Critical Review

Subjective Response to Alcohol as a Research Domain Criterion

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Background: Individual differences in the subjective experience of the pharmacological effects of alcohol have long been implicated in the likelihood that one will drink heavily and develop alcoholism. The theme of this conceptual review and perspective article is to synthesize the literature on subjective responses to alcohol and to set an agenda for the next generation of research in the area. Specifically, we contend that in order for subjective response to alcohol to play a prominent role in alcoholism research, it is critical that it be studied as a multimodal phenotype.

Methods: First, we review the human research on subjective response to alcohol measured under controlled laboratory conditions and draw recommendations for the application of these findings to understanding alcoholism neurobiology in humans. Second, we highlight multimodal approaches, including studies of the genetic and neural substrates of individual differences in subjective response to alcohol. Third, we review treatment implications with a focus on subjective response to alcohol as an intervention target. Upon review of the research on subjective response to alcohol across levels of analyses, we provide recommendations for leveraging these phenotypes in a systematic and methodologically rigorous fashion that can address central questions about alcoholism etiology, disease progression, and personalized treatment.

Discussion : The approach recommended herein is largely consistent with the Research Domain Criteria (RDoC) initiative across the National Institute of Mental Health. The defining feature of such domains is that they inform behavior yet be amenable to examination through multiple units of analysis, such as molecular, genetic, circuit-level, and behavioral measurements. To that end, we contend that subjective response to alcohol represents a behaviorally and biologically plausible phenotype upon which to build using the RDoC framework for understanding alcohol use disorder.

Key Words: Subjective Response, Alcohol, Translational Phenotype, Research Domain Criteria.

THROUGH ITS PHARMACODYNAMIC interaction with a multitude of neurotransmitter systems, consumption of alcohol alters the subjective state of the consumer, termed, subjective response. In particular, alcohol is known to have a variety of effects on subjective states including mood, alertness, and mental clarity. Individual differences in subjective responses to alcohol have long been implicated in the likelihood that one will drink heavily and experience problems related to alcohol, including alcoholism. While the notion that individuals who experience more positive, or reinforcing, subjective effects from drinking alcohol are more likely to drink and those who

experience more negative effects are less likely to drink has a great deal of intuitive appeal, operationalizing and systematically testing these effects remains challenging. Multiple conceptualizations of subjective response have been proposed in the literature (reviewed in more detail below and in Morean and Corbin 2010; Quinn and Fromme, 2011). For this review, we are guided by factor analytic work by our research group (Ray et al., 2009) which, in an attempt to promote consilience between different alcohol challenge "camps," identified 3 factors of subjective response as measured by validated and reliable self-report assessments: (i) stimulation and other pleasant effects; (ii) sedation and unpleasant effects; and (iii) alleviation of tension and negative mood. This factor structure was recently replicated in a larger independent sample (Bujarski et al., 2015b), though with the addition of a fourth "craving" dimension. Although alcohol craving is clearly important for alcoholism risk and treatment development, a detailed review of the vast craving literature is beyond the scope of this present review. Furthermore, while alcohol administration is also known to affect more objective indices (e.g., static ataxia, acetaldehyde levels, fine motor task performance), this review focuses on the effects of alcohol that

are experienced at the level of individual subjectivity, and that are assessed through validated self-report scales.

The approach to studying subjective response to alcohol discussed herein is highly consistent with the Research Domain Criteria (RDoC) initiative across the National Institute of Mental Health (Cuthbert and Insel, 2013; Insel, 2014; Insel et al., 2010). According to the RDoC proposal, scientists are asked to identify key domains of function that can effectively describe the phenomenology of a disorder and offer generative insights into treatment. The defining feature of such domains is that they inform behavior yet are amenable to examination through multiple units of analysis, such as molecular, genetic, circuit-level, and behavioral measurements. Recently, compelling arguments for an Alcohol Addiction RDoC have been raised (Litten et al., 2015). In this paper, we review multimodal research on subjective response to alcohol, thereby strengthening the argument for subjective response as a domain criterion in the RDoC approach to alcohol use disorder.

Although many outcome variables can be measured in these alcohol challenge studies with varying levels of objectivity/subjectivity, subjective responses to alcohol consumption, as measured through validated self-report scales, have emerged as primary predictive factors in multiple prominent etiological models of alcoholism risk (King et al., 2014; Schuckit, 1984; Schuckit and Smith, 1996; Schuckit et al., 1988). Similarly, while alcohol craving represents an important etiological construct that is often measured in alcohol challenge studies (e.g., Bujarski and Ray, 2014; King et al., 2011, 2014; Ray et al., 2013), a detailed review of alcohol craving as an RDoC is deserving of its own critical review. As such, the theme of this review and perspective article is to describe what we have learned thus far about subjective responses to alcohol and to set an agenda for the next generation of research in the area. Specifically, we contend that in order for subjective response to alcohol to play a prominent role in alcoholism research, it is critical that it be studied as a multimodal phenotype.

Multimodal phenotypes, by definition, are those that can be examined across methods and levels of analyses, thereby informing etiological and treatment models of a disorder. To that end, applying findings to subclinical as well as clinical populations requires careful consideration of the samples under study and where they may fit within the progression of the disorder, from initial drinking, to heavy drinking, to early and later stages of alcohol dependence. This review intends to consolidate major findings in this line of research as well as to identify opportunities to enhance the value of subjective response phenotypes that in turn can be carried forward into the era of transdisciplinary addiction science. We begin by reviewing the human research on subjective response to alcohol measured under controlled laboratory conditions and draw recommendations for future studies in the field. Second, we highlight multimodal approaches, including studies of the genetic and neural substrates of individual differences in subjective response to alcohol. Third, we review treatment

implications with a focus on subjective response to alcohol as an intervention target. Finally, we provide a set of conclusions and recommendations to extend upon the rich history of research on subjective response to alcohol and move this line of inquiry into the RDoC era of psychiatric research.

HUMAN LABORATORY MODELS OF SUBJECTIVE RESPONSE TO ALCOHOL

Alcohol administration studies have documented the substantial variability in individuals' subjective responses to alcohol and have shown that such differences impact the predisposition to alcohol use and misuse (King et al., 2014; Schuckit, 1984; Schuckit and Smith, 1996). Schuckit and colleagues pioneered this line of research by assessing subjective response to alcohol during controlled oral alcohol administration in the laboratory (i.e., oral alcohol challenge) (Schuckit, 1984). Although Schuckit's body of research examined multiple indices of alcohol response (e.g., static ataxia and electroencephalography), an early multivariate analysis identified subjective responses to alcohol as measured by the Subjective High Assessment Scale (SHAS; Judd et al., 1977; Schuckit, 1984) as the single strongest predictor of alcoholism risk (Schuckit and Gold, 1988). In terms of alcoholism risk, Schuckit and colleagues demonstrated that a blunted response to the subjective effects of alcohol, measured by the SHAS, represents a risk factor for future alcohol misuse and dependence (Schuckit, 1984, 1994; Schuckit and Smith, 1996). Termed the low level of response model, this theory examined response to alcohol as a unidimensional construct with a particular focus on the more sedative or other unpleasant components of subjective response as evidenced by factor analytic work by Schuckit and Gold (1988). Our group has corroborated that the SHAS is most sensitive to the sedative/unpleasant effects of alcohol (Bujarski et al., 2015b; Ray et al., 2009), although it should be noted that the factor analytic work by our group has utilized intravenous, as opposed to oral, alcohol administration.

Newlin and Thomson (1990) provided a careful review of the alcohol challenge literature available at the time focusing on studies of family history of alcoholism as a risk factor for the disorder. They proposed the influential differentiator model for understanding psychobiological responses to alcohol as a function of family history. The differentiator model proposed that among individuals with a family history of alcoholism, responses to alcohol may be accentuated during the rising blood alcohol curve (BAC) (i.e., acute sensitization) and attenuated during the falling BAC (i.e., acute tolerance). To that end, sons of alcohol-dependent individuals may be both more sensitive to the rewarding and psychomotor stimulating (e.g., increased heart rate) effects of alcohol during the rising limb of the oral alcohol BAC and less sensitive to the unpleasant effects of alcohol when BAC is declining (Newlin and Thomson, 1990). While in broad agreement with the low level of response model in terms of sedative effects, the differentiator model argues for limb of BAC to be

considered along with various dimensions of subjective response.

Following upon the differentiator model, recent studies have challenged the notion of subjective responses to alcohol as a unitary construct. Instead, the pharmacological and behavioral effects of alcohol may be best described using a biphasic model. Specifically, when blood alcohol levels are rising (i.e., the ascending limb of intoxication), alcohol produces robust stimulatory and other pleasurable subjective effects, whereas when blood alcohol levels are declining (i.e., the descending limb of intoxication), alcohol's effects are largely sedative and unpleasant (Earleywine, 1994; Erblich et al., 2003; Martin et al., 1993). This conceptualization of the effects of alcohol argues for the construct of subjective response to be parsed into stimulant and sedative dimensions leading to the development of the Biphasic Alcohol Effects Scale (BAES) (Martin et al., 1993).

Alcohol administration studies have since routinely employed the BAES, including a briefer version which has been recently developed and validated (Rueger and King, 2012; Rueger et al., 2009). However, it was not until recently that a large longitudinal study established the predictive utility of alcohol-induced stimulation and sedation as measured with the BAES during a controlled and blinded oral alcohol challenge with regard to the propensity for heavy drinking and alcohol problems (King et al., 2011, 2014). Specifically, this landmark study demonstrated that individuals who engaged in regular, binge-drinking behavior experienced greater stimulant/pleasant effects during the rising BAC limb than light drinkers, and this heightened alcohol stimulation and reward sensitivity robustly predicted more alcohol use disorder symptoms over time and was associated with greater binge-drinking frequency at 2- (King et al., 2011) and 6-year follow-ups (King et al., 2014). Additionally, heavy drinkers reported lower sensitivity to the sedative effects of alcohol across the duration of BAC, which in turn was also associated with a higher number of alcohol use disorder symptoms at 2- and 6-year follow-ups (King et al., 2014). In sum, this study demonstrated that drinking history is highly related to acute subjective response to alcohol and, beyond the risk associated with a low response to the sedative effects of alcohol as described in the low-response model, enhanced sensitivity to the stimulant subjective effects of alcohol predicts heavier alcohol use and problems at follow-up. This recognition is consistent with a meta-analysis compiling decades of alcohol administration studies and reporting considerable support for the low level of response to alcohol in the context of familial risk as well as support for the differentiator model with regard to its association with drinking patterns (Quinn and Fromme, 2011).

Another important model of subjective response and alcoholism risk is the tension-reduction model which is based on the notion that individuals drink alcohol because of its ability to reduce tension. This theory was initially influenced by the drive reduction theory of the 1940s (Hull, 1943), which emphasized motivational aspects underlying drinking.

Although there is significant intuitive appeal to the notion that individuals drink to reduce tension, an early review by Cappell and Herman (1972) suggested that empirical support for the theory was limited. A related theory was developed in the 1980s, which focused on the stress–response dampening (SRD) effects of alcohol (Levenson et al., 1980; Sher & Levenson, 1982). The SRD model focused on refining the operational definition and laboratory manipulation of stressors (e.g., electric shock, public speaking task) and examining individual differences in the SRD effects of alcohol, making it a more focused and testable theory (Greeley & Oei, 1999). As stated by Greeley and Oei (1999), alcohol, at certain dosages, is capable of reducing some signs of tension in some humans, under certain contextual conditions.

More recent work on the tension-reduction model and related theories emphasize the pharmacological and neurobiological mechanisms by which alcohol may dampen a stress–response as well as the individual and contextual differences that may moderate those effects. Examples of such moderators include hostility (Zeichner et al., 1995), anxiety sensitivity (Stewart et al., 1997), gender (Sinha et al., 1998), type of social situation (Armeli et al., 2003), or life stressor (Hart and Fazaa, 2004). More recently, anxiety and negative urgency were found to operate through coping motives leading to increased risk of alcohol use disorders (Menary et al., 2015). Further, genetic predispositions to stress reactivity, via variations in hypothalamic–pituitary–adrenal axis genes, have been tested as possible mediators of the effects of stress on alcohol consumption (Clarke et al., 2007). Thus, alcohol-induced stress reduction may be especially salient for those individuals with genetically determined heightened stress reactivity. In short, the tension-reduction theory and its most widely researched offshoot, the SRD model, identify alcohol's ability to reduce tension and stress reactivity as central to the motivation to drink and the development of alcohol-related problems.

In summary, subjective response to alcohol represents a multifaceted (Bujarski et al., 2015b; Ray et al., 2009) and replicable construct (King et al., 2015; Roche et al., 2014). Regarding the ability of subjective response to alcohol, measured under controlled laboratory conditions, to predict one's risk to develop alcohol-related problems elegant longitudinal studies have suggested 2 distinct and relatively independent, pathways of risk. The first pathway suggests lower levels of response to the sedative and unpleasant effects of alcohol, and the second suggests higher sensitivity to the stimulant and pleasant effects of alcohol. However, subjective response to alcohol is highly variable between individuals and is influenced by numerous factors, including participant characteristics (e.g., family history of alcoholism, drinking history, recent alcohol exposure) and methodology (dose, measures, timing of measures, route of administration, etc.). As noted by King and colleagues (2011), careful consideration of factors such as the specific response being measured, the dose and rate of alcohol administered, BAC level and the limb of BAC, and the risk factors under examination

should be carefully described so that greater consilience can be reached in the literature.

We would add to this set of recommendations that sample characteristics and additional potential methodological factors, such as route and total duration of alcohol administration be carefully considered as well. For example, when predicting future risk for alcoholism or describing subjective response as a risk factor and treatment target, it is critical to consider that social drinkers that are past the peak age of risk for alcoholism (Grant et al., 2012) are unlikely to adequately inform the literature, ultimately aimed at high risk and/or affected individuals. Additionally, it is currently unclear whether subjective response reliably differs between oral and intravenous alcohol administration, as only a single study has systematically examined differences in alcohol responses between these 2 methods (Ray et al., 2007) and reported greater levels of intoxication, but lower alcohol craving, from intravenous alcohol (possibly due to the absence of alcohol cues). However, recent developments in computerized intravenous alcohol administration paradigms allow for the mimicking of oral BACs (Ramchandani et al., 2009), thus permitting rigorous comparison of subjective response variables across these routes of administration while controlling for BAC-related confounds. It is also worth noting that comparison of drinking groups with different alcohol use histories requires careful consideration of tolerance effects. Considering the limitations noted above, pharmacokinetic tolerance can be controlled through utilization of experimental paradigms that carefully control blood alcohol dose, such as intravenous alcohol administration (Bujarski and Ray, 2014; Ray and Hutchison, 2004; Ray et al., 2013; Zimmermann et al., 2008, 2009, 2013). Pharmacodynamic tolerance, however, is more difficult to account for. Examination of multiple different alcohol responses consistent with the multidimensionality of subjective response (Bujarski et al., 2015b; Martin et al., 1993; Ray et al., 2009) allows researchers to test whether responses to alcohol are blunted across dimensions of alcohol response, consistent with a generalized tolerance syndrome, or whether only specific dimensions of alcohol's effects are altered by drinking status. Recent work by our group has found replicable differences between alcohol dependents and nondependent heavy drinkers in the relationship between stimulatory responses to alcohol and alcohol craving (Bujarski and Ray, 2014; Bujarski et al., 2015a). Although this line of inquiry is early in development, these differences in the coupling of subjective response and craving are potentially less sensitive to tolerance effects than the raw magnitude of subjective responses themselves.

Taken together, decades of human laboratory studies of individual differences in the subjective responses to alcohol have advanced 2 translational phenotypes, namely subjective response to the (i) stimulant/pleasant and (ii) sedative/ unpleasant effects of alcohol. A tension-reduction factor has emerged in factor analytic work (Bujarski et al., 2015b; Ray et al., 2009) and has been recently examined by our group (Bujarski and Ray, 2014) in relation to the proposed transi-

tion from positive to negative reinforcement that is thought to occur during the progression of alcoholism (Koob and Le Moal, 2008b). However, the proper evaluation of this potentially useful phenotype may require testing alcohol self-administration in samples with higher levels of alcoholism severity than those typically enrolled in alcohol administration studies, if in fact this construct can capture negative reinforcement as a maintenance, as opposed to a predisposing, factor for alcoholism. Further, longitudinal studies that can repeatedly measure subjective responses to alcohol, document patterns of change over time, and associate such changes with dynamic changes in alcohol use will ultimately advance these multidimensional phenotypes that can identify risk and also track the progression of alcoholism from the initiation of heavy drinking to its more severe chronic and relapsing forms.

MULTIMODAL APPROACHES TO STUDYING SUBJECTIVE RESPONSE TO ALCOHOL

Subjective response to alcohol has been studied using a host of experimental methods from diverse fields, including behavioral genetics and neuroimaging. The goal of this section is to highlight genetic and neuroimaging studies of subjective response to alcohol, while extensive reviews of these areas can be found elsewhere (Ray et al., 2010d; Roche and Ray, 2015). Using heritability as a starting point to genetic studies, subjective responses to alcohol, measured in an oral alcohol administration twin study, had a heritability estimate of 60% (Viken et al., 2003). This study used a 22-item measure called the Sensation Scale, which included items such as drowsy, lightheaded, and dizzy. Similar estimates, ranging between 40 and 60%, were obtained in an Australian oral alcohol challenge twin study in which subjective response to alcohol was measured across levels of BAC by a single item, namely "how drunk do you feel now" (Heath and Martin, 1991). A more recent laboratory study of the offspring of fathers who completed an alcohol challenge 20 years earlier revealed a significant positive parent–offspring association for subjective feelings of intoxication and body sway after consuming a standardized oral dose of alcohol among family history positive individuals (Schuckit et al., 2005). Although not providing direct evidence of heritability, this study is consistent with prior reports of the genetic influences on these phenotypes and provides support for its reliability. Notably, these studies examine subjective response from the perspective of the low-response model and are less informative about the genetic bases of the stimulant/rewarding phenotype.

A number of behavioral genetic studies have also been conducted using subjective response to alcohol as the outcome variable. Given the experimental nature of the phenotype itself, such studies typically rely on the candidate gene approach, thus borrowing the strengths and weaknesses of this method. An important line of research has dealt with the genes subserving the metabolism of alcohol, which in turn

impacts subjective response. When alcohol is consumed, its metabolic breakdown is a 3-step hepatic process in which the alcohol is first oxidized into acetaldehyde by the enzyme alcohol dehydrogenase (ADH) and is then further metabolized into acetate, and other byproducts, by the enzyme aldehyde dehydrogenase (ALDH). As both acetaldehyde and acetate appear to have pharmacological properties and behavioral effects (Correa et al., 2003, 2012), the genes responsible for the ADH and ALDH enzymes exert important influences on the subjective effects of alcohol because they determine the relative levels of these metabolites over the course of alcohol metabolism. Indeed, genes underlying the pharmacokinetics of alcohol are among the best characterized in terms of their influence on subjective responses to alcohol and alcoholism risk. The behavioral and subjective consequences of possession of genetic variants that affect ADH enzymatic activity to increase the presence of acetaldehyde are acutely aversive in nature, including flushing, headache, tachycardia, and nausea. Genes involved in this pathway include the ALDH gene (*ALDH2*), which has been widely linked to both alcohol use (Sun et al., 2002) and the development of alcohol use disorders (Luczak et al., 2004), as well as *ADH1B*, which has been linked to reduced pleasant subjective effects in Asian Americans (Cook et al., 2005) and greater unpleasant alcohol effects in Caucasians (Wall et al., 2005). A recent study by Peng and colleagues (2014) found that in a sample of Han Chinese men who ingested a small dose of alcohol (0.3 g/kg of alcohol), *ALDH2*2*, rather than *ADH1B2*2*, was a causal variant allele for the accumulation of blood acetaldehyde and the associated facial flushing response. These studies exemplify the application of subjective response models to understanding genetic variance in the pharmacokinetics of alcohol.

Given the large number of neurotransmitter systems potentially involved in alcohol's subjective effects (Spanagel, 2009), numerous studies have also probed genetic variation affecting subjective responses to alcohol via various pharmacodynamics pathways (for recent reviews, see Matsushita and Higuchi, 2014; Roche and Ray, 2015). Several studies using oral alcohol challenge and retrospective assessments have implicated genetic polymorphisms in the gamma-aminobutyric acid (GABA) system, particularly variation in the $GABA_A$ receptor (Pierucci-Lagha et al., 2005; Ray and Hutchison, 2009), as being associated with subjective response to alcohol. Several *GABRA2* variants, which code α2 subunit of the $GABA_A$ receptor, were related to attenuated aversive subjective effects, particularly during the declining BAC limb (Uhart et al., 2013), reduced pleasant subjective effects during the ascending BAC limb (Pierucci-Lagha et al., 2005), and blunted levels of self-reported high and intoxication during intravenous administration (Kareken et al., 2010; Roh et al., 2011). Genetic variation in nicotinic acetylcholine receptors, particularly variants within the *CHRNA5-CHRNA3-CHRNB4* gene cluster on chromosome 15 which encode the α5, α3, and β4 subunits, have also been associated with an attenuated sedative/unpleasant subjective

response as measured by the SHAS during an oral alcohol administration (Joslyn et al., 2008). Finally, a polymorphism in the serotonin transporter gene (*SLC6A4*) resulting in increased transporter activity is associated with reduced SHAS sedation after acute oral alcohol administration (Hu et al., 2005; Schuckit et al., 1999) and lower retrospective self-reports of intoxication levels during drinking episodes (Hinckers et al., 2006).

While the aforementioned studies have focused primarily on the low level of response phenotype, genetic studies of the stimulant/pleasant effects of alcohol have met with some convergence when testing a single nucleotide polymorphism (SNP) in the mu opioid receptor gene (*OPRM1*), the Asn40Asp SNP (rs17799971) (for a review, see Ray et al., 2012). In particular, a series of studies focusing on the stimulant and pleasant subjective effects of alcohol have shown that, compared to Asn40 homozygotes, Asp40 carriers report greater positive subjective effects from an alcohol infusion in the laboratory (Ray and Hutchison, 2004) and in the natural environment, measured using Ecological Momentary Assessment (EMA) methods (Ray et al., 2010e). EMA data revealed that Asp40 carriers consumed more alcohol per drinking episode and that although craving was positively associated with alcohol use in general among Asp40 carriers, craving was less strongly related to alcohol use as compared to Asn40 homozygotes (Ray et al., 2010e). Furthermore, a variable number of tandem repeats in the dopamine transporter 1 gene (*SLC6A3*) was found to moderate the effects of the Asn40Asp SNP on subjective response to alcohol, with Asp40 carriers who were also homozygous for the 10-repeat allele of *SLC6A3* reporting heightened stimulation, vigor, and positive mood after an alcohol infusion (Ray et al., 2014). An interactive effect between *SLC6A3* and *OPRM1* genotypes has also been reported in behavioral (Anton et al., 2012) and neuroimaging (Schacht et al., 2013) studies of naltrexone response. However, a subset of laboratory studies have not supported a relationship between the Asp40 allele and subjective response. Recent studies have found that non-treatment-seeking alcohol-dependent individuals who were homozygous for Asn40 self-reported more alcohol-induced stimulation than Asp40 carriers in a bar-laboratory setting (Anton et al., 2012b) and *OPRM1* genotype was not related to subjective response to intravenous administration in young, heavy drinkers (Hendershot et al., 2014). Yet, the latter study did report that Asp40 carriers self-administer substantially more alcohol and reach a higher BAC than Asn40 homozygotes. This line of inquiry also has important pharmacogenetic implications regarding the prediction of behavioral and clinical response to naltrexone for alcoholism, as discussed in detail elsewhere (Kranzler and Edenberg, 2010; Ray et al., 2012; Roche and Ray, 2015).

A recent review by Jones and colleagues (2015) provides a comprehensive summary of pharmacogenetics of alcohol's subjective effects, including alcohol metabolizing genes, opioidergic genes, dopaminergic genes, and genetic variation in GABAergic, serotonergic, and neurosteroidergic genes,

which is highly consistent with the genetic studies reviewed above. Importantly, the aforementioned review focuses on pharmacogenetics of treatment of alcoholism and calls for increased methodological rigor (e.g., correction for multiple comparison, control for sample heterogeneity) to promote greater consilience across studies. Increased standardization of methods may be critical for genetic studies of subjective response to alcohol, as variation in sample characteristics, alcohol dose, route of administration, and assessment may contribute to the inconsistent findings in the field. Further, the requirement for larger sample sizes in genetic studies along with the realities of time-intensive alcohol administration procedures calls for multisite projects that can effective ascertain a large, homogenous, and methodologically matched large sample from which genetic determinants of alcohol subjective response could be more effective ascertained.

The aforementioned genetic studies are mostly consistent with the hypothesized role of endogenous opioids as mediators of the reinforcing effects of alcohol and suggest that favorable phenotypes to probe for the effect of the Asn40Asp SNP may involve assays of the rewarding subjective effects of alcohol in humans. To that end, a study combining intravenous alcohol administration with positron emission tomography (PET) measuring displacement of a radiolabeled mu opioid receptor agonist, $[^{-11}C]$carfentanil, found that alcohol administration induces endogenous opioid release in the orbitofrontal cortex and nucleus accumbens (NAc) (Mitchell et al., 2012). This study provides a critical demonstration of the involvement of endogenous opioids in the effects of alcohol in humans. Further, this study reported a positive correlation between change in opioid binding in the left NAc and subjective ratings of "best ever" feeling during the alcohol infusion, suggesting that as endogenous ligand release increased in the NAc so did subjective reports of "feeling good" in response to alcohol (Mitchell et al., 2012). A study of intravenous alcohol and PET imaging focused on $[^{-11}C]$-raclopride displacement implicated the Asp40 allele of the *OPRM1* gene in greater striatal dopamine response to alcohol, although associations between striatal dopamine levels and subjective response to alcohol were not reported (Ramchandani et al., 2011). Regarding the relationship between neuroimaging and behavioral measures of response to alcohol, our group has recently reported that subjective responses to alcohol in the laboratory, namely craving, high, and the reinforcing properties of alcohol, predict neural response patterns during alcohol cue presentation in the scanner (Courtney and Ray, 2014).

Last, behavioral studies of the subjective effects of alcohol can help to extend hypotheses from preclinical models of alcoholism to human clinical samples. To that end, our group has recently conducted studies exploring the transition from positive to negative reinforcement, posited by the allostatic model of addiction (Koob and Le Moal, 2005, 2008a), using subjective responses to alcohol as markers of the positive (i.e., stimulant/pleasant effects) and negative (i.e., tension relief) rewarding effects of alcohol in humans. In a study comparing heavy drinkers to alcohol-dependent individuals who received an intravenous alcohol administration, alcohol-induced stimulation was associated with alcohol craving to a significantly greater degree in heavy drinkers, as compared to alcohol-dependent individuals (Bujarski and Ray, 2014). This study provided initial support to hypotheses derived from the allostatic model as individuals with alcohol dependence showed a weaker association between the stimulant effects of alcohol and craving than did heavy drinkers, as would be expected if in fact the stimulant and pleasant effects of alcohol become a weaker determinant of drinking as individuals transition from heavy drinking to alcohol dependence. The diminished salience of the positive/hedonic effects of alcohol has since been replicated and extended in a larger sample that includes social drinkers (Bujarski et al., 2015a).

In sum, a host of studies combining oral or intravenous alcohol administration with genetic, imaging, and pharmacology methods have provided unique insights into the biological bases of subjective responses to alcohol and demonstrate a promising level of consilience between findings in humans and predictions from preclinical studies of the neural and behavioral substrates of alcohol's reinforcing effects. And while the findings themselves are encouraging, these studies make valuable contributions by informing the ways in which methodological tools may be employed/combined to answer transformative questions about the nature of addiction in humans.

TREATMENT APPROACHES TARGETING SUBJECTIVE RESPONSE TO ALCOHOL

Because of its predictive relationship with alcohol consumption and alcoholism etiology, subjective response to alcohol has been identified as a potential therapeutic target in medication development for alcoholism (Ray et al., 2010b). As described earlier, individuals with heightened sensitivity to alcohol's rewarding and stimulatory effects or with decreased sensitivity to its sedative and unpleasant effects are at greater risk for the development of alcoholism (King et al., 2011, 2014b; Schuckit and Smith, 1996). Furthermore, in laboratory and naturalistic studies, alcohol-induced stimulation is positively associated with alcohol preference and consumption, whereas the sedative and unpleasant effects of alcohol are negatively associated with these outcomes (Chutuape and de Wit, 1994; Corbin et al., 2008; DeWit et al., 1989; King et al., 2011; de Wit and Doty, 1994). Accordingly, a medication's ability to acutely reduce the stimulant/pleasant or potentiate the sedative/unpleasant effects of alcohol has become a standard biobehavioral marker of efficacy in early phase human laboratory studies of drug development for alcoholism (Ray et al., 2010b).

Several approved or promising pharmacotherapies for alcoholism may reduce the motivation to drink by "blocking

the buzz" (Heilig et al., 2010), or in other words, attenuating the positively rewarding effects of alcohol. For example, naltrexone (Drobes et al., 2004; King et al., 1997; Ray et al., 2008; Swift et al., 1994), nalmefene (Drobes et al., 2004), and topiramate (Miranda et al., 2008) have all been reported to reduce alcohol-induced stimulation in human laboratory studies, while varenicline was shown to reduce the pleasant effects of alcohol (e.g., liking, wanting more on a visual analogue scale; McKee et al., 2009). Naltrexone appears to be particularly effective in blunting alcohol's other pleasant effects; in addition to its mitigating effects on stimulation, it also attenuates reports of liking and wanting more as measured on the Drug Effects Questionnaire (Morean et al., 2013), and vigor, and positive mood as measured by the Profile of Mood States (McNair et al., 1971) after alcohol administration either orally or intravenously (King et al., 1997; McCaul et al., 2000; Ray et al., 2008). A medication that blunts the stimulatory/pleasant effects of alcohol, such as naltrexone, has been theorized to produce a reduction in alcohol consumption through several potential biological and behavioral pathways (Heilig et al., 2010; Ray et al., 2010a). Primarily, it is thought that, rather than promoting long-term abstinence, the blunting of stimulation and other pleasurable effects reduces the likelihood that a single drinking episode during abstinence (i.e., a "slip") would escalate to a heavy drinking event (e.g., if an individual likes a drink less than they anticipated, they may be less likely to continue drinking within that episode). A consistent reduction in heavy drinking episodes would thereby reduce harmful alcohol consumption and potentially prevent a full relapse. In support of this notion, the results of meta-analyses and systematic reviews suggest that naltrexone's predominant therapeutic mechanism of treating alcoholism is gained through a reduction in heavy drinking as opposed to promoting abstinence (Bouza et al., 2004; Pettinati et al., 2006; Rosner et al., 2008). Interestingly, re-analysis of the COMBINE Study focused on individuals who drank during the trial found that a subgroup of nonabstainers, composed primarily of very regular drinkers, benefited from naltrexone in reducing heavy drinking days (Ray et al., 2010c). In sum, several pharmacotherapies, both U.S. Food and Drug Administration approved and currently under development, blunt the rewarding and stimulatory subjective effects of alcohol and, through this behavioral mechanism, may decrease alcohol consumption by decreasing the frequency of heavy and harmful drinking episodes.

Conversely, other medications may contribute to reducing alcohol consumption by potentiating the sedative and unpleasant subjective effects of alcohol. Varenicline has been shown to enhance dysphoria during an oral alcohol challenge (Childs et al., 2012) and weekly retrospective assessments of sedation (Fucito et al., 2011), whereas naltrexone increased sedation, unpleasant feelings, nausea, fatigue, tension, and confusion after both oral and intravenous alcohol administration (King et al., 1997; McCaul et al., 2000; Ray et al., 2008; Swift et al., 1994). While the

mechanistic role that augmented sedative/unpleasant alcohol responses may play in reducing alcohol consumption is not well understood, it is plausible a medication potentiating such subjective effects could simultaneously reduce positive reinforcement (e.g., produce sedative or unpleasant effects that overpower any stimulant/pleasant effects) and block negative reinforcement (e.g., increase tension). This would, in turn, block the tension reduction that is often sought by drinkers during late stages of alcoholism (Heilig et al., 2010; Koob and Kreek, 2007), while also introducing a punishment aspect (e.g., feel tired and unpleasant after drinking), each of which could theoretically contribute to a decrease in drinking behavior, particularly in heavy drinking episodes. Yet, disulfiram provides a cautionary example of using a medication to treat alcoholism via aversive subjective, as well as physiological, responses to alcohol. By disrupting alcohol metabolism and causing an accumulation of acetaldehyde, disulfiram produces headaches, flushing, nausea, and vomiting after alcohol consumption. These effects were intended to lead patients to associate aversive symptoms with alcohol ingestion and avoid future consumption, but the severity of these adverse reactions, coupled with disulfiram's inability to reduce alcohol craving or protracted withdrawal symptoms, instead lead to poor compliance rates and a limited use in clinical practice (Johnson, 2008; Peterson, 2007). Thus, while a medication's efficacy in reducing drinking may occur in part by potentiating alcohol-induced sedation or other unpleasant subjective effects, one must provide a cautious and balanced consideration of how the severity of such subjective responses may affect both medication compliance and drinking outcomes.

Although reducing the pleasurable or increasing the sedative/unpleasant effects of alcohol is commonly used markers of efficacy in the development of alcoholism pharmacotherapies, further refinement in several related areas is still needed to confidently determine whether subjective response is truly a viable target for alcoholism pharmacotherapy. First, future studies must identify whether subjective responses to alcohol in the laboratory are clinically meaningful markers of medication efficacy. To our knowledge, no study has explicitly examined whether a medication's ability to alter subjective response in the laboratory is directly predictive of pharmacotherapy treatment outcomes in a clinical trial setting. It is imperative that future alcoholism medication development studies employ combined laboratory-longitudinal research approaches, particularly in the context of a clinical trial framework, in order to establish the predictive utility of pharmacological manipulation of laboratory-based subjective response to alcohol as a robust and reliable indicator of medication efficacy in clinical settings.

Second, subjective response to alcohol is a multidimensional construct and a moving target that is observably distinct across the progressive stages of alcoholism (e.g., early vs. late stage addiction; Heilig et al., 2010) and between different populations of drinkers (e.g., light drinkers vs. social drinkers vs. heavy drinkers vs. individuals

with alcoholism; Drobes et al., 2004; King et al., 2011; Ray et al., 2013). Unfortunately, it is currently unclear how this complexity and variability may affect medication efficacy. For example, as noted above, the impact of tolerance is an important consideration that requires careful attention in medication development laboratory studies. Relatedly, several prominent theories of addiction theorize that alcohol's positive reinforcing effects convey the greatest influence on motivation to consume alcohol during the transition from heavy drinking to initial development of alcoholism (e.g., "reward drinking"), whereas late stage alcoholism is characterized primarily by negative reinforcement processes (e.g., "relief drinking"; Heilig et al., 2010; Koob and Kreek, 2007). Therefore, a medication that targets a single dimension of subjective response to alcohol may only be clinically effective during a particular stage of alcoholism or in a certain population of problem drinkers. For example, a medication that primarily targets a reduction in the stimulatory or pleasant effects of alcohol could potentially be most effective in heavy episodic drinkers who are either at risk for or still in the early stages of alcoholism, but less so for individuals in late stage alcoholism. Furthermore, novel medications have generally been screened in nontreatment-seeking and nonalcoholic populations due to concerns of ethics in administering alcohol to individuals with alcoholism, which may limit the generalizability and impact of many laboratory studies that reported pharmacotherapy effects on subjective response to alcohol. While recent human laboratory studies have lent initial credence to the transition of subjective responses across the progressive stages of alcoholism (Bujarski and Ray, 2014; Bujarski et al., 2015a), more research focused on both at-risk and affected populations of drinkers is needed to better characterize how subjective response may vary as a function of drinking behavior and disorder severity, as well as how this progression may relate to medication efficacy.

Finally, while subjective response to alcohol may ultimately be found to be a reliable and clinically meaningful treatment target for some alcoholism pharmacotherapies, it must be noted that a medication can be effective in treating alcoholism without affecting acute subjective response to alcohol. Several pharmacotherapies have demonstrated meaningful reductions in alcohol consumption in clinical trials, yet either showed no effect on subjective response to alcohol in the laboratory (e.g., acamprosate [Brasser et al., 2004] and gabapentin [Bisaga and Evans, 2006]) or provided results that were directionally opposite to those hypothesized (e.g., baclofen, increased stimulation; Leggio et al., 2013). When using human laboratory paradigms to screen novel medications for alcoholism, there are many potential biobehavioral markers of drug efficacy in addition to subjective response to alcohol, including, but not limited to, alcohol cue- or stress-induced craving, protracted or acute alcohol withdrawal, and alcohol self-administration. Therefore, despite subjective response to alcohol representing a promising

target for alcoholism treatment, it is recommended that a comprehensive approach utilizing multiple biobehavioral markers of medication efficacy be employed when screening pharmacotherapies for alcoholism to capture the medication-specific effects that may best inform future clinical trials.

CONCLUSIONS AND FUTURE DIRECTIONS

The goal of this review and perspective article was to synthesize a large body of research on subjective response to alcohol and to advance recommendations for a research agenda in this area. We began by advancing the argument that in order for subjective response to alcohol to play a prominent role in alcoholism research it is critical that it be studied as a multimodal phenotype. This was followed by a review of key findings using subjective response to alcohol in the human laboratory, in studies combining imaging and genetic methods, and ending with a review of treatment studies. During each section, we provided recommendations for future research which we summarize below. Figure 1 is provided for a summary and visual depiction of the utility of subjective response in alcoholism etiology and treatment development.

The human laboratory represents the starting point as subjective response to alcohol is best captured under controlled experimental conditions. An important and relatively recent shift has occurred in how subjective response to alcohol is conceptualized. Whereas in the past, subjective response was measured as a unitary construct, there is now increasing recognition that this is a multidimensional construction with distinct etiological and treatment implications. Three phenotypes are advanced for future research including the stimulant and other pleasant effects of alcohol (capturing positive reward), the sedative and unpleasant effects of alcohol, and the relatively less well studied but potentially important, the tension/dysphoria relief effects of alcohol (capturing negative reward). To advance research in this area, it is recommended that careful attention be paid to how these phenotypes are operationalized, including limb of BAC, measurements, alcohol dose, participant characteristics, and risk factors. Ultimately, large-scale longitudinal studies may be most informative in determining correlates of these phenotypes as well as their clinical significance across stages of alcohol use and alcoholism.

The treatment section reviewed ways in which subjective response to alcohol already informs treatment development for alcoholism, with a strong recommendation that studies linking responses to alcohol in the laboratory to clinical response in trials be conducted in order to fully ascertain which, if any, dimensions of subjective response serve as useful and predictive treatment targets.

In conclusion, this paper calls for research leveraging subjective response to alcohol in a systematic and methodologically rigorous fashion that can address central questions about alcoholism etiology, progression, and
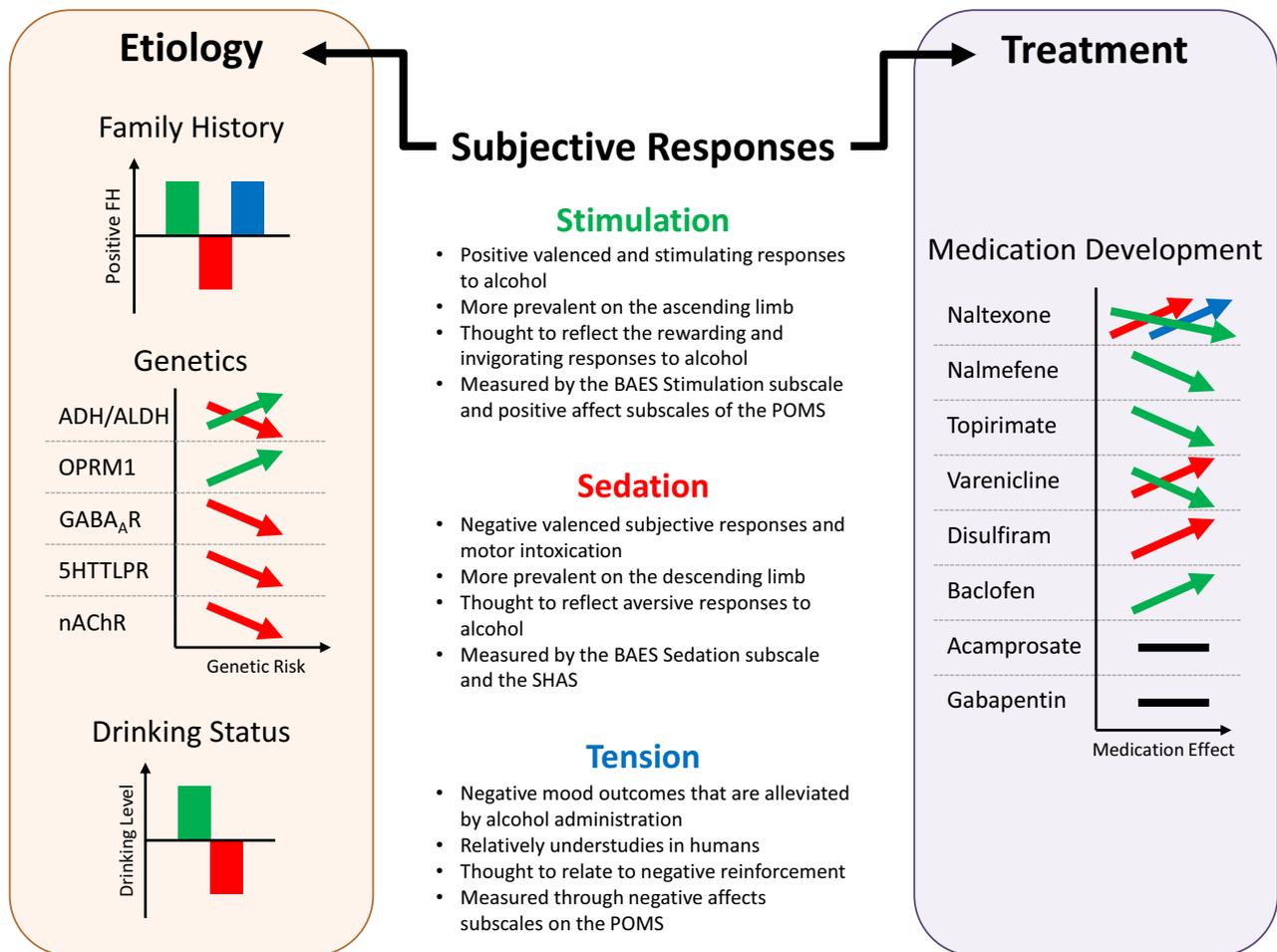
Fig. 1. Subjective responses to alcohol in alcoholism etiology and treatment development research. Subjective response represents a multidimensional construct with the domains of: (i) stimulation, (ii) sedation, and (iii) tension. Etiological studies of subjective response have examined multiple indicators of alcoholism risk including: family history of alcoholism, genetic risk loci, and participants' level of drinking. Treatment studies utilizing subjective response have focused on medication development with a number of approved and promising medications having significant effects on subjective response outcomes. FH, family history; ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; OPRM1, opioid receptor mu 1; GABA$_A$R, gamma-aminobutyric acid type A receptor; 5HTTLPR, serotonin-transporter-linked polymorphic region; nAChR, nicotinic acetylecholine receptor.

treatment development. The approach recommended herein is highly consistent with the RDoC initiative (Cuthbert and Insel, 2013; Insel, 2014; Insel et al., 2010). According to the RDoC approach, scientists are asked to identify key domains of function that can effectively describe the phenomenology of a disorder or set of disorders. RDoC domains are expected to inform behavior yet be amenable to examination through multiple units of analysis, such as molecular, genetic, circuit-level, and behavioral measurements. As reviewed above, subjective response to alcohol represents a behaviorally and biologically plausible phenotype upon which to build using the RDoC framework for understanding alcohol use disorder. And while this approach is not without its limitations and criticisms (Peterson, 2015), there is considerable enthusiasm for the development of an Alcohol Addiction RDoC that can ultimately advance personalized treatment for this disorder (Litten et al., 2015).

CONFLICT OF INTEREST

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