied in traditional gene finding including GWAS studies is inefficient if detection of the effect of the gene is conditional upon environmental risk. This approach assumes that genes have uniform effects across environmental conditions, and that environments affect all genotypes similarly. Alcoholism, given the long-recognized associations between alcohol use disorder in the parental generation and high-risk exposures in the offspring generation (parental separation, assaultive trauma, family conflict etc.), is arguably an ideal case for investigating gene x environment interaction (GXE) effects (Heath and Nelson, 2002). Consequently, consideration of the environment should result in improved gene finding (as well as understanding how gene effects on behavior are mediated and moderated).

The range of potential environmental influences on the development of alcohol dependence and alcohol use disorders (abuse or dependence; AUDs) in humans is vast and ranges from the chemical environment (e.g., ethanol and other drug exposures) to broad social factors (e.g., cultural influences) and includes life-stage specific factors (e.g., prenatal exposures to various biologic and nonbiologic agents, various social roles that vary over the life course). Unlike the genome which contains a very large but finite number of genes, the number and type of environmental influences is unknown. Consequently, we currently have no comparable “environome” to classify the numbers and types of environments that may be relevant for human alcohol dependence or other conditions, making the prospect of environome-wide association studies unfeasible at this time. Indeed, any “scan” for environmental effects is likely to be haphazard and unsystematic at best. When considering the number of unique single-gene by single-environment interactions, the inherent complexity of identifying valid GXE interactions becomes daunting. Clearly, if critical gene-environment interactions are to be detected, strategies must be developed that enhance the likelihood that valid, meaningful interactions are detected and spurious ones minimized. Stressful life events are a known risk factor for psychiatric disease, and perhaps the most celebrated GXE interaction finding in the psychiatric literature is the potentiating effect of multiple stressors and risk-associated effects of a short allele at the serotonin transporter gene on depression and other disorders reported in (Caspi et al., 2003) and in several subsequent studies. In commenting on the negative findings from their meta-analysis on this interaction, Risch et al., (2009) note that “few examples of gene-environment interaction exist for modest gene effects or small environmental impacts, most likely due to lack of power to characterize such an interaction” (p. 2469). When one jointly considers the universe of potential GXE interactions that can be assessed and the inherent low statistical power for detection of interactions in most statistical models (e.g., in a simple factorial ANOVA), the serious challenges that must be overcome in conducting this kind of work must be given careful consideration.

Given the Evident Challenges, How Do We Look for GXE interactions

As noted by Moffitt et al. (2005), there has long been a belief by some in behavior genetics that “GXEs are so infrequent that they can safely be ignored” (p. 473) and this attitude has only recently changed. In order to facilitate further work on human GXE interactions, Moffitt et al. recommend a seven-step strategy that goes beyond brute force scanning and, logically, should help identify the most promising candidate interactions. These steps can be summarized as: (1) “consulting” (i.e., taking leads from) the quantitative behavior-genetic literature (e.g., twin studies), (2) “identifying a candidate environmental pathogen for the disorder in question,” (3) “optimizing environmental risk measurement,” (4) “identifying candidate susceptibility genes,” (5) “testing for an interaction,” (6) “evaluating the specificity of the interaction”, and (7) “replication and meta-analysis.” To this list should be added (5a) evaluating the dependence of the observed interaction on choice of measurement scale (e.g. Jinks and Fulker, 1970) or, particularly in the case of binary phenotypes, the appropriateness of implicit modeling assumptions (e.g. Eaves, 2006; Heath et al., 2008). There is a more restrictive viewpoint that, since only true cross-over interactions cannot be removed by data-transformation, these alone should be the focus of research on gene-environment interaction. But if in biology first-order (main) effects are in general of greater magnitude than second-order interactive effects, such cross-over interactions are likely to be rare and atypical. However, it has recently been argued (Belsky et al., 2009) that such cross-over interactions are not as rare as typically assumed and are substantively meaningful. Specifically, such interactions suggest that a given genotype might be viewed as reflecting a general sensitivity to the environment, with resultant good or bad outcomes. Such cross-over interactions would therefore point to “plasticity” rather than “vulnerability.” Unfortunately, our ability to characterize the strength and form of statistical interactions with confidence is limited because most existing studies are based upon relatively small cohorts of individuals (by the standards of contemporary genetic research), only rarely enriched for specific environmental exposures.

Extension of GXE research to animal models is important scientifically because research in humans (with few, but important exceptions discussed below under *Human Laboratory Models*) is almost exclusively correlational and, thus, incapable of providing strong inferences concerning causation. In humans, additionally, the same environmental exposures that are most plausible candidates for interacting with individual gene effects on risk are also likely to be correlated with genetic risk. For example, alcohol risk genes as well as risky environments are passed down from parents to offspring living in the household: these are the conditions under which the dissection of GXE effects, for a variety of technical reasons, is most challenging (e.g. Purcell, 2002; Rathouz et al, 2008). Animal models provide opportunities for control of both genetic factors and environmental exposures, opportunities to observe the temporal sequencing and unfolding of behaviors and the processes presumably mediating them, and opportunities to conduct analyses across multiple levels of biological organization (e.g., neurocircuitry, cellular, genetic and epigenetic) that involve high levels of invasiveness. As noted in a recent Institute of Medicine (IOM; 2006) report, rodent models can be useful for studying a range of psychosocial environmental variables such as social relationships and many aspects of parenting although they may be limited for investigating more complex social factors such as those involving “cooperation or trust” (p. 133) which may require use of nonhuman primates. In considering ways to model the symptoms of major depression in mice, Cryan and Holmes (2005, Table 1) identified a number of possible models for most DSM-IV criteria including “indecisiveness or diminished ability to think or concentrate” where they suggested “deficits in working and spatial memory and impaired sustained attention.” However, they also concluded that “recurrent thoughts of death or suicide” or “feelings of worthlessness or excessive or inappropriate guilt” could not be modeled in mice (and presumably all other nonhuman

animals). Similarly, some DSM-IV (American Psychiatric Association, 2000) criteria such as “a persistent desire or unsuccessful efforts to cut down or control substance use” and “the substance use is continued despite *knowledge* [emphasis added] of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance” (p. 197) may not be practical phenotypes to model in animals and therefore environmental variables that rely upon uniquely (or largely) human abilities to affect the phenotype may be impossible to model fully in any animal model. Finally, most experimental designs employed in behavior genetic research with animals incorporates enough subjects to detect main effects of genotype or treatment, but not their interaction (Wahlsten, 1991).

Thus, the first task for investigators seeking consilience between human and animal studies of GXE interactions is to identify those environment variables that are ripe for translation across human and animal models of alcohol dependence. This, by necessity, excludes some potent risk and moderating factors for either drinking and/or alcohol use disorders (e.g., culture, Hanson, 1995; religious beliefs, Haber & Jacob, 2007) that have no clear counterparts in nonhuman animal species; and others (e.g. chronic history of childhood sexual or other assaultive trauma; see Sartor et al., 2008) that involve stressors of such severity that they would be prohibited by regulations concerning the use of animals in research. Other important factors such as cost, although in humans determined largely by taxation (see Chaloupka, Grossman, & Saffer, 2002), can, in principle, be modeled via different schedules of reinforcement similarly in both humans and nonhuman animals (Etten, Higgins, & Bickel, 1995). Finally other kinds of psychosocial variables such as parental neglect can be modeled although what is considered to be neglect in humans (e.g., lack of nurturance, inadequate attention to basic physical needs, or supervision) might look phenotypically very different in rodents (e.g., lack of maternal pup retrieval to the nest and licking).

In attempting to judge consilience, the ecological meaning of an environment and the effect it has on underlying neurobiology is more critical than how phenotypically similar it appears to be to its human counterpart. Extraordinary claims require extraordinary evidence and so if one wants to claim that there is an animal model of a specific behavioral process (e.g., guilt) associated with a specific environment (e.g., strong social sanctions), then one would want to see this demonstrated across multiple behavioral paradigms with reference to common neural circuitry (Institute of Medicine, 2006).

Why Do Humans Drink?

Alcohol-seeking, like all addiction-related phenomena, can be viewed as representing the outcome of two competing processes: (1) approach motivation and (2) inhibition/self-control (e.g., Orford, 2001). Full understanding of addictive behavior, then, requires an understanding of impelling and restraining tendencies although a given animal model doesn't necessarily have to address both at the same time.

Approach motivation in humans has been extensively studied in self-report and and factor analyses of self-reported reasons for drinking which reliably yield a multidimensional, four-factor structure (Cooper, 1994): (1) social motives (e.g., “to be sociable”), (2) enhancement motives (e.g., “to get high,” “because it’s fun”), (3) coping motives (e.g., “to forget your worries,” “because it helps when you feel depressed or nervous”), and (4) conformity motives (e.g., “to fit in”). Notably, enhancement and coping motives are strongly associated with drinking, heavy drinking, and drinking problems in both adolescents and adults (Cooper, 1994; Cooper, Frone, Russell & Mudar, 1995), with conformity and social drinking motives somewhat less strongly correlated with consumption levels. A growing body of

literature indicates that the temperamental traits of extraversion and sensation-seeking tend to correlate with enhancement motivation and that neuroticism/negative affectivity tends to correlate with coping motivation (Kuntsche, Knibbe, Gmel & Engels, 2006). These findings point to specific motivational pathways arising from individual differences that are temperamentally based and can help guide the selection of environmental variables and appropriate animal models. For example, to study the effects of alcohol on socialization or conformity (indeed, if conformity in its typical sense is relevant at all to nonhuman animals), one would select a species for study where socialization is an important part of adaptive behavior. Additionally, initial evidence suggests that motives for alcohol use may also be linked to similar genetic factors. Drinking motives involving coping with negative moods appear to be heritable, especially in females, (Agrawal et. al., 2007; Prescott et al., 2004) and a substantial portion of genetic variation in AUDs appears to overlap with drinking to manage mood states (Prescott et al., 2004).

The other side of the approach/restraint conflict is addressed by Dick et al. (in press) who note that impulsivity (arguably, in most but not all cases, the lack of restraint) is, like drinking motivations, multidimensional and so the specific types of phenotypes relevant for consistent translation between human and animal species will depend upon the specific facet of restraint/impulsivity considered (e.g., ability to inhibit a prepotent response, negative affect urgency). (We note that one aspect of impulsivity, novelty seeking is probably best thought of as approach; Dick et al. [in press, this issue] specifically discuss which types of phenotypes are potentially ripe for translation between human and nonhuman animals.)

An important perspective on alcohol dependence is that it is just one manifestation of the types of generalized externalizing behavior problems that first appear in childhood and adolescence (e.g., Achenbach, 1978; Jessor & Jessor, 1977). There are strong genetic correlations among alcohol dependence and conduct disorder (e.g., Slutske et al., 1998) and personality traits associated with disinhibition (e.g., Slutske et al., 2002). In addition, traits-related to disinhibition prospectively predict the onset of alcohol dependence (Sher et al., 1999, 2005). Factor analytic approaches to psychopathology indicate that all externalizing disorders (e.g., conduct disorder, adult antisocial behavior, drug use disorders, and AUDs) are highly correlated and form a distinct psychopathological factor of “externalizing disorder” with common personality correlates (e.g., Krueger et al., 2005; Krueger & Markon, 2006, 2008). While models of generalized externalizing behavior (e.g., Jessor, Donovan, & Costa, 1991; Patterson, Reid, & Dishion, 1992) tend to highlight the importance of parenting and deviant peer groups, both twin studies (e.g., Slutske et al., 1998) and molecular genetics studies (e.g., Dick, 2007) suggest that common genetic influences are also contributing factors. However, there is evidence from twin studies suggesting that there is more complexity to the comorbidity among different forms of substance dependence (and other externalizing behavior problems) than would be expected on the basis of a single spectrum of externalizing behavior. For example, best-fitting multivariate models of the genetic architecture of common genetic factors among abuse of alcohol, nicotine, cannabis, caffeine, and cocaine suggest at least two distinguishable (although very highly correlated) common genetic factors (one principally associated with licit substances and one principally associated with illicit substances) as well as substance-specific genetic factors, especially for nicotine and caffeine (Kendler, Meyers, & Prescott, 2007). These findings were in contrast to a similar study of the genetic architecture of illicit substance dependence which found evidence only for common genetic influences on cannabis, cocaine, hallucinogen, sedative, stimulant, and opiate dependence (Kendler, Jacobson, et al., 2003): individual genetic paths to risk for abuse of each drug separately were not strong in this study. Collectively these findings highlight the importance of shared genetic mechanisms among a range of externalizing and substance pathology but also to a

potentially important role for unique genetic and nongenetic factors on specific types of substance dependence including alcohol dependence.

(At Least) Two Different Ways Environments Can Operate to Affect Alcohol Consumption

Most of the literature on GXE for behavioral phenotypes in animal models focuses on the role of early experiences or later severe stressors inducing some relatively durable change in the organism. Commonly studied environments in other species include maternal behavior, how enriched or impoverished an environment is, various kinds of physical and social stressors, or early drug exposures (e.g., Barr et al., 2004; Cryan & Slattery, 2007; Holmes et al., 2005; Stevens et al., 2009). While these types of experiences appear relevant to drinking in some animal models (esp. the effect of peer-rearing and early exposure to ethanol in primates; Barr et al., 2004), implicit in all of these types of studies is that environmental exposures are creating some functional (and perhaps even structural) change in the organism that persists for some duration of time and is motivationally relevant to general approach or restraint tendencies. Most GXE interactions are studied within this framework.

However, a number of human environmental influences on excessive drinking appear to represent situational goads or constraints that are likely to interact with genetically influenced traits, but not necessarily by getting “under the skin” and influencing underlying physiology. (Clearly, there is a continuum here of “how much” a given environmental exposure induces a transient versus durable effect.) Such situational goads are many and diverse and include simple availability, specific occasions (e.g., celebrations and holiday), specific activities (e.g., tailgating, prepartying, drinking games), housing, social networks, community variables, and price. Some of these types of situational factors (e.g., availability and price) could be modeled in animals and could be important for both identifying GXE interactions highly related to variable aspects of drinking. Moreover, systematically varying these situational variables could prove to be a useful strategy in establishing the robustness of other genetic and environmental manipulations.

It might be tempting to dismiss highly situational effects as not relevant for understanding the genetics of alcoholism in humans. However, such effects may represent some of the most heritable phenotypes. For example, the maximum number of drinks in a drinking day has been shown to be a heritable alcohol consumption-based phenotype for which evidence for genetic linkage is found (Saccone et al., 2000; Saccone et al. 2005) and in a collegiate sample, close to 50% of all 21st birthday celebrants established their highest lifetime maximum drinks (until age 21) on that occasion (Rutledge et al., 2008). While birthday celebrations may not be relevant to animal models, some other drinking situations that promote high consumption (e.g., certain drinking schedules (Crabbe et al, 2009; Falk et al., 1972) could be highly translatable and can be modeled across species.

Using Behavior Genetic Studies to Identify Relevant Environments

Animal models allow us to study environmental effects in genotypes with self-defined levels of alcohol drinking. In the first report of inbred mouse strain differences in two-bottle preference drinking, data on individual mice from 5 inbred strains were presented (McCleary and Rodgers, 1959). Even within the high-drinking C57BL strain, there were individual differences in alcohol preference, and within some other strains such as C3H, the individual differences were substantial. Such differences among individuals within a strain must reflect gene-environment interaction, but the source of the environmental effect is entirely unknown. A strong possibility is that the individual differences within a strain are due to differences in gene expression. Molecular technology now permits the genome-wide

analysis of gene expression differences, and pronounced individual differences within inbred strains have been shown for genes and gene networks. For example, genes in a functional group may be up-regulated in one brain tissue and down-regulated in another in the same individual brain, in addition to differing from expression patterns across individuals of the same genotype (Cowley et al., 2009).

In rodent behavior genetic models of drinking, cross-fostering designs (where the genetic background and rearing environment are experimentally crossed) can be extremely informative for identifying relevant environments and GXEs. Within the limitations to interpretation discussed above, animal models could be used to study the effects of maternal and peer environments on adult drinking. Randall (Randall and Lester, 1975a) compared two inbred mouse strains well known to differ in alcohol preference, the high drinking C57BL/6 strain and the low-drinking DBA/2 strain. She cross-fostered some DBA/2 newborns at birth to C57BL/6 mothers, and vice versa. Mice were tested at adulthood for two-bottle alcohol preference drinking. The strong main effect of genotype was clearly seen (C57BL/6 drank more than DBA/2), however, DBA/2 mice reared by a C57BL/6 dam drank more than those reared by a different DBA/2 dam. Thus, there was a clear GXE effect on adult drinking between genotype and postnatal environment.

Social facilitation could not have contributed to these results (there was no alcohol offered during rearing), but in a subsequent experiment, adult, normally reared C57BL/6 and DBA/2 mice were housed with mice of the opposite or the same strain from weaning (3 weeks) for 7 weeks (Randall and Lester, 1975b). Here, alcohol and water bottles were available. At 10 weeks, mice were individually housed and preference drinking was measured for one week. Both genotypes showed an effect of post-natal rearing. DBA/2 mice reared throughout adolescence with C57BL/6 adults drank more than those reared with other DBAs, and C57BL/6 mice reared with DBAs drank less than the DBAs reared with DBA cage mates.

However, the comparable design in humans, the adoption design, is problematic for several reasons. Human adoptions tend to select for strong genetic effects (due to deviant biological parents) and low variance in rearing conditions (i.e., adoption agencies tend not to place adoptees in problem homes) (Heath et al, 1997). Thus, it is not necessarily surprising that most human adoption studies have failed to find main environmental effects of exposure to parental alcoholism (Cadoret et al., 1985, 1987; Cloninger et al., 1985; Goodwin et al., 1974; McGue, Sharma, & Benson, 1996); and such GXE effects as have been identified (e.g. involving adoptive parent marital status: Cadoret et al. 1986) will be of uncertain generalizability to the general population.

Moreover, in the classic twin design, and in sibling designs more generally, GXE interactions are confounded with additive genetic effects (in the case of genes*shared environment) and with unique environmental effects (in the case of genes*unique environment) (Eaves, 1977; Heath and Nelson, 2002). However, extended twin-family designs that control for genetic background in parents while examining differences in rearing conditions can elucidate where some GXE interactions might occur. Specifically, in one study using this approach, the absence of paternal AUD (a protective environmental factor) reduced the impact of high genetic risk for the development of an AUD in the offspring of (dependence-discordant) twins (Jacob, Waterman, Heath, True, Bucholz, Haber, et al., 2003) although similar findings were not found in another study employing a similar design (Slutske et al., 2008). Thus, perhaps the “biggest news” to come from adoption designs and children-of-twins designs is that the presumed environmental effect of living with an alcohol parent, *per se*, is not an important risk factor for alcohol dependence if genetic factors are adequately controlled.

However, twin studies can provide opportunities for identifying important environmental influences operating both as main effects and as GXE interactions. When information about the environment is explicitly measured, this can be incorporated into twin models to test whether the importance of genetic and environmental effects varies as a function of the measured environment (Dick, Rose, Viken, Kaprio, & Koskenvuo, 2001b; Purcell, 2002). One of the earliest illustrations of gene-environment interaction in the area of substance use research demonstrated that genetic influences on alcohol use were greater among unmarried women, whereas having a marriage-like relationship reduced the impact of genetic influences on drinking (Heath, Jardine, & Martin, 1989). Religiosity has also been shown to moderate genetic influences on alcohol use among females, with genetic factors playing a larger role among individuals without a religious upbringing (Koopmans, Slutske, van Baal, & Boomsma, 1999). Genetic influences on adolescent substance use are also enhanced in environments with lower parental monitoring (Dick et al., 2007c) and in the presence of substance-using friends (Dick et al., 2007b). Similar effects have been demonstrated for more general externalizing behavior: genetic influences on antisocial behavior were higher in the presence of delinquent peers (Button et al., 2007) and in environments characterized by high parental negativity (Feinberg, Button, Neiderhiser, Reiss, & Hetherington, 2007), low parental warmth (Feinberg et al., 2007), and high paternal punitive discipline (Button, Lau, Maughan, & Eley, 2008).

Socioregional or neighborhood-level influences have also been reported to moderate the importance of genetic influences on substance use. Genetic influences for late adolescent alcohol use and early adolescent behavior problems are enhanced in urban environments, communities characterized by greater migration, and neighborhoods with higher percentages of slightly older adolescents/young adults (Rose, Dick, Viken, & Kaprio, 2001; Dick, Rose, Viken, Kaprio, & Koskenvuo, 2001a; Dick et al., 2009). These moderation effects presumably reflect differences in availability of alcohol, role models, neighborhood stability, and community-level monitoring across different areas. Indeed, twin studies suggest that many of the important moderating effects of the environment associated with alcohol use and related externalizing behavior reflect differences in situational constraints and/or opportunities, as discussed above, but this type of GXE has been largely unexplored in measured gene studies.

Examples of Specific Environments that Could be Modeled Across Species: Early Alcohol Exposures and the Peer Environment

Early Alcohol Exposures

Animal models have shown clearly that fetal exposure to alcohol may lead to dysmorphology and behavioral deficits that resemble human Fetal Alcohol Syndrome. In addition, fetal alcohol exposures may lead to the development of specific drug sensitivities and preferences that may contribute to the development of AUDs (Abel, Bush, Dintcheff, 1981; Alati et al., 2006; Arias & Chotro, 2005; Dominguez, Lopez & Molina, 1998; Osborn, Yu, Gabriel & Weinberg, 1998). There is also increasing evidence to indicate that youth exposure to alcohol may be relevant to the development of AUDs. One of the most reliable findings in the epidemiology of AUDs is that early onset of drinking is associated with increased likelihood of developing an AUD (Grant & Dawson, 1997; Hingson, Heeren, & Winter, 2006). What is not clear at this point is the extent that these findings represent a clear causal mechanism (perhaps because of increased sensitivity of the brain to alcohol or alcohol-related cues) or are an artifact of a common “third variable” associated with both early deviant behavior and the development of AUDs. Currently the data are ambiguous, with some evidence suggesting that the early alcohol drinking → AUD link is a spurious effect of correlated disinhibitory problems (Prescott & Kendler, 1999), some a true genotype

x environment interaction effect (Agrawal et al., 2009) and it remains unclear whether common third-variable causation is a sufficient explanation (McGue & Iacono, 2008; Odgers et al., 2008).

It is possible that early alcohol exposure could contribute to risk for dependence by at least two different mechanisms: (1) by altering ethanol sensitivity or alcohol-seeking processes, and (2) by inducing neurocognitive impairment that ultimately could relate to impaired self-control processes. With respect to altering ethanol sensitivity and alcohol seeking, adolescent rats (like humans) tend to consume more alcohol than their adult counterparts and this is not just a function of global consummatory behavior (hyperphagia, hyperdipsia) suggesting enhanced rewarding or decreased aversive responses at this stage of life (Vetter, Doremus-Fitzwater, & Spear, 2007). Adolescent alcohol exposure in rats has been shown to be associated with high levels of appetitive motivation for alcohol (e.g., Pautassi et al., 2008), increased hypothermia (Ristuccia & Spear, 2008), increased stress-induced alcohol consumption (Fullgrabe, Vengeliene, & Spanagel, 2007), altered alcohol-induced social facilitation (Varlinskaya & Spear, 2007), and decreased sensitivity to some but not all symptoms of “hangover” (acute withdrawal; Doremus-Fitzwater & Spear, 2007). At present, it remains unclear to what extent adolescent exposure and drinking behaviors predicts adult variation in alcohol consumption in rats (Vetter et al., 2007). However, adolescence is the primary period of initiation for alcohol consumption in humans and rodent data indicate that adolescents respond differently than adults to both reinforcing and punishing effects of alcohol and they drink different.

Accumulating evidence suggests that adolescent humans and rats may be more sensitive than adults to the neurotoxic effects of alcohol (Monti et al., 2005). Heavy exposure to alcohol in adolescence has been associated with structural and functional brain deficits, and also deficits in cognitive functioning (Clark, Thatcher & Tapert, 2008; De Bellis, Clark, Beers, Soloff, Boring, Hall, et al., 2000; Hargreaves, Quinn, Kashem, Matsumoto & McGregor, 2009; Tapert, Brown, Baratta, Brown, 2004; Zeigler, Wang, Yoast, Dickinson, McCaffree, Robinowitz, et al., 2005). The seemingly heightened sensitivity of the adolescent brain to alcohol-related insult is thought to be associated with neurodevelopmental vulnerability to disruption of the extensive remodeling of the brain that takes place in adolescence (e.g., synaptic pruning; Clark, Thatcher, & Tapert, 2008). The associated neurocognitive deficits, especially those associated with deficits in executive functioning (Monti et al., 2005), could pose added risk for a range of externalizing behavior problems in addition to alcohol dependence. Although a definite causal relation in humans has yet to be established, rodent models of adolescent ethanol exposure (Crews et al., 2000; Spear, 2000; Swartzwelder, Wilson, & Tayyeb, 1995) demonstrate that adolescence appears to be a time of heightened sensitivity to persistent neurologic damage as well as priming enhanced sensitivity for some alcohol effects and tolerance for others.

The Peer Social Environment

Alcohol consumption in humans, at least consumption that leads to intoxication, is largely a social phenomenon. Perhaps the strongest environmental correlate of alcohol use and alcohol problems is peer use, with adolescents and young adults showing a strong resemblance with their peers with respect to their substance use. This similarity reflects two complementary and interacting processes: socialization or causation, and selection (Andrews et al. 2002). Socialization describes the phenomenon where an individual’s alcohol use is shaped by influence from the peer group. In this case, affiliations with substance using peers may encourage greater involvement with alcohol through various mechanisms, including social learning, peer group influence, modeling, and social facilitation (Fergusson et al. 2002; Deater-Deckard 2001). Conversely, the process of selection occurs when adolescents seek affiliation with peers who display similar patterns of substance use or deviant behavior.

Research suggests that adolescents from disadvantaged, dysfunctional, or disturbed environments or those with a predisposition towards antisocial behavior are most likely to become involved with deviant peer groups through the selection process (Fergusson et al. 1999). In either case, the proportion of peer associates who use alcohol and engage in deviant behavior is a powerful predictor of the development of alcohol abuse and dependence in adolescence (Fergusson et al. 2002; Windle 2000).

The peer use environment illustrates some of the dilemmas surrounding the consideration of environmental risk factors since a substantial amount of this ostensible “environmental risk factor,” perhaps as much as 50% by adulthood, is attributable to additive genetic effects (Kendler et al., 2007). The apparent, genetically influenced “niche seeking” should not be interpreted to mean that the environment does not play an important causal role in the outcome of alcohol-related pathology. It does suggest, however, that it is not just naïve but probably incorrect to view the peer environment as an independent, environmental risk factor. Moreover, even in the context of strong selection into high drinking social environments (e.g., college fraternities and sororities), there remains nontrivial socialization effects that appear to reinforce the selection or even lead to onset or escalation in lighter drinkers (Park et al., 2009). Twin studies have suggested that the correlation between peers’ substance use and an adolescent’s own substance use reflects both genetic (selection) and environmental (socialization) processes (Dick et al., 2007a).

When considering the peer environment as an important environmental factor in drinking, simple social influence (e.g., coercive or imitative modeling) and availability are not the only mechanisms that may be considered. Research on drinking motivations (Cooper et al., 1994) and alcohol expectancies (e.g., Brown et al., 1980; Fromme et al., 1993) indicates that drinkers report that alcohol enhances social reinforcement and that they drink to enhance social interaction. Experimental studies (e.g., Sher, 1985) indicate that alcohol is perceived as more pleasurable and activating when consumed in group versus solitary contexts. Indeed, most human consumption occurs in social contexts.

The possibility that some of the most etiologically relevant of alcohol’s reinforcing effects are conditional upon social interaction, at least early in a drinker’s drinking career (e.g., during adolescence), is consistent with neuropharmacological views of alcohol (and other drugs of abuse affecting dopamine circuits; Berridge and Robinson, 1998) increasing the salience of natural incentives. There is direct evidence that interaction with familiar conspecifics is reinforcing in rats (Douglas, Varlinskaya, & Spear, 2004) and that ethanol facilitates social interactions (esp. in adolescents). Moreover, opiate antagonists block some aspects of social interaction (e.g., play fighting) implicating opioid mechanisms in this seemingly consilient ethanol effect (Varlinskaya, & Spear, 2009). Note, however, as drinking progresses to dependence in vulnerable individuals, it seems likely that the salience of the drug effect (independent of enhanced social reinforcement) increases, in effect, “hijacking” brain circuits for social and other natural reinforcers. Thus, the notion of alcohol’s rewarding properties being heightened in the context of social interaction is likely a function of stage of one’s drinking career as well as stage of development.

The role of the social environment in animal modeling of GXE presents a number of interesting opportunities and challenges. The opportunities stem from the ability to carefully manipulate aspects of the social environment to determine the exact nature of the social environmental effect (e.g., imitative modeling, pharmacological enhancement of normal social reinforcement), specifying the neurobiological mechanisms underpinning such an effect, and relating such mechanisms to candidate genes. The challenges arise when trying to find appropriate models or even species where relevant social behaviors “have evolved in their natural ethological and ecological contexts” (IOM [2006], p. 134). From this

perspective, whether or not an animal appears to imitate another animal consuming alcohol isn't a sufficient criterion for deeming it a consilient model. The issue is why it is doing so and whether it serves a similar function.

The Potential Importance of Species Selection for Building Consilient Models

As noted above, alcohol use in humans is largely a social phenomenon. Moreover, human pair bonding (and parenthood) is associated with both general decreases in alcohol consumption ("the marriage effect") and reciprocal dyadic influences within the marital dyad (Leonard & Rothbard, 1999). Use of rat and rodent species that vary greatly from humans in both social activity and pair bonding may limit consilience and, thus, at least for studying some environmental influences, other species may be considered.

Perhaps the most obvious class of animals for building consilient animal models for human alcohol consumption is primates. The value of using primates to study GXE interactions involving childhood and proximal stressors on drinking has been clearly demonstrated (Barr et al., 2004,2008) in the work in Rhesus macaques. However, the cost of conducting this type of research and heightened animal welfare concerns regarding primates constrain the extent that primates can be used and additional species should be considered.

Prairie voles (*Microtus ochrogaster*) are social and monogamous in the wild, forming life-long pair bonds, a trait shared with only 5% of mammalian species (Young et al., 1998). Many of these behavioral characteristics can also be studied in the laboratory. In contrast to a promiscuous and asocial vole species, montane voles (*Microtus montanus*), when studied in triads of one male and two females in a laboratory, male prairie voles huddle with one female selectively after mating with her. The behaviors were shown not to be a function of mate availability or female receptivity, but seem to represent a high degree of affiliative behavior (Shapiro and Dewsbury, 1990). Much of this research has been devoted to defining the neuroendocrine correlates of pair bonding, which predominantly feature signaling differences in arginine vasopressin (especially in the vasopressin 1a receptor) and oxytocin systems (Insel, 2003). Interestingly, one recent study suggested that polymorphisms in the human *AVPR1A* receptor gene were associated with pair bonding in humans (Walum et al., 2008). Some studies have also examined paternal care, male other aspects of social behavior, and various aspects of agonistic behavior (Young et al., 1998).

Could pair bonding, paternal care of pups, or other social behaviors in prairie voles offer an environmental behavioral context for exploring the importance of GXE on alcoholism? One recent study suggests that this might be possible. Bosch et al. allowed male and female prairie voles to pair bond for several days, during which time they presumably copulated and entered the post-copulatory period (after the first 24-72 hr of exposure), although mating was not recorded. Some pairs were then separated. Separated animals showed longer durations of floating in the forced swim test, and increased durations of "passive stress-coping" (i.e., hanging without struggling) in the tail suspension test but showed no differences from controls in the elevated plus maze (Bosch et al., 2009). Further studies in this well-controlled experiment implicated the CRF-1 receptor in these behavioral changes. Thus, the pair bonding behavior appears to be amenable to experimental manipulation.

However, it is not entirely clear how one would interpret such studies. The Bosch study used these particular tests as putative analogs of "depression-like" behavior and "anxiety-like" behavior. In other words, they were used to assess presumed negative emotional states upon removal of the presumably rewarding state of pair bonding. Others have noted that the behavior of floating appears to signify different emotional states and behavioral coping

strategies to different observers – i.e., its construct validity is questionable (Petit-Demouliere et al., 2005). In contrast, most of the literature surrounding the comparison of prairie and montane voles has cast them in the role of an animal model of autistic behavior (Hammock and Young, 2006). Finally, as mentioned above, most of the vole research in this area has been at the molecular level.

A recent study paired adult prairie voles with one male sib for five days and then individually housed the animals. Some were housed with continued “social,” or at least visual, auditory, and olfactory, access to their sibling through a wire mesh screen, and others were housed alone. All had access to water and ethanol and drinking preference was assessed. Isolated voles drank less than those with social access to a littermate. Drinking in littermates housed with access was highly correlated, while sibling drinking in isolated pairs was not. (Anacker & Ryabinin, 2009).

Besides the above unpublished study, that this is an area with intriguing possibilities for alcohol research is based almost entirely on the biological data implicating vasopressin and oxytocin. In the 1980’s, vasopressin was shown to restore normal ethanol drinking in Brattleboro rats genetically lacking vasopressin (Rigter and Crabbe, 1982). More recently, mice with a targeted disruption of the *Avp1r* gene showed increased alcohol consumption compared to wild type (Sanbe et al., 2008). The vasopressin 1A receptor has also been implicated in partially mediating some of the differences in maternal behavior transmitted epigenetically by the group of Michael Meaney and collaborators (Champagne et al., 2003). Other social isolation-related behaviors have been studied extensively in rats and mice, and there is some evidence for a role for vasopressin as well. For example, brain-regional receptor densities for V1aR, oxytocin, and CRF receptors predict the response of rats to isolation housing, specifically the potentiation of the startle reflex induced by isolation (Nair et al., 2005). Manipulations of the pre and postnatal environment using cross fostering and / or ova transplant designs could be applied to prairie voles or other high or low drinking rodent genotypes to begin to tease apart the influences of drinking from observing drinking in cage mates. Similarly, such a study could be performed in a genetically segregating genotype by screening mice at weaning for high or low drinking individuals to use as cage mates. Voles (or possibly mice) could be offered the opportunity to huddle with one of two previous cage mates, a high drinker with which it had previously been paired vs a low drinker. These sorts of designs could be applied to prairie voles or other high or low drinking genotypes to begin to tease apart the influences of drinking from observing drinking in cage mates. It may be useful to pursue the role of vasopressin more widely in such experiments. Similarly, such a study could be performed in a genetically segregating genotype by screening mice at weaning and selecting high or low drinking individuals for cage mates. Such studies might help to sort out GXE from gene-environment correlation.

Human Laboratory Models

Human laboratory models offer an opportunity to examine the effects of GXE interactions on ‘translational phenotypes’ that bridge human and animal models (Hutchison, 2008). Translational phenotypes can be derived from either animal or human studies that are designed to elucidate the neuroanatomical and pharmacological mechanisms that underlie the etiology of addiction. For example, animal models can help identify and evaluate GXE interactions comparing animals with different genetic backgrounds that are exposed to specific environmental variables. Likewise, human laboratory models can be used to compare humans that differ on specific polymorphisms and have been exposed to specific environmental manipulations.

As an example, the motivation to use drugs has been linked to the mesolimbic and mesocortical networks in the brain (the neural substrates that putatively underlie the attribution of incentive motivation to drugs of abuse) and is thought to be an important factor in the etiology of addiction (Berridge & Robinson, 1998; Kalivas & Volkow, 2005; Robinson & Berridge, 1993; Wise, 1988). The most widely used animal model for investigating the neurobiology of drug-seeking behavior is the drug reinstatement model (Epstein, Preston, Stewart, & Shaham, 2006). Here, the animal is exposed chronically to a drug and a drug-related cue, withdrawn from the drug, and then subsequently re-exposed to the cue. Although some concerns regarding the validity of the model have been raised (see Epstein et al., 2006), this approach has been extremely useful for identifying the neurobiological mechanisms that underlie drug-seeking behavior. To examine a gene by environment interaction, animals that have been genetically modified by “knocking in” human genes with different versions of a specific polymorphism or more generally “knocking out” the gene can be exposed to specific environmental variables (e.g., repeated exposure to a drug or drug cues). Key neuroanatomical loci and pathways in the rat include the VTA, nucleus accumbens, prefrontal cortex, dorsal striatum, and basolateral amygdala (see Kalivas & Volkow, 2005). Changes in the loci and pathways that result from the combination of the gene and the environmental exposure can be conceptualized as a GXE interaction.

In the specific example above and more generally, there are three points where animal and human research can make significant contact in terms of the study of GXE interactions. One point is represented by common ground in specific experimental models of exposure to a given environmental variable. A second point of contact is the genetic variable in question (e.g., gene, gene network), and the third point of contact is the biological measures that are analogous across the human and animal studies.

For example, neuroimaging approaches have been used to examine the effect of specific environmental manipulations such as exposure to a drug cue or drug itself on neurocognitive function in humans. In fact, studies with humans have proven to be largely consistent with the animal literature, leading to the integration of translational models that span animal and human findings (Kalivas & Volkow, 2005). Thus, for a GXE study, there are clearly approaches that provide common ground in terms of the environmental manipulation (e.g., exposure to drug cues) and phenotypes (e.g., changes in neurobiological variables). There are also a number of human studies that have examined the effect of GXE interactions in the context of neuroimaging. For example, several studies have demonstrated an interaction between an environmental manipulation (exposure to a drug cue) and a specific polymorphism on brain function (e.g., Hutchison et al., 2008; Filbey et al., 2008, McClernon et al., 2007). It seems likely that these observations actually reflect the long-term consequences of a gene by chronic drug exposure interaction that alters the neurobiological pathways that mediate the attribution of incentive salience to drug related stimuli.

Another point of contact between animal and human studies of G x E interactions can be found in pharmacogenetic studies which we can view as a special case of GXE where the “environmental” variable is exposure to a medication. Recent examples of these studies in humans include studies on the interaction between exposure to alcohol and genetic variation in the OPRM1 gene and naltrexone (Ray & Hutchison, 2007) and the interaction between genetic variation in the CHRNA4 gene and the acute effects of nicotine (Hutchison et al., 2007).

It is important to highlight that with regard to OPRM1, existing studies have generally not found a significant association with substance use disorder diagnoses (Arias et al., 2006). However, a functional single nucleotide polymorphism of the OPRM1 gene may predict

response to naltrexone, an opiate antagonist that has actions at mu opiate receptors. Specifically, carriers of the OPRM1 +118G allele have been found to respond better to naltrexone therapy for alcohol dependence relative to homozygotes for the OPRM1 +118A allele (Anton et al., 2008; Oslin et al., 2003); although not all studies support this finding (e.g., Gelernter et al., 2007).

Human laboratory studies have identified that carriers of the G allele have increased subjective alcohol effects (Ray & Hutchison, 2004), stronger cue-induced craving (van den Wildenberg et al., 2007) and stronger automatic approach tendencies toward alcohol and other appetitive stimuli (Wiers et al., 2009). Moreover, these various facets of alcohol approach motivation and reward such as alcohol stimulation, positive mood, craving and enjoyment are blunted by naltrexone, particularly for those with the G allele (Ray & Hutchison, 2007). It is therefore of considerable interest that seemingly consilient findings can be observed in nonhuman animals. For example, deletion of the mu opioid receptor gene in mice abolishes ethanol drinking (Roberts et al., 2000) and reduces motor impulsivity and the enhancement of motor impulsivity by ethanol (Olmstead et al., 2009). In primates, carriers of a functionally equivalent variant of the mu-opioid receptor had higher alcohol preference that naltrexone reduced providing additional evidence supporting the therapeutic potential of naltrexone. Efforts such as these that work across human and animal studies to examine how genes modify responses to pharmacological agents may ultimately inform our understanding of different pathways to the development of alcohol dependence without finding an association with alcohol dependence *per se* (Weirs et al., 2009).

Finally, one other critical environmental variable to examine in the context of GXE interactions, in both animal and human models, is stress (for review see Clarke & Schumann, 2009). Recent studies have suggested that exposure to stress has a important impact on the progression of psychopathology, especially during specific developmental periods, and this impact is moderated by genetic factors (Stevens et al., 2009). While there are excellent experimental models of the effects of stress in animals (e.g., Heilig & Koob, 2007) and in humans (Greeley & Oei, 1999; Sher, 1987; Sher & Grekin, 2007), it is important to note that the intensity and duration of stressors that can be ethically administered to human participants in the laboratory is limited, thus, restricting our ability to examine traumatic stress exposures in the laboratory. Consequently, the examination of gene x stress interactions may be largely limited to retrospective/observational studies in humans if severe or traumatic stress is the target of inquiry. (Although in recent years electronic diaries and ecological momentary assessment have been used to study alcohol/stress interactions in “real time” in the natural environment [see Sher & Grekin, 2007], the base rate of traumatic exposures is likely too low to employ this technology to assessment traumatic stress.) Animal models can therefore provide critical information that may be difficult to obtain in humans.

Clearly, experimental approaches are more feasible when employing nontraumatic levels of stress in humans. Indeed, some of the largest individual differences in alcohol sensitivity associated with family history of alcoholism are in the domain of autonomic stress reactivity (e.g., Finn, Zeitouni, & Pihl, 1990; Levenson, Oyama, & Meek, 1987). Additionally, there are a number of paradigms for assessing negative affect/stress that translate across human and mammalian species for examining stress reactivity using psychophysiological measures (e.g., affect-potentiated startle) and behavioral measures (e.g., passive avoidance) that have been shown to be alcohol sensitive (e.g., Donohue, Curtin, & Lang, 2007; Sher, 1987; Sher & Grekin, 2005). Moreover, human laboratory models of acute exposure to stress (e.g., Sinha, 2001; Sinha et al., 2006) and the examination of genetic variation that may interact with acute stress (see Clarke & Schumann, 2009) has proven valuable in the study of relapse and clinical alcohol dependence. Given that there is some controversy over the role of stress

in the progression of alcohol dependence, translational models that bridge the animal and human work are sorely needed to develop a better understanding of stress and genetic factors that may interact with exposure to stress.

CONCLUSIONS AND RECOMMENDATIONS

One phenotype where we would expect to find compelling evidence for gene-environment interaction effects is the alcohol dependence phenotype, considering its strong association in the parental generation with childhood environmental adversities in the offspring generation and heightened opportunities for social learning of excessive consumption patterns. It is plausible, but arguably not yet convincingly established, that greater consideration of such GXE effects will facilitate the goals of identifying more of the genes that are contributing to risk of alcohol dependence, as well as of understanding how (including under which environmental conditions) they are having effects. In these undertakings, however, it is critical to remember that much of the genetic effects on alcohol dependence appear to represent broad liabilities to a range of externalizing behaviors and other substance dependence. This suggests that understanding relevant GXE interactions for alcohol dependence may involve studying nonspecific genes and environmental exposures and not focusing exclusively on alcohol-related phenotypes. Characterizing relevant endophenotypes that can be generalized across species and that are relevant to multiple behavior problems would be advanced, but further delineation of the relevant neurocircuitry and behavioral processes that are believed to subserve alcohol dependence more specifically would still be needed.

Achieving consilience faces a number of potent challenges. In the human literature, we lack an organizing taxonomy of environmental exposures. Moreover, the lack of experimental control over environmental exposures, and in particular the tendency of multiple adverse exposures to cluster in the same individuals, families, neighborhoods etc., both cross-sectionally and over time, makes disentangling individual risk-factor effects that might interact with genetic differences a major challenge. While latent variable methods (e.g. inferring genetic effects from twin data) hold considerable promise for identifying major environmental domains that may moderate aggregate effects of genetic variants such methods, involving comparison of differences in familial correlation (e.g. in MZ-DZ correlation differences) as a function of environmental exposure, have relatively low power and thus can detect only large interaction effects (although it remains an open question whether they will yield greater insight into GXE effects than SNP by SNP GXE analyses, given the small effect sizes anticipated for the latter). Isolated reports of GXE effects in individual samples have in general not yet led to the coordinated efforts at cross-study replication, including meta-analyses, that would make findings convincing both in terms of confirmation of GXE effects, and through clarification of the specific aspects of environmental exposure (e.g. of the many environmental differences associated with urban versus rural residence) that may be contributing to interaction effects.

In the domain of human measured genotype studies, GWAS studies offer the prospect of novel genetic findings (albeit most probably on a more limited scale than was initially hoped). However, in the alcohol field, such studies have been designed based on the AUD phenotype, without regard to stratification by environmental exposure history. Thus, they will also have limited power to model GXE effects and use these to inform gene discovery. Despite high initial enthusiasm for the single genetic variant – single exposure approach that was illustrated in the serotonin transporter work of Caspi et al. (2003), the ultimate failure of replication attempts (Munafo et al., 2009; Risch et al), and low power of studies reporting positive findings (Munafo et al., 2009) cautions against undue confidence in the existing literature. In particular, studies based on sample sizes that are at least an order of magnitude

larger than the first generation of studies (which typically had under a thousand individuals per sample) will be needed to give some confidence in findings (esp. for interactions involving rare environmental exposures). Studies in the human experimental laboratory, using experimentally controlled stressors or other manipulations, with human subjects selected on the basis of a genetic variant, and perhaps stratified by early environmental exposure, offer some hope of furthering understanding interaction effects with known genetic variants. Yet, even here, likely modest gene effect sizes (c.f. Flint and Munafo, 2007), except for variables such as metabolism, and greater limitations on feasible sample size, will be an important limiting factor.

We have noted that non-human research offers many attractions for characterizing gene-environment interaction effects, through its ability to work at multiple levels of biological organization (neurocircuitry, cellular, genetic, epigenetic), including in particular specific genotype x specific environment interaction effects. The challenge for work in this area is to identify consilient environmental exposures and associated neurobehavioral processes that are analogous in human and nonhuman species even if not strictly homologous. Such processes can be found in multiple domains including punishment and reward systems (associated with motivations to consume alcohol), self-regulatory systems (associated with the ability to inhibit consumption in the context of drinking motivation), and neurocognitive abilities (e.g. learning processes more generally). It seems possible, if not likely, that more careful consideration of specific species for studying specific environmental variables of relevance to humans will result in more theoretically informed and ecologically valid models.

While most environments studied to date have been viewed as having durable effects on constitutional, motivational propensities and self-regulation, there are a range of possible situational environments that are associated with likelihood of consumption in humans and nonhuman animals. Although some of these would seem to be uniquely human (e.g., various celebrations and socially sanctioned rituals; MacAndrew & Edgerton, 1969), others related to availability, cost, competing demands, and social stimulation would appear to be directly translatable and important for understanding human “real world drinking” where situational goals and constraints represent powerful but not absolute effects on behavior. The ultimate goal is to inform human alcohol use and dependence; establishing meaningful consilience of human and nonhuman animal studies represents considerably more than demonstrating similarity of inputs and genes on alcohol-related behaviors and establishing similar mediating processes linking genes and environments to phenotypes of interest.

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