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Review article

Evidence for incentive salience sensitization as a pathway to alcohol use disorder

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ABSTRACT

The incentive salience sensitization (ISS) theory of addiction holds that addictive behavior stems from the ability of drugs to progressively sensitize the brain circuitry that mediates attribution of incentive salience (IS) to reward-predictive cues and its behavioral manifestations. In this article, we establish the plausibility of ISS as an etiological pathway to alcohol use disorder (AUD). We provide a comprehensive and critical review of evidence for: (1) the ability of alcohol to sensitize the brain circuitry of IS attribution and expression; and (2) attribution of IS to alcohol-predictive cues and its sensitization in humans and non-human animals. We point out gaps in the literature and how these might be addressed. We also highlight how individuals with different alcohol subjective response phenotypes may differ in susceptibility to ISS as a pathway to AUD. Finally, we discuss important implications of this neuropsychological mechanism in AUD for psychological and pharmacological interventions attempting to attenuate alcohol craving and cue reactivity.

1. Introduction

Of all substances of abuse, alcohol is the most commonly used and, arguably, the one with the greatest combined cost to individuals and society (Nutt et al., 2010, 2007). Although many individuals are able to use alcohol without developing an alcohol use disorder (AUD), results from the 2012 to 2013 National Epidemiologic Survey on Alcohol and Related Conditions III (NESARC-III) suggest that approximately 73 % of all non-institutionalized adults in the USA (≥18 years of age) used alcohol at least once in the past year and that 15 % those who used alcohol in the past year met diagnostic criteria for AUD (Grant et al., 2017). This means that, in the USA alone, the number of adult alcohol users with active AUD in any given year is larger than the estimated total number of living adults residing in any one state or territory except California (27,432, 000 or 11 % of the approximate 254, 000, 000 adults estimated to be living in the USA in 2018; Census Bureau, Population Division). Heavy alcohol use puts individuals at greater risk for cancers and cardiovascular disease (Connor, 2017; Wood et al., 2018). The myriad negative medico-legal consequences of excessive alcohol use, such as assault, automobile accidents, gun accidents, rape, suicides, and unwanted pregnancies, create serious costs to society (Bouchery et al., 2011; Hingson et al., 2009; Naimi et al., 2003; Smith et al., 1999; Walsh and Macleod, 1982; Wechsler et al., 2002; Whiteford et al., 2013; Wintemute, 2015). Consequently, there is a great need to understand the biomedical and psychosocial factors that determine excessive alcohol use, including the development of AUD.

An unfortunate reality that hinders this scientific mission is heterogeneity in the clinical presentation and course of AUD (Babor et al., 1992; Cloninger, 1987; Jellinek, 1960). This heterogeneity has been met with numerous attempts to match different “subtypes” of AUD with different treatment approaches, but largely with disappointing results (Allen et al., 1998, 1997). Current approaches to understanding AUD heterogeneity and its consequences for both theory and intervention are informed by broader frameworks for understanding all manner of psychiatric conditions. In particular, the National Institute of Mental Health (NIHM) research domain criteria (RDoC) framework (Insel et al., 2010; Insel and Cuthbert, 2015) has provided an architecture with which multiple causal factors stemming from diverse, biologically grounded systems can be organized for understanding the development and progression of AUD. The RDoC framework emphasizes studying the putative underlying causes (*e.g.*, dysregulated neural circuits) of disorders and aims to generate biologically-meaningful, comprehensive descriptions that might form the basis for new classification schemes, which may be dimensional rather than categorical. The application of the RDoC framework to understanding heterogeneity in AUD has been termed the Alcohol Addiction RDoC (AARDoC) (Litten et al., 2015). The AARDoC organizes research across units of analysis (*viz.*, from genes to brain to behavior, including self-report) relevant to AUD liability and

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promotive processes, and may lead to useful insights about etiology and treatment of AUD.

One of the research domains proposed for the AARDoC is the extent to which alcohol-associated cues acquire "incentive salience."[1] Incentive salience is a construct that refers to the motivational significance attributed to exteroceptive and interoceptive stimuli that reliably predict rewards, via Pavlovian conditioning (Bevins and Besheer, 2014; Paulus et al., 2009; Robinson et al., 2014; Robinson and Berridge, 1993; Saunders and Robinson, 2013). Among the exteroceptive stimuli that can come to predict ethanol ingestion and/or intoxication are the sight, smell, and taste of a preferred alcoholic beverage, the implements used to contain, prepare, and/or consume the beverage, and the sounds of accessing and/or transferring a container's contents. Given that experiencing the diverse interoceptive stimuli involved in or produced by beverage ingestion, including the pharmacological effects of ethanol, is contingent upon the individual's interaction with or manipulation of the alcoholic beverage, its container, and other implements, these cues are especially likely to acquire incentive salience (Tomie, 1996; Tomie and Sharma, 2013). Nevertheless, context matters—the ability of these alcohol-associated cues to promote alcohol use in daily life is likely greatest when they are encountered at the "right" place and time, around the "right" people, and in the "right" emotional state (Marlatt, 1996; Niaura et al., 1988).

One neurobiological theory of addiction that directly addresses how drug-associated cues come to affect individuals' behavior is the incentive salience sensitization theory of addiction (ISST) (Berridge et al., 2009; Berridge and Robinson, 2016, 2003; Robinson and Berridge, 2001, 2000, 1993). The ISST holds that different brain circuits are responsible for attributing hedonic *versus* incentive value to cues and rewards. The ISST posits that addictive behavior stems from the ability of drugs to progressively sensitize the brain circuitry responsible for attributing IS, such that the individual becomes hyper-reactive to the motivational properties of learned drug-predictive stimuli.[2] Critically, the drug-induced sensitization of IS attribution to drug-predictive cues is theorized to progress independently of changes in the hedonic value attributed to either the drug or its cues. The dissociation of hedonic and incentive value can help explain why some people may verbalize explicit goals and reasons for abstaining from or moderating alcohol use, and yet: (1) find themselves drawn toward alcoholic beverages or people and places associated with alcohol use (*e.g.*, bars, neighborhood pub, old drinking buddies); or (2) find it difficult to stop drinking after their first drink; or (3) find it nearly impossible to stop thinking about alcohol under certain circumstances (*e.g.*, after stressful events, certain times of day or the week). Through alcohol-induced incentive salience sensitization (ISS), alcohol-associated cues may be increasingly imbued with the power to instigate alcohol seeking and consumption despite a person's conscious beliefs, goals, and intentions. For this reason, ISS may not only be a mechanism of AUD development but also maintenance and relapse.

In this article, we argue for ISS as a mechanism relevant to AUD in humans. In order to do so, we first provide a summary review of the neural circuitry theorized to mediate attribution of incentive salience (IS) to reward-predictive cues and the behavioral and psychological manifestations of this process. Readers interested in more in-depth coverage of the neurobiology are referred to (Flagel and Robinson, 2017). We then review evidence from work with preclinical non-human animal models for the ability of ethanol, the addictive agent in alcoholic beverages, to induce neuroadaptations that may mediate ISS. Finally, we review evidence for IS attribution to alcohol-associated cues and its sensitization (ISS) in humans and non-human animals.

1.1. Scope and limitations

The current narrative review is not intended as a comprehensive or exhaustive review of all possible scientific evidence that speaks to the potential existence of a unique etiological pathway to AUD captured by the neuropsychological mechanism delineated in the ISST. Rather, we intend to provide an initial and illustrative survey of that body of evidence. The relevance of ISS as a neuropsychological mechanism in AUD could be inferred from its inclusion as an addiction-promotive process in the binge/intoxication and preoccupation stages of the Three Stages of the Addiction Cycle model (Koob and Volkow, 2010). However, to our knowledge, there have been no prior reviews of ISS as a mechanism in AUD; although, the idea is not new (Heinz, 2002). All previous reviews and theoretical papers on ISST have focused on food or other drug rewards, or when focused on alcohol, cover only preclinical data (Valyear et al., 2017). Many commonalities are observed across appetitive stimuli such as food, drugs of abuse, and sex; nevertheless, there are important differences in how these different classes of appetitive stimuli are processed by the brain (Berridge and Kringelbach, 2015; Sescousse et al., 2013). Furthermore, the unique pharmacology of different drugs of abuse means that they are not interchangeable "addictive" stimuli (Badiani et al., 2011; Ozburn et al., 2015); it is thus important to establish a case for the plausibility of the ISST with respect to the specific drug of abuse.

The evidence we review here spans multiple units of analysis in humans and non-human animal models. The reader should not infer from our omission of any particular, relevant study in this review that said study is inadmissible as evidence supporting or disconfirming predictions derived from ISST. That being said, much of the primary scientific literature reviewed here was discovered using a two-step procedure. In the first step, we entered search terms as Boolean strings in Internet search databases (EBSCOhost Academic Search Complete: MEDLINE, PsycARTICLES, PsycINFO; Google Scholar; PubMed). These Boolean strings were always composed of [("alcohol" OR "alcoholic" OR "ethanol" OR "ethyl alcohol")] plus other search terms that varied by the level of analysis and concept (*e.g.*, "adaptation", "approach", "attention", "incentive", "reactivity") as well as whether we were interested in discovering studies involving human participants or non-human animal models. In the second step, we mined the bibliographies of any relevant discovered articles for additional hits. Only studies published in peer-reviewed scientific journals by August 2019 were included.

Readers familiar with ISST (Berridge and Robinson, 2016, 2003; Robinson and Berridge, 2001, 2000, 1993) will note the absence of studies on alcohol-related psychomotor sensitization in the present review. This omission was deliberate. An excellent review on this specific body of work recently was conducted by others (Nona et al., 2018).

2. The incentive salience (IS) circuitry

2.1. Attribution of IS

Attribution of IS to reward-predictive cues is mediated by the mesocorticolimbic dopamine system (Saunders et al., 2018), which is comprised of the ventral tegmental area (VTA) complex and its efferent projections. The VTA complex is a midbrain structure that includes neurons in the lateral and posterior aspects of the ventral tegmental area as well as in the medial aspects of the substantia nigra pars compacta (Yetnikoff et al., 2014). Dopamine release from the VTA complex

[1] The incentive salience of alcohol cues has also been proposed as one of the core domains of neurobiologically-informed clinical assessment for AUD (Kwako et al., 2016).

[2] In terms of the RDoC matrix, the ISST is a framework for understanding how two of the primary constructs, Approach Motivation and Reward Learning, in one research domain, the Positive Valence System, might promote addictive behavior. Of the 39 constructs in the RDoC matrix, 7 were identified as being of utmost importance for understanding addictive behavior by a recent Delphi consensus study (Yücel et al., 2019), and of those 7 constructs, 1 was Reward Learning, and 3 were 3 of the 4 sub-constructs that constitute Approach Motivation.

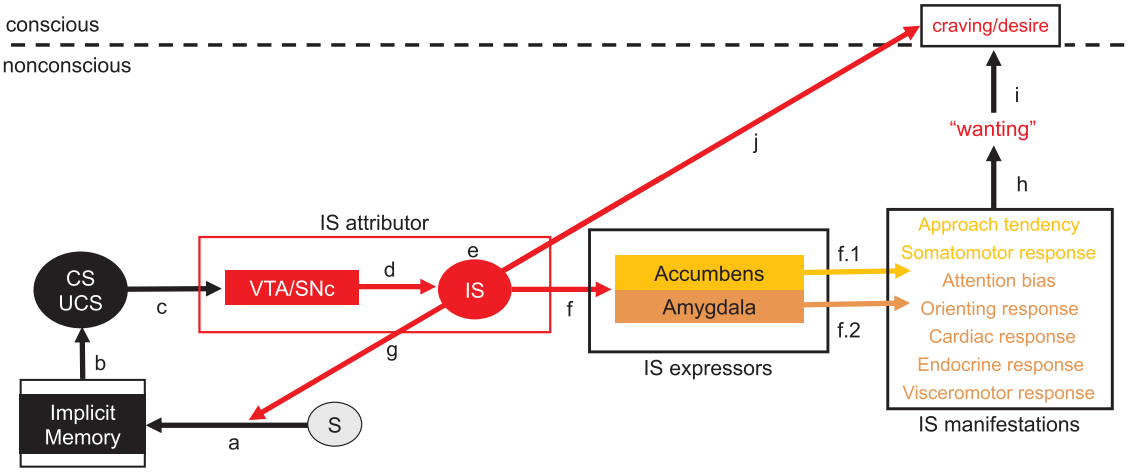

Fig. 1. The incentive salience (IS) attribution and expression system: a simplified schematic. "S" refers to an exteroceptive or interoceptive stimulus. "CS" and "UCS" refer to the Pavlovian conditional stimulus (cue) and unconditional stimulus (reward), respectively. Inspired by Fig. 2 in Robinson and Berridge (1993).

projections modulates on-going activity as well as short- and long-term plasticity at the synaptic and cellular levels in the projections' target structures (Calabresi et al., 2007; Greengard et al., 1999; Lisman et al., 2011; Missale et al., 1998; O'Donnell, 2003; Shen et al., 2008; West and Grace, 2002). Conservation of the VTA complex circuitry across vertebrates establishes the relevance of behavioral neuroscience work on IS attribution and ISS in non-human animals to humans (Boyson et al., 1986; Gaspar et al., 1989; Kubikova et al., 2010; Lavoie et al., 1989; Perez-Fernandez et al., 2014; Smeets et al., 1986).

2.2. Manifestation (expression) of IS

Detection of a reward-predictive cue may automatically activate implicit associations (path a- > b in Fig. 1) involving attitudes (*i.e.*, evaluations) (Bargh et al., 1992), outcome expectancies, and goals (*i.e.*, motivational tendencies) (Bargh et al., 2001). The attribution of IS to a cue (path c- > d- > e in Fig. 1) may not only reinforce its ability automatically activate implicit associations in long-term memory (path g in Fig. 1), but also may amplify the behavioral consequences of implicit associations (path f in Fig. 1) including nonconscious attentional biases (Kappenman et al., 2013; Mogg et al., 1997) and nonconscious approach tendencies (Chen and Bargh, 1999). For example, attribution of IS to a cue may amplify its ability to impel approach and action, which may manifest as enhanced evaluative and response planning at the level of neural processing, covertly as a facilitation or priming of response channels leading to pre-potent responses or faster response times, and/or overtly as movement of the individual toward the cue/reward object and/or engagement with it. These skeletomotor manifestations of IS attribution (path f- > f.1 in Fig. 1) are mediated by an evolutionarily conserved expression circuitry anchored at the nucleus accumbens, a component of the subcortical structure known as the ventral striatum in the rostral forebrain that is situated to integrate diverse functional input from the amygdalar nuclei, cortices, hippocampus, hypothalamus, and thalamus with the IS signal from the VTA complex and to engage the appropriate response systems *via* the basal ganglia (Cho et al., 2013; Groenewegen et al., 1999; Haber, 2003; Haber et al., 2000; Hasue and Shammah-Lagnado, 2002; Parent and Hazrati, 1995; Reynolds and Zahm, 2005; Zahm et al., 1999).

Similarly, attribution of IS to a cue may amplify its ability to capture attention, and this may manifest as enhanced attention at the level of neural processing, an overt orienting response that turns the individual toward the cue/reward object and/or increases visual gaze shifts or fixation on it, and/or a covert orienting response that involves coordinated changes in autonomic physiology. These attentional manifestations of IS attribution (path f- > f.2 in Fig. 1) are mediated by an evolutionarily conserved expression circuitry anchored at the central nucleus of the amygdala, a subcortical structure in the temporal lobe that is situated to integrate diverse functional input from the cortices, hypothalamus, other amygdalar nuclei, thalamus, and brainstem with the IS signal from the VTA complex, and to engage the appropriate systems in the hypothalamus and brainstem (El-Amamy and Holland, 2007, 2006; Hasue and Shammah-Lagnado, 2002; Lee et al., 2011; Veening et al., 1984; Zahm et al., 1999).

The constellation of endocrine, skeletomotor, and visceromotor IS manifestations may constitute a subconscious biobehavioral appetitive-motivational state of "wanting" (path h in Fig. 1). In non-human animals, the cue-triggered "wanting" state is theorized be responsible for the ability of reward-related cues to invigorate actions that are instrumental to seeking or consuming the reward as well as to sustain reward seeking actions in spite of reward omission, punishment, increases in the effort required, or changes to the form the action must take. Given that both IS attribution and expression systems are highly conserved across species, we and others believe that cue-triggered "wanting" is also likely to be conserved across species. Thus, cue-triggered "wanting" may make a person more inclined to act toward the implicitly activated goal, which is to obtain the reward predicted by the cue, and more able to adjust their goal-directed actions according to situational demands.

Some readers may be satisfied to stop here given that much of behavior in humans and non-human animals alike is likely governed by bottom-up, implicit cognitive processes that operate below conscious awareness (Bargh, 2016, 2008; Bargh and Ferguson, 2000; Bargh and Morsella, 2008; Custers and Aarts, 2010; Lewicki et al., 1992). Nevertheless, the subjective experience of desire and craving (at the level of consciousness) is an important phenomenon in humans, and especially relevant to addiction and the ISST. In keeping, human neuroimaging studies of alcohol cue reactivity (reviewed later in Section 4.2.2) tend to find a significant, positive relationship between the level of activation induced by alcohol cues in a person's IS system and that person's self-report of the intensity of desire or craving for alcohol induced by those cues ((Filbey et al., 2008; Fryer et al., 2013; Myrick et al., 2004; Oberlin et al., 2016; Schacht et al., 2013; Tapert et al., 2004; Wiers et al., 2015c); but see: (Ames et al., 2014b; Grüsser et al., 2004; Kim et al., 2014)). Thus, we next propose two ways by which alcohol-associated cue activation of the IS system may drive the emergence of the subjective experience of alcohol-related desire and thought in humans.

According to the Dynamical Model of Desire (Hofmann and Van Dillen, 2018, 2012), which expands on the Elaborated Intrusion Theory of Desire (Kavanagh et al., 2005), subjective experience of a desire *for* the reward predicted by some cue emerges in a person's consciousness

(enters working memory) when neural representations of the cue or the reward or their association capture (neural) attentional resources in excess of some threshold. Below that threshold, a cue can only affect the person's behavioral output via bottom-up, implicit mechanisms (*e.g.*, "wanting"). Thus, it is possible that cue-triggered "wanting" becomes conscious craving when the nonconscious, implicitly-activated behavioral tendencies entailed in "wanting" are interrupted (path h- > i in Fig. 1) because behavioral conflict quickly captures attentional resources (see: Braver, 2012; Saunders et al., 2017; Yeung et al., 2004). In the case of alcohol, this "indirect" pathway to conscious craving may be *at work* when something impedes successful completion of cue-triggered alcohol seeking (*e.g.*, driving or walking by liquor store, but not going in to make a purchase; reaching for a glass, but finding that it has been taken away or that it is empty). It is in these moments that a person may not only become aware of the nonconscious alcohol seeking behaviors that were interrupted, but also of the altered physiological state in which they find themselves, and conclude that they are (or were) experiencing an urge to drink alcohol (Tiffany and Conklin, 2000).

A "direct" pathway from cue detection and IS attribution to the subjective experience of desire or craving may also exist (path j in Fig. 1). Detection of a reward-predictive cue may activate, in parallel to implicit associations, explicit associations in long-term memory, which immediately enter working memory, and thereby bring into consciousness cue- or reward-related attitudes, expectancies, goals, and other thoughts. Attribution of IS to the representation of the cue in working memory may increase the likelihood that cue-elicited thoughts capture the focus of attention in consciousness. When the reward in question is alcohol, the "direct" pathway may be *at work* when a person begins to think about alcoholic beverages, alcohol use, or positive alcohol use outcomes after briefly encountering an alcohol-associated exteroceptive cue in the course of daily life.

3. Evidence for ethanol-induced adaptation of the IS circuitry

According to Robinson and Berridge (1993, 2001), the core criteria for establishing that a drug is able to induce ISS are simple: first, the drug must engage the IS system, and second, its repeated administration should induce sensitization, a non-associative learning process, in the IS system (at the neurobiological level) in a gradual or incremental manner. Inquiry into the neurobiological substrates of sensitization in general, and substance-induced sensitization of the IS system in specific, is an active area of research in neuroscience (*e.g.*, (Areal et al., 2019; Hersman et al., 2019; Stevenson et al., 2019; Weber et al., 2019)). However, some details are clear. The adaptations that mediate ISS are persistent changes at the cellular (*e.g.*, changes in dendritic morphology) or inter-cellular level (*e.g.*, changes in pre- and post-synaptic molecular elements such as voltage-gated ion channels, ionotropic neurotransmitter receptor proteins, neurotransmitter synthesis enzymes and transporter proteins, metabotropic neurotransmitter receptor proteins) that necessarily require changes in gene expression.[3] Persistent functional cellular adaptations (*e.g.*, increased intrinsic excitability, increased neurotransmitter release) entail persistent circuit-level adaptations (*e.g.*, increased excitatory tone, decreased inhibitory tone), which in turn, entail persistent system-level adaptations.[4] Despite all of this, the consequences of a sensitized IS system may only be expressed or manifest in behavior in specific contexts (Leyton, 2007; Vezina and Leyton, 2009). Under certain circumstances, cue- or context-conditioned compensatory (opponent) processes that mediate behavioral tolerance to the effects drugs (*e.g.*, (Weise-Kelly and Siegel, 2001)) may mask the expression of sensitized in cue-conditioned appetitive responses (*e.g.*, (Dalia et al., 1998)).

Consequently, an important issue in establishing ISS as a potential mechanism in AUD is the ability of ethanol exposure to induce persistent adaptations in the IS circuitry, especially adaptations that might underlie non-associative sensitization of the IS system, particularly its functional response to alcohol-associated cues. In this section, we review evidence for adaptations in the IS circuitry of preclinical non-human animal models with ethanol experience that may mediate alcohol cue ISS (Fig. 2) in both humans and other animals.

In considering this evidence, it is necessary to keep in mind the intensity, frequency, and duration of ethanol exposure. In models involving chronic high-intensity exposure, it is necessary to consider when biological or physiological measurements are made relative to the last exposure, because these exposure paradigms are able to induce dependence, as evidenced by signs of acute withdrawal during the first few days after cessation (*e.g.*, lowered seizure threshold, anxiety-like phenotypes) (Macey et al., 1996; Majchrowicz, 1975). Ideally, measurements would be made at various intervals post-cessation. However, the vast majority of studies make measurements only during acute withdrawal. Although studies describing the brain state in acute withdrawal are important (*e.g.*, this state may be conducive to deeper encoding of cue-alcohol associations *via* increased homeostatic value of alcohol or negative reinforcement), ISST assumes that the sensitized response to cues is not constrained to instances of acute withdrawal. In fact, there may be an exposure threshold for ethanol-induced adaptation in different brain and body systems found to be altered in people with AUD. Assuming that this threshold is met, adaptations should begin to arise in the IS circuitry early in the exposure history. Later in the exposure history, the adaptations that mediate ISS should persist after instances of acute withdrawal. For this reason, we review preclinical non-human animal model studies making measurements any time after limited (low-intensity) exposure and at two different timepoints after extensive (high-intensity) exposure: during acute withdrawal and at least a week after it has resolved. Finally, we comment on the role of intermittency in ethanol exposure.

3.1. Precursor for alcohol cue incentive salience sensitization (ISS)

The earliest ethanol-induced adaptation in the IS circuit is the development of phasic[5] dopamine release to ethanol-predictive cues (henceforth: the IS signal), which is necessary for initiation of progressive alcohol cue ISS. We know that outside a self-administration context, *i.e.*, as a purely pharmacological stimulus divorced of its usual motivational significance, ethanol can induce dopamine release in both the prefrontal cortex and nucleus accumbens of people (Boileau et al., 2003; Setiawan et al., 2014; Urban et al., 2010; Yoder et al., 2016, 2007) and rodents alike (Di Chiara and Imperato, 1988; Howard et al., 2008; Imperato and Di Chiara, 1986; Schier et al., 2013; Yim and Gonzales, 2000; Zapata et al., 2006). This occurs putatively as a function of ethanol's acute pharmacological effects on cells in the VTA complex (Brodie et al., 1999, 1990; Brodie and Appel, 1998; di Volo

[3] A comprehensive survey of all the genes and molecules that preclinical research on non-human animal models has demonstrated can change as a function of drug exposure, as a function of associative and non-associative learning, and/or as a function of their interaction, is beyond the scope of this review. Suffice it to say that the list of genes is long and ever-growing.

[4] An appreciation for the coordinated nature of functional adaptation across levels of biological organization (e.g., how changes in different molecules can produce changes synaptic plasticity processes) may be garnered from innovative simulation studies such as (Blackwell et al., 2018).

[5] Phasic refers to event-locked dopamine release on a sub-second timescale due to synchronized bursts of high-frequency action potentials (AP) at axon-terminal boutons, and is contrasted with tonic release due to asynchronous low-frequency AP at the same. Tonic release creates the "basal tone" (steady-state extracellular concentration) that regulates clearance mechanisms (e.g., autoreceptors, transporters, degradative enzymes) in the terminal field. Readers desiring more in-depth coverage of the dopamine neurotransmission system are referred to: (Grace, 2000; Marinelli and McCutcheon, 2014; Rice et al., 2011; Vallone et al., 2000).

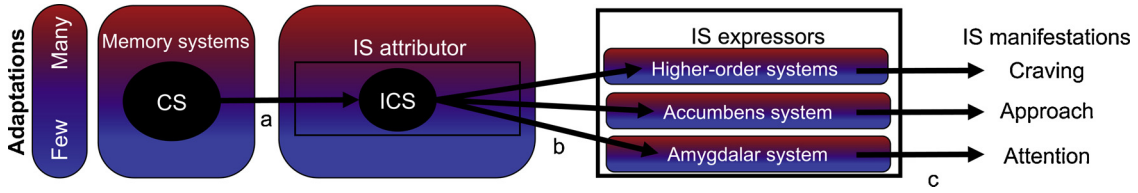

Fig. 2. Paths mediating incentive salience (IS) sensitization (ISS). Components: memory systems, IS attributor, IS expressors, response effector systems. A-type paths: input from memory systems into the IS attributor. B-type paths: IS attributor output to the IS expressors. C-type paths: IS expressors output to response effector systems that are responsible for manifestations of IS in behavioral output across levels of biological organization. The vulnerability of the different paths and IS system components to the adaptations mediating alcohol cue ISS is theorized to increase progressively over the alcohol use history as a function of the frequency, intensity, and pattern of drinking. A 3-color gradient (blue to purple to red) is used to represent an increasing extent or number of adaptations accrued within each component or path. Adaptations may occur in one component or path without occurring in another and the accrual rate may vary by component or path.

et al., 2018; Gessa et al., 1985; Mereu et al., 1984; Xiao et al., 2009).

However, over the course of repeated voluntary oral self-administration by ethanol-experienced non-human animals, explicitly or incidentally-conditioned cues, such as a light or a lever or the flavor of alcohol, acquire the ability to trigger dopamine release in the medial prefrontal cortex and the nucleus accumbens before brain ethanol concentrations reach pharmacologically active levels (Bassareo et al., 2017; Carrillo and Gonzales, 2011; Doherty et al., 2016; Doyon et al., 2005, 2003; Fiorenza et al., 2018; Howard et al., 2009; Shnitko and Robinson, 2015). In the same studies, dopamine levels remain either slightly elevated or return to baseline as brain ethanol concentrations continue to rise. This pattern suggests that one of the early adaptations to chronic ethanol experience in its typical motivational context is a decrease in or loss of VTA complex dopamine neuron sensitivity to the pharmacological effects of ethanol (putatively the rewarding stimulus) and acquisition of VTA complex dopamine neuron sensitivity to ethanol-predictive stimuli (the reward-predictive cues). Interestingly, the same pattern of changes in the IS attributor has been documented as arising in 1/3rd of rodents (so-called "sign-trackers") when they are trained to predict natural reward (food) on the basis of a cue (Flagel et al., 2010). If we accept that the function of the IS attributor is to broadcast whether specific stimuli are "want worthy," then the development of any CS-elicited activity in the IS attributor (*i.e.*, rapid release of dopamine from axon terminal buttons; with or without loss of the US-elicited activity) represents the first step in the process of alcohol cue ISS (formation of type 'a' path in Fig. 2).

3.2. ISS-mediating adaptations arising early in the alcohol use history

Limited (low-intensity) exposure to ethanol is also able to induce adaptations in the IS circuitry that have the functional consequence of increasing the neurobiological (and psychological) relevance of the IS signal. A week of voluntary oral self-administration of moderate ethanol doses (ethanol concentration ≈50 mg/dL whole blood 30 min into the drinking episode) appears to be sufficient to decrease basal extracellular dopamine tone in the prefrontal cortex (Doherty et al., 2016) of rats from a genetically heterogeneous population, whereas longer (*e.g.*, 2 months) voluntary oral self-administration histories may be necessary for similar adaptations to arise in the nucleus accumbens (Doyon et al., 2003; Ericson et al., 2019; Howard et al., 2009). These longer histories can also alter the balance of excitatory and inhibitory drive into the dorsal striatum, the nucleus accumbens, and the orbitofrontal cortex depending on the intensity of alcohol consumption (Adermark et al., 2013; Lagström et al., 2019). The functional consequence of lower basal dopamine tone in either the prefrontal cortex or the nucleus accumbens may be an elevated signal-to-noise ratio in cortical and striatal neurons (Kroener et al., 2009; O'Donnell, 2003; West and Grace, 2002) due to lower tonic dopamine auto-receptor activation (Dreyer et al., 2010). An elevated signal-to-noise ratio would have consequences for the neuromodulatory impact of phasic dopamine release on synaptic activity and plasticity as well as excitatory and inhibitory drive onto those synapses in the IS expressors (changes in the type 'b' paths or their targets in Fig. 2).

A short history of voluntary oral alcohol self-administration in rats from genetically homogenous populations selected for high alcohol preference is also able to increase the number of spontaneously active dopamine neurons in the VTA complex (Morzorati et al., 2010). This suggests that in at least some individuals limited exposure to alcohol can cause a persistent increase in the intrinsic excitability of the IS attributor (which may make it easier for activity in type 'a' paths to drive the IS attributor, *i.e.*, to activate type 'b' paths in Fig. 2). Interestingly, alcohol-naive rats from these more genetically homogeneous populations selected for high alcohol preference and drinking also tend to have lower basal dopamine tone in both the prefrontal cortex and the nucleus accumbens (Engleman et al., 2006; Gongwer et al., 1989; Katner and Weiss, 2006; McBride et al., 1993; Murphy et al., 1982; Quintanilla et al., 2007; Strother et al., 2005), suggesting that selection for high alcohol preference/drinking also selects for neurobiological endophenotypes that may increase vulnerability to alcohol cue ISS.

3.3. ISS-mediating adaptations arising later in the alcohol use history

3.3.1. Adaptations active in acute withdrawal

Depending on alcohol use level and history, abstinence from alcohol can produce an acute withdrawal syndrome, the physical symptoms (*e.g.*, seizures, tremors) of which can begin hours after the last drink yet abate within a few days and the psychological symptoms (*e.g.*, anxiety, depression, trouble sleeping) of which can persist for at least two weeks (Brown et al., 1995; Brown and Schuckit, 1988; Liappas et al., 2002; Schuckit et al., 2015, 1995). During acute withdrawal, cognitive functioning may be especially impaired ((Beatty et al., 2000; Czapla et al., 2016; Loeber et al., 2010; Pitel et al., 2009; Romero-Martínez et al., 2018); for review see: (Bates et al., 2002)) yet alcohol use-directed motivation may be heightened since non-cued craving is at its peak ((Flannery et al., 2003; Martinotti et al., 2008; Schneekloth et al., 2012; Witkiewitz, 2013); but see: (Li et al., 2015)). In non-human animal models, acute withdrawal after extensive (high-intensity) exposure to ethanol is associated with lower basal dopamine tone and greater basal glutamate tone in the nucleus accumbens (Griffin et al., 2015; Hirth et al., 2016; Karkhanis et al., 2015; Uys et al., 2016; Weiss et al., 1996), altered synaptic plasticity in the nucleus accumbens (Jeanes et al., 2011; Renteria et al., 2017b; Spiga et al., 2014), greater excitability in the medial and orbital prefrontal cortices ((Nimitvilai et al., 2016; Pleil et al., 2015), but see: (Renteria et al., 2018)), and altered excitatory drive and synaptic excitability as well as altered phasic and tonic inhibition in the central and basolateral nuclei of the amygdala (Herman and Roberto, 2016; Läck et al., 2007, 2005; Lindemeyer et al., 2014; Papadeas et al., 2001; Pleil et al., 2015; Roberto et al., 2004a, 2004b; Varodayan et al., 2016). In the amygdala, hippocampus, and nucleus accumbens, the number of brain cells activated during the experience of acute withdrawal grows as a function of the number of previous withdrawal episodes (Borlikova et al., 2006), suggesting that repeated cycles of high intensity exposure and acute withdrawal alter the balance of excitation and inhibition in these structures and induce

persistent functional alterations. Finally, although the neurobiology of acute withdrawal from alcohol is primarily informed by post-mortem studies in the mouse and rat brain, a similar neurobiological state, at least in the nucleus accumbens and prefrontal cortices, can be inferred from post-mortem studies in the brains of non-human primates allowed to voluntarily orally self-administer alcohol to intoxication every day for 6 or more months (Acosta et al., 2010; Alexander et al., 2012; Floyd et al., 2004; Hemby et al., 2006; Siciliano et al., 2016a, 2016b, 2015). The functional consequence of these adaptations may be elevated reactivity to alcohol-associated cues in cortical neurons, dysregulated reactivity in amygdalar neurons, and an elevated signal-to-noise ratio in striatal neurons (Kroener et al., 2009; O'Donnell, 2003; West and Grace, 2002) due to lower tonic dopamine auto-receptor activation (Dreyer et al., 2010) that enhances the neuromodulatory impact of event-related dopamine release on synaptic activity and plasticity as well as the thresholds for excitatory and inhibitory drive onto said synapses in the IS expressors (changes in the type 'b' paths or their targets in Fig. 2). Thus, the brain state in acute withdrawal after chronic high intensity exposure appears to be one that may support sensitized responses to alcohol cues (*i.e.*, amplifies or facilitates the impact of alcohol-associated cues on behavioral output) as well as deeper conditioning of those cues if reinforced with alcohol ingestion and/or intoxication.

3.3.2. Adaptations that persist into protracted abstinence/withdrawal

Although physical symptoms of withdrawal from alcohol may abate within days, the psychological symptoms such as anxiety and depression can persist, and may be present in some people up to a year after the last drink (Martinotti et al., 2008). Although cognitive functioning may recover over the periods of months to years of protracted abstinence from alcohol ((Beatty et al., 2000; Czapla et al., 2016; Loeber et al., 2010; Pitel et al., 2009; Romero-Martínez et al., 2018), for review see: (Bates et al., 2002)), alcohol use-directed motivation may remain aberrantly elevated, as evidenced by incubation of alcohol cue-induced conscious craving (Li et al., 2015), even if it is not actively expressed in behavior. During protracted abstinence/withdrawal, some, but not all, components of the IS circuitry appear to have a lower threshold for activation. Specifically, non-human animals exhibit elevated basal glutamate tone (Griffin et al., 2014), increased intrinsic excitability, increased excitability at glutamatergic synapses, and altered synaptic plasticity (Marty and Spigelman, 2012; Renteria et al., 2017a; Zhou et al., 2007), but see: (Adermark et al., 2013)) as well as altered astrocytic excitability (Bull et al., 2014) in the nucleus accumbens. Basal dopamine tone in the nucleus accumbens is found to be either increased (Hirth et al., 2016) or decreased (Kashem et al., 2012; Rothblat et al., 2001) or unchanged (Diana et al., 1992), potentially as a function of the exposure paradigm and its ability to induce changes in local dopamine receptor gene expression and/or its regulation (Eravci et al., 1997; Jonsson et al., 2014). In the medial and orbital prefrontal cortices, synaptic excitability, synaptic plasticity, and its biochemical mediators are perturbed (Henniger et al., 2003; Kroener et al., 2012; Renteria et al., 2018). In the central nucleus of the amygdala, altered tonic inhibition persists due changes in the local expression or regulation of inhibitory neurotransmitter clearance mechanisms (Augier et al., 2018). Finally, dopamine neurons in the VTA complex do not appear to exhibit increased baseline spontaneous firing rates (Diana et al., 1992), but do bear biochemical and electrophysiological signatures of enhanced responsivity to excitatory neurotransmission at synapses along their dendrites (Ortiz et al., 1995; Stuber et al., 2008). Overall, even in the absence of the lower signal-to-noise ratio in the nucleus accumbens observed after acute withdrawal, other nodes of the IS circuitry appear to be more easily driven by alcohol-associated cues in protracted abstinence (changes in the type 'c' paths in Fig. 2). Importantly, the available evidence suggests that long-term ethanol exposure induces adaptations that persist after acute withdrawal into protracted abstinence. Moreover, these ethanol-induced adaptations may support the ability of alcohol-associated cues to affect behavioral output despite non-reinforcement of said cues in protracted abstinence.

3.3.3. On the role of intermittency in the effects of chronic ethanol exposure

Many of the neuroadaptations evident in the acute and protracted withdrawal states after extensive (high-intensity) ethanol exposure that were reported above may hinge upon the intermittency built into many ethanol access/exposure paradigms (*e.g.*, multiple cycles of a 4-day 16-hr/day passive ethanol vapor exposure, every other day 24-hr access or daily 2-hr access schedules). In rodents, these chronic intermittent access/exposure paradigms can induce alcohol addiction-like behavioral phenotypes including: increased alcohol seeking (Augier et al., 2018; Ciccocioppo et al., 2003; Gass et al., 2014; Hauser et al., 2019; Meinhardt et al., 2013; Vendruscolo et al., 2012), development of within-episode drinking patterns that rapidly produce high blood alcohol concentrations (Gilpin et al., 2009; Wilcox et al., 2014), and heavier consumption across episodes (Becker and Lopez, 2004; Bell et al., 2004; Loi et al., 2010; Morales et al., 2015; Simms et al., 2008; Sommer et al., 2008; Wilcox et al., 2014; Wise, 1973) as well as relative insensitivity of alcohol seeking and drinking to alcohol devaluation (Augier et al., 2018; Hopf et al., 2010; Loi et al., 2010; Vendruscolo et al., 2012). Furthermore, rodents that undergo chronic intermittent ethanol access/exposure paradigms exhibit short- and long-term deficits in performance on executive functioning tasks (Gass et al., 2014; Kroener et al., 2012) as well as in learning about aversive, but not appetitive, outcomes (Ripley et al., 2004, 2003; Stephens et al., 2005, 2001). Thus, repeated cycles of intoxication and abstinence may be a critical factor in the progressive loss of control over alcohol use.

3.4. Interim summary 1

In this section, we reviewed evidence for the ability of ethanol, the addictive agent in alcoholic beverages, to induce neuroadaptations that may mediate the ISS process. The evidence, which comes from work in non-human animal models, suggests that several different adaptations capable of mediating the ISS process arise as a function of chronic ethanol exposure (see Fig. 3) in the IS attributor, VTA complex, and the IS expressor systems, amygdala and nucleus accumbens, as well as in the medial and orbital prefrontal cortices, which are innervated by the IS attributor and inter-connected with the IS expressor systems. Given that these prefrontal cortices are believed to mediate cognitive control processes (Barbas, 2000; Braver, 2012; Inzlicht et al., 2015; Ridderinkhof, 2004), complex higher-level psychological functions in humans such as emotion regulation and self-control (Ochsner et al., 2012; Robinson et al., 2010) may be vulnerable to dysregulation as ISS progresses.

4. Evidence for incentive salience (IS) attribution to alcohol cues and its sensitization (ISS)

Based on the behavioral indicators of IS attribution described in (Robinson et al., 2014), if an alcohol-associated cue has been attributed with IS, then: (1) that cue should be able to elicit approach-oriented responses (*e.g.*, attention, approach, conscious craving for alcohol), (2) that cue should be able to serve as a conditional or secondary reinforcer,[6] and (3) that cue should be able to induce or invigorate

[6] Conditional or secondary reinforcers are stimuli that support new learning and/or behavioral performance as a function of their learned, meaningful relationship to a primary reinforcer such as resources necessary for survival. When learned cues acquire conditional reinforcing properties, they can motivate behavior in the absence of primary reinforcement and sometimes even in the face of punishment. The most commonly cited "real world" example of a secondary reinforcer is token money. In some societies, token money is able to motivate some individuals to learn and perform new actions, often vigorously and repeatedly, for long stretches of time. The value of token money to a person in such societies is conditional upon learning about the extent to which and

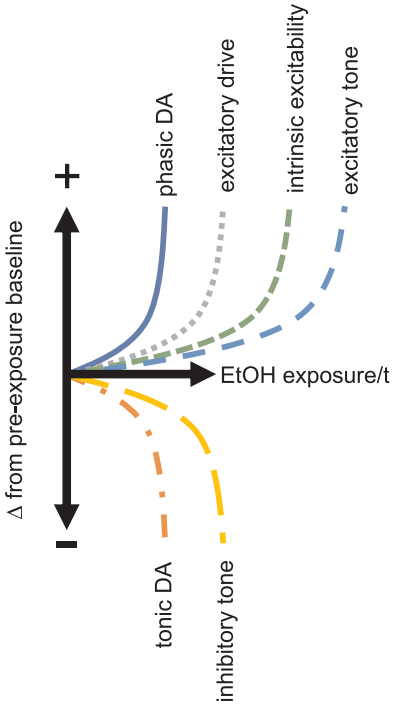

Fig. 3. Example of the kinds of persistent adaptations ethanol (EtOH) exposure might induce over time (t) to mediate alcohol cue ISS and how these might unfold over exposure relative to one another. Conjecture is informed by findings reviewed in the main text. Increased phasic DA release (from synchronized high-frequency action potentials at terminal boutons arising from the IS attributor) must occur at synapses involved in maintaining memory for the alcohol cue or its expression (*viz.*, synapses in memory systems or in the IS expressors). Increased excitatory drive may occur at specific synapses across the IS system components including at the IS attributor. Decreased tonic DA release (from asynchronous low-frequency action potentials at terminal boutons arising from the IS attributor) will naturally affect many more synapses than those immediately involved in alcohol cue memory/expression. Increased excitatory tone, decreased inhibitory tone, and increased intrinsic excitability will naturally affect many cells across the IS system components including at the IS attributor.

instrumental alcohol seeking actions (*e.g.*, choice, consumption). At the brain-level, the IS-attributed alcohol-associated cue should engage the IS circuitry, *i.e.*, activate the IS attributor and/or expressors (Fig. 1).

Applying ISST to AUD, all else being equal, if ISS is a mechanism in AUD, then it holds that an individual's degree of reactivity to alcohol-associated cues should covary with alcohol use levels. There should be a positive relationship between alcohol consumption or exposure and degrees of reactivity. Consequently, with more exposure: (1) the IS-imbued alcohol-predictive cue should be able to elicit *greater* levels of alcohol seeking reactions (*e.g.*, attention, approach, conscious craving for alcohol), (2) the cue should have *higher* conditional rewarding value, and (3) the cue should *more easily* induce or invigorate instrumental alcohol seeking actions (*e.g.*, choice, consumption). Finally, (4) a similar pattern of sensitization should be evident in brain-level responses to the cue. However, all else may not be equal, and it rarely is. It is important to keep in mind that the reliability of the predicted positive association between alcohol use and cue reactivity level in humans is likely to be low because alcohol use level is subject to the influence of many different trait and state factors at the psychological, social, and cultural levels.

(*footnote continued*)
ways in which token money can be traded for desired and/or needed goods and services.

4.1. In non-human animal models

In this section, we review evidence for attribution of IS to alcohol-predictive cues and its sensitization in non-human animal models.

4.1.1. Alcohol cue-related behavioral responses

4.1.1.1. Attentional responses. In discrete alcohol cue conditioning paradigms involving voluntary oral alcohol self-administration by rats, the alcohol-predictive cue can come to elicit an attentional orienting response (Cofresí et al., 2019a, 2019b). However, it remains to be seen whether individual differences in pre-conditioning voluntary alcohol consumption predict conditioned attentional response levels or whether the latter relate to alcohol self-administration in the conditioning task.

4.1.1.2. Approach responses. In the same type of paradigm where alcohol-related attentional responses can be seen in rats, the alcohol-associated discrete cue can also come to elicit an approach response (Cofresí et al., 2019a, 2019b, 2018; Krank, 2003; Krank et al., 2008; Sparks et al., 2014; Srey et al., 2015; Villaruel and Chaudhri, 2016). In keeping with what we might expect from applying ISST to AUD phenotypes, individual differences in pre-conditioning task voluntary alcohol consumption can predict later alcohol cue-conditioned approach levels (Cofresí et al., 2019a). Furthermore, rats with greater magnitude alcohol cue-conditioned approach response also self-administer more alcohol in the cue conditioning paradigm (Cofresí et al., 2019b, 2018). Similarly, alcohol-associated *contextual* cues, such as distinct places paired with experimenter-administered alcohol, can come to elicit place preference, an approach-like response, in mice (Cunningham et al., 2002a, 2002b; Gremel and Cunningham, 2008) and rats (Bozarth, 1990; Nentwig et al., 2017; Torres et al., 2014). Furthermore, there is a positive association between levels of this approach-like response and levels of voluntary alcohol consumption in rodents (Green and Grahame, 2008).

4.1.1.3. Cue as conditional reinforcer effects. Alcohol-associated cues alone can reinforce learning of new instrumental actions in rats (Milton et al., 2012; Schramm et al., 2016; Srey et al., 2015). Alcohol-associated cues and contexts are also able to cause the return of extinguished instrumental actions that previously produced alcohol and maintain that instrumental responding for some time in the absence of alcohol (Bertholomey et al., 2016; Bienkowski et al., 2004; Burattini et al., 2006; Chaudhri and Sahuque, 2008; Ciccocioppo et al., 2002, 2001; Dayas et al., 2007; Hauser et al., 2019, 2016; Jupp et al., 2011; Katner et al., 1999; Katner and Weiss, 1999; Knight et al., 2016; Martin-Fardon and Weiss, 2017; O'Brien et al., 2011; Radwanska et al., 2008; Randall et al., 2017; Rodd-Henricks et al., 2003, 2002; Zironi et al., 2006).

Evidence for sensitization of conditioned reinforcement comes from studies in rats demonstrating changes in the magnitude of conditioned reinforcement-related effects following termination of access or exposure to alcohol. In the hours to days following termination of access/exposure, alcohol dependent rats will: (1) work harder for alcohol (Gilpin et al., 2009; Gilpin and Koob, 2010; Kissler and Walker, 2015; Roberts et al., 1996; Vendruscolo et al., 2012; Walker and Koob, 2007), (2) self-administer more (Weiss et al., 1996), even if it has been adulterated with bitterant (Vendruscolo et al., 2012), and (3) exhibit larger alcohol-associated cue- and context-induced instrumental response reinstatement effects (Ciccocioppo et al., 2003; Liu and Weiss, 2002a; Weiss et al., 1996). As time post-termination of access/exposure increases from days to weeks or months, alcohol-associated cue- and context-induced instrumental response reinstatement effects can be observed to grow in magnitude ((Bienkowski et al., 2004; Hauser et al., 2019, 2016; Radwanska et al., 2008; Rodd-Henricks et al., 2003, 2002), but see: (Jupp et al., 2011; O'Brien et al., 2011)).This incubation effect is in agreement with known time-dependent increase in the magnitude

of spontaneous recovery of extinguished reactivity to alcohol-associated cues (LeCocq et al., 2018; Remedios et al., 2014). From a Pavlovian perspective, these effects demonstrate acute withdrawal and protracted abstinence state-dependent increases in IS attribution to alcohol-associated cues.

4.1.1.4. Pavlovian to instrumental transfer effects. The Pavlovian to instrumental transfer (PIT) construct developed in animal models addresses the ability of incidental exposure to Pavlovian cues to initiate or invigorate an instrumental action. The formal test for PIT involves separately training cue reactivity and instrumental action and then observing behavior during a probe test in which the cue is intermittently presented to the animal while the opportunity for instrumental action is concurrently available. Typically, primary reinforcement is withheld during the test to prevent confounding the effect of cues with the effect of primary reinforcement. In rats, alcohol-associated cues can produce PIT test effects that are specific to alcohol reward as well as PIT test effects that generalize to other rewards ((Alarcón and Delamater, 2018; Corbit et al., 2016; Corbit and Janak, 2016, 2007; Glasner et al., 2005; Krank, 2003; Krank et al., 2008; Lamb et al., 2016); but see: (Lamb et al., 2019, 2016)). Interestingly, alcohol-associated cues do not appear to exert any stronger PIT test effect in rats with a history of physical ethanol dependence than rats without such a history (Glasner et al., 2005). However, in rats without any history of physical dependence, alcohol cues exert a stronger PIT test effect after extensive as opposed to limited voluntary oral self-administration histories ((Corbit and Janak, 2016), but see: (Lamb et al., 2019)).

If we accept that drinking alcohol is itself an action instrumental for the experience of alcohol's primary reinforcing properties, then we can admit as evidence of PIT in non-human animal models those situations in which conditioned alcohol cue reactivity facilitates alcohol drinking behavior (*e.g.*, initiation of a sip, faster sipping, larger sips). Such PIT-like effects have been observed in rats (Cofresí et al., 2019b, 2018). Here, there is a positive relationship between the degree of Pavlovian alcohol cue reactivity and the speed and intensity of alcohol drinking behavior (Cofresí et al., 2019b, 2018).

4.1.2. Alcohol cue-related brain responses

4.1.2.1. Immediate early gene expression. When neurons and astrocytes are activated, the transcription and translation of immediate early genes (*e.g.*, *arc*, *c-fos*, *erk*) occurs, and this allows researchers to use the relative density of transcripts or translated protein product as an index of regional brain activity (typically, post-mortem) (Herdegen and Leah, 1998; Morgan and Curran, 1989; Sheng and Greenberg, 1990). Using these indices, alcohol cues conditioned by voluntary oral alcohol self-administration have been shown to activate cells in various IS circuit nodes in the rat brain, including the medial and orbital prefrontal cortices, insular cortex, basolateral nucleus of the amygdala, nucleus accumbens, and central nucleus of the amygdala (Barak et al., 2013; Cofresí et al., 2019a; Dayas et al., 2007; Jupp et al., 2011; Radwanska et al., 2008).

These alcohol cues appear gain incentive salience as a function of time since acute withdrawal from alcohol. Specifically, after 6 months since cessation of alcohol access compared to after only 1 month, alcohol cues were able to induce activation of more cells in IS circuit nodes including the medial and orbital prefrontal cortices and central nucleus of the amygdala (Jupp et al., 2011). Other IS circuit nodes (*e.g.*, nucleus accumbens, basolateral nucleus of the amygdala) also exhibited cue-induced activation, but the number of activated cells did not scale with time post-cessation of alcohol access. To our knowledge, no studies have looked at whether alcohol cues activate more cells in these brain regions as a function of alcohol exposure levels per se.

4.1.2.2. Dopamine neurotransmission. Changes in phasic and tonic dopamine release, which differentially affect signaling *via* different post-synaptic dopamine receptors (Dreyer et al., 2010; Venton et al., 2003), can be measured using fast-scan cyclic voltammetry (Rodeberg et al., 2017) and microdialysis (Zapata et al., 2009), respectively, in awake, freely-behaving non-human animals. Using these two neurochemical monitoring techniques, alcohol-associated cues have been demonstrated to elicit increases in both phasic and tonic dopamine release at IS circuit nodes such as the prefrontal cortices and nucleus accumbens in the rat (Bassareo et al., 2017; Carrillo and Gonzales, 2011; Doherty et al., 2016; Doyon et al., 2005, 2003; Fiorenza et al., 2018; Gonzales and Weiss, 1998; Howard et al., 2009; Katner and Weiss, 1999; Melendez et al., 2002; Robinson et al., 2009; Shnitko and Robinson, 2015; Weiss et al., 1993).

We were unable to find any published studies that have set out to investigate whether alcohol cues elicit greater dopamine release as a function of alcohol exposure levels. Only one study has looked at whether alcohol-associated cues elicit greater dopamine release as a function of time since acute withdrawal due to termination of alcohol access/exposure. In this single study using microdialysis in rats (Weiss et al., 1996), when alcohol-dependent rats were allowed to orally self-administer alcohol a few hours into acute withdrawal, within 10 min, extracellular dopamine levels in the nucleus accumbens reached 200 % of the baseline extracellular level observed during acute withdrawal. However, in the same study, the baseline extracellular dopamine level in the nucleus accumbens was found to be lower during those first few hours of acute withdrawal than before the induction of physical dependence. Another study from the same group provides indirect evidence for increased cue-elicited dopamine release in the nucleus accumbens during withdrawal. In this study, the potency and efficacy of systemically-administered dopamine receptor antagonists to inhibit the ability of alcohol-associated cue/contexts to reinstate extinguished instrumental response rates were found to be greater after a history of physical dependence (Liu and Weiss, 2002b). Together, these findings are in keeping with the idea (discussed earlier) that ethanol exposure induces adaptations that enhance the neuromodulatory impact of dopamine in the nucleus accumbens.

4.1.2.3. In vivo neuronal firing. Transient changes in the firing rate of neurons also can be measured in awake, freely-behaving animals by implanting electrodes into the brain regions of interest (Woodward et al., 1999). Alcohol-associated cues have been demonstrated to elicit changes in the firing rate of neurons in the nucleus accumbens of rats from genetically heterogeneous populations (Janak et al., 1999; Robinson and Carelli, 2008; Woodward et al., 1998). In rats from a genetically homogenous population selected for high alcohol preference, alcohol-associated cues may also elicit changes in the firing rate of neurons in the prefrontal cortex (Linsenbardt and Lapish, 2015). To our knowledge, no studies have looked at whether alcohol access-related cues induce greater changes in neuronal firing as a function of alcohol use or exposure levels or as a function of time since acute withdrawal due to termination of alcohol access or exposure.

4.2. In humans

In this section, we review evidence for attribution of IS to alcohol-predictive cues and its sensitization in people.

4.2.1. Alcohol cue-related behavioral responses

4.2.1.1. Attentional responses. In this section, we review the evidence for attentional capture by alcohol-predictive cues, an index of IS attribution. Readers interested in the topic of the attentional capture by cues associated with drugs of abuse (including alcohol) in general, including alternative theoretical and methodological explanations for any measured bias in visual attention, its relationship to drug craving, and its clinical relevance are referred to comprehensive review articles conducted by others (Christiansen et al., 2015b; Field et al., 2016, 2014; Field and Cox, 2008).

The best evidence for or against the ability of alcohol cues to elicit oculomotor behavior (*viz.*, capture visual attention) in humans comes from studies measuring eye movement initiation, latency, and duration. In one such study (Monem and Fillmore, 2016), the duration of gazes toward non-alcoholic beverages decreased across two sessions in a simulated *in vivo* "recreational" setting whereas the duration of gazes toward alcoholic beverages in the same setting did not such that in session 2, an attentional bias toward the alcoholic beverages was visible at the sample-level. Monem and Fillmore (2016) also found that within-person differences in gaze duration between alcoholic and non-alcoholic beverages in both sessions were positively related to typical alcohol use levels. Similarly, inside complex visual scenes presented on a computer screen, alcoholic beverages can elicit a greater number of cue-directed eye movements and the extent to which they do appears to be relate to alcohol use levels (Roy-Charland et al., 2017). More eye movements tend to be directed toward alcohol use scenes when they are presented alongside other scenes and gaze duration tends to be longer (Vincke and Vyncke, 2017). Similarly, the duration of gazes toward alcoholic beverage pictures and words tend to be longer than the duration of gazes toward concurrently presented non-alcohol pictures and words and this bias tends to be positively related to typical alcohol use ((Ceballos et al., 2015; Christiansen et al., 2015a; Fernie et al., 2012; Field et al., 2011b; Friese et al., 2010; Laude and Fillmore, 2015; Lee et al., 2014; Melaugh McAteer et al., 2015; Miller and Fillmore, 2011, 2010; Rose et al., 2013; Weafer and Fillmore, 2013, 2012), but see: (Schoenmakers et al., 2008)).

Additional evidence for or against the ability of alcohol cues to elicit oculomotor behavior (*viz.*, capture visual attention) in humans comes from tasks where visual attentional capture by alcohol cues can be inferred based on changes in the accuracy and/or latency of other (non-ocular) responses to visual stimuli. For example, the ability and latency to detect alcoholic beverage-related changes within complex visual scenes as well as simple multi-item display grids in the flicker-induced visual change blindness paradigm in the laboratory (Hobson et al., 2013; Jones et al., 2002, 2006, 2003; Schoenmakers et al., 2007) and in the natural environment (Schoenmakers and Wiers, 2010). The ability and latency to detect alcohol-related changes in the flicker-induced change paradigm tend to be, respectively, positively and negatively related to typical alcohol use levels (Hobson et al., 2013; Jones et al., 2002, 2006, 2003; Schoenmakers and Wiers, 2010). Similarly, in the attentional blink paradigm, which measures the efficiency of early visual attention as a decrease in an experimentally-induced stimulus misidentification rate, greater early visual attention efficiency has been found for both alcoholic beverage pictures and alcohol-related words relative to non-alcohol pictures and words as a positive function of typical alcohol use levels (DePalma et al., 2017; Tibboel et al., 2010). In the modified visual dot probe detection task, an alcoholic beverage picture and non-alcohol beverage picture are presented simultaneously on the left or right-side of a computer screen and a response-target probe is presented shortly after picture offset in the same location as one of the two pictures on the screen. In this task, the latency to respond to the probe tends to be shorter (*i.e.*, people are faster to detect it) when the probe is presented in the same location as the alcoholic beverage picture and this tends to be positively related to typical alcohol use levels ((Christiansen et al., 2015a; Clerkin et al., 2016; Duka and Townshend, 2004; Field et al., 2013, 2007, 2004; Field and Eastwood, 2005; Field and Quigley, 2009; Garland et al., 2012a, 2012c; Manchery et al., 2017; Miller and Fillmore, 2010; Ramirez et al., 2015b, 2015a; Roberts and Fillmore, 2015; Schoenmakers et al., 2007; Shin et al., 2010; Vollstädt-Klein et al., 2012), but see: (Fernie et al., 2012; Field et al., 2005; Jones et al., 2018; Miller and Fillmore, 2011; Schoenmakers et al., 2008; Townshend and Duka, 2007; Wiers et al., 2017)). Additionally, in AUD patients, this measure of attentional capture by alcohol cues appears to "incubate" (*i.e.*, detection of targets in alcohol cued locations becomes increasingly faster) across abstinence (Rinck et al., 2018; Schoenmakers et al., 2010). In the modified color-naming Stroop interference task with words (Stroop, 1935), participants tend to be less accurate and/or slower to identify the color when alcohol-related words are used and this tends to be positively related to typical alcohol use ((Bauer and Cox, 1998; Cox et al., 2003, 2000, 1999; Duka et al., 2002; Fadardi and Cox, 2009, 2006; Field et al., 2013; Grant et al., 2007; Johnsen et al., 1994; Lusher et al., 2004; Modi et al., 2019; Murphy and Garavan, 2011; Ryan, 2002; Sharma et al., 2001; Snelleman et al., 2015; Stautz et al., 2017; Stetter et al., 1995, 1994; Stormark et al., 2000, 1997), but see: (Albery et al., 2015; Christiansen and Bloor, 2014; Duka and Townshend, 2004; Fridrici et al., 2013; Spanakis et al., 2019)) and may "incubate" with repeated cycles of withdrawal (Duka et al., 2002).

Visual attention capture by alcohol cues, across direct and indirect measures, tends to be more consistently related to differences in typical alcohol use than it is related to differences in AUD status, duration, and severity. However, direct and indirect measures of attentional capture by alcohol cues may be confounded by neurocognitive impairments among individuals with AUD (Beatty et al., 2000; Czapla et al., 2016; Loeber et al., 2010; Pitel et al., 2009; Romero-Martínez et al., 2018); for review see: (Bates et al., 2002)). Accounting for these neurocognitive impairments may be necessary in measuring attentional bias among individuals with AUD and when evaluating relationships between attentional bias scores and differences in AUD status, duration, and/or severity (Fadardi and Cox, 2006; Loeber et al., 2009).

4.2.1.2. Approach responses. The best evidence for or against the ability of alcohol cues to elicit skeletomotor behavioral manifestations of IS attribution (*viz.*, approach responses) in humans might be acquired by measuring beverage-directed approach movement initiation and its latency, time spent within proximity, postural changes, or skeletal muscle 'priming' following presentation of alcoholic beverages at a distance. Currently, the best available evidence comes from two computer-based tasks using visual proxies for alcoholic beverages and approach v. avoidance responses. The first task is a modified version of the Simon task (De Houwer et al., 2001) in which people use arrow keys to move a manikin toward or away from alcohol-related and control pictures presented on the computer screen (Field et al., 2005). On this task, people tend to be faster to respond when instructed to move the manikin toward rather than away from alcohol pictures ((Barkby et al., 2012; Christiansen et al., 2012; Field et al., 2011a, 2008, 2007, 2005; Pieters et al., 2012; Schoenmakers et al., 2008; van Hemel-Ruiter et al., 2011), but see: (Snelleman et al., 2015; Spruyt et al., 2013)), an alcohol approach bias that appears to be positively related to alcohol use level ((Barkby et al., 2012; Christiansen et al., 2012; Field et al., 2011a, 2008, 2005; Pieters et al., 2012), but see: (van Hemel-Ruiter et al., 2011)), and not AUD status (Barkby et al., 2012). The second task is a modified version of the Approach-Avoidance task (Chen and Bargh, 1999) in which participants use a joystick to pull (approach) or push (avoid) pictures of alcoholic and non-alcoholic beverages among other objects presented on the computer screen (Wiers et al., 2009). On this task, people tend to be faster to pull alcoholic beverage pictures toward themselves than they are to push them away (Eberl et al., 2013; Ernst et al., 2013; Fleming and Bartholow, 2014; Leeman et al., 2018; Loijen et al., 2018; Peeters et al., 2013, 2012; Sharbanee et al., 2014; Wiers et al., 2011, 2010, 2009, 2015b, 2014), an alcohol approach bias that appears to be positively related to alcohol use level and/or AUD status (Fleming and Bartholow, 2014; Peeters et al., 2013, 2012; Sharbanee et al., 2014; Wiers et al., 2017, 2014).

Arguably, there is a third measure of the approach response in humans. Some researchers have used the Implicit Association Task (IAT) (Greenwald et al., 1998) to assess how strongly the concept of "alcohol" (primed by words or pictures of different brands or types of alcoholic beverages) is linked to other concepts such as "active" (primed by words like 'energetic', 'lively', 'cheerful') or "positive" (primed by words like 'good', 'pleasant', 'nice') (Wiers et al., 2002) as well as "approach" (activated by words like 'approach', 'advance', 'closer')

(Palfai and Ostafin, 2003). In many cases, IAT scores have been found to be positively related to alcohol use levels ((Houben and Wiers, 2009; Jajodia and Earleywine, 2003; Ostafin and Marlatt, 2008; Ostafin and Palfai, 2006; Palfai and Ostafin, 2003; Wiers et al., 2017, 2002), but see: (Tibboel et al., 2015)). It is an open question, however, whether the IAT truly measures the same construct as the modified Simon Task and modified Approach-Avoidance Task described above (cf. (Wiers et al., 2017). Conceptually, it seems that the IAT might be more likely to reveal the structure of the implicit alcohol-associative memory network whereas the modified Simon Task and modified Approach-Avoidance Task might be more likely to detect expression (manifestation) of IS in human skeletomotor behavior.

4.2.1.3. Autonomic responses. Autonomic responses can be registered in many different physiological units including the activity of the cardiovascular system, hormone-secreting glands (*e.g.*, the adrenal glands, the pancreas), smooth muscle (*e.g.*, lining blood vessels or the gut), and the neurons that innervate them. For simplicity, we chose to review evidence from only a single physiological unit of analysis: heart rate. Heart rate is useful summary index of autonomic response because heart rate is sensitive to the interactive effects of many physiological processes including circulating hormones, nervous system activity, respiratory rate, and smooth muscle activity. Presentation of alcoholic beverages is able to elicit an increase in heart rate (measured as more beats per minute) that is sustained as the person performs the act of ingesting the presented beverage, but dissipates shortly thereafter (Kaplan et al., 1985; Newlin, 1986, 1985; Pomerleau et al., 1983; Staiger and White, 1991; Turkkan et al., 1988). The smell, the taste, and the sight of alcoholic beverages can also increase heart rate when presented in isolation from each other (*e.g.*, smell only, sight only) (McCaul et al., 1989; Payne et al., 1992; Stormark et al., 1995; Turkkan et al., 1989; Witteman et al., 2015). Increases in heart rate have also been observed following personalized alcohol use-related mental imagery (Seo et al., 2013; Sinha et al., 2009). The latter has also been demonstrated to produce greater increases in heart rate among people with AUD (Seo et al., 2013; Sinha et al., 2009) whereas *in vivo* exposure to alcoholic beverages can do so sometimes (Kaplan et al., 1985), but not others (Thomas et al., 2005). Presentation of alcoholic beverage sights or smells or tastes in isolation can raise heart rate to a greater extent in some people with AUD (Ingjaldsson et al., 2003; Stormark et al., 1995), but not all (McCaul et al., 1989; Turkkan et al., 1989). Presentation of alcohol-related words is able to increase heart rate to the same extent in people with and without AUD (Stormark et al., 2000).

4.2.1.4. Conscious craving/subjective experience of desire for alcohol.. The construct of craving has a long history in the study of alcoholism (Drummond, 2001; Edwards and Gross, 1976; Jellinek, 1960; Tiffany and Conklin, 2000). The ability of IS-attributed cues to provoke an explicit desire for alcohol is important not only because “strong urges, cravings, or desires to use alcohol” are now one of the diagnostic criteria for AUD (Diagnostic and statistical manual of mental disorders (DSM-5{®}), 2013), but also because the greater a person’s retrospective subjective experience of alcohol craving in daily life, the greater the number of alcohol-related problems and symptoms of AUD they are likely to be experiencing (Chakravorty et al., 2010; Murphy et al., 2014; Ray et al., 2017; Rohn et al., 2017; Yoon et al., 2006). Consequently, the development of cue-provoked craving for alcohol could be considered one of the earliest signs of alcohol cue ISS. In keeping, presentation of alcoholic beverages is able to provoke self-reported explicit desire for alcohol (*viz.*, conscious craving) measured using single-item visual analog scale or multi-item questionnaires (Amlung and MacKillop, 2014; Blaine et al., 2019; Cooney et al., 1984; Curtin et al., 2005; Field et al., 2005, 2004; Hollett et al., 2017; Kambouropoulos and Staiger, 2004; Kaplan et al., 1985; Kareken et al., 2010a; Kiefer et al., 2015; Kreusch et al., 2017; MacKillop, 2006; MacKillop et al., 2015; MacKillop and Lisman, 2008, 2005; Monti et al., 1987; Ostafin et al., 2008; Pomerleau et al., 1983; Ramirez et al., 2015a, 2015b; Rohsenow et al., 1994; Staiger and White, 1991; Willner et al., 1998). Isolated presentation of alcohol-related smells, tastes, and pictures or videos can also provoke craving ((Bragulat et al., 2008; Christiansen et al., 2017; Courtney et al., 2015; Fey et al., 2017; Field et al., 2007; Field and Eastwood, 2005; Filbey et al., 2008; Lovett et al., 2015; Lukas et al., 2013; Manchery et al., 2017; Mccusker and Brown, 1990; Oberlin et al., 2016, 2013; Ostafin et al., 2008; Payne et al., 1992; Pronk et al., 2015; Schneider et al., 2001; Stauffer et al., 2017; Stormark et al., 1995; Veilleux et al., 2018; Vollstädt-Klein et al., 2012; Witteman et al., 2015; Yoder et al., 2009), but see: (Mucha et al., 2000)) as can personalized alcohol use-related mental imagery (Blaine et al., 2019; Fox et al., 2007; Seo et al., 2013; Sinha et al., 2009).

In theory, as ISS progresses the magnitude of cue-provoked craving for alcohol should increase. In line with this prediction, presentation of alcoholic beverages can provoke greater craving among people with AUD compared to controls ((Pomerleau et al., 1983; Reid et al., 2006; Thomas et al., 2005) but see: (Kaplan et al., 1985; Monti et al., 1987)). People with AUD are also more likely than controls to report greater increases in craving following presentation of the isolated sight or smell or taste of alcoholic beverages (George et al., 2001; Ingjaldsson et al., 2003; Myrick et al., 2004; Reid et al., 2006; Schneider et al., 2001; Wiers et al., 2015c) and following exposure to personalized alcohol use-related mental imagery (Reid et al., 2006; Seo et al., 2013; Sinha et al., 2009). Among people without AUD, higher levels or more hazardous alcohol use also predict greater craving following presentations of actual beverages or pictures of them (Blaine et al., 2019; Curtin et al., 2005; Hollett et al., 2017; Lovett et al., 2015; Pronk et al., 2015; Stauffer et al., 2017; Veilleux et al., 2018). Furthermore, the magnitude of craving produced by alcohol’s interoceptive stimuli is also positively related to both alcohol use and AUD severity (Bujarski et al., 2018, 2017, 2015; Bujarski and Ray, 2014; Duka et al., 1999; King et al., 2016, 2014, 2011, 2002; Morean et al., 2013). Together, these findings suggest sensitization of exteroceptive and interoceptive alcohol cue-elicited craving responses. Finally, it also appears that the level of craving induced by at least exteroceptive alcohol cues can become elevated after at least 2 months of abstinence from alcohol, at least among people with AUD (Li et al., 2015; Monti et al., 1993a), which is in keeping with theorized state-dependent modulation of IS attribution and expression.

4.2.1.5. Cue as conditional reinforcer effects.. To our knowledge, currently there are no published reports of direct tests for the conditioned rewarding value of alcohol cues in humans (*i.e.*, alcohol cue-based reinforcement of a new instrumental response, alcohol cue-based reinforcement of a new cue), or even indirect tests such as measuring the extent to which an alcohol-associated cues can reinstate extinguished instrumental actions that previously produced alcohol reward. This precludes any investigation of whether conditional reinforcing value increases as a function of alcohol use level or AUD status, severity, and duration that would be predicted by ISST.

4.2.1.6. Pavlovian to instrumental transfer effects. In people, the alcohol-specific PIT construct developed in non-human animal models of alcohol seeking maps onto situations in which exposure to alcohol-predictive Pavlovian cues increases the likelihood of actions taken to acquire or consume alcoholic beverages. The increases in action likelihood are believed to be at least in part a consequence of cue-triggered Pavlovian alcohol seeking reactions. However, it is important to keep in mind that in non-human animal model paradigms, the subject is typically already in a place associated with alcohol availability, and the instrumental action to obtain or consume alcohol does not require the subject to leave that place. That is, the alcohol-specific PIT construct developed from the non-human animal models may only naturally apply to specific situations in which people may find

themselves. Nonetheless, there have been numerous demonstrations of the alcohol-specific PIT construct in the human laboratory. Instrumental responding for alcohol, measured as ingested alcohol volume or ingestion speed in bogus beverage evaluation tasks or number of alcohol beverage-earning responses in computerized tasks, has been shown to increase following isolated presentation of alcoholic beverage cues within specific sensory modalities (Field and Eastwood, 2005; Field and Jones, 2017; Hodgson et al., 1979; Martinovic et al., 2014; Roehrich and Goldman, 1995; Rose et al., 2018; Stein et al., 2000; Van Dyke and Fillmore, 2015), but see: (Carter and Tiffany, 1999; Field et al., 2007, 2005; Jones and Field, 2013; Kersbergen and Field, 2017; Stautz et al., 2017) as well as following presentation of alcoholic beverages and/or the interoceptive stimuli produced by ingestion ((Amlung and MacKillop, 2014; Bigelow et al., 1977; Blaine et al., 2019; Christiansen et al., 2017; Chutuape et al., 1994; Corbin et al., 2008; Farris and Ostafin, 2008; Fernie et al., 2012; Fromme and Dunn, 1992; Hodgson et al., 1979; Holdstock and de Wit, 1998; Johnson and Fromme, 1994; Larsen et al., 2012; Leeman et al., 2009; Ludwig et al., 1978, 1974; MacKillop and Lisman, 2005; Marlatt et al., 1973; Ostafin et al., 2008; Perkins et al., 2003; Rose and Duka, 2006; Stockwell et al., 1982; Wetherill and Fromme, 2009; Williams and Brown, 1985), but see: (Paredes et al., 1973)). In keeping with ISST, these PIT effects have been found to differ in magnitude based on AUD status ((Higgins and Marlatt, 1973; Hodgson et al., 1979; Ludwig et al., 1978; Marlatt et al., 1973; Stockwell et al., 1982), but see: (Bujarski et al., 2018)) as well as individual differences in typical alcohol use levels ((Blaine et al., 2019; Corbin et al., 2008; Leeman et al., 2009; Van Dyke and Fillmore, 2015), but see: (Kersbergen and Field, 2017; Martinovic et al., 2014)).

4.2.2. Alcohol cue-related brain responses

In most cases, functional brain responses to alcohol-related cues in people are measured using simple tasks that involve only repeated presentation of alcohol-related stimuli (*e.g.*, pictures). This allows for unambiguous interpretation of changes in measured brain activity. In part, the simplicity of tasks reflects the technical difficulty of non-invasively measuring activity in the living human brain.

4.2.2.1. Brain responses measured using the fMRI-BOLD technique. Behavioral responses to alcohol-associated cues, such as attentional bias and approach tendency, are theorized to be a downstream consequence of cue-induced activation of IS neurocircuitry components. Therefore, it is important to verify the ability of alcohol-associated cues to activate the IS attributor and expressors in the living human brain. Functional magnetic resonance imaging (fMRI) provides a way to visualize cue-induced neuronal activation or de-activation in specific areas of the living human brain using the regional blood oxygen level-dependent (BOLD) contrast imaging technique (Logothetis, 2003; Logothetis and Pfeuffer, 2004). As a previous meta-analysis showed (Schacht et al., 2013), using the fMRI-BOLD technique, alcohol cue-induced activation (*i.e.*, more positive BOLD signals) has been reported in the IS attributor, VTA complex, and the IS expressor systems, amygdala and nucleus accumbens, as well as in the medial and orbital prefrontal cortices, which are innervated by the IS attributor and inter-connected with the IS expressor systems. Specifically, activation has been reported in response to isolated alcohol cues presented in the following sensory modalities: sight (Ames et al., 2014a,b; Braus et al., 2001; Brumback et al., 2015; de Sousa Fernandes Perna et al., 2017; Fryer et al., 2013; Grüsser et al., 2004; Ihssen et al., 2011; Kim et al., 2014; Lee et al., 2013; Lukas et al., 2013; Nikolaou et al., 2013; Schad et al., 2018; Sekutowicz et al., 2019; Tapert et al., 2004; Vollstädt-Klein et al., 2010; Wiers et al., 2015c, 2014; Wrase et al., 2002), smell ((Kareken et al., 2004; Schneider et al., 2001) but see: (Lukas et al., 2013)), and taste (Claus et al., 2011; Courtney et al., 2015; Filbey et al., 2008; Oberlin et al., 2016), as well as their combinations ((George et al., 2001; Myrick et al., 2004), but see: (Bragulat et al., 2008)).

In keeping with an alcohol cue ISS mechanism, typical alcohol use levels and AUD status or severity tend to be positively related to the magnitude of BOLD signals during exposure to isolated alcohol-related sights (Ames et al., 2014a, 2014b; Braus et al., 2001; Brumback et al., 2015; Fryer et al., 2013; Grüsser et al., 2004; Heinz et al., 2004; Ihssen et al., 2011; Kim et al., 2014; Lee et al., 2013; Tapert et al., 2004; Wiers et al., 2015c, 2014); but see: (de Sousa Fernandes Perna et al., 2017; Oberlin et al., 2018; Schad et al., 2018; Vollstädt-Klein et al., 2010; Wiers et al., 2015c)), smells (Kareken et al., 2004; Schneider et al., 2001), and tastes (Claus et al., 2011; Courtney et al., 2015; Filbey et al., 2008) as well as their combinations (George et al., 2001; Myrick et al., 2004). In agreement with a previous meta-analysis (Schacht et al., 2013), we found that across studies, cue-induced BOLD in either the ventral striatum (*i.e.*, nucleus accumbens) or prefrontal cortices (esp. orbital and lateral) were the most frequently associated with clinical or drinking measures.

As mentioned in Section 2.2, many of the studies reviewed here reported a significant positive relationship between the level of activation induced by alcohol cues in a person's IS system (esp. amygdala, nucleus accumbens, and prefrontal cortical partners) and that person's self-report of the intensity of desire or craving for alcohol induced by those cues ((Filbey et al., 2008; Fryer et al., 2013; Myrick et al., 2004; Oberlin et al., 2016; Schacht et al., 2013; Tapert et al., 2004; Wiers et al., 2015c); but see: (Ames et al., 2014b; Grüsser et al., 2004; Kim et al., 2014)). Other studies reviewed here did not test the relationship, but implied it in describing their findings (Bragulat et al., 2008; Brumback et al., 2015; George et al., 2001; Heinz et al., 2004; Huang et al., 2018; Kareken et al., 2010b, 2010a, 2004; Lee et al., 2013; Lukas et al., 2013; Schneider et al., 2001; Seo et al., 2013; Vollstädt-Klein et al., 2010). To the extent that it reflects the transformation of "wanting" into a subjective feeling of wanting, then this relationship is important for the ability of ISST to explain changes in the subjective experience of reactivity to alcohol cues in AUD, and warrants further study.

4.2.2.2. Brain responses measured using the PET technique. Alcohol cue-induced activation measured using the fMRI BOLD technique in the brain structures we are referring to as the "IS expressors" could reflect something other than IS signal-related processing; for example, it could reflect processing of a signal from the motivational system involved in avoidance, aversion, and defensive responses. However, since the IS signal is theorized to be encoded by dopamine release from projections that originate in the VTA/SNc complex, one way to ensure that alcohol cue-induced activation of the IS expressors measured with fMRI *can* reflect IS signal-processing is to measure the IS signal generated upon presentation of said cues. In other words, researchers need to measure cue-induce dopamine release in the IS expressors in the living human brain. Positron emission tomography (PET) can reveal cue-induced neurochemical release in specific areas of the living human brain using radioactive ligands (Phelps and Mazziota, 1985). Using radioactive raclopride, a dopamine receptor antagonist, PET has been used to show cue-induced dopamine release in the ventral striatum as a decrease in raclopride binding potential, which contains the IS expressor system labeled "Accumbens" in Fig. 1, in response to the taste of alcohol (Oberlin et al., 2013). However, this does not appear to scale with alcohol use levels or AUD status or severity (Oberlin et al., 2013). It remains to be seen whether this null relationship will replicate in a larger sample or when more intense cues are presented (*i.e.*, combinations of alcohol sight, smell, and taste).

4.2.2.3. Brain responses measured using the EEG-ERP technique. Although both fMRI BOLD and PET inform us about which brain systems (at the circuit and biochemical levels) are engaged by alcohol-associated cues, they do not directly measure the neuronal response to those cues. The fMRI BOLD signal does not reflect neural activation directly but rather reflects changes in a complex

hemodynamic response that hinges upon neuro-vascular coupling *via* perivascular astrocytes (Shetty et al., 2012). The PET signal can reflect neurochemical release, but it is based on changes in binding of the radioactive tracer at both specific and non-specific binding sites, which may be present on both neuronal and non-neuronal cells (Phelps and Mazziota, 1985). Furthermore, both techniques measure biological signal variations that unfold over seconds (by design in fMRI or by signal-to-noise or tracer kinetics-based limitations in PET) rather than on the millisecond timescale of phasic neuronal activity (synaptic transmission) (Zoli et al., 1999). In contrast, the event-related potential (ERP) technique, derived from the scalp-recorded electroencephalogram (EEG), reflects the phasic activity across different neuronal populations following stimulus presentation (Luck and Kappenman, 2017). Studies using the ERP technique assure us that alcohol cue-related activation and dopamine release in nodes of the IS circuit using fMRI-BOLD and PET-raclopride, respectively, reflect alcohol cue-related activation of relevant *neuronal* populations in a variety of different stimulus presentation paradigms (Bailey and Bartholow, 2016; Bartholow et al., 2018, 2010; Dickter et al., 2014; Fleming and Bartholow, 2014; Herrmann et al., 2001; Kroczek et al., 2018; Martinovic et al., 2014; Martins et al., 2019; Petit et al., 2012; Ryerson et al., 2017; Shin et al., 2010).

In keeping with an alcohol cue ISS mechanism, alcohol use levels are positively related to the magnitude of various components in the ERP waveform (specifically, the P1, P2, N1, N2, P3, LPP, and FSW) elicited by alcohol-related visual stimuli in a variety of stimulus presentation paradigms ((Bailey and Bartholow, 2016; Bartholow et al., 2010, 2003; Fleming and Bartholow, 2014; Herrmann et al., 2001; Kroczek et al., 2018; Petit et al., 2012; Ryerson et al., 2017; Shin et al., 2010); but see: (Martinovic et al., 2014)). Less consistently, AUD status appears to be positively related to the magnitude of some of the ERP waveform components (*e.g.*, P3) elicited by alcohol-related visual stimuli ((Dickter et al., 2014; Matheus-Roth et al., 2016; Namkoong et al., 2004); but see: (Hansenne et al., 2003; Littel et al., 2013; Petit et al., 2015)), in keeping with meta-analytic findings across substance use disorders (Littel et al., 2012). Together, these findings suggest that alcohol use levels and AUD may increase neuronal communication related to attentional (P1, P2, N1) and affective or motivational (P3, LPP) processing of alcohol-related visual stimuli as well as the need to recruit additional cognitive control resources (N2, FSW) in order regulate behavior according to task demands in the presence of task-irrelevant alcohol-related stimuli.

4.2.3. On the origin of alcohol cue-related reactivity

The ISST holds that IS attribution transforms “cold” Pavlovian conditioned reward-predictive stimuli to “hot” Pavlovian conditioned reward-predictive stimuli that act as motivational “magnets” (Berridge et al., 2009; Berridge and Robinson, 2016, 2003; Robinson and Berridge, 2001, 2000, 1993). Thus, a critical feature of the application of ISST to alcohol is that reactivity to alcohol-predictive cues reflects Pavlovian (aka classical) conditioning-like associative learning processes. The vast majority of work in preclinical non-human animal models confirms that alcohol can serve as an unconditional stimulus for appetitive (and aversive) Pavlovian conditioning (*e.g.*, (Cofresí et al., 2019a; Cunningham et al., 2002a, 2002b; Krank, 2003; Krank et al., 2008; Srey et al., 2015)). However, it is important to establish, as best we can, that this is also true for people.

The idea that the ability of the stimulus features of alcoholic beverages to elicit attention and conscious craving for alcohol in people is due to naturally-occurring Pavlovian conditioning processes is supported by at least two controlled conditioning studies. In the first study (Field and Duka, 2002), the sight and smell of a beverage that contained a low dose of ethanol (0.2 g/kg or ≈ 10 mg/dL at 30 min post-ingestion) during training acquired the ability to elicit greater attention (measured as number of stimulus-directed gaze shifts using eye-tracking systems) and self-reported alcohol craving at test relative to the sight and smell of a beverage that did not contain ethanol during training. In the second study (Mayo and de Wit, 2016), pictures of the beverage that contained a moderate dose of ethanol (0.6 g/kg or ≈ 40 mg/dL at 30 min post-ingestion) during training acquired the ability to elicit greater attention (measured as number of stimulus-directed gaze shifts using eye-tracking systems) in a modified visual dot-probe task relative to pictures of the beverage that did not contain ethanol during training.

The idea that the ability of the stimulus features of alcoholic beverages can come to elicit autonomic state changes in people is due to naturally-occurring Pavlovian conditioning processes is supported by at least one controlled conditioning study. In this study (Staiger and White, 1988), the sight and smell of a beverage that contained a moderate dose of ethanol (0.5 g/kg or ≈ 30 mg/dL at 30 min post-ingestion) during training acquired the ability to elicit anticipatory increases in heart rate (an index of autonomics) at test relative to the sight and smell of a beverage that did not contain ethanol during training.

Some empirical support for the idea that alcohol-related stimuli elicit changes in regional brain activity in people is due to naturally-occurring Pavlovian conditioning processes can be derived from a study conducted by David Kareken and colleagues (Oberlin et al., 2018). An arbitrary neutral visual stimulus (a geometric shape) was repeatedly paired with alcohol (18 mg/dL per intravenous infusion), and consequently, it acquired the ability to elicit an expectation of subsequent alcohol infusion. This was revealed by the fact that presentation of the newly conditioned stimulus (in the absence of alcohol) produced statistically significant activation (positive fMRI BOLD contrast) in the frontoparietal, orbitofrontal networks, anterior cingulate, and insular cortices as well as sub-threshold activation in the ventral striatum. As discussed by Kareken and colleagues, the study boasts a much larger (n = 60) and better characterized sample than previous work (Kareken et al., 2012); thus, the conflicting findings in the latter were likely the result of type 1 error. However, two majors caveats apply to the (Oberlin et al., 2018) study: (1) the pattern of conditioned alcohol cue-elicited regional brain activity may reflect the particular demands of the decoy reaction time task (*i.e.*, goal-directed search for visual stimuli); and (2) the conditioned alcohol cue failed to produce detectable biases in attention as measured by reaction time (although, as the authors argue, their paradigm was designed to measure cue-related brain activity, not cue-related attentional biases). Despite these caveats, the (Oberlin et al., 2018) study provides the strongest direct evidence to date that ethanol can serve as a purely pharmacological unconditional stimulus that supports learning about antecedent conditional stimuli in humans.

4.3. Interim summary 2

In this section, we have reviewed evidence for attribution of IS to learned alcohol-predictive cues. We found that in humans and non-human animal models alike, alcohol-predictive cues are attributed with IS. Specifically, alcohol-predictive cues acquire the ability to: (1) elicit alcohol seeking reactions (*e.g.*, affective state change, attention, approach, and conscious craving for alcohol); (2) serve as conditional or secondary reinforcers (at least in non-human animal models) that can maintain reactivity in the absence of immediate primary reinforcement; (3) induce or invigorate instrumental alcohol seeking actions; and (4) engage the IS circuitry. We have also reviewed the evidence that alcohol cues undergo ISS. We found that in humans and non-human animal models alike, the amount of IS attributed to alcohol-predictive cues appears to increase as a function of alcohol involvement. Specifically, greater alcohol involvement makes alcohol-predictive cues able to: (1) elicit *higher* levels of alcohol seeking reactions; (2) *better* serve as conditional reinforcers (at least in non-human animals); (3) more *strongly* induce or invigorate instrumental alcohol seeking actions (at least in non-human animals); and (4) more strongly activate the IS circuitry (at least in humans). In humans, the in-the-moment intensity

of conscious craving for alcohol induced by alcohol cues appears to be positively related to the degree of activation these cues induce in the IS circuitry, especially the amygdala, ventral striatum (nucleus accumbens), and prefrontal cortices, a relationship requiring further study that is important for the ability of ISST to explain changes in the subjective experience of alcohol cue reactivity in AUD. Finally, given that the prefrontal cortices are believed to mediate cognitive control processes (Barbas, 2000; Braver, 2012; Inzlicht et al., 2015; Ridderinkhof, 2004), the present findings also suggest that incidental exposure to alcohol cues may impair on-going alcohol use-unrelated behavior and goal pursuit by drawing away attentional resources available to cognitive control processes or releasing inappropriate behavioral responses that create conflict and require the recruitment of additional cognitive control resources for successful completion of on-going behavior. These kinds of effects from incidental alcohol cues have been reported in human behavioral laboratory tasks (Fryer et al., 2013; Nikolaou et al., 2013; Sommer et al., 2017).

5. Discussion

5.1. General

Nona, Hendershot, and Lê (2018) recently reviewed the evidence for sensitized behavioral, physiological, and/or subjective responses to alcohol intoxication as a mechanism in AUD. In the present review, we set out to examine the evidence for sensitized IS attribution to alcohol-predictive cues (*viz.*, sensitized cue-triggered "wanting") as a neuropsychological mechanism in AUD. It is important to note that it remains an open question whether the construct of IS attribution developed in non-human animals truly exists in humans, and if so, whether it manifests in the same ways, undergoes sensitization, and affects subjective experience. The answers to these questions have implications for the ability of the ISST to explain important behavioral phenomena in alcohol addiction such as the progressive loss of control over use, use despite negative consequences, and the subjective experience of desire and craving including preoccupation with alcohol-related thoughts. It may turn out to be the case that ISST can explain the former, but not the latter. Our review cannot provide definite answers to these questions. Nevertheless, it indicates that across different units of analysis that may reflect manifestations of IS attribution in humans and non-human animals, the available evidence tends to be consistent with predictions for sensitized alcohol cue-triggered "wanting" (*viz.*, alcohol cue IS sensitization [ISS]) as a mechanism in AUD.

Many predictions for alcohol cue ISS as a mechanism in AUD remain underexamined across levels of biological organization in humans and non-human animals. Some underexamined predictions at the behavioral and neurobiological units of analysis are especially low-hanging fruit worth pointing out to researchers. First, to the extent that the IS attributor can be identified with dopamine cells in the VTA complex, alcohol-associated cues should be able to activate dopamine cells in the VTA complex of non-human animals, but we were unable to find direct evidence bearing on this prediction. Although, to the extent that the IS signal can be identified with cue-induced phasic dopamine release from dopamine terminals in the IS expressors, it should be noted that there is a growing body of evidence indicating that the IS signal can occur in the absence of IS attributor activation (Cachope and Cheer, 2014). Second, we do not know whether chronic ethanol exposure is able to shift the balance of excitatory and inhibitory drive or tone on those cells or their intrinsic excitability. Third, a systematic empirical exploration of chronic ethanol exposure profile parameter-dependent functional changes within and between IS system components that could mediate alcohol cue ISS is lacking. Fourth, IS-attributed alcohol cues are predicted to elicit changes in autonomic state that support alcohol seeking reactions and actions at the level of physiology. However, little to no attention has been paid to autonomics when modeling alcohol cue reactivity in non-human animals, and in humans, little attention has been paid to sensitization of cue-induced autonomic changes as a function of alcohol involvement. Fifth, IS-attributed alcohol cues are predicted to serve as secondary or conditional reinforcers that are able to maintain reactivity and behavior in the absence of immediate primary alcohol reinforcement (*i.e.*, post-ingestive psychopharmacology). There is substantial evidence from non-human animal models consistent with this prediction, but no systematic examination of how the level of ethanol exposure determines the degree to which alcohol cues serve as secondary reinforcers for alcohol seeking. This is an important, if underappreciated, behavioral function of IS-attributed cues because it is theorized to mediate the persistence of alcohol cue reactivity. Despite the relevance of this particular property to AUD treatment and relapse, we were unable to find any studies examining the conditioned reinforcing property of alcohol-associated cues in humans. Sixth, given the multitude of different behavioral and brain measures collected as putative indicators of IS attribution and/or advanced as reflecting ISS in humans, factor analytic work is warranted to test which of these measures load onto the same latent construct as well as to determine which measures are the most reliable and/or valid indicators of that construct (Wardle et al., 2018).

It is important to note that gender/sex differences continue to emerge for the acute effects of alcohol and its cues in the human laboratory model literature (Bates et al., 2011; Chaplin et al., 2008; Hartwell and Ray, 2013; Kaplan et al., 1985; Rubonis et al., 1994; Udo et al., 2009). Yet female organisms are often absent in studies from preclinical non-human animal model literature. Although this omission is being addressed, much work is ahead for preclinical researchers working with non-human animal models. Once the omission has been corrected, a thorough examination of potential gender/sex differences in ISST-derived predictions for this unique etiological pathway to AUD may be conducted in the vein of (Barker and Taylor, 2017).

A major issue worth raising is that the degree to which 'natural' alcohol cues (*e.g.*, the sight, smell, and taste of the preferred alcoholic beverage) in humans operate like the conditioned alcohol cues studied in human and non-human animal laboratory models remains to be established. This is an important issue for the applicability and translation of ISST into a unique etiological pathway for AUD (and more broadly, for SUD). ISST addresses a psychological property (IS) that may or may not be attributed to learned conditional predictive stimuli for unconditional rewarding stimuli including drugs of abuse such as alcohol. However, not much attention has been paid to the ability of alcohol to serve as a pharmacological unconditional stimulus (US) for conditional stimulus (CS) or 'cue' learning in humans. Our literature review identified only a handful of controlled alcohol cue conditioning studies in humans, each using different administration procedures, different conditioning parameters, and different measures of cue reactivity. Consequently, more controlled conditioning studies are warranted, especially within-subject studies comparing 'artificial' alcohol cues conditioned in the human laboratory to 'natural' alcohol cues that were putatively conditioned over the person's alcohol use history.

A related issue is that if 'natural' alcohol cues are truly conditioned over a person's alcohol use history, then these cues are conditioned within specific emotional, physical, social, and temporal contexts. The natural contexts for alcohol use, and thus, the contexts in which 'natural' cues are conditioned, are difficult to simulate in the human laboratory. Thus, a major caveat applies to human laboratory studies, especially those using functional neuroimaging techniques, which involve the use of equipment—and supine body posture (Harmon-Jones and Peterson, 2009; Price and Harmon-Jones, 2011)–that in many cases opposes any degree of natural physical and motivational context. These studies are typically done in a context that has never been associated with alcohol use, and often explicitly signal the non-availability of alcohol to participants. This experimental setting confounds the interpretation of negative results. In order to study reactivity to 'natural' alcohol cues in their 'natural' contexts, researchers should consider the combined use of ambulatory assessment and mobile human

neuroimaging technology.

A final consideration for evaluating the model-derived predicted relationship between IS attribution and alcohol involvement in humans is that the latter has multiple causes and functions. Additionally, there may be other liability factors that moderate the magnitude of association between and within individuals. Some individuals may be more vulnerable than others to ISS as a pathway to AUD, and samples that contain more of these individuals may show stronger sample-level evidence for alcohol cue ISS.

5.2. Alcohol subjective response (ASR) may moderate AUD risk via alcohol cue ISS pathway

One trait-like liability factor that strongly moderates risk for AUD, alcohol subjective response (ASR) phenotype, may do so by conferring differential vulnerability to ISS as a pathway to AUD. We introduce ASR phenotype and discuss evidence in favor of this idea below.

5.2.1. The link between alcohol subjective response (ASR) phenotype and risks for AUD

The subjective experience of alcohol's pharmacological effects primarily can be ascribed to two factors. The first, pharmacokinetics, refers to factors that determine the amount of alcohol circulating through the body at any given point in time following ingestion. Variation in pharmacokinetic factors can be due to both state (*e.g.*, amount of food in the stomach, dehydration, other drugs in circulation, acquired metabolic tolerance) and trait factors (*e.g.*, baseline expression level and activity profiles of alcohol-metabolizing enzymes) as well as ingestion route and rate (Cederbaum, 2012). The second, pharmacodynamics, refers to factors that determine the biochemical and physiological effects of alcohol. Variation in pharmacodynamic factors can be due to both state (*e.g.*, current level of certain hormones, other drugs in circulation) and trait factors (*e.g.*, baseline activity level and dynamics in certain brain circuits) (Brown et al., 2007; Haughey et al., 2008; Sharko et al., 2016, 2013; Yoder et al., 2005).

In humans, the subjective experience of alcohol's pharmacological effects, *i.e.*, the construct of a subjective response to alcohol as a pharmacological stimulus, can be summarized along 3–4 dimensions, some of which appear to develop over the course of a person's drinking history, *viz.*, as the person gains experience with alcohol as a pharmacological stimulus (Bujarski et al., 2015; Ray et al., 2009). Importantly, even after controlling for inter-individual variation in pharmacokinetics, there is considerable inter-individual variation in self-reported subjective response to the pharmacological effects of alcohol (Bujarski et al., 2015; Gilman et al., 2012; Ray et al., 2007).

There are at least two broadly defined alcohol subjective response (ASR) phenotypes. Specifically, some individuals may have (an initially) low level of subjective response (LLR)—they recollect having required more drinks to feel any effect, dizziness, or stumbling than other individuals in questionnaire-based studies (Schuckit et al., 1997). Similarly, some individuals appear to be less sensitive to alcohol's sedative-like properties yet more sensitive to its stimulant-like properties (LSedHStim)—they feel less "down" or "sluggish" or "slow thoughts" and more "excited" or "excited" or "up" than other individuals after equivalent alcohol doses in controlled laboratory studies (Davidson et al., 2002; Holdstock and de Wit, 1998; King et al., 2002; Martin et al., 1993; Newlin and Thomson, 1990; Rueger et al., 2009; Rueger and King, 2013) Given differences in how these groups of individuals (LLR *versus* HLR and LSedHStim *versus* HSedLStim) were identified, it remains to be seen whether they stem from different or overlapping subpopulations. However, we can tentatively treat LLR and LSedHStim individuals as belonging to one population—the low sensitivity (LS) ASR phenotype population—and HLR and HSedLStim individuals as belonging a different population—the high sensitivity (HS) ASR phenotype population.

The LS ASR phenotypes confer risk for AUD that the HS ASR phenotypes do not (Morean and Corbin, 2010; Quinn and Fromme, 2011). LS individuals present more AUD symptoms than HS individuals (Bartholow et al., 2010; Fleming and Bartholow, 2014; King et al., 2016, 2014). LS individuals tend to drink more frequently, more heavily, and more hazardously than HS individuals (Bartholow et al., 2010; Fleming and Bartholow, 2014; Hinckers et al., 2006; King et al., 2011, 2002; Schuckit et al., 2005; Shin et al., 2010). Compared to HS individuals, LS individuals are also more likely to experience negative legal, social, and occupational consequences of alcohol use (Bartholow et al., 2010; Fleming and Bartholow, 2014; Schuckit et al., 2017, 2005; Schuckit and Smith, 2006). LS individuals are more likely to experience hangovers than HS individuals, but only because LS individuals drink much more—in fact, they are less likely to experience hangover per unit alcohol (Piasecki et al., 2012). Similarly, LS women are more likely to report regretted sexual activity than HS individuals, but only because LS women drink much more—in fact, they are less likely to report regretted sexual activity per unit alcohol (Hone et al., 2017). The unique risk for AUD conferred by LS ASR phenotype may be at least in part explained by ISST/alcohol cue ISS. The rest of the unique risk conferred by LS ASR phenotype might relate to other psychological mechanisms such as heavy drinking-induced adaptations in the motivations for alcohol use (Cooper et al., 1995) and self-selection into heavy drinking environments and social groups (Schuckit, 1998; Schuckit and Smith, 2000).

To the extent that ASR phenotype is inherited, it may be a cause, rather than consequence, of heavy alcohol use. Twin studies have estimated that its heritability is 0.60 (Heath et al., 1999; Heath and Martin, 1991; Viken et al., 2003). ASR phenotype has also been shown to be relatively stable within individuals (King et al., 2016, 2014). However, there is also evidence for some degree of change in phenotype within individuals (King et al., 2016; Morean and Corbin, 2008), perhaps as a function developmental stage-related changes in alcohol involvement.

5.2.2. The link between ASR phenotype and the alcohol cue ISS pathway to AUD

The biases in attention and approach tendency predicted by ISST applied to alcohol and observed in heavy drinking individuals and individuals with AUD may be a function of ASR phenotype. In keeping with this idea, compared with HS individuals, LS individuals exhibit faster reaction times to alcohol cued locations in the modified dot-probe task controlling for past 30 day alcohol use (Shin et al., 2010). Similarly, LS individuals exhibit greater implicit alcohol approach tendency as measured by the alcohol AAT as well as faster reaction times to alcohol-cued targets in the Cued Go/NoGo Task (CGNT) compared to HS individuals (Fleming and Bartholow, 2014). Unlike HS individuals, LS individuals exhibited lower accuracy on response inhibition (NoGo) probe trials in the CGNT when the cue was an alcoholic beverage image relative to a neutral image, indicating that LS individuals were less able to inhibit pre-potent Go responses in the face of an alcohol cue (Fleming and Bartholow, 2014).

LS individuals also appear to be more susceptible to increases in conscious alcohol craving elicited by real-world drinking-associated contexts (*e.g.*, time of day, weekend, bar/restaurant location, recent tobacco use) than HS individuals (Trela et al., 2018). This may help explain why LS individuals tend to drink more frequently than HS individuals. More hazardous alcohol use patterns among LS individuals may be explained by the fact that these individuals tend to "drink too much, too fast" in their drinking episodes than HS individuals (Trela et al., 2016). It is also likely that "overdrinking," *i.e.*, drinking more than intended (Bishop and Rodriquez Orjuela, 2018), may be more frequent among LS individuals, although this remains to be determined.

The exaggerated brain response to alcohol cues predicted by ISST applied to alcohol and observed in heavy drinking individuals and individuals with AUD may be a function of ASR phenotype. In the modified dot-probe task, LS individuals exhibit larger amplitude P1,

indicating greater early attentional orienting, and a smaller amplitude IIN (ipsilateral invalid negativity), indicating lower attentional re-orienting (away from alcohol-cued locations), than HS individuals (Shin et al., 2010). Unlike HS individuals, LS individuals also exhibit a larger amplitude P3 to pictures of alcoholic beverages than to pictures of other beverages and/or neutral objects in visual categorization and evaluation tasks (Bartholow et al., 2010; Martins et al., 2019), putatively indicating that, at the level of neural processing, alcohol cues were evaluated as having greater affective/motivational significance. Additionally, in the CGNT, in the few response inhibition probe trials on which LS individuals *were* able to inhibit pre-potent Go response in the face of an alcohol cue, LS individuals exhibited larger amplitude N2, indicating increased stimulus-related conflict, and larger amplitude P3, indicating that more processing was necessary to successfully inhibit the pre-potent Go response in the face of an alcohol cue, relative to HS individuals (Fleming and Bartholow, 2014).

Work in non-human animals provides additional support for the idea that individual differences in sensitivity to alcohol intoxication are linked to individual differences in sensitivity to the appetitive conditioning effects of alcohol, and thus, increased susceptibility to alcohol cue ISS. Rodents bred for LS-like phenotypes tend to be more sensitive to the appetitive conditioning effects of alcohol (Beckstead and Phillips, 2009; Crabbe et al., 1992; Fish et al., 2012; Risinger et al., 1994; Shen et al., 1995), but see: (Files et al., 1996; Sanchez et al., 1996)). Similarly, rodents bred for greater sensitivity to some of the appetitive conditioning effects of alcohol tend to be more sensitive to its other appetitive conditioning effects ((Ciccocioppo et al., 2001, 1999; Murphy et al., 1989; Oster et al., 2006; Toalston et al., 2008), but see: (Stewart et al., 1996)), and more importantly, tend to exhibit LS-like phenotypes (Agabio et al., 2001; Colombo et al., 1998; Murphy et al., 2002; Päivärinta and Korpi, 1993; Waller et al., 1986). There is also some support for this covariation in rodent populations that were not selected for one trait or the other ((Chappell and Weiner, 2008; Spuhler and Deitrich, 1984), but see: (Gauvin et al., 1993; Khanna et al., 1990)). More extensive testing of this covariation is warranted in non-human animals, especially using paradigms that measure different facets of IS attribution to alcohol cues. Additionally, there is uncertainty about the degree to which LS-like phenotypes in non-human animals can model human LS phenotypes given that the latter are defined in terms of subjective responses to alcohol as opposed to objective responses that can be measured across species (Crabbe et al., 2010). Nevertheless, the available evidence from non-human animals is consistent with a link between ASR phenotype (at least its inherited/genetic component) and susceptibility to alcohol cue ISS.

Together, these pieces of evidence suggest that LS individuals may be more susceptible to alcohol cue ISS than HS individuals. However, more work is warranted to test this hypothesis. There are at least three ways in which LS ASR phenotype, alcohol ISS, and AUD could be interrelated. First, LS ASR phenotype may be the overt manifestation of a neurobiological endophenotype that is a trait marker for vulnerability to ISS as a pathway to AUD (or addictions, in general). Second, LS ASR phenotypes foster heavy alcohol use, and heavy alcohol use can induce alcohol cue ISS, such that alcohol cue ISS is a downstream consequence of LS ASR phenotype. Third, a combination of the former two. Prospective studies are needed to tease apart these possibilities.

5.3. Treatment implications of alcohol cue ISS as a pathway to AUD

Alcohol cue ISS has implications for certain approaches to treatment and more generally, for treatment outcomes, especially relapse. These implications underscore the need for further investigation of this unique etiological pathway in both humans and non-human animal models.

5.3.1. Post-treatment susceptibility to alcohol cue-related risk for lapses and relapse to AUD

It is highly unlikely that alcohol cue ISS accounts for all cases of ineffective AUD treatment. However, individuals who undergo alcohol cue ISS may comprise a large proportion of the population of people who relapse more quickly or more frequently after treatment. There are 2 lines of evidence supporting this idea. First, the higher levels of cue reactivity among individuals suffering from AUD (reviewed earlier). Second, the role of cue reactivity in post-AUD treatment lapse/relapse rates.

Post-treatment recovery/relapse rates are strongly determined by alcohol-related cues in at least two ways (Marlatt, 1996). First, individuals with AUD may have learned to cope with stress related to environmental demands (*e.g.*, accidents, evaluations, financial difficulty, interpersonal conflict, social pressure) by using alcohol. The negative feelings induced by these stressors may become conditioned as alcohol-predictive cues in some individuals (Hogarth and Hardy, 2018; Litt et al., 1990; Rubonis et al., 1994; Stasiewicz et al., 1997; VanderVeen et al., 2016). Second, individuals with AUD may encounter alcohol-predictive cues in their everyday environments (*e.g.*, hidden bottles, passing by a bar, alcoholic beverage advertising, drinking buddies). Cue-triggered behavioral and physiological reactivity levels (*e.g.*, attentional bias, brain circuit activation, heart rate, salivation) measured at treatment time can predict subsequent lapses to drinking and relapse to AUD (Braus et al., 2001; Cox et al., 2002; Garland et al., 2012b; Grüsser et al., 2004; Papachristou et al., 2014; Rohsenow et al., 1994), but see (Snelleman et al., 2015). Given the possibility that alcohol cue ISS entails exaggerated cue-triggered Pavlovian alcohol seeking reactions, individuals that underwent this pathway to AUD may be driving the relationship between alcohol cue reactivity and post-treatment lapse/relapse rate.

One way in which treatment may leave individuals vulnerable to the situational re/lapse-risk that cue reactivity creates is that many psychosocial treatment options do not directly address or attempt to reduce cue reactivity, and those that do have limited efficacy. A second way in which this alcohol cue reactivity-based vulnerability may persist is that existing pharmacological treatment options alone may or may not be able to reverse the neuroadaptations that mediate alcohol ISS.

5.3.2. Response to behavioral treatments for alcohol cue-elicited reactivity

Broadly speaking, there are two behavioral treatments for AUD that aim to reduce reactivity to alcohol cues and thereby reduce relapse rates. The first, older treatment is cue exposure therapy (CET). In CET for AUD, individuals are repeatedly presented with the sights, smells, sounds, and tastes experienced during alcohol use without subsequent ingestion and/or intoxication until these cues cease to elicit behavioral, physiological, and/or subjective (craving) reactions (Monti et al., 1993b; Monti and Rohsenow, 2003; Rankin et al., 1983; Vollstädt-Klein et al., 2011). Importantly, decreased drinking and reduced AUD relapse rates have been reported following use of CET as either an adjunct to standard treatment or as a stand-alone treatment (Drummond and Glautier, 1994; Loeber et al., 2006; Monti et al., 2001, 1993b; Rohsenow et al., 2001). The second, more recently developed treatment is cognitive bias modification (CBM). This family of interventions uses modified versions of behavioral tasks typically used to measure alcohol cue-elicited attentional capture and approach tendency—as well as modified versions of tasks used to measure implicit or explicit attitudes toward alcohol and its cues, *viz.*, "liking" responses—to train the opposite behavioral response to the same cues (Wiers et al., 2013). It works: attentional capture and approach tendency are found to be reduced and/or replaced with attentional disengagement and avoidance tendency, respectively, at least immediately after CBM (Eberl et al., 2013; Fadardi and Cox, 2009; Field et al., 2007; Field and Eastwood, 2005; Rinck et al., 2018; Schoenmakers et al., 2010, 2007; Wiers et al., 2011, 2010). Importantly, decreased drinking and reduced AUD relapse rates have been reported following use of CBM as an adjunct to

standard treatment (Cox et al., 2015; Eberl et al., 2013; Rinck et al., 2018; Schoenmakers et al., 2010; Wiers et al., 2015a, 2011).

It would thus seem that two exceptionally effective treatments are available against alcohol cue reactivity. Unfortunately, this is not the case. The treatments do work, but not as well as clinicians, patients, and researchers might like. Recent meta-analyses across existing randomized clinical trials have indicated that CET (Mellentin et al., 2017) and CBM (Boffo et al., 2019) alike have at best a small effect of unknown reliability on AUD treatment outcomes. One explanation for this state of affairs is that even when CET and CBM are successful in reducing alcohol cue reactivity measured in the treatment setting, people may remain at risk for the return of alcohol cue reactivity in their natural environment due to constraints inherent to the learning and memory process on which they both rely.

Although some researchers might see CET and CBM as strikingly different approaches to reducing conditioned cue reactivity, their limited clinical effects likely stem from a shared reliance on training new (alternative) responses to cues for which associations already exist in long-term memory. CBM effects are believed to reflect, at least in part, the training of a specific alternative response to a previously conditioned cue: a response in the opposite direction than the previously-reinforced response (Wiers et al., 2013). Similarly, despite concerns about procedural differences between CET and the non-human animal learning paradigms that inspired it (Conklin and Tiffany, 2002), CET effects may reflect, at least in part, the training a specific alternative response to a previously conditioned cue: omission of the previously-reinforced response (Colwill, 1991; Rescorla, 1997, 1993). Nevertheless, studies of non-human animals in which a response is first conditioned to a cue, and then "treated" by training the animal to omit or suppress that response have shown unequivocally that the original cue reactivity can and does readily reemerge after seemingly successful "treatment." This is evidenced by the post-"treatment" return of reactivity phenomena known as spontaneous recovery and cue-induced reinstatement (Bouton and Bolles, 1979a, 1979b; Rescorla and Heth, 1975; Robbins, 1990). With the exception of context (place cue)-induced reinstatement (Pitchers et al., 2017; Saunders et al., 2014), these relapse-like effects are especially pronounced with IS-attributed cues in non-human animals (Saunders et al., 2013; Saunders and Robinson, 2011; Yager et al., 2015; Yager and Robinson, 2015, 2013, 2010). The rate of reduction of alcohol cue reactivity within- and between-"treatment" sessions, and the size of post-"treatment" relapse-like return of reactivity phenomena, are likely to be a function of how much ISS has taken place. In part, this may be because more ISS means that IS-attributed cues provide greater conditional reinforcing value, a property of IS that may make it difficult for some individuals to distinguish reinforcement from non-reinforcement of the original cue associations—something which has been demonstrated in non-human animals (Ahrens et al., 2016)—precluding subsequent reinforcement of alternative responses to the cue. Despite these limitations, it is people who progressed to AUD *via* alcohol cue ISS who may derive the most clinical benefit, at least in the long run, from CBM and CET since reductions in alcohol cue reactivity may be irrelevant to recovery from AUD in people who progressed to AUD *via* other etiological pathways.

Finally, it is worth mentioning that overcoming these limitations is the focus of an active area of research. Work in this area suggests that it may be possible to enhance within-session therapeutic learning for both CBM and CET using transcranial stimulation of the prefrontal cortices (den Uyl et al., 2018, 2017, 2016; Wietschorke et al., 2016) or acute pharmacological augmentation of memory consolidation (Kiefer et al., 2015; MacKillop et al., 2015). Additionally, it may be possible to harness a period of memory lability induced by memory retrieval—the so-called memory reconsolidation window (Nader and Einarsson, 2010; Nader and Hardt, 2007)—to alter or "erase" alcohol cue reactivity by interfering with or disrupting its neurobiological substrates using pharmacological tools (*e.g.*, in non-human animal models: (Barak et al., 2013; Milton et al., 2012; Schramm et al., 2016; von der Goltz et al., 2009); initial evidence in humans: (Das et al., 2018). It may also be possible to "update" alcohol cues to a lower level of IS simply by deploying therapeutic learning during the memory reconsolidation window (*e.g.*, in non-human animal models: (Cofresí et al., 2017); initial evidence in humans: (Das et al., 2015; Hon et al., 2016)).

5.3.3. Response to pharmacological treatments attempting to dampen alcohol craving

To the extent that the subjective experience of craving for alcohol (*viz.*, a strong explicit desire or urge to drink, perceived difficulty in resisting a drink if it were offered) is a core symptom of AUD and/or an important factor in lapse/relapse to AUD, medications that attempt to dampen the subjective experience of craving for alcohol among individuals with AUD (for review, see: (Haass-Koffler et al., 2014)) can play a critical role in harm reduction approaches to management of AUD among non-treatment seeking individuals as well as supporting behavior change and psychosocial treatment engagement among treatment-seeking individuals. In short, anti-craving medications can improve and/or save lives. Among these medications are several pharmaceuticals already approved for AUD treatment (*e.g.*, acamprosate, naltrexone), some pharmaceuticals that are used off-label for AUD treatment (*e.g.*, fluoxetine, bupropion), and others at earlier stages of the medication development pipeline (*e.g.*, aripiprazole).

Given diverse mechanisms of action, different anti-craving medications may differentially disrupt subjective experiences of craving arising from the two IS system pathways to craving (Fig. 1: paths [i] and [j]). Alcohol use-related obsessive or intrusive thoughts or desires may reflect hyperactivity in either the indirect path (i) and/or the direct path to craving (j), and anti-craving medications may decrease the level of activity in these IS system pathways such that craving is not experienced. In this light, it might be tempting to see anti-craving medications as the pharmaceutical equivalent to behavioral treatments like CET and CBM. That is, it may be tempting to conceptualize the anti-craving effects of these pharmaceuticals as "response prevention" or "response modification." Indeed, acutely or chronically disrupting activity in pathways (i) and (j) may prevent alcohol use that would have otherwise occurred as a response to conscious craving for alcohol. However, implicit alcohol "wanting" (Fig. 1: paths [f], [f.1], [f.2], and [h]) may still impel alcohol seeking and drinking behaviors in certain contexts despite the absence of conscious craving for alcohol and/or in spite of conscious intentions to abstain from or moderate alcohol use. Moreover, the subjective experience of craving may most often arise from brain systems other than the IS system, such as those involved in mediating non-automatic appraisal/evaluation processes that operate at the level of consciousness. Craving originating in these systems may be entirely unamenable to acute or chronic disruption of IS system activity. Moreover, to the extent that certain brain systems are in place to gate the direct and indirect IS system pathways to craving, then in some individuals alcohol-related obsessive or intrusive thoughts may arise not from hyperactivity in IS system pathways, but rather from hypoactivity at the gates. Amplifying activity at the gates may require medications that attempt to boost or restore activity in high-level executive function and response control-related brain systems. Nevertheless, to the extent that currently available and future anti-craving medications facilitate reductions in the intensity and/or frequency of alcohol exposure, they may be able to arrest the progression of alcohol cue ISS and begin to reverse its underlying neuroadaptations. In doing so, they may help treat a potential substrate for pathological craving and preoccupation with alcohol. Thus, the efficacy of anti-craving medications and their ultimate clinical benefit may be greater among individuals who have progressed to AUD *via* alcohol cue ISS.

5.4. Conclusion

There is sufficient empirical evidence to support the idea that the mechanism originally outlined in the incentive salience sensitization

theory of addiction (ISST) (Robinson and Berridge, 1993) may be at the core of alcohol use disorder (AUD) etiology for some individuals. Throughout this review article we have referred to this etiological pathway as "alcohol cue ISS" to emphasize that it is the motivational significance and behavioral impact of alcohol-predictive cues that is predicted to undergo sensitization, *not* the hedonic response to alcohol ingestion. In other words, the mechanism of ISS involves sensitization of alcohol "wanting," *not* "liking." Susceptibility to this etiological pathway may be moderated by individual differences on traits such as differential sensitivity to alcohol ingestion-induced feelings stimulation v. sedation. Individuals who have undergone this etiological pathway may find themselves especially at risk for cue reactivity-based relapse to AUD after treatment. In general, there is need for continued investigation of ISST-predicted mechanisms, across units of analysis, in the development of disordered alcohol use.

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Declaration of Competing Interest

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