Faculty/Presenter Disclosure

- **Faculty:** Linda Mah

- **Relationships with commercial interests:** None.
Disclosure of Commercial Support

None.

- Potential for conflict(s) of interest:
  None.
Mitigating Potential Bias

Not applicable.
Negative emotional memory bias in late-life depression and mild cognitive impairment

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Assistant Professor, Department of Psychiatry, University of Toronto
Everything you need to know about the pathogenesis of AD in 5 minutes + original data

Linda Mah, MD, MHS, FRCPC
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Acknowledgements

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Learning Objectives

1. Learn why it is critical that we be able to identify individuals at risk for Alzheimer's disease (AD).

2. Understand the challenges of screening for preclinical AD.

3. Be familiar with the association between neuropsychiatric symptoms and development of AD.
The take home is...

1. Brain changes due to AD begin early. They may be irreversible.
2. Screening tools for preclinical AD do not yet exist.
3. Emotion dysregulation may be an early signature of AD risk.
Terminology

- **Alzheimer’s disease (AD)** = cognitive deficits that impair ability to function independently

- **Mild cognitive impairment (MCI)** = cognitive deficits with intact function. It may be a prodrome of AD. 10-15% progress to AD/year

- **Late-life depression** = anyone with depression >=60 years

- **Late-onset depression (LOD)** = first
Clinical Diagnosis of AD

- NIA-AAA (National Institutes of Aging-Alzheimer’s Association of America) criteria for Probable AD (McKhann et al. 2011, Alzheimers Dement May; 7(3): 263–269)

- APA DSM-V Major Neurocognitive Disorder
AD is a neuropathologic diagnosis

ABC criteria

- A. Amyloid-β plaque score (based on Thal et al. 2002)
- B. NFT stage (Braak 1991, 2006).
- C. Neuritic plaque CERAD score (Mirra et al. 1991)

Hyman et al. 2012 NIA-AA guidelines for neuropathologic assessment of AD. Alzheimer’s and Dementia, 8, 1–13
Stages of the Pathologic Process in Alzheimer Disease: Age Categories From 1 to 100 Years

Heiko Braak, MD, Dietmar R. Thal, MD, Estifanos Ghebremedhin, MD, and Kelly Del Tredici, MD, PhD

Development of AT8-ir pathology (n = 2332)
Tangles and Plaques in Nondemented Aging and “Preclinical” Alzheimer’s Disease

Joseph L. Price, DPhil,*† and John C. Morris, MD†‡§

Ann Neurol 1999;45:358–368
Tangles and Plaques in Nondemented Aging and "Preclinical" Alzheimer's Disease

Joseph L. Price, DPhil,*† and John C. Morris, MD†‡§

Tangle Density vs. Age, by Plaque Group
CDR = 0, Entorhinal Cortex

- Age<75, no plaques, Group A
- Age>75, no plaques, Group A
- Age>75, few plaques, Group B
- Age>75, many plaques, Group C

Ann Neurol 1999;45:358–368
The diagram illustrates the progression of clinical disease stages from normal to preclinical, mild cognitive impairment (MCI), and dementia. Different lines represent various biological markers:

- **Amyloid-β accumulation (CSF/PET)**
- **Synaptic dysfunction (FDG-PET/fMRI)**
- **Tau-mediated neuronal injury (CSF)**
- **Brain Structure (volumetric MRI)**
- **Cognition**
- **Clinical Function**

The preclinical stage is highlighted, indicating the early stages of disease before the onset of MCI or dementia.
Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease

Reisa A. Sperling\textsuperscript{a,*}, Paul S. Aisen\textsuperscript{b}, Laurel A. Beckett\textsuperscript{c}, David A. Bennett\textsuperscript{d}, Suzanne Craft\textsuperscript{e}, Anne M. Fagan\textsuperscript{f}, Takeshi Iwatsubo\textsuperscript{g}, Clifford R. Jack Jr.\textsuperscript{h}, Jeffrey Kaye\textsuperscript{i}, Thomas J. Montine\textsuperscript{j}, Denise C. Park\textsuperscript{k}, Eric M. Reiman\textsuperscript{l}, Christopher C. Rowe\textsuperscript{m}, Eric Siemers\textsuperscript{n}, Yaakov Stern\textsuperscript{o}, Kristine Yaffe\textsuperscript{p}, Maria C. Carrillo\textsuperscript{q}, Bill Thies\textsuperscript{q}, Marcelle Morrison-Bogorad\textsuperscript{r}, Molly V. Wagster\textsuperscript{r}, and Creighton H. Phelps\textsuperscript{r}
Preclinical AD

Stage 1
- Asymptomatic amyloidosis
  - High PET amyloid tracer retention
  - Low CSF Aβ1-42

Stage 2
- Amyloidosis + Neurodegeneration
  - Neuronal dysfunction on FDG-PET/fMRI
  - High CSF tau/p-tau
  - Cortical thinning/ Hippocampal atrophy on sMRI

Stage 3
- Amyloidosis + Neurodegeneration + **Subtle Cognitive Decline**
  - Evidence of subtle change from baseline level of cognition
  - Poor performance on more challenging cognitive tests
  - Does not yet meet criteria for MCI

Mild Cognitive Impairment

Alzheimer’s Disease

Sperling et al. 2011
Imaging Brain Amyloid in Alzheimer’s Disease with Pittsburgh Compound-B

William E. Klunk, MD, PhD,1 Henry Engler, MD,2 Agneta Nordberg, MD, PhD,3,4 Yanming Wang, PhD,5 Gunnar Blomqvist, PhD,2 Daniel P. Holt, BS,5 Mats Bergström, PhD,2 Irina Savitcheva, MD,2 Guo-feng Huang, PhD,5 Sergio Estrada, PhD,2 Birgitta Ausén, MSC,4 Manik L. Debnath, MS,1 Julien Barletta, BS,6 Julie C. Price, PhD,5 Johan Sandell, PhD,2 Brian J. Lopresti, BS,5 Anders Wall, PhD,2 Pernilla Koivisto, PhD,2 Gunnar Antoni, PhD,2 Chester A. Mathis, PhD,5 and Bengt Långström, PhD2,6

Pittsburgh Compound B and the Postmortem Diagnosis of Alzheimer’s Disease

Dana M. Niedowicz, PhD\textsuperscript{1,2,*}, Tina L. Beckett, HBSc\textsuperscript{1,*}, Sergey Matveev, PhD\textsuperscript{1,2}, Adam M. Weidner, PhD\textsuperscript{1,2}, Irfan Baig, PhD\textsuperscript{1,2}, Richard J. Kryscio, PhD\textsuperscript{1,3,4}, Marta S. Mendiondo, PhD\textsuperscript{1,4}, Harry LeVine III, PhD\textsuperscript{1,2}, Jeffrey N. Keller, PhD\textsuperscript{6}, and M. Paul Murphy, PhD\textsuperscript{1,2,5}
PET Imaging of Tau Deposition in the Aging Human Brain

Michael Schöll,1,2,6 Samuel N. Lockhart,1,6 Daniel R. Schonhaut,3 James P. O’Neil,4 Mustafa Janabi,4 Rik Ossenkoppelle,1,3,5 Suzanne L. Baker,4 Jacob W. Vogel,1 Jamie Faria,4 Henry D. Schwimmer,1 Gil D. Rabinovici,1,3,4 and William J. Jagust1,4,*

1Helen Wills Neuroscience Institute, University of California, Berkeley, Berkeley, CA 94720, USA

0.5 1.0 2.5

Schöll et al., 2016, Neuron 89, 971–982
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http://dx.doi.org/10.1016/j.neuron.2016.01.028
Severe AD
Mild AD
No dementia
No amyloid
Amyloid
Tau pathology

Tangle Density vs. Age, by Plaque Group
CDR = 0, Entorhinal Cortex

- \( y = 1.6x - 114.3 \)
- \( y = 0.5x - 33.3 \)
- \( y = 0.5x - 33.6 \)
- \( y = 0.1x - 3.2 \)

Ann Neurol 1999;45:358–368
Revealed, the 'ground zero' of Alzheimer's: Scientists pinpoint the exact area of the brain where devastating disease begins

Vulnerable region in the brain, the locus coeruleus, has been identified


Follow us: [@MailOnline on Twitter](https://twitter.com/MailOnline) | [DailyMail on Facebook](https://www.facebook.com/DailyMail)
Locus coeruleus (LC)

- [Image: https://commons.wikimedia.org/wiki/File:Neurones_noradrenergiques.png]

- [Link: https://commons.wikimedia.org/wiki/File:Neurones_noradrenergiques.png]
Location of the locus coeruleus (LC) in the brainstem.
Relationship between basic physiological processes modulated by the LC–noradrenergic system (Rectangles) and potential clinical relevance of these actions (Ovals).

ADHD, PTSD, Stress/Anxiety, Depression, Drug Abuse.
Clinical and neuropathological correlates of depression in Alzheimer's disease

HANS FÖRSTL, ALISTAIR BURNS, PHILIP LUTHERT, NIGEL CAIRNS, PETER LANTOS AND RAYMOND LEVY

From the Section of Old Age Psychiatry and the Department of Neuropathology,
Locus coeruleus neurofibrillary degeneration in aging, mild cognitive impairment and early Alzheimer’s disease

Aneta Grudzien\textsuperscript{a}, Pamela Shaw\textsuperscript{a}, Sandra Weintraub\textsuperscript{a}, Eileen Bigio\textsuperscript{a}, Deborah C. Mash\textsuperscript{b}, M. Marsel Mesulam\textsuperscript{a,}\textasteriskcentered
Summary of stages in the development of Alzheimer disease (AD)-associated tau pathology.
Detection of changes in the locus coeruleus in patients with mild cognitive impairment and Alzheimer’s disease: High-resolution fast spin-echo T1-weighted imaging

Junko Takahashi,1 Toshihide Shibata,1 Makoto Sasaki,2 Masako Kudo,1 Hisashi Yanezawa,1 Satoko Obara,1 Kohsuke Kudo,3 Kenji Ito,2 Fumio Yamashita2 and Yasuo Terayama1

1Department of Neurology and Gerontology, School of Medicine, 2Division of Ul Medical University, Morioka, and 3Department of Diagnostic and Interventional
Relationship between basic physiological processes modulated by the LC–noradrenergic system (Rectangles) and potential clinical relevance of these actions (Ovals).

ADHD, PTSD, Stress/Anxiety, Depression, Drug Abuse

Learning Memory
- PFC
- Hippocampus
- Amygdala

Sensory Processing
- Cortex
- Thalamus
- Brainstem

Attention/Orienting
- PFC
- Parietal Cortex
- Thalamus
- Amygdala

Motor
- Cortex
- Cerebellum
- Thalamus
- Spinal Cord

Arousal
- Waking
- Forebrain Activity State

Insomnia
- Narcolepsy

MS
- MPOA

Brainstem
- Thalamus
- Cortex

Salient Stimuli
- Novel
- Noxious/Stressors
- Rewards

LC-NE SYSTEM

Abnormal

- Amyloid-β accumulation (CSF/PET)
- Synaptic dysfunction (FDG-PET/fMRI)
- Tau-mediated neuronal injury (CSF)
- Brain Structure (volumetric MRI)

Emotion
Cognition
Clinical Function

Normal
Preclinical
MCI
Dementia

Clinical Disease Stage
Survival curves for depressed patients (lower curve) and nondepressed patients (upper curve).

Recent review

NIH Public Access
Author Manuscript

Published in final edited form as:

Depression and Risk of Developing Dementia

Amy L. Byers, PhD, MPH and Kristine Yaffe, MD
Departments of Psychiatry (ALB, KY), Neurology (KY), and Epidemiology & Biostatistics (KY), University of California, San Francisco and San Francisco Veterans Affairs Medical Center (ALB, KY)
Anxiety Symptoms in Amnestic Mild Cognitive Impairment Are Associated with Medial Temporal Atrophy and Predict Conversion to Alzheimer Disease

Linda Mah, M.D., M.H.Sc., F.R.C.P.C., Malcolm A. Binns, Ph.D.,
David C. Steffens, M.D., M.H.Sc., for the Alzheimer’s Disease Neuroimaging Initiative*

Am J Geriatr Psychiatry 2015; 23:466-476

No anxiety

Anxiety

HR = 1.42, p = 0.0002
Emotional memory?

“Well, I'm here to develop some false memories so I can forget about my own rotten past!”
Negative emotional memory bias in late-life depression and mild cognitive impairment

EVLT List A
Presented → Immediate recall List A → Procedure repeated for 4 additional trials

EVLT List B (new)
Presented → Immediate recall List B → Short Delay Recall List A

EVLT = emotional verbal learning test

Mah et al. (submitted)
Positive memory bias score = \# positive words recalled - \# neutral words recalled

Negative memory bias score = \# negative words recalled - \# neutral words recalled
Negative emotional memory bias in late-life depression and mild cognitive impairment

CN = cognitively normal
sd-aMCI = single-domain amnestic MCI
LOD = late-onset depression

Mah et al. (submitted)
Association between executive function and emotional memory

Association between negative emotional memory and executive function in CN

Association between positive emotional memory and working memory in sd-aMCI

Mah et al. (submitted)
ASRP study: Emotional memory in subjective cognitive decline (SCD)

Hypothesized findings:

- Hypothesized findings are represented in a bar chart showing the recall of emotional words for different conditions: CN, sd-aMCI, and SCD. The chart shows the number of emotional words recalled under positive (POS-bias) and negative (NEG-bias) conditions, with error bars indicating variability.

- For CN, the recall under POS-bias is slightly higher than under NEG-bias.
- For sd-aMCI, the recall under NEG-bias is significantly higher than under POS-bias.
- For SCD, the recall under NEG-bias remains high, indicating a bias towards recalling negative emotional words.

The chart helps visualize how emotional memory recall differs across these conditions, with a particular focus on the negative bias observed in SCD.
Screen for emotion dysregulation?
Learning Objectives

1. Learn why it is critical that we be able to identify individuals at risk for AD.
2. Understand the challenges of screening for preclinical AD.
3. Be familiar with the association between neuropsychiatric symptoms and development of AD.
The take home is

1. Brain changes due to AD begin early. They may be irreversible.
2. Screening tools for preclinical AD do not yet exist.
3. Emotion dysregulation may be an early signature of AD risk.
Thank you for your attention