

# Alcohol and the Brain: Neuronal Molecular Targets, Synapses, and Circuits

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Ethanol is one of the most commonly abused drugs. Although environmental and genetic factors contribute to the etiology of alcohol use disorders, it is ethanol's actions in the brain that explain (1) acute ethanol-related behavioral changes, such as stimulant followed by depressant effects, and (2) chronic changes in behavior, including escalated use, tolerance, compulsive seeking, and dependence. Our knowledge of ethanol use and abuse thus relies on understanding its effects on the brain. Scientists have employed both bottom-up and top-down approaches, building from molecular targets to behavioral analyses and vice versa, respectively. This review highlights current progress in the field, focusing on recent and emerging molecular, cellular, and circuit effects of the drug that impact ethanol-related behaviors. The focus of the field is now on pinpointing which molecular effects in specific neurons within a brain region contribute to behavioral changes across the course of acute and chronic ethanol exposure.

Humans consume and abuse ethanol, and thus understanding ethanol's effects on the nervous system necessarily involves knowing the pharmacology of the drug. This two-carbon molecule is only able to interact with other biomolecules via hydrogen bonding and weak hydrophobic interactions, limiting its potency. Thus, it is no surprise that ethanol has a reputation as a nonspecific drug. Indeed, ethanol's effects on brain function mainly occur across a range from the low millimolar range to 100 mM in naive and occasional users. Ethanol's effects at doses that produce blood ethanol concentrations (BECs) of ~28 mg/dL (~6 mM) can be reliably distinguished in humans and animals (Ando, 1975; Schechter, 1980). Acute intoxication grows progressively stronger as BECs rise to higher levels associated with anxiolytic and euphoric effects (~12 mM) and legal intoxication (~18 mM), where slowed reaction times, motor incoordination, and cognitive impairment occur. At concentrations up to 50 mM, locomotor disruption, cognitive impairment, and sedation escalate. Above this level, strong sedation and respiratory depression can lead to coma or death (Alifimoff et al., 1989). According to the 2015 National Survey on Drug Use and Health (NSDUH), injuries and fatalities due to acute intoxication (including toxicity due to respiratory depression), accidents, violence, and traffic fatalities affect tens of thousands of people (Bose et al., 2016; Mokdad et al., 2004).

Chronic ethanol exposure and alcohol use disorder (AUD) have an even greater negative impact on society, including failed relationships, loss of employment, psychiatric symptoms, overt neurotoxicity, liver failure, and severe cognitive disruption (Bose et al., 2016). These chronic problems consume considerable resources for psychiatric care, organ transplants, and long-term medical treatment. As tolerance to the acute effects of ethanol develops, humans can survive with BECs up to 8 times those that would kill an ethanol-naive person. Indeed,

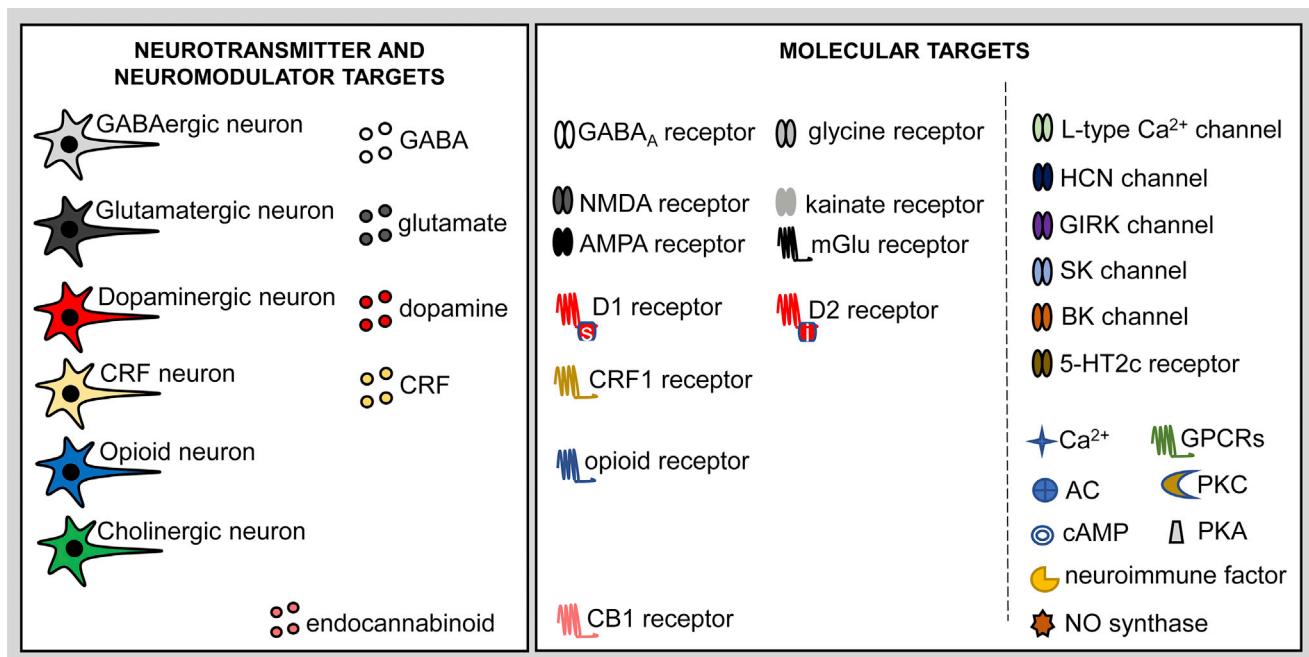
awake individuals with blood concentrations near 300 mM have been reported (Johnson et al., 1982). Overall, the global consequences of AUD include 3.3 million annual deaths (5.9% of all deaths) and 5.1% of the burden of disease and injury, with an economic burden of ~\$250 billion annually in the United States (WHO, 2014; Sacks et al., 2015). Given this huge societal impact, the US Surgeon General recently issued a first of its kind report, "Facing Addiction in America: The Surgeon General's Report on Alcohol, Drugs, and Health," highlighting alcoholism and addiction (US DHHS, 2016). Thus, a review of the current state of knowledge about ethanol effects on the brain is warranted.

In light of this large societal impact, the field seeks to understand how ethanol alters brain function across a range of concentrations and time frames/phases of drinking. Indeed, several phenotypic phases of ethanol consumption and AUD that occur over weeks to years have been proposed (Koob and Volkow, 2016). We will focus on the latest findings from neurobiological studies examining acute and chronic ethanol effects on the brain, with emphasis on neuronal molecules, synapses, and brain circuits with important roles in behavioral effects of the drug. The entire scope of the neural actions of ethanol cannot be covered in this limited format (unfortunately including topics such as fetal alcohol effects, ethanol effects on glia, neuroinflammatory mechanisms, and extracellular matrix), but references for some topics are provided to allow the reader to gain a deeper understanding of the field.

## A Multi-level, Integrative Analysis of Ethanol's Effects on the Nervous System: Bottom-Up and Top-Down Approaches to Finding Ethanol Targets

Ethanol distribution in the body and brain is similar to water, with equilibration throughout organs and cells within a few minutes of drinking. This property contributed to the idea that





**Figure 1. Neurotransmitter/Modulator Systems and Molecular Targets of Ethanol**  
The symbols and definitions shown here are used in Figures 2 and 3.

many of ethanol's effects involve its occupation of water-filled cavities in proteins and subsequent alteration of function. Considering the ubiquity of distribution and low drug potency, ethanol acts on numerous molecular targets in neurons and synapses throughout the brain. This lack of specificity can be daunting to those who study potent and specific drugs, including drugs of abuse with circumscribed primary molecular targets (e.g., opiates). However, even these target-specific drugs produce complex secondary neuroadaptations that contribute to drug use disorders. It is worth noting that the function of many molecules in mammalian neurons appears to be remarkably insensitive to ethanol (Yamakura et al., 2001). Thus, earlier ideas about ubiquitous molecular effects due to changes in membrane fluidity are not helpful in understanding how ethanol alters neuronal function (Peoples et al., 1996). Even if fluidity changes occur, these changes lead to altered neuronal function, and thus, we must examine the proteins that dictate neuronal function. Thankfully, the tools available to modern neuroscientists have enabled examination of ethanol effects at multiple levels. We can now determine how a given molecular effect on a specific neuronal or synaptic subtype contributes to ethanol-induced behavioral changes. Both bottom-up and top-down approaches are being used in such studies.

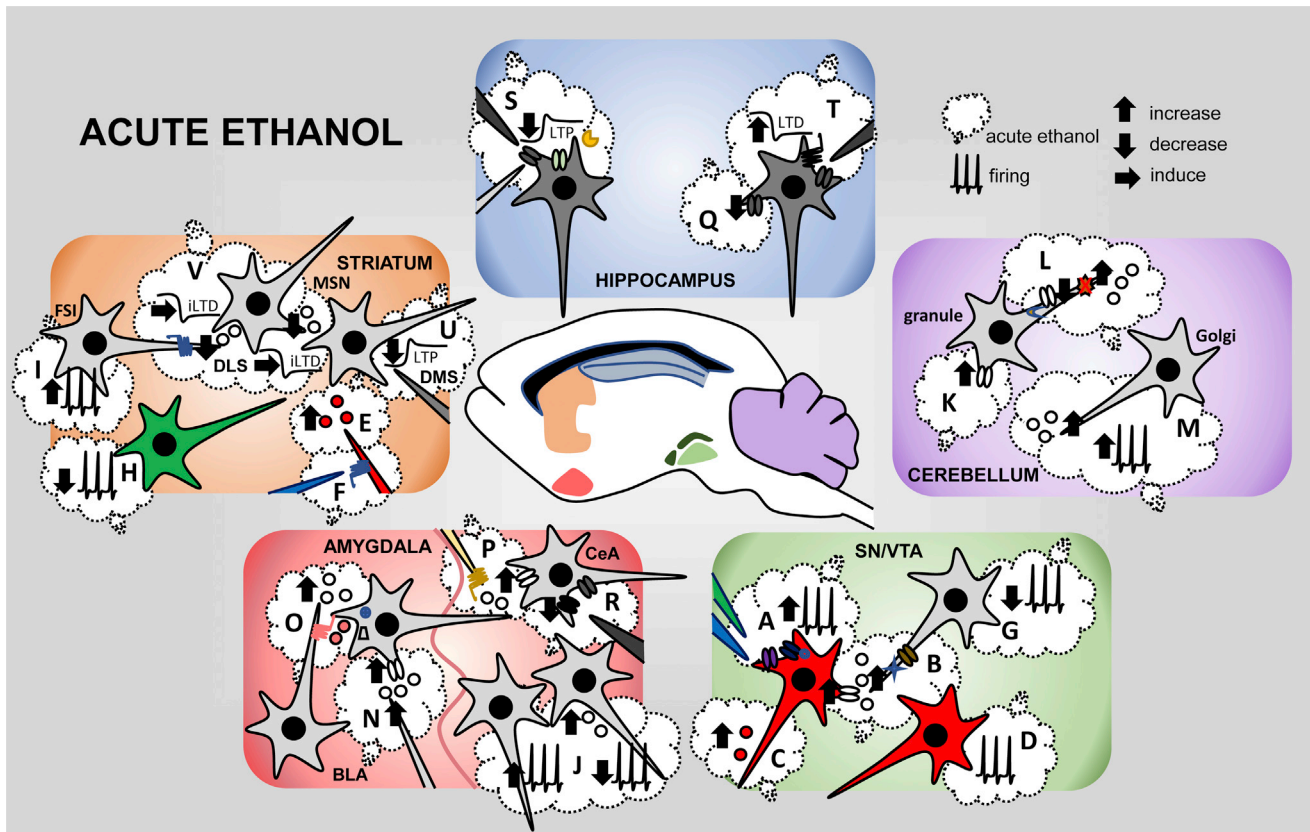
The bottom-up approach builds from the identification of an ethanol-sensitive molecule followed by determination of its role in acute and chronic ethanol changes in physiology and behavior. On the other hand, top-down approaches begin with ethanol-related physiological or behavioral changes leading to the study of specific molecular mechanisms and brain circuits contributing to these effects.

### Molecular Targets

Recent theories have posited specific ethanol-binding sites on several proteins that may act directly or indirectly to produce a biological effect (Figure 1). To understand how ethanol affects the brain and behavior using a bottom-up approach, it is important to first distinguish between the direct and indirect effects of ethanol. To that end, the following criteria have been proposed to classify direct ethanol targets (Harris et al., 2008; Trudell et al., 2014):

1. The putative target protein should be affected by ethanol at both low and high concentrations.
2. The molecular binding site and ethanol interaction should be characterized biochemically or modeled. Manipulation of the amino acids making up the putative binding site should alter the ethanol interaction and, consequently, the biological effect of ethanol.
3. Structural biological evidence should indicate that ethanol inhabits the putative binding site.
4. Genetic alteration of the target protein (e.g., knockout) should result in a readily discernable ethanol-related phenotype.

These criteria allow for the clear identification of direct ethanol targets. However, the low-affinity and transient molecular interactions of ethanol make fulfillment of all four criteria challenging. Thus, some of the molecular targets we discuss will be referred to as "putative" direct targets to indicate only partial fulfillment of the preceding criteria. Targets that do not meet any of the criteria above or that do not have any molecular structures indicative of an ethanol-binding site are referred to as indirect targets.



**Figure 2. Acute Effects of Ethanol on the Hippocampus, Striatum, Cerebellum, Amygdala, and Midbrain**

BLA, basolateral amygdala; CeA, central amygdala; DLS, dorsolateral striatum; DMS, dorsomedial striatum; FSI, fast-spiking interneuron; iLTD, inhibitory long-term depression; LTP, long-term potentiation; LTD, long-term depression; MSN, medium spiny neuron; SN/VTA, substantia nigra/ventral tegmental area. See text and Figure S1 for references related to each letter and highlighted effect.

### Direct Molecular Targets

Low concentrations of ethanol can directly interact with several molecules (Cui and Koob, 2017). The best example of a direct ethanol target (though not brain exclusive) is alcohol dehydrogenase (ADH). Ethanol has been shown to interact with ADH at low millimolar concentrations, the binding site is well characterized, and manipulation of ADH results in biological effects (Goto et al., 2015).

Ethanol has rapid acute effects on the function of proteins involved in excitatory and inhibitory synaptic transmission (Figures 1 and 2). Ethanol generally potentiates cys-loop ligand-gated ion channels (LGICs) (e.g., GABA<sub>A</sub> and glycine receptors [GlyRs]) but inhibits ionotropic glutamate receptors (reviewed in Lovinger and Roberto, 2013; Söderpalm et al., 2017). The different ligand-binding and transmembrane domains of these proteins likely underlie this difference. The current thinking is that ethanol interacts with membrane-spanning domains within these proteins and the subsequent allosteric changes in conformation produced differ for the different LGIC subtypes (Möykkynen and Korpi, 2012; Olsen et al., 2014). However, more work is needed to understand the structural basis of these differences. Ethanol also modulates nicotinic acetylcholine receptor (nAChR) function in a subunit-specific manner (Davis and de Fiebre, 2006; Hendrickson et al., 2013; Rahman et al., 2016) and potentiates 5HT<sub>3</sub>Rs (McBride et al., 2004).

Primary ethanol-binding sites that fulfill the four criteria have yet to be identified for all of these LGICs, but there is evidence of direct interactions with several of the cys-loop LGICs (Howard et al., 2014). For example, the structural basis for a direct interaction of ethanol with the prototypic *G. violaceus* LGIC has been determined and is thought to be a transmembrane cavity between two membrane-spanning domains (Sauguet et al., 2013). Identifying the expression sites and cellular actions of the subunits of these ethanol-sensitive channels is an important next step in understanding how the molecular effect of ethanol translates into altered neuronal and circuit function.

Studies of ethanol interactions with GlyRs are a good example of the bottom-up approach. These studies initially focused on the molecular mechanisms of ethanol's potentiation of GlyRs (Burgos et al., 2015; Mascia et al., 1996; Mihic, 1999; Perkins et al., 2010) and moved to studies of how ethanol's effects on GlyRs contribute to changes in circuit function and behavior (Aguayo et al., 2014; Blednov et al., 2012, 2015). Ethanol's effects on GlyR function have been identified in several brain regions (Badanich et al., 2013; Förster et al., 2017; McCracken et al., 2017). There is also evidence for a glycinergic "tone" or steady-state receptor activation that can be potentiated by ethanol (Salling and Harrison, 2014; Zhang et al., 2008), but the site and basic mechanisms of glycine release remain unclear.

The use of genetically engineered mice with alterations in receptor subunit expression or structure (knockouts and knockins) allow investigators to exploit the bottom-up approach and analyze the behavioral consequences of ethanol's effects on specific targets. Mice lacking the GlyR alpha 2 subunit show reduced ethanol intake, but GlyR alpha 3 knockout mice show increased intake (Mayfield et al., 2016). More evidence of the cellular and brain region location of the GlyRs involved in these behaviors is needed. For example, glycine transporter blockade in the ventral medial prefrontal cortex (PFC) contributes to increased motor impulsivity during protracted abstinence from long-term ethanol exposure (Irimia et al., 2017). Targeted conditional knockout mice may help us to better understand the contribution of GlyRs to ethanol intoxication, consumption, and AUD.

Ethanol inhibition of NMDA receptor (NMDAR) function has been studied in depth, but the details of the ethanol-receptor interaction are poorly understood (Bell et al., 2016). Interactions appear to involve the N-terminal and transmembrane 3 (TM3) domains of receptor subunits, as mutation of these sites alters ethanol inhibition of NMDARs (Smothers et al., 2013). Based on this work, a bottom-up approach using an ethanol-resistant TM3 domain mutation (Ronald et al., 2001; Smothers and Woodward, 2006, 2016) found altered ethanol-associated behaviors (den Hartog et al., 2013). Further investigation is needed to fully understand how this mutation and other alterations in NMDAR function can affect pharmacological and behavioral effects of ethanol.

The putative direct interaction of ethanol with the large-conductance  $\text{Ca}^{2+}$ -activated  $\text{K}^+$  channel (BK channel) has spurred research on a molecular target that affects neurons and circuit function using both bottom-up and top-down approaches. Early studies showed that acute ethanol enhances BK channel function (Dopico et al., 2014). More recently, Bukiya et al. (2014) characterized an ethanol-sensing site in the channel-forming  $\alpha$  subunit. Bottom-up studies have examined how changes in ethanol's effects on BK channels alter behavior. For example, ethanol potentiates  $\alpha$  and  $\alpha\beta 4$  BK channel open probability, but the potentiation of an  $\alpha$ -only-containing BK channel shows rapid tolerance (Martin et al., 2008; Velázquez-Marrero et al., 2014), which could be related to behavioral tolerance (Treisman and Martin, 2009). Studies using genetic manipulation of BK channels have identified a role for these channels in ethanol-induced depressive behavior in *C. elegans*, tolerance in *Drosophila*, and several behavioral responses in rodents (reviewed in Bettinger and Davies, 2014). A top-down approach revealed molecular mechanisms responsible for these behavioral effects. Blocking BK channel transport to the presynaptic plasma membrane alters ethanol-induced locomotor depression in *C. elegans* (Oh et al., 2017), while Wnt/ $\beta$ -catenin-signaling-dependent trafficking of BK channels out of the membrane contributes to ethanol tolerance at the cellular level (Palacio et al., 2015; Pietrzykowski et al., 2004; Velázquez-Marrero et al., 2016). However, no data have associated these molecular events with ethanol-induced behaviors, including tolerance.

Another ion channel with notable ethanol sensitivity is the G-protein-coupled inwardly rectifying  $\text{K}^+$  channel (GIRK). Ethanol enhances GIRK channel function (Bodhinathan and Slesinger,

2013; Glaaser and Slesinger, 2017), and genetic studies have identified a 43-amino-acid C-terminal region that is crucial for this action of ethanol (Lewohl et al., 1999). Mice carrying a missense mutation in the GIRK channel showed a loss of ethanol-induced analgesia (Kobayashi et al., 1999), and GIRK3 subunit knockout mice showed ethanol conditioned place preference, which was absent in controls (Tipps et al., 2016). Using a crystal structure of a mouse inward rectifier containing a bound ethanol molecule and structure-based mutagenesis, investigators probed a putative hydrophobic ethanol-binding pocket in the cytoplasmic domains of GIRK channels (Aryal et al., 2009).

Ethanol can also interact directly with non-ion-channel targets, including intracellular signaling molecules such as protein kinase C (PKC) (Pany and Das, 2015; Ron and Barak, 2016) and adenylate cyclase (AC) (Yoshimura et al., 2006). The physiological consequences of these effects of ethanol are not fully clear, but roles in the effects of drugs on synaptic transmission are emerging, as discussed later in this review.

#### Indirect Molecular Targets

Indirect ethanol targets include ion channel subunits, intracellular signaling proteins, growth factors, transcription factors, proteins involved in epigenetic regulation of gene expression, and even membrane lipids. In most cases, there is no clear evidence of an ethanol-binding site or that acute ethanol alters the expression or function of these molecules, but they show prominent alterations following chronic ethanol exposure and intake. Examples of indirect targets are highlighted in this and later sections of the review.

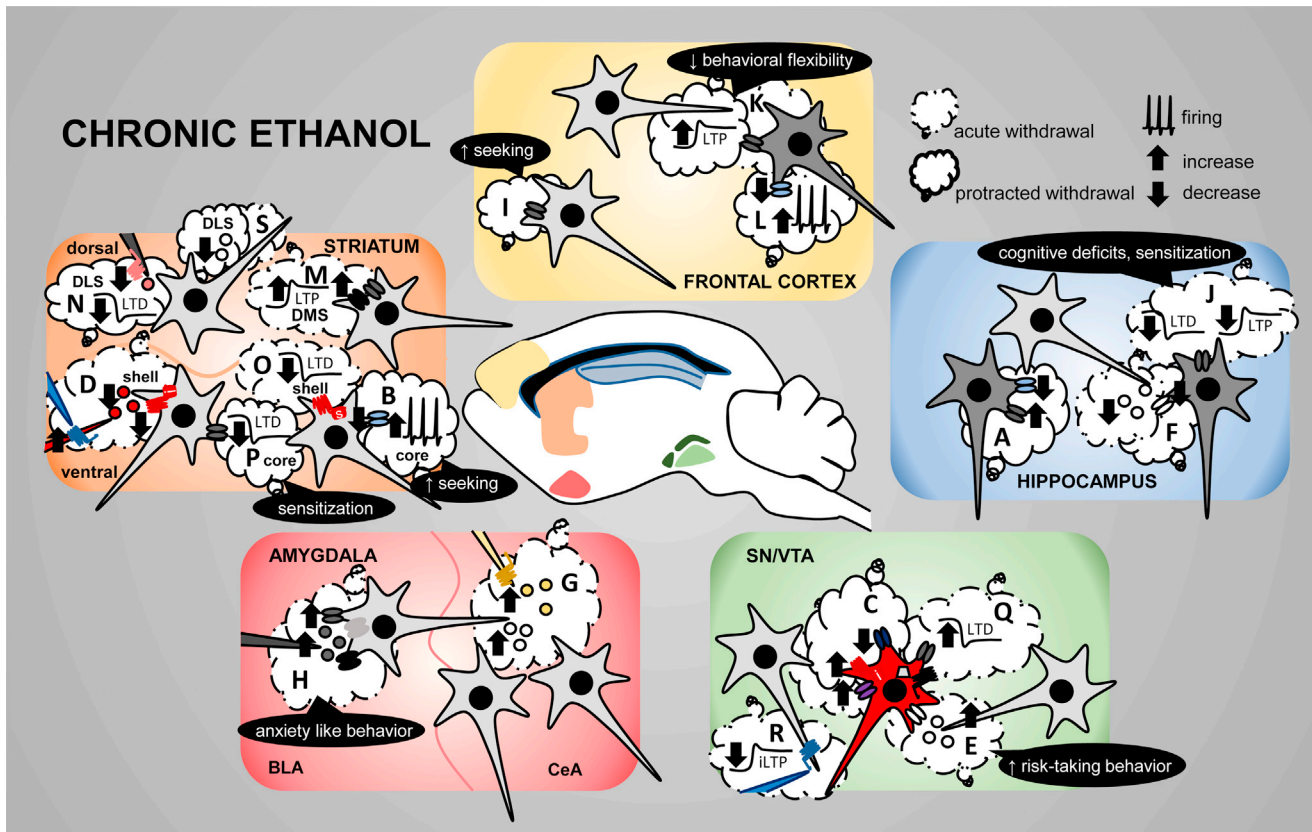
An intriguing example that has been the subject of recent study is the small-conductance  $\text{Ca}^{2+}$ -dependent  $\text{K}^+$  (SK) channel. Ethanol inhibits SK2 channel currents in a heterologous expression system (Dreixler et al., 2000), but there is no evidence of direct ethanol interactions with this channel. However, a number of studies indicate that chronic ethanol exposure and withdrawal reduce SK channel function in the ventral tegmental area (VTA) dopamine, hippocampal CA1 (Figure 3A), and cortical neurons (reviewed in Mulholland et al., 2009, 2011; Nimitvilai et al., 2016a; Korkotian et al., 2013). Furthermore, decreased SK channel expression and function were observed in the nucleus accumbens (NAc) core after ethanol self-administration. This effect was associated with greater ethanol seeking and was blocked by administration of an SK channel activator into the NAc after abstinence (Hopf et al., 2010). Similarly, NAc SK channel inhibition increases ethanol intake in mice (Padula et al., 2015), supporting the association between SK channels and ethanol intake (Figure 3B). Clearly, the SK channel has important roles in neuroadaptations that alter ethanol-related behaviors.

In the following sections, we will consider the neurophysiological and behavioral effects of ethanol. The emphasis will be on the effects of ethanol in particular brain circuits and their ramifications for ethanol-related behaviors.

#### Ethanol Effects on Intrinsic Excitability, Synaptic Transmission, and Plasticity

##### Effects on Neuronal Firing

Ethanol has well-known locomotor and reinforcing effects, and certainly the latter contribute to drinking in some capacity.



**Figure 3. Chronic Effects of Ethanol on the Frontal Cortex, Striatum, Hippocampus, Amygdala, and Midbrain**  
 BLA, basolateral amygdala; CeA, central amygdala; core, nucleus accumbens core; DLS, dorsolateral striatum; iLTP, inhibitory long-term potentiation; LTP, long-term potentiation; LTD, long-term depression; shell, nucleus accumbens shell; SN/VTA, substantia nigra/ventral tegmental area. See text and Figure S2 for explanation and references related to each letter and highlighted effect.

Thus, top-down approaches based on these behavioral outcomes led scientists to study ethanol's effects on midbrain dopamine neurons that have prominent roles in locomotion and reward (Melis et al., 2007; Samson et al., 1992). Although findings suggest that lesions of the mesolimbic dopamine system do not change ethanol self-administration (Rassnick et al., 1993), rodents do self-administer ethanol into the VTA (Gatto et al., 1994; Rodd et al., 2004), and dopamine is clearly implicated in ethanol-induced increases in locomotion and sensitization (Phillips and Shen, 1996). Ethanol facilitates action potential firing of midbrain dopamine neurons (Figure 2A) and increases extracellular dopamine levels in the VTA (Deehan et al., 2016) (Figure 2C). The physiological mechanisms thought to underlie this ethanol potentiation were reviewed by Morikawa and Morisset (2010) and include reductions of a barium-sensitive potassium and M-type currents. Furthermore, GIRK channels (Herman et al., 2015) and the hyperpolarization-activated and cyclic nucleotide-gated (HCN) channel current (Ih) (Appel et al., 2003; McDaid et al., 2008; Nimitvilai et al., 2016b) may also be involved in ethanol stimulation of dopamine neuron firing. Synaptic mechanisms also contribute to this stimulatory ethanol effect. Opioid (Xiao and Ye, 2008; Xiao et al., 2007), GABA, cholinergic, and serotonergic transmission modulate ethanol excitation of VTA dopamine neurons (Adermark et al., 2014; Theile et al., 2009,

2011; Xiao and Ye, 2008; Xiao et al., 2007; but see Nimitvilai et al., 2016b) (Figures 2A and 2B). It is now clear that dopamine neurons are heterogeneous, and recent reports have identified a subset of VTA dopamine neurons with greater sensitivity to ethanol's effects (Avegno et al., 2016; Mrejeru et al., 2015; Tateno and Robinson, 2011) (Figures 2A and 2D). The chronic and withdrawal effects of ethanol on dopamine neuron firing are mixed, with decreases observed in anesthetized rats (Diana et al., 1996) but no change (Okamoto et al., 2006; Perra et al., 2011) or increases (Didone et al., 2016) detected in slices. Repeated *in vivo* ethanol downregulates Ih density in dopamine neurons (Okamoto et al., 2006) and induces adaptations in the dopamine D2 receptor and GIRK channels (Perra et al., 2011) (Figure 3C). Thus, while changes in dopamine neuron firing are among the most consistent effects of ethanol, more work is needed to pin down the mechanisms underlying this effect.

The acute ethanol-induced increase in dopamine neuron firing is associated with increased NAc dopamine levels in rodents (Ericson et al., 1998; Yoshimoto et al., 1992) and humans (Aalto et al., 2015; Boileau et al., 2003) (Figure 2E). Interestingly, active and passive ethanol administration produces similar increases in NAc dopamine levels (Bassareo et al., 2017) that may be dependent on taurine (Ericson et al., 2011), GlyRs (Adermark et al., 2011a), and opiate receptors (Benjamin et al., 1993; Zapata

and Shippenberg, 2006) (Figure 2F). In contrast, high concentrations of ethanol dampen dopamine release from terminals measured with fast-scan cyclic voltammetry in the striatum (Budygin et al., 2001; Schilaty et al., 2014). These seemingly contradictory effects of ethanol on the striatal dopamine depend on the ethanol dose, with lower doses increasing dopamine via actions in midbrain and higher doses inhibiting release. Chronic ethanol exposure produces adaptations in dopamine release, and the opioid system may play a role (reviewed in Barbaccia et al., 1980). A nonspecific opioid receptor antagonist blocks dopamine release induced by ethanol drinking in the NAc (Gonzales and Weiss, 1998). Recent work has also shown that the ethanol-induced dopamine increase switches to a decrease after short-term withdrawal, which could be associated with a supersensitivity of kappa opiate receptors (Karkhanis et al., 2016; Rose et al., 2016; Siciliano et al., 2015) (Figure 3D). Interestingly, decreased availability of striatal D2 dopamine receptors is associated with AUD (Volkow et al., 2002; Volkow et al., 2017) (Figure 3D), indicating less dopamine responsiveness after short-term withdrawal from chronic ethanol exposure. Hirth et al. (2016), however, found that while dopamine levels were decreased during acute ethanol withdrawal, protracted withdrawal was accompanied by increased dopamine in rodents. Thus, while the overall trend is a decrease in dopaminergic transmission after chronic ethanol and withdrawal, this may depend on the withdrawal duration.

Neurons that fire spontaneously set a rhythm of tonic activity in many brain areas. Ethanol alters activity of distinct types of these “tonically active” neurons. Although ethanol potentiates the firing of dopamine neurons, it inhibits the firing of midbrain GABAergic neurons (Adermark et al., 2014; Burkhardt and Adermark, 2014; Stobbs et al., 2004) (Figure 2G). Interneurons of the striatum are also differentially affected by acute ethanol (Blomeley et al., 2011; Clarke and Adermark, 2015). Ethanol decreases the tonic firing frequency of cholinergic interneurons in the striatum, which then affects the activity of medium spiny neurons (MSNs) (Adermark et al., 2011b; Blomeley et al., 2011) (Figure 2H). These findings indicate that ethanol’s effects on intrinsic excitability are region and cell-type specific. Indeed, in the globus pallidus external segment, acute ethanol decreases the firing of low-frequency, but not high-frequency, firing neurons. The ethanol-induced inhibition of low-frequency firing neurons is attributable to ethanol activation of the BK channel (Abraham et al., 2017). Thus, this is one neuronal subtype in which the bottom-up approach can be used to assess the circuit and behavioral effects of BK activation by ethanol.

Ethanol also differentially affects the excitability of neurons that are not tonically active. For example, low-threshold spiking striatal interneurons show acute ethanol-induced hyperpolarization, but fast-spiking interneurons (FSIs) show a significant ethanol-induced membrane depolarization (Blomeley et al., 2011). Indeed, *in vivo* electrophysiological recordings show that acute ethanol increases the firing rate of FSIs in the NAc that may be related to the depolarization observed *in vitro* (Burkhardt and Adermark, 2014) (Figure 2I). In the central amygdala (CeA), acute ethanol can increase or decrease the firing of different neurons (Herman and Roberto, 2016) (Figure 2J).

Specific groups of neurons express one or more channels that are direct or indirect ethanol targets, allowing for neuron-specific ethanol modulation of activity. In the case of neurons whose intrinsic activity is ethanol insensitive, it remains to be determined whether they lack ethanol target channels or whether the factors that control sensitivity to ethanol (e.g., post-translational modifications) differ between ethanol-sensitive and insensitive neurons. Future studies should use both top-down and bottom-up approaches to examine how acute and chronic ethanol exposure affects excitability and firing in different neuronal populations in brain regions with key roles in the behavioral actions of ethanol and in which ethanol-sensitive molecules contribute to these changes.

### Fast Inhibitory Synaptic Transmission

Ethanol’s interactions with GABA-mimetic drugs have long been known, and the synergism of ethanol and barbiturates was studied extensively before it was clear that both of these drugs act on GABA<sub>A</sub> receptors (Mihic and Harris, 2011). Thus, a top-down analysis indicated that ethanol’s effect on GABA<sub>A</sub>-mediated fast synaptic transmission was likely to be a fruitful area of study to better understand intoxication and high-dose ethanol actions. Accordingly, it was natural to assume that ethanol would act on GABA<sub>A</sub> receptors in a manner similar to other sedative drugs. Indeed, ethanol potentiates GABA<sub>A</sub> receptors in some neurons and heterologous expression systems (Harris et al., 1997; Mihic, 1999). Examination of “tonic” GABA<sub>A</sub> currents consistently revealed increases in postsynaptic GABA responses in the cerebellum (Diaz and Valenzuela, 2016) (Figure 2K), hippocampus (Liang et al., 2006), and thalamus (Jia et al., 2008). These actions of ethanol often involve the GABA<sub>A</sub>  $\delta$  subunit (Choi et al., 2008). However, there has been debate about the mechanisms involved in this tonic current effect. In the cerebellum, there is evidence that ethanol’s enhancement of interneuron firing is a key factor underlying increased tonic current (Valenzuela and Jotty, 2015), but this may not be the case in other brain regions.

Analysis of intact synapses indicated that while acute ethanol enhanced GABAergic transmission at synapses in several brain regions (Siggins et al., 2005; Weiner et al., 1997; Zhu and Lovinger, 2006), these effects often involved unexpected presynaptic potentiation (Ariwodola and Weiner, 2004; Carta et al., 2004; Nie et al., 2004; Roberto et al., 2003). The clearest evidence for enhanced GABA release at individual synapses comes from studies of isolated neurons from the cerebellum (Figures 2L and 2M) and basolateral amygdala (BLA) (Figures 2N and 2O) that include pinched-off, functional synaptic boutons that spontaneously release GABA. Ethanol potentiates this spontaneous release at concentrations relevant to intoxication. Indices of postsynaptic changes are not observed in the presence of ethanol (Kelm et al., 2007; Zhu and Lovinger, 2006), and this potentiation cannot result from activity of interneurons, as the boutons are no longer connected to somata. This type of experiment provides clear evidence of an increase in GABA release at central synapses.

The mechanisms underlying ethanol potentiation of GABA release are not well-understood. Examination of mice lacking protein kinase A (PKA) or PKC epsilon indicate loss of the presynaptic actions of ethanol (Bajo et al., 2008; Proctor et al., 2003) and inhibition of AC has been shown to prevent this

ethanol effect at some synapses (Talani and Lovinger, 2015) (Figure 2O). Activation of a variety of Gi/o-coupled G-protein coupled receptors (GPCRs) counteracts ethanol's potentiation of GABA release at synapses in several brain regions (Ariwodola and Weiner, 2004; Kelm et al., 2011; Roberto et al., 2010; Talani and Lovinger, 2015). These findings reinforce the idea that signaling through AC and PKA is involved in ethanol's actions and are in accord with findings from invertebrate models (Moore et al., 1998). In cerebellar granule neurons, although ethanol inhibits the function of GABA<sub>A</sub> receptors through a mechanism involving postsynaptic PKC, ethanol also enhances GABA release via inhibition of nitric oxide synthase (Kaplan et al., 2013) (Figure 2L).

Presynaptic ethanol effects at some synapses are secondary to release of neuromodulators that are themselves the direct mediators of increased vesicle fusion. The CeA, for example, expresses a number of neuropeptides (including corticotropin-releasing factor [CRF]) affected by ethanol, and peptides in this region are implicated in the processing of aversive stimuli and emotional salience. As such, CeA is critically involved in the negative affective states accompanying drug and alcohol abuse and addiction (Koob, 2015). CRF enhances GABAergic transmission in the CeA via presynaptic CRF1 receptors (Bajo et al., 2008; Cruz et al., 2012; Roberto et al., 2010). Acute ethanol also enhances this transmission (Kang-Park et al., 2013; Nie et al., 2004; Roberto et al., 2003; Roberto et al., 2004a), and this effect is CRF1 dependent, suggesting that ethanol acts indirectly to increase GABA release by facilitating local CRF release (Bajo et al., 2008; Nie et al., 2004) (Figure 2P). However, in some CeA neurons, the ethanol and CRF effects on GABA transmission are additive, suggesting distinct mechanisms of action. In the dorsolateral striatum, however, ethanol inhibits GABA release by enhancing enkephalin release and presynaptic delta opiate receptor activation (Patton et al., 2016). Thus, ethanol-induced neuropeptide release modulates GABA release in a synapse-specific manner. Neuropeptide release is certainly not involved in ethanol's actions on GABA release at all synapses, as evidenced by potentiation in isolated neuron preparations (Criswell et al., 2008; Zhu and Lovinger, 2006).

Chronic ethanol exposure and intake also alter GABAergic transmission via pre- and postsynaptic mechanisms. These effects were covered in a recent review (Roberto and Varodayan, 2017) and will not be discussed in detail here. Both increases and decreases in GABA release are observed in several brain regions and they appear to be synapse specific (Cuzon Carlson et al., 2011; Herman et al., 2016a; Schindler et al., 2016; Tremwel et al., 1994; Wanat et al., 2009; Wilcox et al., 2014) (Figures 3E–3G). In the CeA, for example, CRF levels and GABA transmission are increased and remain so during acute withdrawal. Interestingly, acute ethanol exposure following chronic ethanol treatment has the same effect as acute ethanol in naive animals, suggesting that acute ethanol-induced facilitation of GABA transmission does not undergo tolerance (Roberto et al., 2004a) (Figure 3G).

#### **Fast Excitatory Synaptic Transmission**

Ethanol has several effects on glutamatergic transmission (Bell et al., 2016; Hwa et al., 2017; Roberto and Varodayan, 2017). Acute ethanol inhibits all glutamate receptors. These effects

occur in the hippocampus (Lovinger et al., 1990) (Figure 2Q), frontal cortex (Weitlauf and Woodward, 2008), and CeA (Kirsan et al., 2017; Roberto et al., 2004b, 2006; Zhu et al., 2007) (Figure 2R), among other brain regions. The acute effects of ethanol on glutamate release vary, with some reports showing presynaptic potentiation (Herman et al., 2016b; Silberman et al., 2015; Xiao et al., 2009) and others showing inhibitory effects (Basavarajappa et al., 2008; Hendricson et al., 2004; Herman et al., 2016b; Maldve et al., 2004; Zhu et al., 2007).

Chronic ethanol exposure can affect NMDARs (Abraham et al., 2013; den Hartog et al., 2017; Hendricson et al., 2007), kainate receptors (Carta et al., 2003; Läck et al., 2009), AMPA receptors (AMPA) (Läck et al., 2007), and metabotropic glutamate receptors (mGluRs) (Ding et al., 2016; Mihov and Hasler, 2016). These ethanol effects in specific brain regions have been linked to different ethanol-related phenotypes. For example, increased glutamatergic transmission in the BLA induced by chronic ethanol is associated with withdrawal anxiety-like behavior (Christian et al., 2013; Läck et al., 2007) (Figure 3H). In addition, selective deletion of the GluN2B NMDAR subunit in cortical interneurons reduces ethanol seeking (Radke et al., 2017a, 2017b) (Figure 3I). Analysis of the role of glutamate and glutamate receptors in ethanol-related behaviors should be extended to additional synapses and brain regions. Chronic ethanol exposure elevates extracellular glutamate levels in several brain regions, inducing a “hyperglutamatergic” state thought to contribute to AUDs (Gass and Olive, 2008; Spanagel, 2009). For example, this increased glutamatergic drive may lead to excessive activation at key synapses in circuits involved in ethanol seeking, including the corticostriatal synapses examined by Meinhardt et al. (2013). Indeed, increased extracellular NAc glutamate, induced by chronic ethanol or glutamate reuptake inhibition, promoted ethanol consumption in mice (Griffin et al., 2014). Based on this line of work, glutamate uptake has been targeted to treat AUD (Rao et al., 2015).

#### **Synaptic Plasticity**

Ethanol alters learning and memory (Oslin and Cary, 2003; White, 2003), and this may involve effects on synaptic plasticity, including long-term depression (LTD) and long-term potentiation (LTP) (reviewed in Zorumski et al., 2014). Most of the data on ethanol effects on synaptic plasticity come from studies in the hippocampus. Acute ethanol inhibits LTP in hippocampal slices (Blitzer et al., 1990; Morrisett and Swartzwelder, 1993), but these results are not consistent (Fujii et al., 2008; Swartzwelder et al., 1995). This variability may be due to many factors, including age, subregion, and stimulus strength. Acute ethanol blocks LTP in apical dendrites but only reduces LTP in basal dendrites (Ramachandran et al., 2015). These effects may be due to NMDAR inhibition (Chandler et al., 1998; Izumi et al., 2005), but recent work posits a role for neurosteroids (Izumi et al., 2015; Tokuda et al., 2013). In contrast to LTP, hippocampal LTD is enhanced by acute ethanol in the CA1 region (Hendricson et al., 2002), and this effect involves NMDARs and mGluR type 5 (mGluR5) (Izumi and Zorumski, 2012; Overstreet et al., 1997) (Figure 2T).

Chronic ethanol exposure reversibly inhibits LTP (Durand and Carlen, 1984; Roberto et al., 2002) and dampens LTD in hippocampal neurons (Thinschmidt et al., 2003) (Figure 3J). Indeed,

high-dose ethanol treatment can transiently abolish NMDA-dependent LTD in hippocampal neurons and elicit cognitive deficits in rats (Silvestre de Ferron et al., 2015). Impairment of mGluR5-LTD in hippocampal slices following ethanol vapor exposure (Wills et al., 2017) indicates that other types of plasticity may be affected by chronic ethanol. Relevant to the role of plasticity in ethanol-related behaviors, mice susceptible to the development of locomotor sensitization to ethanol show normal hippocampal LTD, whereas mice resistant to ethanol sensitization lack LTD (Coune et al., 2017). We still have an incomplete understanding of how changes in synaptic plasticity are associated with behavioral adaptations produced by chronic ethanol treatment.

The PFC is involved in the cognitive symptoms of AUD. Although studies have investigated the acute effects of ethanol on PFC NMDARs (Weitlauf and Woodward, 2008), few have investigated the effect on synaptic plasticity in this area. Chronic ethanol exposure induces an increase in the NMDA/AMPA current ratio in the PFC and enhances expression of NMDAR-mediated spike-timing-dependent LTP, a neuroadaptation likely associated with reduced behavioral flexibility (Kroener et al., 2012; Nimitvilai et al., 2016a) (Figures 3K–3L). It will be interesting to determine how these plasticity changes contribute to ethanol-induced cognitive impairment.

Ethanol can also affect striatal plasticity (Lovinger and Kash, 2015). For example, acute ethanol application blocks LTP (Figure 2U) and has diverse effects on LTD (Clarke and Adermark, 2010; McCool, 2011; Yin et al., 2007). In contrast, chronic ethanol facilitates corticostriatal LTP (Wang et al., 2012; Xia et al., 2006) (Figure 3M) and impairs endocannabinoid-mediated disinhibition in the dorsolateral striatum (Adermark et al., 2011c). Furthermore, chronic ethanol dampens striatal LTD at excitatory synapses (Adermark et al., 2011c; Cui et al., 2011; DePoy et al., 2013) (Figure 3N). With novel optogenetic and transgenic tools, scientists can now study pathway-specific ethanol effects. For example, excessive ethanol intake potentiates AMPA- and NMDA-mediated transmission at the medial prefrontal cortex (mPFC) input and increases glutamate release from BLA afferents to the dorsomedial striatum (DMS). These changes could explain the effect of chronic ethanol exposure on striatal LTP, as paired activation of the mPFC and BLA inputs induces robust LTP of the corticostriatal input to the DMS (Ma et al., 2017).

Acute and chronic ethanol-induced changes in plasticity have also been extensively studied in the NAc, a region implicated in the rewarding effects of ethanol (reviewed in Renteria et al., 2016), and will only be briefly summarized here. Acute ethanol inhibits NMDAR-dependent LTD in the NAc shell in an MSN-subtype-specific manner (Jeanes et al., 2014). In the NAc core, acute ethanol impairs LTP via effects on mGluRs (Mishra et al., 2012). Following chronic ethanol exposure, LTD is altered such that D1-negative MSNs show LTD while D1-positive MSNs lose LTD, and sometimes show LTP (Jeanes et al., 2014; Renteria et al., 2017) (Figure 3O). These effects were lost after 2 weeks of withdrawal. Another study found impaired expression of NMDAR-LTD in the NAc core, but not shell, of mice that showed robust locomotor sensitization to ethanol after 2 weeks of withdrawal from chronic ethanol treatment (Abraham et al., 2013) (Figure 3P). Thus, plasticity deficits in the NAc and hippocampus

may contribute to behavioral adaptations to chronic ethanol (Coune et al., 2017).

Much less is known about ethanol's effects on plasticity in other areas. A single *in vivo* ethanol administration impairs LTP in VTA dopamine neurons in DBA mice, with no effect in C57 mice (Wanat et al., 2009), but unlike other regions, chronic ethanol treatment enhances NMDA-dependent LTD in VTA dopamine neurons (Bernier et al., 2011) (Figure 3Q). Ethanol exposure also inhibits LTP in VTA neuron GABAergic synapses (Guan and Ye, 2010) (Figure 3R). Further study is required to understand the effect of ethanol on midbrain dopamine neurons, especially in light of recent findings on the anatomical and biochemical diversity of dopamine neurons (Lammel et al., 2008; Poulin et al., 2014).

### Circuitry

While much of the past focus has been on ethanol effects on molecules and synapses, there has been increasing realization that these targets must be considered in the context of micro- and larger circuits. This concept has arisen from the findings that ethanol effects on cellular targets vary across brain regions due to differences in the molecular complement of different neurons and differences in ethanol sensitivity. For example, ethanol potentiates GIRK channel function in cerebellar granule neurons, but striatal MSNs do not express GIRK channels (Kobayashi et al., 1995), and thus, this mechanism would not be viable in these neurons. The variability in ethanol potentiation of delta-subunit-containing GABA<sub>A</sub> subunits (e.g., thalamus and hippocampus) also reinforces this point. In addition, there is increasing recognition of how different brain circuits contribute to behavior, and thus, we must understand ethanol's effects on circuitry to fully appreciate the factors underlying the range of behavioral effects of the drug. The increasing appreciation of the larger circuitry in which individual brain regions participate has stimulated systems-level neuroscience in general and spurred increasing work at this level in the alcohol research field.

### Microcircuitry

The acute and chronic effects of ethanol on microcircuits can help reveal changes in local control of synapses that alter the output of key brain regions. As the majority of synapses in microcircuits are GABAergic, this research has focused mostly on changes in the effects of GABA. Some of the ethanol-induced changes in interneuron function and synaptic transmission were mentioned earlier in this review, and we will now focus on recent data from striatum and cerebellum.

In the dorsal striatum, local GABAergic connections include synapses between FSIs and MSNs, as well as collateral MSN-MSN connections (Wilson, 2007). Effects of both acute and chronic ethanol on these GABAergic synapses have been characterized in rodents (Patton et al., 2016; Wilcox et al., 2014) (Figure 2V) and non-human primates (Cuzon Carlson et al., 2011). One theme that has emerged from these studies is that ethanol has opposing actions on GABAergic synapses in two subregions of the striatum. In the "associative" or DMS, ethanol potentiates GABAergic transmission via a presynaptic mechanism, while ethanol inhibits GABAergic transmission in the "sensorimotor" or dorsolateral striatum, with the aforementioned opiate receptor-dependent presynaptic mechanism



implicated in this action (Wilcox et al., 2014). Ethanol also inhibits MSN-MSN synapses via a mechanism that is not as well characterized (Patton et al., 2016). Thus, the net effect of acute ethanol is to inhibit MSN output from associative striatum while disinhibiting output from sensorimotor striatum. These striatal subregions are part of larger circuits that control goal-directed, conscious actions (the associative circuit) and habitual, unconscious actions (the sensorimotor circuit). The combination of associative circuit inhibition and sensorimotor circuit activation could help to promote the learning and performance of habitual actions. Short- and long-term ethanol consumption reduces GABAergic synaptic responses in sensorimotor regions and exacerbates the imbalance in the output of associative and sensorimotor circuits (Cuzon Carlson et al., 2011; Wilcox et al., 2014) (Figure 3S).

Recent work has focused on how differences in genetics and intracellular signaling impact ethanol's actions on microcircuits and the relationship between these effects and alcohol intoxication, reward, and drinking. It is well known that C57Bl6J mice differ from DBA mice in ethanol-related behaviors (Belknap et al., 1993), likely due to differences in genes governing the neural mechanisms underlying reward and aversion (Cunningham et al., 1992). A top-down examination of ethanol's effects on GABA<sub>A</sub>-receptor-mediated transmission in cerebellar microcircuitry revealed differences between these strains that may account for the behavioral differences. Rossi and colleagues observed a differential balance between the GABA-potentiating and inhibiting effects of ethanol in C57Bl6J and DBA mouse strains (Kaplan et al., 2013) that correlate with differences in ethanol intake. More recent studies indicate that enhancing GABAergic transmission in the cerebellum of C57Bl6J mice decreases ethanol drinking to levels seen in DBA mice (Kaplan et al., 2016).

### Projections and Large-Scale Circuits

Ultimately, the scope of alcohol research will have to expand to examine effects on large-scale brain circuitry and how circuits control alcohol-related behaviors. In animal models, this work will be bolstered by techniques allowing for more precise control of neuronal projections (e.g., opto- and chemogenetics), as well as new techniques for widespread measurement of neuronal activity. While these approaches are just beginning to be applied within the field, there are some intriguing findings.

Rinker et al. (2017) reported that reducing the function of CRF-expressing bed nucleus of the stria terminalis (BNST)-VTA projections reduces ethanol intake in a mouse model of binge drinking. This effect was mimicked by blockade of CRF1. Both the BNST and CRF are implicated in ethanol drinking and relapse driven by stress and negative affect (Koob, 2015), and there is evidence that BNST-VTA projection neurons regulate the expression of ethanol conditioned place preference (Pina et al., 2015; Pina and Cunningham, 2017).

The limbic corticostriatal circuitry has long been implicated in drug use disorders (Koob and Volkow, 2016). Recent work on inputs from the mPFC and insula to the NAc is illuminating the role of specific synapses and molecules mediating excessive ethanol drinking. These glutamatergic corticostriatal inputs drive the activity of MSNs, and the NMDAR is key for synaptic function and plasticity at these synapses (Lovinger, 2010). Ethanol drinking

alters the NMDAR subtypes by insertion of the NR2C subunit at mPFC and insula synapses onto MSNs in the NAc core, but it leaves these receptors unchanged at glutamatergic inputs from amygdala (Seif et al., 2013). The mPFC and insula synapses appear to drive drinking in the face of aversive consequences, and the NR2C subunit is implicated in the loss of this control (Seif et al., 2013). In addition, projections from the ventral subiculum to the NAc shell are also important for ethanol seeking in the face of aversive consequences, as selective inhibition of this pathway by chemogenetic techniques decreased context-induced relapse (Marchant et al., 2016). These findings show how synapse-specific molecular changes alter the ability of limbic circuits to control ethanol drinking in relation to negative environmental events that would normally curtail drinking.

mGluR2 has also been implicated in the control of excessive ethanol intake by dampening corticostriatal input. Chronic ethanol exposure reduces mGluR2 expression in infralimbic NAc shell projection neurons (Meinhardt et al., 2013). This downregulation contributes to a hyperglutamatergic state within the NAc shell. In an ethanol self-administration paradigm, cues associated with ethanol elicit responding that is especially strong in ethanol-dependent rats and involves limbic corticostriatal circuitry (Meinhardt et al., 2013). Increasing mGluR2 expression in infralimbic projections to the NAc shell attenuates this responding to levels seen in non-dependent rats. Thus, mGluR2 appears to provide a feedback brake on mPFC-drive for excessive ethanol seeking. Interestingly, the alcohol-preferring P rat is a functional mGluR2 knockout, and enhanced ethanol intake is observed in both this rat and mGluR2 knockout mice (Zhou et al., 2013). Inputs to the DMS are also altered by chronic ethanol exposure. Excessive ethanol consumption potentiates glutamatergic transmission via a postsynaptic mechanism at the corticostriatal input and involves a presynaptic mechanism at the amygdalostriatal input (Ma et al., 2017). Chronic ethanol consumption strengthens glutamatergic input to D1-, but not D2-, receptor-expressing DMS MSNs, and GABAergic synaptic strength is enhanced specifically onto D2 MSNs (Cheng et al., 2017; Wang et al., 2015). Interestingly, a bottom-up-approach study following from these findings demonstrated that chemogenetic excitation of DMS D1 MSNs or inhibition of D2 MSNs promotes ethanol consumption in mice (Cheng et al., 2017).

This circuit-centered work, aided by new technologies, can help to show how specific neuronal pathways and neurotransmitters are implicated in ethanol-specific phenotypes, including reinforcing, appetitive, and consummatory behaviors.

### Conclusions

As this review indicates, the effects of ethanol at the molecular, cellular, and circuit levels are myriad and may appear daunting to those outside the field, especially when compared to drugs that act through one predominant molecular target. However, the number of direct and indirect targets of ethanol's action, while numerous, are still limited enough to allow appreciation of many drug actions that strongly influence circuits and behavior. Furthermore, some targets (e.g., GlyRs, GABA release, NMDARs, GIRK, BK, and SK) mediate ethanol effects on several neurons and synapses throughout the brain. By abandoning a "single-target" view of ethanol's actions and instead examining

which molecules are altered by ethanol in which cells, investigators are beginning to piece together the intoxicating, abuse-promoting, and toxic actions of the drug. With the adoption of new techniques for cellular and circuit manipulation, along with sophisticated measures of neuronal function *in vivo* and in reduced preparations, researchers can link ethanol's effects at all levels to behavioral changes brought about by this widely used and abused drug. This rapidly evolving field is providing information that will be valuable in addressing the large public health problem created by this small drug.

#### SUPPLEMENTAL INFORMATION

Supplemental Information includes two figures and can be found with this article online at <https://doi.org/10.1016/j.neuron.2017.10.032>.

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