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Endophenotypes for Alcohol Use Disorder: An Update on the Field

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Abstract

The endophenotype concept was first proposed as a strategy to use (purportedly) genetically simpler phenotypes in gene identification studies for psychiatric disorders, and is distinct from the closely related concept of intermediate phenotypes. In the area of alcohol use disorder (AUD) research, two candidate endophenotypes have produced replicable genetic associations: level of response to alcohol and neurophysiology markers (e.g., event-related oscillations and event-related potentials). Additional candidate endophenotypes from the cognitive, sensory, and neuroimaging literatures show promise, although more evidence is needed to fully evaluate their potential utility. Translational approaches to AUD endophenotypes have helped characterize the underlying neurobiology and genetics of AUD endophenotypes and identified relevant pharmacological interventions. Future research that capitalizes on the polygenic nature of endophenotypes and emphasizes endophenotypes that may change across development will enhance the usefulness of this concept to understand the genetically-influenced pathways toward AUD.

Keywords

Endophenotypes; alcohol use disorder; addictions; sweet liking; genetics; genomics; delayed reward discounting; brain structure; brain function

Alcohol use disorder (AUD) is genetically complex (i.e., caused by more than one gene) and behaviorally heterogeneous. In view of this heterogeneity, it has been suggested that "alcoholism cannot be reified but reflects a collection of various symptoms and episodic behaviors that collectively make up perhaps as many alcoholisms as there are alcohol abusers" [1]. Against this backdrop, identifying replicable genetic associations for AUD has been challenging.

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Compliance with Ethical Standards

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The concept of using endophenotypes to aid in gene identification was first introduced to the field of psychopathology by Gottesman and Shields [2]. The idea gained widespread attention after Gottesman and Gould [3] reintroduced the concept and argued that psychiatric classification systems by their very nature create heterogeneous groups of affected individuals, and that this heterogeneity hampers our ability to detect susceptibility genes. Further, these broad binary classifications are quite distal from the level of gene action; surely there is no gene "for" AUD, rather, genes affect certain biochemical processes and pathways that alter susceptibility. Since then, there has been a proliferation of interest in endophenotypes across a range of psychiatric disorders [4–6], including AUD [7–11]. A PUBMED search of the terms "endophenotype" plus "alcohol" produces over 150 results (as of November 2014).

Although there are several excellent reviews of specific candidate endophenotypes for AUD, such as subjective responses to alcohol [8] and neurophysiological markers such as brain oscillations [12], as well as novel candidate neurobiological endophenotypes that distinguish between different stages in the development of alcohol dependence [13], there has not been a recent integrative update on where the field stands with respect to using endophenotypes to aid in gene identification for AUD. Our goal here is threefold. First, we evaluate the weight of evidence for various candidate endophenotypes for AUD (including their previously documented genetic associations) and highlight promising candidate endophenotypes from the cognitive/psychological, sensory, and structural neuroimaging domains. Second, we provide illustrative examples of successes and challenges in validating endophenotypes in animal models. Third, we identify themes to guide future research on endophenotypes for AUD.

Evaluating the Weight of Evidence for AUD Candidate Endophenotypes

Gottesman and Gould defined endophenotypes as "measurable components unseen by the unaided eye along the pathways between disease and distal genotype", and argued that endophenotypes should be "simpler clues to genetic underpinnings than the disease syndrome itself" [2], although it has been more recently recognized that there is likely a gradient of endophenotypes, some of which are closer to gene action and others that are closer to the phenotype [14]. They delineated five criteria: A candidate endophenotype should be (1) associated with illness; (2) heritable; (3) state-independent (present whether or not illness is active); (4) co-segregate with illness within families; and (5) found in a higher rate in the unaffected relatives of affected individuals than in the general population [3]. Others have agreed that endophenotypes should reflect causes rather than effects of disorders, and suggest that endophenotypes should be measured quantitatively [15, 16].

The endophenotype concept is similar to, but distinct from, related concepts such as biomarkers and intermediate phenotypes [17]. Biomarkers refer to measurable indicators of a disease state. As noted by Lenzenweger [17], biomarkers are associated with the disease, but do not necessarily reflect a genetically influenced pathway. For example, in a biomedical context the ratio of aspartate aminotransferase to alanine aminotransferase can be used as a biomarker of alcoholic liver disease. In this case, the biomarker is associated with the disease, but does not reflect a genetically influenced enduring vulnerability to the disease.

According to Rasetti and Weinberger, an intermediate phenotype is "a heritable trait that is located in the path of pathogenesis from genetic predisposition to psychopathology" [18]. This concept has been critiqued on account of its ambiguity with respect to where "intermediate" phenotypes lie along the pathway from genes → disorder, which has implications for level of analysis [17]. Thus, although the endophenotype, biomarker, and intermediate phenotype concepts share overlapping goals of clarifying heterogeneity, the terms are not interchangeable. For an extended discussion of these definitional issues, we refer interested readers to Lenzenweger [17].

Flint and Munafo noted that the "endophenotypes" that have been used in studies of different psychiatric diseases typically fell into six categories: anatomical, developmental, electrophysiological, metabolic, sensory, and psychological/cognitive [19], providing a useful framework for classifying potential endophenotypes. We adopted this framework to organize the evidence for a number of AUD candidate endophenotypes according to each of the five Gottesman & Gould [3] criteria (Table 1) as well as genes, regions of interest, and gene sets associated with candidate endophenotypes (summarized in Table 2 and visualized as part of a gene-environment interplay system in Figure 1). We also added a "functional neuroimaging" category in view of the growing number of functional brain candidate endophenotypes for AUD [13]. As Table 1 illustrates, the evidence for many of the strict endophenotype criteria is sparse at present. The two candidate AUD endophenotypes for which there is the greatest evidence, and which have generated the most genetic associations, are neurophysiological phenotypes and level of response to alcohol [for detailed reviews of these as candidate endophenotypes, see 8, 12].

Neurophysiology

Numerous dimensions of resting and event-related EEG measures (e.g., alpha, theta, and beta oscillations) broadly index information processing and cognitive functioning. Neurophysiological measures are highly heritable [20], and individuals affected with AUD and individuals at high-risk for AUD (offspring of male alcoholics) have elevated resting high-frequency (beta; 12–28 Hz) brain oscillations [21] compared to unaffected and low-risk individuals.

A genome-wide linkage study of EEG beta power in the high-risk Collaborative Study on the Genetics of Alcoholism (COGA) sample found a linkage peak (i.e., a statistical indication that a particular section of a chromosome co-segregates with the trait within families) over a $GABA_A$ receptor gene (*GABRA2*) on chromosome 4 [22]. Subsequent studies across multiple, independent samples have found evidence for association between alcohol dependence and variation in *GABRA2* [23–25] (for a recent exception see [26]). A genome-wide linkage study of power for three frequency bands (alpha, theta, and beta) in a sample of Plains American Indians showed evidence for convergent linkage peaks over the corticotropin releasing hormone binding-protein gene (*CRH-BP*) on chromosome 5 [27]. In the same study, variants in *CRH-BP* showed association with AUD in a Caucasian replication sample, and anxiety disorders in the Plains Indians, suggesting that *CRH-BP* may have pleiotropic effects (i.e., associations with multiple disorders). More recently, gene-based tests from a whole-genome sequencing study of EEG beta power identified the

gastrulation brain homeobox 2 gene (*GBX2*) on chromosome 2; however, it is unknown whether this gene is associated with AUD [28].

In another neurophysiology example, the amplitude of the event-related potential P3 wave, which indexes orientation toward novel events and inhibition of ongoing cognitive processing, is reduced in individuals with AUD (and externalizing disorders more generally) and in individuals at familial risk for AUD [29–33], especially in male offspring [34]. Linkage analyses of the frontal theta and parietal-occipital delta event-related oscillations (EROs) underlying the P3 component found a linkage peak over the muscarinic acetylcholine receptor M2 (*CHRM2)* on chromosome 4 [35]. Subsequent association analyses in the COGA sample found significant association among variants in the glutamate receptor, metabotropic 8 (*GRM8)* gene and theta EROs [36]; variants in the corticotropin releasing hormone receptor 1 gene (*CRHR1*) on chromosome 17 and P3 amplitude [37]; and variants in *KCNJ6* on chromosome 21 and frontal theta oscillations [38]. Variation in *CHRM2*, *GRM8*, *CRHR1*, and *KCNJ6* has also been associated with alcohol and/or drug dependence [39, 40, 37, 36].

Level of response

Level of response (LR) to alcohol is the second candidate endophenotype for AUD to meet many of Gottesman & Gould's [3] criteria, with the exception that, to our knowledge, there is not evidence that it co-segregates with AUD within families. LR [also known as subjective response to alcohol; 41] is the degree to which a person responds to a specific dose of alcohol or the number of drinks an individual needs to produce specific psychological and motor effects, and is distinct from acquired alcohol tolerance [42]. Low LR is hypothesized to confer risk for AUD because individuals who are less sensitive to alcohol must consume larger quantities of it in order to experience its effects. A program of research led by Schuckit and colleagues demonstrates that low LR is associated with increased alcohol use and problems across multiple samples [43, 42, 44]. As summarized in a recent meta-analysis, populations at risk for AUD, such as individuals with a family history of alcoholism, typically have lower LR compared to other populations [45]. Heritability (h^2) estimates for LR are approximately 60% [46, 47].

Variation in a number of genes and gene regions is associated with LR. Variation in *GABRA2* [48] and in the 5-HTTLPR polymorphism in the serotonin transporter (*SERT*) gene on chromosome 17 [49] are associated with subjective responses to alcohol and/or body sway in alcohol challenge studies. Variation in the μ opioid receptor gene (*OPRM1)* on chromosome 6 is associated with subjective responses to alcohol in alcohol infusion studies of problem and [50] non-problem drinkers [51] and self-rated effects of alcohol in a Native American sample [52]. A systematic genome-wide scan in the same Native American sample identified regions of interest on chromosomes 6, 10, 12, and 17 that were associated with participants' self-reported subjective LR early in their drinking careers [53]. Variation in the aldehyde dehydrogenase gene *(ALDH2)* on chromosome 12 was associated with self-reported subjective LR early in the drinking careers of a sample of Chinese- and Korean-American college students [54]. Finally, variants in the cholinergic nicotinic receptor gene cluster (*CHRNA5-CHRNA3-CHRNB4)* on chromosome 15 [55, 56] and genes sets

implicated in neuronal signaling [57] were associated with LR in a sample of young adult offspring of alcoholics.

The evidence for association among these genes and AUD is mixed, with the exception of *ALDH2*'s well-replicated association [58]. A meta-analysis indicates an association between variation in the 5-HTTLPR polymorphism and AUD; however, there is some indication that this reflects publication bias [59]. A meta-analysis of the commonly studied *OPRM1* Asn40Asp (A118G) polymorphism indicated no association with substance dependence (opioid, alcohol, nicotine, or cocaine) [60]. There is some evidence for association among variants in the nicotinic receptor gene cluster on chromosome 15 and AUD [61]; however, other studies have reported null effects [62].

Although LR has received much attention as an endophenotype, it is worth noting that some inconsistencies in the alcohol challenge literature have led others to propose a more nuanced "differentiator model" [63] that takes into account subjective and motor responses across the rise and fall of blood alcohol levels. Under this model, individuals at risk for developing an AUD (by virtue of family history) are hypothesized to show acute sensitization to alcohol as blood/breath alcohol level rises, and acute tolerance as blood/breath alcohol level falls. Thus, these individuals are at risk because of two processes: they experience more pleasurable and excitatory effects of alcohol during initial intoxication, and fewer of the sedative effects of alcohol as blood alcohol level declines. A modified version of the differentiator model [64] suggests that these effects are most pronounced at peak breath alcohol concentration. Recent longitudinal work is consistent with this modified differentiator model; individuals who were more sensitive to the stimulant and rewarding effects of alcohol and who were less sensitive to the sedating effects of alcohol at peak breath alcohol concentration in an alcohol challenge study had the highest number of AUD symptoms six years later [65].

Promising Potential Endophenotypes

Although there are only a small number of examples that come close to meeting the strict definition of an endophenotype, there are many additional candidate endophenotypes for AUD for which some criteria are met. This is especially the case for novel promising endophenotypes for which sufficient data are not yet available. We highlight here four psychological/cognitive, sensory, and neuroimaging candidate endophenotypes that show potential.

Delayed reward discounting

AUD shares genetic influences with several other common externalizing disorders (e.g., illicit drug dependence and antisocial behavior) and measures of impulsivity [66, 67]. Disinhibition, or the inability to control one's impulses, is the central feature shared among these disorders [68]. Impulsivity is a multifaceted construct that encompasses diverse behaviors that are poorly planned, inappropriate, or unnecessarily risky [69]. Impulsivity as a whole is likely not tractable for study as an endophenotype because it does not represent a unitary construct unseen to the unaided eye, but specific features, such as the ability to delay rewards (i.e., exhibit self-control) have been proposed as a cognitive endophenotype for

AUD and substance use disorders more generally [70]. Delayed reward discounting is heritable [30–51% in an adolescent sample; 71]. Abstinent alcoholics are less likely to delay rewards [72] and the unaffected adult daughters (but not adult sons) of alcoholic fathers are less likely to delay reward [73]. To date, however, there have not been systematic gene identification efforts for sub-clinical impulsivity phenotypes such as delayed reward discounting, and so its potential to aid in gene identification for AUD is still relatively unknown.

Executive functions

In recent years there has been a proliferation of interest in executive functions (EF) as they relate to alcohol and other substance use disorders. EF refer to an interrelated set of self-regulatory skills and abilities related to goal-directed behavior [74] including attention, working memory, planning, and cognitive flexibility. EF share a highly heritable (99%) common factor [75] and alcohol dependence severity is associated with impaired EF [76]. These EF impairments among alcohol dependent individuals are to be expected given the toxic effects that alcohol has on the frontal lobes; however, it has been proposed that these EF deficits may predate the onset of disorder and qualify as an endophenotype [77]. For example, unaffected relatives of alcohol or drug dependent probands also have lower EF (as measured in tasks tapping cognitive flexibility and inhibition) compared to healthy controls [78, 77]. In one of these samples, analyses of the brain-derived neurotrophic factor (*BDNF*) Val66Met polymorphism found that the Met allele was associated with lower EF [78]. However, variation in this same polymorphism is not associated with AUD [79].

Sweet liking

From the sensory domain, sweet liking (i.e., preference for sweet tasting foods) is also a strong yet understudied candidate endophenotype. Perceived pleasantness of sweet foods, the frequency of sweet food consumption, and sweet food cravings are moderately heritable (31–50%) [80]. In a taste preference test, alcoholic men preferred higher concentration sucrose solutions compared to non-alcoholic men [81], and paternal history of alcoholism (an indicator of genetic risk) in an inpatient psychiatric sample predicted sweet liking above and beyond subjects' own alcohol dependence status [82]. Children with a family history of alcoholism also prefer a higher sucrose concentration compared to children without a family history of alcoholism; however, this was only the case for children who were also experiencing depressive symptomatology [83]. Variation in the taste receptor type one family of genes (*TAS1R1*, *TAS1R2*, and *TAS1R3*) influences sweet liking [84] and there is a linkage peak (LOD = 3.5) on chromosome 16 at 16p11.2 (marker D16S753) for frequency of sweet food consumption [80]. However, whether variation in the *TAS1* genes and other sweet-liking genomic regions are associated with AUD has not been systematically examined, representing an important direction for future research.

Brain structure

The rapid advances and growing interest in neuroimaging have begun to identify a number of structural brain features that may qualify as endophenotypes for AUD [13]. Disentangling premorbid differences from the effects of alcohol on the brain is an inherent difficulty of

work in this area, as it is known that even subclinical alcohol use disrupts typical neurodevelopment [85] and chronic alcohol abuse accelerates loss of white and gray matter volume [86]. Brain structure is highly heritable (e.g., frontal and language-related structures ($h^2 > 80\%$) [87] and white matter volume ($h^2 = 96\%$) [88]). Alcohol-dependent individuals have reduced volume in the right hippocampus compared to unaffected controls [89, 90]. Brain volume differences are also observed in alcohol-naïve children, adolescents, and young adults who are at high familial risk for AUD, as evidenced by reduced gray matter volumes across multiple brain regions (superior frontal, cingulate and parahippocampal gyri, amygdala, thalamus, and cerebellum) compared to matched controls at low familial risk for AUD [91]. In this same study, smaller gray matter volumes in many of these regions were associated with elevated externalizing symptoms (attention deficit, hyperactivity, conduct and oppositional defiant disorder symptoms), suggesting that these gray matter differences may predispose individuals to a range of externalizing-spectrum problems, some of which have been previously shown to be genetically correlated with AUD [92, 93]. Thus, some structural brain features appear to meet many of the endophenotype criteria. Systematic gene identification studies for these features may provide evidence for association with AUD and thus become important directions for future research.

AUD Endophenotypes in Animal Models

Translational approaches to endophenotypes that include the development of relevant animal models are important [94] for elucidating the underlying neurobiology and genetics of AUD, which may in turn support the development of pharmacological treatments [95]. As highlighted below, the efforts to develop animal models for AUD endophenotypes have had varying degrees of success with respect to these goals.

Neurophysiology

In findings that mirror the human literature, an alcohol preferring (P) mouse strain had a reduced P300 amplitude compared to a non-alcohol preferring (NP) mouse strain [96]. A follow-up study further indicated that reductions in evoked delta event-related oscillations and decreases in delta and theta phase synchrony contributed to this P300 amplitude reduction [97]. Additional studies are needed to identify the genetic differences between these selectively bred mouse models that are associated with these neurophysiological endophenotypes.

Level of response

Rat models suggest that P animals have lower LR compared to NP animals; for example, in a conditioned place aversion test, P rats avoided an alcohol-paired location less than NP rats [98], suggesting that P rats are less sensitive to the aversive effects of alcohol. here have also been attempts to translate the body sway dimension of LR into rodent models; however, the lack of concordance between the human phenotype and rodent models makes development of novel behavioral assays an important area for continued refinement [for a review see 99]. A series of eleven rodent behavioral assays broadly indexing body sway were tested across eight inbred mouse strains. Interestingly, there was little genetic correlation across the behavioral assays, suggesting that unique sets of genes contribute to foot slippage and

wobbly gait, for example [100]. The degree to which unique sets of genes contribute to the component processes of human body sway is unknown. Despite these challenges to phenotype consilience across species, convergent evidence from cross-species (humans, mice, and fruit flies) analyses of locomotor responses to ethanol implicated the glypican gene *GPC5* on chromosome 13 [101].

Delayed reward discounting

Delayed reward discounting tasks are very similar in human and non-human animals, making this an ideal translational endophenotype [70]. In findings that mirror the human literature, P mice were more impulsive than NP mice in a delayed reward discounting task [102]. Outbred mice that more steeply discounted delayed rewards also displayed more sensitivity to the stimulant effects of ethanol after repeated exposures [103], suggesting that delayed reward discounting and ethanol sensitization (one component of the differentiator model discussed above) may share underlying predispositions to AUD. We note that this translational literature is not entirely consistent. In one study there were no differences in delayed reward discounting between mice that were bred to either consume high or low amounts of ethanol [104], and there is also some evidence that mice bred to be less sensitive to the reinforcing effects of drugs exhibited greater delay discounting compared to mice that were more sensitive to these reinforcing effects [105]. These differences may be attributable to mouse strain differences, and highlight the difficulties in identifying the appropriate model system for translational studies of candidate endophenotypes.

Sweet liking

Animal models have also provided some validation of sweet liking as a strong candidate endophenotype for AUD and for addiction phenotypes more broadly [106, 84]. Rats selected for high saccharin intake consumed more ethanol relative to rats selected for low saccharin intake [107], and they exhibit greater ethanol withdrawal [108]. Saccharin consumption also appears to offset alcohol consumption. P rats who voluntarily consume saccharin subsequently drink less ethanol compared to alcohol preferring rats who are not given access to saccharin [109]. This suggests that ethanol and saccharin consumption may have overlapping effects on (genetically-influenced) neurobiological systems involved in reward, such as the opioid, serotonin, and dopamine systems [110]. Consistent with this idea, P rats who were administered clonidine (a noradrenergic signaling inhibitor) reduced alcohol consumption and saccharin consumption, but not water consumption [111]. In another example, P rats who were administered TP-10 (a dual-specificity cyclic adenosine monophosphate/cyclic guanosine monophosphate-inhibiting enzyme inhibitor) reduced their alcohol and saccharin self administration [112]. This illustrates the utility of using the endophenotype concept in a translational manner to develop potential therapeutic targets for AUD.

Gene identification for translational endophenotypes

Translational approaches to endophenotypes typically rely on comparisons of mouse strains selectively bred for higher and lower alcohol preference. Mapping these differences to genes and gene networks is critical to fully realizing the promise of a translational approach for

endophenotypes. A meta-analysis of three mouse strains that differed in alcohol preference identified 3,800 genes that were differentially expressed in the brains of N and NP mice, and functional gene groups including mitogen-activated protein kinase signaling and transcription regulation pathways were overrepresented among these differentially expressed genes [113]. These results provide numerous candidate genes and pathways to be tested for association with translational candidate endophenotypes and, if merited, further testing in human samples.

The Endophenotype Concept in AUD Research: Redux

The landscape of psychiatric genetics has changed dramatically since the endophenotype concept was most recently reintroduced in the literature. The field has moved towards large, collaborative gene finding research networks for psychiatric outcomes (such as the Psychiatric Genomics Consortium) that have sample sizes in the tens of thousands, moving away from an endophenotype strategy with its emphasis on heritability. However, the trade-off between large-scale genotyping, where amassing very large samples often comes at the cost of less precise measures, and the study of endophenotypes, which may require deeper, more costly measurement on a smaller number of subjects, is currently unknown.

We recognize that an endophenotype approach shares some of the same weaknesses as large-scale genotyping efforts. One is the issue of reliability. As noted by Kendler and Neale [114], although many candidate endophenotypes may seem scientifically “harder” (because they involve, for example, measures of brain structure) than “softer” clinical diagnoses, they do not necessarily have higher reliabilities. This ultimately impacts the power of one’s analyses, and in this respect it does not appear that endophenotypes offer a particular advantage over diagnoses. A second is the issue of whether candidate endophenotypes are truly less heterogeneous than diagnostic categories; for example, a reduction in P3 amplitude can result from several possible differences in underlying event-related oscillations. Thus, whether some endophenotypes for AUD are more homogenous than the diagnostic category for genetic analysis remains an open question. A third is the issue of replication. Only a few of the genes and genetic variants identified in Table 2 have replicable associations with their respective candidate endophenotypes and with AUD, and thus the replicable yield of AUD-associated genes remains small.

Related to the issue of replication, several of the genes summarized in Table 2 were selected based on their prior association with AUD-related phenotypes. This raises the question of whether studies of candidate endophenotypes have identified novel genes for AUD. Let us put the issue of novelty into context. *GABRA2* exemplifies the success of an endophenotype approach for AUD in that variation in this gene was initially associated with a neurophysiological endophenotype [23] and numerous subsequent studies have documented its association with alcohol dependence [115]. On the other hand, the largest genome-wide association study of alcohol dependence to date [116] produced associations for genes implicated in alcohol metabolism that were initially identified in the early 1990s [117], as well as a handful of other genetic variants for which the replication results were mixed. Thus, in the absence of other, more successful approaches for AUD gene identification (both in terms of novelty and replicability), it seems reasonable that pursuing both large-scale

genotyping strategies and endophenotypes-based approaches may be the most prudent path forward.

There is also a growing recognition that endophenotypes may not be genetically simpler than the psychiatric phenotypes with which they are associated [118], and in fact may reflect the contribution of many genetic variants of small effect from across the genome [119]. A recent special section in the journal *Psychophysiology* (December 2014) devoted to studies of physiological candidate endophenotypes for addiction and schizophrenia in the Minnesota Twin and Family Study reiterates this point. These studies were able to use the same sample of parent and twin pair offspring to conduct biometric modeling (i.e., decomposing variation for a measure into latent genetic and environmental influences based on the pattern of correlations among different degrees of relatives) and genetic association analyses. In one example, biometric modeling indicated that genetic factors accounted for 65% of the variance in P3 amplitude; however, a genome-wide association study in the same sample did not identify any genome-wide significant variants, although a gene-based test did identify the myelin expression factor 2 (*MYEF2*) gene on chromosome 15 [120]. The absence of genome-wide significant effects suggests that P3 amplitude is likely polygenic. We return to the implications of a polygenic architecture for endophenotypes shortly.

Nonetheless, even if these candidate endophenotypes are not simpler clues to the genetic underpinnings than AUD itself [19], they could still be very useful in terms of delineating underlying mechanisms [118]. And, as illustrated in the neurophysiology, level of response, delayed reward discounting, and sweet liking literatures, endophenotypes can also help to begin to bridge human and non-human animal alcohol research and (in the case of sweet liking) identify possible drug targets, both of which are distinct advantages of the endophenotype concept that Gould and Gottesman [94] emphasized.

Future Directions

Polygenic and network approaches to endophenotypes—AUD has a polygenic architecture, meaning that it includes the effects of many variants of small magnitude across the genome [121, 122]. The advent of low-cost genome-wide genotyping has made it possible to measure polygenic risk for psychiatric disorders such as schizophrenia, and polygenic approaches have shown predictive power in instances where no single marker meets the stringent genome-wide significance threshold [123]. Polygenic approaches can be easily applied to studies of endophenotypes to test whether polygenic risk scores for candidate endophenotypes also show association with AUD [124].

Polygenic effects can be further interrogated using gene network analyses and bioinformatic data to evaluate biological plausibility and relevance (e.g., is the gene expressed in the brain or liver?). Gene network analyses permit examination of whether variants included in polygenic scores are located in functionally related networks of genes [125]. This approach can thus identify the different pathways involved in genetic vulnerability, and the routes by which a set of genes may influence pathways of risk. Knowledge of such networks can be capitalized on to develop novel drug targets. Work in model organisms has begun to identify gene networks associated with initial sensitivity to ethanol, a measure closely associated to level of response [126], and there is some preliminary evidence suggesting that variation in

gene networks related to neuronal signaling is associated with level of response in humans [57].

Developmental approaches to endophenotypes—Attention to endophenotypes as developmental phenomena may also provide additional insight into the pathways between genetic predispositions and eventual disorder. To date, the criterion for an endophenotype to be associated with the illness has typically been met using cross-sectional studies that compare individuals with AUD to healthy controls. However, there are also likely to be endophenotypes that emerge or maximally differentiate between those who will and will not go on to have AUD at points earlier in development. In a conceptual example of this, variation in the AUD-associated gene *GABRA2* is also associated with childhood conduct disorder symptoms [127] and increased risk (odds ratios ranging from 2.1 to 2.7) of exhibiting an elevated persistent trajectory of externalizing behavior across adolescence and early adulthood [128]. Neither conduct disorder nor externalizing behavior trajectories meet the endophenotype criteria; however, what this example illustrates is the possibility that there may be endophenotypes earlier in development that predict adult AUD, and these can be capitalized on in gene identification efforts.

A corollary of this point, which is particularly relevant for substance use disorder candidate endophenotypes, is that there is likely to be a dynamic relationship between the genes associated with AUD and a necessary environmental exposure (i.e., alcohol). For example, ethanol exposure induces modest differential gene expression in lymphoblastoid cell lines from alcoholics and non-alcoholics [129]. The possibility of identifying AUD genetic predispositions that interact with environmental factors (e.g., adolescent alcohol exposure) to produce variation in a candidate endophenotype is particularly promising. For example, adolescent alcohol exposure may initiate a cascade of biological changes (e.g., gene expression [130]) that contribute to variation in AUD candidate endophenotypes and eventual disorder.

Developmental considerations have been nearly absent in the literature on endophenotypes [131], although it has been noted that one of the more prominent candidate endophenotypes for AUD—P3 amplitude reduction—is more pronounced in adolescence compared to young adulthood in males with a high-risk paternal history of externalizing disorders [132]. Another promising example of a developmental candidate endophenotype comes from a recent fMRI study of spatial working memory. It found that the pattern of functional brain connectivity in early adolescents (12–14 years) with a family history of AUD was less similar to that of older adolescents/young adults (16–20 years) compared to a control sample of early adolescents without a family history [133]. The pattern of findings suggests that neural connectivity is less mature in adolescents with a family history of AUD. Interestingly, this may represent a neuromaturational lag that can only be detected in adolescence. Additional data are needed to determine whether this neurodevelopmental lag in adolescence is indeed associated with subsequent AUD, but this example illustrates that novel candidate endophenotypes that have “sleeper effects” for AUD may be used in gene finding studies.

Attention to developmental changes in and/or the developmental salience of particular genes for candidate endophenotypes may be important for identifying the relevant genes and gene

networks implicated in AUD. Fully 95% of genes are expressed in the developing fetal brain [134], in contrast to the 84% of genes expressed in the adult human brain [135]. The structure and function of the brain is largely determined during prenatal development, with a second wave of development in adolescence [136]. Thus, the genes and gene networks that influence neuronal development, cellular migration, and brain anatomy and function may be predominantly expressed quite early in development, but their consequences for cognitive, neurophysiological, and functional brain candidate endophenotypes may only emerge later in development.

Conclusions

The endophenotype concept was initially proposed as a strategy for improving gene identification in view of the complex and heterogeneous nature of psychiatric disorders. In the area of alcohol research, level of response to alcohol and resting and event-related neurophysiological measures have received considerable attention as candidate endophenotypes, and have also led to replicable genetic associations (e.g., *CHRM2* [7] and *GABRA2* [115]) for AUD. As these examples illustrate, the past successes of endophenotype strategies for AUD gene identification suggest that the concept will continue to remain relevant to AUD research today, even as gene identification efforts move towards large-scale phenotyping at the diagnostic level. A number of other candidate endophenotypes show promise, including delayed reward discounting, executive functions, sweet liking, and structural brain features. Systematic efforts to continue to refine and validate these as elected endophenotypes, and to identify the genes, polygenes, and gene networks that may influence variation in these traits/behaviors (and in turn AUD) by themselves and in the context of environmental exposures (particularly alcohol) represent important directions for future research.

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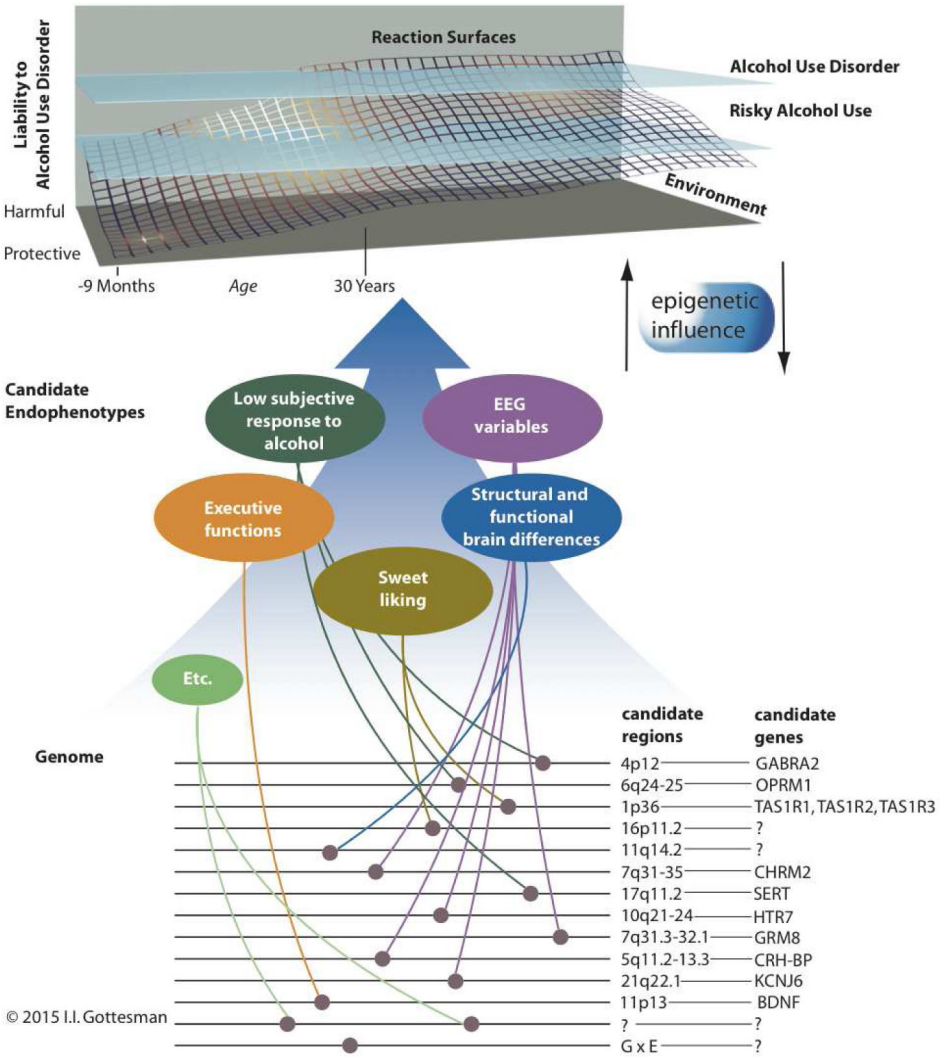

Figure 1.

Depiction of the interplay among genetic and environmental factors that contribute to liability for alcohol use disorder (AUD), and the contribution of candidate endophenotypes and their associated genes and gene regions. Genes and gene regions that are associated with AUD candidate endophenotypes are highlighted here (references are documented in Table 2). These should be considered illustrative and not exhaustive. The “reaction surface” represents the probabilistic interplay among genetic and environmental factors in the development of risky alcohol use (i.e., consuming alcohol in quantities that put individuals at risk for alcohol-related harms) and AUD. Figure adapted from Gottesman & Gould [3] and used with permission.

Table 1

Weight of evidence for candidate endophenotypes for alcohol use disorder, organized by category (anatomical, developmental, electrophysiological, metabolic, sensory, psychological/cognitive, and neuroimaging) and criterion.

Candidate endophenotype	Endophenotype criterion				
	Associated with AUD	**Heritable**	**State-independent**	**Co-segregates with illness within families**	**Presents in nonaffected family members > population**
Anatomical					
Structural brain differences	Boutte et al. [89], Agartz et al. [90], Monnig et al. [137]	Baare et al. [138], Posthuma et al. [139]	Fein, Fein [140], Cheetham et al. [141]		Benegal et al. [91]
Developmental					
Externalizing behavior	Benegal et al. [91]	Young et al. [67]	Englund et al. [142]		Benegal et al. [91]
Electrophysiological					
Resting and event-related EEG phenotypes	Ehlers, Phillips [143] Carlson et al. [144]; Roopesh et al. [145], Roopesh et al. [146]	van Beijsterveldt et al. [20] Perlman et al. [147]	Carlson et al. [144]	c.f. Carlson et al. [144]; c.f. Carlson et al. [32]	Rangaswamy et al. [21]
Metabolic					
HPA axis activity	Wand, Dobs [148], Starcke et al. [149]	Bartels et al. [150]			
Sensory					
Sweet liking	Kampov-Polevoy et al. [81]; c.f. Kranzler et al. [151]	Keskitalo et al. [152]			Mennella et al. [83], Lange et al. [153]
Psychological/Cognitive					
Executive functions	Sjoerds et al. [76]	Friedman et al. [75]			Benzerouk et al. [78], Gierski et al. [77]
Delayed reward discounting	Mitchell et al. [72]	Anokhin et al. [71]	Petry et al. [73]		
Low subjective response to alcohol (LR)	Schuckit et al. [43], Schuckit et al. [42], Schuckit et al. [44]	Schuckit et al. [154]	Schuckit et al. [43]		Schuckit et al. [43]
Functional Neuroimaging					
Functional brain differences during spatial working memory tasks	Pfefferbaum et al. [155], Vollstadt-Klein et al. [156], Tapert et al. [157]				Spadoni et al. [133], Spadoni et al. [158]

Notes.

* Does not meet endophenotype definition itself, but other candidate endophenotypes (e.g., executive functions, delayed reward discounting) are likely to contribute to individual differences in externalizing across development.

** May also be considered a sensory/motor endophenotype. Studies listed should be considered illustrative and not exhaustive.

Table 2

Genes, regions of interest, and gene sets associated with illustrative candidate endophenotypes.

Candidate endophenotype	Chromosome	Gene	Potential relevance	References
Low subjective response to alcohol	4	*GABRA2*	Implicated in central nervous system disinhibition	Uhart et al. [48]
	6	*OPRM1*	Endogenous opioid system involved in alcohol-induced reward	Ray et al. [50] Ray, Hutchison [51] Ehlers et al. [52]
	10	*CYP2E1*	Codes CYP2E1 enzyme; involved in ethanol metabolism	Webb et al. [159]
	12	*ALDH2*	Involved in alcohol metabolism; implicated in conversion of acetaldehyde to acetate	Luczak et al. [54]
	15	*CHRNA5-CHRNA3-CHRNB4* genes	Nicotinic acetylcholine receptor genes	Joslyn et al. [55]
	17	*SERT*	Involved in serotonin transmission	Hu et al. [49]
	multiple	gene sets implicated in neuronal signaling	--	Joslyn et al. [57]
	regions of interest on chromosomes 6, 10, 12, and 17	--	--	Ehlers et al. [53]
EEG variables	13	*GPC5*	Codes for a cell surface proteoglycan implicated in neural development	Joslyn et al. [101]
	2	*GBX2*	Involved in midbrain/ hindbrain development and influences the expression of other genes during embryogenesis	Vrieze et al. [28]
	4	*GABRA2*	Implicated in central nervous system disinhibition	Porjesz et al. [22]
	5	*CRH-BP*	Codes for a high affinity binding protein for corticotrophin releasing hormone; involved in stress response	Enoch et al. [27]
	7	*CHRM2*	Influences the effects of acetylcholine in the central and peripheral nervous system	Jones et al. [35]
	7	*GRM8*	Involved in glutamatergic system	Chen et al. [36]
	10	*HTR7*	Involved in serotonergic system	Zlojutro et al. [160]
	15	*MYEF2*	Transcriptional repressor of the myelin basic protein gene	Malone et al. [120]
	17	*CRHR1*	Involved in the neuroendocrine stress response	Chen et al. [37]

Candidate endophenotype	Chromosome	Gene	Potential relevance	References
	21	*KCNJ6*	Codes for the GIRK2 protein involved in dopaminergic signaling	Kang et al. [38]
Executive functions	11	*BDNF*	Codes for BDNF protein involved in brain development and synaptic plasticity	Benzerouk et al. [78]
Structural brain differences	11	11q14.2	--	Boutte et al. [89]
Sweet liking	1	*TAS1R1, TAS1R2, TAS1R3*	Involved in sweet taste reception	Bachmanov et al. [84]
	16	16p11.2	--	Keskitalo et al. [80]

Notes. -- indicates not applicable or unknown. Studies listed should be considered illustrative and not exhaustive.