Developing Neurobiological Endophenotypes that Reflect Failure to Control Alcohol Consumption and Dependence

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Abstract Alcohol-use disorders (AUDs) are a major public health concern in the United States. To better understand the etiology of alcohol dependence and to identify physiological and behavioral markers that predict alcohol use progression, research has focused on linking diagnostic phenotypes with genetic variation. In recent years, neurobiological endophenotypes have largely surpassed clinical symptoms as the major phenotypes of interest, because they are typically more proximal to underlying genetic mechanisms, and can help to fill the gaps between genetic variation and clinical diagnosis. To date, numerous useful neurobiological endophenotypes for alcohol dependence have been uncovered, including those related to reward dysregulation, impulsivity, and subjective response to alcohol, In general, further work is needed to demonstrate direct associations between AUD endophenotypes and specific genetic variation. Future research would also benefit from applying a theoretical framework emphasizing the shifting imbalance between reward and control networks that occurs during the typical progression from recreational drinking to alcohol dependence. Identifying endophenotypes characteristic of different stages of addiction could have important diagnostic and treatment implications.

Keywords Endophenotypes · Alcohol · Neuroimaging · Genetics · Reward · Impulsivity · Addiction

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Introduction

Alcohol-use disorders (AUDs) are an economically burdensome and widespread problem, with lifetime prevalence an estimated 18 % in the United States [37]. AUDs cost approximately $235 billion per year, accounting for approximately 13 % of annual health-care costs, or 2.7 % of the total gross domestic product [86]. In addition to the financial impact, numerous deleterious health outcomes are associated with alcohol misuse, including cardiovascular disease, cancer, liver disease, and damage to brain structure and function [76,86,102]. Given the substantial heterogeneity among AUDs in terms of clinical symptoms and response to treatment [43], research in this field is tending towards development of a more nuanced understanding of their etiology and maintenance.

Numerous studies over the last 30 years have suggested that risk for AUDs is at least partially determined by genetics—specifically, AUD risk seems to be 50–60 % heritable [38,53,81,91]. Although genetic variation is a crucial differentiating factor [40], current research has yet to characterize genetic variations that can be used to effectively identify at-risk individuals or prescribe effective personalized treatments. Because of the difficulty of linking genetic variation to complex diagnostic phenotypes, the field has shifted its focus to delineating "intermediate" phenotypes, in the hope they might simplify the connection between genes, neurobiological mechanisms, and the development and maintenance of AUDs [66,84].

The term "intermediate phenotype" is generally indicative of a mechanism that mediates the effect of genetic variation on a more distal clinical phenotype. Intermediate phenotypes can relate to a broad range of observable behavior, including behavior patterns (i.e., repeated failed efforts to control drinking) that are not necessarily a form of diagnosed psychopathology. The "endophenotype" concept was first

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used over 30 years ago [36], to describe particular intermediate phenotypes ranging from neuroanatomical features to metabolic processes to psychological characteristics to electrophysiological or hemodynamic brain responses. These physiological markers are more proximal to genes than are diagnostic phenotypes, and can help form the link between upstream genes and downstream phenotypes. Use of endophenotypes in psychiatric genetics research may aid diagnosis, classification, treatment, and the development of animal models [35]. Moreover, better understanding of these components could enable the development of more customized and efficacious treatment options, including improved pharmacotherapy for AUDs [43,66].

It should be noted that the commonly used term "biomarker" refers to any "endogenous, measurable characteristic that indicates *either* risk for or manifestation of a psychiatric illness" [5], whereas endophenotypes—an important subtype of biomarkers—are subject to a more specific set of defining criteria. Cannon & Keller [17] have outlined the characteristics that must be present for a behavior or response to be considered a genetically informative endophenotype:

1. it must be heritable;
2. it must be associated with the causes rather than the effects of a disorder (i.e., the level of the endophenotype should enable prediction of the individual level of genetic risk, and the endophenotype should be expressed in the "deviant range" before and after an individual manifests a particular disorder);
3. it must be less complex than its associated disorder (and numerous endophenotypes may be related to a complex disorder);
4. it must vary continuously in the general population;
5. it should be measureable across more than one level of analysis; and
6. endophenotypes that affect multiple disorders should be found for genetically related disorders [17].

It may also be useful to add an additional criterion, namely, that the endophenotype should fit into a conceptual model for which prior data already provide strong theoretical support. For instance, several commonly accepted models of addiction suggest that substance-use disorders are maintained, in part, through an imbalance between an individual's incentive reward network [48], which creates the urge to use a substance, and the control network [6], which affects whether these impulses are acted upon [43,44]. Briefly, the incentive network refers to structures involved in reward and/or reinforcement, including the ventral tegmental area (VTA), the nucleus accumbens, the thalamus, the insula, and the amygdala [29,52,57,69], and the control network refers to structures involved in executive functioning, including the inferior frontal gyrus (IFG), the orbitofrontal cortex (OFC), and the dorsolateral prefrontal cortex (dlPFC) [12,20,52]. Thus, useful endophenotypes might examine the balance between reward and control networks.

Relatedly, the three-stage model [56] suggests that addiction develops in three stages:

- binge/intoxication;
- withdrawal/negative effect; and
- preoccupation/anticipation

and that this progression is accompanied by neurobiological adaptations that promote the addicted state. Recently, Karoly and colleagues [52] have extended the three-stage theoretical model to demonstrate the shifting imbalance between reward and control networks across each stage of the addiction cycle, as an individual progresses from recreational use to an addicted (dependent) neural state. Briefly, the extended model states that during stage 1 (the "binge/intoxication" stage), the reward network seems to be dysregulated with repeated drug use, such that responses to drug-related rewards increase whereas the incentive value of natural reinforcers decreases [4,27,74,88]. Repeated drug use is associated with an increase in connectivity between regions involved in negative effect and withdrawal [13,68,75,99]. These changes lead to a downstream strengthening of reward areas in response to drug-related cues, and concurrent weakening of control regions [45,108], which serves to perpetuate compulsive substance use, characteristic of the "preoccupation/anticipation" stage. An example of an endophenotype derived from the three-stage model might involve targeting neurobiological adaptations characteristic of the "withdrawal/negative effect" stage, and might measure brain activation in response to visual alcohol cues among heavy drinkers undergoing acute or protracted withdrawal (additional examples are given by [52].

One notable concern regarding the development of endophenotypes for complex psychological disorders is the issue of disorder specificity. Although criterion 6, above, notes that an endophenotype can affect several disorders if those disorders are genetically related, an endophenotype associated with numerous forms of psychopathology (i.e., executive functioning deficits) may have less clinical utility. For AUDs, one possible solution to this problem is testing the "gene X alcohol exposure" interaction for a given endophenotype. If a particular gene alters the effect of alcohol exposure on some endophenotype (i.e., executive control) this interaction would suggest a more specific genetic link between the endophenotype and the disorder. Further, longitudinal studies examining whether a given endophenotype affects future alcohol use or treatment outcome could indicate the presence of a causal relationship between the endophenotype and AUDs.

Endophenotypes for AUDs

Given the complex biopsychosocial etiology of AUDs [70,109] and the significant individual variability in subjective responses to alcohol consumption [23,82], much research effort over the past 10–15 years has attempted to uncover endophenotypes for AUDs [8]. Early work focused on hypotheses related to electrophysiology and alcohol metabolism. Electrophysiological endophenotypes include cortical synchronization [107], the P300 component of the event-related potential [18,80] and event-related brain oscillations during cognitively demanding tasks [49]. Individual differences in alcohol metabolism—the rate at which alcohol is converted to acetaldehyde—is also predictive of disordered alcohol use, given that accumulation of acetaldehyde affects alcohol sensitivity and subjective drinking experience [41]. Much other evidence has linked variation in alcohol-metabolism genes to AUD risk [63,106]. However, although these early endophenotypes are genetically informative and clinically relevant, they are less applicable in the context of more recent conceptual models of loss of control, reward dysfunction and alcohol dependence. Therefore, electrophysiology and alcohol metabolism research will not be reviewed comprehensively here.

In this review, we will discuss three major categories of AUD endophenotypes, noting advantages and limitations of each, and, when appropriate, identifying the stage(s) within our theoretical model of addiction in which each endophenotype is likely to confer AUD risk. Broadly, we will focus on endophenotypes related to:

1. craving and reward dysregulation;
2. impulsivity; and
3. subjective response to alcohol (Table 1).

We will then further discuss the development of theoretically derived endophenotypes for AUDs, and comment on the limitations of current endophenotypes in the context of such models. Finally, we will suggest theoretically derived endophenotypes that simultaneously probe reward and control networks to overcome some of these limitations.

Craving and Reward Dysregulation

Much evidence suggests that neural reward processing that promotes craving in response to drug-relevant cues is altered in substance abusers [64,99,108]. PET imaging studies have revealed that among addicted individuals, impaired dopamine signaling is associated with compulsive drug use, as drug rewards increase in value while natural rewards become less reinforcing [105]. Dysfunctional adaptations in neural reward networks tend to worsen as addiction progresses [58], probably involving numerous brain areas and neurotransmitter systems. For example, while dopaminergic dysfunction seems to promote the loss of control observed in the initial stages of addiction, impaired glutamatergic projections to the nucleus accumbens have been implicated in the reward dysfunction characteristic of later stages of addiction [48]. Further, disturbances in different aspects of reward processing may be a pre-morbid risk factor predisposing individuals to the development of AUDs [79,97•]. Thus, dysfunction within neural reward pathways has been a crucial target for investigation as a possible AUD endophenotype.

Accordingly, neuroimaging research by our group has attempted to identify activation related to craving and AUD severity [19••]. This study demonstrated that brain activation in reward regions (including the nucleus accumbens, amygdala,

Table 1 Proposed endophenotypes related to three AUD-relevant hypotheses

Endophenotype	Specific phenotype	Selected citations	Relevant stage(s)
Craving and reward			
Dysfunctional reward circuitry, altered dopamine signaling, abnormal cue-responding, heightened alcohol craving	Visual cue response (fMRI)	[39,46•,73]	Binge/Intoxication, Preoccupation/Anticipation
	Olfactory cue response (fMRI)	[50]	
	Taste cue response (fMRI)	[19••,28]	
	Dopamine signaling (PET)	[105]	
Impulsivity			
Impaired response inhibition, devaluing delayed rewards, altered resting and functional connectivity in reward and control networks	Delay discounting (fMRI)	[20,24,71,78];	Binge/Intoxication, Preoccupation/Anticipation
	Stop–signal (fMRI)	[51••,61, 72]	
	Functional connectivity	[7,54]	
	Resting state connectivity	[14,15]&c	
Subjective response to alcohol			
Individual differences in acute physiological and/or psychological responses to alcohol	Level of response (LR)	[90,92,93,103]	Binge/Intoxication, Withdrawal/Negative Affect, Preoccupation/Anticipation
	Sensitivity to stimulating and sedating effects of alcohol	[40,55,60,83,84]	

precuneus, insula, and dorsal striatum) elicited by exposure to the taste of a favorite alcohol beverage was predictive of AUD severity. This study also found activation in brain areas associated with craving, including the prefrontal cortex, striatum, and ventral tegmental area, and this activation was positively correlated with measures of alcohol problems. Increased neural responses to alcohol taste cues within the mesocorticolimbic pathway have been linked to variation in two genes, DRD4 and OPRM1, which regulate receptors within the same pathway [28]. Similar activation was found in a study using olfactory alcohol cues among high-risk drinkers [50], and activation in reward and craving areas (i.e., the prefrontal cortex, ventral striatum, thalamus, and insula) after presentation of alcohol images was greater for alcohol-dependent subjects than for healthy control subjects [33,39,46•,73].

Taken together, this work suggests that brain activation in response to alcohol cues is likely to be a useful biomarker for AUDs, and dysfunctional craving and/or reward-responsivity is likely to confer significant risk in the binge/intoxication and preoccupation/anticipation stages of addiction. Additional work should implement cue-elicited craving paradigms among individuals experiencing acute or protracted alcohol withdrawal, to examine the role of craving and reward-responsivity during the withdrawal/negative effect stage. In addition, to determine whether this biomarker is a true endophenotype, studies should examine neural activation in response to alcohol cues among the unaffected siblings of individuals with AUDs. As far as we are aware, no studies have yet tried to directly answer this question. However, one study of individuals who are family history-positive for alcoholism demonstrated altered neural reward processing among unaffected family members [2•]. This finding is promising initial support for craving and/or reward-responsivity as a true endophenotype for AUDs.

Impulsivity

In response-inhibition tasks impulsive responses and poor performance tend to be characteristics of heavy drinkers [11,59,71]. The term "impulsivity" involves both the ability to inhibit pre-potent responses (a measure of "stopping impulsivity"), when necessary, and the ability to determine the subjective value of delayed rewards (a measure of "waiting impulsivity") [21]. Although AUDs are likely to be related to several deficits in executive functioning, impulsivity is a particularly useful endophenotype because it is a heritable [9], pre-morbid risk factor [22] present in AUD sufferers' unaffected siblings [26], and it appears to worsen with increased AUD severity [59]. Neuroimaging research has leveraged several effective impulsivity tasks in an attempt to characterize the altered neural activation patterns observed among heavy drinkers and those at risk for AUDs

First, neural and behavioral responses to stop–signal task (SST; [62]) paradigms (i.e., "stopping impulsivity") may be a particularly informative endophenotype for AUDs. Altered processing during stop–signal inhibition is observed more often among alcohol-dependent individuals than among healthy controls, and higher levels of in-task craving is predictive of impaired frontal activation [61], which suggests that response to this task may be particularly informative during the preoccupation/anticipation stage. In addition, intravenous infusion of alcohol during an SST significantly reduced stop-trial minus go-trial activation in the right PFC among family history-negative but not family history-positive subjects [51••], which suggests that stopping impulsivity may also confer a significant risk at the binge/intoxication stage. Further support for this hypothesis is provided by studies that demonstrate effects of acute intoxication on stop–signal inhibition [30,72], but not other aspects of task performance, for example reaction time. The Kareken study also indicates that genetic variation may affect individual differences in SST performance and neural activation. As far as we are aware, particular genes related to stop–signal inhibition have not yet been identified. Determining how specific genes affect SST response would lend additional support to its utility as an AUD endophenotype.

In addition, behavioral response to delayed reward discounting (DRD) tasks (i.e., "waiting impulsivity") has received substantial support as a behavioral AUD endophenotype [65], and more recent fMRI research has largely corroborated this view. In a study of heavy drinkers, greater discounting of delayed monetary rewards during an fMRI task and greater activation in the supplementary motor area, insula, inferior frontal gyrus, and precuneus were observed for subjects with more severe clinical symptoms [20]. Importantly, abnormally enhanced temporal discounting seems to persist even among abstinent alcohol-dependent subjects [71], and seems to be at least partially genetically mediated. In particular, DRD has been linked to genetic variation in the COMT gene [100], and DRD may confer AUD risk from family history [78]. Studies examining the effects of acute alcohol administration on DRD have furnished inconsistent results [24,77,87], so further research is needed to determine which stage(s) of the cycle may be affected by DRD.

Finally, recent neuroimaging work targeting resting-state connectivity in AUDs has uncovered another potential endophenotype related to inhibitory control. Resting state connectivity is a measure of the brain's functional organization based on communication between brain regions [31]. Alcohol-dependent individuals in early abstinence who later relapsed had significantly less connectivity in executive control networks than those who remained abstinent, and this decreased connectivity was associated with deficits in a response-inhibition task [14]. In contrast, individuals in long-term abstinence had reduced connectivity in

limbic reward areas and increased connectivity in executive control regions [15]. Evidently, as individuals progress from short to long-term abstinence, resting state connectivity progressively decreases within the reward network and increases within the control network [16] which is consistent with our theoretical model, which posits that these changes occur in the opposite direction during the progression from recreational use to addiction. Further, a recent study using an alcohol-cue reactivity (rather than a resting state study) paradigm demonstrated altered functional connectivity in abstinent individuals who later relapsed compared with those who remained abstinent [7]. Alcohol intoxication also seems to affect functional connectivity acutely [54]. Taken together, this evidence suggests that both resting-state and task functional connectivity data may be useful for predicting treatment outcome and assessing AUD progression and severity.

Subjective Response to Alcohol

Subjective responses to alcohol depend on how alcohol-relevant neural pathways are organized within an individual [84], and subjective response to the acute effects of alcohol is known to be a major determinant of individual risk of developing an AUD [93,96]. More specifically, it seems that alcohol causes greater stimulating (rewarding) effects and lower sedative (unpleasant) effects in heavy compared with light drinkers, and these subjective effects predict future alcohol consumption [55]. Higher alcohol-induced stimulation is, thus, a useful AUD vulnerability marker, given its association with greater reinforcement and increased consumption [60].

Subjective responses to alcohol are heritable [95,104], and differences in subjective response to alcohol have been linked to variation in particular genes [85,94]. Ray & Hutchison [83] found that individuals with at least one copy of the A118G allele had greater response to subjective intoxication, sedation, stimulation, and changes in mood states. Level of response to alcohol has also been significantly associated with two SNPs—rs1051730 and rs8034191—within the 15q25.1 region [47], and Hendershot et al. [40] showed that alcohol sensitivity mediated the effects of the ALDH2 genotype on drinking behavior.

One particularly well-studied construct is the "low level of response" to alcohol (LR) endophenotype, which has been consistently supported as an AUD risk marker. Briefly, LR refers to the genetically affected trait that leads some individuals (low responders) to require higher doses of alcohol to obtain the desired effect [90,92]. LR seems to be heritable [91], present in unaffected family members [25], and genetically mediated [42,47]. A recent fMRI study identified differential activation in the inferior frontal and cingulate regions associated with LR [103], and continued investigation of potential neural correlates of LR is warranted. Evidently,

subjective responses to alcohol are affected by numerous interrelated factors, including alcohol pharmacodynamics and metabolism, and the obvious environmental, social, and/or psychological considerations discussed elsewhere [98], and are thus likely to confer risk differentially throughout the addiction cycle [84].

Future Directions in Theoretically-Derived Endophenotype Development

The extent to which the reward network overpowers the control network at a given time theoretically determines whether an individual will act upon the craving for, or urge to use, a substance. Accordingly, the strongest determinant of loss of control over substance use may be the different strength of these two networks [4,10,34]. We propose that an informative endophenotype for AUD should fit within a theoretical framework emphasizing the emergence of a network imbalance in which the increasingly dysregulated reward network (which can become overly responsive to alcohol-related rewards after repeated alcohol use) eventually overpowers the weakened control network, thus promoting alcohol misuse by some individuals. Such a "reward–control–endophenotype" could be refined even further in the context of the three-stage model, given that the balance between reward and control networks shifts as addiction progresses [52]. Although study of the endophenotypes proposed above have clarified several AUD vulnerability factors that confer different risk at different stages of addiction, further research in this area is needed. Neuroimaging of endophenotypes focusing on the relative strengths of the reward and control networks could have significant diagnostic utility in terms of characterizing neural markers of disorder progression by identifying the stage of addiction of an individual at a given time.

Improved AUD Endophenotypes: Reward and Control

In the context of this theoretical model, it should be noted that some of the existing endophenotypes for AUDs are limited in their ecological validity—this is particularly true of tasks that use alcohol cues to probe the reward network, but fail to simultaneously access the control system because the individual is not asked to inhibit behavior while the cue is being presented. In "real life" situations in which an individual attempts to control his or her drinking, cue-induced craving places high demands on both reward and control systems [1], as the individual decides whether or not to drink in response to alcohol cues. For this reason, fMRI tasks aimed at defining an endophenotype for AUDs should ideally involve simultaneous alcohol cue presentation and an inhibitory control task. Implementation of an fMRI task aimed at characterizing the

neural basis for the reward vs. control network imbalance could help to classify individuals in terms of AUD severity, and may have implications for optimizing personalized treatments.

For this reason, our group is developing an fMRI task designed to identify neural activation patterns that characterize the extent to which dysregulated reward processing in response to acute alcohol cue exposure compounds the behavioral effects of impaired response inhibition. This task combines the standard SST paradigm with visual alcohol and control cues. We hypothesize that our task will elicit differential neural activation during stop–signal inhibition, depending upon which cue is presented, and that this difference will depend on severity of alcohol dependence. Similarly, Fryer et al. [32••] have implemented a visual–oddball paradigm using alcohol and control images, and have used this task to categorize altered neural activation patterns throughout the stages of addiction.

In general, existing reward-based decision-making tasks [67] have proved useful for examining the relationship between control processes and specific aspects of reward (i.e., reward prediction, anticipation, etc.). For instance, gambling paradigms have been useful for examining cognitive control and reward *expectation* [89] and delay discounting tasks have been used to study impulsivity in the context of reward *anticipation* [101]. However, a task that taxes control systems while simultaneously activating the reward network using *craving*-inducing cues (rather than the real or imaginary monetary rewards typically used in reward-based decision-making tasks) may have particular relevance for better understanding AUDs, given the clinical implications of altered neural responses to alcohol cues, and the relationship between cue-induced craving and relapse [99]. Ultimately, such a task could be further specified to examine control over drinking behavior itself, perhaps through an fMRI compatible adaptation of a laboratory drinking paradigm [3].

Conclusions

Numerous biologically based endophenotypes that mediate the effects of genetic variations on AUD severity have been identified. Well-supported AUD endophenotypes include alcohol metabolism, electrophysiology measures, and subjective responses to acute alcohol consumption. In recent years, neuroimaging techniques have been used to examine potential endophenotypes related to reward dysregulation and impulsivity. We propose that further research would benefit from expanding this work, and focusing on endophenotypes consistent with a theoretical framework emphasizing the imbalance between neural reward and control networks, and the *shifting* network balance that can occur as individuals progress from recreational drinking to dependence. Gaining a deeper

understanding of the interplay between these two networks—and identifying genetic variation and neural adaptations that affect reward and control processes—are likely to have important implications for diagnosis and treatment of AUDs.

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