Psych 3102
Introduction to Behavior Genetics

Lecture 26

Substance use and abuse

Alcohol

Genetics of substance use disorders (SUDS)

- abuse of drugs is one of the leading public health problems

- societal and personal burdens
  – health care, lost productivity, broken families, ruined careers, violent victimization, increases risks for chronic disabling illness

- aims of behavior genetic research is to get better understanding of origin of use disorders , so that better prevention and intervention methods might be developed

- behavior genetic research has helped transform field - these disorders are no longer viewed as result of moral weakness or as an outcome of unresolved conflict

- widespread recognition there is a neurological basis with genetic influence

- evidence is that these are chronic conditions - the person cannot be ‘cured’

Biological basis

Brain is hard-wired to increase pleasure, decrease pain – underlies use of all drugs

all additive substances share a commonality:

they all increase dopamine levels in nucleus accumbens (main reward center of brain)

amphetamines do this directly

cocaine blocks reuptake

alcohol, narcotics(heroin, pain relievers) suppress neurons that inhibit release

Why do some keep using to their detriment, ie become addicted?

1. Genetic vulnerability
2. Dopamine-regulating circuit changes

The substance use and disorder phenotype

- disorders are relatively common
  – most common mental health problem in nearly all Western countries
  - community based samples, population twin studies will provide large #s with clinically relevant levels of abuse/dependence

- both clinical and sub-clinical patterns of use have health consequences
  - research not limited to disorders

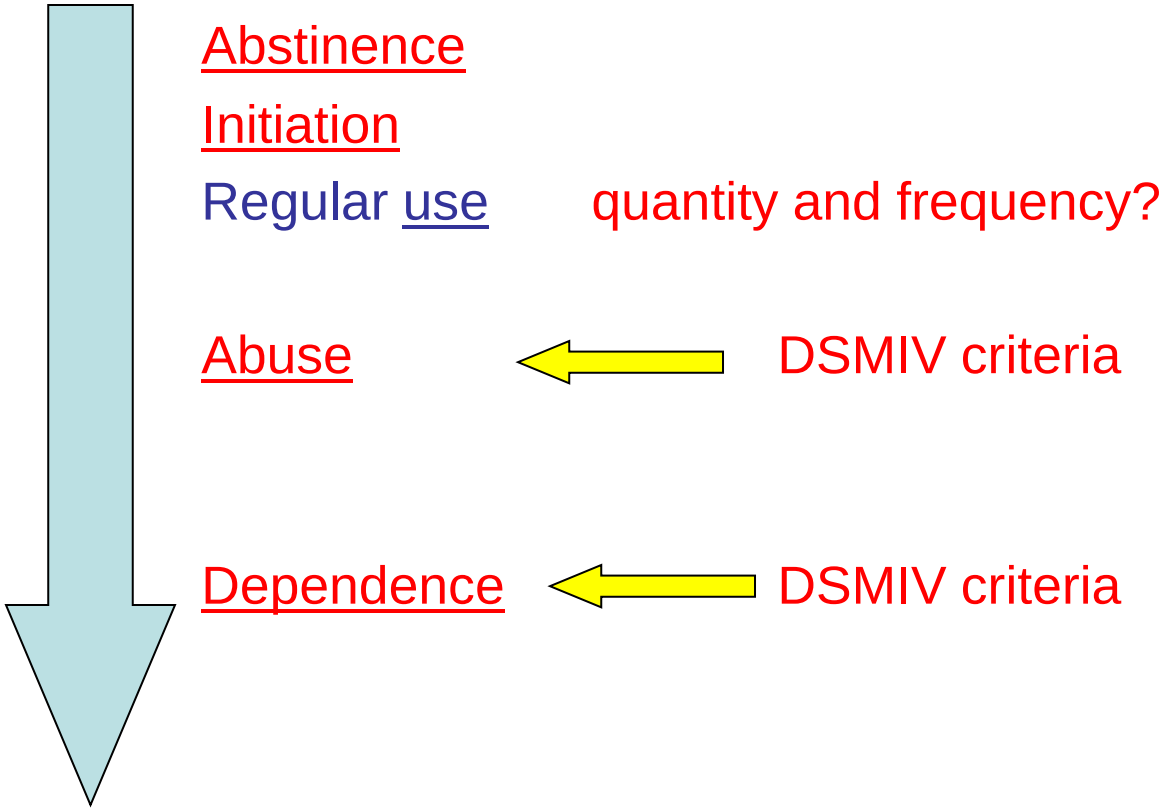
- developmental framework is apparent, with different influences acting at different stages

- a use disorder rarely occurs in isolation
  – comorbidity with other drug use and with psychopathology, personality disorders

- access to substances is obviously necessary
  – there will be genotype/environment interaction and correlation

Levels of substance use

- use is viewed as occurring on a developmental continuum
- different influences act on the different levels
- influences are both substance-specific and substance non-specific



Influences on substance use and abuse

Research shows substance use runs in families

Family risks (over no use) some families are about 3x likely to use than others

	Alcohol	Cannabis	Other drugs .
Use	1.8	2.7	3.2
Abuse	3.5	2.9	1.6
Dependence	3.0	3.2	0.8

+ only a small fraction of those who experiment with or use substances proceed to harmful use

- research indicates health efforts may be more effective if directed

a) at those who are more likely to abuse substances and suffer social and personal impact and

b) at the transition from use to abuse rather than on experimentation

Abuse of prescription drugs

An increasing, more recent problem

psychiatric medications

pain relief drugs

abuse of these dwarfs other illicit drug problems:

- hospitalizations related to these up x5 over last 10 years
- more high school seniors report recreational use of these drugs than heroin and cocaine combined

Alcohol use and use disorders

- Abuse and dependence are complex genetic traits that are influenced by environmental factors

- 2002 WHO report: alcohol is 5th leading cause of death & disability worldwide
  - liver disease (cirrhosis)
  - cancer (especially breast cancer in women)
  - cardiovascular disease (weakening of heart muscle, stroke, hi BP, irregular heartbeat)
  - shrinkage of cerebral cortex

- Heritability for alcoholism (alcohol dependence)
- Similar for alcohol abuse (to be no distinction in DSMV)
- Influences on use (NOT abuse, dependence) of alcohol are largely environmental

developmental framework

–different influences at different ages and levels of use

Sex differences

- prevalence rates
- influences, both genetic and environmental
- women alcoholics are more likely to have comorbid disorders
- women are more likely to have alcoholic partners due to assortative mating on the part of females only
- health problems caused by abuse and dependence are worse in women

Fetal alcohol syndrome and spectrum defects

4 necessary features for syndrome (FAS):

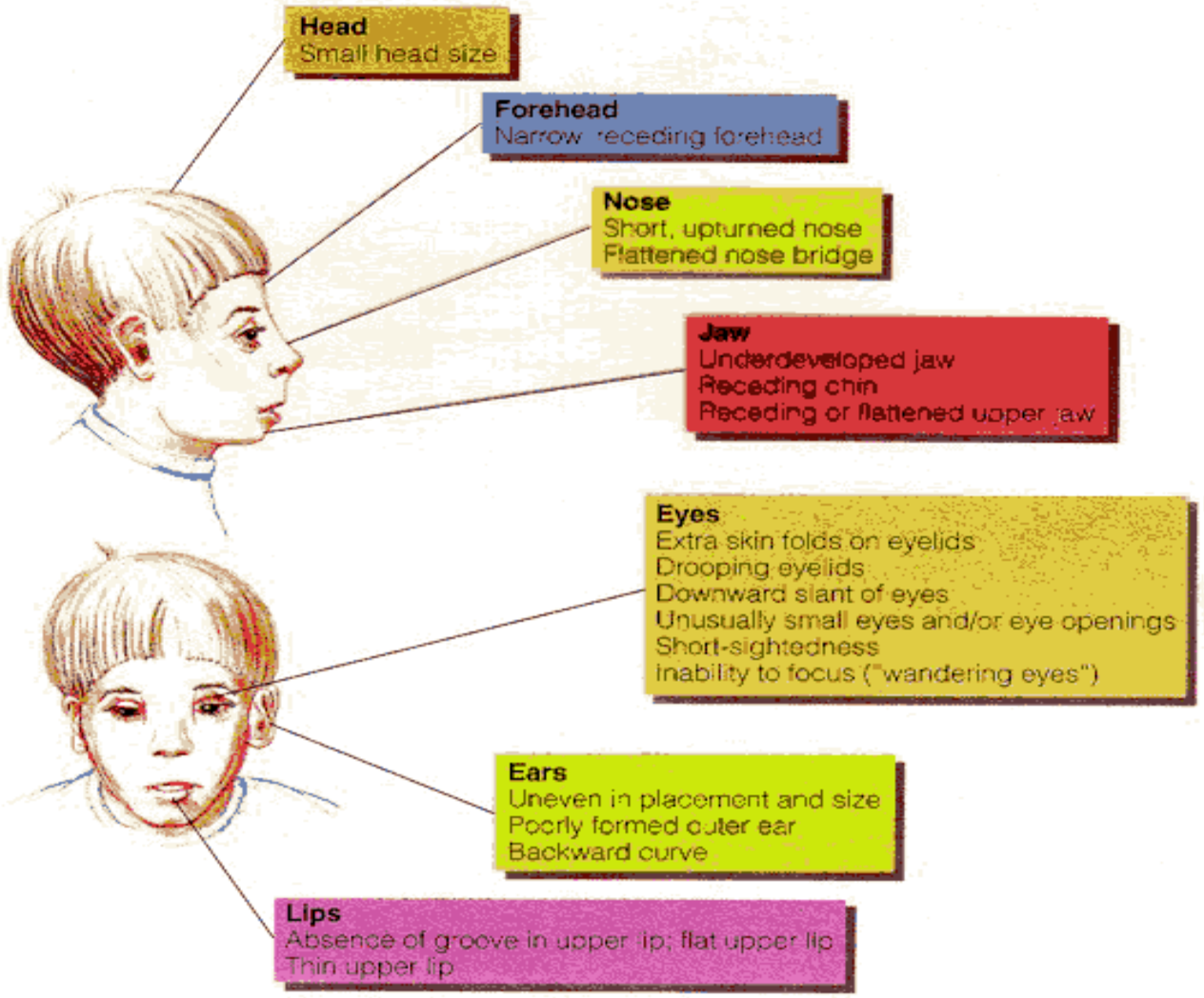
1. maternal alcohol consumption
2. craniofacial features (lack = spectrum diagnosis)
3. CNS dysfunction
4. growth retardation (pre- and post-natal)

- spectrum prevalence = 1 in 100

30,000 babies / year born with alcohol-related defects

- billions of dollars spent on treatment for these babies each year
- not all women who drink whilst pregnant produce children with FAS, genetics of Mom, child and also environmental circumstances (education, SES, time of consumption) are important
- alcohol can act very early in development (gastrulation) probably by changing methylation patterns (ie. epigenetically)
- some syndrome features produced by consumption later in gestation (eg. hyperactivity – may be produced by effect of alcohol on 3rd trimester brain growth spurt)

Typical Facial Characteristics of FAS



Lifetime rates of dependence

= history of dependence at any time in a person's life

- rates are increasing in younger cohorts
- there is tendency to earlier age of onset of dependence

DSMIII-R criteria: USA prevalence of alcoholism

males

females

illicit drug dependence males = 9.2%

females = 5.9%

nicotine dependence ~ 20% in young adults (same both sexes)

- high rate of male alcohol dependence
- family risks are higher

Subclinical use

substantial health burden from those with no diagnosis

- increased risk of driving accidents, violence
- decreased productivity
- increased risk of progressing to abuse and dependence, especially with early use (early adolescence) since use and disorders occur on a continuum
- Subclinical use has largely environmental influences
  - some genetic influences on preference, reaction to alcohol

Behavior Genetic Human studies

Which has the greatest influence on drinking behavior?

friends? parents? genes?

Depends on what age and what level of use we are discussing

at 14 - genes contribute very little, shared e = 40% of variance

at 23 – shared e contributes very little, genetic variance = 40%

Levels of use

1. Abstinence what influences a person to decide not to drink?
2. Initiation what influences a person to start drinking?
   what determines the person's response to alcohol?
3. Progression to abuse and dependency

   what makes a person increase quantity and frequency enough to lead to abuse and dependence?

1. Influences on decision to use alcohol versus abstinence

Most MZ and DZ correlations indicate very small gene effect
shared environment is large influence

- environmental variables more important than genetic

2. Influences on initiation and use

- initiation (USA) typically early to mid adolescence
  initiation after mid-twenties is uncommon

- for initiation, h^2 ~ 26%, shared e ~ 65% (Fowler et al 2007)
  shared sib and peer environment more important than parent

McGue et al (1996) J. Studies on Alcohol Disorders
adoptive sibs: reared together, not biologically related
biological sibs, parents all rated for drinking behavior

Adoptive sibs, age 12-18 same-sex, < 2 years apart in age r = 0.45
opposite-sex, > 2 years apart r = 0.05

adoptive P/O r = 0

P/O biological children = 0.24, so parental contribution genetic not environmental

Influences on level of use

- majority will try alcohol (and tobacco)

- age of initiation and how rapidly use escalates is more important than use itself for predicting future problem use

- for most, environment moderates use in young adults
  marriage career
  responsibilities multiply

So far - most influences have been environmental

Where do genetic risk factors enter into this?

3. Progression of drinking towards abuse/dependence

Different people are going to have different risk factors for abuse/dependence

1. Response to first drink

Protective factors: genetic tendency for low preference

genetic tendency to react badly to alcohol

alcohol dehydrogenase alleles

Risk factors:

hypersensitivity "whoa, this is awesome!"

- increased sensitivity to the stress-response dampening effects of alcohol may put some individuals at greater risk for alcoholism

measurable greater attenuation of cardio-vascular response to unavoidable shock in offspring of alcoholics compared to non-alcoholics, when given alcohol

+ other neurophysiological differences

eg. offspring of alcoholics show more relaxed, comfortable state after drinking

hyposensitivity "what 'whoa'? maybe I need more?"

Why?

- lower response to stress dampening effects - may lead to overconsumption
- lack of feedback inhibition
- need to consume larger amounts to achieve perceived desired effects

tolerance is high

non-alcoholic sons of male alcoholics show reduced sensation of intoxication after standard dose compared to non-alcoholic sons of non-alcoholics (matched for drinking history)

within 10 years: 43% of alcoholics' sons were alcoholic
11% of non-alcoholics' sons were alcoholic

Sensitivity and tolerance to effects of alcohol are genetically influenced
- leads to increased risk for use disorders in some

2. Externalizing behavior

traits associated with behavioral disinhibition increase risk for alcohol use disorders

Conduct disorder
– puts individual at greater risk of encountering alcohol at an early age (environmental)
- lack of ability to inhibit risky behavior increases likelihood of early use and overuse (genetic)

Common genetic risks found in ADHD, other externalizing disorders

Ball & Collier,2002

14 year-old twins (Review of 9 twin studies)

Community-based (clinical samples give biased results through overrepresentation of severe & comorbid individuals)

1% met dependence criteria
3% met abuse criteria
13% met CD criteria males > females

for alcohol symptom counts: $h^2 = 0$, $c^2 = 80\%$ no sex difference

for CD symptom counts: $h^2 = 50\%$ in males 30% in females
$c^2 = 30\%$ in both sexes

correlation between CD and alcohol counts = 0.5 mediated by shared e

genes are not an important influence on early alcohol use

CD behavior, shared environment are important influences

other studies (McGue et al 2001) have reported higher heritabilites in boys for early drinking, but still large shared e

Early use of alcohol is predictive

Grant & Dawson (1997) National Longitudinal Alcohol Epidemiological Survey

27,000 ever-drinking adults

- those trying alcohol before age 15, lifetime rate of dependence = 4 times higher than those trying alcohol after age 20

Males: 55%

Females: 25%

males, risk ~ 45% at 15, 14% after age 19

- early age of first alcohol use is a manifestation of generalized disinhibition (which has a strong genetic component)

early alcohol use was also associated with

Endophenotype common to all externalizing disorders:

p3 amplitude – low amplitude correlates with age of 1st drink, predates alcohol use

predicts onset of new SUDs h^2 = 60-65%

- alcohol use is NOT causal in CD behavior

Alcohol abuse and dependence

- typically onset is late adolescence, early adulthood
- factors affecting abuse and dependence seem similar
- differences in diagnostic criteria between DSMIII-R and DSMIV make little difference in estimates of heritability
- studies on adult community-based samples produce consistent results
- studies on younger cohorts give less consistent results and have focused on studies of quantity & frequency rather than abuse & dependence criteria, but not always looking at age of use
- heritability rises and shared e influences get less as age of ascertainment goes up from adolescence to adulthood

Adult, community-based twin studies - heritabilites

Criteria		Abuse	Dependence
DSMIIIR	males	55%	49%
	females	56%	50%
DSMIV	males	58%	51%
	females	66%	59%

Remainder of variation was e^2, no c^2 found for lifetime abuse or dependence, no sex differences

Results are supported by adoption studies – the adopted away offspring of alcoholic parentage retain higher risk

Samples that include only people who have sought (or been court-ordered to seek) treatment do show shared e:

abuse	h^2 = 48%	c^2 = 34%	e^2 = 18%
dependence	= 63%	= 17%	= 20%

Adolescent/young adult studies report lower heritabilities and more shared environmental influences

Sex differences in alcohol abuse/dependence

- much more prevalent in males, especially type 2
- heritabilities look similar in recent studies but past studies show inconsistencies
- studies of opposite-sex DZ pairs indicate a low correlation for genetic effects r = 0.24

  - this indicates gender-specific genetic factors
- consequences worse in females – health dangers from alcohol itself and from assortative mating

Subtypes of alcoholism

1. Early and late onset alcoholism

Age of onset = person's age at first symptom

Early onset =

Late onset =

McGue et al (1992) clinical sample from treatment centers

Dependence	Males			Females		
	h^2	c^2	e^2	h^2	c^2	e^2
Early onset	73%	23%	4%	0%	73%	27%
Late onset	30%	37%	33%	0%	53%	47%

- genetic influences are less for later onset alcoholism
- environment (both $e^2$and c^2)is more important in male late onset and late and early onset in females in this sample
- no genetic influence in females in this sample
- age of first drink correlated with dependence but less with abuse in this sample:

dependence - 29% of total variance accounted for by age of first drink, both in males and females

abuse – only 12% in females, 3% in males

not all studies, therefore, indicate raising age of first drink would reduce alcoholism

2. Type I no tendency towards aggression when drinking

Type II

associated with variation in 5HT genes influencing 5HT and GABAergic neurotransmission, increased amygdala activity, impaired prefrontal function – predisposes to increased intake, impulsive aggression, intake increases impaired executive function → facilitates aggressive behavior further

Genotype/environment interaction

Cloninger, Swedish adoption data:

Type I alcoholism 3% prevalence

+ve biological background → -ve adoptive home 10-11% risk

+ve biological background → +ve adoptive home 27% risk

Type II alcoholism 2% prevalence

no change in risk with adoptive home risk = 17-18%

Role of genes in use and abuse of alcohol

Animal studies mice rats

psychopharmacogenetics

selection, cross-breeding, inbred-strain studies all indicate genetic influences on every aspect studied :

- preference for alcohol
- sensitivity to alcohol
- susceptibility to withdrawal symptoms
- response to alcohol
- development of tolerance

- alcohol-related aggression

knock-out studies:

DRD2 knock-out –

HTR knock-out -

Genes associated with risk for alcoholism in humans

Alcohol metabolism in the liver:

Acetaldehyde causes DNA damage - some repair, depends on genotype

- thought to be mechanism behind fetal alcohol syndrome, deficits of lesser kind in offspring of drinkers
- also causes bone-marrow failure and cancer

ALDH 2 acetaldehyde dehydrogenase

one of the most transparent gene influences on behavior

- *2 allele of ALDH 2 gene has protective effect against alcoholism since it produces ‘flushing’ response when alcohol is consumed
- allele is only present in Asian populations

Japanese males

ALHD 2 genotype	*1/*1	*1/*2	*2/*2
population	58%	35%	7%
alcoholics	88%	12%	0%

*2 homozygotes –

*2 heterozygotes –

Unemphasized but important fact:

*2 allele also raises risk of digestive system and other cancers due to acetaldehyde build-up

esophageal cancer x6-10 risk with even moderate drinking

ignoring flushing response not recommended

More alcohol pharmacology

- more complex than other drugs

sedative
ataxic
anxiolytic effects
} mediated through GABA glutamate signaling

reward properties
- euphoria
- psychomotor stimulation
} mediated through endogenous opioids, mesolimbic dopamine

Understanding mechanism of action can help with development of new treatments

μ opioid receptor (OPRM1) blockade being developed as treatment

OPRM1 genotype determines response

Variation in genes within pathways is likely to effect vulnerability to overuse, addiction, response to treatment

Current treatments

Antabuse (disulfiram) has same effect as *2 allele (ALDH blocker)

Naltrexone opioid antagonist

Acamprosate functional glutamate antagonist

Replicated genetic effects besides ALDH

GABA-A receptor genes

- chromosome 4
- GABA is major inhibitory neurotransmitter in human CNS
- GABA is involved in many behavioral effects of alcohol
- strong association of GABRA2 alleles with alcohol dependence

Nicotinic acetylcholine receptors CHRN A and B genes

- alcohol dependence frequently co-occurs with smoking
- evidence for shared genetic vulnerability
- CHRNA5 gene associated with both dependences

Dopamine system DRD2 and DRD4

- alleles of both genes may have effects on severity of alcoholism as well as overall risk

association 69% of alcoholics carry A1 allele in region of
20% of non-alcoholics DRD2 locus

Legalize drugs?

- is the current ‘war on drugs’ working to reduce drug use and addiction?
- or is it just serving to give us the largest per capita prison population in the world?

1917 - government estimates 1.3% of US population addicted

1970 - ‘war on drugs’ started under Nixon

- at this time, 2% <12 yrs old used illegal drugs and 1.3% addiction rate

2003 46% <12 yrs old used illegal drugs (2300% increase)

- over 1 trillion dollars, more people imprisoned per capita than any other country in the world, and 39 million arrests later

in 2008 government estimates 1.3% of us are addicted