

Exploring the Impact of Alcohol Use on Cognition and Brain Structure in Older Adults

Ari Cuperfain MD, MSc, FRCPC

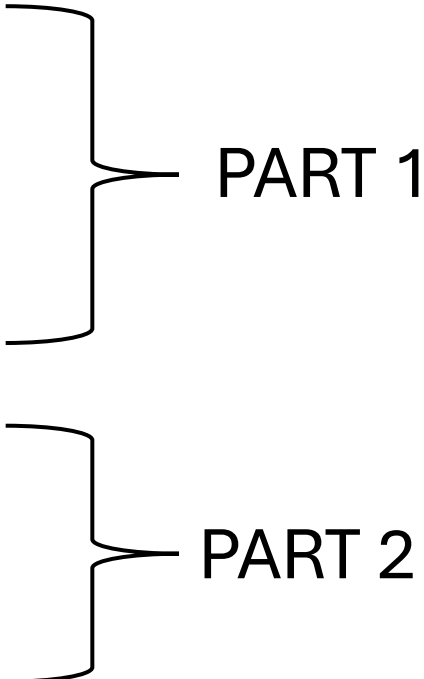
Centre for Addiction and Mental Health

University of Toronto, Department of Psychiatry

Disclosures

- Ari Cuperfain
 - Relationships with commercial interests: None
 - Grants/Research Support: Canadian Institutes of Health Research (CIHR); University of Toronto Department of Psychiatry Excellence Funds; matching contributions from the Centre for Addiction and Mental Health (CAMH).
 - Speakers Bureau/Honoraria: None
 - Consulting Fees: None
 - Patents: None
 - Other: Sub-investigator on a Bristol Myers Squibb-funded clinical trial (no personal remuneration received). No conflicts of interest related to this presentation/study.

Objectives

1. Review the epidemiology, pathophysiology and potential mechanisms underlying alcohol-related cognitive impairment (ARCI)
 2. Discuss approaches to the assessment and management of co-occurring alcohol use and neurocognitive disorders
 3. Present results from neuropsychological and structural brain imaging studies in older adults with neurocognitive disorders and excessive alcohol use
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- PART 1
- PART 2

Case

- 70M, living in supportive housing, history of alcohol use disorder dating back to adolescence
- Consumed approximately 12oz of vodka daily (300mL; 8 SD) for approximately 55 years
- Smoked cigarettes 1ppd, also for 55 years
- PMHx: Mild cirrhosis, asthma
- Past Psychiatric History: no formal Dx aside from SUD, history of childhood trauma
- SHx: English-speaking, Grade 10 education

Case

- Referred for memory assessment
 - Case worker identified new deficits in level of function
 - Testing showed cognitive impairment in multiple domains, diagnosed with a major NCD.
 - Advised he reduce his alcohol use and engage with Addictions treatment.
- Two years later, he had completely abstained from alcohol and connected with Alcoholics Anonymous.
- Repeat cognitive testing demonstrated improvement in his cognitive scores.

Introduction

- Recent update to Canadian guidelines recommends max 2 SD/week



Introduction

- The 2020 update to the Lancet Commission on dementia prevention, intervention, and care included three additional risk factors – traumatic brain injury, air pollution and **excessive alcohol consumption**

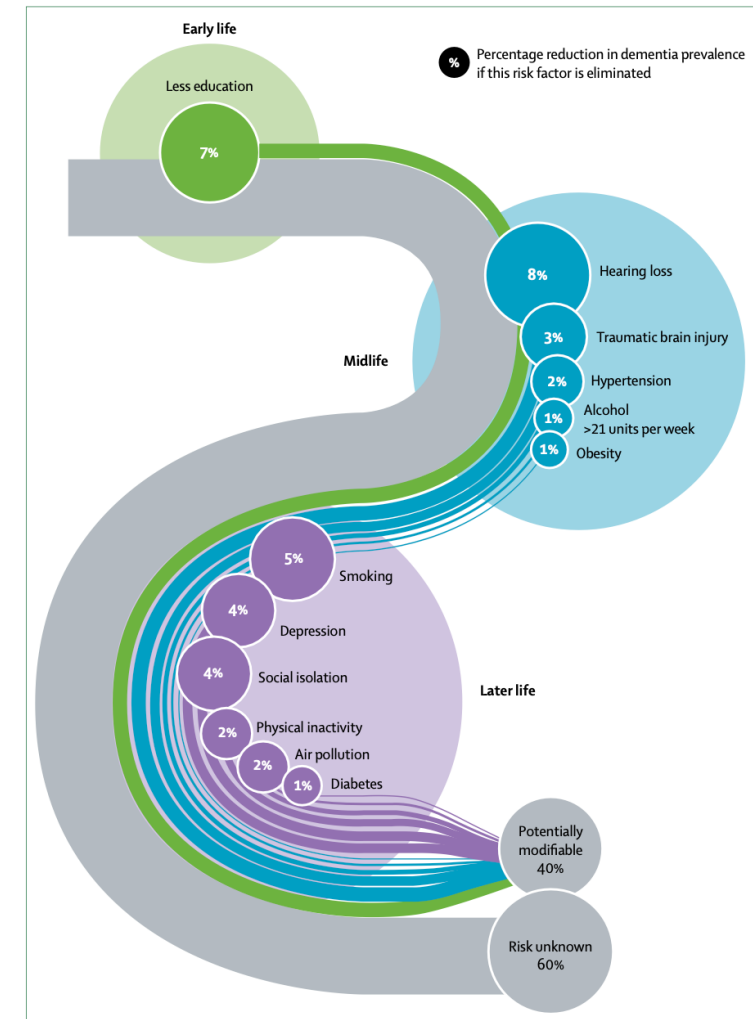


Figure 7: Population attributable fraction of potentially modifiable risk factors for dementia

Question 1

What percentage of total global dementia burden is attributed to excessive alcohol use?

- a) 0.01%
- b) 0.1%
- c) 1%
- d) 10%

Question 1

What percentage of total global dementia burden is attributed to excessive alcohol use?

- a) 0.01%
- b) 0.1%
- c) 1%**
- d) 10%

Answer: C. Per Lancet commission on dementia prevention, intervention, and care, excessive alcohol use in midlife carries a 1% contribution to dementia on a population level

Introduction

- Excessive alcohol consumption is defined as ≥ 21 units*/week (168g)
- Excessive alcohol use was associated with increased risk for developing dementia and accounted for 1% of total dementia cases on population level
 - pooled RR = 1.18 (95% CI 1.06–1.31).

* 21 units are equivalent to 12 standard drinks in North America

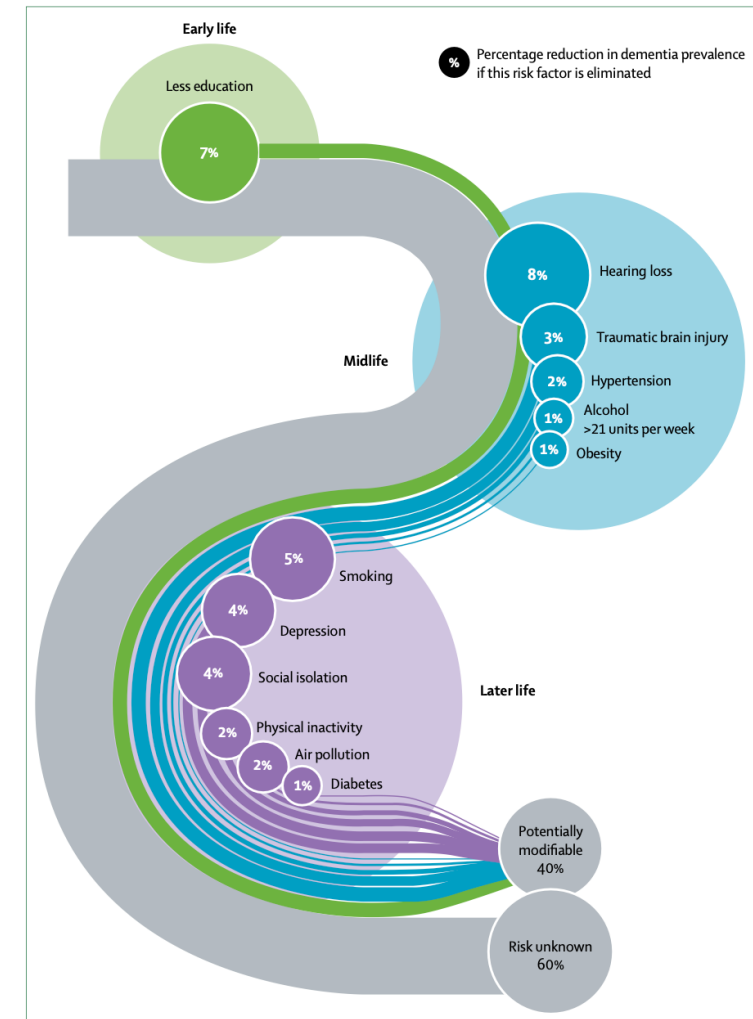


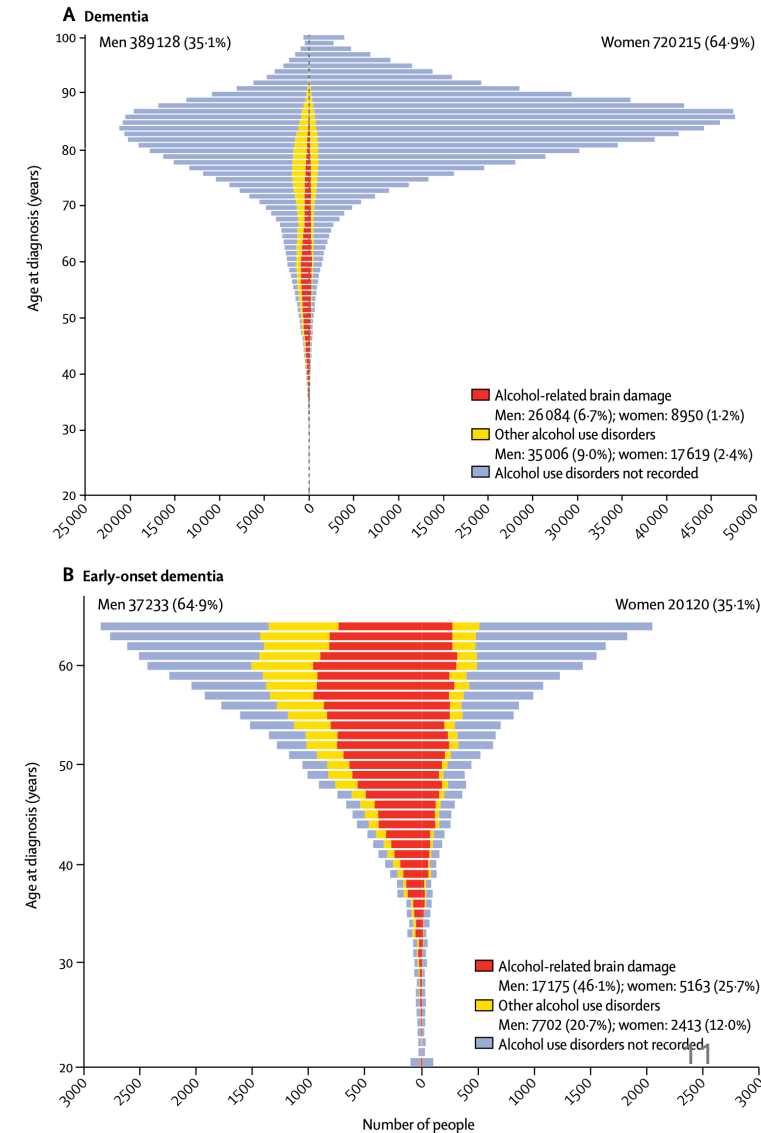
Figure 7: Population attributable fraction of potentially modifiable risk factors for dementia

Epidemiology

- Incidence of alcohol-related dementia is estimated at between 1-10 per 100,000 person years
- Less severe forms of alcohol-related cognitive impairment (ARCI) are more common and may co-occur with other neurocognitive disorders
- It can be difficult to distinguish ARCI from other forms of neurocognitive disorders especially in populations where these conditions overlap (e.g. Memory Clinics)

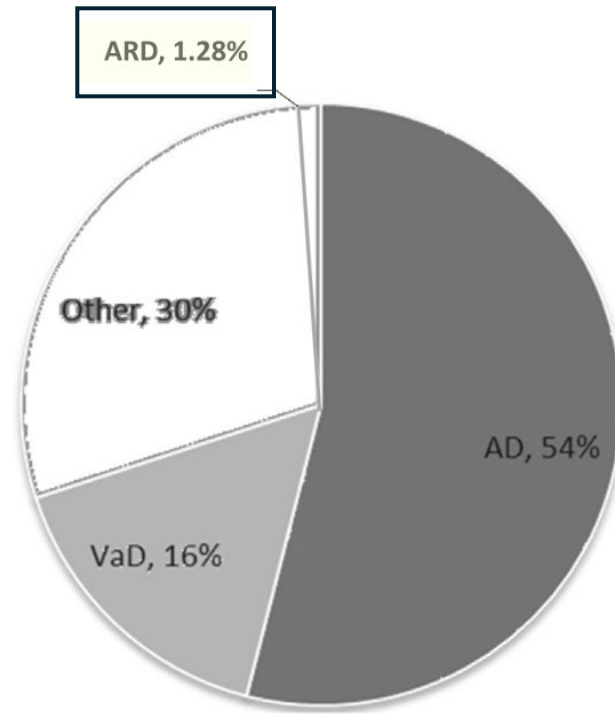
Schwarzinger M, et al. *The Lancet Public Health* (2018)

Palm A, et al. *Int J Geriatr Psychiatry* (2022)

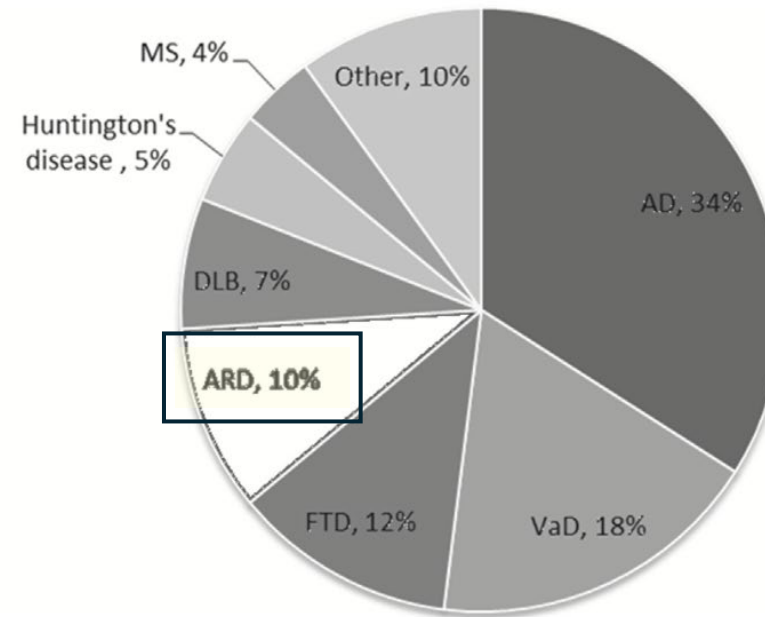


Epidemiology

- The relative proportion of alcohol-related dementia (ARD) is greater in early onset vs late-onset dementia (10% vs. 1.28%)



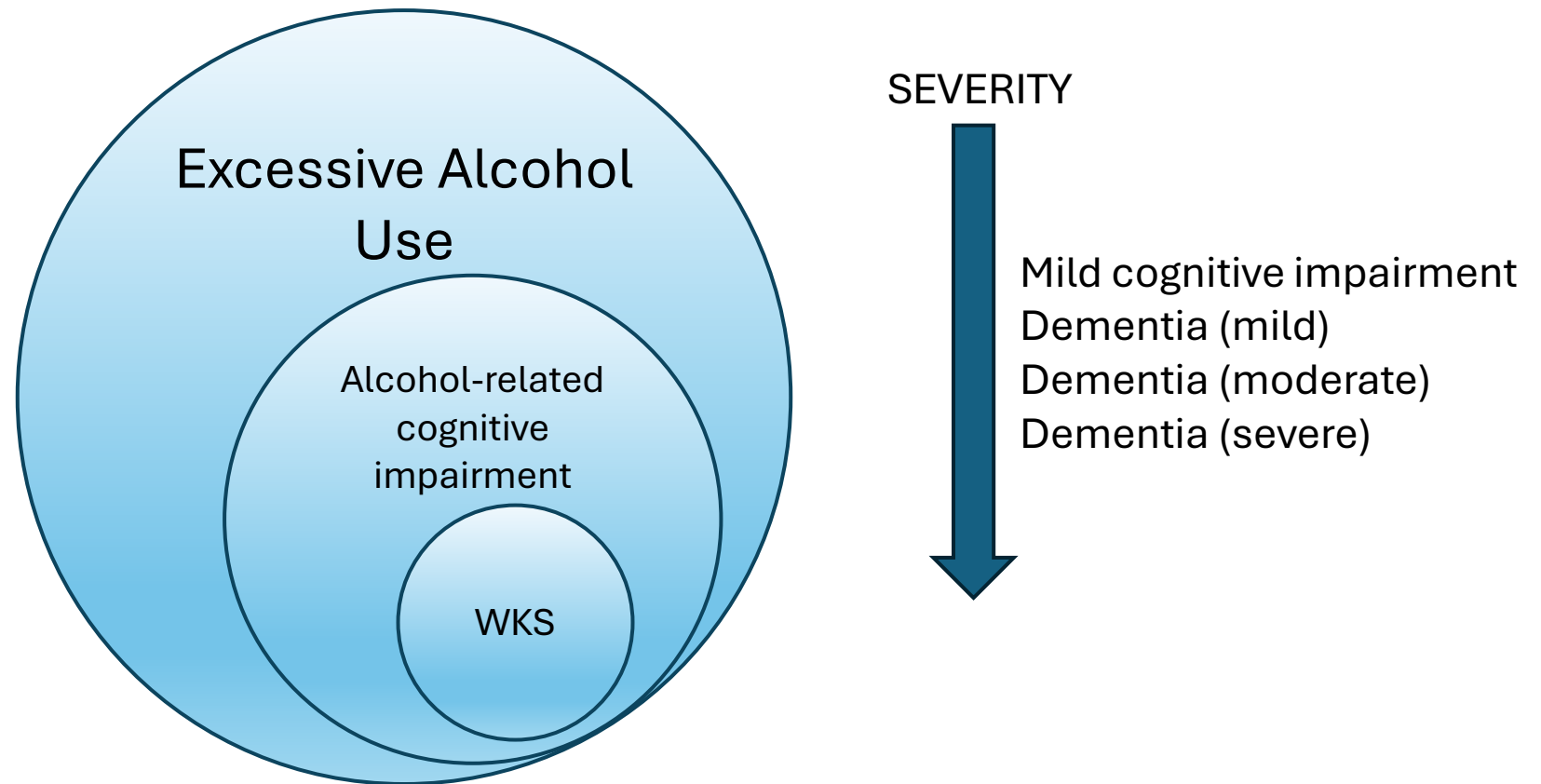
Late-onset dementia



Early-onset dementia

ARCI

- What is meant by “Alcohol-related cognitive impairment”?
- No clear consensus on this term, but for purposes of this talk:



WKS = Wernicke-Korsakoff Syndrome

ARCI

A review proposed the following criteria for ARCI:

1. history of **prolonged and heavy alcohol** consumption (e.g. ≥ 5 years of excessive use)
2. **persistence of cognitive impairment with abstinence** of at least 60 days followed by **stable cognition during abstinence**
3. objective **impairment in one or more cognitive domains**
4. **not attributable to other cause** (e.g. neurodegenerative, psychiatric, medical)

*Some frameworks exclude WKS, while others include it as falling under the umbrella of ARCI

Mechanism of Cognitive Impairment

- Direct
 - Cytotoxic effects due to NMDA receptor modulation
 - Inflammation/oxidative stress
- Indirect
 - Nutritional deficiency (e.g. thiamine)
 - Hepatic injury
 - Cardiovascular disease
 - Head injury
- Pattern of Use
 - Short vs long duration of use
 - Binge-drinking vs consistent use
- Isolated vs Mixed
 - Pure ARCI vs. mixed AD, vascular, etc.

Cognitive Impairment

- ARCI affects a broad range of cognitive domains:
 - Executive function
 - Visuospatial
 - Memory
 - Emotional/social cognition
- In comparison to other neurocognitive disorders, ARCI shows deficits in specific memory retrieval processes
 - Verbal memory intrusions

Stephen R, et al. *The American Journal of Drug and Alcohol Abuse* (2016)

Stavro K, et al. *Addiction Biology* (2013)

Cuperfain AB, et al. *Journal of Clinical Psychiatry* (2025)

Cuperfain AB, et al. *Journal of Alzheimer's Disease* (2026)

Cognitive Impairment

- ARCI is generally non-progressive and may even be reversible
- In contrast to other dementias, the decline in cognitive functioning in ARCI is relatively non-progressive in abstinent ex-drinkers (or partially reversible)
- With abstinence, ~10-20% of those affected will show improvement in cognitive function
- Exception: Wernicke-Korsakoff Syndrome

Goldman MS. *American Psychologist* (1983)

Oslin DW and Cary MS. *American Journal of Geriatric Psychiatry* (2003)

Weytingh MD, et al. *Journal of Neurology* (1995)

Wernicke-Korsakoff Syndrome

- Due to thiamine deficiency, often secondary to excessive alcohol use
- Progression from Wernicke encephalopathy (WE) to Korsakoff syndrome (KS) if thiamine deficiency is untreated
- This condition is generally not reversible

Wernicke-Korsakoff Syndrome

- Wernicke encephalopathy (WE)
 - Ataxia, ophthalmoplegia, altered LOC
 - Bilateral symmetrical hyperintensities, classically in mammillary bodies, on T2-weighted and FLAIR sequences
 - Treatment is with high-dose parenteral thiamine
- Korsakoff syndrome (KS)
 - Amnesia, memory impairment, confabulations
 - Generalized cerebral atrophy, especially in the mammillary bodies and thalamus

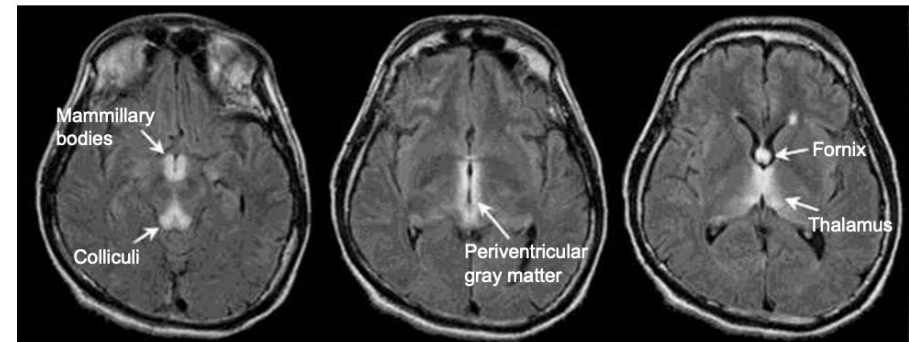


Figure 3 Three fluid-attenuated inversion recovery (FLAIR) images (5 mm thick with a 2.5 mm skip) of a 35-year-old man with schizophrenia and acute nutritional deficiency-induced Wernicke encephalopathy (WE). Note the hyperintense signal in the characteristic loci for WE pathology. Reproduced with permission from Sullivan & Pfefferbaum,⁷² © 2008 Sullivan & Pfefferbaum, Department of Psychiatry & Behavioral Sciences, Stanford University, Stanford, CA, USA.

Management

- Alcohol cessation should be encouraged
 - Reduced alcohol availability
 - Dealcoholized beverages are an option
- Thiamine supplementation in setting of recent/ongoing alcohol use
 - Parenteral thiamine in patients at high risk of Wernicke's encephalopathy ($\geq 200\text{mg/day}$ x 3-5 days per CCSMH guidelines)
 - Oral thiamine can be prescribed in the outpatient setting ($\geq 50\text{mg/day}$ per CCSMH guidelines)
- Anticraving medications
- Assess driving safety
- Community and caregiver supports

Management

- Cognitive enhancers
 - Cholinesterase inhibitors – did not show efficacy
 - Memantine – global cognitive improvement shown over 28 weeks
 - Clonidine – improvements in executive function measures
 - Modafinil – conflicting results showing either improvement or worsening in cognitive measures
- All studies were small
- Overall, more research is needed to guide treatment recommendations
- In cases of mixed disease, can treat based on other condition

Question 2

In what way does alcohol-related cognitive impairment differ from other neurodegenerative disorders such as Alzheimer's disease?

- a) Management includes addressing alcohol use and associated nutritional deficiencies
- b) Cognitive impairment may be (at least partially) reversible with abstinence
- c) It is associated with younger average age at onset
- d) All of the above

Question 2

In what way does alcohol-related cognitive impairment differ from other neurodegenerative disorders such as Alzheimer's disease?

- a) Management includes addressing alcohol use and associated nutritional deficiencies
- b) Cognitive impairment may be (at least partially) reversible with abstinence
- c) It is associated with younger average age at onset
- d) All of the above**

Answer: D. These are all features of ARCI.

Part 2

Research Questions

- What is the cognitive profile of ARCI in comparison to that of other neurocognitive disorders?
- How does alcohol interact with patients with or at risk for neurocognitive disorders?
- Is alcohol use contributing to this patient's cognitive symptoms?
- Why is this important?
 - Mechanism (i.e. how does alcohol lead to cognitive impairment)
 - Prognosis (i.e. is cognition likely to continue declining or remain stable)
 - Treatment (i.e. is there a targeted treatment)

TDRA Study

- We compared cognitive domain and subdomain scores on the TorCA between those with and without ARCI

Toronto Cognitive Assessment (TorCA) Cognitive Domains and Subdomain Tests

ORIENTATION	IMMEDIATE RECALL	DELAYED RECALL	DELAYED RECOGNITION	VISUOSPATIAL FUNCTION	EXECUTIVE FUNCTION	LANGUAGE
Orientation	CERAD Trial 1 CERAD Trial 2 CERAD Trial 3	CERAD Delayed Recall Benson Figure Delayed Recall	CERAD Delayed Recognition Benson Figure Delayed Recognition	Benson Figure Copy Clock Draw	Serial 7s Serial 3s Forward Digit Span Reverse Digit Span Trails A Trails B Alternating Sequences Similarities Verbal Fluency – Phonemic	Verbal Fluency - Semantic MINT Naming Repetition Single Word Comprehension Single Word Reading Comprehension Sentence Comprehension Single Word Reading Semantic Knowledge

Abbreviations: CERAD = Consortium to Establish a Registry for Alzheimer Disease, MINT = Multilingual Naming Test.

TDRA Study

- Participants with ARCI had more delayed recall intrusions compared to those without excessive alcohol use on the CERAD verbal memory test



TDRA Study

- Deficit in response inhibition, i.e., the inability to suppress incorrect information on a test of verbal memory
- We hypothesized that this cognitive deficit may reflect susceptibility of the ventral medial prefrontal cortex (vmPFC) to the effects of alcohol
- Not all cognitive tests include measures of verbal memory intrusions or response inhibition more generally

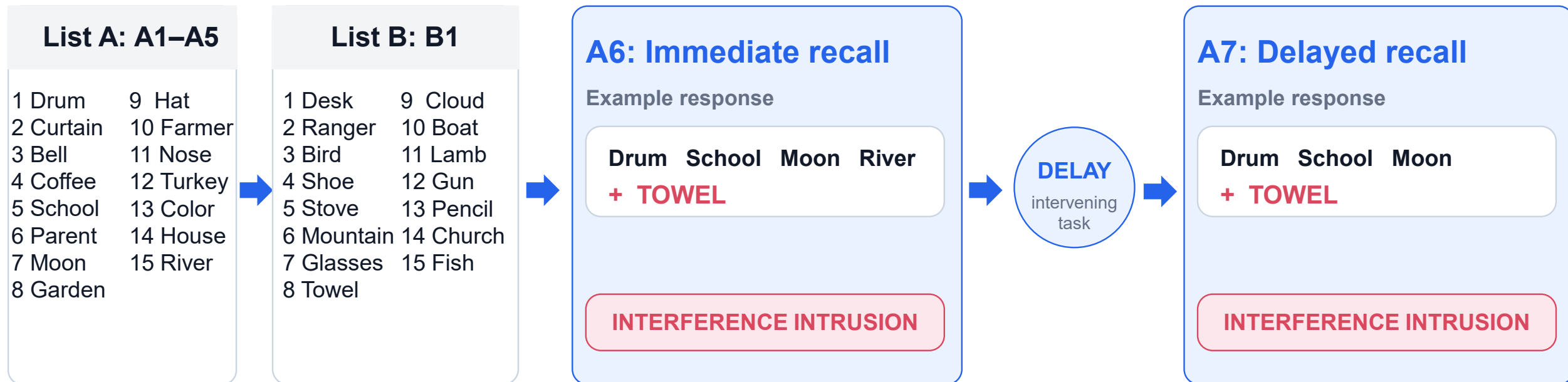
Intrusion Subtypes Study

- To further explore the mechanisms underlying verbal memory intrusions in ARCI, we aimed to investigate relative between-group differences in specific intrusions subtypes
- Cohort: CCNA COMPASS-ND and ONDRI

Semantic	Word sharing similar meaning
Phonemic	Word sharing similar sound
Interference	Word recalled from list B on list A task, or vice versa
Root word	Word sharing same tense
Unrelated	Word without any of the alternative subtype features

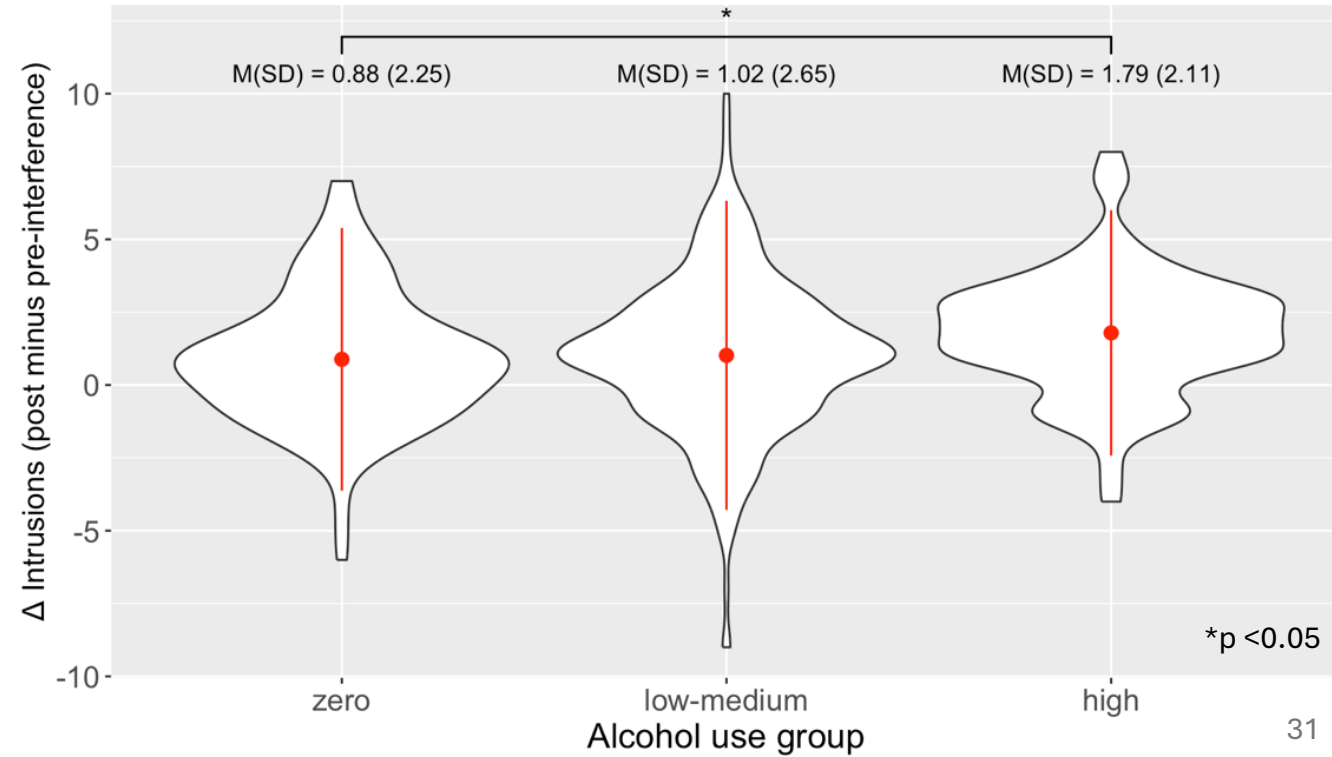
Intrusion Subtypes Study

- Neuropsychological test: Rey auditory verbal learning test (RAVLT)



Intrusion Subtypes Study

- High alcohol use was associated with increase in post-interference intrusions on the RAVLT
- These cognitive processes have been associated with activity in similar ventral brain regions



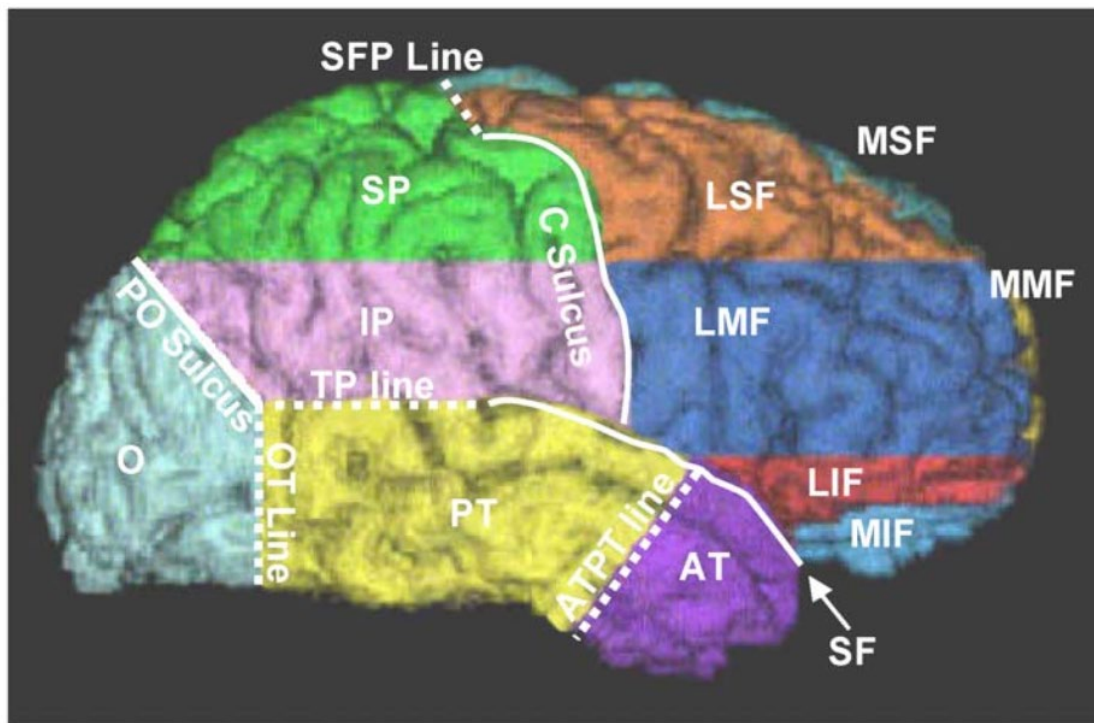
Intrusion Subtypes Study

- Excessive alcohol use disrupts specific memory retrieval processes related to inhibitory control and proactive interference
- These cognitive processes have been associated with activity of the ventromedial prefrontal cortex (vmPFC)

Hypothesis: Higher alcohol use will be associated with lower vmPFC volume, and lower vmPFC volumes will be associated with greater interference intrusions

Neuroimaging Study

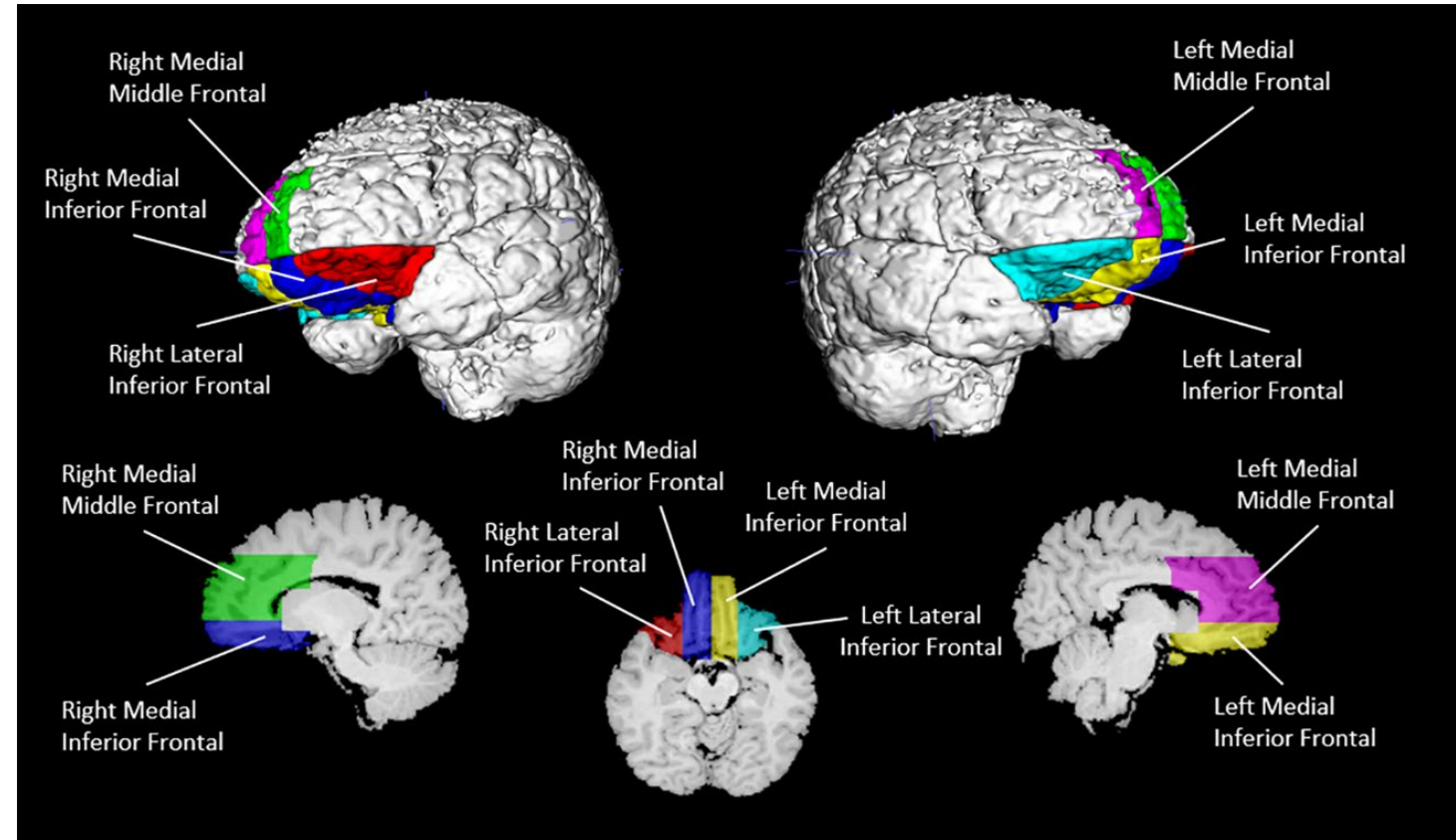
- Cohort: ONDRI
- Imaging protocol: Semi-Automated Brain Region Extraction (SABRE) to generate 13 regions of interest (ROIs) per hemisphere



Frontal	Temporal	Parietal	Occipital
Lateral Superior Frontal	Anterior Temporal	Superior Parietal	Occipital
Medial Superior Frontal	Posterior Temporal	Inferior Parietal	
Lateral Middle Frontal	Anterior Basal Ganglia and Thalamus		
Medial Middle Frontal	Hippocampus		
Lateral Inferior Frontal			
Medial Inferior Frontal			

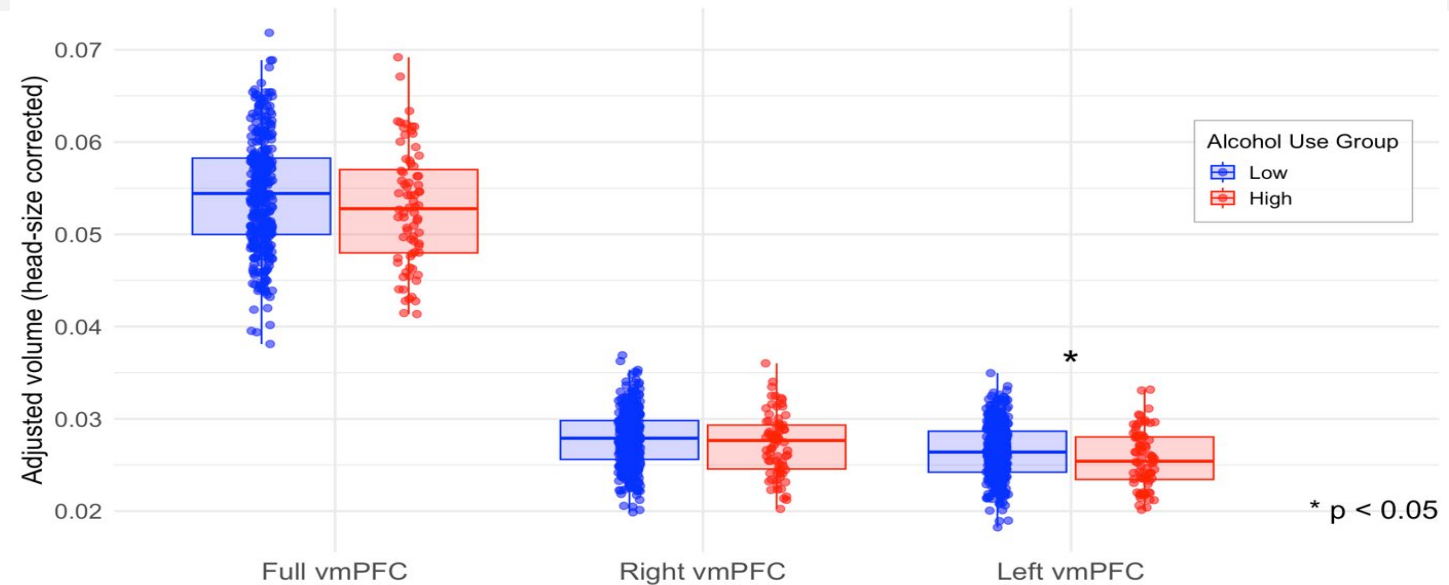
Neuroimaging Study

- We defined the vmPFC as the medial inferior frontal, medial middle frontal and lateral inferior frontal lobe regions bilaterally



Neuroimaging Study

- High alcohol use was associated with smaller left vmPFC gray matter volumes

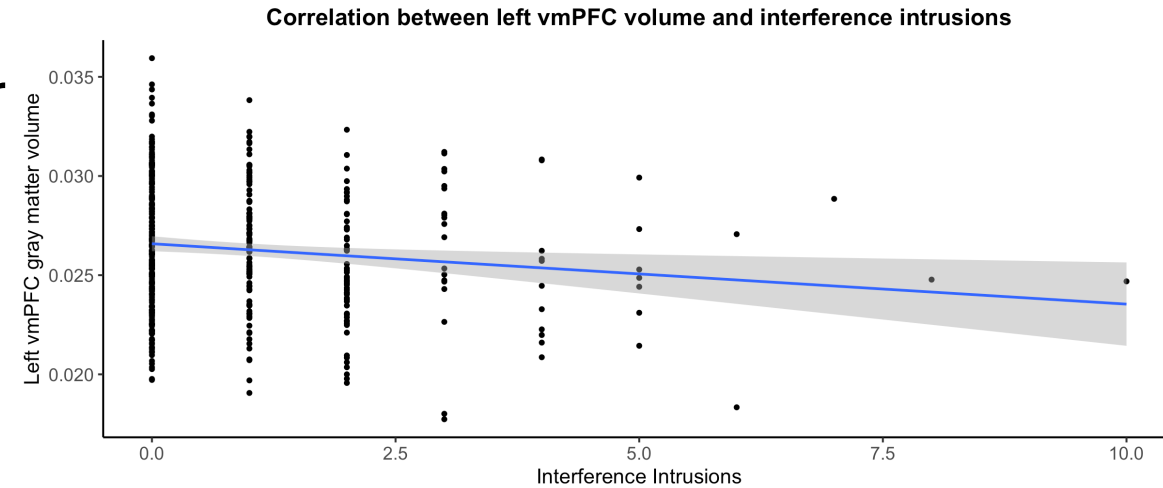


High vs. Low Alcohol Use (n = 427)

	% Change	beta	SE	p-value
Ventromedial prefrontal cortex (vmPFC) Gray Matter – Full				
Full vmPFC	-2.81%	-0.23	0.12	0.057
Ventromedial prefrontal cortex (vmPFC) Gray Matter – Divided				
Right vmPFC	-2.23%	-0.19	0.12	0.124
Left vmPFC	-3.37%	-0.26	0.12	0.030

Neuroimaging Study

- Smaller left vmPFC gray matter volumes were associated with greater number of interference intrusions



Interference Intrusions (n = 427)			
	beta	SE	P-value
Ventromedial prefrontal cortex (vmPFC) Gray Matter – Full			
Full vmPFC	-0.14	0.05	0.007
Ventromedial prefrontal cortex (vmPFC) Gray Matter – Divided			
Right vmPFC	-0.14	0.05	0.006
Left vmPFC	-0.14	0.05	0.011

Neuroimaging Study

- These findings suggest that vmPFC atrophy may play a role in ARCI
- The vmPFC may represent a potential target for future interventions aimed at mitigating ARCI

Question 3

Volume reduction in which brain region may be associated with both heavy alcohol use and interference intrusions on tasks of verbal memory?

- a) ventromedial prefrontal cortex (vmPFC)
- b) occipital lobe
- c) hippocampus
- d) basal ganglia

Question 3

Volume reduction in which brain region may be associated with both heavy alcohol use and interference intrusions on tasks of verbal memory?

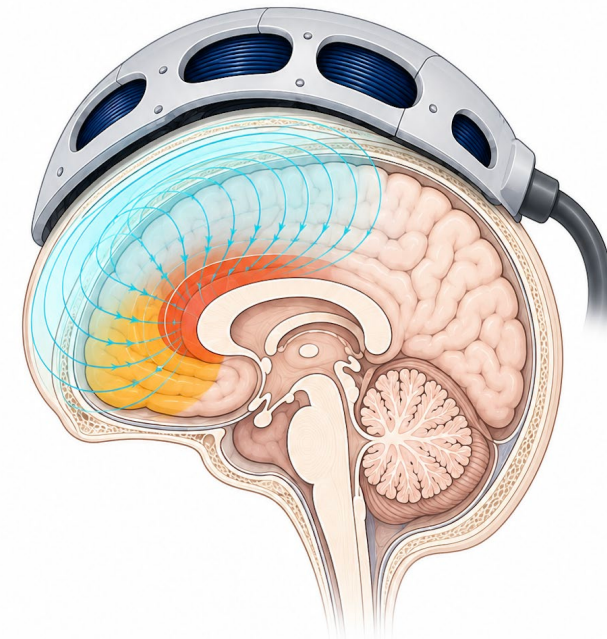
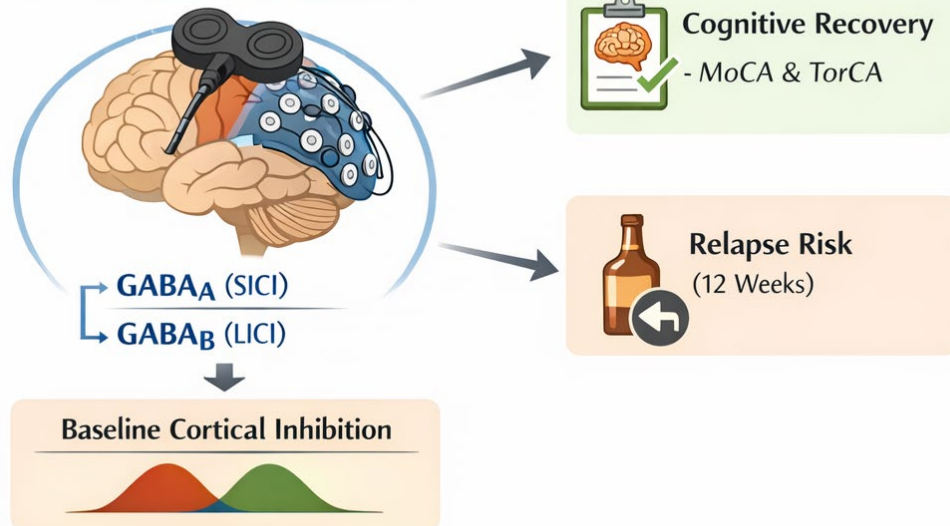
- a) ventromedial prefrontal cortex (vmPFC)**
- b) occipital lobe
- c) hippocampus
- d) basal ganglia

Answer: A. Ventromedial prefrontal cortex (vmPFC). This is the finding of our recent study.

Future Directions

- Identifying biomarkers of ARCI using larger datasets
- Mechanistic understanding to explain why some develop cognitive impairment and others do not
- Specific treatments targeting both dependence and cognition

TMS-EEG of Prefrontal Cortex
Excitatory-Inhibitory Balance



Conclusions

- Chronic heavy alcohol use is a risk factor for the development of dementia
- Alcohol-induced neurocognitive disorders are phenotypically similar to other neurocognitive disorders complicating accurate and timely diagnosis and management
- Alcohol cessation and thiamine supplementation are the mainstay of treatment for ARCI
- Reduced vmPFC volume may mediate the association between excessive alcohol use and memory retrieval deficits, and may be a target for non-invasive neuromodulation approaches aimed at mitigating ARCI

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Thank You For Listening

- Questions?
 - E-mail: ari.cuperfain@camh.ca

