Neuropsychology of Addiction: Implications and Recommendations for Practice

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Disclosures

Emily MacKillop, PhD	Unrestricted research funding: McMaster University St Joseph's Healthcare Hamilton Research Foundation Ownership: MacKillop Psychology Professional Corporation
James MacKillop, PhD	Unrestricted research funding: Peter Boris Chair in Addictions Research Boris Family Foundation DeGroote Centre for Medicinal Cannabis Research Canadian Institutes of Health Research Canada Research Chair Program National Institute on Alcohol Abuse and Alcoholism Correctional Services of Canada Health Canada Ownership: Principal, BEAM Diagnostics, Inc. MacKillop Psychology Professional Corporation

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General Outline

- Part 1: Primer - Addiction Neuropsychology and Neurobiology
- Part 2: Applied Learning: Clinical Cases, Clinical Relevancy
- Part 3: Implications: Neuropsychological Research and Practice

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Addiction Neuropsychology and Neurobiology

Part 1

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Relevance of Addiction Neuropsychology

Understanding addiction as a behavior associated with brain dysfunction

What areas of the brain are impacted?

The impact of substance use has broad relevance to neuropsychology:

ADHD	TBI	Dementia	Chronic Pain	Psychiatric

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Core Rationale

- SUD+ pts frequently present with neurocognitive concerns:
  - Complaints of attention, memory, and EF deficits that may predate or be consequences of substance use
  - + screens for multiple comorbidities
  - Trajectories typically unclear
- Neuropsychological evaluation can be critically informative.
- This, in turn, can be integrated into optimal treatment planning

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Effects on Cognition

- Acute effects (state-like)
  - Acute intoxication effects
  - Acute post-intoxication effects
  - Acute withdrawal effects
  - Residual sub-withdrawal effects
- Chronic effects (trait-like)
  - Etiological antecedents (not technically effects)
  - Acute brain damage
  - Progressive brain damage
  - Teratogenic effects*

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Defining Addiction

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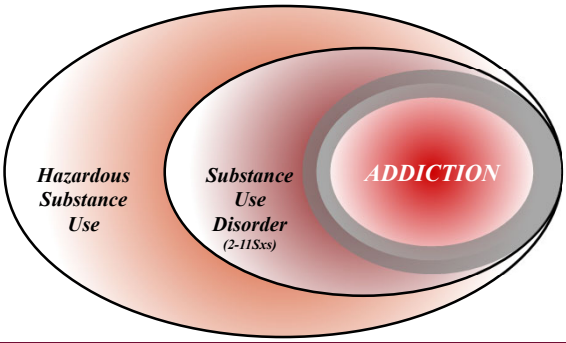
Risk vs. SUD vs. Addiction



Heilig et al. (2021) *Neuropsychopharmacology*

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DSM-5 Substance Use Disorder

1. Substance used in **larger amounts or over a longer period of time** than intended.

Inability to regulate consumption (loss of control)

4. Persistent and/or intense **cravings** for the substance
5. Continued use **despite knowledge of physical or psychological problem** caused or exacerbated by the substance
6. Substance use results in **failure to fulfill major role obligations** at work, school or home

Consumption in spite of adverse consequences

8. Important social, occupational or recreational **activities are given up or reduced** due to substance use
9. Substance use in situations in which it is **physically hazardous**
10. *__Tolerance__,
    (a) A need for markedly increased amounts of cannabis to achieve intoxication or desired effect

Physiological dependence

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    (b) Substance is taken to relieve or avoid withdrawal symptoms

APA (2013) DSM-5

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ICD-11 Harmful Use/Dependence

- Harmful Use
  - A pattern of psychoactive substance use that is causing damage to health (physical or mental)
- Dependence
  - A strong desire or sense of compulsion to take the substance
  - Difficulties in controlling substance-taking behaviour in terms of its onset, termination, or levels of use
  - Progressive neglect of alternative pleasures or interests because of psychoactive substance use, increased amount of time necessary to obtain or take the substance or to recover from its effects
  - Persisting with substance use despite clear evidence of overtly harmful consequences
  - Withdrawal
  - Tolerance

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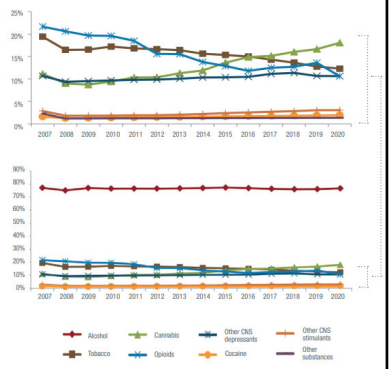
Substance Use Prevalence Estimates



Canadian Substance Use Costs and Harms 2007–2020 (csuch.ca)

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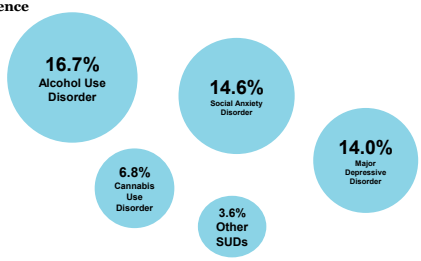
SUD Prevalence in Canada

Lifetime Prevalence



Statistics Canada, 2023

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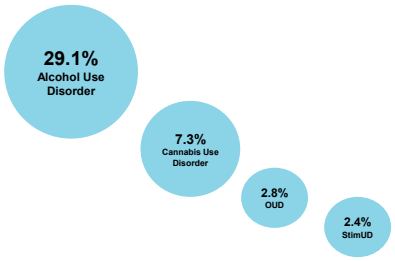
SUD Prevalence in United States

Lifetime Prevalence



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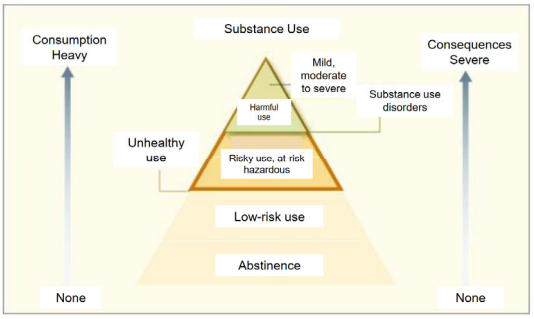

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Person-first Language: Individuals with Substance Use Disorders

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Neurobiology of Addiction

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Neurocircuitry of Addiction

Neuropsychopharmacology www.nature.com/npp

REVIEW ARTICLE OPEN

Addiction as a brain disease revised: why it still matters, and the need for consilience

Markus Heilig[1], James MacKillop[2,3], Diana Martinez[4], Jürgen Rehm[5,6,7,8], Lorenzo Leggio[9] and Louk J. M. J. Vanderschuren[10]

The view that substance addiction is a brain disease, although widely accepted in the neuroscience community, has become subject to acerbic criticism in recent years. These criticisms state that the brain disease view is deterministic, fails to account for heterogeneity in remission and recovery, places too much emphasis on a compulsive dimension of addiction, and that a specific neural signature of addiction has not been identified. We acknowledge that some of these criticisms have merit, but assert that the foundational premise that addiction has a neurobiological basis is fundamentally sound. We also emphasize that denying that addiction is a brain disease is a harmful standpoint since it contributes to reducing access to healthcare and treatment, the consequences of which are catastrophic. Here, we therefore address these criticisms, and in doing so provide a contemporary update of the brain disease view of addiction. We provide arguments to support this view, discuss why apparently spontaneous remission does not negate it, and how seemingly compulsive behaviors can co-exist with the sensitivity to alternative reinforcement in addiction. Most importantly, we argue that the brain is the biological substrate from which both addiction and the capacity for behavior change arise, arguing for an intensified neuroscientific study of recovery. More broadly, we propose that these disagreements reveal the need for multidisciplinary research that integrates neuroscientific, behavioral, clinical, and sociocultural perspectives.

Neuropsychopharmacology (2021) 46:1715–1723; https://doi.org/10.1038/s41386-020-00950-y

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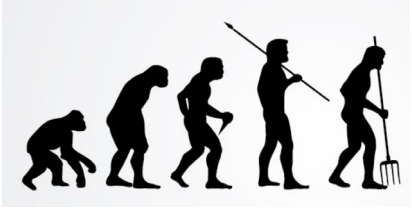
Neurocircuitry of Addiction

Ancient Mammals in a Brave New World

Psychoactive drugs hijack ancient brain circuits subserving classical fitness drives



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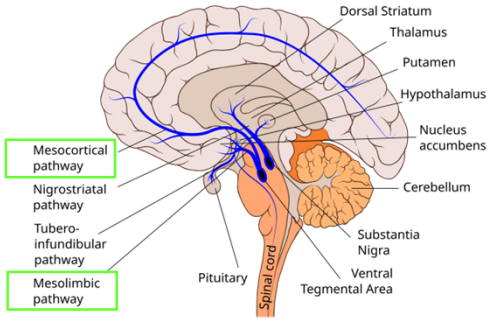
Common Neural Pathway for Addiction



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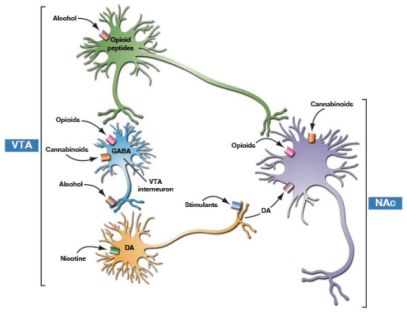
Diverse Mechanisms with a Common Neural Pathway



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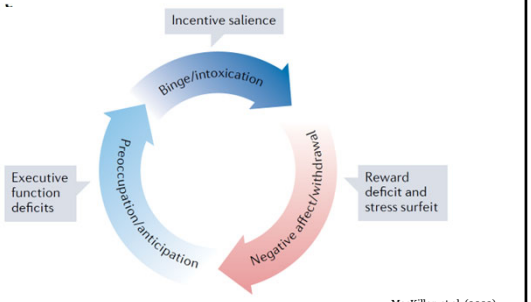
Three Stage Cycle of Addiction



MacKillop et al. (2022)
Nature Reviews Disease Primers

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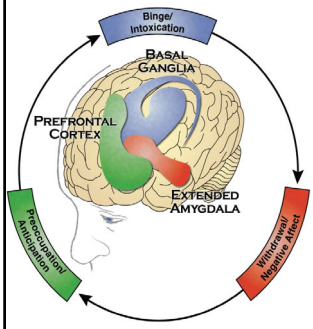

1. Binge/intoxication: Basal Ganglia
   - ❑ Striatum
   - ❑ VTA
2. Withdrawal/negative affect: Amygdala
   - ❑ BLA
   - ❑ Central Amygdala
3. Preoccupation/anticipation: PFC
   - ❑ PFC
   - ❑ Hippocampus

Adolescence as a critical "at risk" period due to significant development and remodeling

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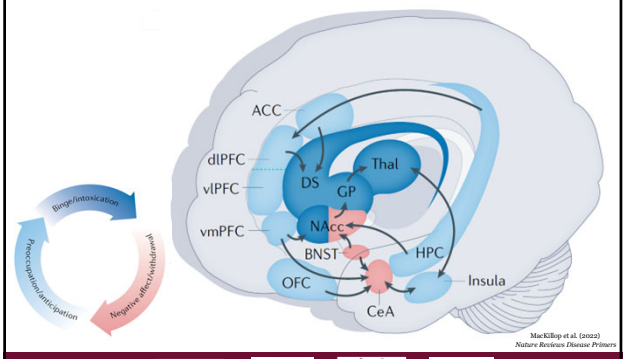
Changes in Brain Function Over Time



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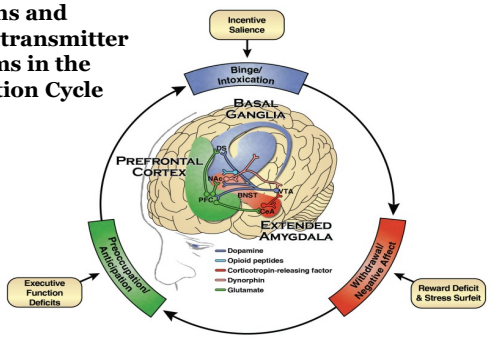
Primary Brain Regions and Neurotransmitter Systems in the Addiction Cycle



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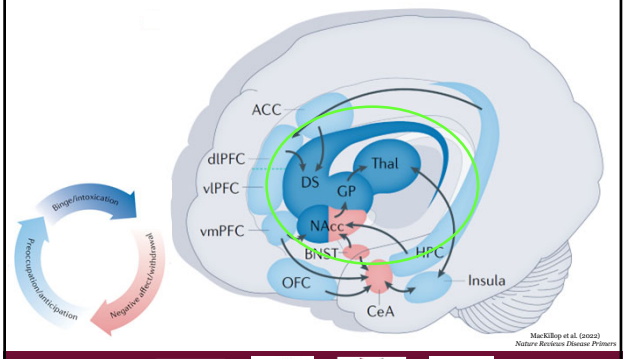
Changes in Brain Function Over Time



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Stage 1: Binge/Intoxication Stage

- Rewarding/reinforcing effects of substance use
  - Nucleus Accumbens:
    - motivation and experience of reward, reward salience
  - Dorsal Striatum:
    - forming new habits and routine behaviors
- Activating the dopamine system
  - Features of all addictive substances, particularly stimulants
  - Activating the opioid system (liking)
  - Repeated activation of this system leads to compulsive substance seeking

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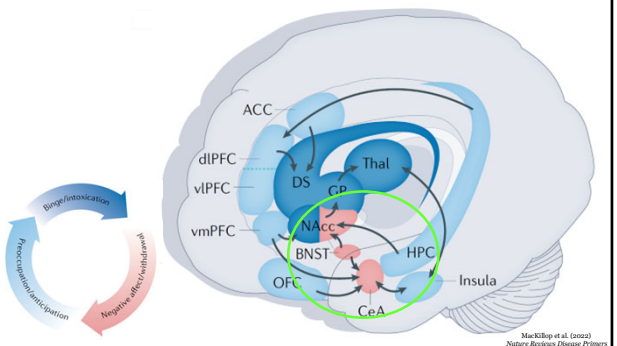
Changes in Brain Function Over Time



MacKillop et al. (2022) *Nature Reviews Disease Primers*

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Stage 2:Withdrawal/Negative Affect System - Amygdala & Limbic System

- Regulation of "fight or flight" drives
- Emotional information: Negative emotions from diminished pleasure
  - Fear replaced by avoidance of withdrawal
- Inputs are integrated in the NAcc
  - Lesions show preference for smaller immediate rewards*

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Stage 2:Withdrawal/Negative Affect System - Amygdala & Limbic System

- Stress response dysregulation
  - ❑ Interaction with the hypothalamus which controls activity of hormone-producing glands (e.g., pituitary; adrenal)
  - ❑ Activation of stress neurotransmitters (CRF), NE, dynorphin
  - ❑ eCB neuroadaptations also increase stress reactivity
- Hippocampus
  - ❑ Vulnerable to teratogenic effects of ETOH
  - ❑ Stroke in cocaine*
  - ❑ Reductions in neurogenesis in SUD

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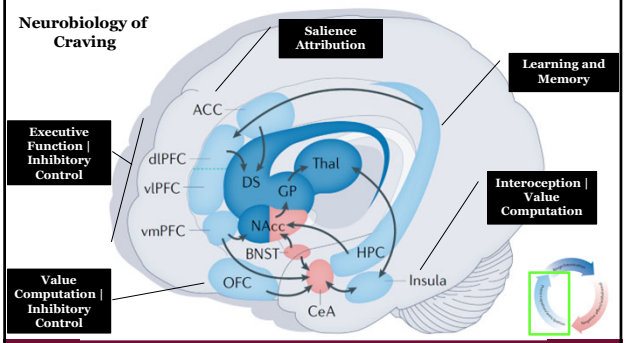
Changes in Brain Function Over Time



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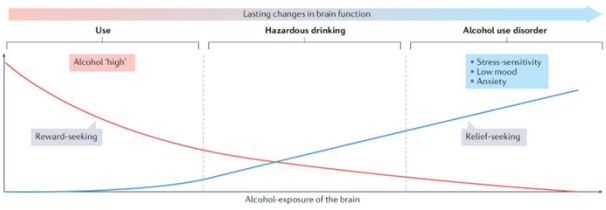

MacKillop et al. (2022)
Nature Reviews Disease Primers

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Review of Neuroadaptive Models

- Psychostimulant theory of addiction
  - Dopamine as a final common pathway
- Incentive sensitization approach
  - *Liking vs. wanting*
- Hyperkatifeia approach
  - *Positive to negative reinforcement transition*
  - Reward-seeking to relief-seeking
- Automaticity approach
  - *Ventral-to-dorsal striatum transition*
  - Goal-directed choice to habit learning

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Transitions in Psychological Processes in the Addiction Cycle

- Impulsivity
  - Deficits in self-regulatory control
- (to) Compulsivity
  - Diminished volitional control over time
- Positive Reinforcement
  - Diminished with repeated use and tolerance
- (to) Negative Reinforcement
  - Withdrawal effects, use to reduce withdrawal effects
  - Negative emotions, stress reactivity and physical illness

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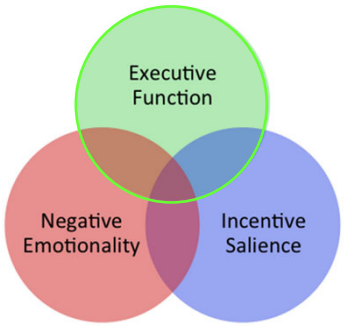
Addictions Neuroclinical Assessment



Kwako et al. (2016)
Biological Psychiatry

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Addictions Neuroclinical Assessment

Measure	Time to Complete	Type of Task
Executive Function		
Stop Signal Reaction Task (123)	10 minutes	Behavioral
Appetitive Go-NoGo (124)	10 minutes	Behavioral
Continuous Performance Test (125)	15 minutes	Behavioral
Tower of London (126)	15 minutes	Behavioral
Wisconsin Card Sorting Test (127)	15 minutes	Behavioral
Delay Discounting (128)	15 minutes	Behavioral
N-Back (129)	10 minutes	Behavioral
Beads in a Jar Task (130)	5 minutes	Behavioral
Barratt Impulsiveness Scale (131)	5 minutes	Self-report
Negative Emotionality		
Approach Avoidance Task (132)	10 minutes	Behavioral
Cyberball (133)	10 minutes	Behavioral
Trier Social Stress Test (134)	20 minutes	Behavioral
Cold Pressor Task (135)	10 minutes	Behavioral
Digit Span (136)	5 minutes	Behavioral
Two-Step Task (Model-Free Model-Based) (137)	15 minutes	Behavioral
Beck Depression Inventory (138)	5 minutes	Self-report
Beck Anxiety Inventory (139)	5 minutes	Self-report
Fawcett-Clark Pleasure Scale (140)	5 minutes	Self-report
Toronto Alexithymia Scale (141)	5 minutes	Self-report
Childhood Trauma Questionnaire (142)	5 minutes	Self-report
Facial Emotion Matching Task (143)	10 minutes	Neuroimaging
Incentive Salience		
Choice Task (Explicit Version) (144)	15 minutes	Behavioral
Dot-Probe Attentional Bias Task (Cues) (145)	10 minutes	Behavioral
Obsessive-Compulsive Drinking Scale (146)	5 minutes	Self-report
Cue Reactivity Task (80)	10 minutes	Neuroimaging
Monetary Incentive Delay Task (147)	10 minutes	Neuroimaging

Kwako et al. (2016) *Biological Psychiatry*

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Addictions Neuroclinical Assessment

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Wisconsin Card Sorting Test (127)	15 minutes
Delay Discounting (128)	15 minutes
N-Back (129)	10 minutes
Beads in a Jar Task (130)	5 minutes
Barratt Impulsiveness Scale (131)	5 minutes

Kwako et al. (2016) *Biological Psychiatry*

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Impact of Substances on Brain Function

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Substances Alter Immune Response

- Chronic Cocaine, opiates, alcohol, THC have immunosuppressive, neuroinflammatory effects
  - Degree varies by type and duration of use
  - increased susceptibility to infections
  - Substances of abuse affect integrity of BBB
  - cerebral dysfunction related to viruses and diseases
- More rapid progression of diseases (e.g., HIV to AIDS)
- Increase postoperative risks
- Substances interact and exacerbate virus and disease courses and increase risk of neuropsychological impairment.

(e.g., Malkiewicz et al., 2020)

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Alcohol and Neurocognitive Impairment

- Approx. half of individuals with AUD show mild-severe cognitive dysfunction some will progress
- Cerebral atrophy
  - Frontal lobes, cerebellum, limbic structures
- Cessation has been linked with brain recovery
  - Cortical thickness increases (Durazzo et al., 2024; Schroth et al., 1988)
  - Neuropsychological improvement
  - ARD effects/course may not be reversible but can slow/stabilize with abstinence

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Alcohol: Persisting Effects

- Wernicke's encephalopathy – acute presentation
  - thiamine deficiency
  - Distinct: Confusion, ataxia, and nystagmus
- Korsakoff syndrome –
  - If WE is not treated promptly, persistent effects
  - Diencephalon: Mammillary bodies/hypothalamus, thalamus
  - Cerebellum and frontal cortex can also be affected
- Alcohol Related Dementia
  - Persistent long-term use of alcohol, not necessarily due to thiamine deficiency

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Dementia and Substance Use

- A relationship between dementia and substance use is well established
  - VaD: Stroke, co-occurring chronic illness, cerebrovascular vulnerability
- Alzheimer's disease susceptibility has also been linked with alcohol and substance use (Justo et al., 2025)
  - ETOH can change the presentation (frontal features) and course (earlier)
- Co-occurring conditions are common, making etiological classifications challenging
  - DSM-5-TR: Substance-Induced or Mixed Major vs. Mild Neurocognitive Disorder, Persistent

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Co-Occurring Factors Influence Progression & Course of Neurocognitive Impairment in SUD

- Medical
  - CVD, hepatic diseases, malnutrition, cancer risk
- Neurological
  - TBI, FASD, Inflammation/encephalopathy
- Psychiatric
  - Depression, anxiety, PTSD, ScZ, BPD (Grant et al., 2004)
- Genetics
  - ~40% heritability SUD
- Other SUD

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Cocaine

- Dopamine dysfunction (Volkow et al., 2007)
- Structural and functional changes in the PFC (Rando et al., 2013)
- Amygdala, altering emotional processing (Koob & Volkow, 2010)
- Hippocampus damage, volume (McHugh et al., 2013)
- Striatum: motor and habitual behaviors (Calabrese et al., 2007)
- Cerebellar function, atrophy (Stein et al., 2005)
- White matter integrity (Ottino-Gonzalez et al., 2022)
- Risk factor for ischemic and hemorrhagic stroke
- More rapid progression of chronic illnesses and infections

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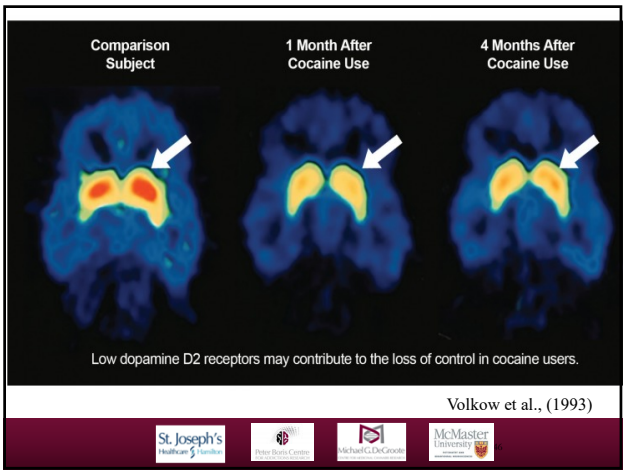

Volkow et al., (1993)

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Neuropsychological Effects of Cocaine

- Long-term neuropsychological consequences vary largely due to methodological differences across studies (Frazer et al., 2018)
  - Common findings are impairment in impulsivity and decision-making
- Cocaine confers risks for other conditions associated with cognitive impairment:
  - Psychiatric symptoms
  - Social/environmental problems
  - Risk factor for stroke (Renton et al, 2023)

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Cannabis and the Neurocognition

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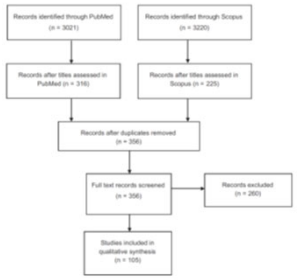
Systematic Review on Cannabis and Cognition (Broyd et al., 2016)



Broyd et al., 2016, *Biological Psychiatry*

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Cognitive Domain	Acute[b]	Chronic[b]	Persistence With Abstinence[b]	Pertinent Cannabis Use Parameters
Memory				
Verbal learning and memory	+++	+++	+−	Frequency; lifetime use; duration; age of onset; sex
Working memory	+−	+−	+−	Frequency; lifetime use; recency; sex
Other memory function	+	+−	−	Age of onset; frequency; recency
Attention				
Attention	+++	+++	+−	Dose; age of onset; length of abstinence; withdrawal effects
Attentional bias	+	+++	NA	Craving; dependence; frequency; CBD
Psychomotor Function	+++	+	+	
Executive Function				
Planning, reasoning, interference control, and problem solving	+−	+−	+−	Neurodevelopmental stage; age of onset; frequency
Inhibition	++	+−	NA	Frequency; task complexity
Verbal fluency	−	+−	+−	
Time estimation	+−	−	−	
Decision Making	+−	+−	−	Age of onset; lifetime exposure; frequency; cannabis use disorder

Broyd et al., 2016, *Biological Psychiatry*

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Broyd et al., 2016, *Biological Psychiatry*

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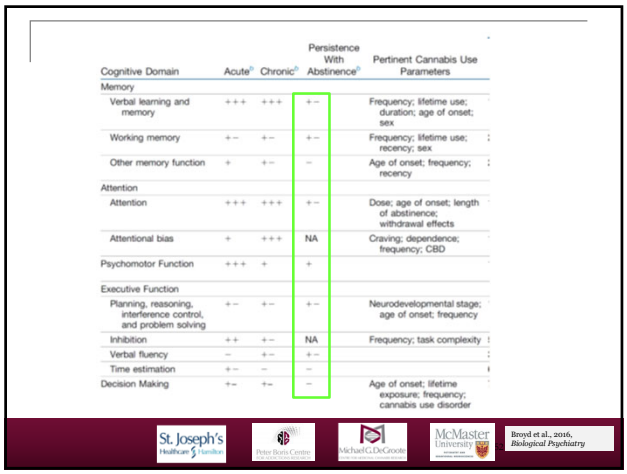

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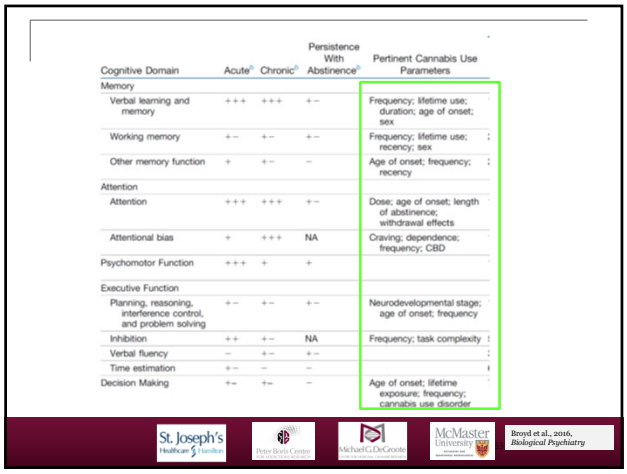

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Broyd et al., 2016, *Biological Psychiatry*

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Nicotine

- Confers risks for other conditions associated with neurocognitive impairment:
  - ❑ COPD, stroke, cerebrovascular disease, VaD
- Reduces survival rates in cancer, HIV
- Grey and White matter integrity (e.g., Fritz et al., 2014; Ottino-Gonzalez, 2021))
- Acute effects: lower regional cerebral blood flow
  - ❑ Abstaining can improve cerebral circulation following 1 year in elderly individuals who have a 30–40-year smoking history (Rogers et al., 1985)

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Benzodiazepine

- Acute effects of associated with factors correlating with cognitive impairment:
  - Postoperative confusion;
  - Falls: hip fractures; TBIs;
  - MVAs;
  - risk for decline in overall physical health; (e.g., urinary incontinence)
  - alcohol misuse
- Longer term direct cognitive effects - research is equivocal.
  - Meta-analyses show reduced cognitive function in many domains (Barker et al., 2004b) while newer research shows no direct link (Joyce et al., 2022)
  - Chronic users are 2x as likely to show lower cognitive performances than non-users, linked to factors above and/or reasons why they are prescribed the meds
  - Polypharmacy effects, older adults who are prescribed benzos are twice as likely to take >10 medications

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Pons & Cerebellar Dysfunction

- Postural, motor dysfunction and coordination
- Structural changes related to cognitive deficits, particularly in tasks requiring executive control and spatial attention
- Central Pontine Myelinolysis
- Cerebellar Degeneration is common in long-term AUD
  - Alcoholic cerebellar degeneration
    - Associated with thiamine deficiency, oxidative stress
    - Psychiatric and cognitive changes
- Nicotine, Cannabis, Cocaine, Opioids
  - Receptors present in cerebellum with associated dysfunction
  - Nicotine, cocaine use correlated with reduced gray matter

(Chan et al., 2003; Blithikioti et al., 2019; Moreno-Ruis, 2019).

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Relevancy of Addiction to Clinical Neuropsychology

Part 1; Section 3:

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Addiction: A Behavior Associated with Brain Dysfunction

- Chronic Illness impacting health, social function
- Loss of voluntary behavioral control
- Addiction shares many similar features of chronic medical conditions:
  - Subject to relapse
  - Influenced by genetic, behavioral, developmental, environmental factors
  - Difficulties complying with treatment
  - Suboptimal treatment/management can cause neuropsychological impairment.
  - Treatment/management can cause neuropsychological improvement
  - Stress and emotional factors can exacerbate effects and dysfunction

(Saitz et al., 2008; Wu et al., 2019)

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Substance use is a causative and aggravating factor in neurocognitive disorders

- Awareness of substance use history can impact the neuropsychological assessment
  - High co-morbidity in clinical populations of interest to neuropsychologists
  - History of use can affect disease presentation and course
- Substance use can contribute to directly to dementia and also accelerate/exacerbate effects of dementia and cognitive impairment.

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Clinical Relevancy: Addiction occurs with Common Conditions Seen by Neuropsychologists

Condition	Comorbidity rate with SUD
mTBI	Up to 75%
Mod-Severe TBI	25%
Stroke	2-5 times higher stoke risk with SUD
Dementia	10% of all dementias due to AUD; AUD = 3-6 times higher likelihood of developing dementia Relationship with VaD is strongly established.
ADHD	Increased odds for SUD (1.33-3.58 odds ratio); 25-40%
Chronic Pain	16-30%
Psychiatric	50% (NIDA), higher in SZ, Bipolar
HIV	15-30%, higher in IV drug users

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Neuropsychological findings in SUD

- Impulsivity
- Self-Control
- Response-Inhibition
- Episodic Memory
- Steeper delayed discounting

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Frontal Dysfunction

- Individuals with alcohol, cocaine, or opioid use disorders show impairments in executive function,
  - disruption of decision-making and behavioral inhibition.
- Disruptions in decision making in the "Go" and "Stop" systems.(Goldstein & Volkow, 2002)
- Smaller volume of the prefrontal cortex in abstinent, previously addicted individuals. (Rando et al., 2011)
- Diminished prefrontal cortex control over the extended amygdala is prominent in humans with PTSD, commonly comorbid with SUD (Mahan et al., 2012).
  - Impairment in these circuits after prolonged use.

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Is Self-Control a Neuropsychological Construct?

- Self-control
  - Working memory
  - Response-Inhibition
  - Episodic Memory
- Working memory
  - Effective choice bundling, shifting attention between two choices
  - Consideration of alternatives
- Perseveration
  - Fixation - opposite of mental flexibility

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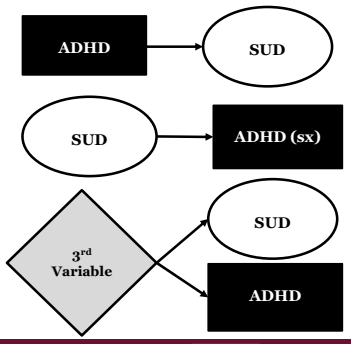
Substance Use and ADHD



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Clinical Relevancy: SUD and ADHD

- Co-occurrence of ADHD and SUD
- Same pathways in the brain (BG; Amygdala; PFC; ACC) contribute to similar symptoms:
  - Impulsivity
  - Self-control
  - Decision-making
  - Self-regulation
  - Behavioural Disinhibition
  - Emotional dysregulation
  - Task persistence
  - Hyperarousal

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Clinical Relevancy: Chronic Pain & Opiates

- SUD and Chronic pain: 16-30% comorbidity
- Opiate suppresses immune response, which may contribute more rapid disease progression
- Opiate use enhances pain response, increasing use
- Opioids promote sleep disturbances
- Contribute to memory, impulsivity, cognitive flexibility deficits (Baldacchino et al., 2020).
- Sickle cell Disease
  - Chronic pain, opioid therapy is commonly utilized
  - 20-50% have problematic opioid use
  - Health disparities and biases play a role in accessing treatment, care, chronic disease management including alternative therapies and treatments.

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Cultural Addiction Neuropsychology

- Additional research is needed to better understand and address the interaction of substance use, addiction, and cognition across various groups.
  - Interplay between genetic vulnerabilities, but also differences in social factors, such as types and patterns of use between cultures and various groups.
  - Differences are seen between sexes regarding substance use and its effects
  - Racial and ethnic group differences are seen in how substances effect the brain and body differently
    - Gene variants
    - Susceptibility to cancers
    - Differences in metabolism rates, neuroadaptation rates
  - Awareness and sensitivity to individual and cultural factors are important during an assessment.

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Illustrative Case Study

Part 2

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The Man Who Forgot He was Addicted

(MacKillop et al., 2025)

- Mr. J. Doe, early 50's who was admitted to the ED after cocaine intoxication/accidental overdose
- Confusion, rhabdomyolysis, AKI and signs of end organ dysfunction at the time of admission, GCS = 13
  - Found by paramedics after a welfare check was initiated
  - Unclear how long he had been unconscious
- Fomepizole and Narcan administered preventatively for potential toxic alcohol and opioid ingestion
- Referred to neuropsychology to assess memory and other cognitive sequelae during admission, with 1-year outpatient follow-up.

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Background Information JD:

- Living alone in apartment, living with sister after admission, and then living with son
- Three adult children
- Adopted, limited knowledge of health history of biological family
- Incarcerated several times previously for breaking into houses and stealing cars as well as assaults when intoxicated

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Background information JD:

Relationship Status: Single

Employment Status: Industrial worker for past 30 years

Developmental: To his knowledge, unremarkable

Education: Formal education through grade 9. Behavioral problems in school, no learning problems.

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Psychiatric History

- Previous psychiatric diagnoses: None noted.
- Hospitalizations: Hospitalized as young teenager for behavioral problems – no elaboration
- Suicidal behaviour: Previous non-suicidal self-harm behaviours (e.g., cutting wrist for attention); unable to recall specific details
- ECT: None

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Substance Use Before Stroke:

- Pieced together by self and collateral report
- Alcohol: heavy drinking with binge drinking and black-out episodes; drug of choice (with cocaine) at time of stroke.
- Cocaine: Significant use; noted that he would spend entire paycheck on cocaine; drug of choice (with ETOH) at time of stroke.
- Tobacco: 5-6 cigarettes per day (per collateral)
- Cannabis: One joint per day
- IVDU: Previous history but denied recent use
- Other substances: Tried acid, coke, mescaline, oxycodone, ecstasy

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Medical Diagnoses

- Cocaine overdose
- non-ST elevated myocardial infarction
- Hypoxic episode/ischemic stroke
- Acute kidney injury
- Hyperkalemia
- Rhabdomyolysis
- High blood pressure

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Mental Status During Admission:

- Temporal disorientation (date/time)
- 2 years retrograde amnesia and <5 min. anterograde amnesia
  - Unable to recall immediate history prior to hospital admission or details of his course in hospital.
  - Unable to recall where he lived, the year,
  - did not recognize providers between contacts,
  - unaware of COVID, which occurred 18 months prior to the stroke.
  - 1-2 minute memory span for new information, before the rapid loss of information
  - No improvements in memory during his approximate 2-week admission

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Behavioral Observations

Inpatient Assessment

- Full range affect, mood congruent, euthymic/affable
- Linear, logical, and goal-directed, mildly perseverative speech
- Intact comprehension
- Impaired judgment/insight
- No psychotic symptoms, SI/HI
- No effort/validity concerns
- Hospital gown, not disheveled
- Excellent rapport

Outpatient Assessment (12 months)

- Full range affect, mood congruent, euthymic/affable
- Improved, no perseverative speech
- Intact comprehension
- Improved judgment/insight
- No psychotic symptoms, SI/HI
- No validity/effort concerns
- Casually dressed, appeared stated age
- Excellent rapport

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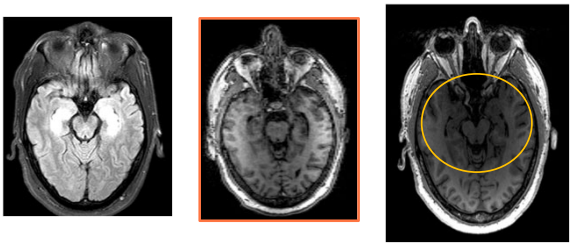
JD MRI History

s/p ~1 day | s/p ~1 week | s/p ~1 year



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Volumetric differences of hippocampal subfields between JD and comparative samples, one-year post-stroke

		LEFT			RIGHT		
Subregion	Hippocampal Subfield	JD	Community Adults		JD	Community Adults	
		Volume	M Volume	% Difference	Volume	M Volume	% Difference
HEAD	Parasubiculum	63.96	76.12	15.97%	58.91	72.89	19.18%
	Presubiculum Head	108.62	158.27	31.37%	100.56	153.27	34.39%
	Subiculum Head	135.7	215.44	37.01%	124.08	214.69	42.21%
	CA1 Head	355.97	568.69	37.41%	388.44	598.82	35.13%
	CA3 Head	83.29	128.57	35.22%	103.29	139.97	26.21%
	CA4 Head	80.3	134.24	40.18%	91.33	141.15	35.30%
	GC-ML-DG Head	94.35	164.18	42.53%	106.61	172.31	38.13%
	Molecular Layer HP Head	226.33	363.72	37.77%	232.35	375.16	38.07%
	HATA	46.71	67.87	31.18%	57.41	69.94	17.92%
BODY	Presubiculum Body	106.36	182.66	41.77%	101.99	164.03	37.82%
	Subiculum Body	148.96	268.19	44.46%	151.05	248.77	39.28%
	CA1 Body	76.3	131.15	41.82%	74.66	140.73	46.95%
	CA3 Body	60.57	87.56	30.82%	58.3	95.07	38.68%
	CA4 Body	76.24	127.75	40.32%	74.62	125.82	40.69%
	GC-ML-DG Body	86.17	145.16	40.64%	83.66	141.49	40.87%
	Molecular Layer Body	136.88	242.92	43.65%	134.18	242.16	44.59%
	Fimbria	57.96	114.12	49.21%	57.22	106.96	46.50%
FISSURE	Hippocampal Fissure	130.79	149.44	12.48%	125.22	162.82	23.09%
WHOLE	Hippocampal Tail	271.02	612.7	55.77%	302.2	638.04	52.64%
	Hippocampal Body	749.45	1299.5	42.33%	735.68	1265	41.84%
	Hippocampal Head	1195.2	1877.1	36.33%	1262.99	1938.2	34.84%
	Hippocampus	2215.7	3789.3	41.53%	2300.87	3841.3	40.10%

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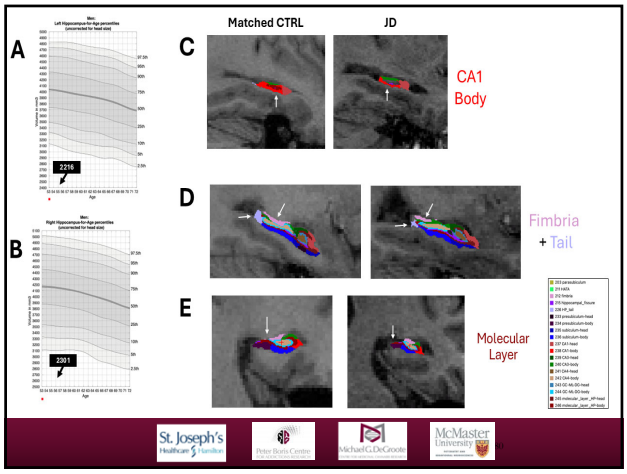

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	Inpatient: s/p stroke 6 days		Outpatient: s/p stroke 12 mos	
	SS	%ile²	SS	%ile²
MMSE-2-SV	78	7	93	31
TOPF	96	40	-	-
WASI-II				
Vocabulary	109	73	105	63
Similarities	111	77	116	86
Matrix Reasoning	106	66	114	82
Block Design	108	70	109	73
VCI	110	75	111	77
PRI	107	68	112	79
FSIQ	110	75	112	79

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	Inpatient: s/p stroke 6 days			Outpatient: 12 mos	
RBANS (FORM B)	**SS**	**%ile**		**SS**	**%ile**
List Learning	70	2		80	9
Story Memory	90	25		95	37
Figure Copy	76	5		70	2
List Recall		≤2			≤2
List Recognition		10-16			51-75
Story Recall	<55	<1		70	2
Figure Recall	<55	<1		55	<1
Picture Naming		51-75			51-75
Line Orientation		51-75			25-50
Coding	95	37		100	50

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	Inpatient: s/p stroke 6 days			Outpatient: 12 mos	
BVMT-R	**SS**	**%ile**		**SS**	**%ile**
Total Recall	65	1		72	3
Delay	<55	<1		<55	<1
% Retention		<1			<1
Hits		3-5			>16
False Positive		>16			3-5
WMS-III					
Orientation		6			6
LM I	85	16		80	9
LM II	<55	<1		60	<1
Spatial Span	105	63		115	84
LNS	80	9		90	25

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	Inpatient: s/p stroke 6 days			Outpatient: 12 mos	
WAIS-IV	**SS**	**%ile**		**SS**	**%ile**
Digit Span	95	37		80	9
Arithmetic	85	16		85	16
D-KEFS C-W					
Color	100	50		85	16
Word	90	25		105	63
CW	95	37		105	63
Interference	60	<1		60	<1
WCST (128)					
# Categories		>16			>16
Errors	106	66		112	79
Perseverative Responses	99	47		124	95
Trials to Complete First Category		>16			6-10
Set Failure		>16			>16
Generative Fluency					
Phonemic Fluency	91	42		110	75
Animal Fluency	115	84		99	47
TMT A	115	84		122	93
TMT B	120	91		116	86
NAB Judgement	18/20 (raw)	WNL		18/20 (raw)	WNL

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Mood Rating shows more mood symptoms after 1 year.

DASS	6 days Score	rating		12 mos Score	rating
Depression	0	WNL		22	Mild
Anxiety	0	WNL		6	WNL
Stress	6	WNL		14	WNL
Total	6	WNL		42	WNL

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JD: Neuropsych Summary

- Temporal disorientation (date/time), intact orientation otherwise
- Marked impairment in memory
  - Impaired encoding → pronounced deficits in storing and retrieving information
    - consistent with damage to his bilateral hippocampi and cerebellar hemispheres
- Inhibition deficits, generally intact EF otherwise
- Visual organization and wayfinding deficits

Overall stable with mildly improved insight, temporal orientation with mild symptoms of depression at 1 year follow up

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Outpatient Follow-Up 12 months

- Abstinent from cocaine use, minimal alcohol and nicotine use*
- Visuospatial navigation issues
- Subjective reports
  - improvements in memory;
  - Problems with sustained attention and multi-tasking
  - Repeats self during conversations
  - Frequently forgets what he is doing in the moment
- Unsuccessful attempts to use compensatory strategies
- Cognitive abilities worsen with stress
- Independent of IADLs/ADLs, confirmed by collateral

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Why Did He "Forget" He was Addicted?

- Hippocampal stroke disrupted the addiction memory circuit:
  - BG; HPC; BLA; PFC
  - Cerebellar changes – not apparent on examination
- Basal Ganglia:
  - Motivational drive changed, reward salience was gone even though remote memories for use were intact
- Hippocampus/Amygdala:
  - Emotional salience of memories are reduced
  - Affective changes occurred (less sensitive to distress),
  - negative reinforcement or habitual, compulsive behavior was disrupted
- PFC:
  - Anticipating and craving is gone – no drug-seeking behavior

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Clinical Applications and Research Implications

Part 3

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Assessment

- History
- Screening and Assessment Tools
- Biomarkers
- Neuropsych tasks

The Alcohol Use Disorders Identification Test: Self-Report Version

PATIENT: Because alcohol use can affect your health and can interfere with certain medications and treatments, it is important that we ask some questions about your use of alcohol. Your answers will remain confidential so please be honest. Place an X in one box that best describes your answer to each question.

Questions	0	1	2	3	4	
1. How often do you have a drink containing alcohol?	Never	Monthly or less	2-4 times a month	2-3 times a week	4 or more times a week	
2. How many drinks containing alcohol do you have on a typical day when you are drinking?	1 or 2	3 or 4	5 or 6	7 to 9	10 or more	

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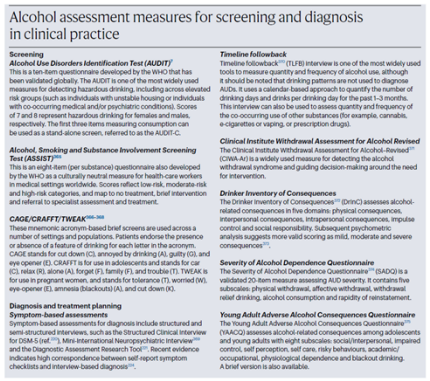
CUDIT

DUDIT



Alcohol assessment measures for screening and diagnosis in clinical practice

Screening

Alcohol Use Disorders Identification Test (AUDIT)[7]
This is a ten-item questionnaire developed by the WHO that has been validated globally. The AUDIT is one of the most widely used measures for detecting hazardous drinking, including across elevated risk groups (such as individuals with unstable housing or individuals with co-occurring medical and/or psychiatric conditions). Scores of 7 and 8 represent hazardous drinking for females and males, respectively. The first three items measuring consumption can be used as a stand-alone screen, referred to as the AUDIT-C.

Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)[359]
This is an eight-item (per substance) questionnaire also developed by the WHO as a culturally neutral measure for health-care workers in medical settings worldwide. Scores reflect low-risk, moderate-risk and high-risk categories, and map to no treatment, brief intervention and referral to specialist assessment and treatment.

CAGE/CRAFFT/TWEAK[366–368]
These mnemonic acronym-based brief screens are used across a number of settings and populations. Patients endorse the presence or absence of a feature of drinking for each letter in the acronym. CAGE stands for cut down (C), annoyed by drinking (A), guilty (G), and eye opener (E). CRAFFT is for use in adolescents and stands for car (C), relax (R), alone (A), forget (F), family (F), and trouble (T). TWEAK is for use in pregnant women, and stands for tolerance (T), worried (W), eye-opener (E), amnesia (blackouts) (A), and cut down (K).

Diagnosis and treatment planning

Symptom-based assessments
Symptom-based assessments for diagnosis include structured and semi-structured interviews, such as the Structured Clinical Interview for DSM-5 (ref.[369]), Mini-International Neuropsychiatric Interview[370] and the Diagnostic Assessment Research Tool[371]. Recent evidence indicates high correspondence between self-report symptom checklists and interview-based diagnosis[124].

Timeline followback
Timeline followback[372] (TLFB) interview is one of the most widely used tools to measure quantity and frequency of alcohol use, although it should be noted that drinking patterns are not used to diagnose AUDs. It uses a calendar-based approach to quantify the number of drinking days and drinks per drinking day for the past 1–3 months. This interview can also be used to assess quantity and frequency of the co-occurring use of other substances (for example, cannabis, e-cigarettes or vaping, or prescription drugs).

Clinical Institute Withdrawal Assessment for Alcohol Revised
The Clinical Institute Withdrawal Assessment for Alcohol–Revised[373] (CIWA-Ar) is a widely used measure for detecting the alcohol withdrawal syndrome and guiding decision-making around the need for intervention.

Drinker Inventory of Consequences
The Drinker Inventory of Consequences[374] (DrInC) assesses alcohol-related consequences in five domains: physical consequences, interpersonal consequences, intrapersonal consequences, impulse control and social responsibility. Subsequent psychometric analysis suggests more valid scoring as mild, moderate and severe consequences[375].

Severity of Alcohol Dependence Questionnaire
The Severity of Alcohol Dependence Questionnaire[376] (SADQ) is a validated 20-item measure assessing AUD severity. It contains five subscales: physical withdrawal, affective withdrawal, withdrawal relief drinking, alcohol consumption and rapidity of reinstatement.

Young Adult Adverse Alcohol Consequences Questionnaire
The Young Adult Adverse Alcohol Consequences Questionnaire[377] (YAACQ) assesses alcohol-related consequences among adolescents and young adults with eight subscales: social/interpersonal, impaired control, self perception, self care, risky behaviours, academic/occupational, physiological dependence and blackout drinking. A brief version is also available.

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Screen for Medications with Abuse Liability

- Opioids
  - Hydrocodone (Norco, Vicodin)
  - Oxycodone (OxyContin, Percocet)
  - Fentanyl
  - Codeine
- CNS Depressants
  - Benzodiazepines
    - Clonazepam (Klonopin)
    - Alprazolam (Xanax)
    - Diazepam (valium)
  - Barbiturates
    - Phenobarbital
    - Butalbital (Fioricet; Fiorinal)
- Stimulants
  - Amphetamines (Adderall, Vyvanse)
  - Methylphenidates (Ritalin, Concerta)

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Medication Dependence

- Time/activities associated/interrupted by medication use?
- Have they used longer than originally planned or indicated?
- Increased dose higher than planned?
- Unsuccessful attempt to cut down?
- Continued to use medication even if it's causing problems with physical or emotional health
- Experienced withdrawal symptoms when medications are stopped or skipped

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SUD Biomarkers: Alcohol Biomarkers

Alcohol biomarkers

Level or recency of alcohol use

- Blood alcohol content (BAC) reflects circulating alcohol in the bloodstream, which correlates with level of impairment.
- Breath alcohol (BrAC), measured via a breathalyser, is a valid proxy for BAC.
- Transdermal alcohol is another valid proxy for BAC but transdermal alcohol is available over a longer time window than BrAC via continuous monitoring devices.
- Urinary ethyl glucuronide is a minor metabolite of alcohol that is dose-dependently detectable for up to 72h after drinking has ended.
- Phosphatidyl ethanol (PEth) is a cellular membrane phospholipid produced from the interaction of alcohol with phospholipase D, and can reliably detect heavy drinking over extended durations.

Alcohol burden on the liver and other systems

- Aspartate aminotransferase and alanine aminotransferase (AST and ALT) reflect liver burden from alcohol metabolism. Reference ranges are 0–35 IU/L and 0–45 IU/L respectively. An AST to ALT ratio of 2:1 or higher is an indicator of heavy drinking.
- γ-Glutamyl transferase (GGT) is a liver enzyme that reflects injury to the liver, particularly to the bile ducts and in response to alcohol. Reference ranges are 0–30 IU/L, but GGT is not specific enough be used alone. Elevated GGT in conjunction with elevated AST may be used as an indicator of heavy drinking.
- Percentage carbohydrate-deficient transferrin (%CDT) reflects proportionate levels of deficiency of an iron transport protein in the serum. In general, consumption of 50–60 g of alcohol per day for two or more weeks increases %CDT, which normalizes after three or more weeks of abstinence. The commonly used cut-off is 2.5% and %CDT can be used in conjunction with measurement of GGT.

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SUD Biomarkers: Breath Screening

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SUD Biomarkers: Urine Screening

SUBSTANCE TESTED
Amphetamines (AMP)
Barbiturates (BAR)
Benzodiazepines (BZO)
Buprenorphine (BUP)
Cocaine (COC)
Ecstasy (MDMA)
Marijuana (THC)
Methadone (MTD)
Methadone Metabolite (EDDP)
Methamphetamines (MET)
Opiates (MOP) or (OPI300)
Oxycodone (OXY)
Phencyclidine (PCP)
Tricyclic Antidepressants (TCA)
** Cotinine / Nicotine (COT)
** Ethyl Glucuronide (ETG)
** Fentanyl (FEN)
** Gabapentin (GAB)
** Kratom (KRA)
** Synthetic Marijuana (K2)
** Tramadol (TRA)

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SUD Biomarkers: Urine Screening

***ADULTERANTS**

- Creatinine (C)
- Glutaraldehyde (G)
- Acidic or Alkaline pH (P)
- Nitrite (N)
- Oxidants (O)
- Specific Gravity (S)

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SUD Biomarkers: Urine Screening

This color highlights drug panels included with this specific test

	CUT-OFF LEVEL	MINIMUM DETECTION	MAXIMUM DETECTION
Amphetamines (AMP)	500 ng/mL	2 - 7 hours	2 - 4 days
Barbiturates (BAR)	300 ng/mL	2 - 4 hours	1 - 3 weeks
Benzodiazepines (BZO)	300 ng/mL	2 - 7 hours	1 - 4 days
Buprenorphine (BUP)	10 ng/mL	4 - 24 hours	3 - 6 days
Cocaine (COC)	150 ng/mL	1 - 4 hours	2 - 4 days
Ecstasy (MDMA)	500 ng/mL	2 - 7 hours	2 - 4 days
Marijuana (THC)	50 ng/mL	2 hours	Up to 40+ days
Methadone (MTD)	300 ng/mL	3 - 8 hours	1 - 3 days
Methadone Metabolite (EDDP)	300 ng/mL	3 - 8 hours	1 - 3 days
Methamphetamines (MET)	500 ng/mL	2 - 7 hours	2 - 4 days
Opiates / Morphine (OPI300)	300 ng/mL	2 hours	2 - 3 days
Oxycodone (OXY)	100 ng/mL	1 - 3 hours	1 - 2 days
Phencyclidine (PCP)	25 ng/mL	4 - 6 hours	7 - 14 days
Tricyclic Antidepressants (TCA)	1,000 ng/mL	8 - 12 hours	2 - 7 days
** Cotinine / Nicotine (COT)	200 ng/mL	18 - 24 hours	7 - 10 days
** Ethyl Glucuronide (ETG)	500 ng/mL	1 - 2 hours	1 - 2 days
** Fentanyl (FEN)	25 ng/mL	1 - 5 hours	1 - 2 days
** Gabapentin (GAB)	2000 ng/mL	5 - 7 hours	1 - 3 days
** Kratom (KRA)	100 ng/mL	7 - 24 hours	2 - 9 days
** Synthetic Marijuana (K2)	25 ng/mL	2 - 4 hours	7 - 10 days
** Tramadol (TRA)	100 ng/mL	3 - 8 hours	1 - 3 days

** Drug panel not CLIA Waived. Intended for forensic use only. Forensic use only means the drug test has not yet been FDA (510k) cleared and is intended to only be used for law enforcement or criminal justice purposes.

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Even if substance use is not part of the presentation or referral question, biomarkers offer objective 'rule-out' data

Observed findings are not attributable to recent substance

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Neuropsychological Constructs

- Reward Valuation
- Expectancy/Reward Prediction Error
- Action Selection/Preference-Based Decision-making
- Reward Learning
- Habit
- Response Selection/Inhibition
- Compulsivity

(Delphi consensus study; Yucel et al., 2018)

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Traditional Neuropsychological Measures

- Behavioral features, observation and interview
- Impulsivity, disinhibition, self-control, decision-making
- Wisconsin Card Sort
  - Perseveration
- Stroop or C-W
  - Inhibition elements
- Iowa Gambling Task
  - Deliberate longer; Choose unfavorable decks
  - A lifetime SUD diagnosis associated with performance on the IGT after controlling for covariates, while other neuropsych tests performances were similar (Barry & Petry, 2009).
- Continuous Performance Test (CPT-3)
  - Impulsivity elements; signal detection

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Development of Measures for Real-World Behavioral Dysfunction

- Tools to assess cognitive dysfunction related to SUD are needed (VMPFC/OFC)
  - Understanding cognitive profile of individuals with SUD
  - Predict prognosis
- Delayed discounting
- Impulsivity
  - Risk factor for SUD and a consequence of use
  - Associated with worse tx outcomes
- Inhibition "stop"
- Cognitive Control, Behavioral reward- valuation motivation
  - "Real-world" applications
- Decision-making

(Zald & Andreatti, 2010; Verdejo-Garcia & Albein-Urios, 2021; Barreno et al., 2019)

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Clinical Research Implications

Part 3

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mTBI and SUD

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Head Injury and SUDs (Levitt, MacKillop, et al., 2025)

Trauma type	% yes (n) Total	Male (n)	Female (n)	Chi-square test $\chi 2$	*p*
Hospitalized or treated in emergency room following injury	52.6% (891)	55.6% (454)	49.9% (437)	5.48	0.019
Car accident or from crashing other moving vehicle	36.3% (615)	39.8% (325)	33.1% (290)	8.14	0.004
Fall or being hit by something or playing sports or on playground	54.5% (922)	60.8% (497)	48.5 (425)	25.86	<.001
Fight, from being hit by someone or from being shaken violently or ever been shot in the head	40.7% (689)	46.5% (380)	35.3% (309)	22.12	<.001
Nearby when an explosion or a blast occurred	7.3% (124)	10.8% (88)	4.1% (36)	27.64	<.001
Mean (SD)	1.91 (1.50)	2.13 (1.59)	1.71 (1.39)	5.88*	<.001
Frequencies					
0 injuries reported	26.1% (442)	23.9% (195)	28.2% (247)		
1 injury reported	15.4% (260)	13.5% (110)	17.1% (150)		
2 injuries reported	20.0% (338)	16.8% (137)	22.9% (201)		
3 injuries reported	21.5% (364)	23.0% (188)	20.1% (176)		
4 injuries reported	13.7% (232)	17.0% (139)	10.6% (93)		
5 injuries reported	3.4% (57)	5.9% (48)	1.0% (9)		

Overall = 73.9%
Male = 76.1%
Female = 71.8%

***N* = 1693**

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Head Injury and SUDs

Disorder	M (SE) Head injury	M (SE) No head injury	ANCOVA F	ANCOVA *p*	ANCOVA ηp^2	% Above Cut off Head injury	% Above Cut off No head injury
Alcohol use disorder (AUDIT) (≥8)	18.44 (0.37)	16.13 (0.61)	10.56	0.001	0.006	69.0%	62.9%
Cannabis use disorder (CUDIT) (≥6)	7.98 (0.24)	6.91 (0.40)	7.74	0.005	0.005	41.4%	35.7%
Drug use disorder (DUDIT) (≥6)	18.51 (0.48)	15.77 (0.77)	11.20	0.001	0.007	60.9%	55.9%
Depression (PHQ-9) (≥10)	15.57 (0.21)	14.78 (0.35)	5.87	0.015	0.003	74.3%	69.9%
Anxiety (GAD-7) (≥10)	12.84 (0.18)	12.02 (0.30)	8.12	0.004	0.005	66.6%	60.0%
PTSD (PCL-5) (≥33)	40.59 (0.59)	34.11 (1.02)	43.49	5.6967E-11	0.025	64.8%	50.9%
ADHD (ASRS) (≥14)	13.31 (0.16)	12.05 (0.28)	22.59	0.000002	0.013	50.5%	41.2%

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Hx of Head Injury @ SJHH

Disorder	Mean (SE) Hx of Head Injury	Mean (SE) No Hx of Head Injury	ANCOVA *F*	ANCOVA *p*	ANCOVA η_p^2
Negative Urgency (UPPS)	12.28 (0.07)	11.80 (0.14)	14.34	0.0002	0.008
Positive Urgency (UPPS)	9.74 (0.09)	8.96 (0.15)	22.67	0.000002	0.013
Lack of Perseverance (UPPS)	7.73 (0.07)	7.88 (0.11)	0.762	0.383	0.000
Lack of Premeditation (UPPS)	8.79 (0.08)	8.62 (0.13)	2.76	0.097	0.002
Sensation Seeking (UPPS)	10.46 (0.09)	9.50 (0.14)	33.73	7.5393E-9	0.020
Delay Discounting $100 ($ED_{50}$)	-1.38 (0.03)	-1.53 (0.06)	5.94	0.015	0.004
Delay Discounting $1000 ($ED_{50}$)	-1.64 (0.03)	-1.79 (0.05)	5.00	0.026	0.003
Distress tolerance (DT-R)	12.85 (0.03)	13.80 (0.06)	11.35	0.001	0.007

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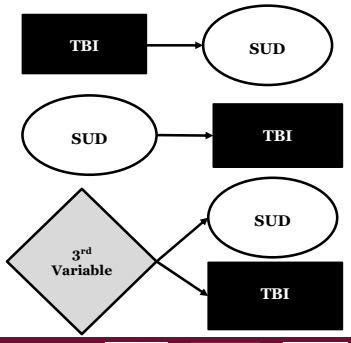
Substance Use and TBI



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Behavioral Addiction and SUD in Adolescence

Adolescent brain development

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Social Media and Adolescent Brain Development

- Social media stimulates ventral striatum, disrupting reward pathways
  - Compulsive behavior
- Disrupts social cognition development
- Increases depression and anxiety
- Diminishes attention span, elevates rates of ADHD
- Disrupts sleep
- Does is cause lasting brain damage?

Sherman et al., 2016; Berridge et al., 2017; Haight et al., 2014; Rosen et al., 2013; LeBourgeois et al., 2017; Haight, 2024.

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Gaming Addiction

Young Brains & Video Games - Brain Connections

https://Brainconnections.ca

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ADHD is also related to behavioral addiction

- There is a strong relationship between substance use, behavioral addiction (social media/gaming) and ADHD (Becker et al., 2015; Primack et al., 2017; *Haight, 2024*).
- Overlapping symptoms
  - ❑ deficits in attention, working memory, impulsivity, self-control
- Neuropsychologists in clinical and research roles are needed to disambiguate:
  - ❑ Increase awareness of the relationship between ADHD with substance and behavioral addiction
  - ❑ Identify targets for intervention
  - ❑ Reduce rates of prescription stimulant use/misuse when addiction is present

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Delay Discounting as a Future Clinical Measure of Self-regulation

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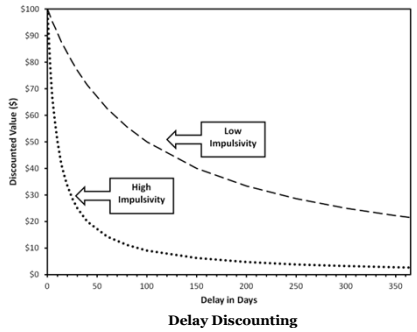
Delay Discounting



Delay Discounting

MacKillop (2016) *Alcoholism: Clinical and Experimental Research*

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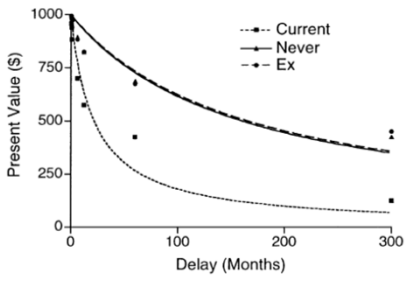
Delay Discounting



Bickel et al. (1999)
Psychopharmacology

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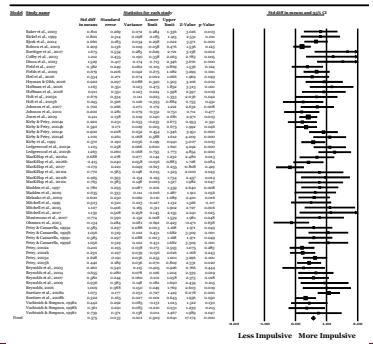
Meta-Analysis of Case-Control Studies



Overall d = .49, p<10^{-8}

Clinical d = .67, p<10^{-5}

Subclinical d = .46, p<10^{-10}

Almost all individual substances and gambling significant

Minimal evidence of publication bias

MacKillop et al. (2011)
Psychopharmacology

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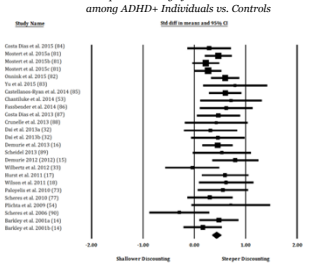
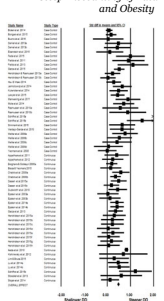
Meta-Analyses of ADHD and Obesity

Steep Discounting of Future Rewards among ADHD+ Individuals vs. Controls



d =.43; p <10^{-15}
N=3913

Steep Discounting of Future Rewards and Obesity



d =.43; p <10^{-14}
N=10,278

Amlung et al. (2016)
Psych Med; Jackson & MacKillop (2016)
BP: CNNI

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Other Health Behaviors

- Disease prevention
  - Blood pressure testing
  - Cholesterol testing
  - Cancer prevention (mamograms, pap smears, prostate exams)
  - Physician advice/medication compliance
  - Flu shot
  - Seat belt usage
  - Dental visits
  - Exercise
- Inverse associations with anorexia nervosa and OCPD
- Cognitive decline and neurodegenerative disorders

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Delay Discounting and Neurodegeneration

Neuroscience and Biobehavioral Reviews 146 (2023) 105048

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Altered delay discounting in neurodegeneration: insight into the underlying mechanisms and perspectives for clinical applications

Valérie Godefroy [a,b,c,*], Idil Sezer [a], Arabella Bouzigues [a], Maxime Montembeault [d,e], Leonie Koban [f], Hilke Plassmann [b,c], Raffaella Migliaccio [a,g,h,*]

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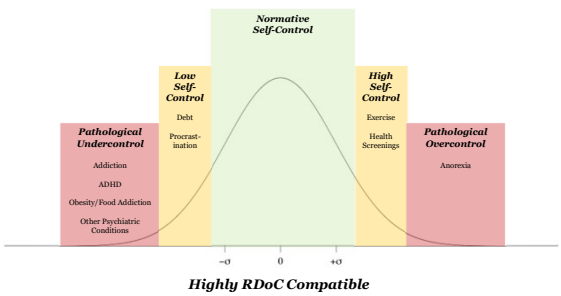
Delay Discounting as a Dimensional Trans-diagnostic Process



Highly RDoC Compatible

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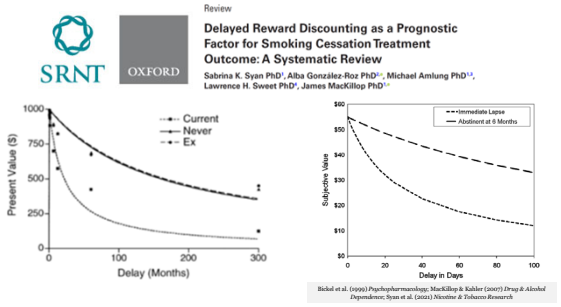
Delay Discounting and Treatment Response



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Neuromodulation Treatment for SUDs

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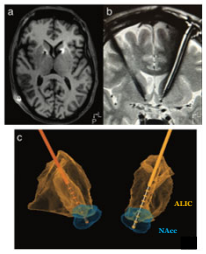
Neuromodulation Interventions

Deep Repetitive Transcranial Magnetic Stimulation (Deep rTMS)

Deep Brain Stimulation (DBS)

Transcranial Direct Current Stimulation (tDCS)



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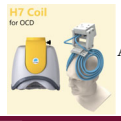
Deep rTMS

Medial Prefrontal Cortex (mPFC)

Lateral Prefrontal Cortex & Insula (lPFC +AI)



Anterior Cingulate Cortex (ACC)

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d_rTMS for Tobacco Use Disorder

RESEARCH REPORT

Repetitive transcranial magnetic stimulation for smoking cessation: a pivotal multicenter double-blind randomized controlled trial

Abraham Zangen[1], Hagar Moshe[1], Diana Martinez[2], Noam Barnea-Ygael[1], Tanya Vapnik[3], Alexander Bystritsky[3], Walter Duffy[4], Doron Toder[1,5], Leah Casuto[6], Moran Lipkinsky Grosz[1], Edward V. Nunes[7], Herbert Ward[8], Aron Tendler[9], David Feifel[10], Oscar Morales[11], Yiftach Roth[1], Dan V. Iosifescu[12], Jaron Winston[13], Theodore Wiredu[14], Alaxs Stein[15], Frederic Deutsch[16], Xinghao Li[17], Mark S. George[17,18]

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation method increasingly used to treat psychiatric disorders, primarily depression. Initial studies suggest that rTMS may help to treat addictions, but evaluation in multicenter randomized controlled trials (RCTs) is needed. We conducted a multicenter double-blind RCT in 262 chronic smokers meeting DSM-5 criteria for tobacco use disorder, who had made at least one prior failed attempt to quit, with 68% having made at least three failed attempts. They received three weeks of daily bilateral active or sham rTMS to the lateral prefrontal and insular cortices, followed by once weekly rTMS for three weeks. Each rTMS session was administered following a cue-induced craving procedure, and participants were monitored for a total of six weeks. Those in abstinence were monitored for additional 12 weeks. The primary outcome measure was the four-week continuous quit rate (CQR) until Week 18 in the intent-to-treat efficacy set, as determined by daily smoking diaries and verified by urine cotinine measures. The trial was registered at ClinicalTrials.gov (NCT02126124). In the intent-to-treat analysis set (N=234), the CQR until Week 18 was 18.4% following active and 8.7% following sham rTMS (X²=5.655, p=0.017). Among completers (N=169), the CQR until Week 18 was 28.0% and 11.7%, respectively (X²=7.219, p=0.007). The reduction in cigarette consumption and craving was significantly greater in the active than the sham group as early as two weeks into treatment. This study establishes a safe treatment protocol that promotes smoking cessation by stimulating relevant brain circuits. It represents the first large multicenter

H4 Coil
15 + 3 Sessions
3-weeks daily
+ 3-weeks weekly

Primary Outcome:
4-week CQR

Secondary Outcome:
Craving

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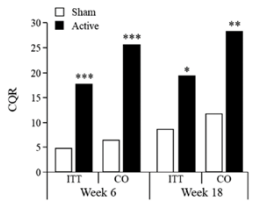
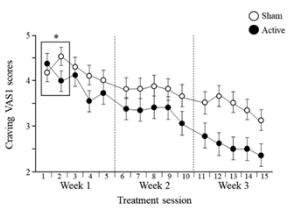
d_rTMS for Tobacco Use Disorder





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d_rTMS for Tobacco Use Disorder

Week	Number of cigarettes smoked		Change from baseline in TCQ total score	
	Adjusted mean difference (95% CI)	p	Adjusted mean difference (95% CI)	p
Intent-to-treat set				
2	−16.64 (−27.91 to −5.37)	0.004	−3.94 (−8.63 to 0.76)	0.100
3	−19.14 (−31.14 to −7.14)	0.002	−7.17 (−12.16 to −2.18)	0.005
4	−18.02 (−30.22 to −5.82)	0.004	−6.44 (−11.52 to −1.35)	0.013
5	−18.87 (−31.27 to −6.48)	0.003	−4.83 (−9.99 to 0.33)	0.067
6	−16.14 (−28.79 to −3.48)	0.012	−5.56 (−10.70 to −0.42)	0.034
Completer analysis set				
2	−20.35 (−32.73 to −7.98)	0.001	−5.50 (−10.56 to −0.43)	0.033
3	−19.18 (−31.66 to −6.69)	0.003	−7.69 (−12.78 to −2.61)	0.003
4	−16.56 (−29.08 to −4.05)	0.010	−5.97 (−11.04 to −0.89)	0.021
5	−18.55 (−31.15 to −5.95)	0.004	−5.61 (−10.71 to −0.50)	0.031
6	−15.01 (−27.85 to −2.17)	0.022	−5.71 (−10.81 to −0.62)	0.028

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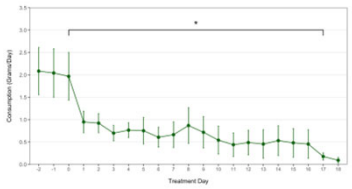
Pilot Trial for Cannabis Use Disorder

PFC + Insula



Average Consumption by Day

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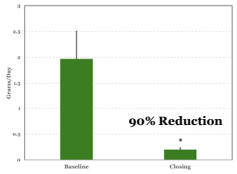
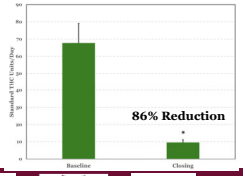
Pilot Trial for Cannabis Use Disorder

PFC + Insula





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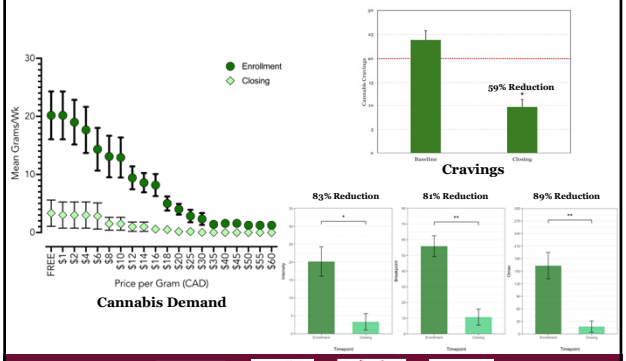
Cannabis Cravings and Reinforcing Value



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Deep Brain Stimulation for SUDs

The Canadian Journal of Neurological Sciences (2025), 1–4
doi:10.1017/cjn.2025.12

Canadian Journal of Neurological Sciences
Journal Canadien des Sciences Neurologiques

Letter to the Editor: New Observation

Deep Brain Stimulation for Substance Use Disorder: Case Report of Fentanyl Use Disorder and Review of the Literature

Andrew Z. Yang[1,2,3], James MacKillop[3,4,5], Alexandre Boutet[6,7], Anton Fomenko[1], Artur Vetkas[1], Matthew E. Sloan[1,2,8,9,10,11,12,13], Can Sarica[1], Brendan Santyr[1], Dana Abdel Hafeez[14], Sharmane Villafuerte[1], Jürgen Germann[1,7,15], Ivan Skelin[15], Luka Milosevic[1,7,15,16,17,18], Benjamin Davidson[1,19,20], Suneil K. Kalia[1,7,15,18], Taufik A. Valiante[1,7,12,15-19,20,21], Andres M. Lozano[1,7,12,15-19] and Victor M. Tang[1,8,9,10,12,13]

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Deep Brain Stimulation for SUDs

- Pt: 46-year-old male with a 20-year history of SUD
  - ❑ Alcohol→ prescription opioids→ heroin → fentanyl
- Hx: alcohol-induced pancreatitis and attention deficit hyperactivity disorder
- Extensive treatment hx:
  - ❑ methadone (up to 130 mg daily), oral buprenorphine (up to 32 mg daily), long-acting injectable buprenorphine (up to 300 mg monthly), in-patient detoxification/residential, psychosocial interventions (e.g., sober living housing)
- Offered DBS on compassionate grounds

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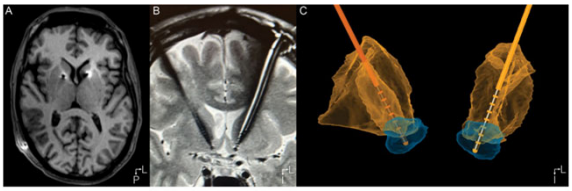
Deep Brain Stimulation for SUDs



Orange = ALIC
Turquoise = NAcc

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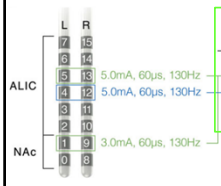
Deep Brain Stimulation for SUDs



Weeks from DBS	Fentanyl (g/day)	Craving (0–10)	PHQ-9 (0–27)	GAD-7 (0–21)	QOL (0–100)
Baseline	3.0	9	24	21	40
1 to 30	0 | 100%	0 | 100%	2.4 | 90%	1.3 | 94%	74.1 | 85%
30 to 48	0.6 | 80%	6.0 | 33%	6.7 | 72%	4.3 | 80%	47.3 | 18%
All Weeks	0.1 | 97%	1.4 | 84%	3.4 | 86%	2.0 | 90%	70.5 | 76%

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Brain-based treatments require insights from clinical neuropsychology

- ❑ Mechanisms of action (mediators/moderators)
- ❑ Adverse events (side effects)

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Conclusions

- Addiction is a behavior that is a product of brain dysfunction
  - Behaviors affected: decision-making, self-control, impulsivity
  - Areas affected: PFC, Limbic System, BG
- SUD co-occur with common clinical populations, and may impact disease presentation and course
- Neuropsychologists are uniquely qualified to understand the impact of substance use and disambiguate the clinical presentation

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