The Neuropsychology and Neurobiology of Alcoholism and Substance Abuse

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Neuropsychological Aspects of Substance Use Disorders: Evidence-Based Perspectives

by Daniel N. Allen and Steven Paul Woods

Has great individual chapters on specific substances
Neuropsychological Bias

- All behavioral experiences lead to physiological change of brain, not just psychological change

- Substance abuse leads to physiological changes in cognitive, behavioral, and emotional ability

- Ignore these facts at the risk of failure as a therapist
87% reported drinking alcohol, lifetime; 71%, past year; 56%, past month.

25%, binge drinking, and 7%, heavy drinking in the past month.

17 million adults (7%) had an AUD, 11% of men and 6% of women. Only 8% in need of treatment at a specialized facility received it.

3% of adolescents ages 12 to 17 (3%) have an AUD; Only 8.5% treated.

31% of driving fatalities = alcohol-related.

2015 California: 50% of “drunk” driving is “drugged"
Alcohol

- A central nervous system (CNS) depressant.

- Moderate to high doses suppress neural activity

- Low doses stimulates neural activity, often increasing social interaction
Neuropathology

- **Chronic heavy consumption** leads to **dose-related neurotoxic CNS damage** and a pattern of **neuropsychological dysfunction**.

- There is a pattern of **alcohol-specific damage** known as the **neurotoxicology of essential alcoholism**.

- **Brain atrophy** occurs largely due to **white matter atrophy**, as well as **neuronal loss in PFC, hypothalamus, and cerebellum in Korsakoff's**.
Risk factors for developing AUD

- Greater activation of the reward circuit accompanied by blunted executive control systems
- Impulsivity, poor affect regulation, and poor executive function
- Antisocial tendencies
- Early adversity
- Genetics (e.g., family history, genotypes): 50% of risk
- Earlier onset of drinking, greater the addiction

Alcohol Use Disorder

Old: Alcohol Dependence & Alcohol Abuse (dx combined)

Dx: requires problematic pattern of alcohol use leading to clinically significant impairment or distress as manifested by at least 2 of 11 specified symptoms within a 12 month period
DSM-5: Neurocognitive Disorder

1. Cognitive decline from previous level of performance in 1 or more cognitive domains
   1. Concern of person, informant, or clinician of a mild cognitive decline
   2. Cognitive impairment on NP testing

2. Deficits do not interfere with capacity for independence in everyday activities in Mild NCD; do interfere, in Major NCD

- Substance/Medication-Induced Major or Mild Neurocognitive Disorder

- NP Testing:
  - 1-2 s.d. (3 to 16\textsuperscript{th} %tile) for Mild NCD;
  - 2+ s.d. for Major NCD
Social Drinking

Mixed results in the research related to whether there is an association between daily levels of alcohol and cognitive function.

Framingham Heart Study: modest positive effect of social drinking for women on all cognitive test performances except WAIS Similarities and for men WMS Delayed Memory.

Social Drinkers (.75 to 1.5 oz.): evidence of neuropsychological deficits “remains inconclusive, inconsistent, and open to a variety of explanations” per I. Grant

Elias, et al, 1999
Alcohol Benefits in Normals = 1 drink only per day

- 2009 prospective study: 12,000 people,

- Moderate alcohol consumption was associated with a **28 percent reduction in the risk for dying**. Those who had more than three drinks a day increased their risk by 11 percent.

- **Modest alcohol**, especially red wine, use may **lower the risk of dementia**
  - Protective effect on cardiovascular and cerebrovascular health

Klatsky, 1994; Reinke & McCay, 1996)
30% don’t drink; 
Next 30%: 1 drink per day; 
top 20%: 2 drinks per day; 
Top 10%, 74 alcoholic drinks per week (10 drinks per day) 
= (70% of the alcohol consumed in any year by everyone) 

Median = 3 drinks per week; 51% of adults = regular drinkers 

Who drinks & how much: 

(WNESARC) data
Booze & Calories: Distilled liquor the most
Moderate & Binge Drinking

- **Moderate drinking** is up to 1 drink per day for women and up to 2 drinks per day for men.

- **Binge Drinking**: (NIAAA) = blood alcohol concentration (BAC) levels to 0.08 g/dL; 4 drinks for women and 5 drinks for men—in about 2 hours.

- **SAMHSA**: 5 or more alcoholic drinks on the same occasion on at least 1 day in the past 30 days.
Alcoholism

2001-2005: **79,000 alcohol deaths**;

3rd leading cause of death (due to cirrhosis, cancers, injury, violence)

In 2010, **10,228 alcohol related driving deaths** (33,804 total driving deaths vs. 33,636 gun deaths)

#1 disability by 2020;

10% have severe neuropsychological impairments meeting criteria for DSM alcohol-related mild or major NCD

Chronic condition associated with: increased mortality, unemployment, homelessness, treatment costs, social costs ($300 billion)
Guns and booze: Risky behaviors flock together

- 48% of gun related deaths are alcohol involved
- Those who drink 5+ drinks at one time are twice as likely to have a gun at home.
- 50% of successful suicides are done under the influence

Joseph B. Kuhns, et al., 2015
Defining the “Standard Drink”

- A standard drink = 14 g ethanol
  - 12 oz of regular beer or cooler (5% alcohol)
  - 5 oz of table wine (12% alcohol)
  - 1.5 oz of hard liquor (40% alcohol, 80 proof)
- The average person metabolizes about 1 standard drink per hour

Alcohol Use Disorder (AUD)
(Dependence/Abuse)

- Heavy intake – 4 or 5 drinks per day
- Craving
- Social & occupational dysfunction
- Tolerance
- Withdrawal
- Continued use despite negative consequences
Dependence

Three C’s…

- Compulsion to Drink
- Loss of Control
- Negative Consequences
Addictive Drugs in the brain

- All drugs are Trojan horses in the brain.
- All addictive chemicals are mimics which look and act like an existing brain neurotransmitter, esp. dopamine (anticipation & reward chemical).
- Increases available amount of dopamine which produces a high; brain responds by reducing dopamine receptors.
- Drugs capture reward pathways in the brain which control motivation & compulsion.
They can hold their booze: Low response to alcohol

- Individuals with low response to alcohol can drink much more alcohol before becoming drunk

- Low response correlates with becoming alcoholic

- More alcohol per session of drinking in your brain; greater chance for long term neuronal damage

- Greater chance of low response with family history of alcoholism
Genetics

- Heritability in twin studies: .39 for hallucinogens to .72 for cocaine

- Alcoholism: .50

- The single most reliable indicator of risk for future alcohol and drug problems is Family History.

- Epigenetics: chronic cocaine use changes the pattern of acetyl and methyl tags on hundreds of genes within the brain’s reward center; and these changes make these genes more active when subsequently exposed to cocaine.
Among 90% of alcoholics without severe impairment,

- 50% have no detectable NP deficits with 3 weeks of abstinence
- other 50% experience mild to moderate NP deficits

With abstinence, those mild to moderate deficits resolve in 70-90% of individuals over a 6 month period and persist in the other 10-30%.

This persistent condition is known as the *intermediate-duration neurocognitive disorder associated with alcoholism* (dx = mild NCD)
Range of Impairment

- **Mild (subtle)** = may or may not evidence impairment in daily life

- **Moderate** = more likely show some impairment in daily life

- **Severe** = Wernicke’s Encephalopathy (WE) (acute), Korsakoff’s Disease, Intermediate-duration neurocognitive disorder associated with alcoholism (chronic)
Substance Abuse: Cognitive Consequences

- Brain damage is a common and potentially severe consequence of long-term, heavy alcohol consumption.
- Even mild-to-moderate drinking can adversely affect cognitive functioning.
- Persistent cognitive impairment, with an established pattern of chronic heavy drinking, can contribute to:
  - poor job performance in adult alcoholics,
  - can interfere with learning and academic achievement in adolescents.

Cognitive impairment impedes recovery from alcoholism.
Prevalence of NP Impairment

- 33 – 75% of alcoholics entering treatment display neuropsychological deficits, most in the mild to moderate range

- Executive Functioning (Problem-solving, Abstract thinking, Concept shifting)
- Learning / Memory
- Visualspatial ability
- Balance & Gait

Eckardt & Martin, 1986; Meek et al., 1989; Parsons & Leber, 1981; Tabakoff & Petersen, 1988
Prevalence of Frontal Impairment

- Categories = 50%
  - Abstract thinking
- COWAT = 50%
  - Verbal fluency
- Trails-B = 17%
  - Cognitive flexibility
- Stroop = 12%
  - Response inhibition
- Shipley Vocabulary = 13%
  - Verbal skills

Morgenstern & Bates, 1999
Substance Abuse: Neuropsychological Deficits

Substance abuse causes a wide range of neuropsychological deficits

These NP deficits associated with:
- Treatment process and outcome.
- Patient ability to learn and have insight.

NP results correlate with:
- Clinician ratings of impairment
- Therapeutic progress,
- Relapse
- Employment status
Importance of Neuropsychological Deficits

- **Neuropsychological Deficits** interfere with **Treatment**:
  - Memory limitations
  - Executive Functional Deficits

- **Psychogenic or Neurogenic Interpretation**:
  - Psychological lack of motivation vs. neurological impairment:
    - Nature of denial/lack of awareness: **anosognosia**
    - **Alcoholics with significant PFC deficits will exhibit neurogenic denial of deficits (anosognosia) – they truly do not know they have a problem**
Clinical Recommendations 1

- There is no cure for addiction; it is a brain disorder & long term behavioral memory conditioning; but treatment & AA can lead to long-term sobriety

- Need to do some brief cognitive assessment early

- MoCA: Montreal Cognitive Assessment

- http://www.mocatest.org/

- If significant deficit, may need formal NP testing.
Neuropsychological Testing Performance

Neuropsychological testing performance outcome in alcoholics is highly multifactorial in nature.

Alcohol is not the only cause of deficits.
Neuromedical Risk Factors

- Separate from dose-related neurotoxic effects of chronic alcohol consumption:
  - Metabolic factors resulting from intoxication and withdrawal syndrome
  - Cerebrovascular disease
  - Hepatic encephalopathy
  - Alcohol-related physical complications (gastritis, esophagitis)
  - Traumatic brain injury (TBI)
Factors affecting Neuropsychological Performance

**Prior Neuro-Medical Status:**

- Pre-abuse cognitive deficits (ADHD)
- Malnutrition
- Traumatic Brain Injury
- Organ Disease (cirrhosis of liver, seizures)
- Infections (HIV)
Factors affecting Neuropsychological Performance 2

**Comorbid Psychiatric Conditions:**

Higher levels of Substance Abuse comorbidity:

- Schizophrenia
- Major Depressive Disorder
- ADHD
- Antisocial Personality Disorder

*All have associated neuropsychological deficits*
Alcohol Abuse factors:

Acute vs. Chronic Effects
Drinks per occasion
Duration of drinking
Recent Amount
Maintenance vs. Binging
Abstinence Length
Factors affecting Neuropsychological Performance

Demographics:

Age: younger you start, worse the addiction
Sex
Education: Cognitive Reserve Capacity
Social Class

Genetics, Epigenetics
Factors affecting Neuropsychological Performance

Brain Structure And Function:

Congenital status: IQ, etc.

50% of alcoholics have alcoholic parents:
  Physical abuse,
  ACA = LOC 7x higher;
  Fetal Alcohol Syndrome
  Higher ACEs scores
Test Characteristics:

Motivation
Effort
Affect and Mood

Example: Teenager on MJ & IVA

30 day testing rule
Newly Dry Brains: Neuropsychological Impairment in Abstinent Alcoholics

**Bad News**: Alcohol is neurotoxic

**Good News**: Abstinence reverses damage

Overwhelming evidence:

**Significant pattern of cognitive deficits** in alcoholics/CD: 33-60 % with detectable deficits, long before liver, neurological and medical symptoms

Filley, 2001
Specific etiology not established

Contaminants in conclusions: age, brain injuries, nutrition, pre-morbid IQ, length of abstinence, amount of recent drinking, withdrawal effects, liver function, vascular damage
Predictors of NP Impairment 1

Age: more important than length of drinking history

Family history, genetics

Age of beginning drinking

Years of drinking, esp. 10 years +
Predictors of NP Impairment 2

- Maintenance drinkers worse than binging
- Amount of ETOH per session > frequency
- Presence of classic sx (DTs, blackouts, Sz) unrelated to NP impairment
- Years of ETOH, # of drinks not strongly related to NP impairment (.3 to .4 correlation; 20% of variance)
Childhood Experiences vs. Adult Alcoholism

ACE Score vs. % Alcoholic

- ACE Score 0: 2%
- ACE Score 1: 6%
- ACE Score 2: 12%
- ACE Score 3: 16%
- ACE Score 4+: 4+
ACE Score and Drug Abuse

Ever addicted to drugs

Ever injected drugs

Percent With Health Problem (%)
ADHD and Chemical Dependency

Compared with controls, adults with ADHD have a:

- 3 to 4-fold higher rate of marijuana and cocaine use
- 3-fold higher rate of alcohol abuse
- utilize tobacco 40% more

ADHD Treatment with stimulants reduces CD relapses
Why do most 16-year-olds drive like they're missing a part of their brain?

BECAUSE THEY ARE.

Even bright, mature teenagers sometimes do things that are “stupid.”

But when that happens, it’s not really their fault. It’s because their brain hasn’t finished developing. The underdeveloped area is called the dorsal lateral prefrontal cortex. It plays a critical role in decision making, problem solving and understanding future consequences of today’s actions. Problem is, it won’t be fully mature until they’re into their 20s.

It’s one reason 16-year-old drivers have crash rates three times higher than 17-year-olds and five times higher than 18-year-olds. Is there a way for teens to get their driving experience more safely — giving their brains time to mature as completely as their bodies? Allstate thinks so.

STRENGTHEN GRADUATED DRIVER LICENSING (GDL) LAWS.

GDL laws put limitations on teen driving so kids can gain experience safely. Since North Carolina implemented one of the most comprehensive GDL laws in the country, it has seen a 25% decline in crashes involving 16-year-olds.

HAVE THE DRIVING TALK.

75% of teens surveyed said their parents would be the best influence in getting them to drive more safely. The Allstate Parent-Teen Driving Contract can help start the conversation. Contact an Allstate Agent to get a free copy or visit Allstate.com/teen for the interactive contract.

It’s time to make the world a safer place to drive. That’s Allstate’s Stand.

Allstate. You're in good hands.
Drug Use starts early and peaks in Adolescence
Substance Abuse is a Developmental Disease:
% who develop first time dependence (Alcohol, Tobacco, THC)

Influence of alcohol on brain maturation

Neuroimaging findings in adolescents

• Smaller PFC in teens with AUDs and correlation of smaller volume with greater alcohol consumption

• Hippocampal volume correlate with age at AUD onset (younger age at initiation, smaller volume) and duration (shorter duration, larger volume)

• Both binge drinkers and marijuana users have poorer white matter integrity; binge drinkers show even poorer white matter health in several cortical and subcortical regions.

Jacobus & Tapert, 2013)
NP findings in adolescents

- Worse performance in attention and information processing, memory, visuospatial functioning, language abilities, and executive functioning compared to nondrinking controls.

- Consuming more drinks per drinking day was related to poorer performance on measures of attention and EF.
NP in adolescents

• **Protracted alcohol use over a 4-year follow-up period resulted in poorer neurocognitive functioning,**

• **Similar 8-year follow-up study showed worse attention, learning, and VS functioning.**

• **Withdrawal symptoms are associated with poorer learning and memory performance.**
Deficit Source

ETOH neurotoxicity:

- Mice with 4 m ETOH—50% HC dendritic loss

- Cerebral atrophy most common finding
  - White matter more affected than gray
  - Frontal and parietal regions most affected

- Disrupts hippocampal connections

- Subcortical atrophy
  - Cerebellum
  - Caudate nucleus
  - Limbic system

Brust, 1993; Jernigan, et al., 1991
Deficit Source 2

Nutrition: thiamine deficit

Liver disease: hepatic encephalopathy: lower PIQ

Vascular pathology: reduced Cerebral Blood Flow

Brain trauma

Age of drinking onset: Cloninger’s Type 2 (early onset: symptoms of antisocial personality disorder, more social consequences of drinking and higher sensation-seeking scores, worse prefrontal)

Fetal Alcohol Syndrome

Smoking: COPD
Alcohol and Brain Damage

Alcohol does not kill neurons in adults.

Alcohol damages dendrites and white matter, reducing message traffic between neurons and transmission speed.

Damage is mostly reversible, but neuronal structure is changed in the process.
Clinical Recommendation 2

- Damaged brains do not output normal cognition and behavior

- Let patients know that is part of reason why recovery is so hard is because their brain functioning is not currently normal
Chronic Heavy Drinking

- Chronic heavy alcohol consumption is frequently associated with cognitive compromise.

- On average, NP test performance of heavy drinkers falls with the average to low average range.

- Heavy drinkers (26 drinks): performance reductions in word-list generations, VS skills, memory & psychomotor speed
No support for Ryback’s *continuity hypothesis* (linear increase of NP deficits with increasing alcohol consumption)

Support for *threshold model* beyond which a significant level of daily alcohol consumption begins to compromise cognitive function.

Consumption of 3-4 drinks for 7 days a week are associated with reduced cognitive function.
Tx Presentation & Course

Treatment presentation:
- at 19 years for men and 16 years for women after onset of heavy drinking

5 stages (male):
- heavy drinking in late 20s;
- life functioning effected in early 30s (MVAs);
- loss of control over drinking;
- intensified job/social problems in mid 30s;
- severe long term consequences by late 30s (liver disease)
Non-Korsakoff Alcoholism

- **Non-Korsakoff alcoholism (chronic AUD) cognition**: deficits in problem solving, abstraction, perceptual motor skills

- **Age & maximum quantity & frequency of recent alcohol use predict deficit level**: Mild not Major NCD

- **Younger than 40-45**: better recovery & less severe deficits than older
Non-Korsakoff Alcoholism 2

- No correlation between years of alcoholism and severity of NP deficits

- Quantity and frequency of consumption in 6-month period prior to evaluation are best predictors of NP impairment

- Lower extremity motor deficits are correlated with length of drinking

- 2 systems of brain deficit in alcoholism:
  - Cerebellar-pontine-prefrontal (motoric)
  - Prefrontal-parietal corticocortical (cognitive)
AWS, DTs, Wernicke’s

- **Alcohol Withdrawal Syndrome (AWS):** anxiety, depression, difficulty thinking, fatigue, jumpiness, shaky, headache, insomnia, irritability or excitability, loss of appetite, nausea, pale skin, palpitations, rapid emotional changes, sweating, vomiting.

- **Dementia Tremens (DTs):** Any of the AWS sx$s in worsened form. Especially rapid muscle tremors, rapid or irregular heartbeat, heavy sweating, and hallucinations/delusions. Fatal in 30%.

- **Wernicke’s Encephalopathy (WE):** Confusion/disorientation, optic ataxia and/or ataxia of gait, abulia, apathy, and global amnesia.
Subacute deficits in non-Korsakoff Alcoholism

- Problem-solving/executive functioning, recent memory, VS ability, and perceptual and motor skills deficits

- Executive function often more resistant to recovery of function.
  - Influenced by family hx of alcoholism and is a predisposing vulnerability to alcoholism
  - Influenced by psychiatric comorbidity,
  - And may be less mediated by dose-effect relationships.

- During intermediate duration phase, recovery in any or all functions, but deficits may be long-standing among 10-30% who display them beyond subacute phase.
Individual differences among Non-Korsakoff Alcoholics

- Alcoholics:
  - uncomplicated types vs
  - those with complex neuromedical risks (hepatic, neurological, nutrition, hypoxemia, alcohol withdrawal, psychiatric)

- Minimal Hepatic encephalopathy (MHE) is:
  - most likely manifestation of cirrhosis from alcoholism
  - most likely to complicate the severity and duration of NP presentation (esp. psychomotor slowing, attention & EF, involving fronto-subcortical networks)
Individual differences in Non-Korsakoff alcoholism 2

- Among **women**, anxiety & mood disorders are common co-morbidities;

- **Among men**, substance abuse & ASP are most common.

- **Combo of alcohol neurotoxicity & ASP results in greater EF and VP deficits.**
Neuroimaging in “uncomplicated” alcoholics

- Ventricular enlargement, particularly the third ventricle
- Gray and white matter volume loss
  - Prefrontal cortex (PFC), most notably the dorsolateral PFC
  - Hippocampus
  - Cerebellum
  - Corpus callosum
- Associated with longer lifetime alcohol use and poorer NP functioning
- Can partially recover with abstinence through regeneration
- Future relapses had smaller brain volumes than future abstainers in regions of the reward system
Recovery in Non-Korsakoff Alcoholism

- Acute (1-2 weeks), sub-acute (3 weeks to 2 months), and intermediate (2-6 months)

- Recently detoxified: general NP deficits (excluding intact vocabulary) within 1st week or 2 of detoxification

- First 24-72 hours: characterized by alcohol withdrawal syndrome (AWS)

- 5% have DTs
Wernicke’s encephalopathy is a potentially permanent neuropsychiatric syndrome that can happen during DTs.

Benzos are Tx for AWS.

Neuroimaging reveals:

- improvement in white matter and thalamic atrophy;
- there is VS improvement with 3rd ventricle volume reduction;
- linked to neural & glial regeneration
In general, if deficits are present in non-Korsakoff alcoholism, the same deficits tend to be present and possibly more serious, in Korsakoff alcoholism.
Modal Neuropsychological Findings

**Big 4 Major Neuropsychological Deficits:**

Executive Functioning
Explicit Memory, esp. nonverbal
Visual Spatial
Motor Ability

Deficits are mild to severe
NP in uncomplicated, recently detoxified Alcoholics

- All cognitive domains except IQ are affected.
- Executive dysfunction may be both a determinant and consequence.
- Most recovery occurs during the first month of abstinence;
- 30-80% have cognitive dysfunction after 1 mo. of abstinence
- If deficits persist beyond the first month, recovery may take months or years; 20% will not recover fully.
NP in uncomplicated detoxified

- Deficits also are related to age of onset, duration of abuse, and amount of alcohol consumed.

- 10% have permanent alcohol-related amnesia or major NCD.

- Same pattern of deficits and recovery whether chronic or episodic user.
Neuropsychological Deficits

- IQ: At risk for lower performance on NART-estimated IQ
- Lower performance on Perceptual Reasoning & Processing Speed on WAIS4
- Attention: complex attention ↓↓
- Working memory: consistently impaired ↓↓
Neuropsychological Deficits 2

- Processing speed ↓↓: one of the most consistently impaired

- Language: normal

- Visuoperceptual & Visuospatial ↓↓: commonly impaired

- EF dysfunction ↓↓↓↓: categorical thinking, set establishment and maintenance, and decision making deficits

- Korsakoff: severe EF deficits
Neuropsychological Deficits 3

- **Sensorimotor functions**: ataxia of gait and reduction in manual dexterity are common; fine motor control and grip strength normal

- **Test engagement**:
  - Secondary gain does not typically play a large role
  - Psychiatric comorbidity & personality disorders can lead to high degree of low motivation, oppositional behavior and acting out
  - Use SVTs for impact of motivation on test performance

- **Emotion & Personality**: MMPI, PAI: depressed mood, antisocial
Neuropsychological Deficits 4

- **Memory:**
  - Recently detoxified: reduced word-list learning & paired associate learning
  - Non-Korsakoff: learning deficits, working memory deficits; subcortical retrieval pattern of memory deficits, with ok retention & recognition
  - Korsakoff: profound encoding & retrieval of episodic memory

- **Procedural memory is intact:**
  - AA had it right

- **Abstinence crucial:**
  - 3 weeks to cognitive recovery in younger alcoholics; longer for older
Clinical Recommendation 3

Dissociation:
- Knowledge or ability to describe appropriate behavior **does not equal ability to do it appropriately**

Implications:  **Don’t depend on verbal insight**

- Neurologically challenged/impaired, not unmotivated

Do a MoCA!

Work on behavioral memory enhancement, a la AA.
Neuropsychological Battery

- Baseline IQ
- WAIS
  - Attention, working memory
  - Speeded information processing \(\downarrow\downarrow\): Digit Symbol
  - Visuospatial functioning \(\downarrow\downarrow\): Block Design

- Verbal learning, memory:
  - CVLT (subcortical retrieval profile vs encoding deficit)
  - RCF
Rey Complex Figure Recall
Neuropsychological Battery

- Executive functioning
  - Wisconsin Card Sorting Test (Set-shifting, working memory, responsiveness to feedback, cognitive flexibility)
  - Category Test
  - Trailmaking Test A & B (Visual scanning, attention, cognitive flexibility)
- Controlled Oral Word Association (verbal fluency)
- Stroop Color Word Test
- Iowa Gambling Test
- Tower of Hanoi
State dependent learning / Context dependent memory:
Where is that bottle?

Blackouts = Temporary Amnesia:
BAC level of .2
9 hours to 3 days in length
51% undergraduates = 1x
alcohol suppresses CA1 in hippocampus: encoding deficit

Acute effects on Memory:
Retrieval poorer than Recognition
Retrieval cues aid alcoholics
Alcohol and Neurogenesis

- Moderate alcohol consumption significantly decreases neurogenesis in the adult hippocampus.

- In rats, the number of cells produced in the dentate gyrus of the hippocampus was reduced by nearly 40%.

- Moderate consumption of alcohol for a relatively short period of time can have profound effects on structural plasticity in the adult brain.
Alcohol → Neurogenesis ↓ ↓ in rats

High doses of alcohol lead to a disruption in the growth of new brain cells

He J, Nixon K, Shetty AK, Crews FT, 2005
Episodic/factual Memory impaired, esp. visual/nonverbal

Procedural Memory preserved (secret of AA’s success)

Poorer semantic encoding strategies (EF):
  higher intrusions,
  less semantic category usage

Ryan & Butters, 1986
Memory and Alcohol 3

Normal forgetting rates

Continuum of memory effects:

social drinkers to alcoholics (retrieval deficit) to Korsakoff (amnesia), esp. nonverbal memory
Prefrontal activation in deep memory encoding: not in Alcoholics

This figure shows a comparison between the fMRI activations observed in chronic alcoholics (n=13) vs. healthy controls (n=15) during “deep” encoding of words and faces. The data were analyzed with a stringent random effect model. The most striking differences between the alcoholic patients and healthy controls were in prefrontal brain regions. Face stimuli in particular reliably evoked a bilateral prefrontal activation in healthy controls but not in the alcoholic group. The activation to words had a different pattern in both subject groups. As expected, these differences are particularly obvious in the “deep” encoding condition, as it evoked prefrontal activation.
The black, open circle is the old location and the solid red circle is the new location. Control rats (left) rapidly learn to find the new location. Weeks after treatment when alcohol was no longer present, binge treated rats (right) perseverated on the old location. They never found the new location.
Clinical Recommendation 4: Memory

- **AA is right:** use procedural memory not insight or talking, esp. in early recovery

- **Behavioral repetition** is target

- But also **external reminder systems** to reinforce poor memory

- **Download CJV’s Executive Skills & Metacognitive Therapy booklet from website**
Clinical Recommendation 4: Memory

- Keep it simple: Modify written material to make it concise and to the point.

- Paraphrase concepts, use concrete examples, incorporate visual aids, or otherwise present an idea in more than one way.
Clinical Recommendation 4: Memory

- If it helps, allow the individual to take notes or at least write down key points for later review and recall.

- **External prosthesis**: Encourage the use of a calendar or planner; if the treatment program includes a daily schedule, make sure a "pocket version" is kept for easy reference.

- Make sure homework assignments are written down.
Clinical Recommendation 4: Memory

- Do not take for granted that something learned in one situation will generalize to another.

- Procedural memory is sensorimotor specific

- Repeat, review, rehearse, repeat, review, rehearse.
Visualspatial Functions

Simple visualspatial functions intact

Impaired color vision, visual search

Visual-spatial organizational functioning impaired, esp. slowness

Emotional processing impaired:
  Emotional cues and facial emotion expression interpretation ↓
Clinical Recommendation 5: EF

- US Law vs neuroscience: **Knowledge of right & wrong can be present along with total inability to inhibit behavior**

- Executive Dysfunction is cause of **neurogenic lack of awareness & loss of inhibition**

- Impairments in Self-Awareness; Introspection

- **Neurologically based Poor Self Monitoring** leads to **inability to understand the consequences of one’s actions.**
Clinical Recommendation 5: EF

- Caution: when making inferences about motivation based on observed behaviors.

- Non-compliance may not arise from lack of motivation or resistance.

- Unawareness of deficits can be due to executive dysfunction and may not always be due to psychological denial.
Clinical Recommendation 5: EF

- **Confrontation** shuts down thinking and **elicits rigidity**; roll with resistance.

- **Do not just discharge for non-compliance**; follow-up and find out why someone has no-showed or otherwise not followed through.
Clinical Recommendation 5: EF

- Inflexibility can lead to perseveration i.e. repeating an inappropriate behavior

- Poor ability to inhibit a response can lead to a broad range of inappropriate behaviors: safety issues; striking out; verbal outbursts; sexual remarks or behaviors; socially inappropriate comments
Clinical Recommendation 5: EF

- Let a person know a behavior is inappropriate.

- **Do not assume the individual knows** and is choosing to do so anyway.

- Provide straightforward feedback about **when and where behaviors are appropriate**.

- Test prospective memory by having them remember to remind you of something 15 minutes later.
Specific Test Deficit Patterns

WAIS: normal VIQ, impaired PIQ

Halstead Reitan Battery:
significant impairment
(Category, nondominant TPT, Tapping, TMT)

Impaired domains: Executive functioning, Memory, Visual Spatial Ability, Motor speed
WAIS & Halstead Reitan Battery

**WAIS:**
- VIQ normal in 75%
- Vocabulary normal in 93%
- PIQ lower in 67% (BD, Digit Symbol)
- VIQ>PIQ by 17-20 pts; crystallized>fluid

**HRB:**
- 50% of neurologically WNL showed HRB↓
- Category - 87% ↓
- TPT – 100% ↓ nondominant hand
- TMT – B – 92% ↓

**WCST:**
- 86% ↓
Chronic Alcoholism: Neuropsychological Deficits

Language: normal

Sensorimotor: color vision, visual search, response slowing ↓, peripheral neuropathy

Motor Speed: ↓

Memory: common ↓, but not universal; superficial encoding, intrusions, visual memory ↓
Chronic Alcoholism: Neuropsychological Deficits 2

**Visual spatial**: VS organization ↓

**Executive Functioning**: ↓ ↓
   flexibility, problem solving, cognitive and behavioral inhibition, search strategy

**Age** is **significant variable in reversibility of deficits**

**Continuum**: 10% severe; 50-70% some cognitive deficits; 20% normal
Alcoholics have smaller brains than healthy controls (Agartz, Shoaf, Rawlings, Momenan, & Hommer, 2003; Hommer, Momenan, Kaiser, & Rawlings, 2001).

Performance on Block Design decreases as alcoholics age, and this decrease is predicted by brain shrinkage.
Summary: Neurocognitive Impairments

- **Specific Deficits**

- Often **Subclinical Levels**:
  - Often significantly inferior to community controls

- Accessible via either neuropsychological or neurocognitive techniques

- **Not associated with withdrawal processes**

- Equivalent impairment for males/females
Grade Point Average and Alcohol

![Average Number of Drinks Per Week by GPA](chart.png)

Source: Core Institute, 1996

- A: 3.3 drinks per week
- B: 4.8 drinks per week
- C: 6.1 drinks per week
- D or F: 9.0 drinks per week

Grade point average (GPA)
Intoxication: Neurological Condition

Intoxication: alcohol is a CNS depressant with neurocognitive deficits:

- Slurred Speech
- Ataxia
- Neuropsychological Deficits (Memory, Executive deficits)
- Behavioral disinhibition
- Reaction Time ↓
Stages of Neuropsychological Recovery:  Acute

Acute deficits: 1 week abstinence:

Most impaired immediately after cessation

Younger improve over 3-4 weeks to WNL

Older (>40) have slower recovery

Memory and Visual-motor improve markedly

Improvement diminishes or reverses if relapse

Ryan & Butters, 1986
Stages of Neuropsychological Recovery: **Short Term**

Short term: 2-5 weeks

Younger (<35 age, 5-10 years use) recover to WNL

More chronic history and older age, poorer NP performance:
- Executive, perceptual-motor, LT verbal and nonverbal memory (latter worse), visual-spatial deficits
Characteristic Behaviors of detoxified Alcoholics: EF

- impaired judgment
- blunted affect
- poor insight
- social withdrawal
- reduced motivation
- distractibility
- cognitive rigidity
- inattention
- perseveration

Frontal Lobe Dysfunction
Characteristic Behaviors of Alcoholics: VS

- poor sense of direction
- impaired constructional ability
- impaired spatial placement
- impaired drawing ability

→ Parietal Lobe Dysfunction
Characteristic Behaviors of Alcoholics: Motor

- impaired timing
- impaired tracking
- impaired balance
- impaired gait
- increased falls

→ Cerebellar Dysfunction
Stages of Neuropsychological Recovery:  **Long Term**

Long Term:  **13 months+**

Less conclusive evidence for deficits:
- Nonverbal learning and memory, esp. Visual memory↓
- Complex memory, esp. encoding strategy ↓
- Executive functioning ↓

5 years: significant improvement but not as good as controls

Poorer recovery:  **TMT-B, Digit Symbol**
NP of uncomplicated alcoholic: at 7-12 years abstinence

- Meta-analysis of cognitive functioning after 7-12 years of abstinence

<table>
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<th>Domain</th>
<th># studies</th>
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<th>Weighted mean abstinence (weeks)</th>
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Gender Differences

Majority of studies: recently detoxified males

Males to Females: 5:1; Men drink 2.5 times more alcohol in lifetime

Women have similar pattern & degree of NP deficits as men

Women metabolize alcohol differently; display NP deficits sooner

Women develop cirrhosis, cardiomyopathy, & peripheral neuropathy sooner

Sullivan, ’02: women 3 months sober: ST nonverbal working memory and visualspatial (BD)↓; related to lifetime ETOH consumption
Personality Consequences

- **SA produces Disinhibition:**
  - 40-80% of all assaults,
  - 47% of homicides,
  - 34% of drownings,
  - 42% of injuries,
  - 47% of young male car crashes;
  - 50% of date rape;
  - 16% of child abuse; burglaries, spousal abuse, suicide attempts
- 50% of successful suicides done under influence of alcohol
- Depression
- Action orientation
- Alexithymia
Neuroimaging Findings

Recent detoxified: **Cerebral atrophy and volume loss, esp. in older**

Prefrontal **sensitive** to effects of aging & ETOH

Prolonged *abstinence* (6 m) causes **White Matter increase, decreased 3rd Ventricle volume**

PET studies: NP deficits related to **decreased glucose metabolism and hypoperfusion in frontal cortex & subcortical structures**

SPECT: **reduced rCBF**
Neuroimaging

- **Structural MRI:**
  - Smaller cortical gray and white matter volumes & larger ventricles
  - Pronounced in frontal, limbic and cerebellar areas
  - Older show greater volume deficits, esp. frontal
  - Hippocampal volume deficits in adolescent and young adults
  - Younger age of onset and longer duration of use correlates with smaller hippocampal volumes

- **Functional MRI:**
  - Alcoholics use more higher order cognitive processes to do simple tasks

- **Diffusion Tensor Imaging:**
  - Poor WM integrity, esp. corpus callosum
  - Demyelination
Decreased P3 wave in Evoked Response Potential and alcoholism risk

The P3 component in ERP is reduced in alcoholics compared with control subjects. And in young sons of alcoholic fathers.
Emotional Perception and Alcoholism

- Alcoholic individuals display abnormalities in their perceptions of facial and linguistic emotional stimuli
  - Impairment in emotional facial-expression recognition
  - Deficits in processing affective cues in speech
  - See more fear and less anger in facial expressions
  - Enhanced fear responses

- They perceived the valence of negative facial stimuli to be more neutral as a function of age

U. Clark, et al., Neuropsychology, 2007
Brain in Recovery

- Brain is clearly a dynamic organ
- **Structural brain abnormalities can be partially reversible with sustained sobriety, possibly reflecting remyelination & cellular revoluming:**
  - Increase in glucose utilization post 30 days of sobriety
  - Increase in cortical grey volume, even more WM volume, & hippocampal volume with 30 days
  - Neurogenesis increase with sobriety in rats
  - With 5 years sobriety, increased brain volume
  - Increased frontal and limbic areas with recovery
Alcohol relate Neurological Syndromes

Alcoholic Cerebellar Degeneration: ataxia (38%)
Alcoholic Dementia (4%)
Stroke: Coronary Artery Disease ↑ in heavy use
Marchiafava-Bignami Disease: CC demyelinization
Peripheral Neuropathy (34%)
Seizures (14%)
Frontal Lobe deficits (58%)
Memory dysfunction (32%)
Fetal Alcohol Syndrome

Tuck, 1991
Alcohol Effects on Neurotransmitters

- Increases Dopamine (pleasure ↑)
- Decreases Serotonin (Inhibition ↓)
- Stimulates Opiate Neuropeptide Release – Endorphins (euphoric)
- Potentiates GABA receptor function – (sedation)
- Inhibits Glutamate receptor function – memory ↓
Alcoholic Peripheral Neuropathy

- Abnormal sensations
  - Pain
    - Feels like "pins and needles"
  - Numbness
  - Muscle weakness, cramps, or aches
  - Muscle spasms / contractions
  - Tingling
- Constipation
- Diarrhea
- Incontinence (leaking urine) or difficulty with urination
- Impotence in men
- Nausea / vomiting
Elected as best beer in the world!
Delirium Tremens

**Delirium tremens** (Latin for "shaking frenzy", also referred to as DTs, "the horrors", "the bottleache", "quart mania", "ork orks", "gallon distemper", "barrel fever", "the shakes", or "the fear") is:

- an acute episode of [delirium](#) that is usually caused by withdrawal from alcohol,
- first described in 1813
- usually caused by [withdrawal](#) or [abstinence](#) from benzodiazepines or barbiturates, or alcohol

When caused by alcohol, it occurs only in individuals with a history of constant, long-term alcohol consumption.
Five percent of cases of acute ethanol withdrawal progress to delirium tremens.

Delirium tremens can be fatal:
- up to 35% if untreated;
- if treated early, death rates range from 5-15%.
The main symptoms are:

- confusion,
- disorientation
- agitation
- signs of severe autonomic instability (fever, tachycardia, hypertension).

Hallucinations such as visions of insects, snakes or rats (or stereotypically, pink elephants or tiny figures). These may be related to the environment, e.g., patterns on the wallpaper that the patient perceives as giant spiders attacking him or her.
Delirium tremens hallucinations:
- primarily visual,
- but can be tactile hallucinations such as sensations of something crawling on the subject - a phenomenon known as formication.

Sometimes be associated with severe, uncontrollable tremors of the extremities and secondary symptoms such as anxiety, panic attacks and paranoia.

Delirium tremens due to alcohol withdrawal can be treated with benzodiazepines.
Wernicke-Korsakoff Syndrome

Carl Wernicke, b Poland 1848

Sergei Korsakoff, b Russia 1853
Wernicke’s syndrome

► In 1881, Carl Wernicke described a neurologic syndrome of acute onset characterized by:
  ► a global confusional state,
  ► ataxia,
  ► ophthalmoplegia (eye muscle weakness),
  ► nystagmus,
  ► polyneuropathy in the arms and legs

► Thiamine (B1) deficiency + heavy drinking

► 10% fatal
Korsakoff Syndrome

In 1887 Korsakoff added the characteristic:
- problems in new learning (anterograde amnesia)
- as well as the deficits in remembering past events (retrograde amnesia),
- and emphasized that these occurred in the context of clear attention and consciousness

Some patients tended to confabulate, sometimes making up stories or events entirely, but more frequently confusing the temporal context of actually experienced events.
Gudden, several years later, realized that the symptoms described by Wernicke and Korsakoff often occur sequentially in the same patients (Gudden 1896).

The syndrome is referred to as Wernicke Korsakoff syndrome.

But two syndromes can be independent.
Wernicke-Korsakoff’s Syndrome 1

Up to 80 percent of alcoholics have a deficiency in thiamine (Vitamin B).

ETOH interferes with gastrointestinal transport of Thiamine and chronic liver disease reduces thiamine metabolism.

N. Butters, 1985; Lishman, 1997
Wernicke’s Encephalopathy (WE)

• Acute neuropsychiatric disorder resulting from thiamine deficiency, most often in the context of chronic alcohol use.

• Characterized by:
  • Mental status change (34-82% that usually improve within 1-2 days but may take 2-3 weeks
  • Ocular abnormalities (15-29%), usually ophthalmoplegia or nystagmus, often improve within days to weeks
  • Ataxia (23-25%) usually improves within the first week but can take months to resolve
  • Can also present with hypotension, hypothermia, seizures, and progressive hearing loss.
  • If undiagnosed or inadequately treated, usually proceeds to Korsakoff’s
Wernicke’s Encephalopathy

Lesions may occur in the vicinity of the 3rd and 4th ventricles, in the thalamic nuclei and in mammillary bodies.

Brust, 1993; Victor et al. 1971
Wernicke Korsakoff Syndrome

**Hemorrhages** in **Dorsomedial Thalamic nuclei and Mammillary Bodies** via
- thiamine deficiency
- fencing foils (Case N.A.) via nostril
- snooker cues (Case B.J.) via nostril

**Treatment**: large doses of Thiamine over 4 weeks
T2 and FLAIR are better able to detect WE-related neuropathology than CT.

Wernicke’s encephalopathy

- A medical emergency; fatal in up to 20% of cases; requires high-dose intravenous thiamine Tx.

- WE is difficult to differentiate from sx of Acute Withdrawal & DTs.

- An ensuing chronic Korsakoff syndrome in 85% of those surviving WE; 25% will require long term institutionalization.

- Wernicke-Korsakoff syndrome = alcohol-induced mild or major NCD.

- Acute confusion subsides over 3 months, but severe memory disorder (diencephalic amnesia) persists.
Wernicke-Korsakoff’s Syndrome 3

Persistent (Korsakoff’s):

- Normal IQ
- Severe Anterograde and temporally graded retrograde amnesia imposed over typical neurotoxic alcohol effects:
  - defective encoding;
  - severe retrieval deficit;
  - but can recall stores of sexual content
  - better with recognition;
  - but 2 of 3 recalled 9/11/2001 event

Butters & Stuss, 1989
Wernicke-Korsakoff’s Syndrome 4

Executive dysfunction; lack of awareness if frontal; blandness, confabulation

Processing speed impaired

28% slight recovery, 26% permanent syndrome
Confabulation

- Primarily happens in the acute (Wernicke) stage of the disorder.

- Confabulation is not specific to Korsakoff syndrome, also seen in patients with lesions in the frontal lobes, basal forebrain, or both.

- Caused by disruption in one or more frontal cognitive processes needed for effective reality monitoring, such as temporal discrimination, source monitoring, and self-initiated memory retrieval.

Johnson et al 1997
Korsakoff Syndrome

- Due to alcohol neurotoxicity syndrome, as well as neuronal loss, microhemorrhages, and gliosis of the paraventricular and periaqueductal gray matter resulting from thiamine deficiency.
- Lesions in the dorsomedial nucleus of the thalamus, anterior thalamic nuclei, mammillary bodies, and mammillothalamic tract all implicated in KS.
- Lack of consensus as to the lesion critical to emergence of memory disorder.
- Thiamine deficiency has been identified as principal pathogenic factor in degeneration of the cerebellum.
NP findings in KS

- Dense amnesia for both recent and remote information
- Executive dysfunction
  - Abstract thinking
  - Cognitive flexibility
  - Disinhibition
  - Poor judgment
  - Confabulation
  - Emotional processing
  - Volition
  - Awareness of deficits
- Attention deficits
Visuospatial and visual-perceptual deficits are also observed on a variety of concept formation tests that require discrimination and classification of complex visual stimuli.

Abnormally long time to identify visually presented material.

Kopelman 1995; Oscar-Berman, 1980
Korsakoff’s Syndrome 2

- Deficits in planning, decision making, and problem solving, deficits linked to impaired frontal executive control

- Perform poorly on clinical tests of frontal function such as the Wisconsin Card Sorting test, verbal fluency, and Trails B (Squire 1982; Jacobson et al 1990)
Korsakoff’s Syndrome 3

- Retrograde amnesia a typical feature, commonly extending back 25 years or more

- Memory for autobiographical information as well as knowledge of public events and facts are affected

- Memories from childhood and early adulthood are remembered better than memories from the recent past. (Kopelman 1989; Fama et al 2004)
COGNISTAT: Korsakoff’s
Variability in the level of general intellectual functioning

Score in the average range on standard IQ tests, but others demonstrate more widespread cognitive deficits

Jacobson et al 1990
Korsakoff’s Syndrome 5

- **Changes in personality**
  - Patients lack insight
  - Blandness and apathy about ongoing events
  - Unconcerned about personal appearance.
  - A lack of interest in alcohol is also striking.
Comparing Korsakoff and non-Korsakoff alcoholics

Sudden Onset in Korsakoff’s

Korsakoff patients are impaired on tests of memory, fluency, cognitive flexibility, and perseveration

Non-Korsakoff alcoholics may show some frontal system deficits as well, but these are milder

Oscar-Berman et al 2004
Korsakoff’s vs. Alcohol induced NCD

- In Korsakoff syndrome patients have a disproportionate disorder of memory.

- Patients with Alcohol induced major NCD have more global cognitive impairment (Salmon et al 1993).
Korsakoff’s vs. Alcohol Major NCD

- No distinct neuropathological basis has been established for alcoholic major NCD (Victor and Adams 1995)

- Cognitive disorders secondary to alcoholism can more appropriately be seen as varying along a continuum of severity (Bowden 1990)
Portal-Systemic/Hepatic (liver) Encephalopathy

- Portal-Systemic or Hepatic Encephalopathy (PSE) caused by cirrhosis (advanced stage liver disease due to alcohol, viral hepatitis, or metabolic or acetaminophen poisoning)

- Impairment of liver blood flow, which leads to portal hypertension and reduced capacity to remove and detoxify toxins (esp. ammonia)
Hepatic Encephalopathy 2

- PSE occurs as **florid neuropsychiatric disorder, low grade chronic or acute condition**

- Sxs: day-night reversal, visual spatial deficits; non-synchronized, intermittent flapping motion at the wrists (asterixis); euphoria, depression, mental slowing, inappropriate affect, behavioral and sleep disturbance; apathy, stupor, coma; often diagnosed as anxiety reaction, psychotic depression
Cirrhosis in Hepatic Encephalopathy

**Cirrhosis of liver**: 30% of alcoholics; most common medical consequence of excessive drinking

**Cirrhosis effects**: worse STM, eye tracking, hand-eye coordination, PIQ ↓

Elevated nitrogen in serum: Visual Spatial ↓

**Subclinical encephalopathy**: significant memory deficits and motor slowing

**Liver transplant**: memory capacity does not improve
Neuropsychological and Neurological Deficits Associated with Cirrhosis

- NP deficits are independent of other liver disease symptoms (PSE)
- Deficits esp. in spatial, practic, and perceptual-motor: VS, handwriting, VIQ, memory
- Neuropathology: frontal atrophy, cortical hypoperfusion, neuronal necrosis, demyelination
- EEG: triphasic wave pattern
- Issue of some covariance with alcohol effects
50-85% of people who have schizophrenia are heavy cigarette smokers

As are 60% to 70% of people with bipolar disorder

They smoke two to three times as much as an average smoker.

Estimated that 44% of all cigarettes used in the US are smoked by the mentally ill.

Prefer high tar, high nicotine cigarettes
2000 Smoking Prevalence

- 70% of all cigarettes smoked in the United States are consumed by people with psychiatric and/or substance abuse disorders; smoking prevalence in US was 23%.

- Smoking rate in individuals with major depression and other mood and anxiety disorders is 41%.

- Smoking rate in individuals with alcoholism, heroin dependence or other illicit drug use is 68%.
Schizophrenia and Smoking: Nicotine as poor man’s Stimulant

- 50-85% of people who have schizophrenia are heavy cigarette smokers (and ~65% of people with bipolar disorder)
- They smoke 2 to 3 times as much as an average smoker.
- Schizophrenia pts. do better on NP tests when smoking; poor man’s stimulant?
Smoking and neuropsychological variables in Schizophrenics: Quitting Smoking & Attention

- Greater deficits in WM task and WCST performance correlated with smoking cessation failure
- "Self medicate" to remediate the chemical imbalance in the brain (dopamine hypofunction in the PFC)
- Information processing speed ↑↑, increased attention
- Poor man’s Ritalin

Cattapan-Ludewig et al, 2009
TBI and Alcoholism

- Alcohol is present in:
  - 41% of fatal TBI
  - 7% of falls
  - 60% of MVA
  - >70% of MVA comas
  - 1 person injured every 2 min where alcohol present
TBI and Substance Abuse: Alcohol 2

Alcoholics have:

- Higher rates of medical complications
- Longer periods of post-injury agitation
- Poorer cognitive functioning at discharge
- Greater neurological impairment
Long Term Complications: Alcohol

- Increased risk of another TBI
- Lowered seizure threshold
- Lowered levels of recovery
- Degradation of rehabilitation gains
- Increased risk of psychological adjustment difficulties
- Exacerbation of premorbid behavioral characteristics (impulsivity, risk taking, psychiatric disorders)
Alcohol caused Major NCD

25% of elderly alcoholic;
24% of institutionalized

Multifactorial causation

Onset is insidious, but often 10 years younger
Major NCD
More White matter atrophy, esp. frontal
Permanent
Executive deficits
Fluency, language normal
Subcortical and Cortical variants

Filley, 2001; Lishman, 1997
Brain Atrophy and Drinking

- Brain volume normally decreases with age at an estimated rate of 1.9 percent per decade, accompanied by an increase in white matter lesions.

- N=1,839 adults (average age 60), between 1999-2001

- The more alcohol an individual drank, the smaller the total brain volume.

- The association between drinking and brain volume was stronger in women.

- Alcohol consumption does not have any protective effect on brain volume.

Neurology, 2008
Alcoholism with Cerebral Atrophy

Severe atrophy of Mammillary bodies and thalami
Alcoholism, Smoking and Alzheimer’s:
7 year earlier onset of dementia

N = 938 people age 60 and older who were diagnosed with possible or probable Alzheimer's disease

7 percent of the study participants had a history of heavy drinking (more than two drinks per day). 20% had a history of heavy smoking (one pack of cigarettes or more per day); 27% had the APOE-4 variant.

Heavy drinkers and heavy smokers develop Alzheimer's disease years earlier than people with Alzheimer's who do not drink or smoke heavily.

Ranjan Duara, Neuropsych. Review, 2009
Alcohol related Atrophy, esp. Prefrontal

Pfefferbaum et al. 1997
Alcohol & Aging and Dementia

- Protective effect of light-to-moderate alcohol consumption on cardiovascular system
- Raises blood levels of high-density lipoprotein (HDL) cholesterol
- Increases insulin sensitivity
- Prevents blood clots by preventing platelet aggregation and inhibiting thrombin activity
- Increases the natural breakdown of blood clots (i.e., fibrinolysis)
- Protective effect of light-to-moderate alcohol consumption against cognitive decline
- Presence of the APOE genotype may modify or worsen these factors
HIV and substance abuse

- Up to 75% of HIV+ have history of past or current substance abuse.

- History of drug abuse associated with degree of cognitive impairment.

- Injection drug use accounts for >30% of all HIV/AIDS cases in US.

- Either directly or because of drug use, HIV associated with increased risky sexual behaviors.
HIV & Substance Abuse #2

- Opiates and other IV drug use seem to increase vulnerability to effects of virus on CNS (Vazquez/Justo 2003)

- HIV + substance abuse can lead to greater impulsivity even when CD4 count WNL, leading to impulsive decisions/behaviors

- Suspected synergistic adverse effects on motor and visuomotor functioning

- Drinking severity, WCST failures to maintain set, and higher Beck Depression scores assoc w/ more frequent medication non-compliance (they forget to take them!)
HIV & Substance Abuse #3

- Recent heavy alcohol use may represent a potential risk factor for more rapid or pronounced cognitive decline. This may be even more pronounced with comorbid substance abuse.

- Decrement more pronounced in domains preferentially affected by both HIV and ETOH
  - Psychomotor/motor speed
  - Reaction time
HAD (HIV-Associated Dementia) vs. Alcohol-Related Deficits

- If CD4 is high, probably not HAD
- If pt no longer drinking and memory problems developed suddenly, probably is HAD
- Alcohol will lead to cerebellar problems such as wide-based gait
- HAD: look for cognitive ↓↓ and motor slowing
- Memory problems similar in both
Etiological Theories

Premature aging
Global deterioration: wrong
Right hemisphere
Frontal-limbic-diencephalon
Subcortical
Pre-morbid susceptibility

Two-systems compromise model
Preexisting EF vulnerabilities

- Nonalcoholic adult offspring of alcoholic individuals showed increased impulsiveness and decreased EF, suggesting weakness of 2 distinct neurobehavioral decision systems.

- Findings support evidence that EF weaknesses may qualify as a suitable endophenotype (genetically based behavior pattern) candidate for alcoholic disease.
Two-systems compromise model

- **Best fits current data**

- Posits alcohol neurotoxic compromise of
  - Cerebellar-pontine-prefrontal (motoric)
  - Prefrontal-parietal cortico-cortical system (cognitive)
  - producing motor and cognitive compromise, respectively

- It is based on a pattern of compromise of executive function, visuospatial abilities, and ataxia of gait, along with relative sparing of declarative memory and upper limb speed and strength
Recovery and White Matter

- Reversal of atrophy: abstinence followed by reversal of sulcal and ventricular enlargement

- Increased cortical grey matter after 2-4 weeks of sobriety

- Increase in white matter volume related to decrease in 3rd ventricular size, 2-7 months
There was a substantial decrease in reported symptoms in the first 2 years of sobriety. Importantly, however, recovery continued for years with recovering individuals approaching controls only at ~1 decade into recovery.

DeSoto, O’Donnell & DeSoto, 1989
Recovery of Deficits

With longer sobriety, NP and Neuroimaging studies indicate that, there is significant improvement in brain structure and function.

De-atrophication: dendritic & white matter regrowth

3 weeks as typical recovery

Drinking pre and post 40

Neuropsychological deficits improve over 4 to 5 years

Grant, 1987; Parsons & Nixon, 1998
Recovery 2: Reversal of Atrophy

- Cognitive functions and motor coordination improve within 3 or 4 weeks of abstinence; cerebral atrophy reverses after the first few months of sobriety. (Oscar-Berman, A. Alcohol Health Research World., 21, 65-75, 1997)

- Structural pathology often disappears with long-term abstinence. (Neuropsychology of Alcoholism - Parsons et al. 1987)

- Frontal lobe blood flow continues to increase with abstinence, returning to approximately normal levels within 4 years. (Gansier D. et al. Journal of studies of Alcohol, 61, 32-37. 2000)
Recovery 3: Executive Functioning is slowest to recover

- Skills that require novel, complex, and rapid information processing take longest to recover.

- New verbal learning is among the first to recover. Visual-spatial abilities, abstraction, problem solving, and short-term memory, are the slowest to recover.

- May be persistent impairment in these domains, particularly among older alcoholics [over 40]

Neuropsychology of Alcoholism - Parsons et al. 1987
Solvents: Neurotoxic Injury

- **Demyelination** and ischemic effects

- **Cognitive**: memory acquisition, processing speed deficits

- **Psychiatric Symptoms**: depression, impaired behavioral control
Cannabis / Marijuana/ THC (tetrahydrocannabinol)

Intoxication: widespread Cognitive ↓

Acute Deficits (24 hours): Attention, Executive, immediate recall, RT, time underestimation

Long Term Deficits, Chronic Use:
► increasing evidence that teenage cannabis use onset results in greater neurocognitive deficits compared with adult onset. Weekly cannabis use before age 18 has been linked with reduced performance on IQ tests, attention, visual search, & EF. Also amotivational syndrome

Dependence: Memory, sustained attention, RT ↓

Schwartz, 1991; I. Grant, 1978
Acute Effects of MJ

Produces sedation, mood elevation & hallucinations.

There is no dispute that cannabis produces cognitive impairment during acute intoxication; effects can be shown using driving or flight simulators; esp. memory & learning.

Primary adverse effect of acute marijuana use is diminished psychomotor performance: marijuana has been found to play a significant role in car accidents with 33 percent of drivers arrested at the scene of the accident being positive for marijuana.
Effects of Cannabis

- Physiological: sedation, mood elevation & hallucination

- Primary immediate cognitive effect: adverse effects on learning & memory

- Chronic Cognitive Effects

- Primary neurotransmitter system: binding to endogenous cannabinoid receptor (CB1)
THC Potency today

- Much of what we know from earlier research is based on smoking marijuana with much lower doses of THC than are commonly used today.

- Potency: in 1978 = 1.4%, in 1988 = 3.6%, in 1998 4.4%, and in 2008 8.5%.

- The highest tested sample had 22.04% THC.

- The highest tested sample ever tested between 1975 and 2009 had 33.12% THC.
Latest studies

- Frequent marijuana use (1x a week) can have a significant negative effect on the brains of teenagers and young adults, including cognitive decline, poor attention and memory, and decreased IQ.

- 2012 study: 6.5% of high school seniors reported smoking marijuana daily; 31% of young adults (ages 18 to 25) reported using marijuana in the last month.

- People who have become addicted to marijuana can lose an average of 6 IQ points by adulthood: 2012 longitudinal study of 1,037 participants who were followed from birth to age 38.

Krista Lisdahl, 2014
Brain imaging studies of regular marijuana users have shown significant changes in their brain structure, particularly among adolescents.

Abnormalities in gray matter, which is associated with intelligence, have been found in 16- to 19-year-olds who increased their marijuana use in the past year.

Recent 2015 study: Marijuana use may be major predictor of bipolar cycling in at risk bipolar individuals.
Chronic cannabis users, by their own admission, are not happy campers

<table>
<thead>
<tr>
<th></th>
<th>Positive</th>
<th>Neutral</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>What effect has marijuana had on your...</strong></td>
<td></td>
<td></td>
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<tr>
<td>Social Life?</td>
<td>5%</td>
<td>25%</td>
<td>70%</td>
</tr>
<tr>
<td>Physical Health?</td>
<td>0</td>
<td>19%</td>
<td>81%</td>
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<tr>
<td>Mental Health?</td>
<td>24%</td>
<td>16%</td>
<td>60%</td>
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<tr>
<td></td>
<td>Positive</td>
<td>Neutral</td>
<td>Negative</td>
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<tr>
<td>----------------------</td>
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<tr>
<td><strong>What effect has marijuana had on your...</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Cognition?</td>
<td>2%</td>
<td>8%</td>
<td>91%</td>
</tr>
<tr>
<td>Memory?</td>
<td>0</td>
<td>8%</td>
<td>91%</td>
</tr>
<tr>
<td>Career?</td>
<td>0</td>
<td>21%</td>
<td>79%</td>
</tr>
</tbody>
</table>
Marijuana Effects

- Subtle chronic effects even with adolescent users. There also may be dose relationship.

- Reduced memory efficiency, at least during THC use

- Primary adverse effect of acute marijuana use is diminished psychomotor performance: marijuana has been found to play a significant role in car accidents with 33 percent of drivers arrested at the scene of the accident being positive for marijuana
MJ Conclusions

- There is no clear consensus on whether cannabis produces long-term or irreversible effects on the brain; but newer research indicates more deficits.

- Regular cannabis use (several times a week) is associated with impaired functioning – both by objective measures and by the admissions of users themselves.
Cocaine

CNS stimulant; increases dopamine availability; chronic heavy use is neurotoxic

Stimulant: negative consequences: vasoconstriction, HTN, strokes, seizures, MI (all produce cognitive ↓)

Moderate NP effects (size = .35): memory↓, WM ↓, attention↓, executive↓, disinhibition

PET indicates functional neurological abnormalities in F, T, BG areas

Chronic usage with seizures: higher white matter atrophy

Abstinence from heavy chronic use: frontolimbic hypometabolism & down-regulation of dopamine receptors

Bauer, 1993
Effects of Cocaine

- Physiological: euphoria, increases in energy & motor activity
- Primary immediate cognitive effect: improved attention, processing speed, & inhibition
- Chronic Cognitive Effect: decreased attention, WM, & visual memory
- Primary neurotransmitter system: increased dopamine availability in limbic system
Amphetamines

**Long term use**: serotonergic damage, neuronal pruning

**Acute**: Attention, motor speed, verbal fluency, verbal memory ↓

**Long Term Deficits**: Attention, motor, verbal memory ↓

**MDMA (ecstasy)**: memory, executive ↓
Effects of amphetamines

- **Physiological**: increased neural firing, euphoria, vasoconstriction, appetite suppression, increases in respiration, energy, & libido

- **Primary immediate cognitive effect**: enhanced attention & speed of info processing, paranoid psychosis

- **Chronic Cognitive Effect**: decreased verbal memory, complex info processing, PS, WM, inhibition, problem solving & decision making

- **Primary neurotransmitter system**: Nigrostriatal dopaminergic projections
Stimulant Drugs Inhibit Dendritic Growth in Response to Environment

Relocating rats from standard cages to an enriched environment led to a significant increase in dendrite branching in the nucleus accumbens, but not if the rats were first exposed to amphetamine or cocaine.

Kolb, B. 2003
Eroding the Mind
Researchers have mapped brain decay caused by methamphetamine use. The damage affected memory, emotion, and reward systems.
Opiates (Oxycodone/Heroin): serious public-health problem

- Heroin is major illicit drug of abuse; Vicodin & Oxycodone are major licit opiate drugs of abuse
- By 2010, the United States, with about 5% of the world’s population, was consuming 99% of world’s hydrocodone (the narcotic in Vicodin), along with 80% of the oxycodone
- Opiate abuse associated with cortical atrophy & enlarged ventricles & orbitofrontal & ACC anomalies on imaging
- Neuropsychological data indicate deficits in attention, concentration, WM, recall, visuospatial skills, EF, & psychomotor speed with both acute and chronic opioid use.
- The long-term effects of opiate use appear to have the greatest impact on executive functions, including the ability to shift cognitive set and inhibit inappropriate response tendencies.

Hartman, Gruber, 2007
Opiates (Heroin) 2

- Opiate users are **usually poly-substance abusers**. Poly-substance abuse has been shown to produce significant neuropsychological deficits ever since Grant investigated it about 25 years ago. Plus, demographic and premorbid factors are a big unknown in these users.

- **Acute**: Attention & Memory↓;

- **Chronic Use**: Executive↓

- **Treatment**: Methadone; Suboxone (partial opioid agonist buprenorphine)
Effects of opiates

- **Physiological:** decreased pain perception, sedation, respiratory depression, constipation, & euphoria

- **Primary immediate cognitive effect:** attention, WM, psychomotor speed, problem solving, & decision making

- **Chronic Cognitive Effect:** deficits in EF, WM & impulsivity

- **Primary neurotransmitter system:** binding to endogenous opioid receptors
FMRI: Opiates
Volume deficits in Frontal and Temporal areas
Benzodiazepines

Benzodiazepines include branded prescription drugs like Valium, Ativan, Klonopin, and Xanax. Among the most commonly misused prescription drugs, they work on GABA receptors.

Elderly: 40% of prescriptions

Even low dosage can impair cognitive abilities.

Reduction in neural firing reduces NP performance, mental slowing, and anterograde amnesia.

Long Acting: Memory, RT, motor speed ↓
Short Acting: Attention & Memory ↓
Memory & motor deficits can persist with lengthy abstinence.
Deficits at 6 months post discontinuation in chronic users.
Effects of benzodiazepines

- **Physiological**: reduced neural firing, sedation
- **Primary immediate cognitive effect**: mental slowing, anterograde amnesia
- **Chronic Cognitive Effect**: memory and motor deficits
- **Primary neurotransmitter system**: GABA receptor
- **2 recent major studies**: Taking the drug for three to six months raised the risk of developing Alzheimer’s disease by 32 percent, and taking it for more than six months boosted the risk by 84 percent
Effects of barbiturates

- **Physiological**: reduced neural firing, sedation, euphoria, anxiolytic, respiratory depression, decreased blood pressure

- **Primary immediate cognitive effect**: decreased concentration, confusion, impaired coordination, impaired decision making

- **Chronic Cognitive Effect**: risk of cognitive impairment & depression

- **Primary neurotransmitter system**: GABA receptor
Hallucinogens

- Profound distortions in user’s perception of reality & intense emotional swings

- 3 major compounds: LSD, Peyote, Psilocybin

- All case reports; not addictive substance

- Serotonin effect

- LSD: in some, persistent flashbacks – hallucinogen-induced persisting perceptual disorder
Effects of hallucinogens

- **Physiological**: marked alteration in sensory gating, perception, mood & thought; acute psychosis; dreamlike states; pseudohallucinations

- **Primary immediate cognitive effect**: heightened response to internal stimuli, reduced effectiveness responding to external stimuli

- **Chronic Cognitive Effect**: no studies

- **Primary neurotransmitter system**: Serotonin
Effects of Ecstasy

- **Physiological**: euphoria, extroversion, elevated mood, hallucination, confusion
- **Primary immediate cognitive effect**: few studies; possible memory deficits
- **Chronic Cognitive Effect**: decreased short and long term memory and attention
- **Primary neurotransmitter system**: serotonin
## Chronic effects on NP evaluation

<table>
<thead>
<tr>
<th>Domain</th>
<th>IQ/Achv</th>
<th>Atten</th>
<th>PSpeed</th>
<th>Lang</th>
<th>Vspatial</th>
<th>Mem</th>
<th>EF</th>
<th>SensMot</th>
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<tr>
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<tr>
<td>Amphetamine</td>
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<td>-</td>
<td>?</td>
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<td>+++</td>
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</tr>
<tr>
<td>Barbiturates</td>
<td>?</td>
<td>+++</td>
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<td>-</td>
<td>+++</td>
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<tr>
<td><strong>Benzos</strong></td>
<td>+++</td>
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<td>-</td>
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<td>+++</td>
<td>+++</td>
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</tr>
</tbody>
</table>

? = unk
Neurologically challenged/Impaired, not unmotivated

Wait 2-3 weeks for cognitive assessment

Neurogenic lack of awareness: incapable of insight

Don’t depend on insight: insight therapy inappropriate early on, phase appropriate
Clinicians’ misattributions of patients’ behaviors
- Verbal skills (previously learned information) remain relatively preserved, so patients appear unimpaired
- Clinicians fail to identify cognitive impairment in at least 40% of patients
- Neuropsychological dysfunction may result in more rule violations in treatment and drop out rates

(Fals-Stewart et al., 1993; 1994)
Factors that May Influence Treatment Outcome

What about neuropsychological function?

Do these patients have the cognitive capacity to participate in treatment aimed at changing thoughts and behaviors related to their substance use disorder?

i.e., Are their brains intact enough to learn, process, and apply new relapse-prevention skills?
Low motivation and minimization and denial may be attributable to cognitive deficits.

Cognitively impaired patients might benefit from cognitive rehabilitation in addition to traditional alcohol treatment.

(Allen, Goldstein & Seaton, 1997)
Think *external prosthetics* for neurological vs. psychological Tx

Different treatment approaches for cognitively impaired clients: *different levels of care*

Need for *Mental Status screening*, i.e. MoCA
Clinical Implications of NP perspective

- **Patient – Treatment Matching**
  - Pre-treatment neuropsychological assessment
  - Target skills to individual patient’s neuropsych profile
  - Reduction in number of skills taught in CBT
  - Behavioral possibly better than cognitive focus
  - Extensive repetition
  - Extra role-plays

- **Cognitive Rehabilitation**
  - A la TBI, schizophrenia cog rehab
NP Rehabilitation

► Allow extra processing and retrieval time

► Employ errorless learning strategies for simple verbal information (http://www.projectlearnet.org/tutorials/errorless_learning.html)

► Encourage elaborative processing (http://adaptivereading.pbworks.com/w/page/3949397/FrontPage)

► Provide clear rules for actions and structure tasks/routines
A Neuropsychological Perspective on Treatment Tactics 4

- Use of **Exercise**: neurogenesis enhancement

- **Replace use of executive function with procedural memory/prospective memory tactics**

  - Airline Pilot research: Flip procedure books

- **Implementation Intentions (50%↑):**
  - “When situation \( x \) arises, I will perform response \( y \)”

- Steps: the **how, the when and the where** of doing any goal
A Neuropsychological Perspective on Treatment Tactics 5

- Use of reminder strategies
  - Calendars, dayminders
  - Google calendar (text message reminders)
Emphasize Procedural memory:

AA had it right – walk the walk

Behavioral strategies:
- behavioral repetition
- concrete
- sponsor model
- avoid triggers
Evidence-Based Practices Resources:

- SA and MH Services Admin:
  - http://www.nrepp.samhsa.gov/

- National Institute on Alcohol Abuse:

- National Institute on Drug Abuse

- Univ. of Washington Alcohol & Drug Abuse Institute:
  - www.pscyhologicaltreatments.org
Bibliography

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- Neurobehavioral Toxicology: Neurological and Neuropsychological Perspectives – J/ Albers & S. Berent (2005)