BUZZED:
Using Neuroscience to Understand Alcoholism

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Presentation Outline

• Why do we study alcohol?  
  A widespread problem

• Current treatment options  
  Why they’re not good enough

• Basic research  
  Animal models and neuroscience

• The future of research  
  And the future of treatment?
Ingrained in Culture
In 1956, the American Medical Association (AMA) stated alcoholism was a disease, as it met the five criteria needed in order to be considered a disease: pattern of symptoms, chronic, progression, subject to relapse, and treatability.
DSM-V Criteria for Alcohol Use Disorders (AUDs)

*Integrated alcohol use and dependence into one disorder; two or more symptoms qualify an individual for AUD (ranked mild-severe)*

1. Alcohol consumed in larger amounts or over a longer period than intended.
2. Unsuccessful efforts to cut down or control alcohol use.
3. Great deal of time obtaining, using, or recovering from alcohol.
4. Craving or desire to use alcohol.
5. Recurrent use despite failure to full major obligations (work, school, home).
6. Continued use despite social/interpersonal problems.
7. Participation in social, occupational, recreational activities suffers due to alcohol use.
8. Recurrent alcohol use in physically hazardous situations.
9. Continued use despite knowledge of associated physical and/or psychological problems.
10. Tolerance.
Alcohol use (and abuse) is extremely prevalent

- In 2012, 87.6% of people ages 18 or older reported that they drank alcohol at some point in their lifetime.

- In 2012, 24.6% of people ages 18 or older reported that they engaged in binge drinking in the past month – 7.1% reported that they engaged in heavy drinking in the past month.

- Approximately 17 million Americans meet the criteria for an AUD.

Alcohol use (and abuse) is extremely prevalent

- An estimated 15% of individuals with an AUD seek treatment.

- Nearly 80,000 people die from alcohol-related causes annually, making it the third leading preventable cause of death in the US.

- In 2006, alcohol problems cost the U.S. $224 billion, primarily from lost productivity but also from health care and property damage costs.

Current Treatment Options: Behavior

• Mutual help groups (e.g., AA), cognitive behavioral therapy, couples and family therapy, supportive individual therapy, relapse prevention therapy etc.

• Technological advancements have increased availability of behavioral treatments (e.g., internet, smartphone use)

• More effective when combined with pharmacological treatment; higher rate of relapse when behavioral intervention is used without concomitant pharmacotherapy (Anton et al., 2006; Weiss et al., 2008)
Current Treatment Options: Pharmacotherapy

- Naltrexone
  - Reduces cravings
- Acamprosate
  - Reduces cravings
- Disulfiram (Antabuse)
  - Aversion medication

Other drugs under investigation
- Topirimate, Nalmefene, SSRIs, dopamine antagonists, CRF antagonists, NPY antagonists, varenicline

Moderate levels of efficacy, although improved by combinatorial treatment

Side effects, patient adherence, heterogeneity of patient population
Why haven’t we found a cure?

Or: Given the prevalence of AUDs, and the abundance of time, money, and research that has already been invested, why aren’t we closer to finding a solution?
AUDs are extraordinarily complex

- No “one size fits all” diagnosis ... or treatment
- Incredibly diverse patient population
  - Individual differences
  - Drinking history, patient history
  - Family history
  - Age at onset of drinking
  - Socioeconomic standing
- Treatment-seeking? Non-treatment seeking?
- High degree of comorbidity with other disorders
Same Symptoms, Different Disorders

Mood Disorders
- Anhedonia/Hyperhedonia
- Guilt
- Impulsivity

Alcohol Dependence
- Changes in motivation
- Pleasure and anhedonia (withdrawal)
- Guilt
- Impulsivity
- Habit formation

Gambling Disorders
- Habit formation
- Impulsivity
- Reward (tolerance)
- Guilt
Comorbidity: Beyond Chance

**Alcohol Use Disorder**

Sample of over 43,000 US adults indicated a lifetime prevalence of alcohol abuse was 17.8%; prevalence of lifetime dependence was 12.5% (Hasin et al., 2007)

**Pathological Gambling**

Numerous studies indicate that pathological and problem gambling affect between 0.5-2% of the population in western countries. (Hodgins, Stea & Grant, 2011)

AUD and PG display an incredible degree of comorbidity

(Daghestani, Elenz, & Crayton, 1996; Giacopassi, Stitt, & Vandiver, 1998; Lejoyeux, Feuche, Loi, Solomon, & Ades, 1999)

In one study of 75 treatment-seeking Australian gamblers, 73% had a coexisting AUD

(Maccallum and Blaszczynski 2002)
Understanding Disease States and Comorbidity

- **Disease States** (e.g., alcohol use disorder and pathological gambling)
- **Symptoms** (e.g., craving, tolerance, withdrawal)
- **Individual Brain Region** (e.g., nucleus accumbens)

How do we determine which brain region(s) are important?
The Whole is Greater than the Sum of the Parts
Refining our Understanding

Disease States
(e.g., alcohol use disorder and pathological gambling)

Symptoms
(e.g., craving, tolerance, withdrawal)

Individual Brain Region
(e.g., nucleus accumbens)
Refining our Understanding

- **Disease States**
  (e.g., alcohol use disorder and pathological gambling)

- **Symptoms**
  (e.g., craving, tolerance, withdrawal)

- **Brain Circuits**
  (e.g., mesolimbic reward circuitry)

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- **Diagnostic and Statistical Manual of Mental Disorders (DSM)**
- **Research Domain Criteria (RDoC)**
We use imaging techniques to compare and contrast the brains of control subjects and alcoholics.
Human Research is Limited

- **Resolution**
  - Spatial, Temporal

- **Ethics**
  - Cause and Effect

- **Environment**

Q: How do we model human disease in an animal?

A: We don’t.

Instead, we use animal models that probe specific aspects of neuropsychiatric illness (e.g., ethanol preference or anxiety-like behavior).
Animal Models of AUDs

• The benefits of using animal models

• Choosing the proper animal model
  – Species, strain

• Ethical considerations
Selective Breeding

- Genetic and biochemical mechanisms

- Examine selective traits
  - Sensitivity to hypnotic effect of alcohol (long-sleep and short-sleep mice)
  - Hypothermic effect (COLD and HOT mice)
  - Locomotor stimulant effect (FAST and SLOW mice)
  - Alcohol withdrawal seizures (WSP and WSR mice)
  - Acute functional tolerance (HAFT and LAFT mice)
Selective Breeding

- Ethanol preferring and non-preferring mouse strains
  - C57BL/6J vs. DBA/2J
  - HAP and LAP (Chester et al., 2003)
  - HDID1 and HDID 2 (Crabbe et al.)

- Individual variation, even within strains

Important consideration: selective breeding allows us to examine various aspects of alcohol use and alcohol effects, but there is not an “alcoholic mouse”
Selective Breeding

- Alko Alcohol (AA) and Alko Nonalcohol (ANA) (Eriksson 1968);
- Alcohol preferring (P) and non-preferring (NP) (McBride and Li 1998);
- Sardinian alcohol-preferring (sP) rats (Colombo 1997);
- High alcohol drinking (HAD) and low alcohol drinking (LAD) rats (Li et al., 1993).
Modeling specific facets of AUDs

• Fetal alcohol exposure (FASD models)

• Ethanol preference (voluntary consumption)

• Specific responses to ethanol
  – Anxiolytic effects, tolerance, hangovers, etc.

• Low/moderate drinking

• Excessive (or binge-like) drinking

• Ethanol dependence (and withdrawal)
Binge-like Alcohol Consumption

• Pattern of drinking resulting in blood alcohol concentrations of 0.08 g% (80 mg%) or above
  – 4 drinks (F) or 5 drinks (M) over a 2-hour period (NIAAA)

• Common pattern of drinking
  – Majority of binge drinking episodes in the United States involve adults over the age of 26 (Nelson et al., 2009; Naimi et al., 2003)
Binge Drinking: Risks

- Aggressive and violent behavior  (Brewer et al., 2005)

- Risky choices
  - Impaired driving, unprotected sex  (Naimi et al., 2003; Miller et al., 2007)

- Health consequences
  - Mental distress, decreased quality of life, metabolic syndrome, heart disease, type-II diabetes, stroke  (Fan et al., 2008, Okoro et al. 2004)

- Increased risk of developing alcohol dependence in individuals that binge drink early in life  (Miller et al., 007, Hingson et al., 2006)
Modeling Binge-Like Drinking

• Intragastric administration (Faingold et al., 2001; Coleman et al., 2011)

  Bertola et al., 2013

• Intermittent access and scheduled high alcohol consumption (SHAC) (Finn et al., 2005; Szumlinski et al., 2007; Cozzoli et al., 2009)
Modeling Binge-Like Drinking

- Drinking in the Dark (DID) 
  (Rhodes et al. 2005 and 2007; Crabbe et al., 2011; Lowery-Gionta et al., 2012)

- 3 hours into dark cycle, homecage water bottles are replaced with bottles containing 20% (v/v) ethanol or sucrose

- Days 1-3

- Day 4

- Immediately following bottle removal, 10μl of tailblood collected for BEC analysis
Drinking in the Dark (DID)

- Capitalizes on innate consummatory behavior
  - Provides ethanol access during period of naturally high drinking (Gill et al., 1986)

- High levels of voluntary ethanol consumption
  - Utilizes a 2-4 hr access period (Rhodes et al., 2005)
  - Pharmacologically relevant BEC (Rhodes et al., 2007)

- Ethanol consumption not dependent upon food availability (Lyons et al., 2008)

- Induces motor deficits akin to those experienced by humans (Rhodes et al., 2007)
Current treatments display predictive validity using the DID model.

**Naltrexone**

Kamdar et al., 2007

**Acamprosate**

Gupta et al., 2008
In fact, many systems have been implicated as playing a role in binge-like drinking...

- **Glutamate** (Gupta et al., 2008)
- **GABA** (Melon and Boehm, 2011; Moore et al. 2007)
- **Dopamine and opioid systems** (Kamdar et al., 2007)
- **Endocannabinoid** (Lisenbardt et al., 2009)
- **Nicotinic** (Henderson et al., 2007)
- **Corticotrophin releasing factor (CRF)** (Sparta et al., 2008; Lowery-Gionta et al., 2012)
- **Neuropeptide Y (NPY)** (Sparrow et al., 2012)
- **Melanocortin** (Navarro et al., 2008)
CRF antagonism blunts binge-like ethanol consumption in mice...

Lowery-Gionta et al., 2012
Additionally, binge-like drinking may recruit different mechanisms than non-binge-like drinking (Lowery-Gionta et al., 2012).
Does DID model dependence?

• Are binge-drinking mice dependent or non-dependent?
  – Many changes in neuropeptide systems echo those observed in dependent animals
  – Similar phenotypes may suggest overlapping pathways

• Dependence-like state associated with:
  – Increases in voluntary EtOH consumption and self-administration (Becker and Lopez, 2004)
  – Elevated anxiety-like behaviors (Kliethermes et al., 2004)
  – Increased ataxia (Philibin et al. 2012)
  – Increased sensitivity to handling-induced convulsions (HICs) after 24+ hrs of withdrawal (Homanics et al., 1998)
Following many DID cycles, mice do not show signs of dependence

- Moderate increases in voluntary alcohol consumption (greater in animals with longer ethanol experience)
- No change in anxiety-like behaviors
- No change in ataxia
- No change in sensitivity to handling-induced convulsions or ethanol withdrawal

Cox et al., 2013
Repeated binge-like drinking: a way to model the transition to dependence?

Lowery-Gionta, 2011
Rodent models of dependence

• *Intragastric* (Majchrowicz, 1975)
  – Repeated exposure, 3-5x a day
  – Intensive, difficult, difficult to maintain BEC; risk of overdose

• **Ethanol diet** (Moy et al., 1997)
  – Sole source of calories; individual variability; consume fewer calories than from normal chow

• Long-term voluntary drinking

• **Ethanol vapor** (Rodgers et al., 1979)
  – Combined with intermittent alcohol (CIE/IA)
Chronic Intermittent Exposure (CIE) to Ethanol Vapor

Gilpin et al., 2008
CIE Induces Dependence-Like Phenotypes

O’Dell 2004

Cagetti 2004
CIE Induced Dependence-Like Phenotypes

- CIE produces increases in *initiation* and *maintenance* of alcohol self-administration following seven weeks of exposure (Rimondini et al., 2003).

- In rats, increased anxiety (and sensitized anxiety response) persists for many weeks following the end of CIE (Baldwin et al., 1991; Rassnick et al., 1993; Gatch et al., 1999; Rasmussen et al., 2001; Valdez et al., 2002, 2003).

- Vapor exposure produces increases in alcohol-drinking behavior in rats, an effect augmented by multiple withdrawals (Roberts et al., 1996, 2000; O'Dell et al., 2004).

- Alcohol-dependent rats exhibit increases in anxiety-like behavior both early in alcohol withdrawal and well into protracted abstinence from alcohol (Kliethermes, 2005).

- Rats exhibit increases in ICSS current thresholds (Schulteis et al., 1995) and decreases in operant responding for natural reinforcers (Slawecki, 2006) following termination of chronic alcohol vapor exposure.
Advancing Our Understanding Of Neuropsychiatric Illness

- Evolving understanding of disease and comorbidity
- Development of appropriate animal models
- Identification of neuronal circuitry underlying symptoms
- Understanding multi-circuit interactions that may inform selective therapeutics
Plentiful Targets

Moonat et al., 2010

Koob and Vokow, 2010
In vivo electrophysiology
Examining communication between different brain regions

Dzirasa et al., 2011
Combining animal models of AUDs with *in vivo* electrophysiology

- Examine individual differences
  - Pre- and post-exposure
- Identify changes induced by different patterns of drinking
- Examine the effect of concomitant drug exposure
- Identify both short-term and long-term alterations
- Determine whether deficits in neurocommunication may be rescued by pharmacotherapy

...and much more!
Using Neuroscience to Understand Alcoholism

- Patient experiences
- Clinical research
- Basic research
- Animal models
- Double-blind drug trials
- Human imaging
- In vivo electrophysiology
Basic Research and the Clinic: A Two-Way Street
The Future of Treatment?

Where do we go from here?

Identify Relevant Neurocircuitry
   Develop targeted therapeutic options

Develop Appropriate Animal Models
   Model most relevant symptoms

Translate Knowledge
   Open communication between clinic and basic science
Where do we go from here?

Identify Relevant Neurocircuitry
   Develop targeted therapeutic options

Evaluate Efficacy
   Clinical observations

Translate Knowledge
   Open communication between clinic and basic science

Develop Appropriate Animal Models
   Model most relevant symptoms
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