Mild Behavioral Impairment (MBI): Symptoms, Prodrome, or False Alarm?

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Disclosures
(since 1993)

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- Consultant/Advisor
  - Astra-Zeneca, Glaxo-Smith Kline, Eisai, Novartis, Forest, Supernus, Adlyfe, Takeda, Wyeth, Lundbeck, Merz, Lilly, Pfizer, Genentech, Elan, NFL Players Association, NFL Benefits Office, Avanir, Zinfandel, BMS, Abvie, Janssen, Orion, Otsuka, Astellas, Merck
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THANK YOU!

Zahinoor Ismail MD FRCPC

Hotchkiss Brain Institute, University of Calgary

Mary Ganguli MD MPH FRCPC

University of Pittsburgh

for background and some slides

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Talk overview[1]

- NPS: close link to dementia well established for over a decade, intimate link with neurodegenerative process
- NPS: affect at least 50% of patients with MCI and are associated with accelerated progression to dementia
- NPS in the absence of a cognitive syndrome associated with accelerated progression to MCI and dementia
- MBI: review the construct; discuss its emerging status

[1] **NPS = neuropsychiatric symptoms**

The meaning of words

- Symptoms: expressions of “psychiatric disease”
- Prodrome: a harbinger of dementia
- False alarm: “psychological reaction”

A common presentation

- 72 year old, married, retired nurse with anxiety, irritability, worry, loss of interest, & social withdrawal of 2-3 years duration. Onset was gradual, progressive. No major sleep, appetite or weight change. Husband noted uncharacteristic outbursts of anger without provocation.
- No significant family history. Patient in good health all her life with no prior substance use or other psychiatric history.
- Referred by her GP to a psychiatrist who diagnosed major depression and initiated treatment with CBT & sertraline with some improvement.
- Switch to venlafaxine and addition of buproprion led to remission.
- Subsequently began complaining of memory loss and getting lost while driving. Cognitive testing indicated amnestic MCI.
- Enrolled in IDEAS and had POSITIVE florbetapir PET scan

Mental Disorders in Later Life

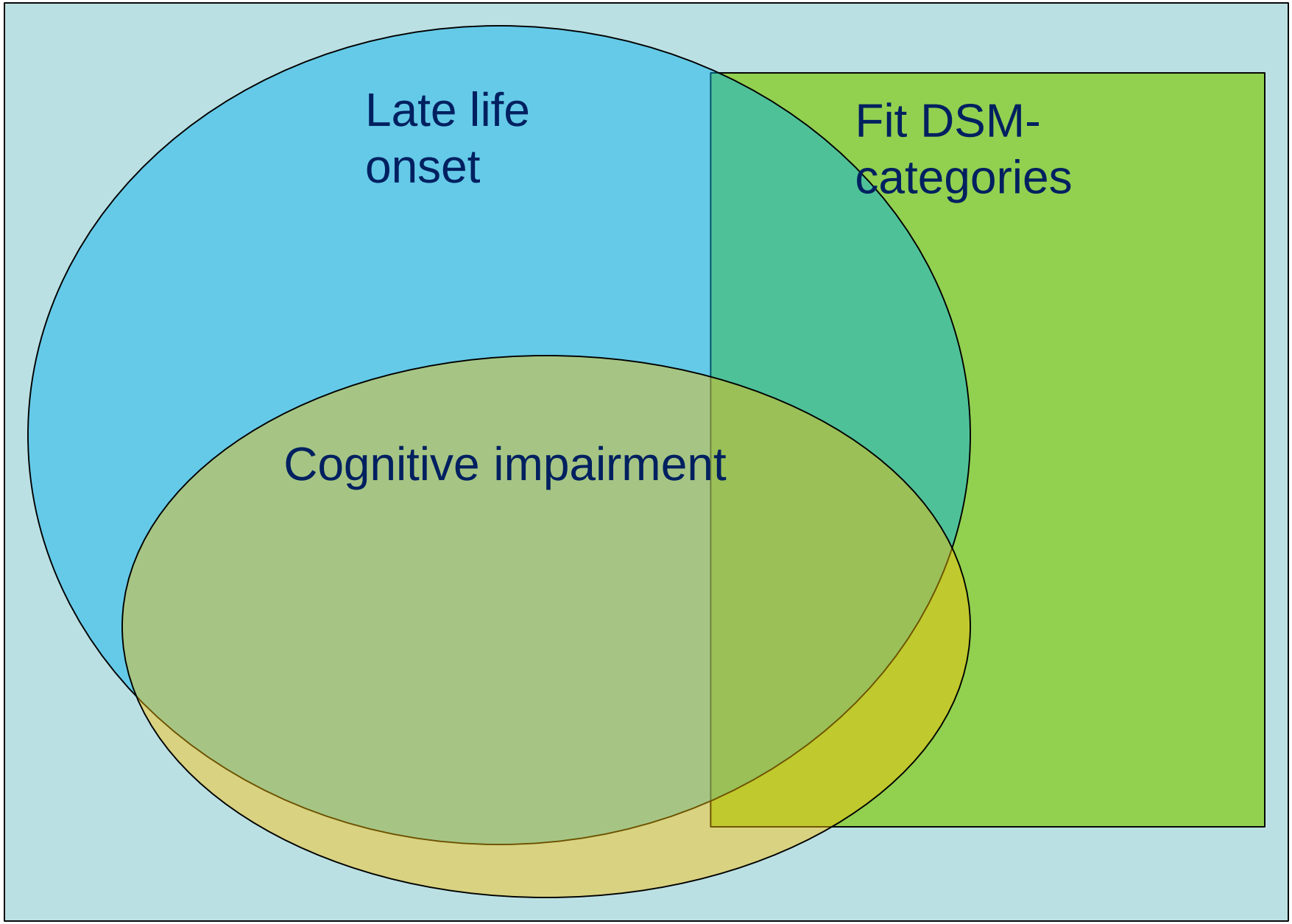
- ~45% of older adults report current NPS
- ~25% criteria for Mental Disorder by APA's Diagnostic & Statistical Manual (DSM)
- 2nd peak of mood disorder incidence~55y.o.
- Presentations often differ from earlier life
  - 30-40% of mood disorders "without sadness"
- Closely linked to cognitive decline
  - 40-60% of mood disorders with cognitive decline

Important observations

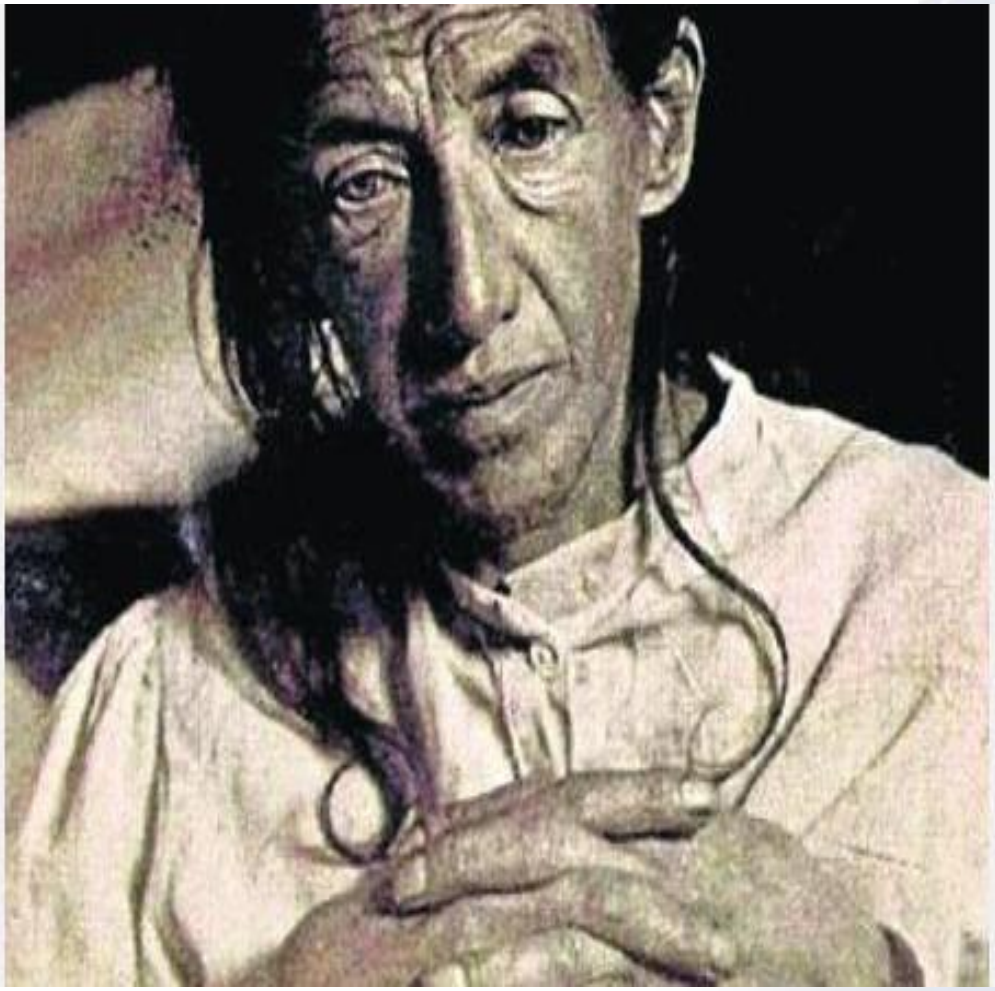
- ½ do not fit traditional DSM phenotypes
- ½ comorbid with cognitive syndromes

- Two groups
  - Persistence/recurrence of early onset “DSM” disorders
  - Late life onset of “atypical” disorders
- New etiologies: brain conditions of later life
  - Cerebrovascular disease
  - Neurodegenerative disease (AD, PD+, etc.)

Mental disorders occurring in later life

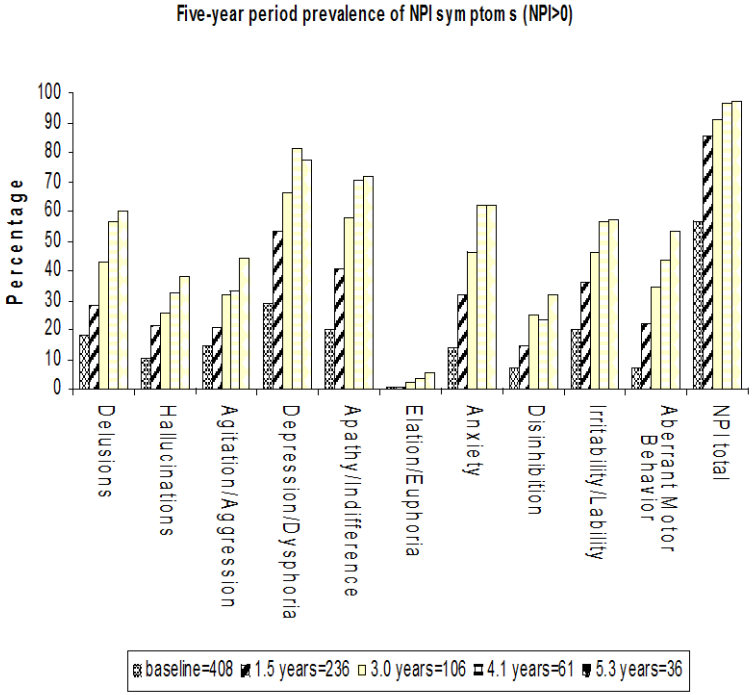


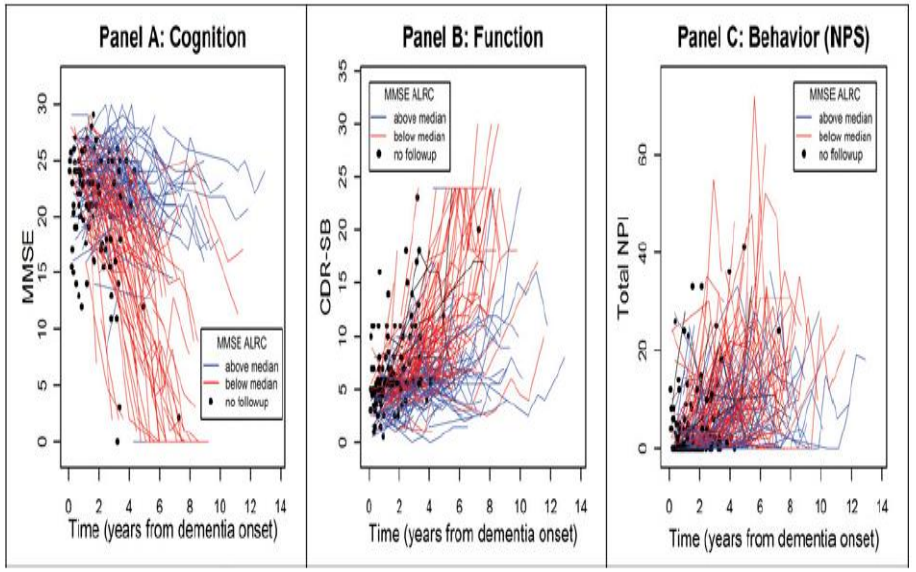
August D: hospitalized for delusions and change in personality, not cognitive impairment



NPS are UNIVERSAL (97%) & fluctuate

Cache County Dementia Progression Study





Steinberg et al, Int J Ger Psychiatry 2008

Tschanz et al, Am J Geriatr Psychiatry 2012

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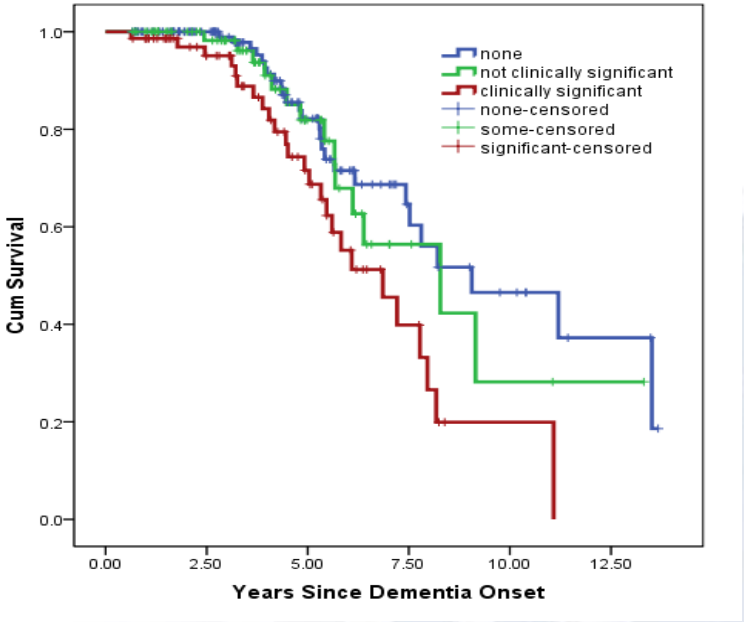
NPS are “bad” for patients & caregivers

- Greater ADL impairment[1]
- Worse quality of life[2]
- Earlier institutionalization[3]
- Major source of burden[4]
- Higher costs[5]
- Faster to severe dementia[6]
- Accelerated mortality[6]



[1]Lyketsos et al, 1997; [2]Gonzales-Salvador et al, 1999; [3]Steele et al, 1990;

[4]Lyketsos et al, 1999; [5] Murman et al, 2002; [6] Peters et al, 2015

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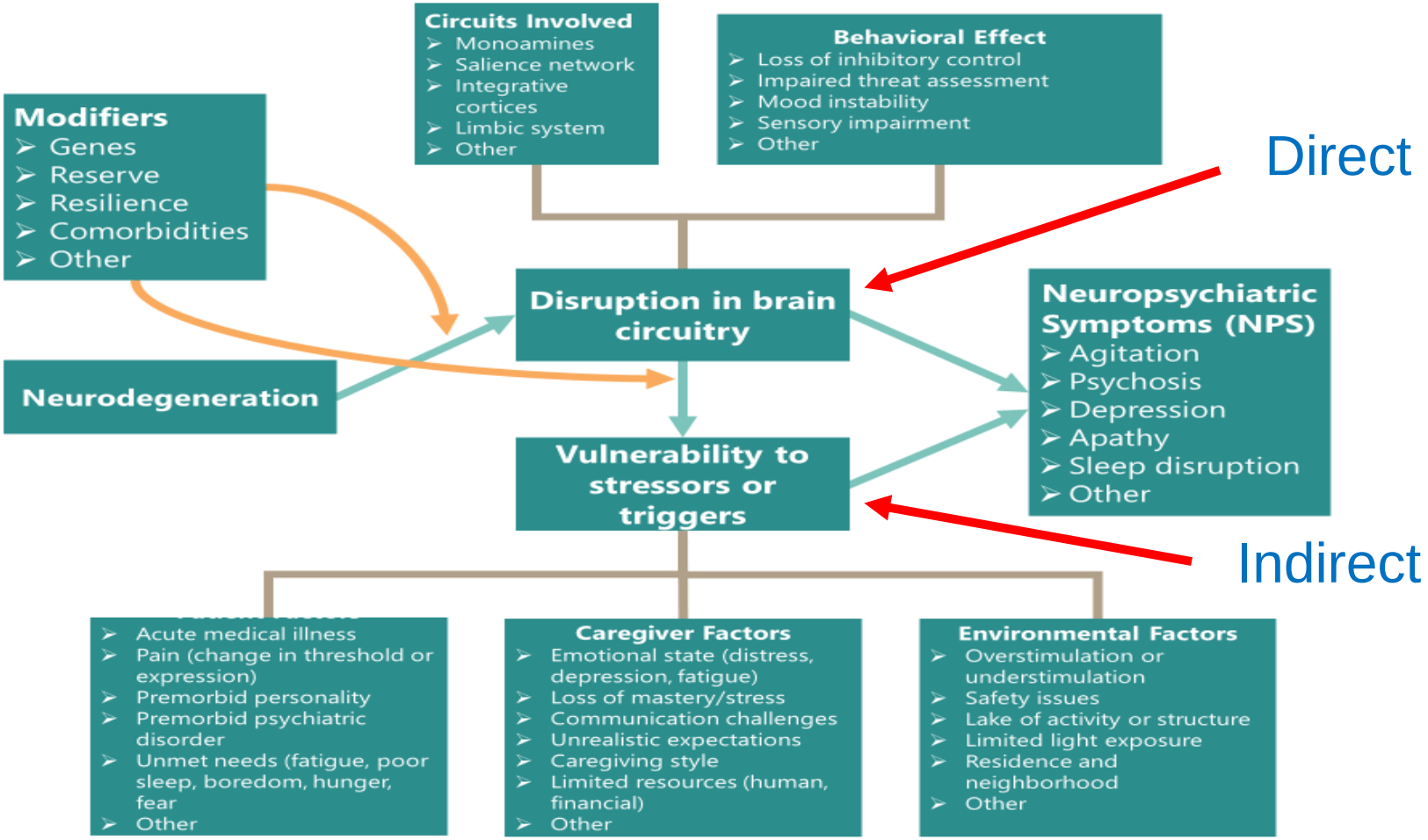
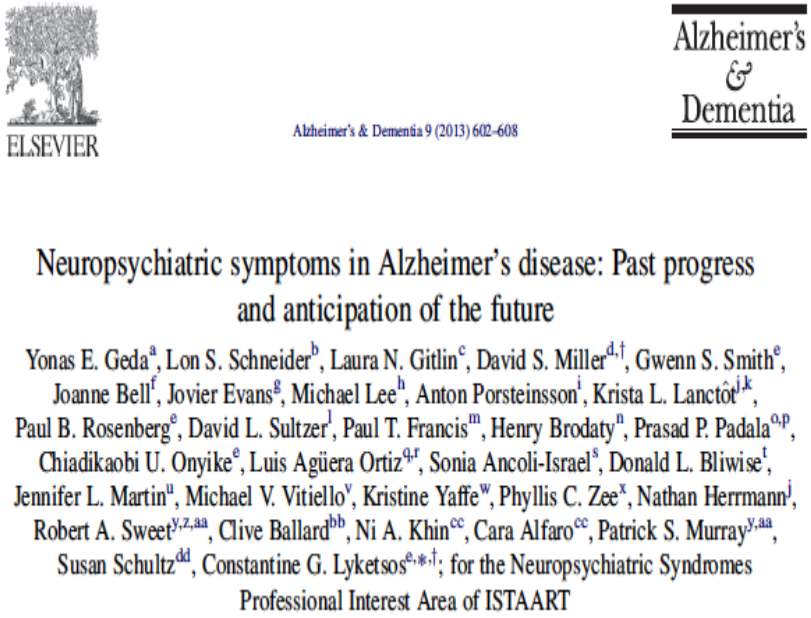
Etiologies of NPS



British Medical Journal 2015; NIMH/NIA Panel May 2017

Three *(overlapping)* neurobiological models proposed by the ISTAART NPS-PIA



ELSEVIER

Alzheimer's & Dementia 9 (2013) 602-608

Alzheimer's & Dementia

Neuropsychiatric symptoms in Alzheimer's disease: Past progress and anticipation of the future

Yonas E. Geda[a], Lon S. Schneider[b], Laura N. Gitlin[c], David S. Miller[d,†], Gwenn S. Smith[e], Joanne Bell[f], Jovier Evans[g], Michael Lee[h], Anton Porsteinsson[i], Krista L. Lanctôt[j,k], Paul B. Rosenberg[e], David L. Sultzer[l], Paul T. Francis[m], Henry Brodaty[n], Prasad P. Padala[o,p], Chiadikaobi U. Onyike[e], Luis Agüera Ortiz[q,r], Sonia Ancoli-Israel[s], Donald L. Bliwise[t], Jennifer L. Martin[u], Michael V. Vitiello[v], Kristine Yaffe[w], Phyllis C. Zee[x], Nathan Herrmann[j], Robert A. Sweet[y,z,aa], Clive Ballard[bb], Ni A. Khin[cc], Cara Alfaro[cc], Patrick S. Murray[y,aa], Susan Schultz[dd], Constantine G. Lyketsos[e,*,†]; for the Neuropsychiatric Syndromes Professional Interest Area of ISTAART

1. Fronto-subcortical circuit disruption
2. Cortico-cortical circuit disruption
3. Monoamine regulatory imbalance

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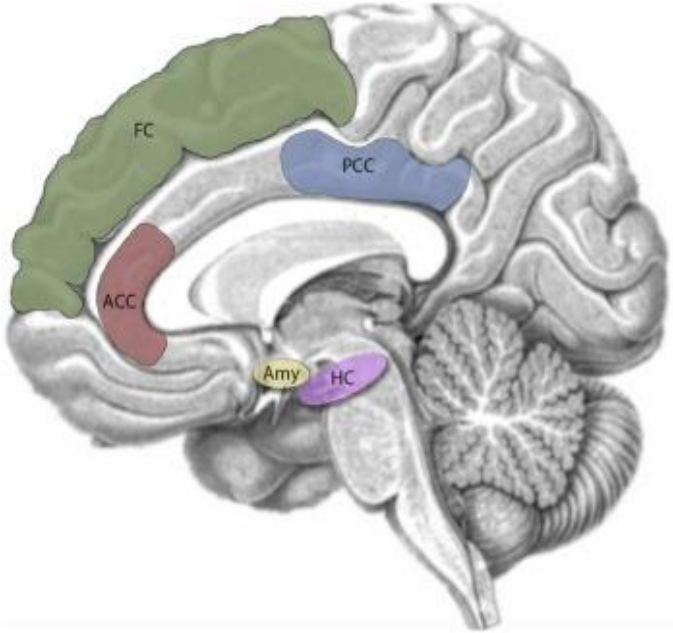
journal homepage: www.elsevier.com/locate/mam

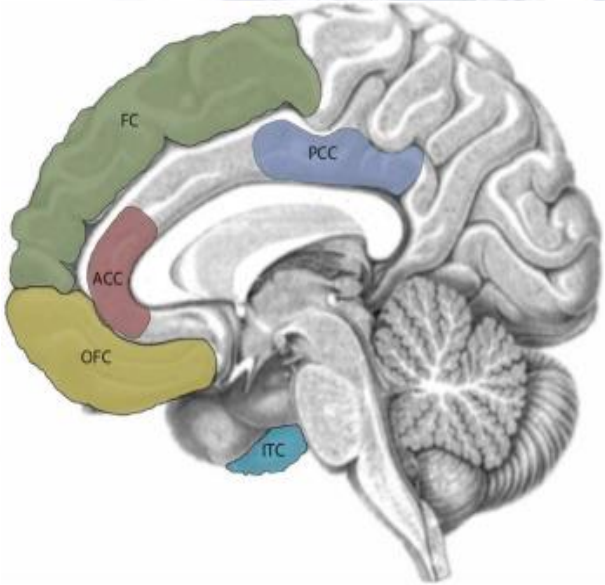
Review

Neuropsychiatric symptoms in Alzheimer's disease: What might be associated brain circuits?

Paul B. Rosenberg *, Milap A. Nowrangi, Constantine G. Lyketsos

Department of Psychiatry and Behavioral Sciences, Division of Geriatric Psychiatry and Neuropsychiatry, Johns Hopkins School of Medicine, USA





Agitation circuit

Apathy circuit

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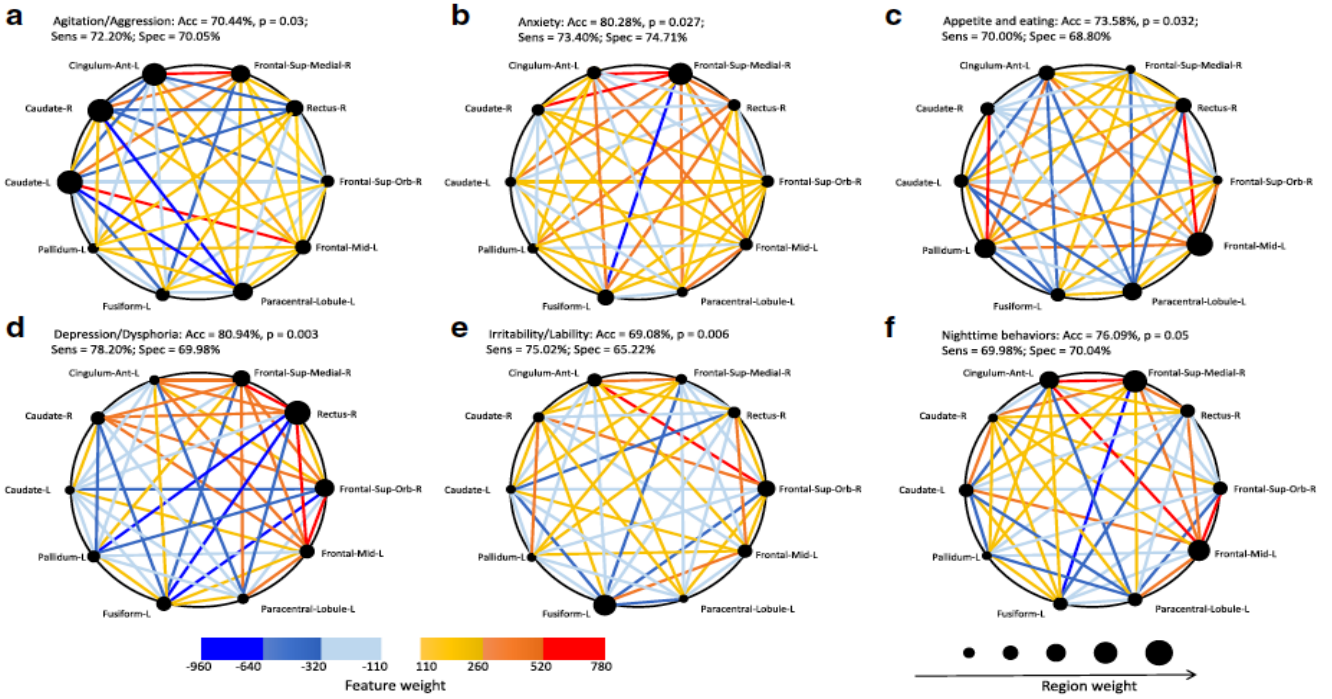
Brain Imaging and Behavior
DOI 10.1007/s11682-017-9767-y

ORIGINAL RESEARCH

Identify a shared neural circuit linking multiple neuropsychiatric symptoms with Alzheimer's pathology

Xixi Wang[1] · Ping Ren[2] · Mark Mapstone[3] · Yeates Conwell[4] · Anton P. Porsteinsson[4] · John J. Foxe[5] · Rajeev D. S. Raizada[6] · Feng Lin[2,4,5,6] · and the Alzheimer's Disease Neuroimaging Initiative



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Monoamine regulatory imbalance

J Alzheimers Dis. 2014;41(3):819-33. doi: 10.3233/JAD-140309.

Brain region-specific monoaminergic correlates of neuropsychiatric symptoms in Alzheimer's disease.

Vermeiren Y[1], Van Dam D[1], Aerts T[1], Engelborghs S[2], De Deyn PP[3].

Neuropsychologia. 2005;43(3):442-9.

Cholinergic-serotonergic imbalance contributes to cognitive and behavioral symptoms in Alzheimer's disease.

Garcia-Alloza M[1], Gil-Bea FJ, Diez-Ariza M, Chen CP, Francis PT, Lasheras B, Ramirez MJ.

Arch Neurol. 2004 Aug;61(8):1249-53.

Association of the serotonin transporter and receptor gene polymorphisms in neuropsychiatric symptoms in Alzheimer disease.

Assal F[1], Alarcón M, Solomon EC, Masterman D, Geschwind DH, Cummings JL.

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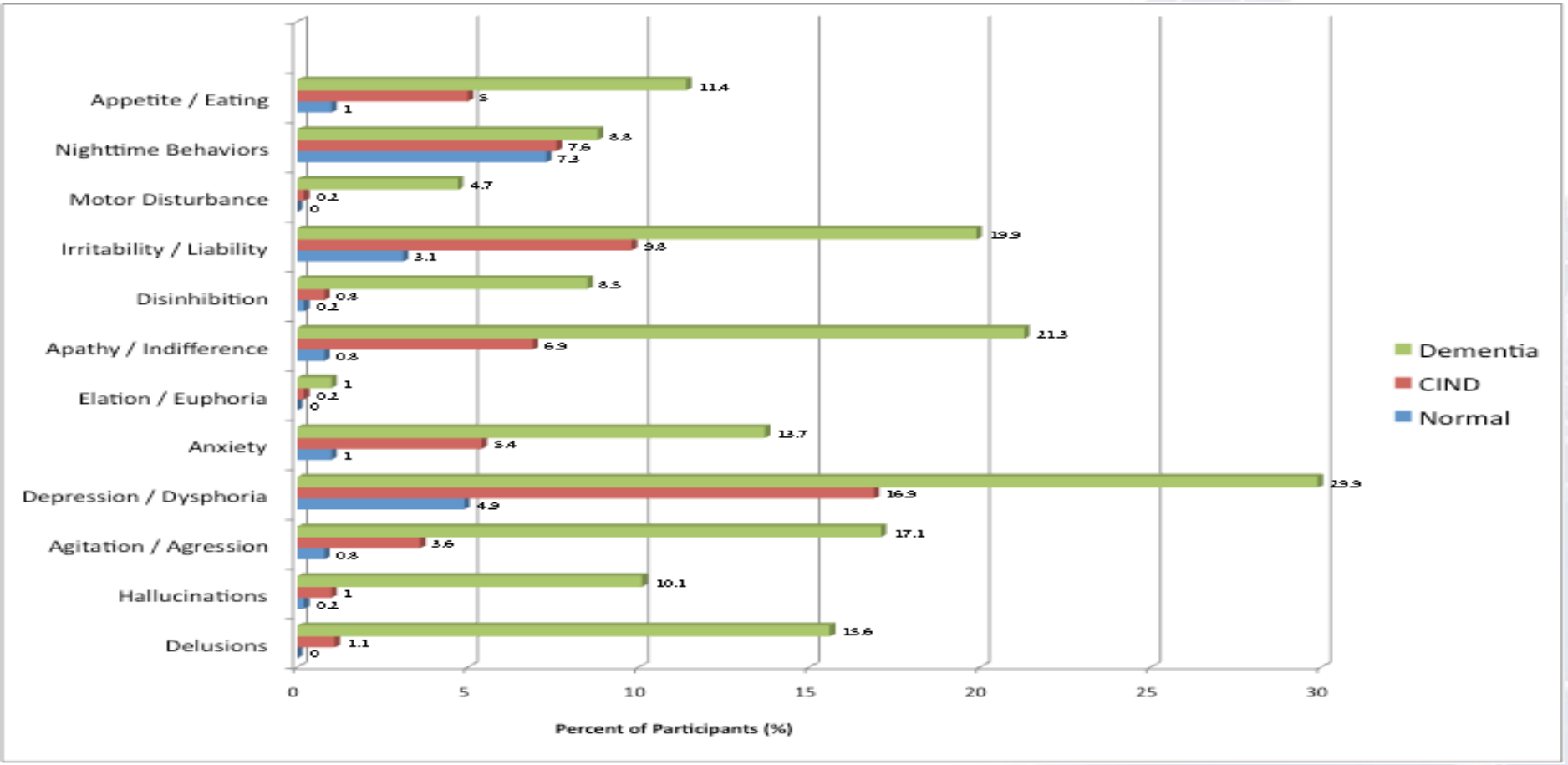
NPS are common in MCI

Cache County Memory Study



Peters et al, AJGP 2011

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Depression in MCI: 57 studies, N=20,892

Omnibus prevalence 32% (25% community, 40% clinical)

Zahinoor Ismail, MD; Hoba Elbayoumi, BScPharm; Corinne E. Fischer, MD; David B. Hogan, MD; Colleen P. Millikin, PhD; Tom Schweizer, PhD; Moyra E. Mortby, PhD; Eric E. Smith, MD; Scott B. Patten, MD, PhD; Kirsten M. Fiest, PhD

IMPORTANCE Depression is common in individuals with mild cognitive impairment (MCI) and may confer a higher likelihood of progression to dementia. Prevalence estimates of depression in those with MCI are required to guide both clinical decisions and public health policy, but published results are variable and lack precision.

OBJECTIVE To provide a precise estimate of the prevalence of depression in individuals with MCI and identify reasons for heterogeneity in the reported results.

DATA SOURCES A search of literature from database inception to March 2016 was performed using Medline, Embase, and PsycINFO. Hand searching of all included articles was performed, including a Google Scholar search of citations of included articles.

STUDY SELECTION Articles were included if they (1) were published in English, (2) reported patients with MCI as a primary study group, (3) reported depression or depressive symptoms using a validated instrument, and (4) reported the prevalence of depression in patients with MCI.

DATA EXTRACTION AND SYNTHESIS All abstracts, full-text articles, and other sources were reviewed, with data extracted in duplicate. The overall prevalence of depression in patients with MCI was pooled using a random-effects model. Heterogeneity was explored using stratification and random-effects meta-regression.

MAIN OUTCOMES AND MEASURES The prevalence of depression in patients with MCI, reported as a percentage with 95% CIs. Estimates were also stratified by population source (community-based or clinic-based sample), method of depression diagnosis (clinician-administered, informant-based, or self-report), and method of MCI diagnosis (cognitive vs global measure and amnestic vs nonamnestic).

RESULTS Of 5687 unique abstracts, 255 were selected for full-text review, and 57 studies, representing 20 892 patients, met all inclusion criteria. The overall pooled prevalence of depression in patients with MCI was 32% (95% CI, 27-37), with significant heterogeneity between estimates (I^2 = 90.7%). When stratified by source, the prevalence of depression in patients with MCI in community-based samples was 25% (95% CI, 19-30) and was 40% (95% CI, 32-48) in clinic-based samples, which was significantly different ($P < .001$). The method used to diagnose depression did not significantly influence the prevalence estimate, nor did the criteria used for MCI diagnosis or MCI subtype.

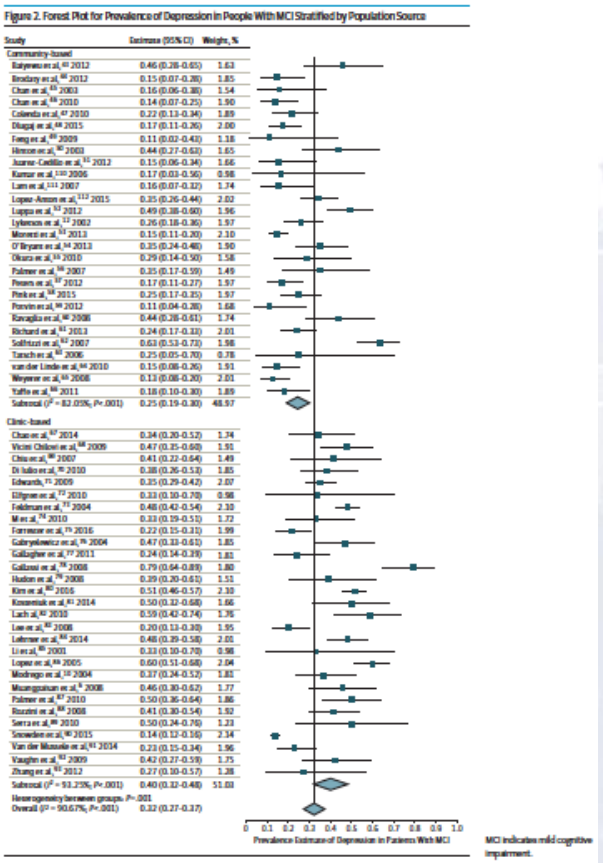
CONCLUSIONS AND RELEVANCE The prevalence of depression in patients with MCI is high. A contributor to heterogeneity in the reported literature is the source of the sample, with greater depression burden prevalent in clinic-based samples.

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Zahinoor

Figure 2. Forest Plot for Prevalence of Depression in People With MCI Stratified by Population Source



MCI indicates mild cognitive impairment.

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NPS in MCI:
faster conversion to dementia

The Association of Neuropsychiatric Symptoms in MCI with Incident Dementia and Alzheimer Disease

Paul B. Rosenberg, M.D., Michelle M. Mielke, Ph.D., Brian S. Appleby, M.D., Esther S. Oh, M.D., Yonas E. Geda, M.D., Constantine G. Lyketsos, M.D. M.H.S.

Objectives: *Individuals with mild cognitive impairment (MCI) are at high risk of developing dementia and/or Alzheimer disease (AD). Among persons with MCI, depression and anxiety have been associated with an increased risk of incident dementia. We examined whether neuropsychiatric symptoms in MCI increased the risk of incident dementia (all-cause) and incident AD.* **Design:** *Longitudinal cohort study followed annually (median: 1.58 years).* **Setting:** *National Alzheimer's Coordinating Center database combining clinical data from 29 Alzheimer's Disease Centers.* **Participants:** *A total of 1,821 participants with MCI.* **Measurements:** *1) Progression to dementia (all-cause) or AD, 2) Neuropsychiatric Inventory Questionnaire (NPI-Q), 3) Geriatric Depression Scale (GDS), 4) Clinical Dementia Rating Global Score and Sum of Boxes, and 5) Mini-Mental State Examination (MMSE). The association of covariates with risk of incident dementia or AD was evaluated with hazard ratios (HR) determined by Cox proportional-hazards models adjusted for age, ethnicity, Clinical Dementia Rating Global Score and Sum of Boxes, and MMSE.* **Results:** *A total of 527 participants (28.9%) progressed to dementia and 454 (24.9%) to AD. Baseline GDS > 0 was associated with an increased risk of incident dementia (HR: 1.47, 95% CI: 1.17–1.84) and AD (HR: 1.45, 95% CI: 1.14–1.83). Baseline NPI > 0 was associated with an increased risk of incident dementia (HR: 1.37, 95% CI: 1.12–1.66) and AD (HR: 1.35, 95% CI: 1.09–1.66).* **Conclusions:** *Neuropsychiatric symptoms in MCI are associated with significantly an increased risk of incident dementia and AD. Neuropsychiatric symptoms may be among the earliest symptoms of preclinical stages of AD and targeting them therapeutically might delay transition to dementia.* (Am J Geriatr Psychiatry 2013; 21:685–695)

Key Words: Alzheimer disease, dementia, depression, longitudinal study, mild cognitive impairment, neuropsychiatric symptoms

Neuropsychiatric Symptoms as Risk Factors for Progression From CIND to Dementia: The Cache County Study

M. E. Peters, M.D., P. B. Rosenberg, M.D., M. Steinberg, M.D., M. C. Norton, Ph.D., K. A. Welsh-Bohmer, Ph.D., K. M. Hayden, Ph.D., J. Breitner, M.D., M.P.H., J. T. Tschanz, Ph.D., C. G. Lyketsos, M.D., M.H.S., and the Cache County Investigato

Objectives: *To examine the association of neuropsychiatric symptom (NPS) severity with risk of transition to all-cause dementia, Alzheimer disease (AD), and vascular dementia (VaD).* **Design:** *Survival analysis of time to dementia, AD, or VaD onset.* **Setting:** *Population-based study.* **Participants:** *230 participants diagnosed with cognitive impairment, no dementia (CIND) from the Cache County Study of Memory Health and Aging were followed for a mean of 3.3 years.* **Measurements:** *The Neuropsychiatric Inventory (NPI) was used to quantify the presence, frequency, and severity of NPS. Chi-squared statistics, t-tests, and Cox proportional hazard ratios were used to assess associations.* **Results:** *The conversion rate from CIND to all-cause dementia was 12% per year, with risk factors including an* APOE *ε4 allele, lower Mini-Mental State Examination, lower 3MS, and higher CDR sum-of-boxes. The presence of at least one NPS was a risk factor for all-cause dementia, as was the presence of NPS with mild severity. Nighttime behaviors were a risk factor for all-cause dementia and of AD, whereas hallucinations were a risk factor for VaD.* **Conclusions:** *These data confirm that NPS are risk factors for conversion from CIND to dementia. Of special interest is that even NPS of mild severity are a risk for all-cause dementia or AD.* (Am J Geriatr Psychiatry 2012; 00:1–9)

Key Words: agitation, anxiety, Cache County, CIND, dementia, depression, MCI, NPS, NPI

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"pre-MCI"

MCI on clinical exam but normal cognitive testing

Pre-MCI and MCI: Neuropsychological, Clinical, and Imaging Features and Progression Rates

Ranjan Duara, M.D., David A. Loewenstein, Ph.D., Maria T. Greig, M.D., Elizabeth Potter, Ph.D., Warren Barker, M.S., Ashok Raj, M.D., John Schinka, Ph.D., Amy Borenstein, Ph.D., Michael Schoenberg, Ph.D., Yougui Wu, Ph.D., Jessica Banko, Ph.D., Huntington Potter, Ph.D.

Objective: *To compare clinical, imaging, and neuropsychological characteristics and longitudinal course of subjects with pre-mild cognitive impairment (pre-MCI), who exhibit features of MCI on clinical examination but lack impairment on neuropsychological examination, to subjects with no cognitive impairment (NCI), nonamnestic MCI (naMCI), amnestic MCI (aMCI), and mild dementia.* **Methods:** *For 369 subjects, clinical dementia rating sum of boxes (CDR-SB), ApoE genotyping, cardiovascular risk factors, parkinsonism (UPDRS) scores, structural brain MRIs, and neuropsychological testing were obtained at baseline, whereas 275 of these subjects received an annual follow-up for 2–3 years.* **Results:** *At baseline, pre-MCI subjects showed impairment on tests of executive function and language, higher apathy scores, and lower left hippocampal volumes (HPCV) in comparison to NCI subjects. Pre-MCI subjects showed less impairment on at least one memory measure, CDR-SB and UPDRS scores, in comparison to naMCI, aMCI and mild dementia subjects. Follow-up over 2–3 years showed 28.6% of pre-MCI subjects, but less than 5% of NCI subjects progressed to MCI or dementia. Progression rates to dementia were equivalent between naMCI (22.2%) and aMCI (34.5%) groups, but greater than for the pre-MCI group (2.4%). Progression to dementia was best predicted by the CDR-SB, a list learning and executive function test.* **Conclusion:** *This study demonstrates that clinically defined pre-MCI has cognitive, functional, motor, behavioral and imaging features that are intermediate between NCI and MCI states at baseline. Pre-MCI subjects showed*

- N=369
- Apathy associated with higher incidence of MCI at 2-3 years

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“pre MCI” Alzheimer’s

Subjective Cognitive Concerns and Neuropsychiatric Predictors of Progression to the Early Clinical Stages of Alzheimer Disease

Nancy J. Donovan, M.D., Rebecca E. Amariglio, Ph.D., Amy S. Zoller, B.A., Rebecca K. Rudel, B.A., Teresa Gomez-Isla, M.D., Deborah Blacker, M.D., Sc.D., Bradley T. Hyman, M.D., Ph.D., Joseph J. Locascio, Ph.D., Keith A. Johnson, M.D., Reisa A. Sperling, M.D., Gad A. Marshall, M.D., Dorene M. Rentz, Psy.D.

Objective: *To examine neuropsychiatric and neuropsychological predictors of progression from normal to early clinical stages of Alzheimer disease (AD).* **Methods:** *From a total sample of 559 older adults from the Massachusetts Alzheimer's Disease Research Center longitudinal cohort, 454 were included in the primary analysis: 283 with clinically normal cognition (CN), 115 with mild cognitive impairment (MCI), and 56 with subjective cognitive concerns (SCC) but no objective impairment, a proposed transitional group between CN and MCI. Two latent cognitive factors (memory-semantic, attention-executive) and two neuropsychiatric factors (affective, psychotic) were derived from the Alzheimer's Disease Centers' Uniform Data Set neuropsychological battery and Neuropsychiatric Inventory brief questionnaire. Factors were analyzed as predictors of time to progression to a worse diagnosis using a Cox proportional hazards regression model with backward elimination. Covariates included baseline diagnosis, gender, age, education, prior depression, antidepressant medication, symptom duration, and interaction terms.* **Results:** *Higher/better memory-semantic factor score predicted lower hazard of progression (hazard ratio [HR] = 0.4 for 1 standard deviation [SD] increase, $p < 0.0001$), and higher/worse affective factor score predicted higher hazard (HR = 1.3 for one SD increase, $p = 0.01$). No other predictors were significant in adjusted analyses. Using diagnosis as a sole predictor of transition to MCI, the SCC diagnosis carried a fourfold risk of progression compared with CN (HR = 4.1, $p < 0.0001$).* **Conclusion:** *These results*

- n=454
- Depression, irritability and agitation predicted more rapid progression to a worse diagnosis across all groups

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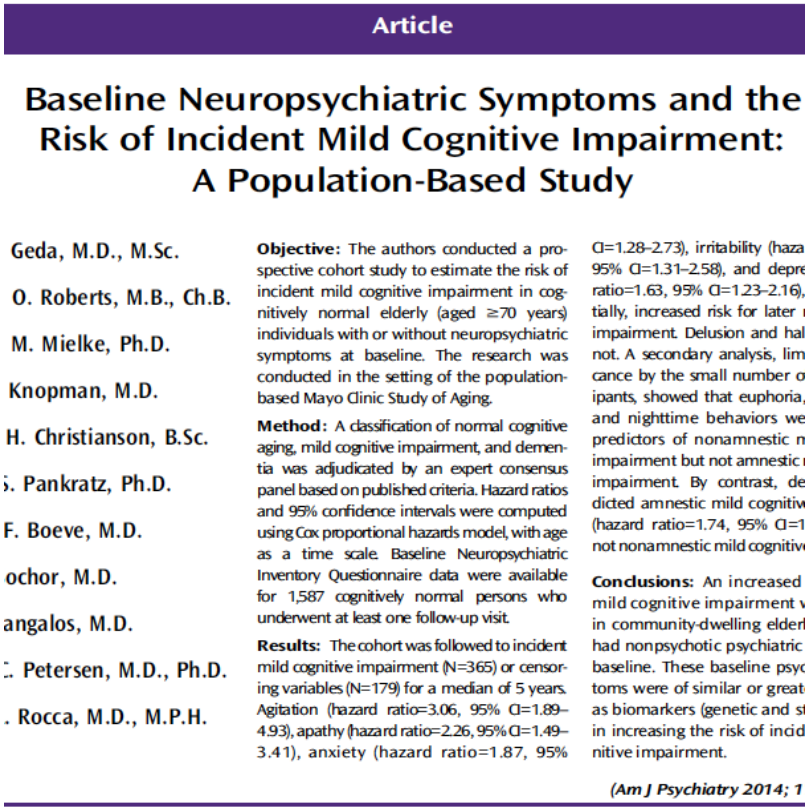
NPS in cognitive “normals”



Article

Baseline Neuropsychiatric Symptoms and the Risk of Incident Mild Cognitive Impairment: A Population-Based Study

Geda, M.D., M.Sc.
O. Roberts, M.B., Ch.B.
M. Mielke, Ph.D.
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H. Christianson, B.Sc.
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F. Boeve, M.D.
ochor, M.D.
angalos, M.D.
. Petersen, M.D., Ph.D.
. Rocca, M.D., M.P.H.

Objective: The authors conducted a prospective cohort study to estimate the risk of incident mild cognitive impairment in cognitively normal elderly (aged ≥70 years) individuals with or without neuropsychiatric symptoms at baseline. The research was conducted in the setting of the population-based Mayo Clinic Study of Aging.

Method: A classification of normal cognitive aging, mild cognitive impairment, and dementia was adjudicated by an expert consensus panel based on published criteria. Hazard ratios and 95% confidence intervals were computed using Cox proportional hazards model, with age as a time scale. Baseline Neuropsychiatric Inventory Questionnaire data were available for 1,587 cognitively normal persons who underwent at least one follow-up visit.

Results: The cohort was followed to incident mild cognitive impairment (N=365) or censoring variables (N=179) for a median of 5 years. Agitation (hazard ratio=3.06, 95% CI=1.89–4.93), apathy (hazard ratio=2.26, 95% CI=1.49–3.41), anxiety (hazard ratio=1.87, 95% CI=1.28–2.73), irritability (haza
95% CI=1.31–2.58), and depre
ratio=1.63, 95% CI=1.23–2.16),
tially, increased risk for later
impairment. Delusion and hal
not. A secondary analysis, lim
cance by the small number o
ipants, showed that euphoria,
and nighttime behaviors we
predictors of nonamnestic n
impairment but not amnestic
impairment. By contrast, de
dicted amnestic mild cognitiv
(hazard ratio=1.74, 95% CI=1
not nonamnestic mild cognitiv

Conclusions: An increased
mild cognitive impairment
in community-dwelling elder
had nonpsychotic psychiatric
baseline. These baseline psyc
toms were of similar or great
as biomarkers (genetic and s
in increasing the risk of incid
nitive impairment.

(Am J Psychiatry 2014; 1

- N=1587
- NPS higher risk of MCI
  - Agitation HR=3.06
  - Anxiety HR= 1.87
  - Irritability HR=1.84
  - Depression HR=1.63

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“early anxiety and depression may be the harbingers of future cognitive decline”

EXTRA Dementia and Geriatric Cognitive Disorders

Dement Geriatr Cogn Disord Extra 2014;4:509–516
DOI: 10.1159/000357775
Published online: December 18, 2014

1664–5464/14/0043–0509$39.50/0
www.karger.com/dee

Karger Open access

Original Research Article

The Alzheimer’s Disease Cooperative Study Prevention Instrument Project: Longitudinal Outcome of Behavioral Measures as Predictors of Cognitive Decline

Sarah Jane Banks[a] Rema Raman[b] Feng He[b] David P. Salmon[b]
Steven Ferris[c] Paul Aisen[b] Jeffrey Cummings[a]

[a]Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas, Nev., [b]University of California, San Diego, Calif., and [c]New York University Langone Medical Center, New York, N.Y., USA

Key Words
Aging · Depression · Anxiety · Mild cognitive impairment · Alzheimer’s disease

Abstract
Background/Methods: The Alzheimer’s Disease Cooperative Study Prevention Instrument Project is a longitudinal study that recruited 644 cognitively healthy older subjects (aged between 75 and 93 years, 58% women) at baseline and evaluated their cognitive change over 4 years. The study was structured like a clinical trial to anticipate a prevention trial and to determine the performance of novel trial instruments in a longitudinal non-interventional trial framework. Behavioral symptoms were assessed at baseline. ***Results:*** The existence of participant-reported behavioral symptoms at baseline predicted conversion to Clinical Dementia Rating scale score ≥0.5 over the 4-year period. ***Conclusions:*** The results imply that early anxiety and depression may be harbingers of future cognitive decline, and that patients exhibiting such symptoms, even in the absence of co-occurring cognitive symptoms, should be closely followed over time.

- n=644
- Anxiety and depression predicted conversion to CDR ≥0.5 over 4-year follow up period

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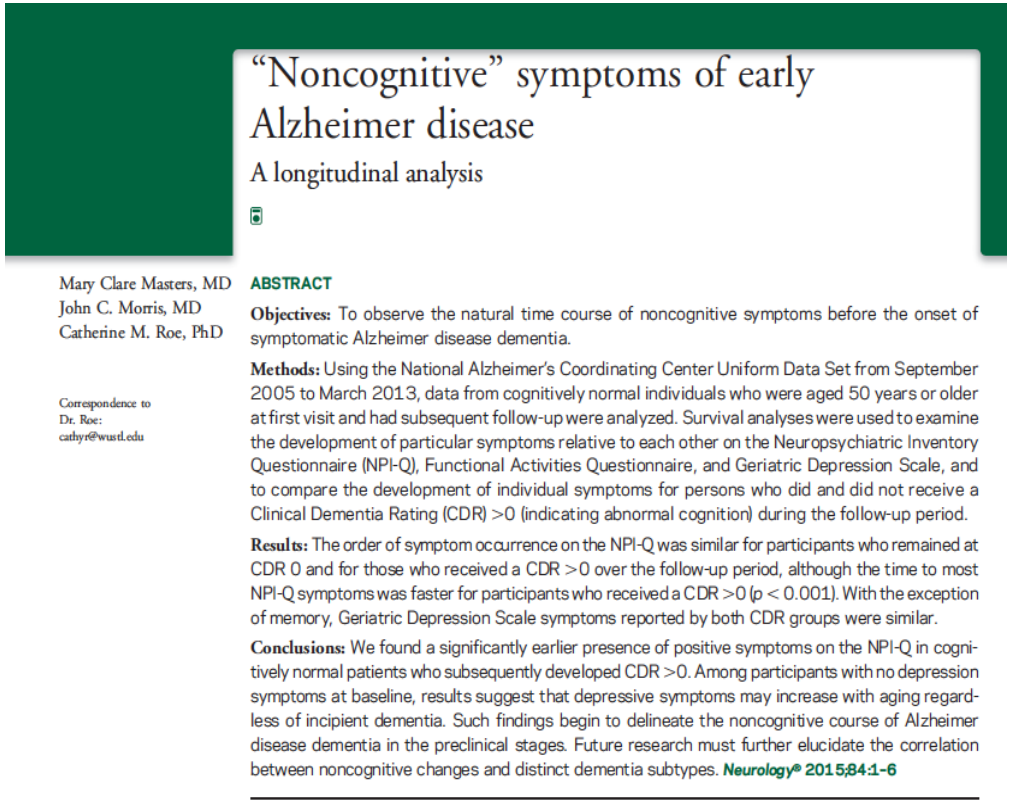
“Non-cognitive” AD



“Noncognitive” symptoms of early Alzheimer disease

A longitudinal analysis

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ABSTRACT

Objectives: To observe the natural time course of noncognitive symptoms before the onset of symptomatic Alzheimer disease dementia.

Methods: Using the National Alzheimer's Coordinating Center Uniform Data Set from September 2005 to March 2013, data from cognitively normal individuals who were aged 50 years or older at first visit and had subsequent follow-up were analyzed. Survival analyses were used to examine the development of particular symptoms relative to each other on the Neuropsychiatric Inventory Questionnaire (NPI-Q), Functional Activities Questionnaire, and Geriatric Depression Scale, and to compare the development of individual symptoms for persons who did and did not receive a Clinical Dementia Rating (CDR) >0 (indicating abnormal cognition) during the follow-up period.

Results: The order of symptom occurrence on the NPI-Q was similar for participants who remained at CDR 0 and for those who received a CDR >0 over the follow-up period, although the time to most NPI-Q symptoms was faster for participants who received a CDR >0 ($p < 0.001$). With the exception of memory, Geriatric Depression Scale symptoms reported by both CDR groups were similar.

Conclusions: We found a significantly earlier presence of positive symptoms on the NPI-Q in cognitively normal patients who subsequently developed CDR >0. Among participants with no depression symptoms at baseline, results suggest that depressive symptoms may increase with aging regardless of incipient dementia. Such findings begin to delineate the noncognitive course of Alzheimer disease dementia in the preclinical stages. Future research must further elucidate the correlation between noncognitive changes and distinct dementia subtypes. *Neurology*® 2015;84:1–6

- n=2416
- Earlier presence of NPS in NC who went on to develop a CDR>0

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Mild worry symptoms?

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Mild Worry Symptoms Predict Decline in Learning and Memory in Healthy Older Adults:

A 2-Year Prospective Cohort Study

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Abstract

Objective—Theoretical models of cognitive aging are increasingly recognizing the importance of anxiety and depressive symptoms in predicting age-related cognitive changes and early dementia. This study examined the association between mild worry and depressive symptoms, and cognitive function in healthy, community-dwelling older adults.

Method—A total of 263 healthy older adults participated in an observational prospective cohort study that assessed worry and depression symptoms, and a broad range of cognitive functions over a 2-year period.

Results—Older adults with mildly elevated worry symptoms at baseline performed worse than older adults with minimal worry symptoms on measures of visual and paired associate learning. They were also more likely to show clinically significant (> 1.5 standard deviation) decline in visual learning and memory at a 2-year follow-up assessment (9.4% versus 2.5%; odds ratio = 3.8).

Conclusion—Assessment of worry symptoms, even mild levels, may have utility in predicting early cognitive decline in healthy, community-dwelling older adults.

- N=263
- Mild worry more likely to show clinically significant decline in visual learning and memory at 2-year follow-up

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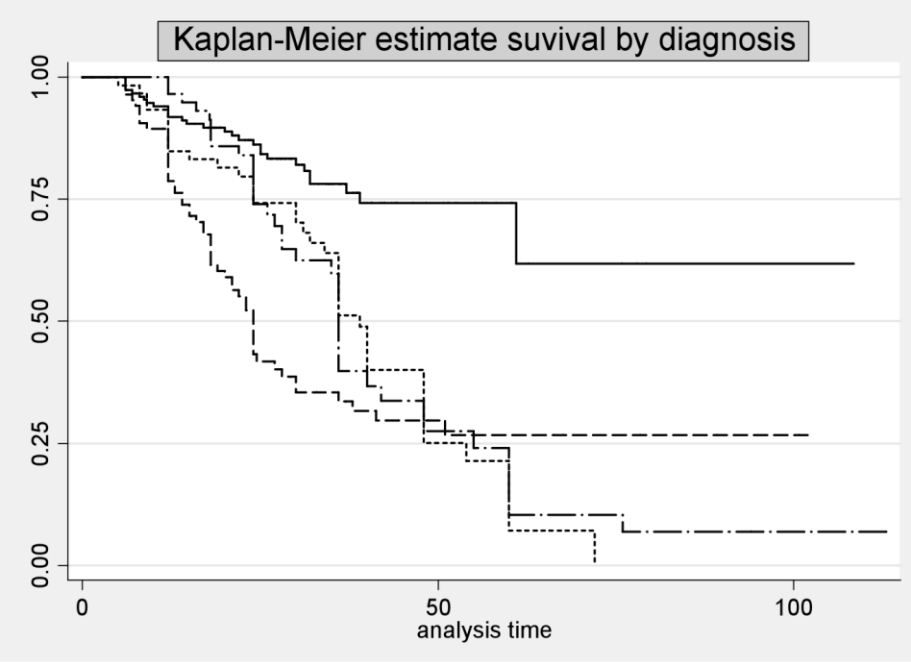
Mild Behavioral Impairment (MBI): stronger risk of dementia than MCI alone?



Type of dementia matters:

- MCI alone (n=154)
  - 28 (18%) dementia: 27 AD
- MCI with NPS (n=85)
  - 54 (63%): 37 AD and 15 FTD
- MBI with abnormal cognition (n=59)
  - 41 (69%): 25 AD and 12 FTD
- MBI normal cognition (n=60)
  - 44 (73%): 41 FTD and 3 AD

- 358 patients at CEMIC Buenos Aires, Argentina
- Referred to the memory clinic (collaborative)
- Followed for five years

Taragano et al, J Clinical Psychiatry, 2009

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The psychiatric flipside

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The diagnostic challenge of psychiatric symptoms in neurodegenerative disease; rates of and risk factors for prior psychiatric diagnosis in patients with early neurodegenerative disease

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Abstract

Objective—To identify rates of and risk factors for psychiatric diagnosis preceding the diagnosis of neurodegenerative disease (ND).

Method—Systematic, retrospective, blinded chart review of patients with a ND diagnosis [behavioral variant frontotemporal dementia (bvFTD n=69); Alzheimer's disease (AD n=65); semantic dementia (SemD n=41); progressive non-fluent aphasia (PNFA n=17); corticobasal degeneration (n=25); progressive supranuclear palsy (n=15); and amyotrophic lateral sclerosis (ALS n=20)].

Results—28.2% of patients with a ND received a prior psychiatric diagnosis. Depression was the most common psychiatric diagnosis in all groups. BvFTD patients received a prior psychiatric diagnosis significantly more often (52.2%) than patients with AD (23.1%), SemD (24.4%), or PNFA (11.8%), and were more likely to receive diagnoses of bipolar affective disorder or schizophrenia than patients with other NDs ($p<0.001$). Younger age, higher education and a family history of psychiatric illness increased the rate of prior psychiatric diagnosis in patients

- Neurodegenerative disease retrospective
- 28.2% initially had a psychiatric Dx

- FTD: 52.2%
- AD: 23.1%

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Alzheimer's & Dementia

Perspective

Neuropsychiatric symptoms as early manifestations of emergent dementia: Provisional diagnostic criteria for mild behavioral impairment

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MBI criteria: rationale

- NPS as prodrome of all dementias, not just bvFTD
- Provide clear operationalized criteria
- Define relationship between MBI and MCI
- Standardize assessment to identify target population
- Develop novel treatments based on these targets

ISTAART MBI Criteria

- Change in behavior or personality with onset after 50 years that persists for ≥6 months
- Five domains
  - Drive and Motivation
  - Mood and Affect
  - Impulse Control
  - Social Appropriateness
  - Thought and Perception
- IADL/ADL function maintained
- Impaired social, interpersonal, or workplace functioning
- Not due to “typical” psychiatric or medical illness or substance
- Dementia not present

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How to measure MBI

The Mild Behavioral Impairment Checklist (MBI-C): A rating scale for neuropsychiatric symptoms in pre-dementia populations

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What is your call?

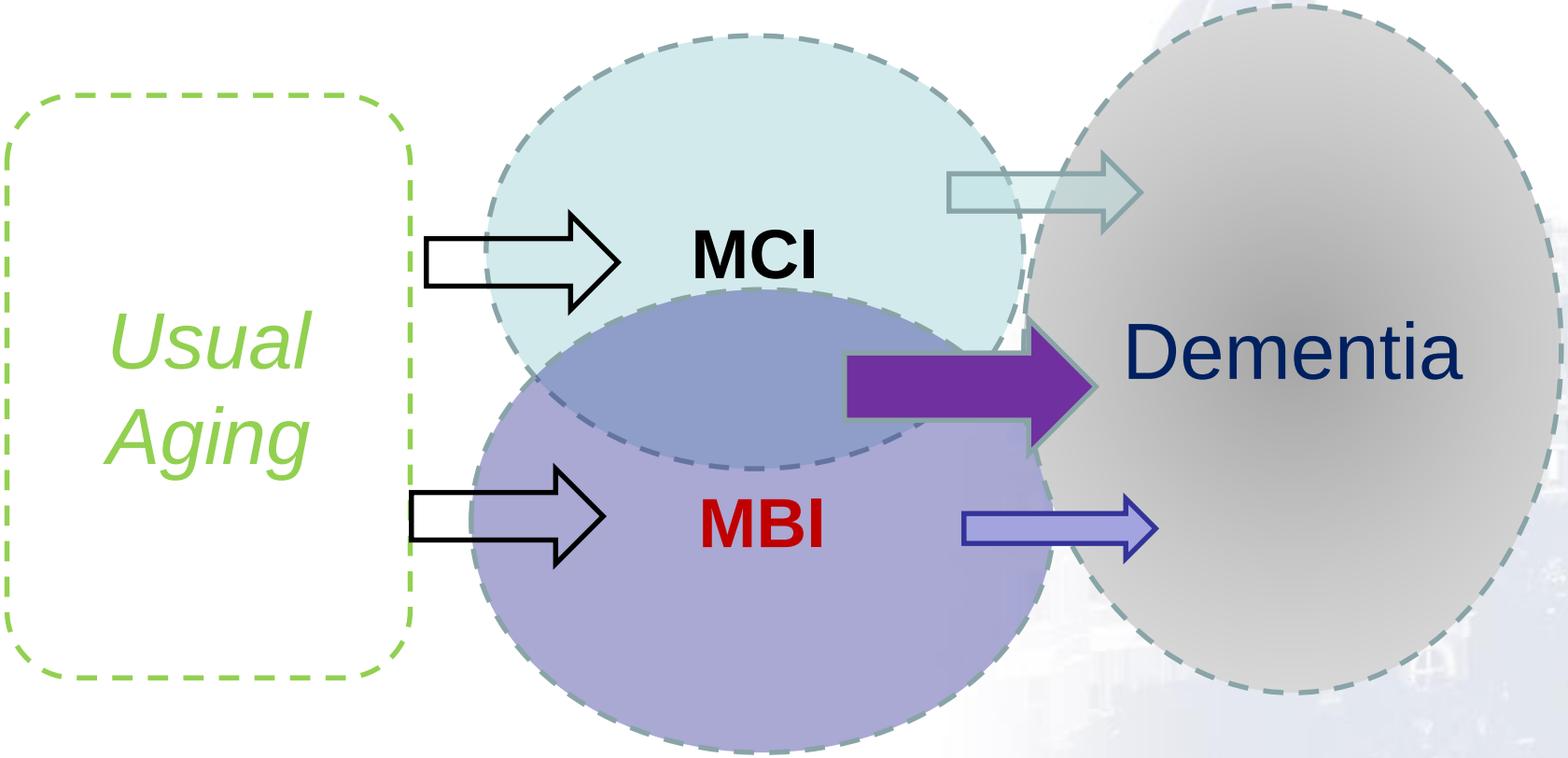
- Symptoms
- Prodrome
- False alarm

My call about MBI?

A dementia prodrome

- Partial overlap of behavioral & cognitive symptoms
- Discrete brain underpinnings for different symptoms

The theory: “Mild Behavioral Impairment (MBI)”



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Ultimate goals of proposing MBI

- Research into nature of later-life onset NPS with or without cognitive symptoms
- New treatment targets
- New approach to prevention

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Thank you!
Ευχαριστω!

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