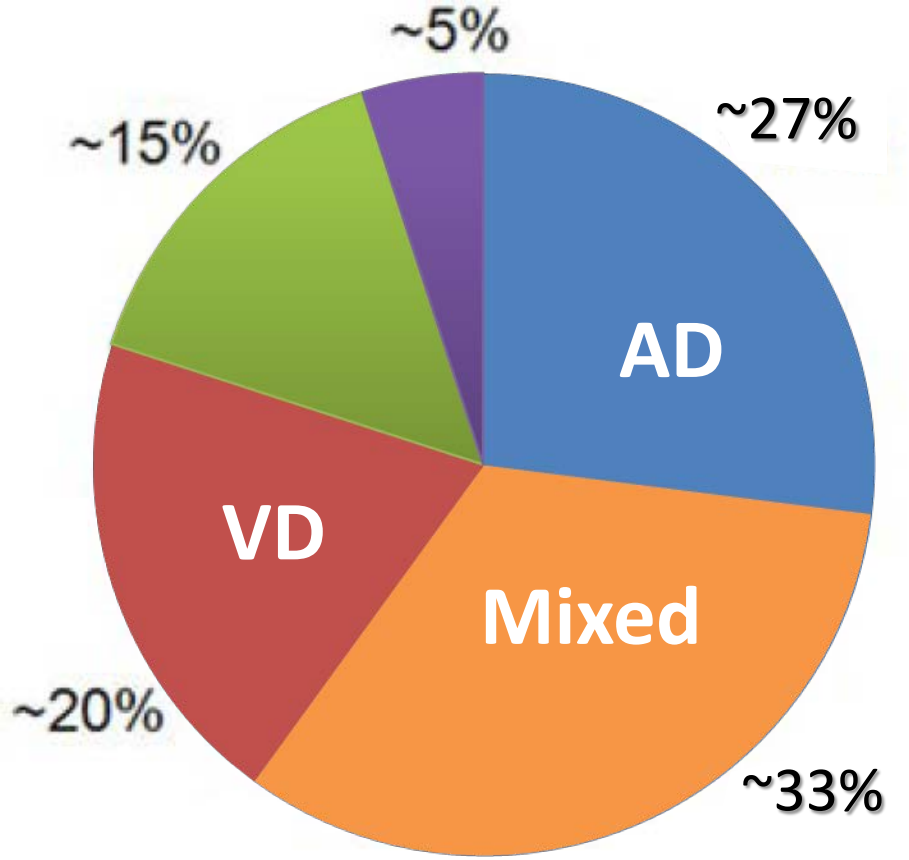
Brain, Behaviours, and Biomarkers

Research from the Lanctôt Lab

Presenter: Jinghan Jenny Chen
Supervisor: Dr. Krista Lanctôt

Introduction

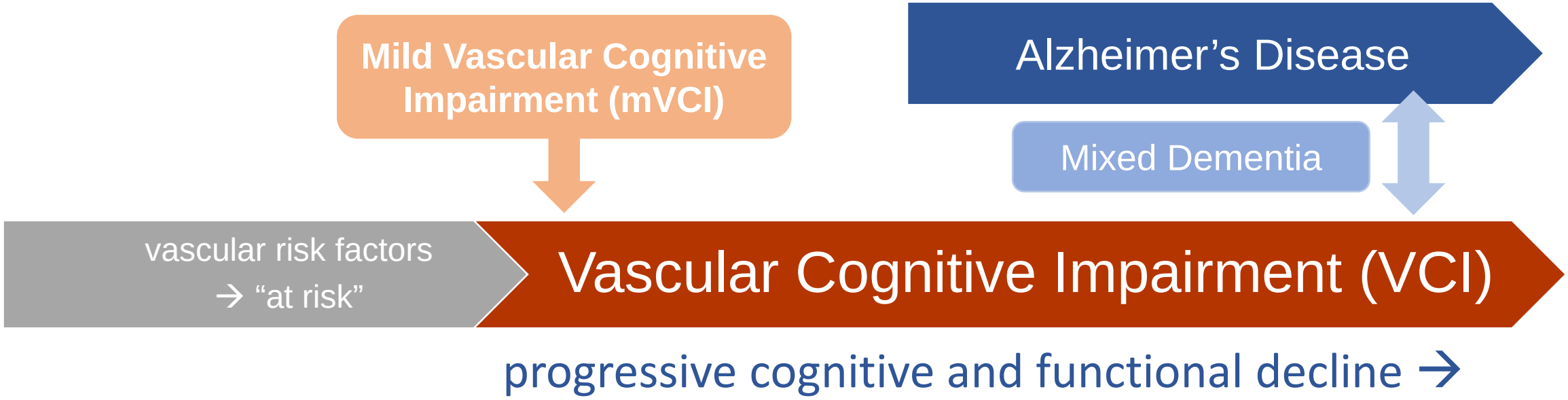
- Dementia has an overwhelming impact on the health care system and caregivers
- Vascular contributions plays an important role in dementia
- Cerebral vascular changes seen in 46-70% of clinically-diagnosed **A**lzheimer's **D**isease (AD) cases



Adapted from Niedowicz, D. M., et al. (2011). "Alzheimer's disease: pathological mechanisms and recent insights." Current neuropharmacology **9**(4): 674-684.

Mild Vascular Cognitive Impairment (mVCI)

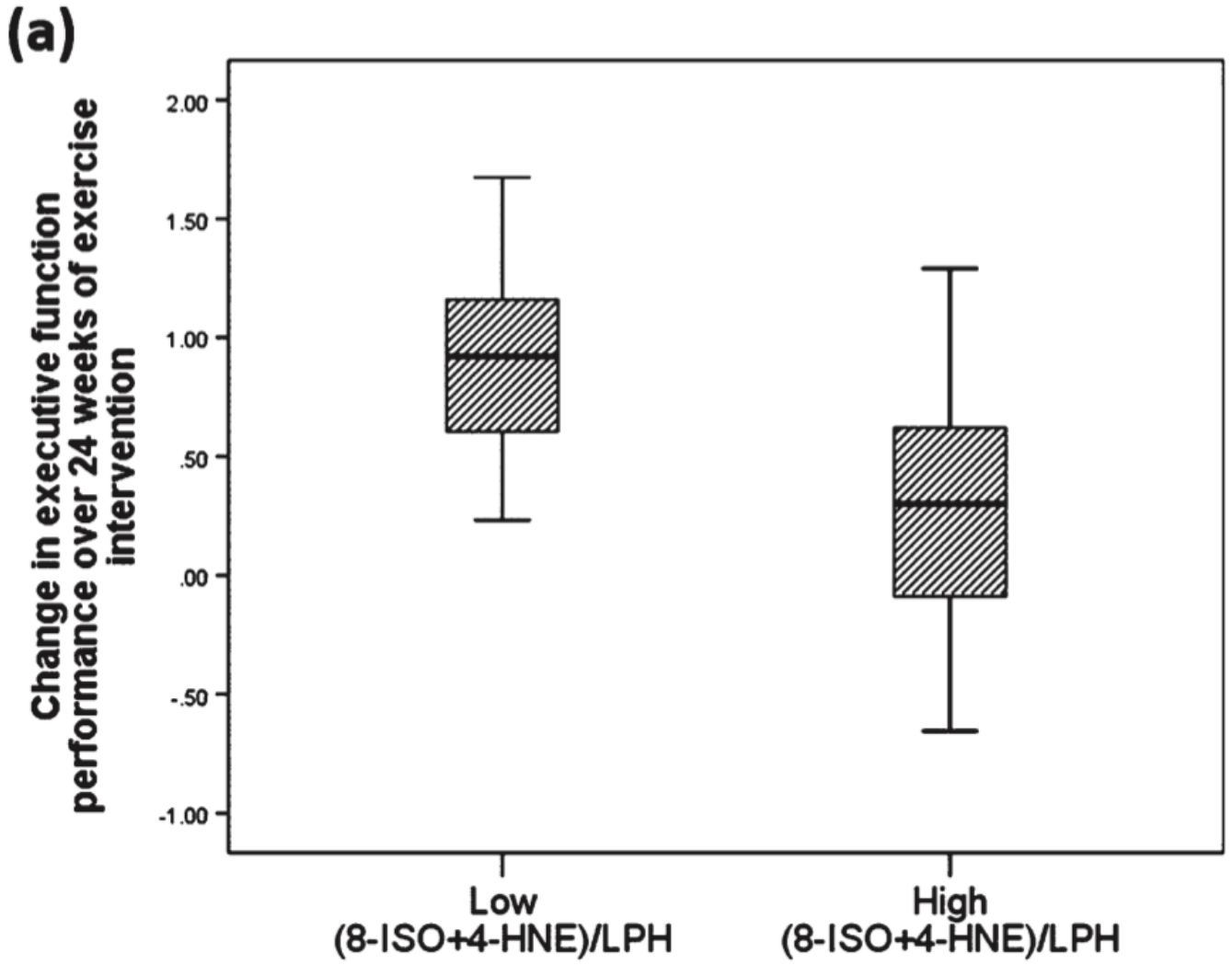
- The most prevalent form of VCI
  - Cognitive impairment + vascular comorbidities
  - Without functional impairments



Coronary Artery Disease and Exercise

- Those with Coronary Artery Disease (CAD) are at risk for mVCI
- Exercise - current recommendation to manage vascular risk factors
- Positive effects in cognition

But… those with mVCI do not benefit from exercise



Suridjan, I., Herrmann, N., Adibfar, A., Saleem, M., Andreazza, A., Oh, P. I., & Lanctot, K. L. (2017). Lipid Peroxidation Markers in Coronary Artery Disease Patients with Possible Vascular Mild Cognitive Impairment. *J Alzheimers Dis, 58*(3), 885-896.

MOVE-IT: Efficacy and Safety of N-Acetylcysteine (NAC) in Patients with Mild Vascular Cognitive Impairment

Principal Investigator: Dr. Krista L. Lanctôt
Qualified Investigators: Drs. Paul Oh, Damien Gallagher
Co-investigators: Drs. Nathan Herrmann, Sandra Black, Ana Andreazza, Walter Swardfager, Simon Graham, Alex Kiss, Joel Ramirez

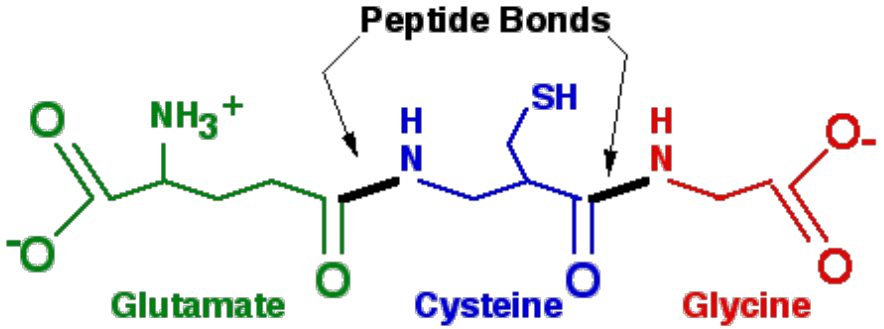
What is the goal of MOVE-IT?

- **N-acetylcysteine (NAC)** supplementation will be used as an add-on therapy to improve cognitive function in patients undergoing cardiac rehabilitation
- **We hypothesize that NAC will increase the efficacy of exercise in improving cognitive performance, by reducing oxidative stress in mVCI patients**

Why NAC?

Glutathione (GSH) - tripeptide antioxidant

- Primary antioxidant molecule in the brain
- Level in depends on precursors availability
- Depletion linked to neuronal death
- May be altered by increased OS



NAC - natural health product

- ↑ availability of cysteine → ↑ intracellular GSH
- Cross blood brain barrier
  - ↓ OS species

MOVE-IT Study Design

- Randomized, double blind, placebo controlled, parallel group study (gold standard for clinical trials)
- 128 patients with mVCI enrolled in a 6 month cardiac rehabilitation program, recruited over 5 years
- Intervention: oral NAC 2400 mg/daily or placebo (lactose)

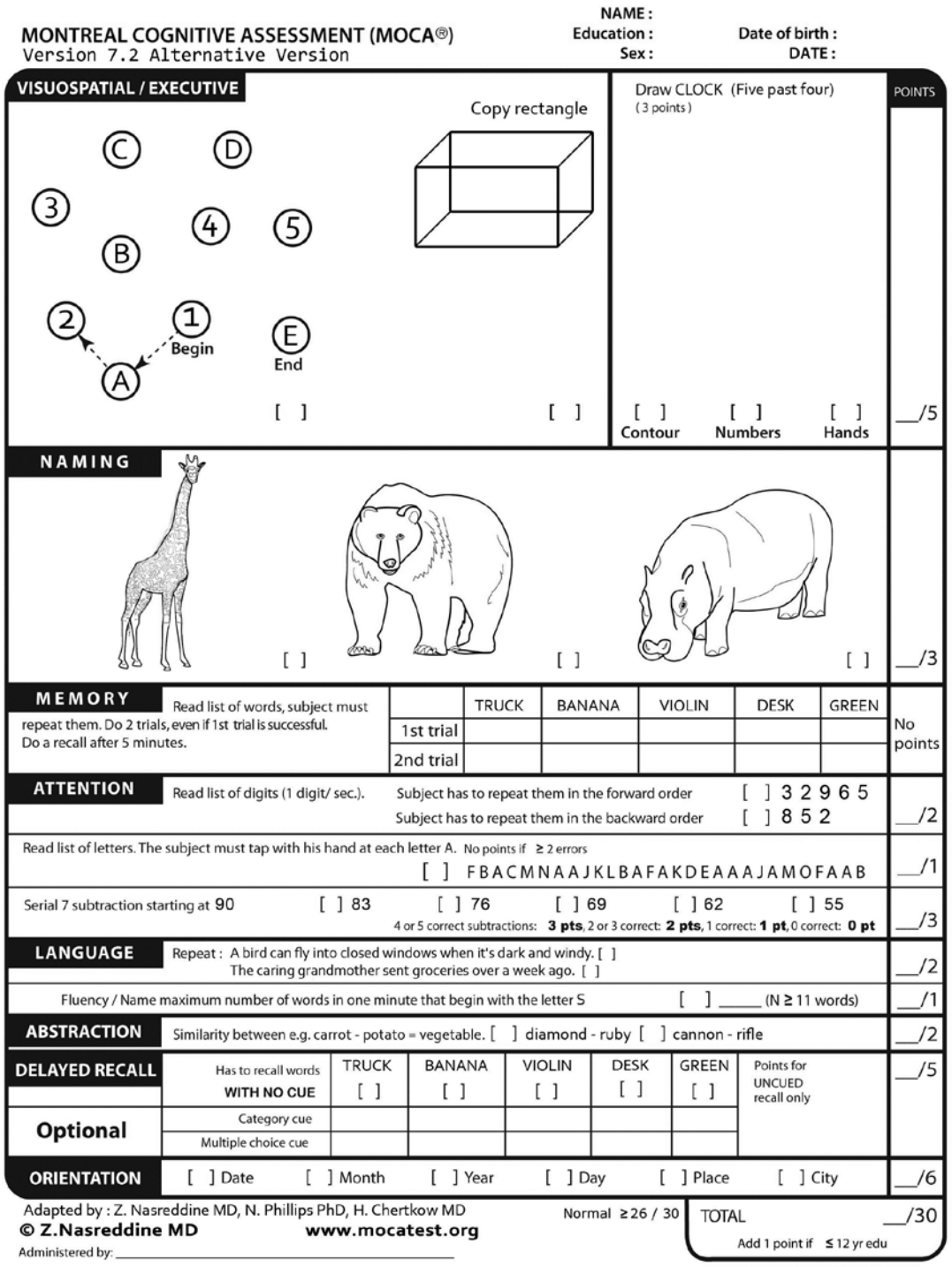
Primary Hypothesis: in patients with mVCI, those randomized to NAC will demonstrate greater improvement in executive function over 6 months as compared to those on placebo

MoCA

The Montreal Cognitive Assessment (MoCA) is a brief cognitive screening tool for Mild Cognitive Impairment

Assess global cognition:

- Short term memory
- Visuospatial abilities
- Executive function
- Attention and working memory
- Language
- Orientation



MONTREAL COGNITIVE ASSESSMENT (MOCA®)
Version 7.2 Alternative Version

NAME :
Education :
Sex :
Date of birth :
DATE :

VISUOSPATIAL / EXECUTIVE — POINTS

Copy rectangle

Draw CLOCK (Five past four) (3 points)

[ ] Contour [ ] Numbers [ ] Hands

__/5

NAMING

[ ] [ ] [ ]

__/3

MEMORY — Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	TRUCK	BANANA	VIOLIN	DESK	GREEN
1st trial					
2nd trial					

No points

ATTENTION — Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 3 2 9 6 5

Subject has to repeat them in the backward order [ ] 8 5 2

__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Serial 7 subtraction starting at 90 [ ] 83 [ ] 76 [ ] 69 [ ] 62 [ ] 55

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

__/3

LANGUAGE — Repeat : A bird can fly into closed windows when it's dark and windy. [ ]
The caring grandmother sent groceries over a week ago. [ ]

__/2

Fluency / Name maximum number of words in one minute that begin with the letter S [ ] _____ (N ≥ 11 words)

__/1

ABSTRACTION — Similarity between e.g. carrot - potato = vegetable. [ ] diamond - ruby [ ] cannon - rifle

__/2

DELAYED RECALL

	Has to recall words WITH NO CUE	TRUCK	BANANA	VIOLIN	DESK	GREEN
		[ ]	[ ]	[ ]	[ ]	[ ]
Optional	Category cue					
	Multiple choice cue					

Points for UNCUED recall only

__/5

ORIENTATION — [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

__/6

Adapted by : Z. Nasreddine MD, N. Phillips PhD, H. Chertkow MD
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Normal ≥ 26 / 30

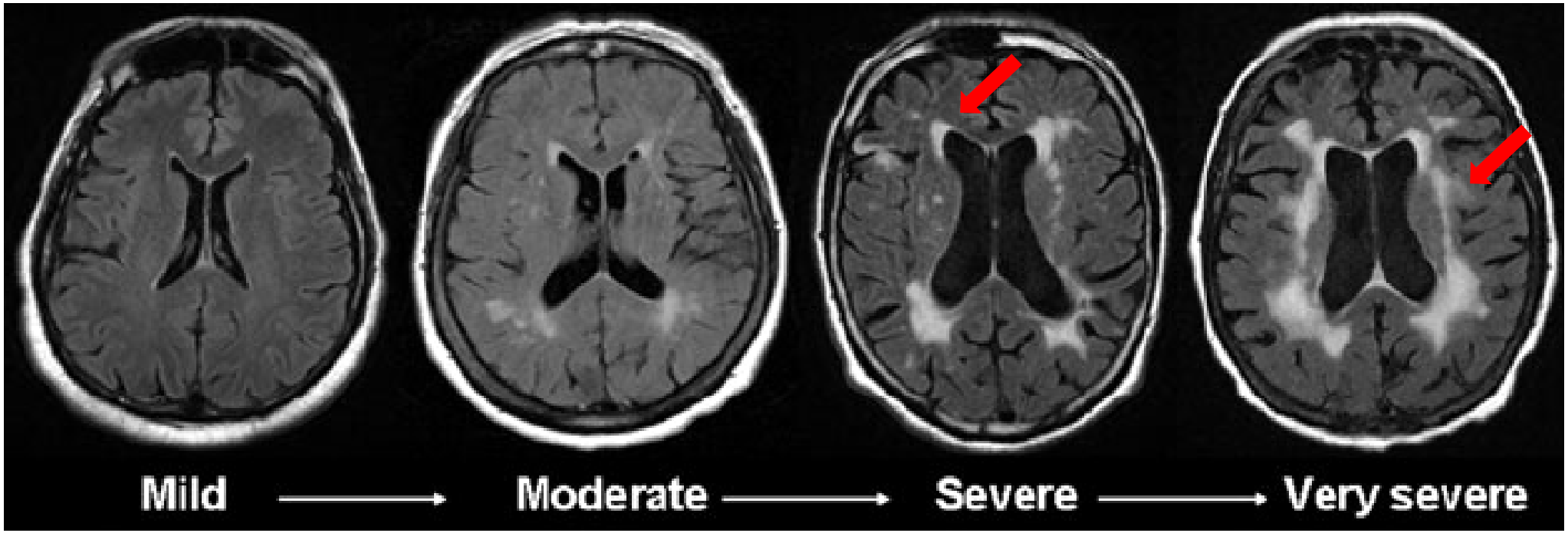
TOTAL __/30

Add 1 point if ≤ 12 yr edu

Administered by: _____

White Matter Hyperintensities (WMH)

- Lesions observed on T2-weighted images on brain MRI
- Multi-factorial

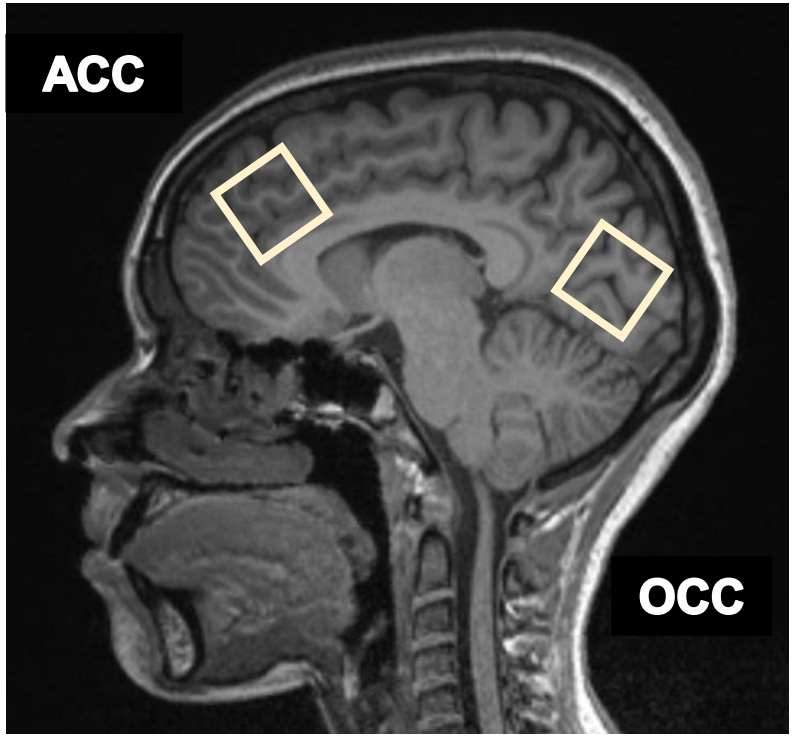


Chutinet, A., & Rost, N. S. (2014). White matter disease as a biomarker for long-term cerebrovascular disease and dementia. *Current treatment options in cardiovascular medicine*, *16*(3), 292.

Why do we use biomarkers?

Brain GSH

- Measured *in vivo* using Magnetic Resonance Spectroscopy (MRS)
  - Anterior cingulate (ACC)
  - Occipital cortex (OCC)
- Concentration (mM) relative to water calculated using open-source toolkit (Gannet)



Occipital Cortex Voxel – location and spectra

Other biomarkers

- Blood
  - Oxidative stress markers
  - GSH
  - Astrocyte/neurodamage markers
- Cerebral blood flow
- Amyloid PET imaging

Study Status: Currently Recruiting

Looking forward to results!

alzheimer's association®

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Société Alzheimer Society CANADA

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Neuropsychopharmacology Research Group

Thank you!