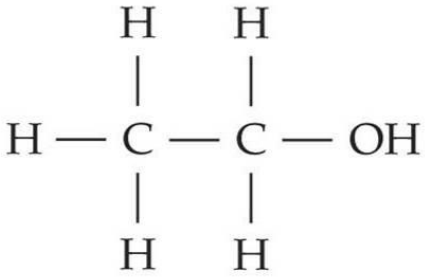
Alcohol



Ethyl alcohol (ethanol)

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Selected aspects of the psychopharmacology of alcohol (ethanol)

- Primary neuropharmacological targets of alcohol

- Acute psychological effects of alcohol

- Decreased tension/anxiety (anxiolysis)
- Impaired memory (amnesia, ‘black out’)
- Directly ‘rewarding’ effects of alcohol?

- Psychological effects of chronic (excessive) alcohol consumption

- Neuropharmacological adaptations, withdrawal symptoms and alcohol dependence
- Severe and chronic cognitive deficits due to brain shrinkage (Wernicke-Korsakoff Syndrome)

Today

Alcohol-induced memory loss (‘amnesia’)

- Alcohol interferes with memory, especially with the encoding of new information into long-term declarative memory. Alcohol-induced anterograde amnesia may range from little memory lapses (‘cocktail party memory deficits’) to ‘fragmentary’ or ‘en block black outs’, i.e. partial or complete absence of memory, for experiences under alcohol influence, if large amounts of alcohol have been drunk rapidly (‘binging’).

- Aaron White and colleagues (2002, JAmerCollHealth 51:117) asked 772 undergraduates the following question:

"Have you ever awoken after a night of drinking not able to remember things that you did or places that you went?"

51% of those who had ever consumed alcohol answered YES.

White (2003) *Alcoh. Res. Health* 27:186

Possible mechanisms of alcohol-induced amnesia I: State-dependence

- Information encoded/learnt in a drugged state, may be remembered better if tested in a comparable drugged state, than in a non-drugged state (Overton, 1964, JCompPhysiolPsychol 57:3). Such state-dependence of memory may partly account for alcohol-induced amnesia.

- Experiments testing for state-dependence typically include 4 groups in a 2X2 design:

Group	Encoding drug state	Retrieval drug state
AA	alcohol	alcohol
SS	sober	sober
AS	alcohol	sober
SA	sober	alcohol

- Alcohol has been shown to render some aspects of declarative memory state dependent. There is also evidence for asymmetric state dependence, i.e. retrieval was especially reduced in the AS group, but less so in the SA group.

Goodwin et al. (1969) *Science* 163:1358; Duka et al. (2003) *Psychopharmacology* 153:295-306

State-dependent effect of alcohol on word-association memory

Word-association test

•*Learning phase (Day 1):*
Subjects were asked to respond to 10 words with the first word that comes to mind.

•*Recall phase (Day 2):*
Subjects were cued with the words and asked to recall their response from Day 1.

Group	Word association Errors
AA	2.50 ± 1.57
SS	1.25 ± 1.14
AS	4.58 ± 2.13
SA	2.25 ± 1.43

Which finding supports state-dependent recall?

a) **Recall is worse in group AA than in SS.**

b) **Recall is better in group AA than in AS.**

c) **Both a) and b).**

d) **None of the above.**

Difference between AA and AS groups is best explained by state-dependence

Goodwin et al. (1969) *Science* 163:1358

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SA	sober	alcohol

- Alcohol has been shown to render some aspects of declarative memory state dependent. There is also evidence for asymmetric state dependence, i.e. retrieval was especially reduced in the AS group, but less so in the SA group.

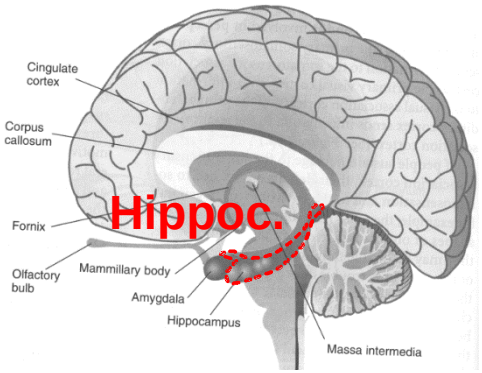
- However, state-dependency appears to account mainly for little memory lapses or fragmentary blackouts – en block blackouts seem to be due to other mechanisms (Goodwin, 1969, BrJPsychiatry 115:1033-1038).

Goodwin et al. (1969) *Science* 163:1358; Duka et al. (2003) *Psychopharmacology* 153:295-306

Possible mechanisms of alcohol-induced amnesia II: Selective interference with hippocampal memory mechanisms

- Alcohol mainly interferes with encoding of new declarative information, similar to damage to the hippocampus (such as in patient H.M.). Thus, interference with hippocampal synaptic mechanisms of memory may contribute to alcohol-induced amnesia.

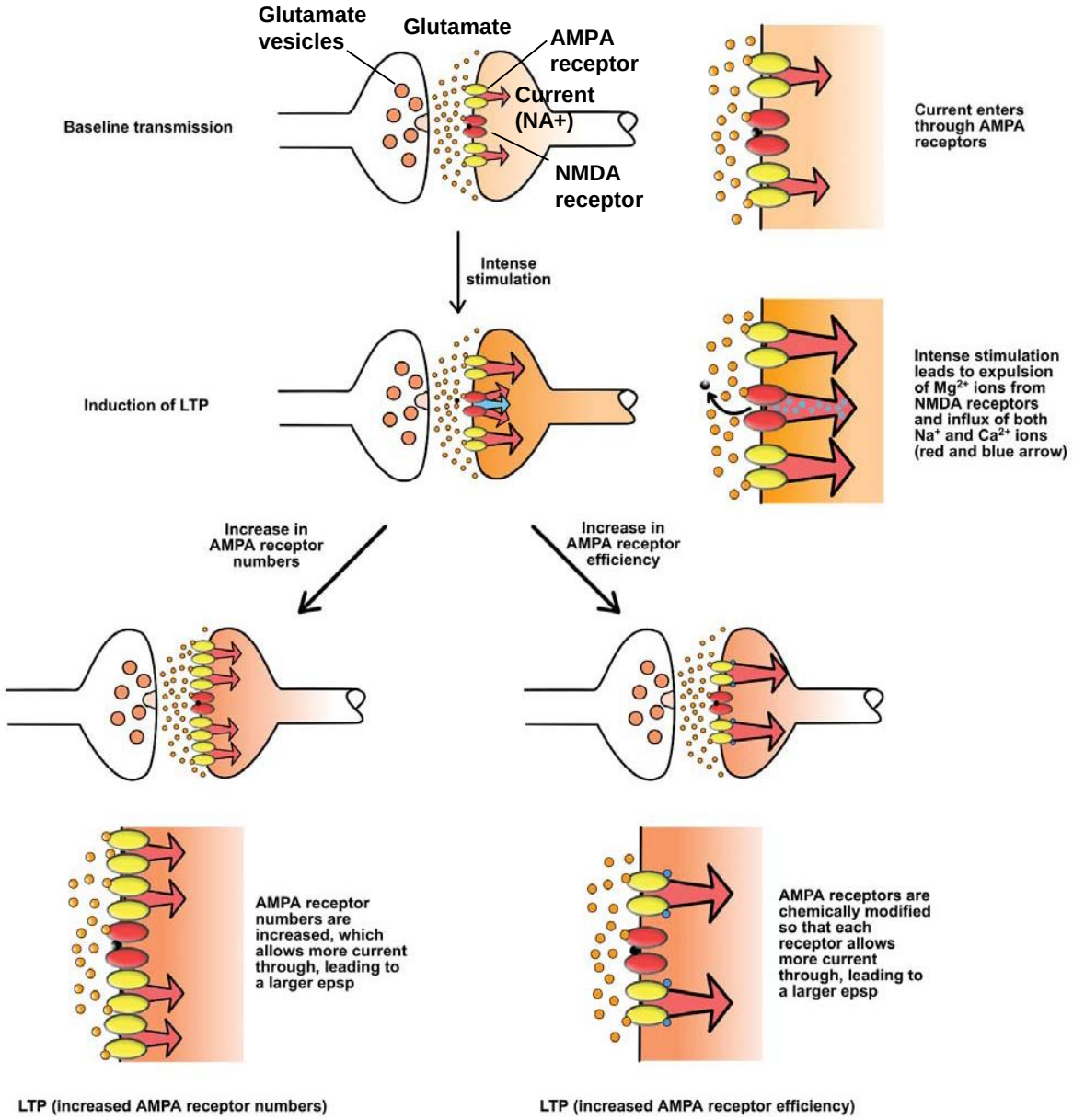
White (2003) *AlcohResHealth* 27:186



- For example, alcohol disrupts the induction of hippocampal long-term potentiation (LTP) – an activity-dependent long-lasting increase in synaptic strength and a candidate physiological mechanism of memory (Bliss & Collingridge, 1993, Nature 361:31).

Givens & McMahon (1995) Brain Res 688:27

Long-term potentation (LTP): the basics



Neuroscience - Science of the Brain: An Introduction for Young Students; p. 28 (http://www.bna.org.uk/publications/brain_sci.html)
Further reading: Carlson, Physiology of Behavior, Chpt. 14; Bliss & Collingridge (1993) *Nature* 361:31

Possible mechanisms of alcohol-induced amnesia II: Selective interference with hippocampal memory mechanisms

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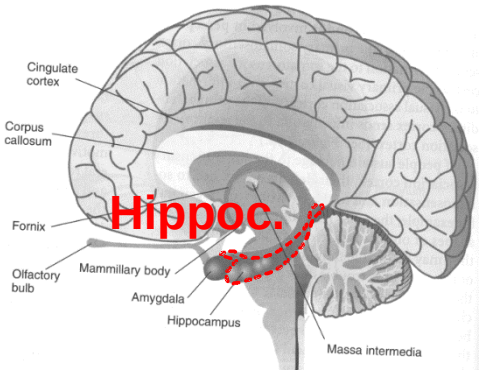

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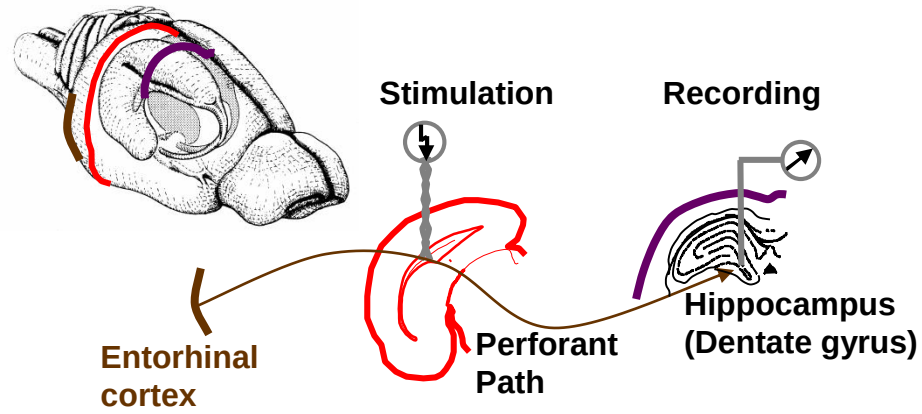
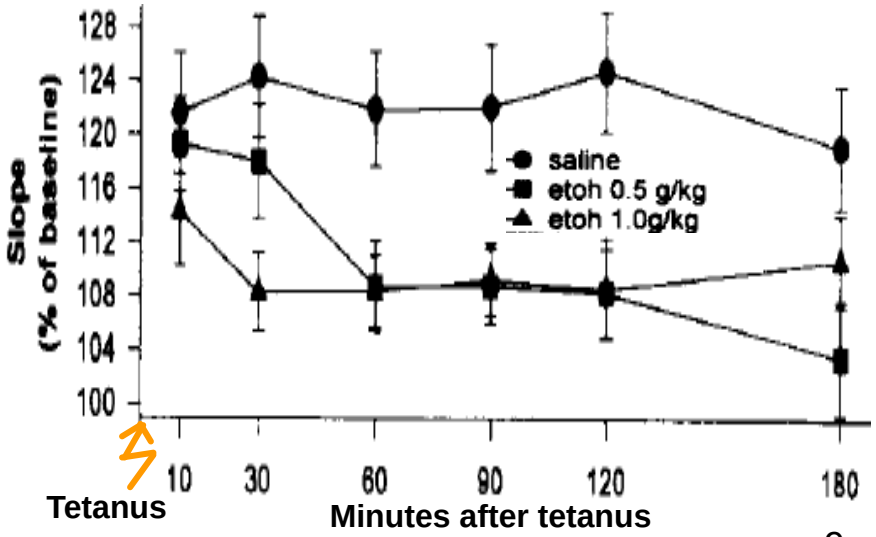




Givens & McMahon (1995) Brain Res 688:27

TABLE 9.5 Percentage of Binge Drinkers Reporting Alcohol-Related Problems Since the Beginning of the School Year by Gender[a]

Alcohol-related problem	Percentage[b]	
	Women	Men
General disorientation		
Have a hangover	81%	82%
Do something you later regret	48%	50%
Forget what you did	38%	41%
Sexual activity		
Engage in unplanned sex	26%	33%
Not use protection before sex	15%	16%
Violence		
Argue with friends	29%	32%
Damage property	6%	24%
Disciplinary action		
Have trouble with campus/local police	4%	10%
Personal injury		
Get injured	14%	17%
Get medical treatment for overdose	<1%	1%
School performance		
Miss a class	42%	45%
Get behind in schoolwork	31%	34%

Source: Wechsler et al., 1995a.

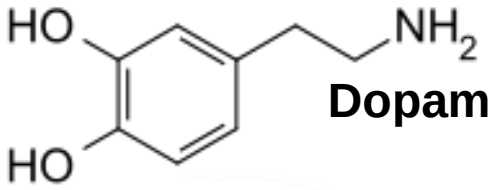
[a] Women binge drinkers report having four or more drinks in a row at least once during the past 2 weeks. Men binge drinkers report having five or more drinks in a row.

[b] Percentage of binge drinkers who report that, since the beginning of the school year, their drinking has caused them to experience each problem one or more times.

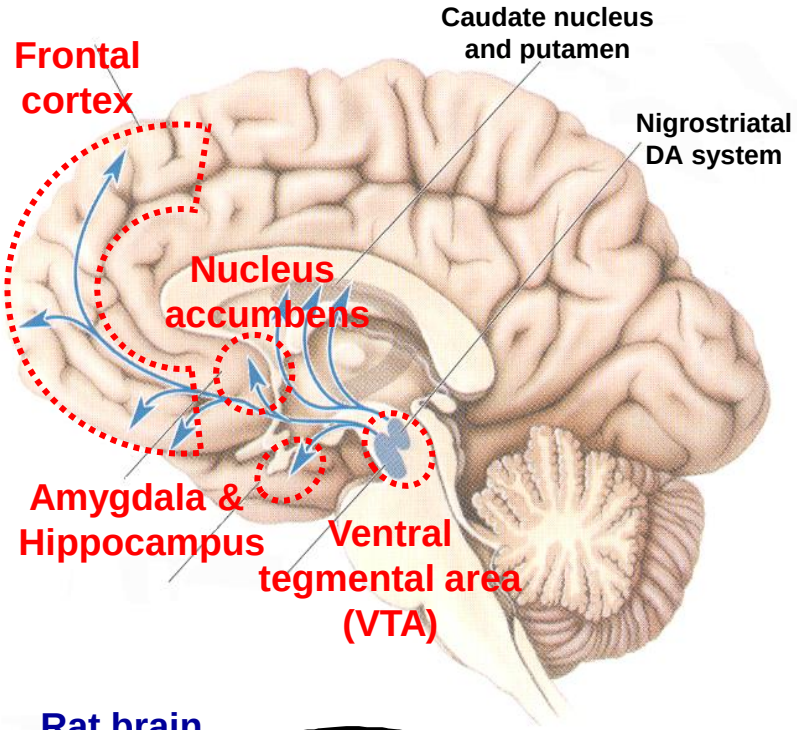
Many of alcohol's effects are unpleasant –

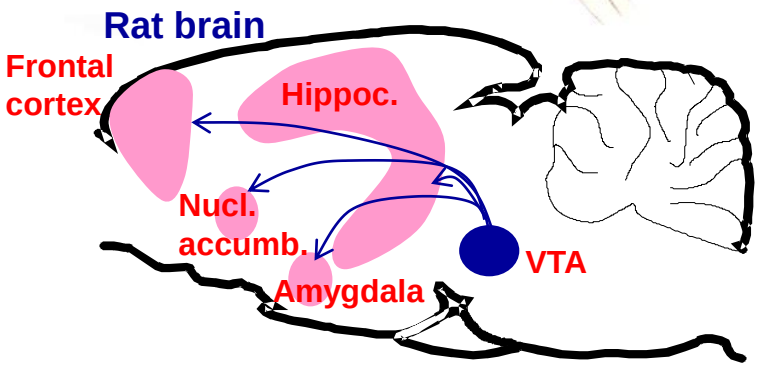
why do so many people consume alcohol?

Meso-corticolimbic dopamine system and reward

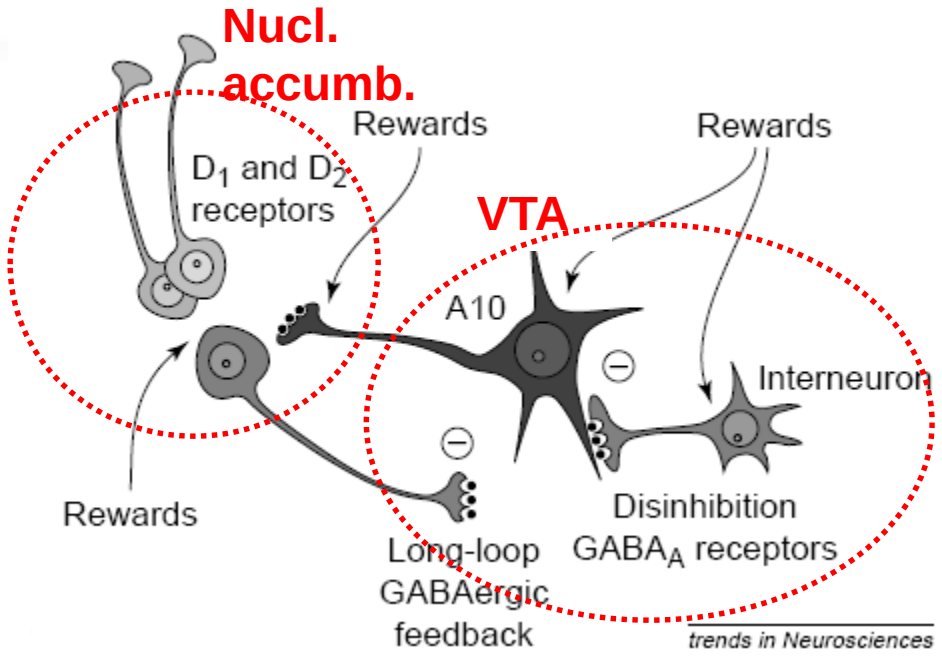


Dopamine



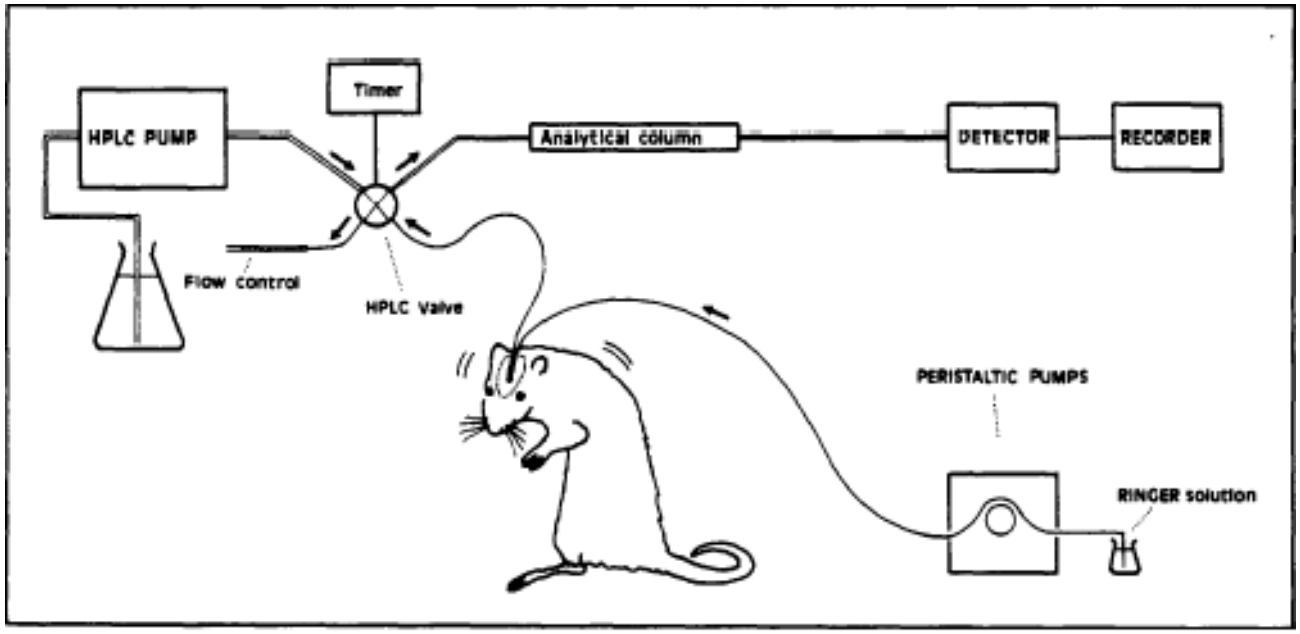


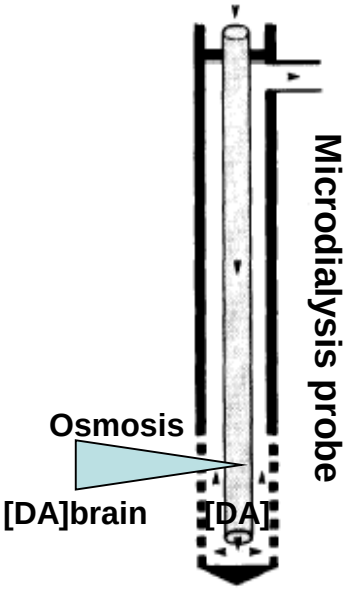
Rewards activate meso-corticolimbic dopamine transmission



For critical review see:
Spanagel & Weiss (1999) *Trends Neruosci.* 22:521

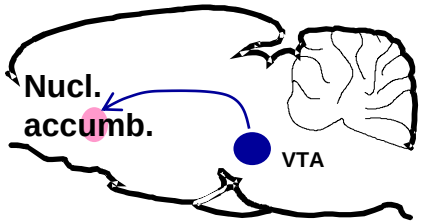
Intracerebral microdialysis to measure neurotransmitters





Westerink (1995) *Behav Brain Res* 70:103

Drugs of abuse, including alcohol, increase accumbal dopamine levels



DA (% baseline)

1mg/kg

amphetamine

5mg/kg

cocaine

DOSE (mg/kg s.c.)
0.5
1.0
2.5
10

morphine

DOSE (g/kg i.p.)
0.25
0.5
1.0
2.5

ethanol

6mg/kg

nicotine

Time after drug injection

Dichiara & Imperato (1988) *Proc. Natl. Acad. Sci.* 85:5274

Chronic excessive alcohol use can lead to alcohol dependence

TABLE 9.4 Diagnostic Criteria of Substance Abuse and Substance Dependence

Substance abuse occurs when the drug

- impairs the ability of the individual to function at school, at work, or in the home.
- causes legal problems like arrests for violence or driving under the influence.
- is used in a dangerous manner.
- is used despite legal, social, or medical problems.

Substance dependence occurs when the drug fulfills the criteria for abuse and also includes:

- development of tolerance;
- physiological or cognitive signs of withdrawal at abstinence;
- frequent desire and effort to reduce drug use;
- preoccupation with securing, consuming, and recovering from drug use so that most daily activity is directed by the drug.

Source: American Psychiatric Association, 1994.

PSYCHOPHARMACOLOGY, Table 9.4 © 2005 Sinauer Associates, Inc.

Neuropharmacological adaptations to repeated and chronic alcohol use contribute to dependence:

- **Tolerance** in response to repeated use leads to reduced acute alcohol effects
- **Long-term compensatory changes** in neural mechanisms in response to chronic excessive alcohol use lead to **chronic psychological changes when sober**

-Compensatory changes are opposed to acute effects of alcohol

Little (1999) *Pharmacol. Ther.* 84:333;
Vengeliene et al. (2008) *Br. J. Pharmacol* 154:299

Whithdrawal hyperexcitability

Altered balance between excitatory and inhibitory neurotransmission in response to chronic alcohol:

•Decreased GABA-A receptor function (compensating for acute GABA enhancing effects of acute alcohol)

•Increased glutamate receptor stimulation and function (compensating for decreased glutamate release and decreased NMDA receptor function in response to acute alcohol)

⇒ Possible effects:

•Many withdrawal symptoms: seizures, tremor, withdrawal anxiety, alcohol craving

•Excitotoxic brain damage (resulting in long-term cognitive deficits)

For reviews see: Little (1999) *Pharmacol. Ther.* 84:333-353; Vengeliene et al. (2008) *Br. J. Pharmacol.* 154:299

Amy Winehouse 'died from seizure as body shocked from lack of alcohol'

Amy Winehouse's family believe she died from a seizure as her body couldn't cope with her sudden decision to stay off alcohol for three weeks, it has been reported.

Related Tags:
Amy Winehouse

Amy Winehouse's family believed she died after ignoring doctor's orders to wean off alcohol gradually

Metro, 28 July, 2011

http://www.metro.co.uk/showbiz/870656-amy-winehouse-died-from-seizure-as-body-shocked-from-lack-of-alcohol

Amy Winehouse died of alcohol poisoning, second inquest confirms

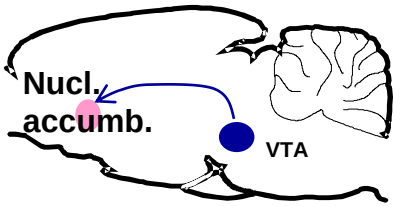
Second inquest into singer's death was held after original coroner was found not to have correct qualifications

▲ The second inquest into the death of Amy Winehouse confirmed that she died of alcohol poisoning after binge drinking following a period of abstinence. Photograph: Yui Mok/PA

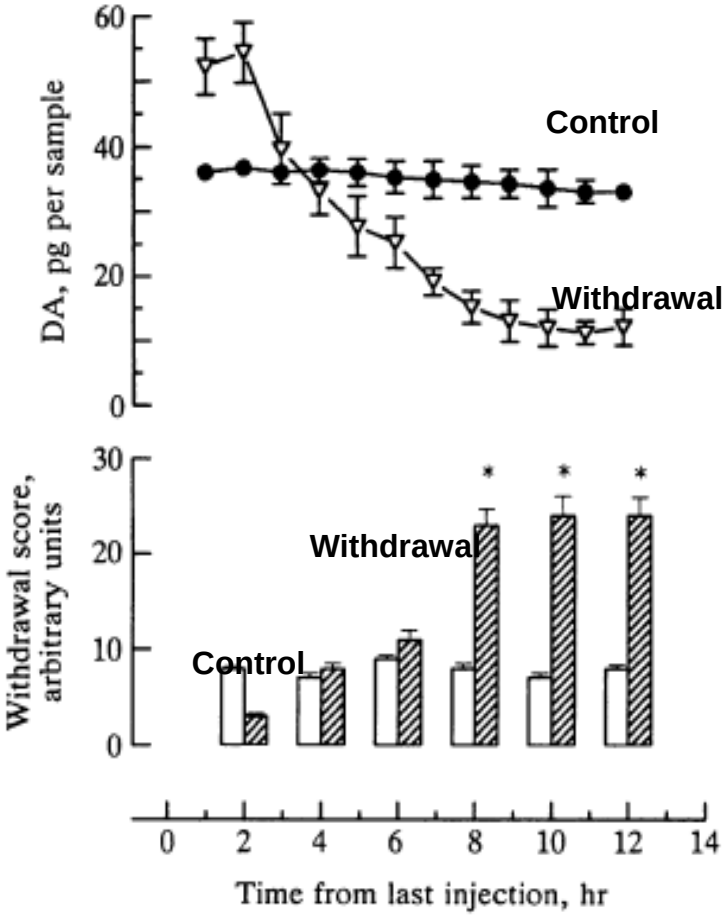
Guardian, 8 January, 2013

https://www.theguardian.com/music/2013/jan/08/amy-winehouse-alcohol-poisoning-inquest

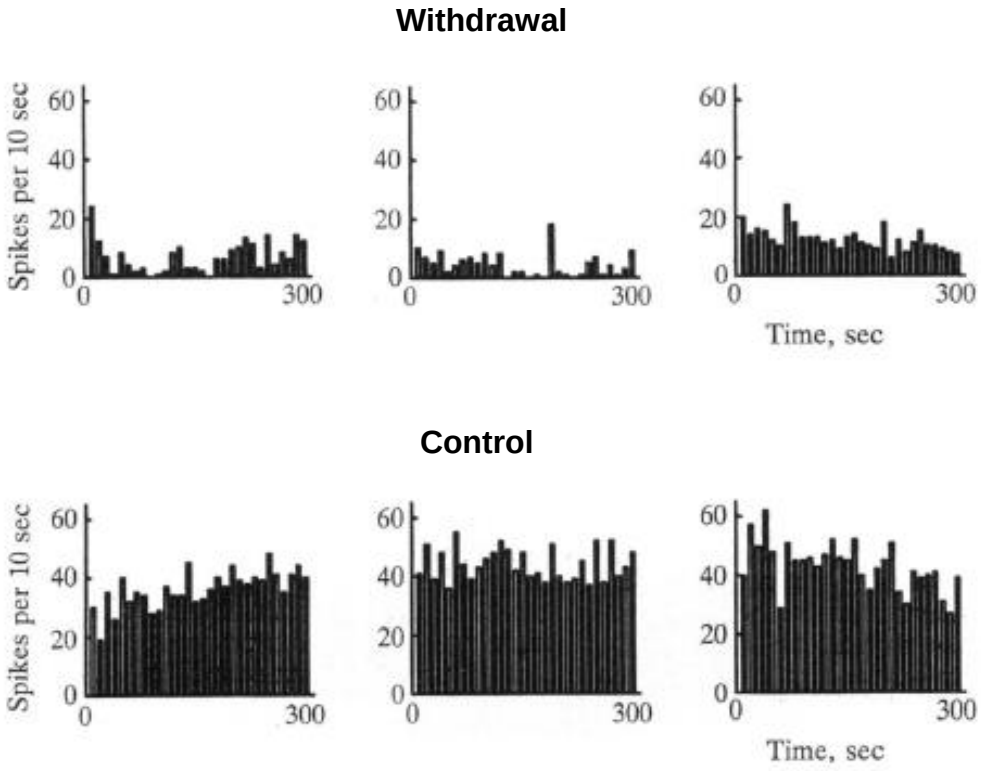
Reduced dopamine transmission during withdrawal



Reduced nucleus accumbens dopamine during withdrawal



Reduced spontaneous activity of dopaminergic neurons in the VTA



⇒ Possible effect:

Reduced sensitivity to (natural) rewards and reduced motivation

Diana et al. (1993) *Proc. Natl. Acad. Sci.* 7966

Chronic excessive alcohol consumption may cause alcohol tolerance and withdrawal symptoms:

a) by inducing compensatory neurophysiological changes that are opposite to the effects of acute alcohol.

b) by inducing neurotoxicity.

c) both a) and b).

d) none of the above.

Severe cognitive impairments and brain shrinkage associated with chronic excessive alcohol consumption

Wernicke-Korsakoff Syndrome:

•Caused by thiamine deficiency, most commonly in association with alcoholism

•Wernicke Syndrome: acute stage, characterised by ophtalmoplegia (paralysis of eye muscles), confusion, ataxia

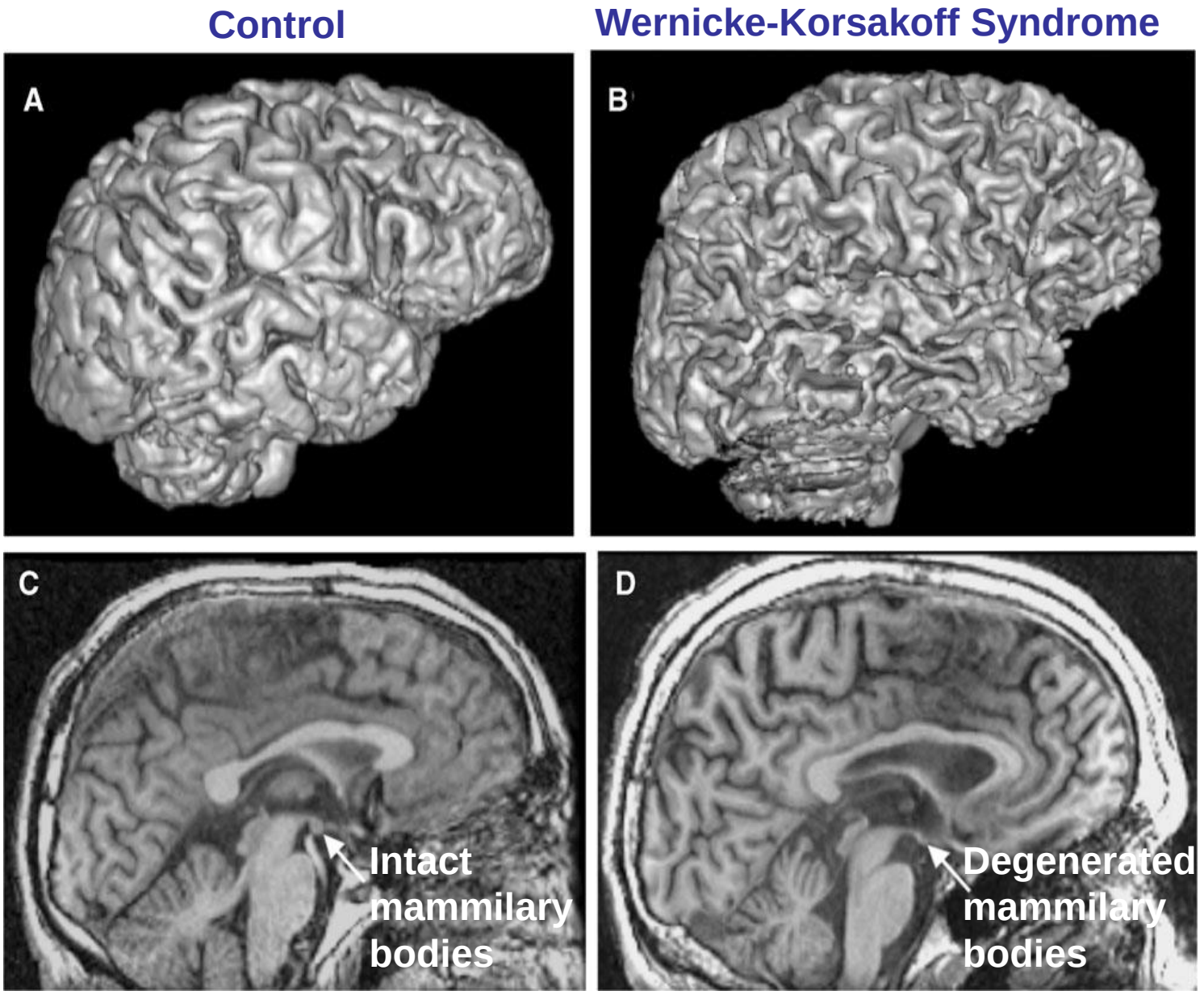
•Korsakoff Amnesia: remains after treatment of acute Wernicke Syndrome if thiamine deficiency lasted too long; global impairment in forming new declarative memory; severe brain 'shrinkage', especially striking degeneration of the mammilary bodies

Cognitive deficits and brain shrinkage in 'uncomplicated' alcoholics

Even alcoholics without WKS, may present with deficits in sensori-motor and executive functions, learning and memory and show marked fronto-cerebellar brain damage.

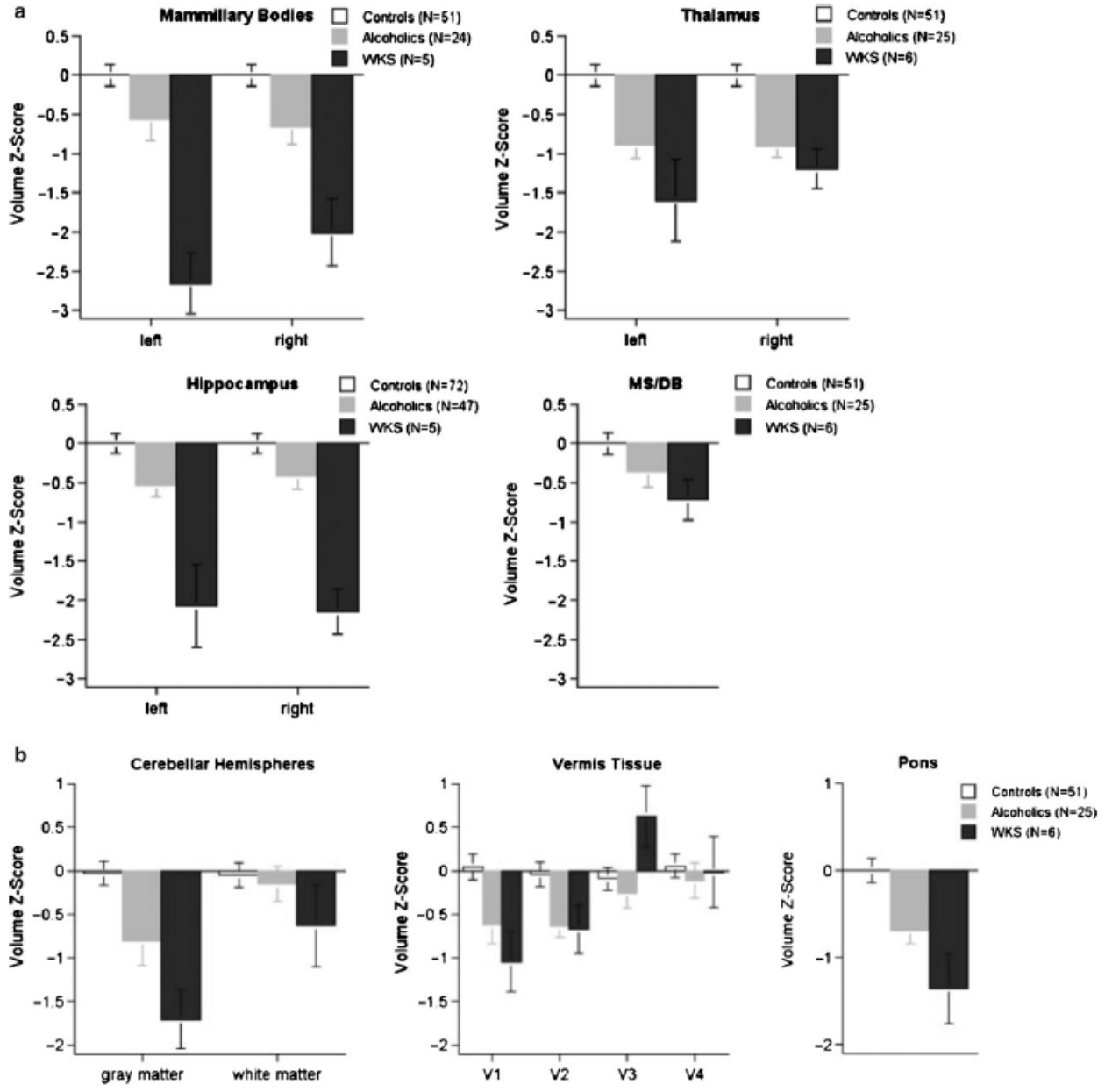
Harper & Matsumoto (2005) *Curr. Opin. Pharmacol.* 5:73;
Sullivan & Pfefferbaum (2009) *Alcoh.Alcoholism* 44:155

Brain shrinkage associated with chronic excessive alcohol use



Sullivan & Pfefferbaum (2009) *Alcoh.Alcoholism* 44:155

Brain shrinkage associated with chronic excessive alcohol use



Sullivan & Pfefferbaum (2009) *Alcoh.Alcoholism* 44:155

Selected reading – Alcohol II

***Textbook chapter*:**

Chpt. on Alcohol – for general overview

Selected overviews of topics discussed today:

V Vengeliene, A Bilabo, A Molander, R Spanagel (2008) Neuropharmacology of alcoholism. *Br. J. Pharmacol* 154:299-315.

AM White (2003) What happened? Alcohol, memory blackouts, and the brain. Alcohol Research & Health 27:186-196.

C Harper, I Matsumoto (2005) Ethanol and brain damage. Curr. Opin. Pharmacol. 5:73-78.

All articles, as well as all references given in lecture, are available online via Nottingham University access.

Questions for revision

- How may alcohol interfere with our memory?

- By which common mechanism may drugs of abuse, including alcohol, act as 'reward'?

- Which neuropharmacological adaptations may lead to alcohol dependence?

- Can you drink your brain away? Which neurodegenerative changes are associated with alcoholism?

The exam MCQs related to alcohol will all be based on the material dealt with in my two lectures on alcohol.

The MCQs put up during the lecture give you a good idea of the level of detail I would expect a student to know or understand, respectively, in order to do well in the exam.

If you understand the material, so that you can answer the lecture MCQs and the revision questions well, you should have no difficulties with the exam MCQs.