Neuroscience of Alcohol: Practical considerations

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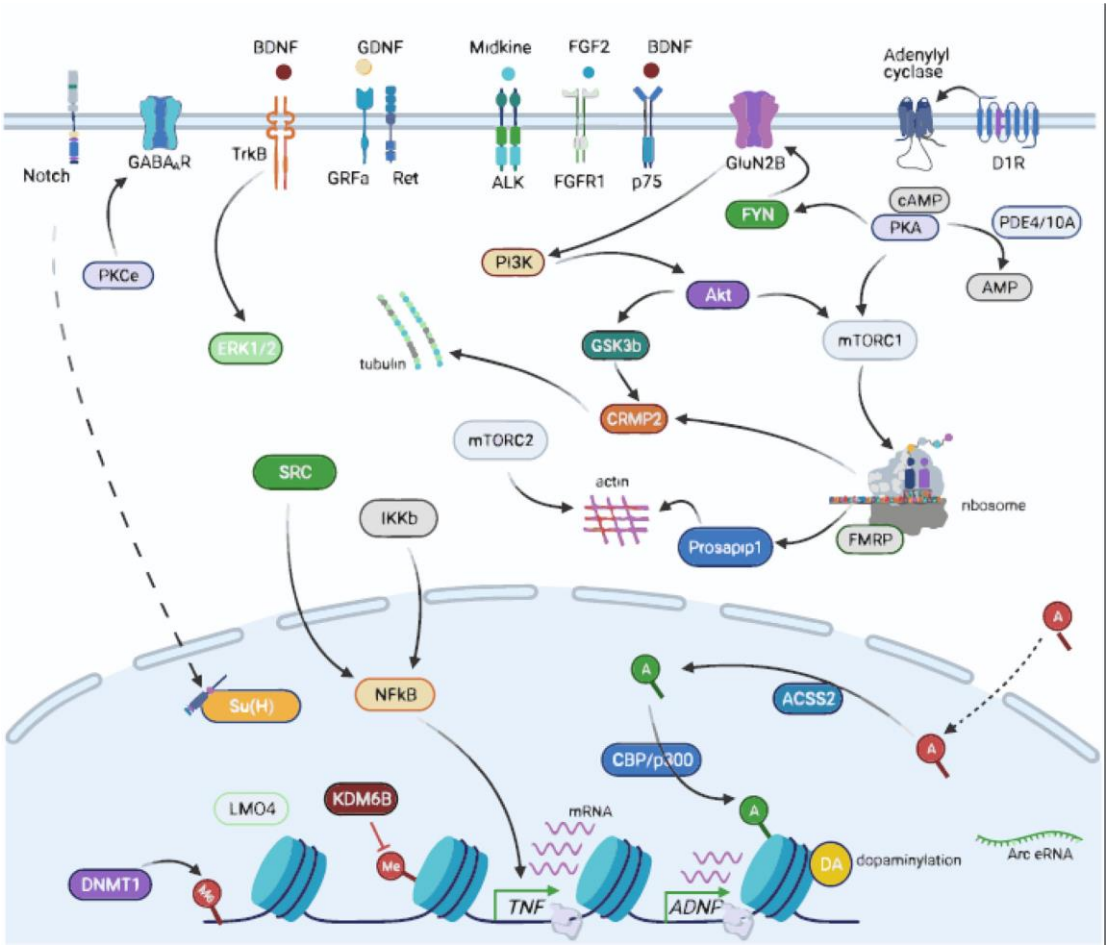
Introduction

- **Ethanol is one of the most commonly abused drugs**
- **Alcohol use disorder (AUD) affects about 10–15% of the global population, causing significant medical, social, and economic burdens**
- **There are complex and multi-faceted ways by which intake of alcohol affects the nervous system**
- **Both acute and chronic alcohol exposure produce molecular and cellular neuroadaptations influencing discrete brain regions and cell types.**
- **Consequently, these neuronal adaptations that underlie AUD are influenced by diverse interactions between alcohol and intracellular signaling, the epigenome, neurotransmitters and modulators as well as the activity of neuronal circuits,**
- **Drive behaviors such as heavy alcohol use, anxiety, craving, and relapse**

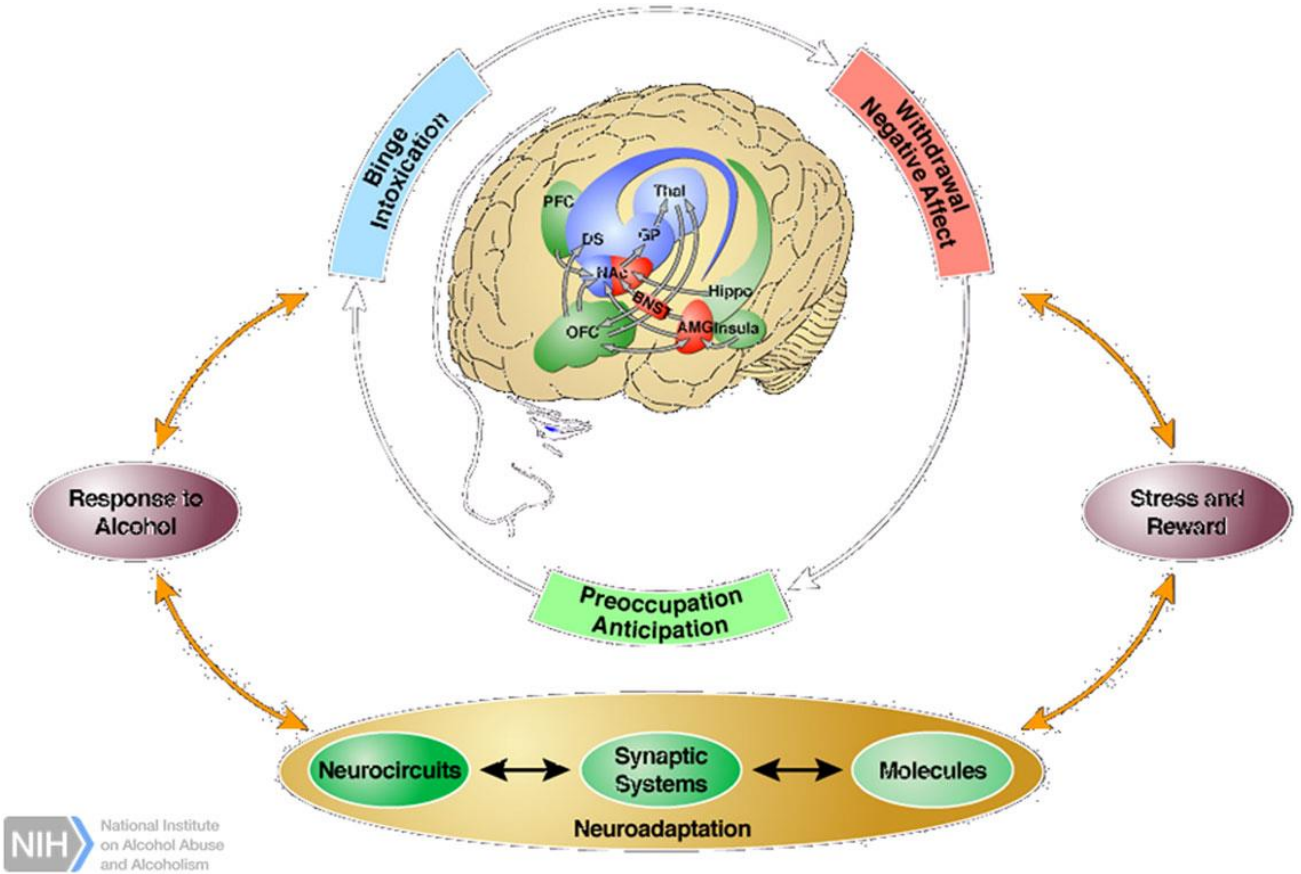
Levels of alcohol's effects on the brain

- **Level 1: Genetic factors in AUD**
- **Level 2: Alcohol-induced alterations in epigenetic regulation**
- **Level 3: Alcohol's effects on transcriptional activity**
- **Level 4: Alternative splicing**
- **Level 5: Alcohol and protein translation**
- **Level 6: The role of posttranslational modifications**
- **Level 7: Impact of chronic drinking on neuromodulators and neural circuits**

Molecular pathways in alcohol use disorder



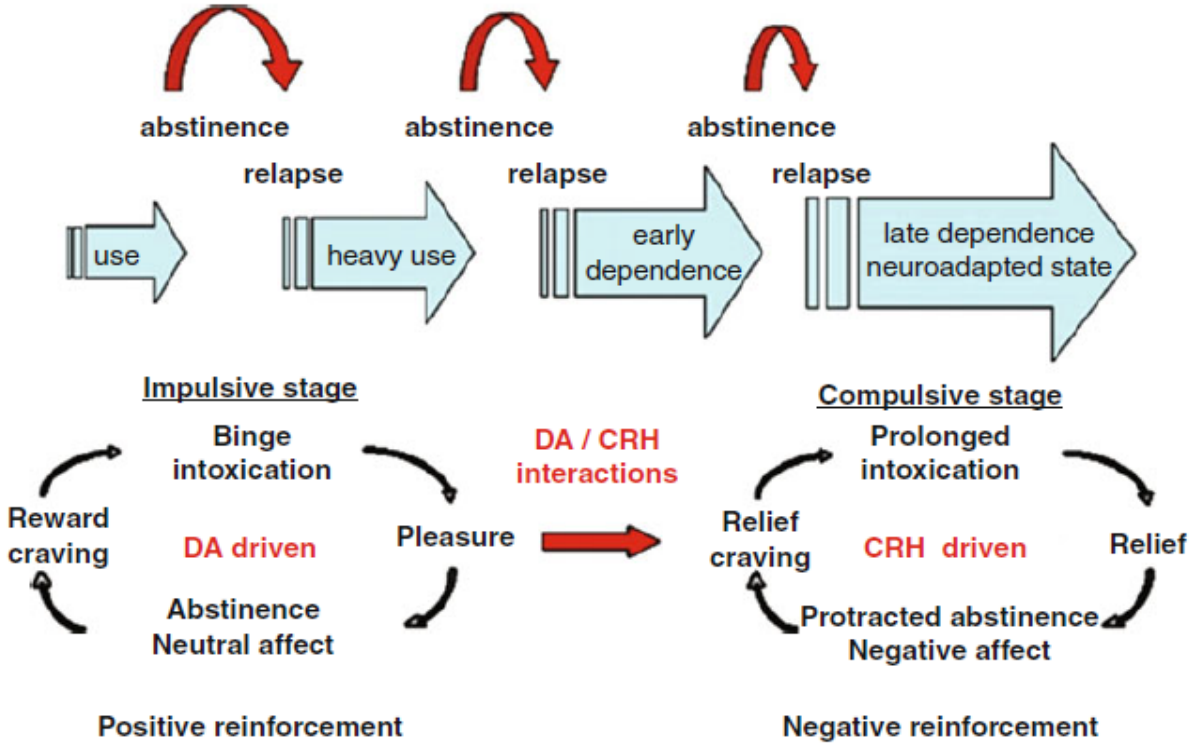
The neurobiology of addiction



The neurobiology of addiction

- **Three-stage addiction cycle framework:**
- **binge/intoxication,**
- **withdrawal/negative affect, and**
- **preoccupation/anticipation.**
- **multiple neuroadaptations in three corresponding domains:**
- **(1) increased incentive salience,**
- **(2) decreased brain reward and increased stress, and**
- **(3) compromised executive function;**
- **and in three major neurocircuits: basal ganglia, extended amygdala, and prefrontal cortex**

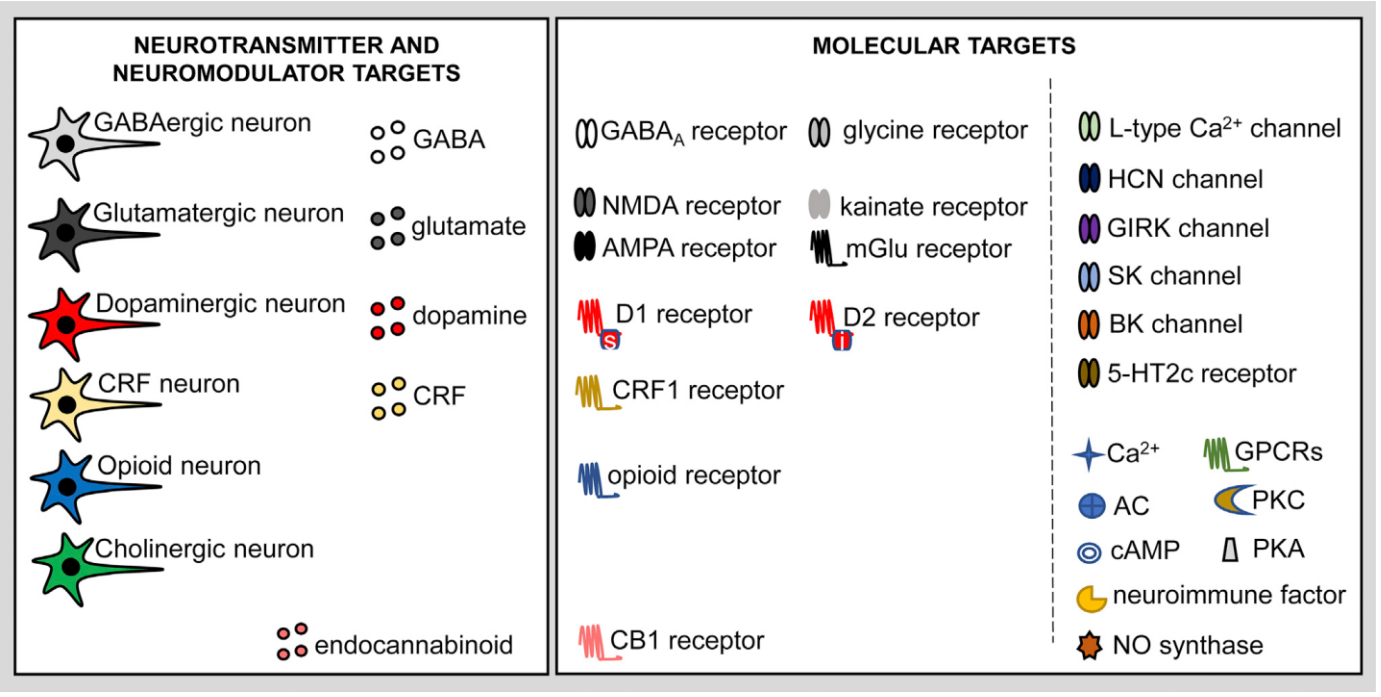
Conceptual framework for the progression of alcohol addiction over time



Integrative Analysis of Ethanol's Effects on the Nervous System: Bottom-Up and Top-Down Approaches

- **Ethanol distribution in the body and brain is similar to water,**
- **Equilibration throughout organs and cells is achieved within a few minutes of drinking**
- **many of ethanol's effects involve its occupation of water-filled cavities in proteins and subsequent alteration of function**
- **ethanol acts on numerous molecular targets in neurons and synapses throughout the brain.**
- **lack of specificity**
- **The bottom-up approach builds from the identification of an ethanol-sensitive molecule followed by determination of its role**
- **top-down approaches begin with ethanol-related physiological or behavioral changes leading to the study of specific molecular mechanisms and brain circuits**

Neurotransmitter/Modulator Systems and Molecular Targets of Ethanol



Direct Molecular Targets

- **Ethanol has rapid acute effects on the function of proteins involved in excitatory and inhibitory synaptic transmission**
- **Ethanol generally potentiates ligand-gated ion channels (LGICs) (e.g., GABAA and glycine receptors [GlyRs]) but inhibits ionotropic glutamate receptors**
- **ethanol interacts with membrane-spanning domains within these proteins**
- **Ethanol also modulates nicotinic acetylcholine receptor (nAChR) function and potentiates 5HT3Rs**
- **Ethanol inhibition of NMDA receptor (NMDAR) function has been studied extensively**
- **acute ethanol enhances BK channel function which could be related to behavioral tolerance**
- **Ethanol enhances GIRK channel function**
- **Ethanol can also interact directly with non-ion-channel targets, including intracellular signaling molecules such as protein kinase C (PKC) and adenylate cyclase (AC)**

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.**
- **Ethanol inhibits SK2 channel currents**
- **the SK channel has important roles in neuroadaptations that alter ethanol-related behaviors.**

Ethanol Effects on Intrinsic Excitability, Synaptic Transmission, and Plasticity

- **Ethanol has well-known locomotor and reinforcing effects**
- **Ethanol facilitates action potential firing of midbrain dopamine neurons and increases extracellular dopamine levels in the VTA**
- **Opioid, GABA, cholinergic, and serotoninergic transmission modulate ethanol excitation of VTA dopamine neurons**
- **lower doses increasing dopamine via actions in midbrain and higher doses inhibiting release**
- **Ethanol alters activity of distinct types of ‘‘tonically active’’ neurons and also differentially affects the excitability of neurons that are not tonically active**

Ethanol Effects on Intrinsic Excitability, Synaptic Transmission, and Plasticity

- Fast Inhibitory Synaptic Transmission
- **Ethanol's interactions with GABA-mimetic drugs have long been known**
- **both of these drugs act on GABAA receptors**
- **acute ethanol enhanced GABAergic transmission at synapses in several brain regions**
- **Chronic ethanol exposure and intake also alter GABAergic transmission via pre- and postsynaptic mechanisms**
-

Ethanol Effects on Intrinsic Excitability, Synaptic Transmission, and Plasticity

- **Fast Excitatory Synaptic Transmission**
- **Ethanol has several effects on glutamatergic transmission**
- **Acute ethanol inhibits all glutamate receptors**
- **Chronic ethanol exposure can affect NMDARs, kainate receptors , AMPA receptors (AMPARs), and metabotropic glutamate receptors (mGluR)**
- **Linked to different ethanol-related phenotypes.**
- **Chronic ethanol exposure elevates extracellular glutamate levels in several brain regions, inducing a ‘‘hyperglutamatergic’’ state thought to contribute to AUDs**
- **glutamate uptake has been targeted to treat AUD**

Synaptic Plasticity

- Ethanol alters learning and memory, and this may involve effects on synaptic plasticity, including long-term depression (LTD) and long-term potentiation (LTP)
- **The PFC is involved in the cognitive symptoms of AUD.**
- **Chronic ethanol exposure induces an increase in the NMDA/AMPA current ratio in the PFC**
- **a neuroadaptation likely associated with reduced behavioral flexibility**
- **Ethanol can also affect striatal plasticity**
- **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**
- **plasticity deficits in the NAc and hippocampus may contribute to behavioral adaptations to chronic ethanol**

Circuitry

- much of the past focus has been on ethanol effects on molecules and synapses
- these targets must be considered in the context of micro- and larger circuits
- ethanol effects on cellular targets vary across brain regions due to differences in the molecular complement of different neurons and differences in ethanol sensitivity
- 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.
- This circuit-centered work can help to show how specific neuronal pathways and neurotransmitters are implicated in ethanol-specific phenotypes, including reinforcing, appetitive, and consummatory behaviors

From signalling to circuitries

- **AUD is a complex disorder, with various clusters of behavioural phenotypes characterizing different stages of the condition**
- **(for examples, binge drinking and intoxication, withdrawal and negative affect, preoccupation and anticipation, craving and relapse)**
- **intracellular signalling cascades affected by alcohol drinking must be taken in the context of their effects on brain circuits**
- **the potential interplay between molecular signalling cascades and circuits**

The mesolimbic system

- consists of projections from the VTA to limbic regions such as the NAc, hippocampus and amygdala.
- has a major role in learning, memory, motivation and reward, and drugs of abuse are considered to 'hijack' this circuit
- During episodes of alcohol intake, the activity of the mesolimbic system increases, resulting in enhanced release of dopamine in the NAc, which correlates with reinforcement of drug taking
- the transition from drug use to abuse is typically associated with a decrease in mesolimbic activity, and a reduction in dopamine levels in the NAc is associated with abstinence
- This dopaminergic deficiency is thought to have a key role in the allostatic mechanisms that cause a progressive reduction in the hedonic set point, resulting in increased alcohol seeking and intake

The nigrostriatal system

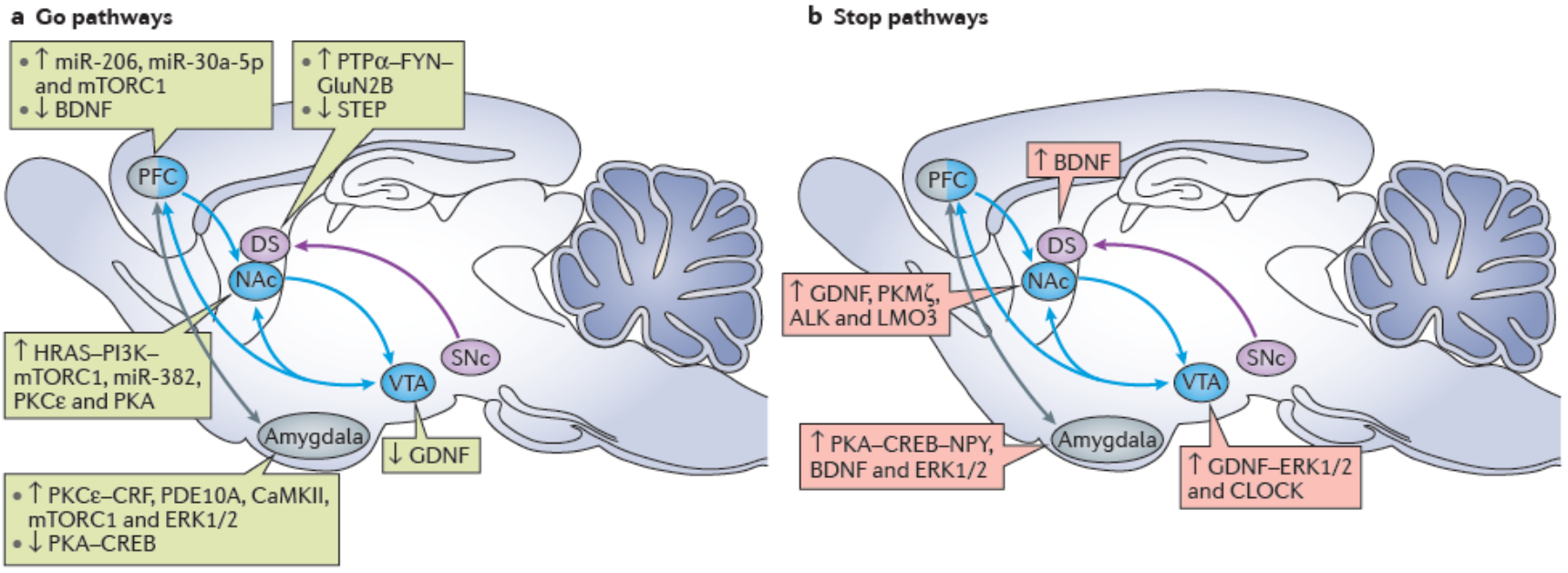
- **the dopaminergic nigrostriatal system, which projects from the substantia nigra to the dorsal striatum, has a crucial role in the habitual and compulsive nature of alcohol addiction**
- **Alcohol consumption is initially maintained by goal-directed behaviours, which are controlled by the NAc and the DMS**
- **chronic drug and alcohol intake attenuates cortical control, and the subcortical dominance shifts from the DMS to the DLS, a brain region that drives habit learning**
- **thus leading to impulsive and compulsive behaviours associated with addiction**

The extended amygdala

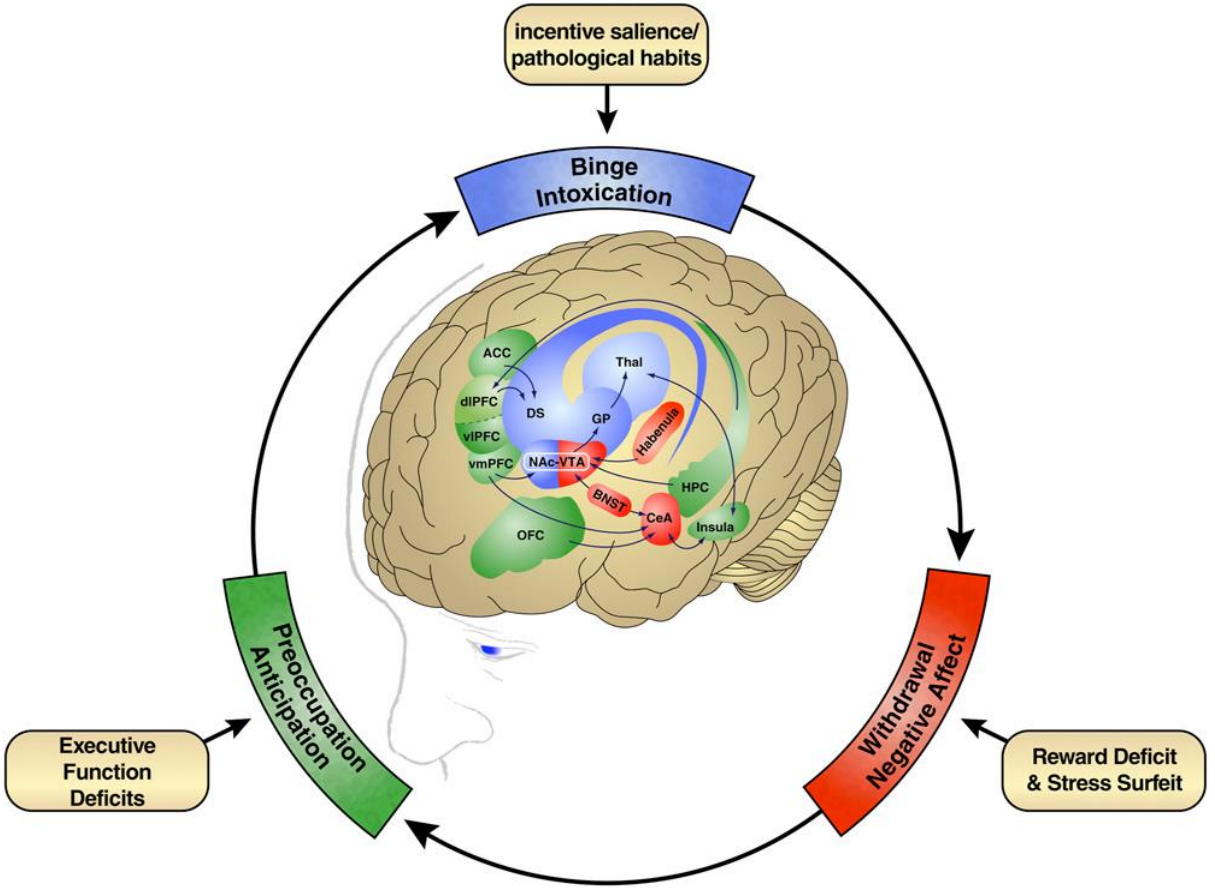
- **the negative emotional state that often accompanies alcohol withdrawal is thought to engage the extended amygdala**
- **an area composed of several basal forebrain regions, including the bed nucleus of the stria terminalis, the BLA, the CeA and the posterior shell of the Nac**
- **The extended amygdala includes major components of the stress regulatory system of the brain, which also have a major role in negative reinforcement, in which alcohol intake serves to suppress negative states**

Cortico-amygdalar pathways

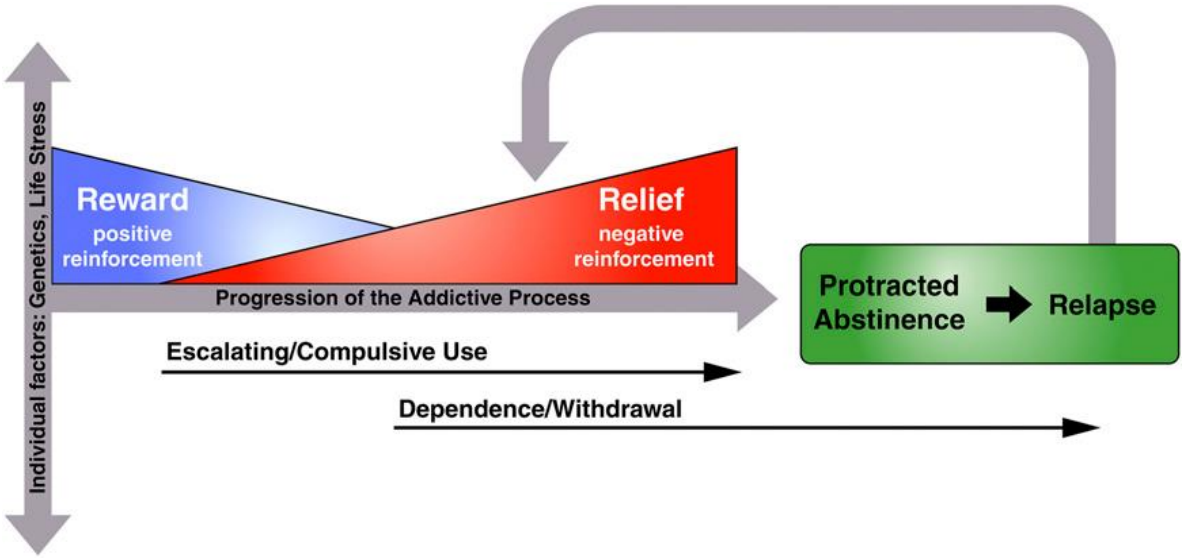
- The cortico-amygdalar networks mediate the retrieval and maintenance of long-term fear memories, as well as fear extinction
- implicated in synaptic plasticity changes in the cortico-amygdalar circuitries that drive the retrieval and reconsolidation of these persistent memories, leading to relapse to alcohol seeking and drinking
- Alcohol can cause a multi-target imbalance in various signalling pathways within several brain circuitries, which drive and maintain excessive, compulsive alcohol- drinking behaviours.
- A major challenge is identifying a direct link between the molecular cascades and the brain circuitries


a Go pathways
• ↑ miR-206, miR-30a-5p and mTORC1
• ↓ BDNF
• ↑ PTPα–FYN–GluN2B
• ↓ STEP
PFC
DS
NAc
↑ HRAS–PI3K–mTORC1, miR-382, PKCε and PKA
SNc
VTA
↓ GDNF
Amygdala
• ↑ PKCε–CRF, PDE10A, CaMKII, mTORC1 and ERK1/2
• ↓ PKA–CREB
b Stop pathways
↑ BDNF
PFC
DS
NAc
↑ GDNF, PKMζ, ALK and LMO3
SNc
VTA
↑ PKA–CREB–NPY, BDNF and ERK1/2
Amygdala
↑ GDNF–ERK1/2 and CLOCK

Conceptual framework for the neurobiological basis of substance use disorders



Conceptual framework of sources of reinforcement in addiction



Allostatic change in emotional state associated with the transition to addiction

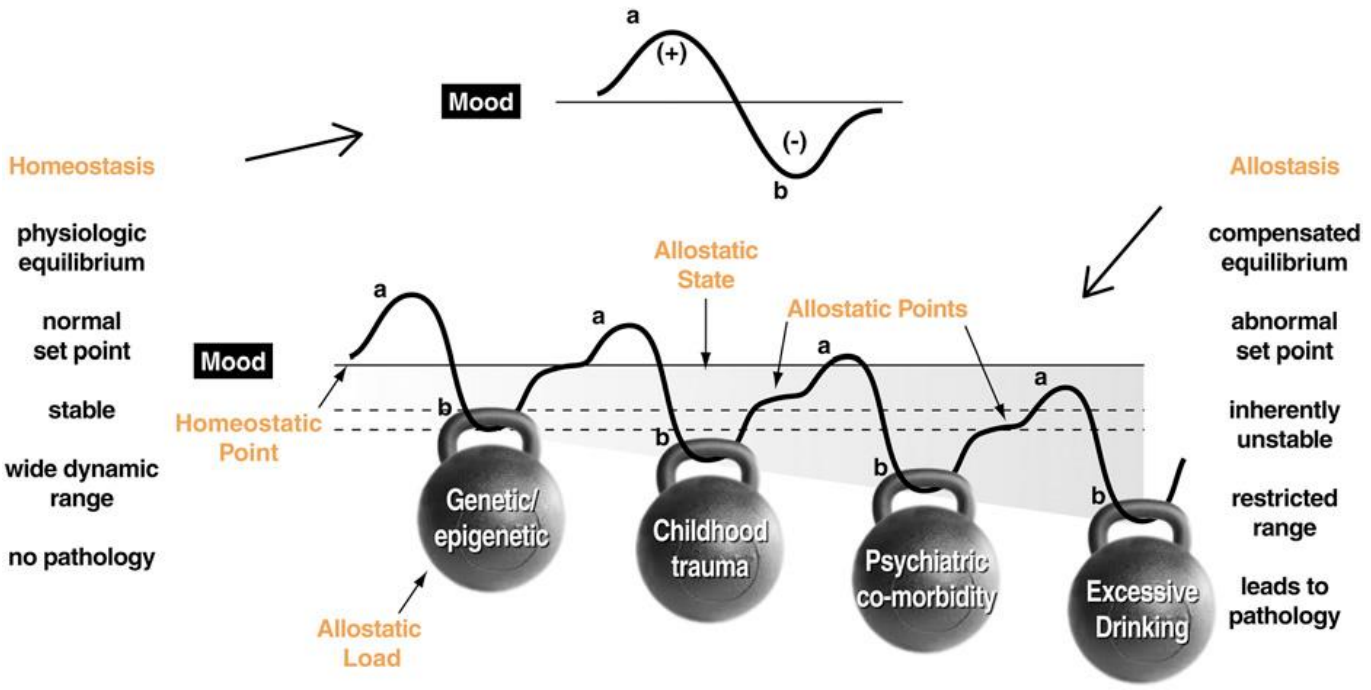


Table 1.1 Journey from responsible alcohol drinking to alcoholism.

Stages of alcohol addiction	Possible mechanisms discussed in the review
Acute phase: positive reinforcement[a]	Rising BAC, DA_{ergic}, OP_{ergic}, $GABA_{ergic}$, and 5-HT_{ergic} neurons and respective receptors
Acute phase: negative reinforcement[b]	Falling BAC, NMDAR and GABAR, and receptor/voltage-gated Na^+ channels
Hangover/tolerance/ craving	Alcohol metabolism, acetaldehyde accumulation, excitatory NT signaling, and 5HTRs
Alcohol addiction	Adenosine, DAR, 5HTR, GABAR, and gluR
Withdrawal symptoms	NMDA/GluRs, GABA, hyperexcitation, and seizures

NT system	Existing and potential pharmacotherapies
Dopamine system Normalization of DA_{ergic} response Alcohol drinking Adjuvant treatment for the withdrawal symptoms (WS)	Dopamine receptor partial agonists *Aripiprazole—D_2 receptor partial agonists* *Bromocriptine*—WS adjuvant therapy Dopamine receptor antagonists *GSK 598809—D_3 receptor antagonists*
GABA system Prevents relapse Suppresses the WS	GABA receptor modulators *Gabapentin—$GABA_B$ receptor modulator* *Benzodiazepines*
5-HT systems Decrease in craving and drinking • Brain stress system • Stress Management • Manage alcohol Drinking • Prevents relapse • Reduce alcohol drinking • Adjuvants for the WS	Selective serotonin uptake inhibitor *Fluoxetine, Sertraline, Citalopram* 5-HT Antagonist *Ondansetron* CRF-related targets *Antalarmin, pexacerfont—CRF receptor antagonists* Non-CRF-related targets *Prazosin*—α1 Adrenergic receptor antagonist *Naltrexone/β-Funaltrexamine*—μ opioid receptor antagonists *Norbinaltorphimine*—κ opioid receptor antagonist *Naltrindole*—δ opioid receptor antagonist *Nalmefen*—μ and δ opioid receptor antagonist Neuropeptide Y receptor agonist

NT system	Existing and potential pharmacotherapies
Glutamate system	Glutamate receptor agonists and antagonists
Increases duration of abstinence	*Acamprosate*—*N*-methyl-D-aspartate (NMDA) receptor partial agonist
Reduces drinking and facilitates	*Topiramate*—α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist
Abstinence	3-[(2-methyl-1,3-thiazol-4-yl) ethynyl] pyridine (MTEP) mGluR5 antagonist
Alcohol dependence and drinking	LY-379,268—mGluR2 and mGluR3 agonist
Stress management and alcohol craving	(1S,2R,5R,6R)-2-amino-4-oxabicyclo [3.1.0]hexane-2,6-dicarboxylic acid
Antipsychotic activity	Aripiorazole

Molecular and neurocircuitry targets for medications development to reverse hyperkatifeia of the withdrawal/negative affect stage for OUD and AUD

Target	Manipulation	Opioids	Alcohol
Within-system			
Dopamine	Dopamine receptor partial agonists	✓	✓
Opioid peptides	G protein modulators	✓	—
	CREB	✓	—
	cAMP/PKA modulators	—	✓
	CREB	—	✓
GABA/glutamate	GABA subunit receptor agonists	✓	✓
	Glutamate receptor antagonists	✓	✓
Between-system			
CRF	CRF_1 receptor antagonists	✓	✓
Dynorphin	κ-Opioid receptor antagonists	✓	✓
Vasopressin	V_{1b} receptor antagonists	✓	✓
Norepinephrine	α_1-Adrenergic receptor antagonists	✓	✓
	α_2-Adrenergic receptor agonists	✓	✓
	β-Adrenergic receptor antagonists	✓	✓
Hypocretin	Hcrt-1 receptor antagonists	✓	✓
	Hcrt-2 receptor antagonists	✓	✓
Neuroimmune system	Neuroimmune modulators		
	Tumor necrosis factor	✓	✓
	Phosphodiesterase inhibitors	—	✓
Antistress modulators			
NPY	Y_1 receptor agonists	✓	✓
	Y_2 receptor antagonists	✓	✓
Nociceptin	Nociceptin receptor agonists	✓	✓
Endocannabinoids	FAAH inhibitors	✓	✓
	MAGL inhibitors	✓	✓
Oxytocin	Oxytocin receptor agonists	✓	✓
Hyperalgesia/pain			
Glutamate	NMDA receptor antagonists	✓	✓
CRF	CRF_1 receptor antagonists	✓	✓
Dynorphin	κ-Opioid receptor antagonists	✓	—
Melanocortin	Melanocortin receptor 4 antagonists	✓	✓
PKC	PKCε inhibitor	—	✓
	PKCγ inhibitor	✓	—
Serotonin	5-HT_{2A} receptor antagonist	—	✓

Medication	Main mechanism of action	Common clinical indication
Disulfiram	Acetaldehyde dehydrogenase inhibitor; blocks the metabolism of alcohol	Alcohol dependence
Naltrexone	Opioid receptor antagonist	Alcohol dependence
Acamprosate	Precise mechanism is unknown; potentially modulates glutamatergic and GABAergic neurotransmission and modifies neuronal excitability	Alcohol dependence
Topiramate	Precise mechanism is unknown; potentially enhances GABAergic activity and antagonizes Glutamate (kainate and [or] AMPA type) receptors	Epilepsy, prophylaxis of migraine headaches, investigated for alcohol dependence

Medication	Main mechanism of action	Common clinical indication
Baclofen	GABA-B agonist	Spastic movement disorders, investigated for alcohol dependence
Clozapine[a]	DA—5-HT antagonists	Schizophrenia
Olanzapine, quetiapine[a]	DA—5-HT antagonists	Schizophrenia, BD
Flupentixol[b]	DA antagonist	Schizophrenia
Lamotrigine[c]	Precise mechanism is unknown; potentially stabilizes neuronal membranes and inhibits the release of excitatory neurotransmitters	Epilepsy, BD
Valproate	Precise mechanism is unknown	Epilepsy, BD
Lithium	Precise mechanism is unknown	BD
Imipramine, desipramine[d]	SNRIs	MDD, anxiety disorders
Fluoxetine, paroxetine, sertraline	SSRI[e]	MDD, anxiety disorders
Nefazodone	5-HT2 receptor antagonist and moderate SNRI	MDD
Buspirone presynaptic	5-HT1A partial agonist	Anxiety disorders
Prazosin	NE (α-1) antagonist	Hypertension

Evolutionary perspectives

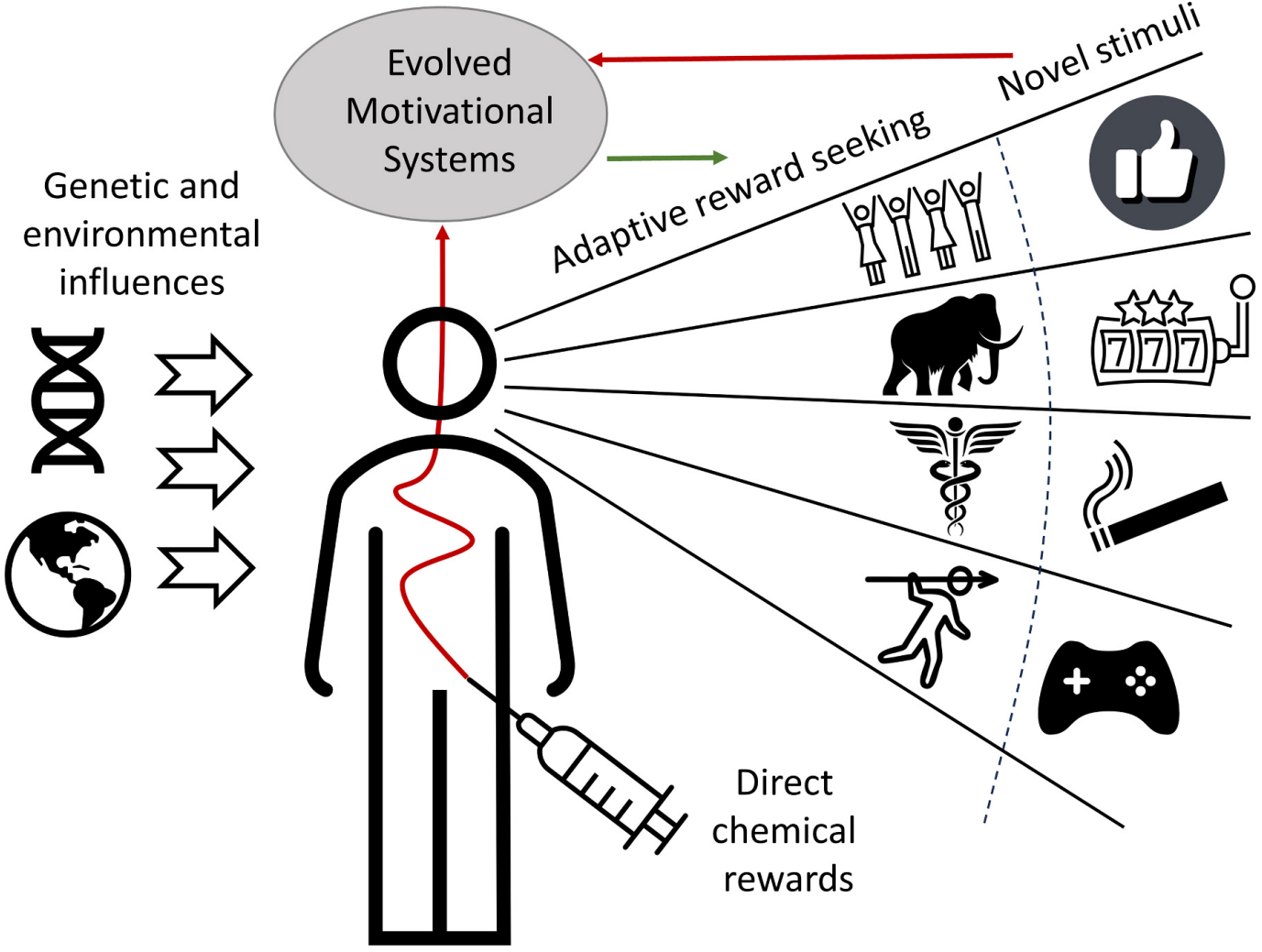
- **In explaining addiction, evolutionary perspectives most commonly reference the concept of ‘evolutionary mismatch’**
- **genotypes and phenotypes were shaped by natural selection for millions of years within ancestral environments**
- **evolutionary accounts generally propose evolutionary mismatch occurs in a ‘hijacking’ of previously adaptive systems**
- **Drugs of abuse are generally framed as overriding adaptive functions of primary emotional systems by increasing positive affect or decreasing negative affect**
- **The novelty of these compounds (in structure, purity or quantity) means we lack evolved mechanisms limiting artificial reward experiences**

Evolutionary perspectives

- humans have been involved in a multi-million year co-evolutionary relationship with psychotropic plant substances
- Plants have evolved specific allelochemicals mimicking the structure of neurotransmitters and thus binding to multiple neural receptors, including acetylcholine, nicotinic, muscarinic, adrenergic, serotonin, dopamine, adenosine, opioid and cannabinoid receptors
- It is these adaptations that predispose humans to substance-seeking behaviour by exploiting the neurotransmitter-analog plant chemicals instead of having to produce the neurotransmitters endogenously, which would be metabolically costly
- Other accounts have considered pharmacological uses such as analgesia, stimulation and sedation as possible psychotropic effects which enhanced reproductive success in human evolutionary history

Evolutionary perspectives

- **Homo sapiens' relationship with alcohol likely predates records by millions of years- "drunken monkey" hypothesis**
- **primates, evolved the ability to digest ethanol, a natural product of ripening fruit which can be converted into energy, along with a preference for ethanol-rich ripe fruits**
- **Alcohol exposure is inevitable among frugivores- whenever a high concentration of carbohydrates is reached, ethanol (and, to a lesser extent, methanol) production occurs**
- **eating alcohol-rich food has been correlated with eating sugar-rich foods and higher calorie intake**
- **a functional benefit in social interactions, particularly for its role in rituals and group bonding**
- **shift to a more omnivorous diet exposed hominins to zoonotic parasites and pathogens against which plant-derived substances can help**
- **Non-human primates and other animals self-medicating in various ways, including in leaf-eating for anti-parasitic properties and dirt eating to aid digestion**


Evolved
Motivational
Systems
Genetic and
environmental
influences
Adaptive reward seeking
Novel stimuli
Direct
chemical
rewards

Outstanding questions

- **How do the specific levels of alcohol-induced adaptations interact and influence each other to result in complex behavioral changes?**
- **Which molecular pathways and circuits could serve as the most promising potential therapeutic targets for alcohol use disorder (AUD)?**
- **Which mechanisms determine individual vulnerability to excessive alcohol consumption?**
- **AUD is a polygenic disorder. How is it possible that manipulating single genes in animal models can result in animals that are resilient to AUD?**
- **Are there additional, currently unknown variants that confer susceptibility for or resilience against developing problem drinking and AUD?**

Conclusions

- alcohol use leads to brain region-specific and, potentially, neuron- and circuit-specific neuroadaptations that prevent or promote the transition from moderate to excessive alcohol use
- alcohol-induced activation or inhibition of intracellular signalling seems to be determined by the amount of alcohol consumed and by the duration of exposure.
- the same signalling molecules contribute to both the go and stop pathways, making it likely that the opposing actions of these molecules are determined by the locus of activity.
- how does alcohol exactly work?
- it is unclear how a seemingly nonspecific agent such as alcohol can produce such restricted signalling events
- elucidating the molecular mechanisms underlying alcohol-drinking behaviours should allow us to move forward to translational paths for the treatment of AUD.

Thank you!

- **“To alcohol! The cause of... and solution to... all of life's problems”**
- **— Matt Groening**