

11.05.2022

המרכז הבינלאומי לכנסים
אקספו תל אביב



הכנס השנתי
של האיגוד הישראלי
לרפואה גריאטרית



הסתדרות
הרופאים הישראליים
Israel Medical
Association

Dementia And MCI: More Than Just Cognition

Oren Tene MD, Tel-Aviv Sourasky Medical Center

May 2022



TEL AVIV SOURASKY
MEDICAL CENTER
ICHILOV



Conflicts of interest

- Sponsored lecture: Dr. Samuelov



- Lecturer for: Janssen



- Advisory board: Lundbeck



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הכנס השנתי

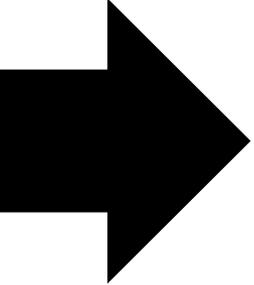
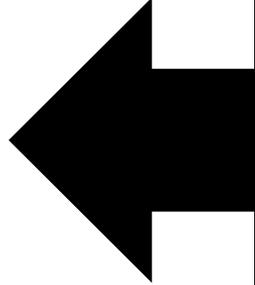
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לרפואה גריאטרית



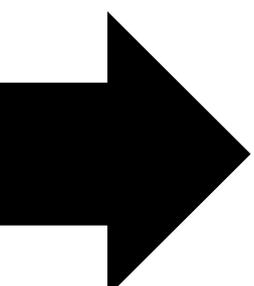
DR. SAMUELOV
BETTER PHARMA





- 
- “Many hands” are involved in cognition; different languages
 - MCI does **not** necessarily mean memory impairment
 - MCI is common, but if we won’t look for it – we won’t find it
 - We have very few treatment options for MCI
- 



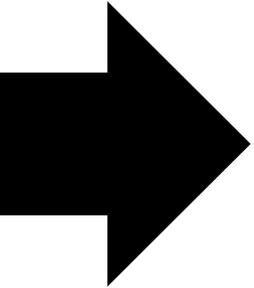
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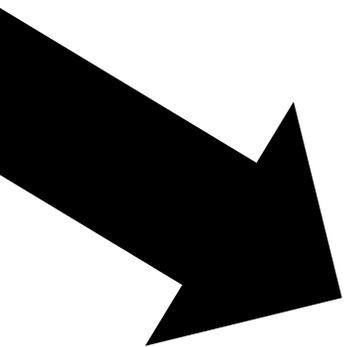


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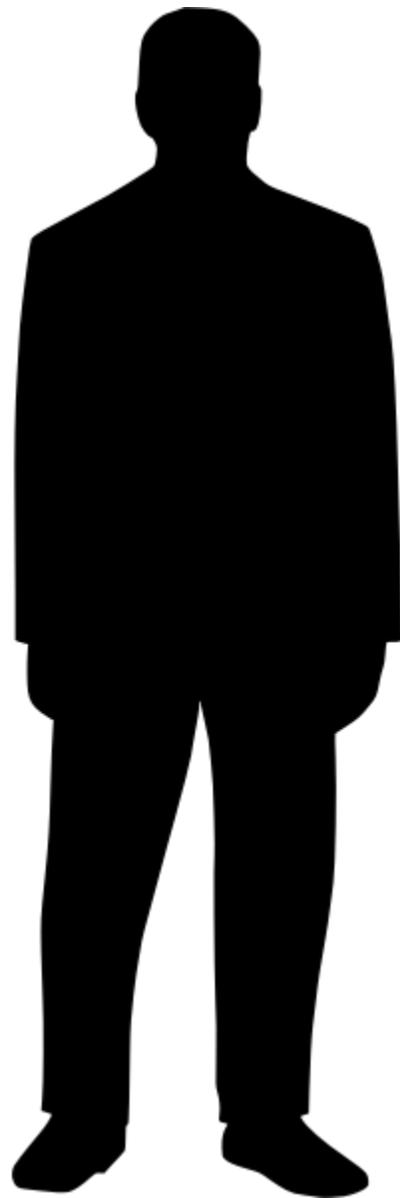


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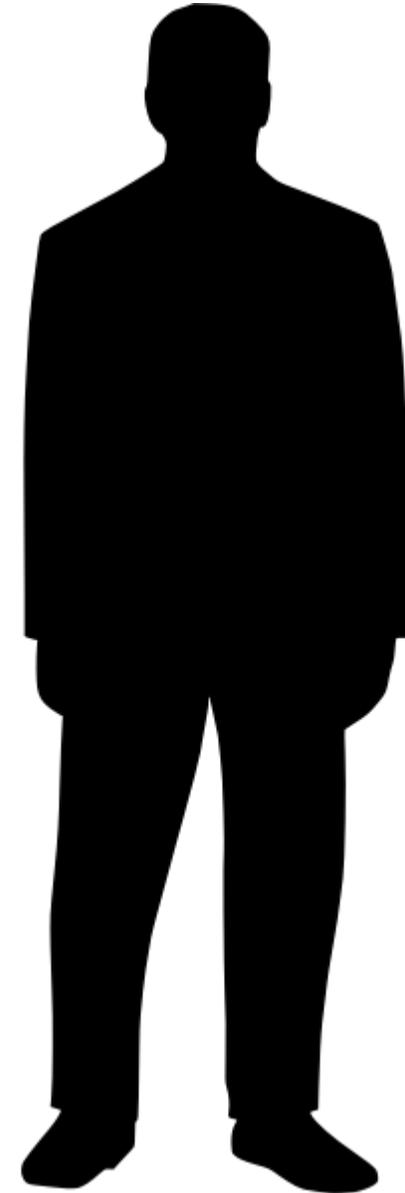


Mr. M



Mr. M

- 74, retired
- Brought in by his wife
- “He’s apathetic, stopped being interested in everything”
- He didn’t complain





Mrs. T



Mrs. T

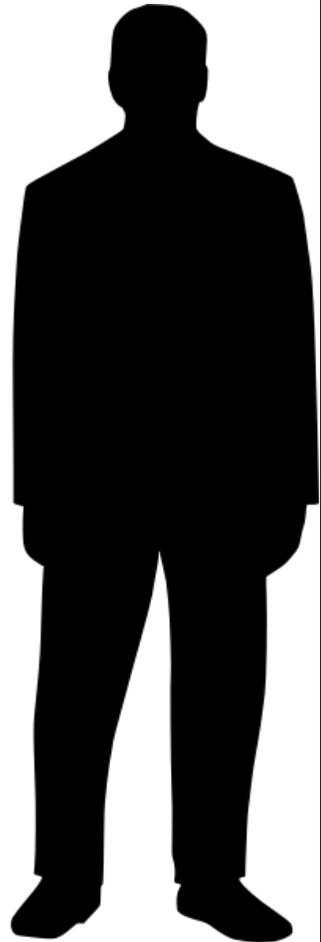
- 78, brought in by her daughter
- Doesn't sleep well, anxious and depressed for the 1st time in her life

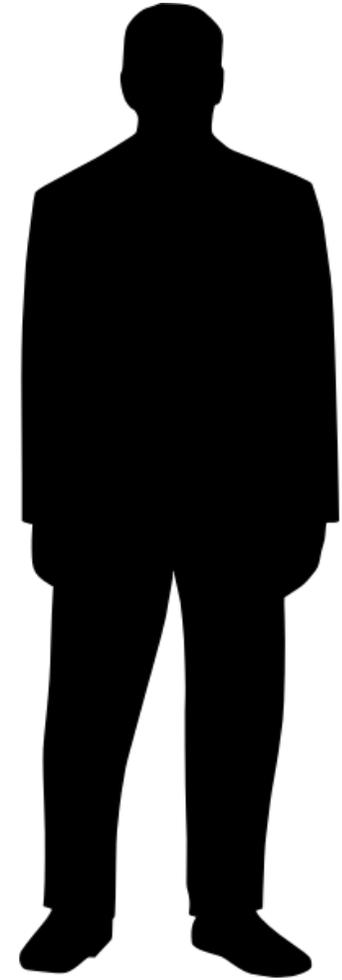


Mr. S

- 79, brought in by his son
- Religious man
- Started “talking dirty” to his sisters in law

What do the 3 of them have in common?



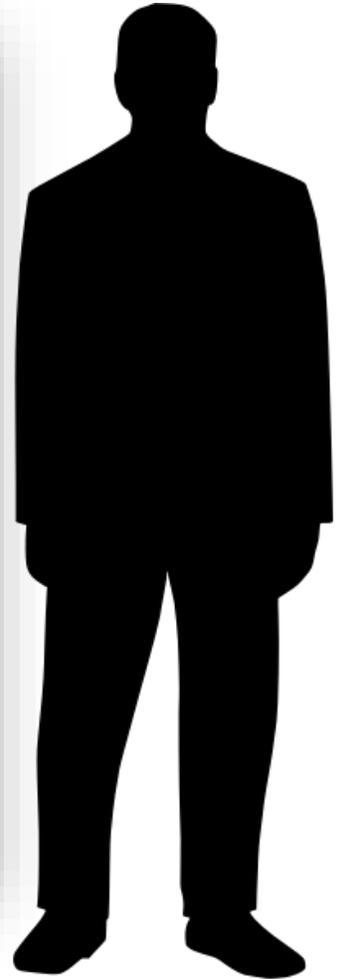
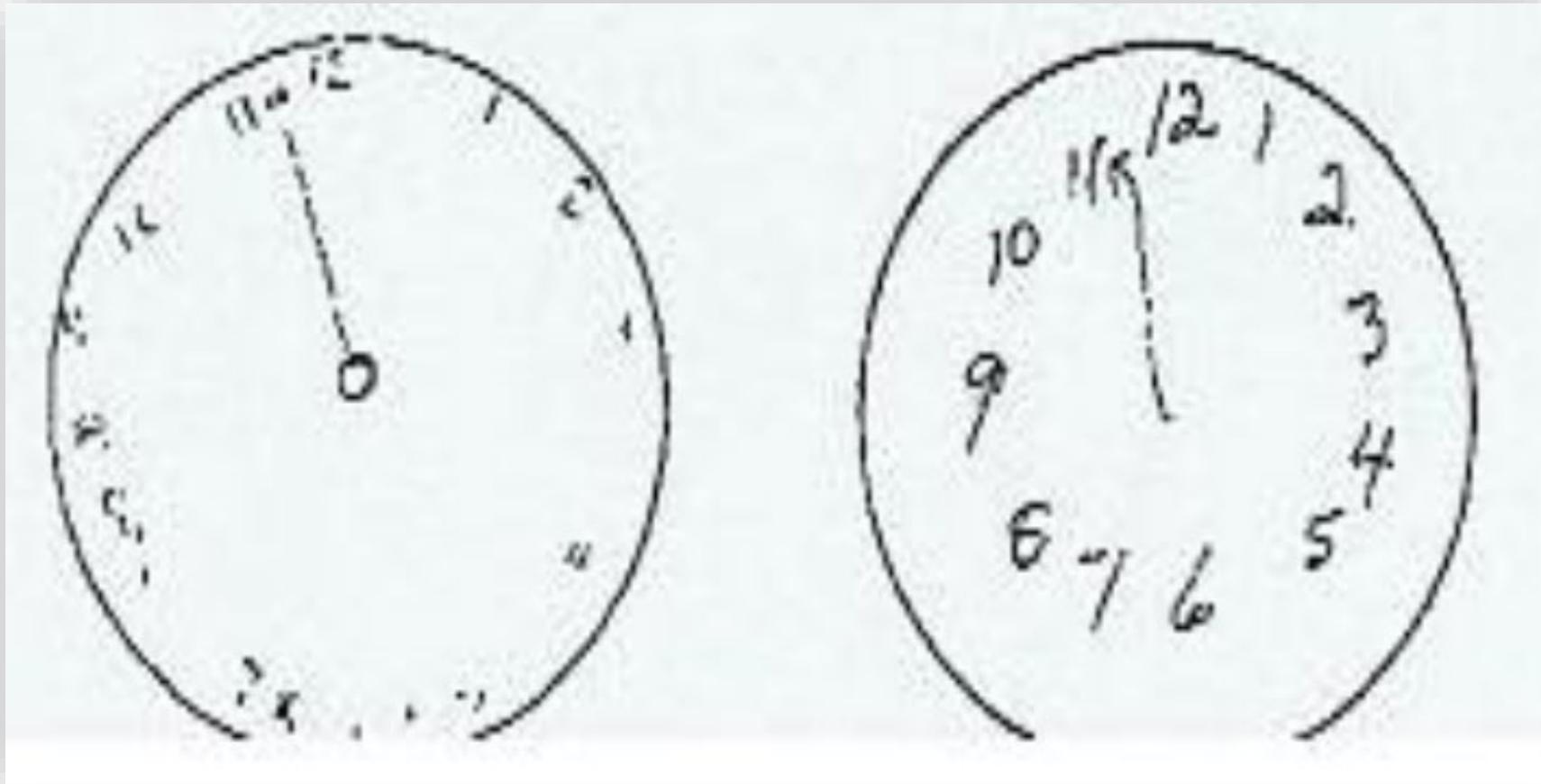


And what don't they all have?

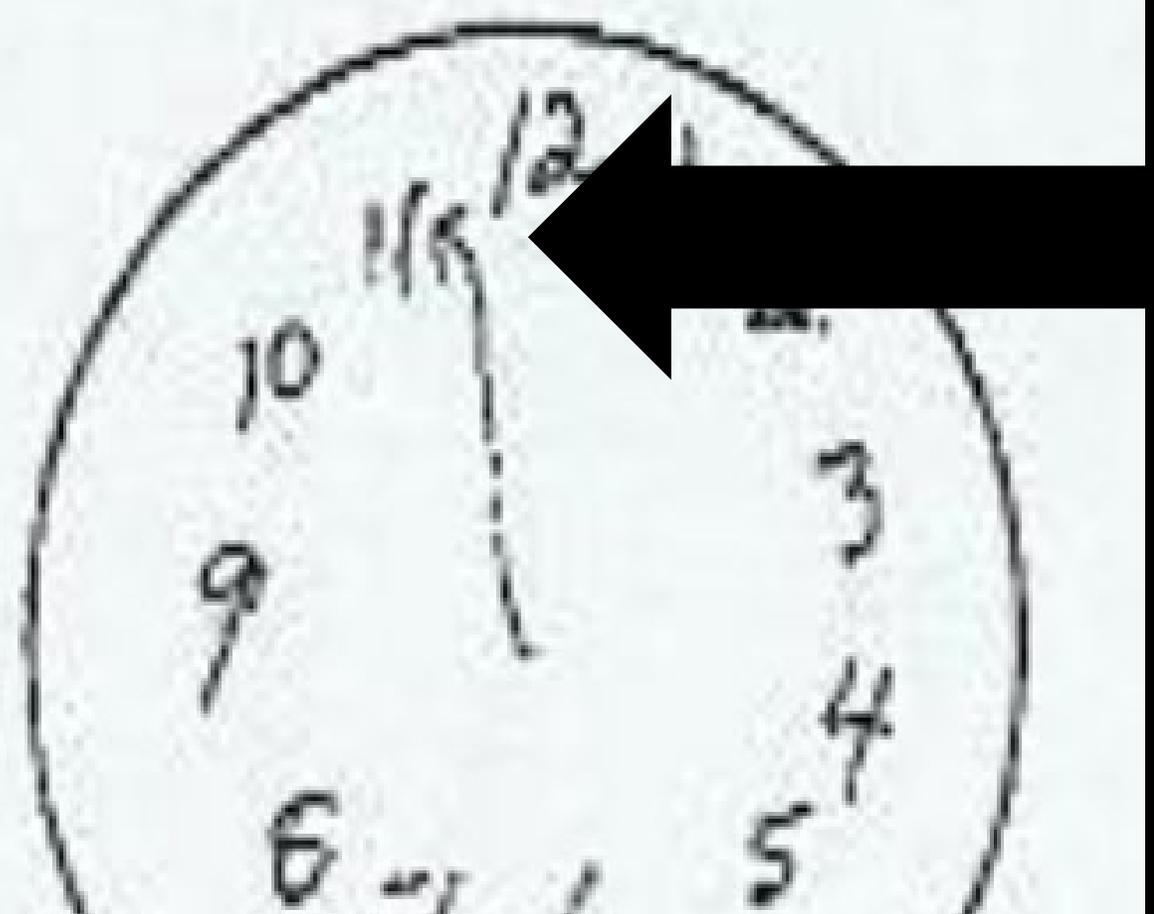
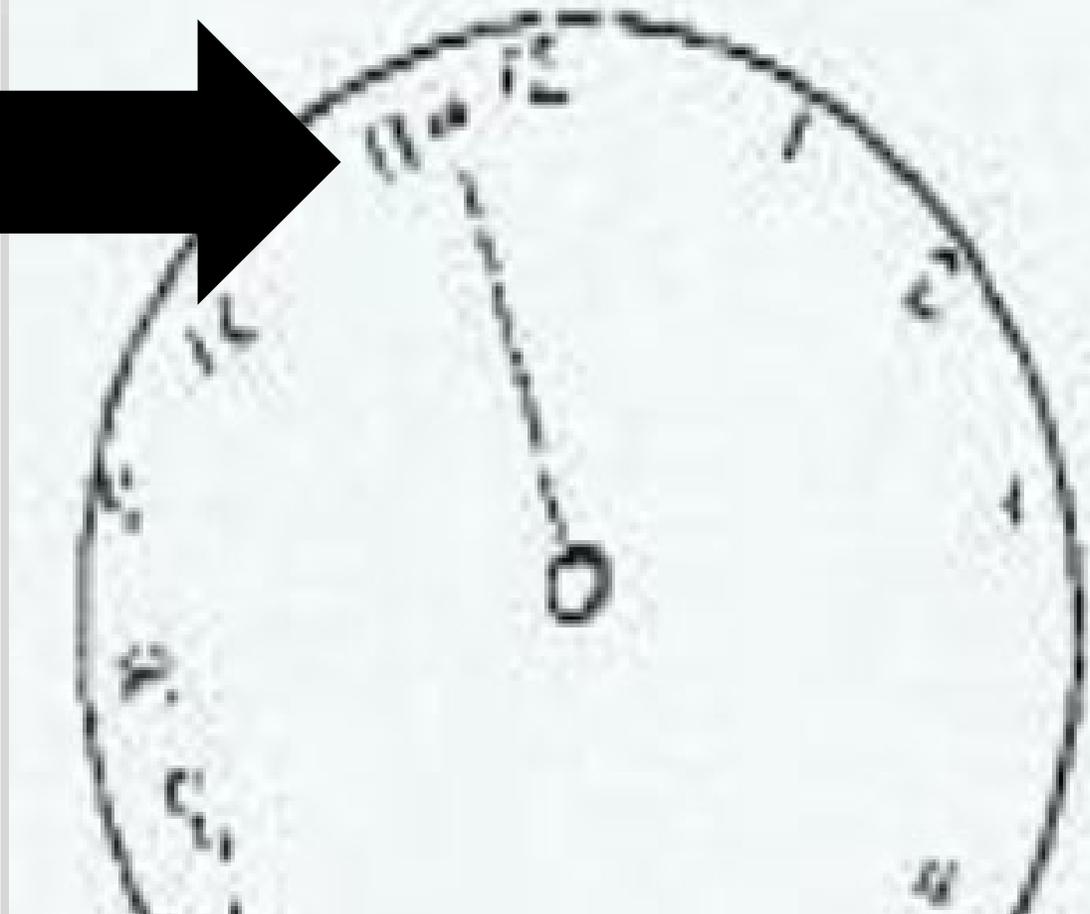


A “cognitive” complaint

Clock drawings of Mr. S and Mr. M:



Clock drawings of Mr. S and Mr. M:



Clock drawings of Mr. S and Mr. M:

Am I supposed to treat them?

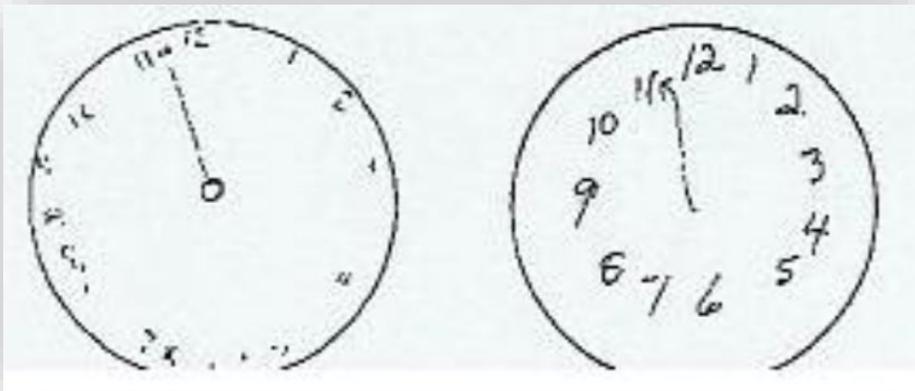
Who's supposed to be the
case-manager of cognitive
disorders?

Primary care physicians?

Neurologists?

Psychiatrists?

Geriatrics?



Primary care physicians?

Neurologists?

Psychiatrists?

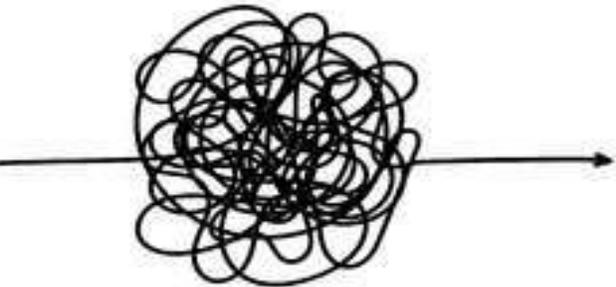
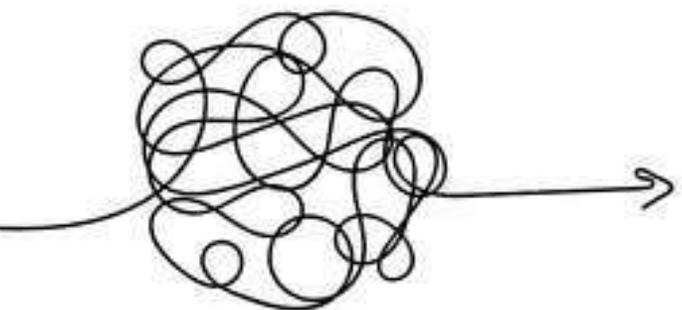
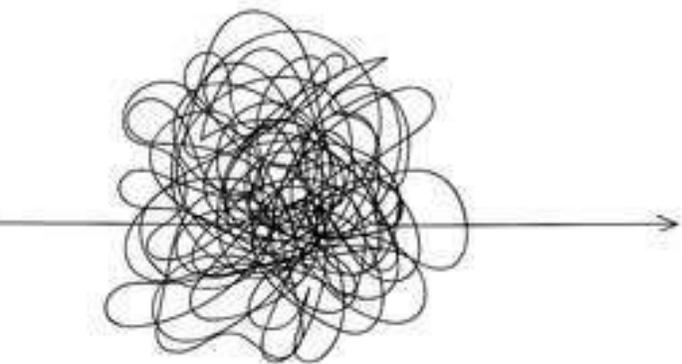
Geriatrics?

All of us together!

Current situation:

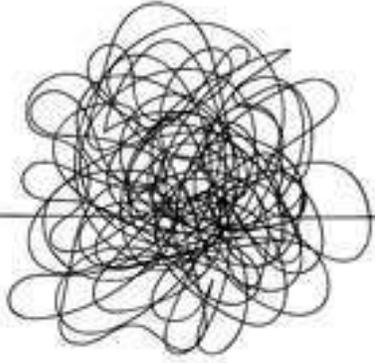
- Diverse etiologies
- Separate groups determining criteria for each disorder
- The result: an array of terms to describe the same syndrome





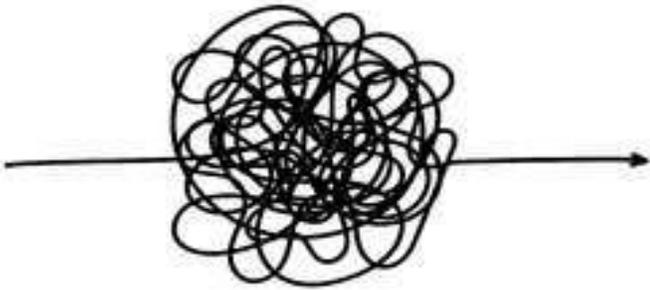
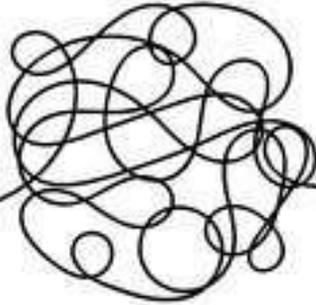
Clinically it's a challenge

- Patients with dementia have very different presenting symptoms



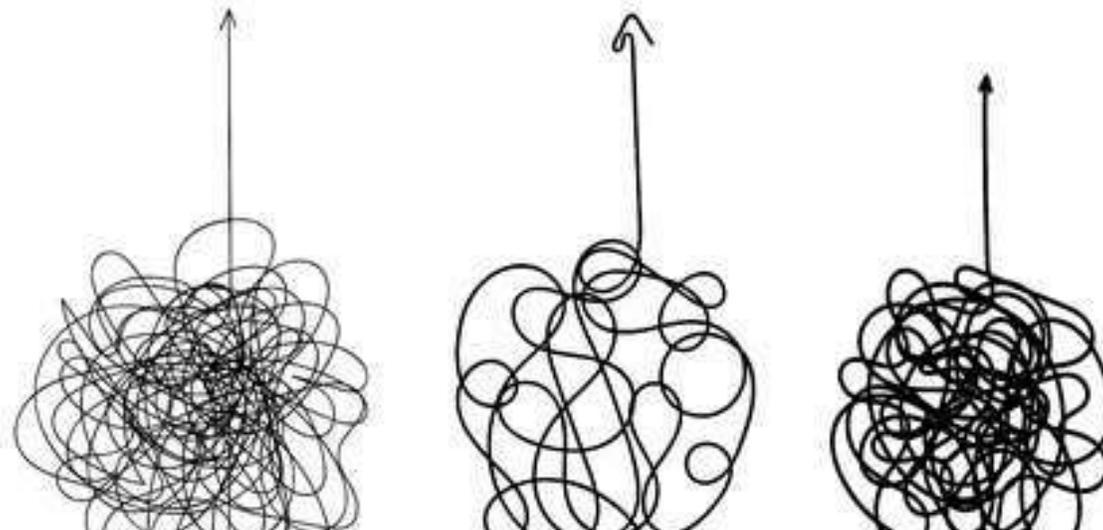
Biologically it's complex...

- A surprising truth:
neuropathological studies reveal mixtures of Alzheimer's, vascular, and Lewy body
- “Pure” syndromes are uncommon

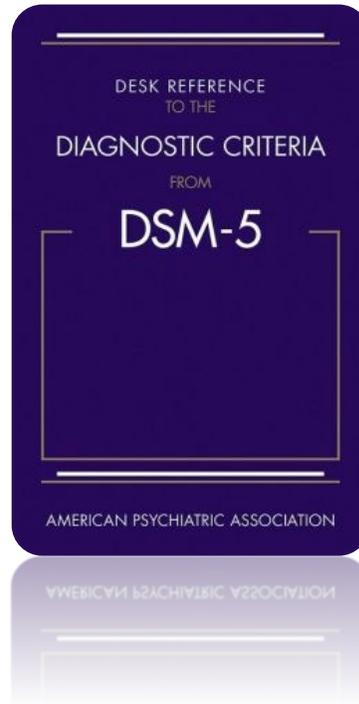


A multi-factorial,
multi-symptomatic syndrome...

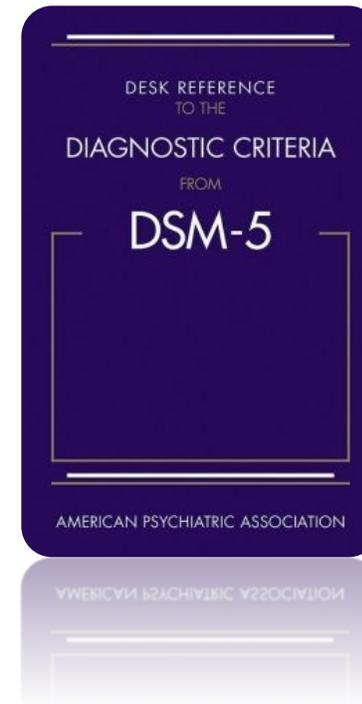
Do we have multi-modal
strategies to face it?



DSM-5 proposes to start with standardizing the classification...



What's new?





1. Say bye to dementia*, say hi to Major Neurocognitive Disorder (NCD)...

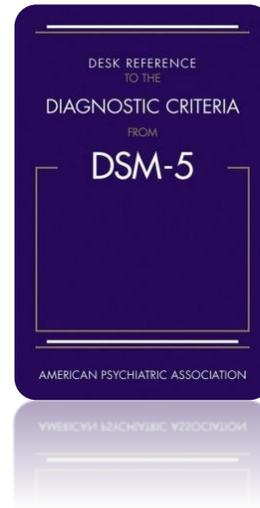
* The term dementia is retained in DSM-5 for continuity and may be used in settings where physicians and patients are accustomed to it

Why not dementia?

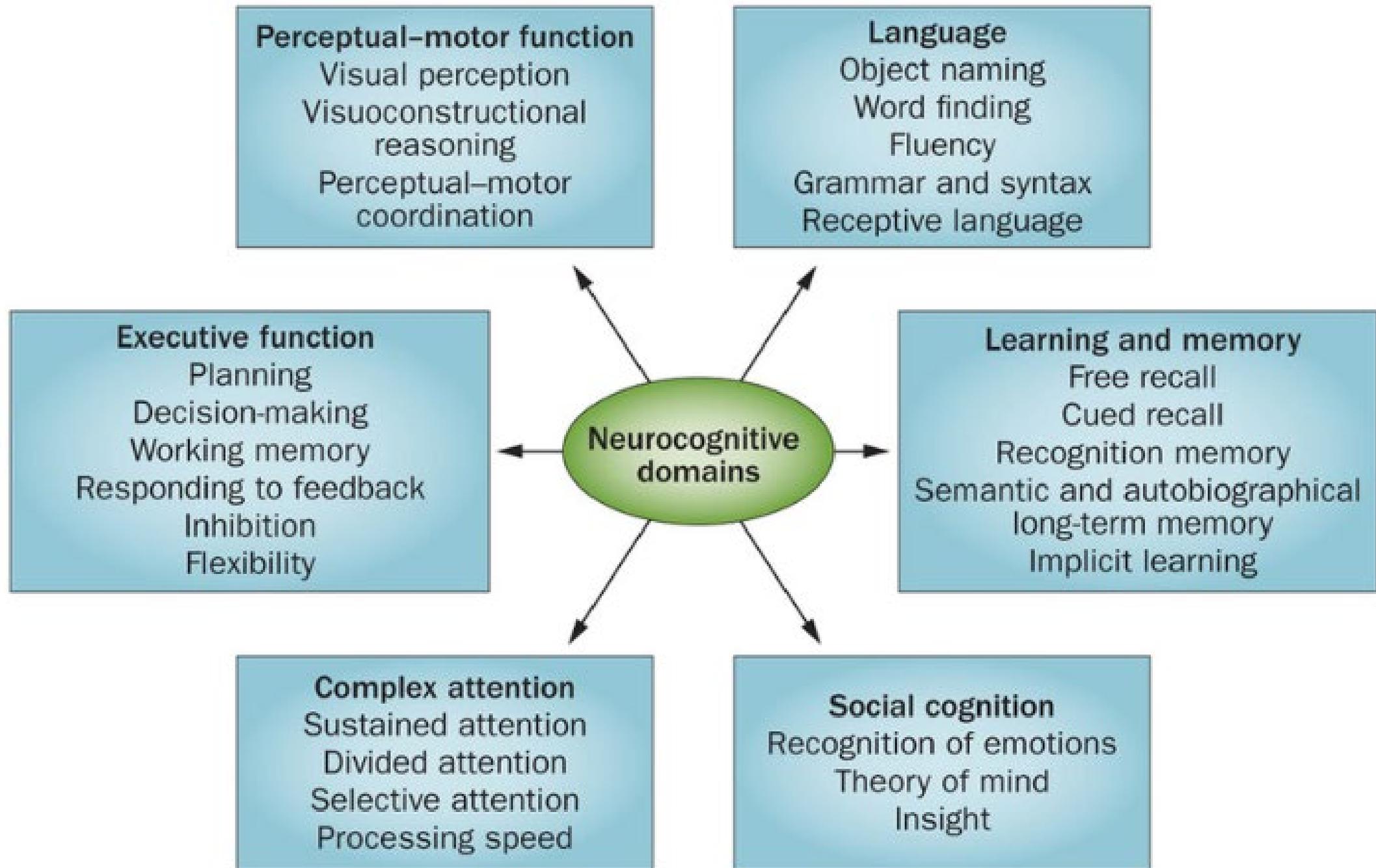


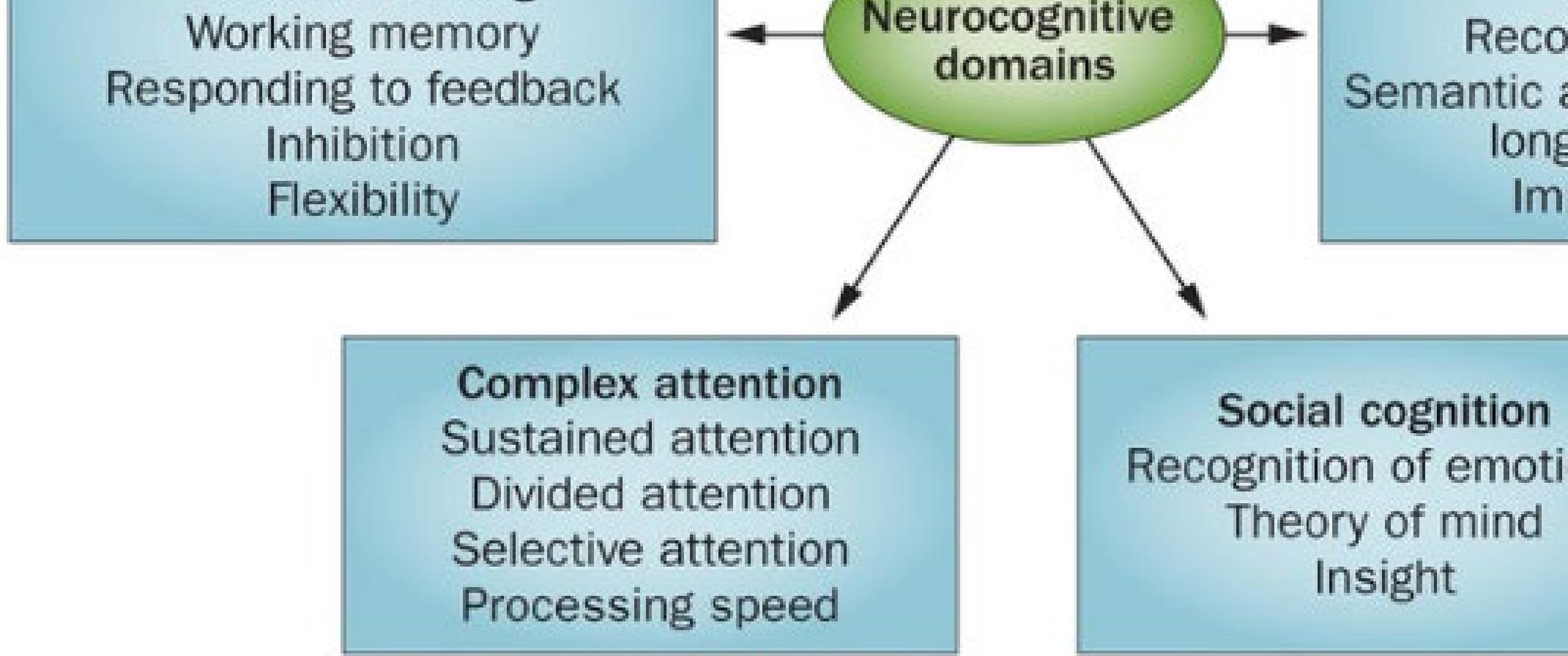
NCD is a broader
definition – a substantial
decline in a **single**
domain is enough for
diagnosis

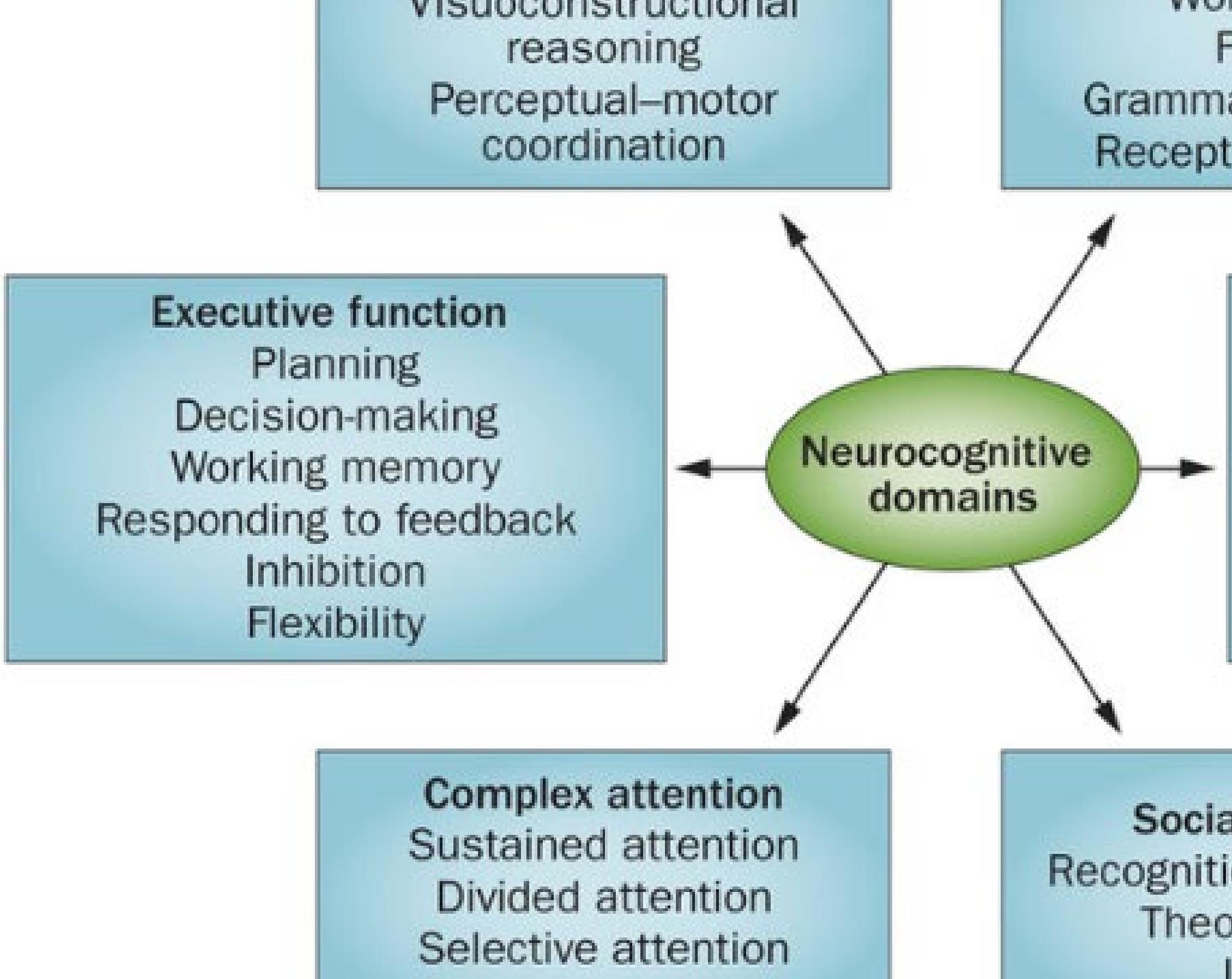




2. It's not just about memory – look at domains







Perceptual-motor function

Visual perception
Visuoconstructional reasoning
Perceptual-motor coordination

Language

Object naming
Word finding
Fluency
Grammar and syntax
Receptive language

Executive function

Planning
Decision-making
Working memory
Responding to feedback

Neurocognitive domains

Learning

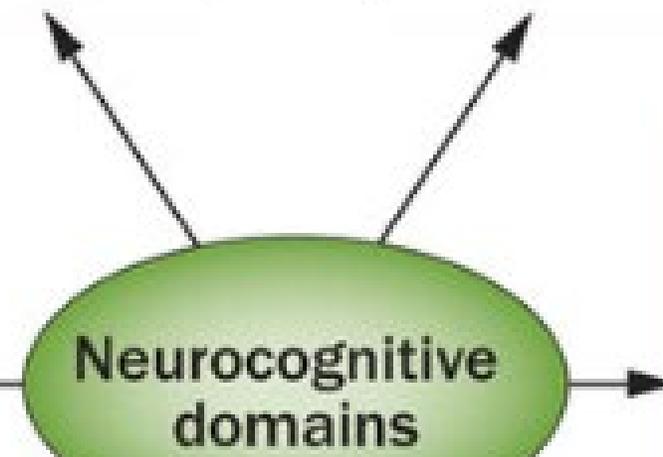
Fr
Cu
Recogn
Semantic

Perceptual-motor function
Visual perception
Visuoconstructional reasoning
Perceptual-motor coordination

Language
Object naming
Word finding
Fluency
Grammar and syntax
Receptive language

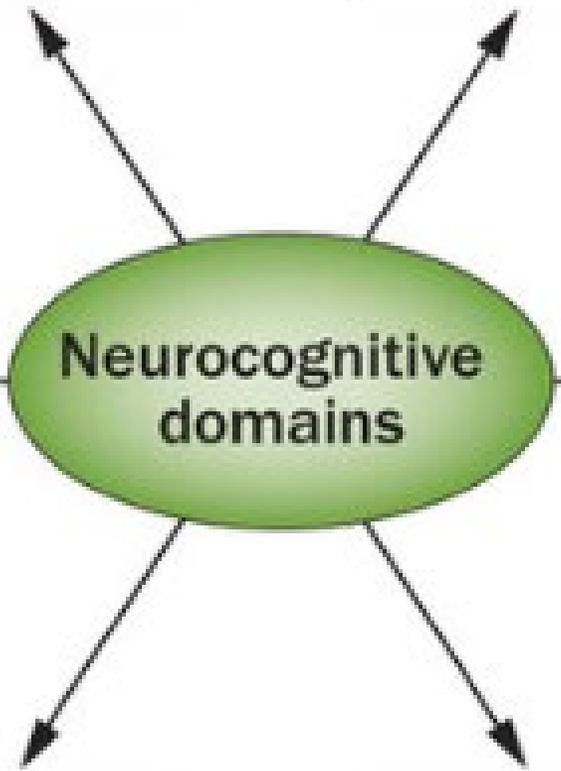
Executive function
Planning
Decision-making
Working memory
Response to feedback

Learning and memory
Free recall
Cued recall
Recognition memory
Semantic and autobiographical



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Object naming
Word finding
Fluency
Grammar and syntax
Receptive language



Neurocognitive domains

Learning and memory
Free recall
Cued recall
Recognition memory
Semantic and autobiographical long-term memory
Implicit learning

Social cognition
Recognition of emotions
Theory of mind

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Memory
Feedback
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y



Recognition memory
Semantic and autobiographical
long-term memory
Implicit learning

Complex attention
Sustained attention
Divided attention
Selective attention
Processing speed

Social cognition
Recognition of emotions
Theory of mind
Insight

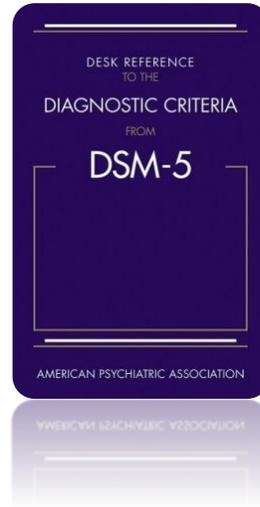


Neuropsychiatric symptoms

Its not just about “cognition”!

Sometimes the 1st signs of cognitive decline will be:

- Apathy / anhedonia
- Depression
- Anxiety
- Sleep problems
- Inappropriate behavior



And finally:

3. Say bye to MCI, say hi to Mild NCD



Why mild?

(The opposite of major is minor)

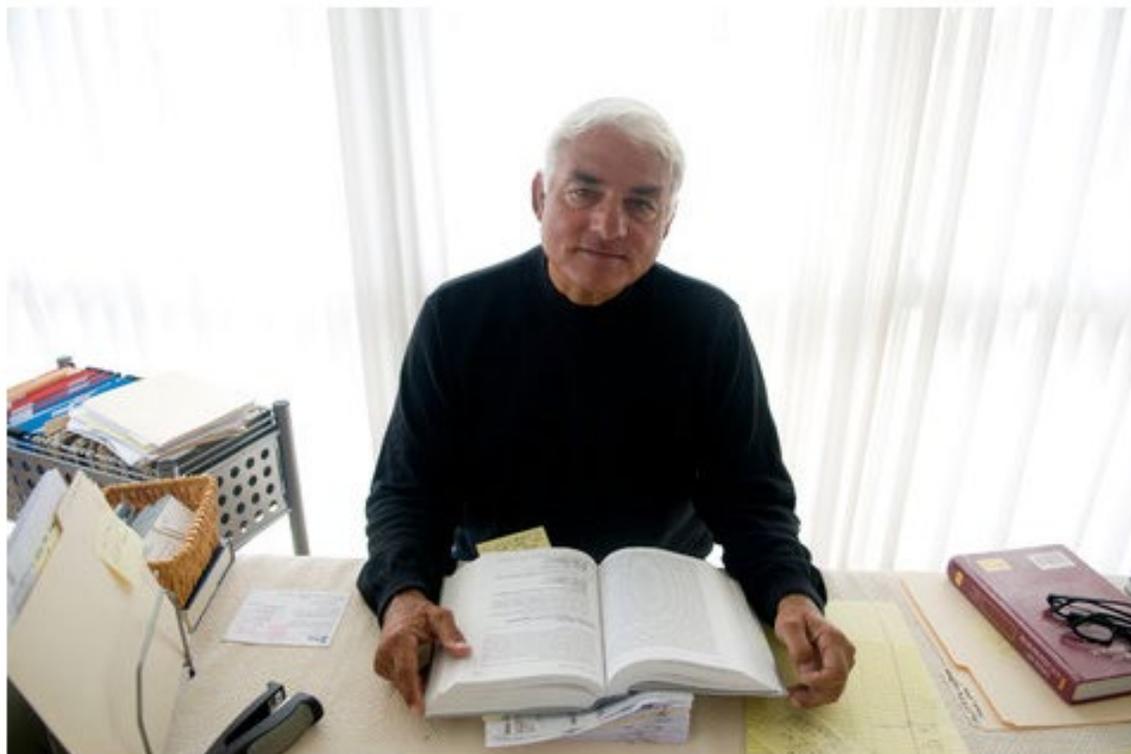


Say bye to MCI

- Mild NCD represents a new framework for the commonly used MCI
- Test performance: 1–2 SD below the normative mean (3rd and 16th percentiles)

Time to Recognize Mild Cognitive Disorder?

By PAULA SPAN JANUARY 25, 2013 5:47 AM 37 Comments



Dr. Allen Frances, chairman of the task force that developed the previous Diagnostic and Statistical Manual of Mental Disorders, predicts inclusion of mild neurocognitive disorder in the new version will lead to "wild overdiagnosis." Sam Hodgson for The New York Times

The Diagnostic and Statistical Manual of Mental Disorders, published and periodically updated by the American Psychiatric Association, is one of those documents few laypeople ever read, but many of us are affected by.



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Neurocognitive Disorders in DSM-5

The introduction of the diagnosis “mild neurocognitive disorder” is the crucial change in the diagnostic criteria for the neurocognitive disorders chapter of DSM-5 (previously entitled “Delirium, Dementia, and Amnesic and Other Cognitive Disorders” in DSM-IV) (1). Except in the case of delirium, the first step in the diagnostic process will be to differentiate between normal neurocognitive function, mild neurocognitive disorder (mild NCD), and major neurocognitive disorder (major NCD or dementia). The second step will be to assign an etiological category, such as Alzheimer’s NCD, vascular NCD, or frontotemporal NCD. Although neurocognitive dysfunction in older adults is usually analogous in the clinician’s mind to learning and memory problems, DSM-5 also includes complex attention, executive function, language, perceptual motor problems, and social cognition among the neurocognitive domains that can be impaired by an NCD.

The movement to diagnose NCDs upstream reflects an emerging literature that confirms both the improvement in early diagnostic determinations and the recognition that the neuropathology underlying these disorders emerges well before the onset of clinical symptoms. This change, however, has been criticized in the scientific literature and in the popular press (2, 3). Distinguishing between mild NCD and major NCD is challenged by some neurologists to be an artificial threshold dependent upon the subjective judgment of the clini-

*The time for intervention will be early
in the development of the disease,
whatever the etiology.*

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*The time for intervention will be early
in the development of the disease,
whatever the etiology.*

So, we have to actively look for NCD's,
otherwise we will miss the chance to go upstream...



MONTREAL COGNITIVE ASSESSMENT (MOCA)

NAME :

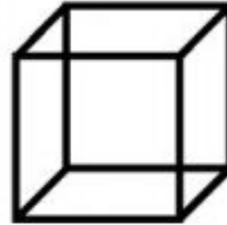
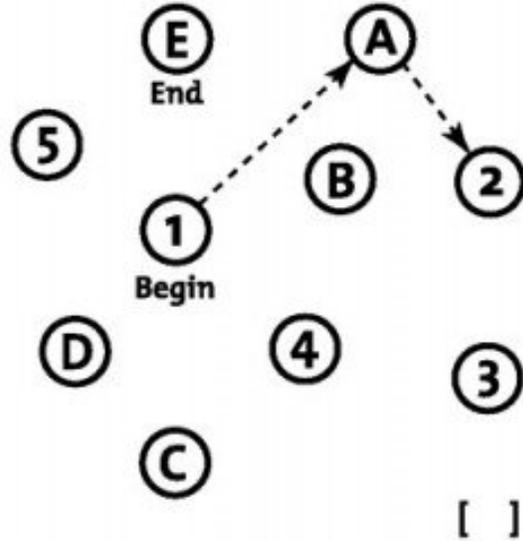
Education :

Sex :

Date of birth :

DATE :

VISUOSPATIAL / EXECUTIVE



Copy cube

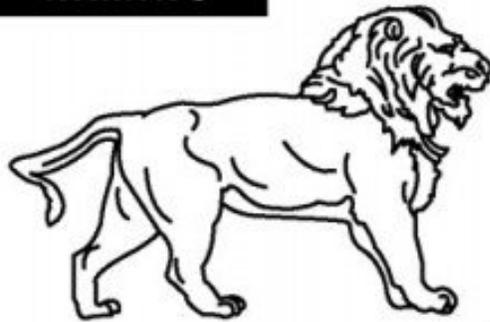
Draw CLOCK (Ten past eleven)
(3 points)

POINTS

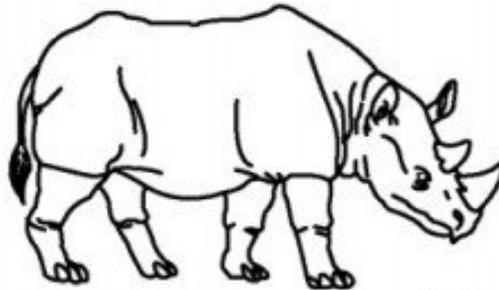
[] [] []
Contour Numbers Hands

___/5

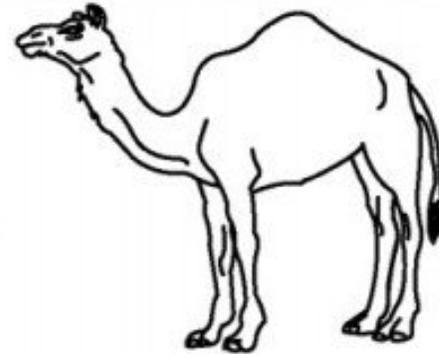
NAMING



[]



[]



[]

___/3

MEMORY

Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION	Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order [] 2 1 8 5 4						___/2	
	Subject has to repeat them in the backward order [] 7 4 2							
	Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors						___/1	
	[] FBACMNAAJKLBAFAKDEAAAJAMOF AAB							
	Serial 7 subtraction starting at 100	[] 93	[] 86	[] 79	[] 72	[] 65	___/3	
	4 or 5 correct subtractions: 3 pts, 2 or 3 correct: 2 pts, 1 correct: 1 pt, 0 correct: 0 pt							
LANGUAGE	Repeat : I only know that John is the one to help today. []						___/2	
	The cat always hid under the couch when dogs were in the room. []							
	Fluency / Name maximum number of words in one minute that begin with the letter F [] ____ (N ≥ 11 words)						___/1	
ABSTRACTION	Similarity between e.g. banana - orange = fruit [] train - bicycle [] watch - ruler						___/2	
DELAYED RECALL	Has to recall words WITH NO CUE	FACE []	VELVET []	CHURCH []	DAISY []	RED []	Points for UNCUED recall only	___/5
Optional	Category cue							
	Multiple choice cue							
ORIENTATION	[] Date	[] Month	[] Year	[] Day	[] Place	[] City	___/6	
© Z.Nasreddine MD Version 7.0		www.mocatest.org		Normal ≥ 26 / 30		TOTAL	___/30	
Administered by: _____		Add 1 point if ≤ 12 yr edu						

Cut-off: 25-26

Sensitivity of 80-100%; Specificity 50-76%

ID: _____ Date: _____

Step 1: Three Word Registration

Look directly at person and say, "Please listen carefully. I am going to say three words that I want you to repeat back to me now and try to remember. The words are [select a list of words from the versions below]. Please say them for me now." If the person is unable to repeat the words after three attempts, move on to Step 2 (clock drawing).

The following and other word lists have been used in one or more clinical studies.¹⁻³ For repeated administrations, use of an alternative word list is recommended.

Version 1Banana
Sunrise
Chair**Version 2**Leader
Season
Table**Version 3**Village
Kitchen
Baby**Version 4**River
Nation
Finger**Version 5**Captain
Garden
Picture**Version 6**Daughter
Heaven
Mountain

Step 2: Clock Drawing

Say: "Next, I want you to draw a clock for me. First, put in all of the numbers where they go." When that is completed, say: "Now, set the hands to 10 past 11."

Use preprinted circle (see next page) for this exercise. Repeat instructions as needed as this is not a memory test. Move to Step 3 if the clock is not complete within three minutes.

Step 3: Three Word Recall

Ask the person to recall the three words you stated in Step 1. Say: "What were the three words I asked you to remember?" Record the word list version number and the person's answers below.

Word List Version: _____ Person's Answers: _____

Scoring

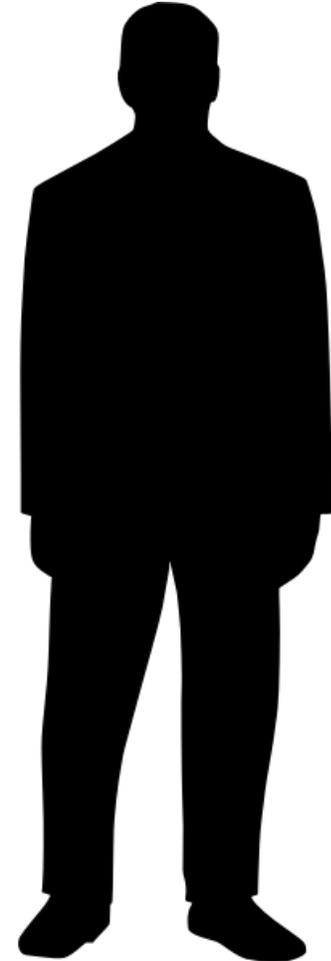
Word Recall: _____ (0-3 points)	1 point for each word spontaneously recalled without cueing.
Clock Draw: _____ (0 or 2 points)	Normal clock = 2 points. A normal clock has all numbers placed in the correct sequence and approximately correct position (e.g., 12, 3, 6 and 9 are in anchor positions) with no missing or duplicate numbers. Hands are pointing to the 11 and 2 (11:10). Hand length is not scored. Inability or refusal to draw a clock (abnormal) = 0 points.
Total Score: _____ (0-5 points)	Total score = Word Recall score + Clock Draw score. A cut point of <3 on the Mini-Cog™ has been validated for dementia screening, but many individuals with clinically meaningful cognitive impairment will score higher. When greater sensitivity is desired, a cut point of <4 is recommended as it may indicate a need for further evaluation of cognitive status.

Mini-Cog™ © S. Borison. All rights reserved. Reprinted with permission of the author solely for clinical and educational purposes. May not be modified or used for commercial, marketing, or research purposes without permission of the author (soob@uw.edu).
v. 01.19.16

Cut-off: 2

Sensitivity of 39-84%; Specificity 78-88%

What about our patients?





Mr. S

- 79. Started “talking dirty”
- MMSE: 21
- MoCA: 18
- Diagnosis: major NCD
(dementia)

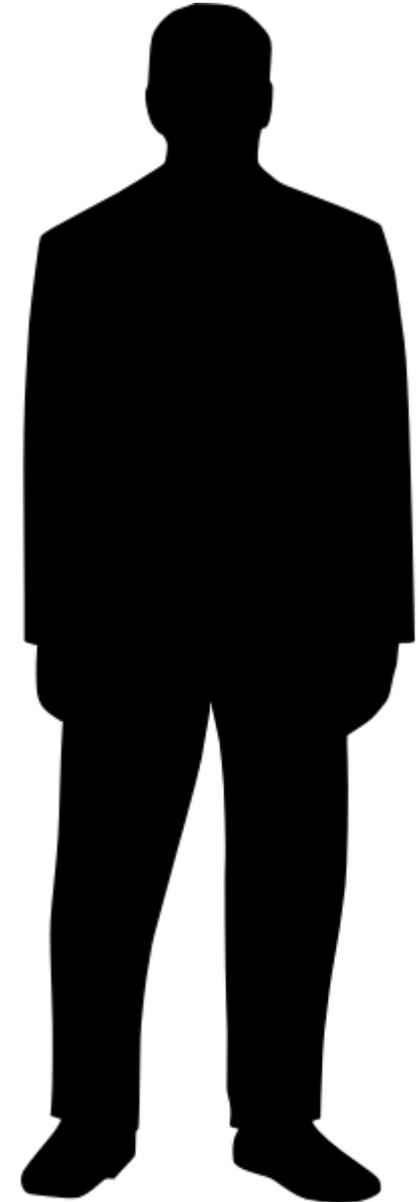


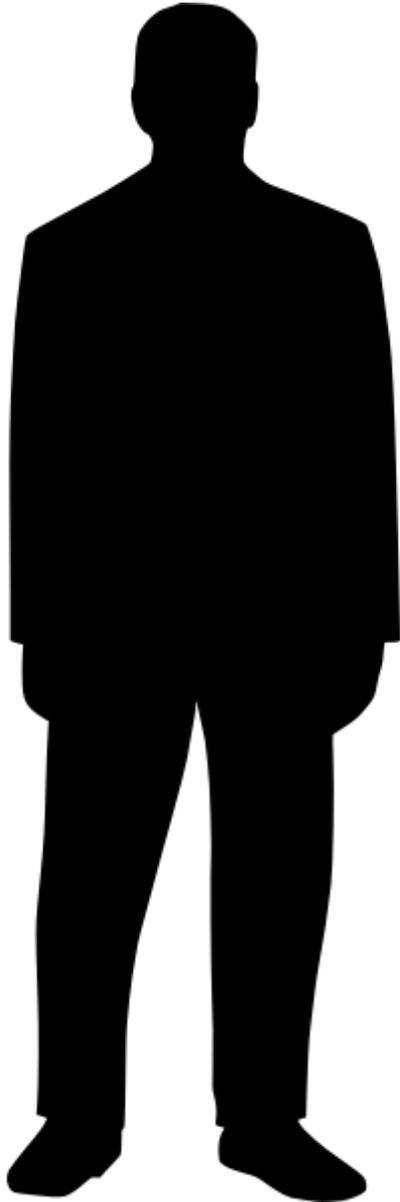
Mrs. T

- 78, anxious and depressed for the 1st time in her life
- MMSE: 28
- MoCA: 28
- Diagnosis: ?

Mr. M

- 74, “apathetic”
- MMSE 26
- MoCA: 24
- Probable mild NCD (MCI)





So, we diagnosed mild NCD.

Do we need to treat it?

Kasper S et al.

**Management of mild
cognitive impairment
(MCI): The need for
national and international
guidelines**

2020 Feb. *World J Biol
Psychiatry*. 2020;1-16.





From mild to major NCD



- ~10–15% of mild NCD → will develop major NCD per year
- Positive for AD biomarkers: three-year progression rate to AD-type dementia - 59%



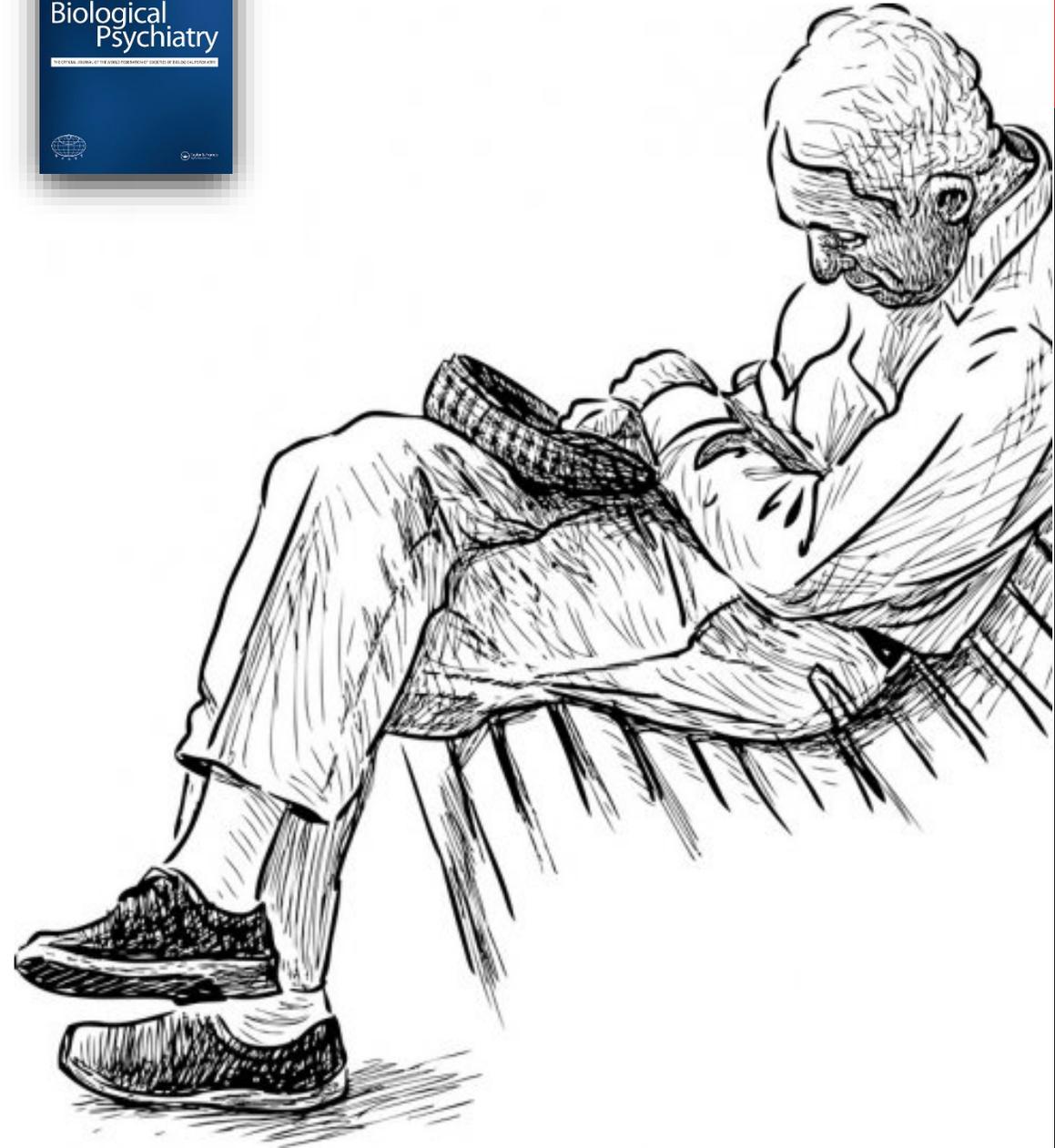
From mild to major NCD



- Compared to the general population, the risk of dementia in MCI patients is 3 to 18 times higher

Rationale to intervene in mild NCD

- Behavioral and neuropsychiatric symptoms (NPS) are common in mild NCD
- Depression, apathy, anxiety
 - in 40% of adults with MCI
- Important to reduce the burden on caregivers



WATCHFUL

WAITING?



“A questionable option...”



What are our treatment options with
Mild NCD and Major NCD?

What are our treatment
options with Mild NCD
and Major NCD?



Prevention



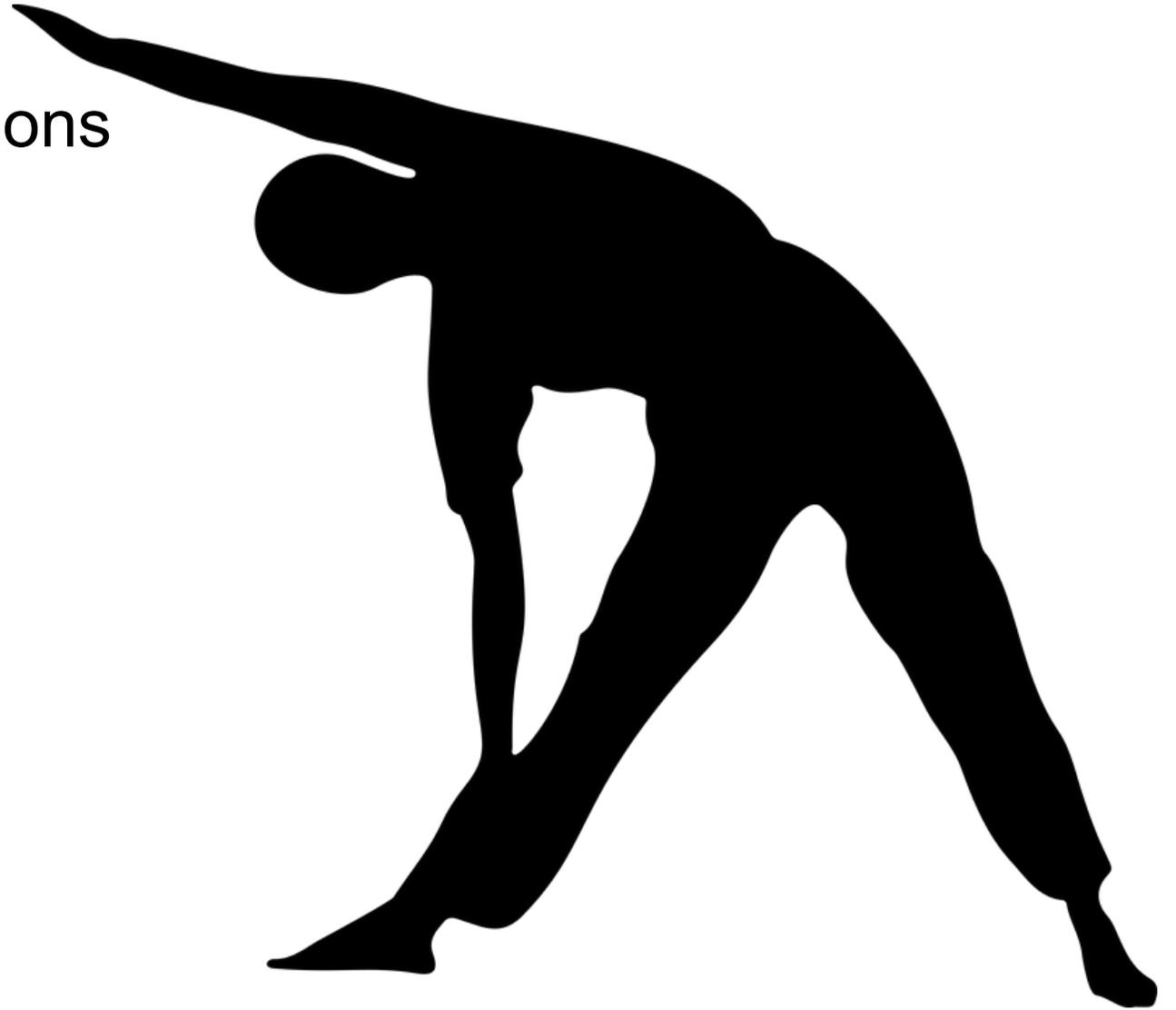
Prevention (WHO recommendations 2019)

- Sleep disorders
- Sensory deprivation
- Depression and stress
- No physical activity
- Alcohol abuse
- Social isolation
- Air pollution
- HTN
- Obesity
- Smoking
- NIDDM
- Infections
- Head trauma



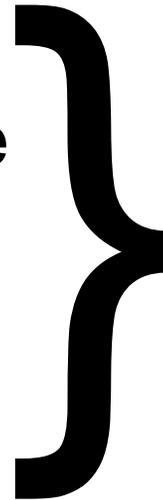
Non-pharmacological interventions

- I. Cognitive training
- II. Moderately intensive physical exercise
- III. Diet
- IV. Socialization

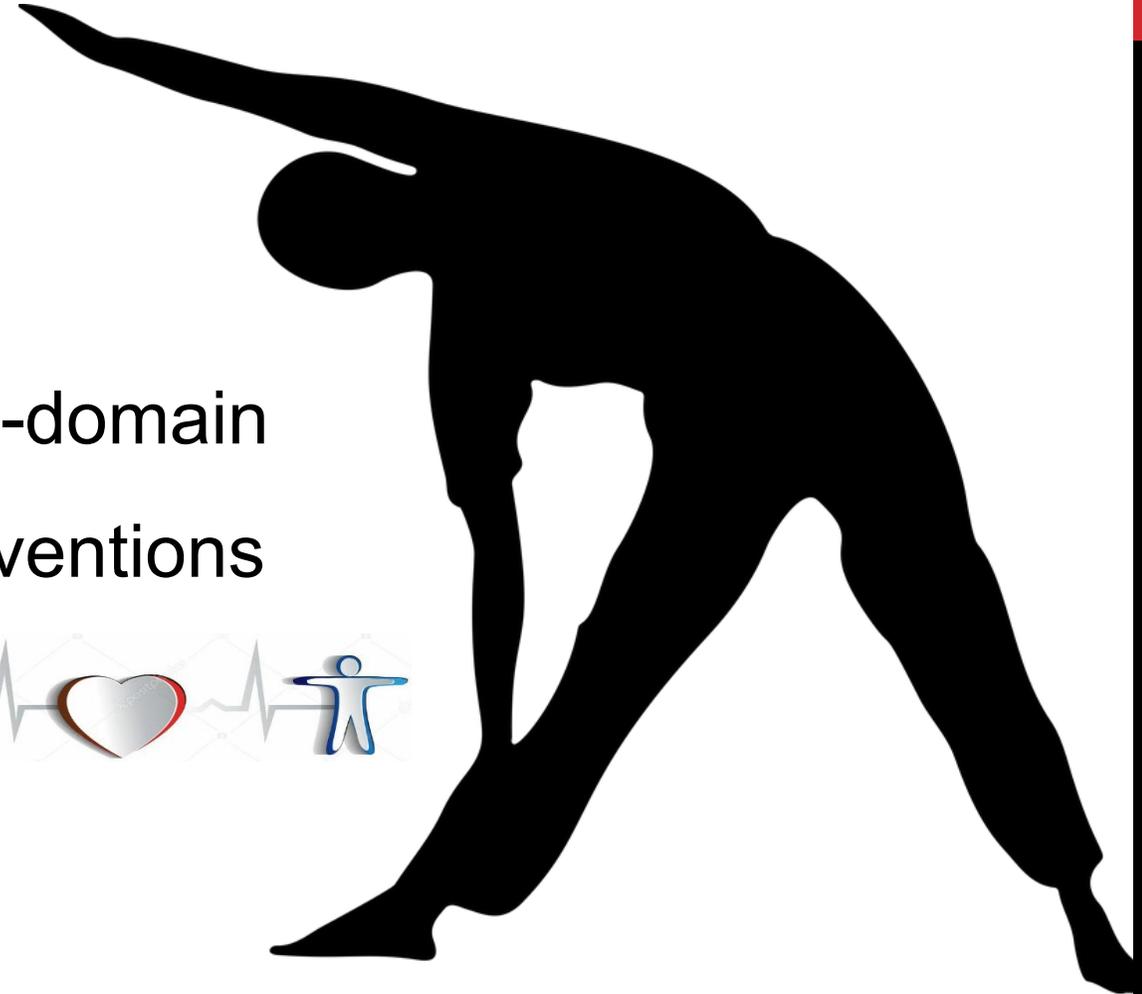


Non-pharmacological interventions

- I. Cognitive training
- II. Moderately intensive physical exercise
- III. Diet
- IV. Socialization



Multi-domain interventions



Multi-domain
interventions are
probably good



What about
adherence?





Nutritional supplements



Nutritional supplements

No results or very modest results



Drugs?

Drugs?

- Numerous RCT's in MCI
- Some show symptomatic relief
- **No study to date has proven a drug to be disease modifying**



B-Amyloid as a potential target in MCI



B-Amyloid as a potential target in MCI

- “The pharmacological relevance of this hypothesis at this stage of disease is questionable”





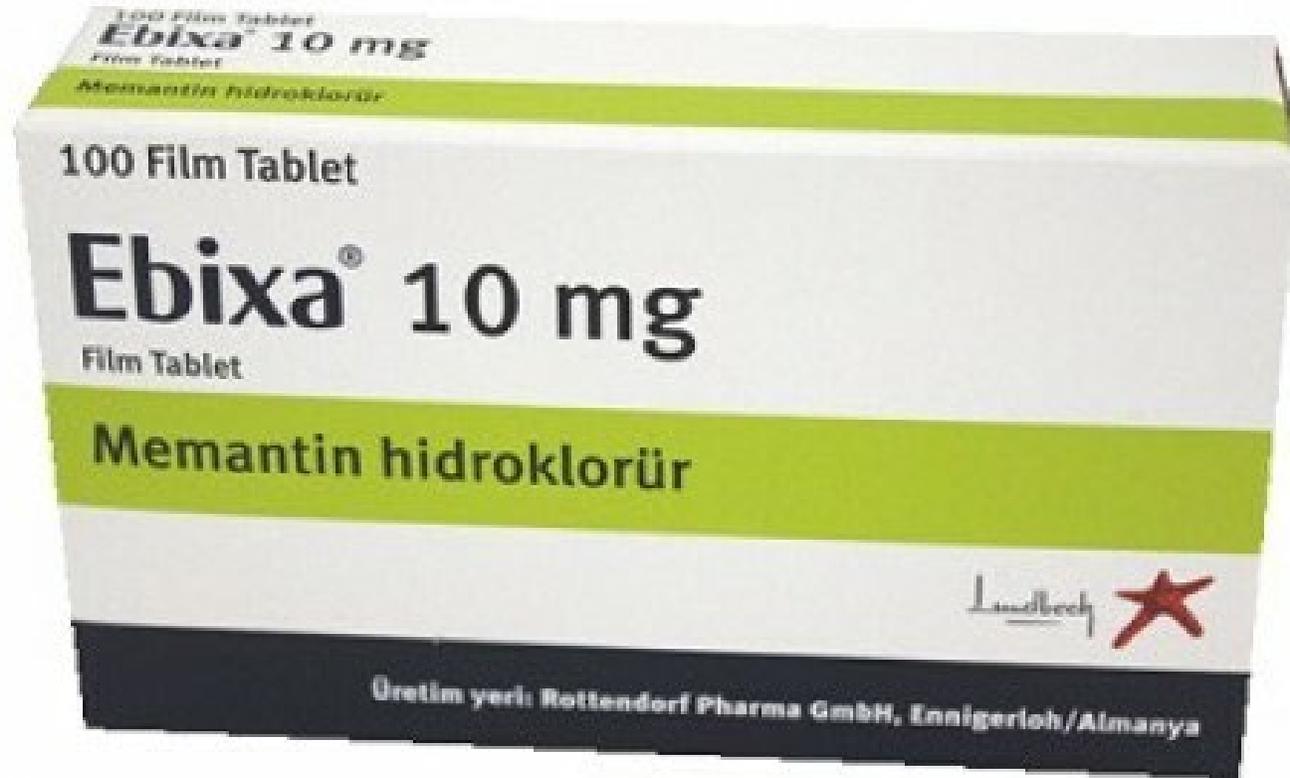
Cholinesterase inhibitors

Cholinesterase inhibitors

- Large RCT's fail to show clinically significant results in MCI
- Indicated in initial phases of Major NCD



Memantine: NMDA receptor antagonists



Memantine: NMDA receptor antagonists

- Not well studied in MCI
- Indicated in late phases of major NCD



Ginkgo Biloba special extract – EGb 761®

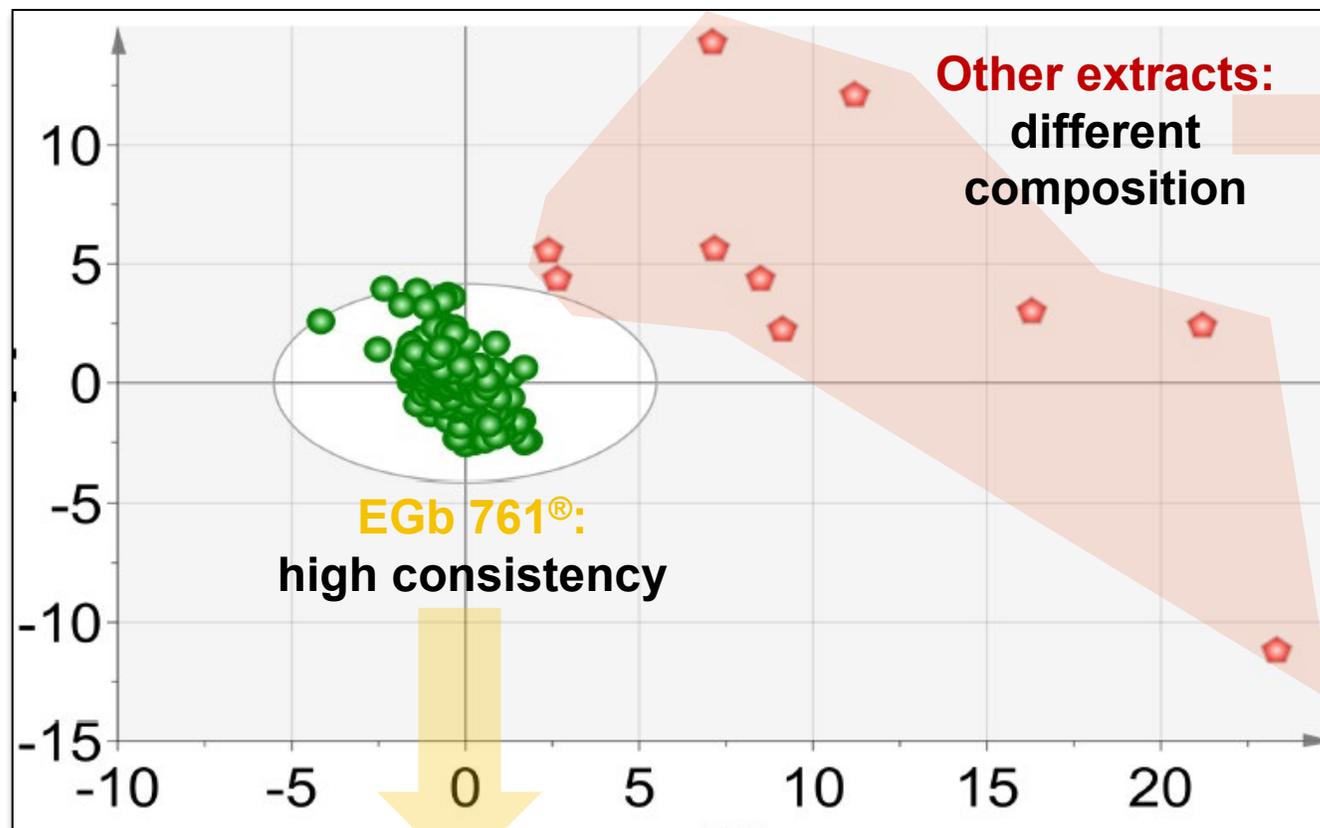


Ginkgo Biloba special extract – EGb 761®

- Not every “Ginkgo product” is EGb 761®
- Medical Ginkgo extract:
 - 24% Ginkgo Flavone Glycosides
 - 6% Terpene lactones
 - Mustn't include more than 5 ppm of Ginkgolic acids!



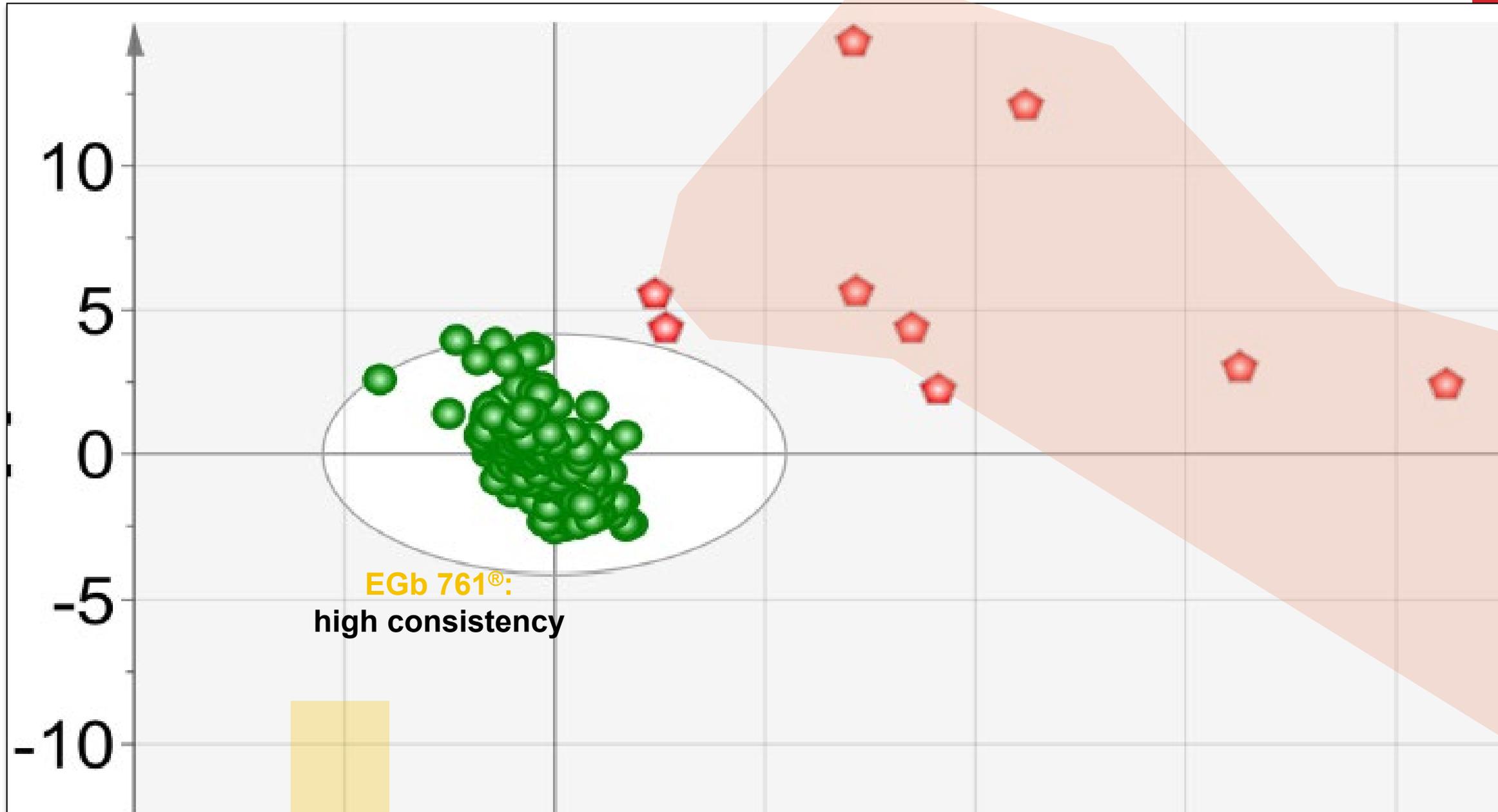
EGb 761[®] ≠ Ginkgo



Clinical Results for EGb 761[®] cannot be generalized

Reproducible efficacy: Every single batch of EGb 761[®] has the very same composition (throughout almost 50 years of production)

Source: Principal Component Analysis (PCA)



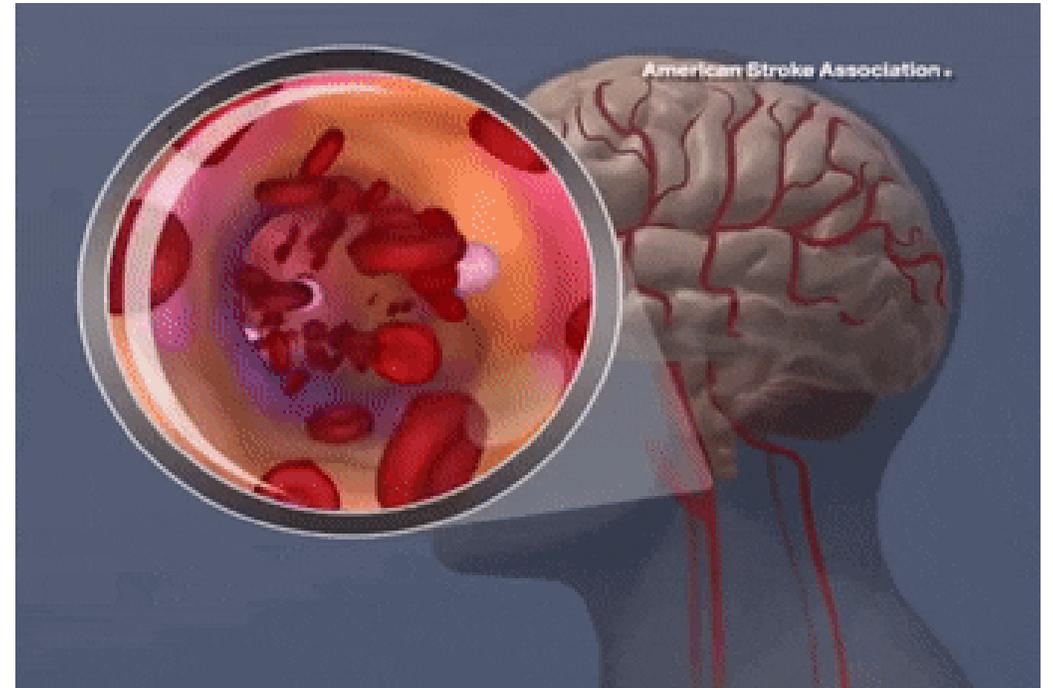
Ginkgo Biloba special extract – EGb 761®

- Efficacy in cognitive and neuropsychiatric symptoms and function of patients with Alzheimer's dementia, vascular and mixed dementia



Ginkgo Biloba special extract – EGb 761®

- Efficacy in cognitive and neuropsychiatric symptoms and function of patients with Alzheimer's dementia, **vascular and mixed dementia**



EGb 761[®] in mild NCD

RESEARCH ARTICLE

International Journal of
Geriatric Psychiatry

Efficacy and safety of *Ginkgo biloba* extract EGb 761[®] in mild cognitive impairment with neuropsychiatric symptoms: a randomized, placebo-controlled, double-blind, multi-center trial

S. I. Gavrilova¹, U. W. Preuss², J. W. M. Wong², R. Hoerr³, R. Kaschel⁴, N. Bachinskaya⁵ and the GIMCIPlus Study Group[†]

¹Mental Health Research Center of the Russian Academy of Medical Sciences, Moscow, Russia

²Department of Psychiatry, Psychotherapy and Psychosomatics, Hospital Prignitz, Perleberg, Germany

³Clinical Research Department, Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany

⁴Department of Psychology, University of Osnabrück, Osnabrück, Germany

⁵Institute of Gerontology, Academy of Medical Sciences, Kiev, Ukraine

Correspondence to: R. Hoerr, MD, PhD, E-mail: robert.hoerr@schwabe.de

[†]The GIMCIPlus Study Group: Gavrilova SI, Mental Health Research Center of the Russian Academy of Medical Sciences, Moscow; Vilyanov VB, City Hospital No. 2 "V. I. Razumovskiy", Saratov; Sholomov II, City Clinical Hospital No. 9, Saratov; Voskresenskaya ON, Saratov State Medical University of Roszdrav, Saratov; Shiryayev OY, Voronezh Regional Clinical Psychoneurological Polyclinic, Voronezh; Chefranova ZY, Belgorod Regional Clinical Hospital, Belgorod; and Gubarev YD, Belgorod State University Chair of Nervous Diseases, Belgorod.

Objective: The study was conducted to explore the effects of EGb 761[®] (Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany) on neuropsychiatric symptoms (NPS) and cognition in patients with mild cognitive impairment (MCI).

Methods: One hundred and sixty patients with MCI who scored at least 6 on the 12-item Neuropsychiatric Inventory (NPI) were enrolled in this double-blind, multi-center trial and randomized to receive 240 mg EGb 761 daily or placebo for a period of 24 weeks. Effects on NPS were assessed using the NPI,

EGb 761[®] in mild NCD

- Double blind RCT
- 160 patients with MCI and neuropsychiatric symptoms
- 24 weeks

Gavrilova SI et al. Int J Geriatr Psychiatry. 2014

RESEARCH ARTICLE

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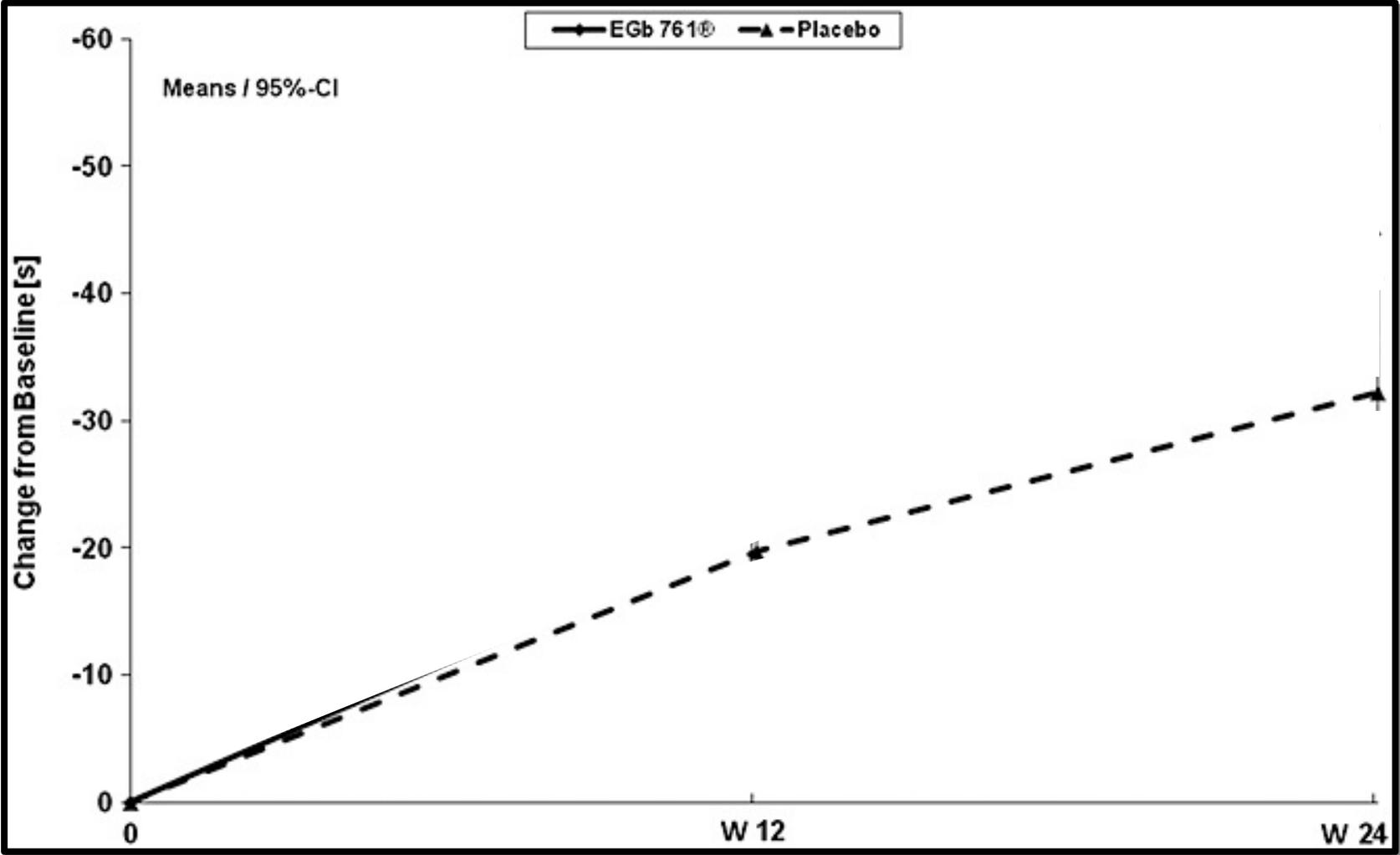
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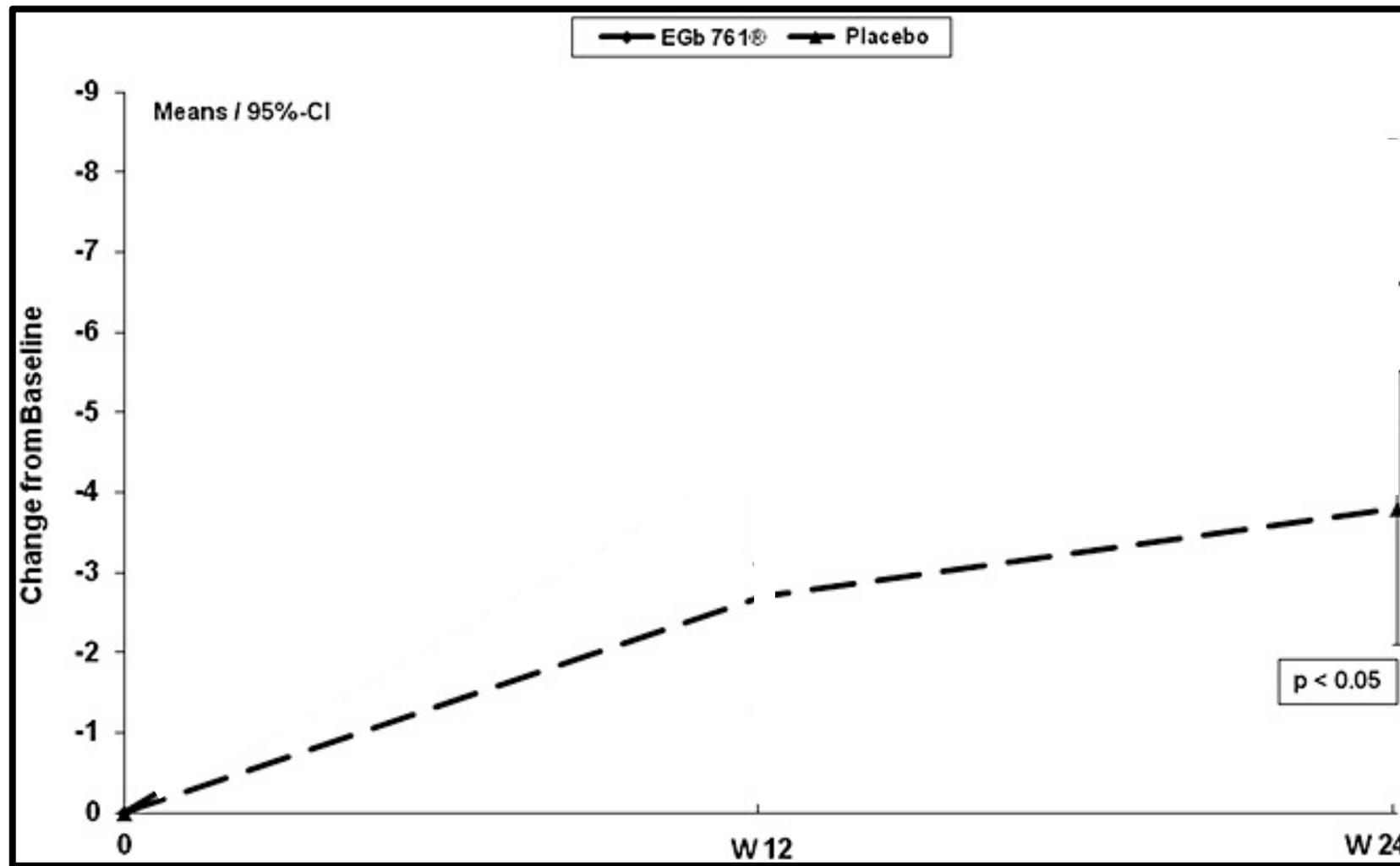
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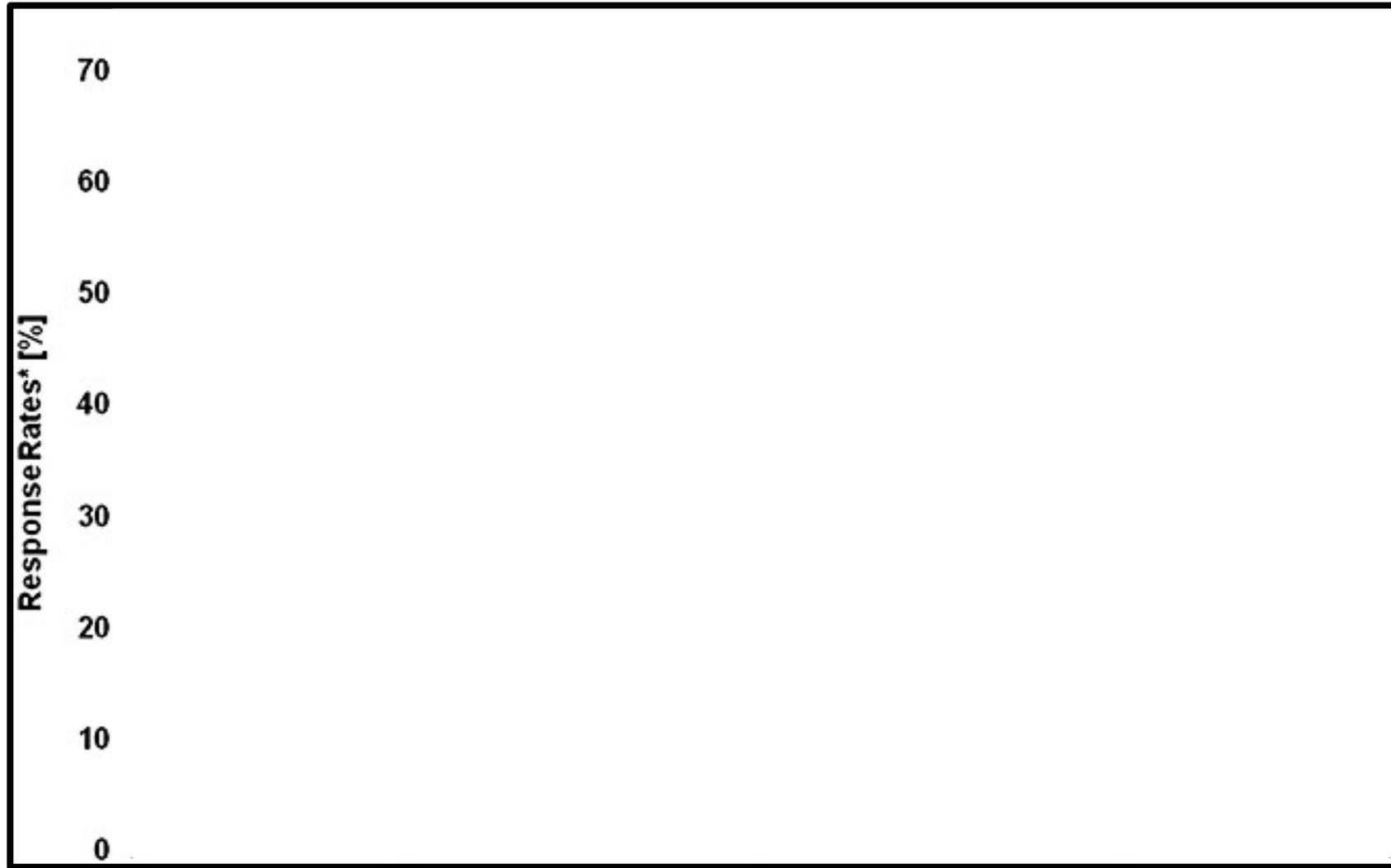
Change in trail making



Change in state anxiety



Response rates in neuropsychiatric inventory



EGb 761[®] in very mild NCD

Effects of Ginkgo Biloba Special Extract EGb 761[®] in Very Mild Cognitive Impairment (vMCI)

Brigitte Grass-Kapanke¹, Arija Busmane², Andris Lasmanis³, Robert Hoerr⁴, Reiner Kaschel⁵

¹Alexian Hospital Krefeld, Krefeld, Germany; ²Adoria Clinic, Riga, Latvia; ³Alma Clinic, Riga, Latvia; ⁴Dr. Willmar Schwabe GmbH & Co. KG Pharmaceuticals, Karlsruhe, Germany; ⁵University of Osnabrueck, Osnabrueck, Germany.
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Received January 12th, 2011; revised March 5th, 2011; accepted March 10th, 2011.

ABSTRACT

Objective: To assess effects of EGb 761[®] on cognition and quality of life in subjects with very mild cognitive impairment. Methods: We randomized 300 subjects aged 45 to 65 with cognitive complaints and low functioning (more than one standard deviation below appropriate norm) in at least one cognitive test to double-blind treatment with once daily 240 mg EGb 761[®] or placebo for 12 weeks. Results: The exploratory intention-to-treat analysis showed significant improvement ($p < 0.025$, one-sided) beyond practice effects for EGb 761[®] in a measure of attention (Vienna Test System-Work Performance Series) and trends in favour of EGb 761[®] in measures of memory (Wechsler Memory Scale III-Faces I, Appointments Test—delayed recall), and perceived physical health (SF36-factor score Physical Health). Cognitive effects were more pronounced and more consistent ($p < 0.025$ in 4 of 5 tests) in subjects with lower memory function at baseline. Specifically, practice effects in the more demanding tests were attenuated or absent in these subjects. Conclusion: Ginkgo biloba extract EGb 761[®] improved cognitive functioning and aspects of quality of life in subjects with very mild cognitive impairment.

Keywords: Ginkgo Biloba, EGb 761[®], Mild Cognitive Impairment, Memory, Concentration, Randomised Controlled Trial

EGb 761[®] in very mild NCD

- Double blind RCT
- 300 subjects
- 12 weeks

Grass-Kapanke et al. 2011, Neuroscience & Medicine 2:48-56

Effects of Ginkgo Biloba Special Extract EGb 761[®] in Very Mild Cognitive Impairment (vMCI)

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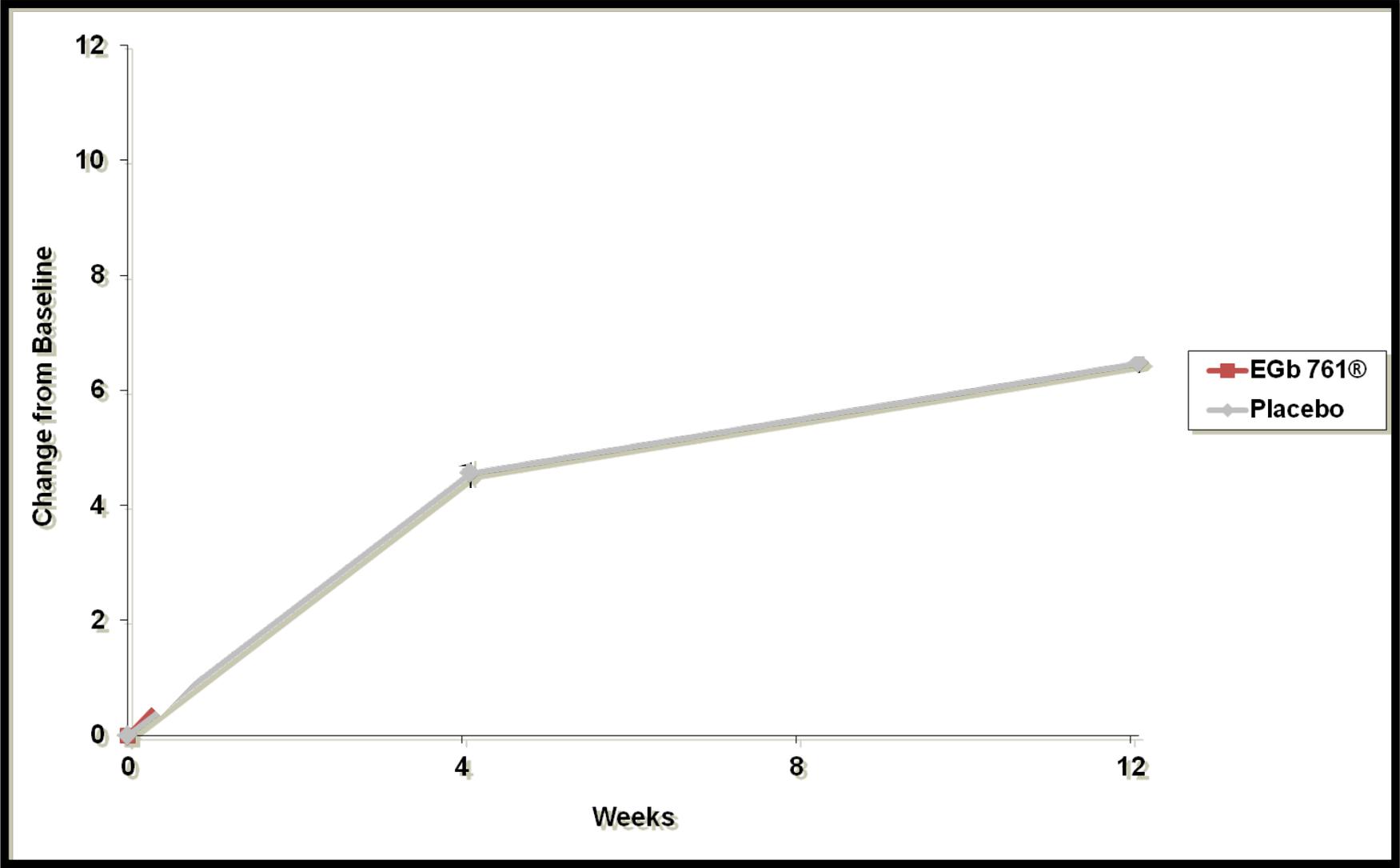
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Change in the “faces 2” task:



EGB 761[®] – 20 year follow up: PAQUID Trial

OPEN ACCESS Freely available online

PLOS ONE

Ginkgo Biloba Extract and Long-Term Cognitive Decline: A 20-Year Follow-Up Population-Based Study

Hélène Amieva^{1,2*}, Céline Meillon¹, Catherine Helmer¹, Pascale Barberger-Gateau¹, Jean François Dartigues¹

¹ University of Bordeaux, ISPED, Centre INSERM U897-Epidemiologie-Biostatistique, Bordeaux, France, ² University of Bordeaux, Department of Psychology, Bordeaux, France

Abstract

Background: Numerous studies have looked at the potential benefits of various nootropic drugs such as Ginkgo biloba extract (EGb761[®]; Tanakan[®]) and piracetam (Nootropyl[®]) on age-related cognitive decline often leading to inconclusive results due to small sample sizes or insufficient follow-up duration. The present study assesses the association between intake of EGb761[®] and cognitive function of elderly adults over a 20-year period.

Methods and Findings: The data were gathered from the prospective community-based cohort study 'Paquid'. Within the study sample of 3612 non-demented participants aged 65 and over at baseline, three groups were compared: 589 subjects reporting use of EGb761[®] at at least one of the ten assessment visits, 149 subjects reporting use of piracetam at one of the assessment visits and 2874 subjects not reporting use of either EGb761[®] or piracetam. Decline on MMSE, verbal fluency and visual memory over the 20-year follow-up was analysed with a multivariate mixed linear effects model. A significant difference in MMSE decline over the 20-year follow-up was observed in the EGb761[®] and piracetam treatment groups compared to the 'neither treatment' group. These effects were in opposite directions: the EGb761[®] group declined less rapidly than the 'neither treatment' group, whereas the piracetam group declined more rapidly ($\beta = -0.6$). Regarding verbal fluency and visual memory, no difference was observed between the EGb761[®] group and the 'neither treatment' group (respectively, $\beta = 0.21$ and $\beta = -0.03$), whereas the piracetam group declined more rapidly (respectively, $\beta = -1.40$ and $\beta = -0.44$). When comparing the EGb761[®] and piracetam groups directly, a different decline was observed for the three tests (respectively $\beta = -1.07$, $\beta = -1.61$ and $\beta = -0.41$).

Conclusion: Cognitive decline in a non-demented elderly population was lower in subjects who reported using EGb761[®] than in those who did not. This effect may be a specific medication effect of EGb761[®], since it was not observed for another nootropic medication, piracetam.

Citation: Amieva H, Meillon C, Helmer C, Barberger-Gateau P, Dartigues JF (2013) Ginkgo Biloba Extract and Long-Term Cognitive Decline: A 20-Year Follow-Up Population-Based Study. PLoS ONE 8(1): e52755. doi:10.1371/journal.pone.0052755

Editor: Sonia Brucki, University Of São Paulo, Brazil

EGb 761[®] – 20 year follow up: PAQUID Trial

- Prospective community-based cohort
- 3612 non demented patients > 65 years
- 589 used EGb 761[®]
- 149 used Piracetam

Amieva H et al. PLoS One. 2013

OPEN ACCESS Freely available online 

Ginkgo Biloba Extract and Long-Term Cognitive Decline: A 20-Year Follow-Up Population-Based Study

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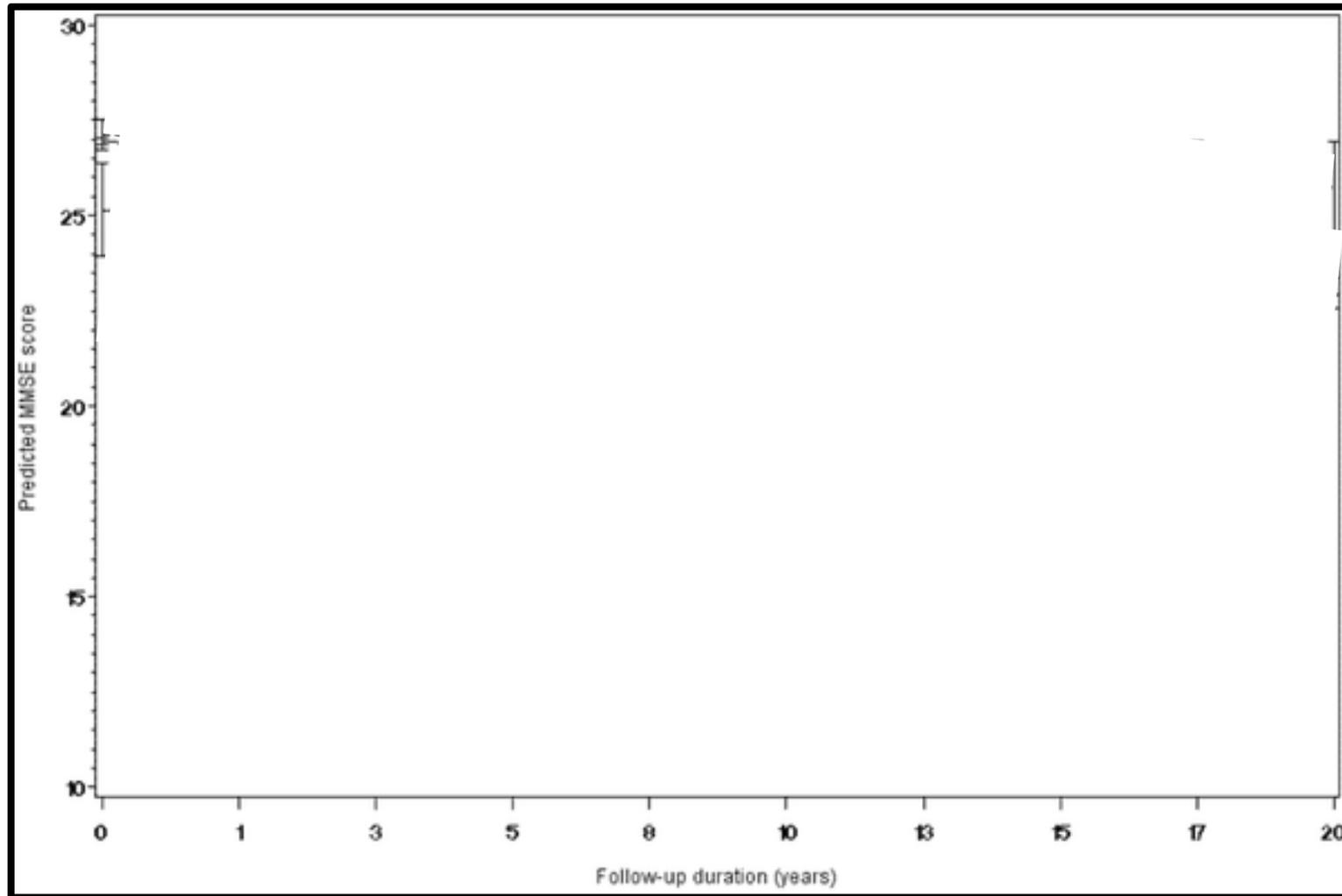
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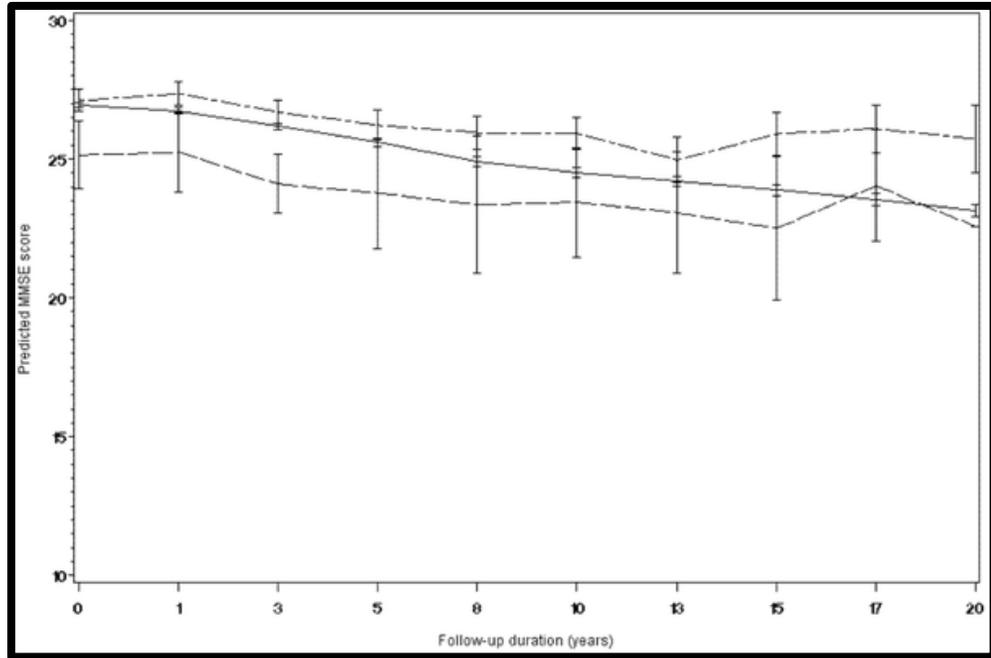
Editor: Sonia Brucki, University Of São Paulo, Brazil

Change in MMSE score over the 20-year follow-up:



Amieva H et al. (2013) PLOS ONE

EGb 761[®] – 20 year follow up: PAQUID Trial



- First longitudinal study with such a long period of time and so many participants
- MMSE decline in EGb 761[®] users significantly slower than in controls
- Difference of 5 MMSE points over 20 years

Association Between *Ginkgo Biloba* Extract Prescriptions and Dementia Incidence in Outpatients with Mild Cognitive Impairment in Germany: A Retrospective Cohort Study

Jens Bohlken^a, Oliver Peters^{b,c} and Karel Kostev^{d,*}

^a*Institute for Social Medicine, Occupational Medicine, and Public Health (ISAP) of the Medical Faculty at the University of Leipzig, Leipzig, Germany*

^b*Department of Psychiatry, Charité-Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany*

EGb 761[®] prescriptions and cognitive outcome

- 24,483 patients \geq 65 years old
- An initial MCI diagnosis between January 2000 and December 2019
- Observation up to 20 years

Bohlken et al. Journal of Alzheimer's disease 2022

Journal of Alzheimer's Disease 86 (2022) 703–709
DOI 10.3233/JAD-215348
IOS Press

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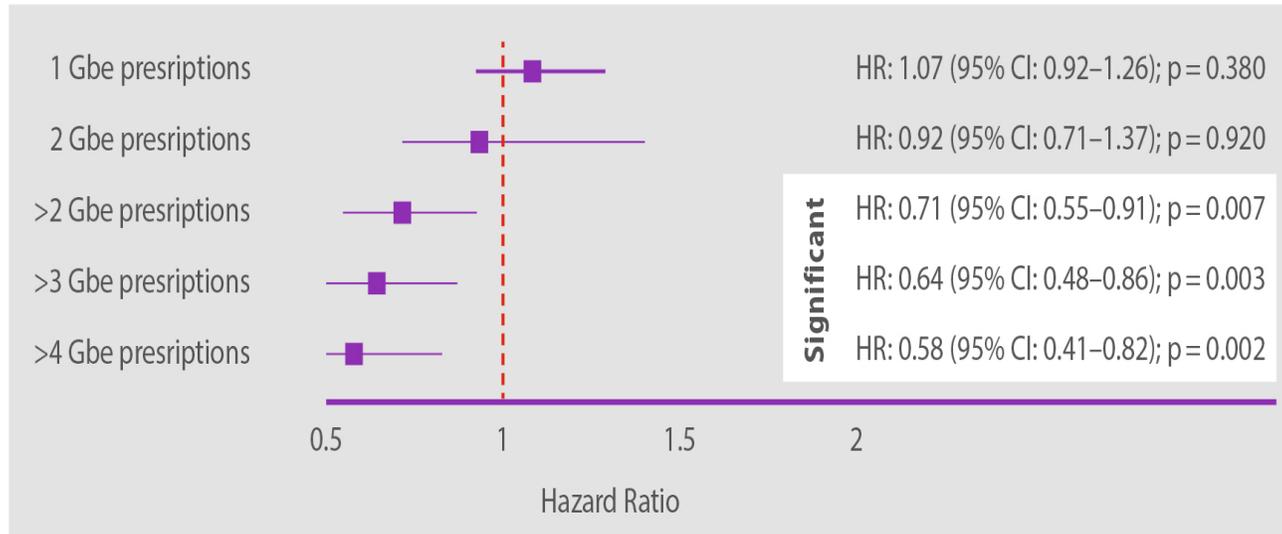
Association Between *Ginkgo Biloba* Extract Prescriptions and Dementia Incidence in Outpatients with Mild Cognitive Impairment in Germany: A Retrospective Cohort Study

Jens Bohlken^a, Oliver Peters^{b,c} and Karel Kostev^{d,*}

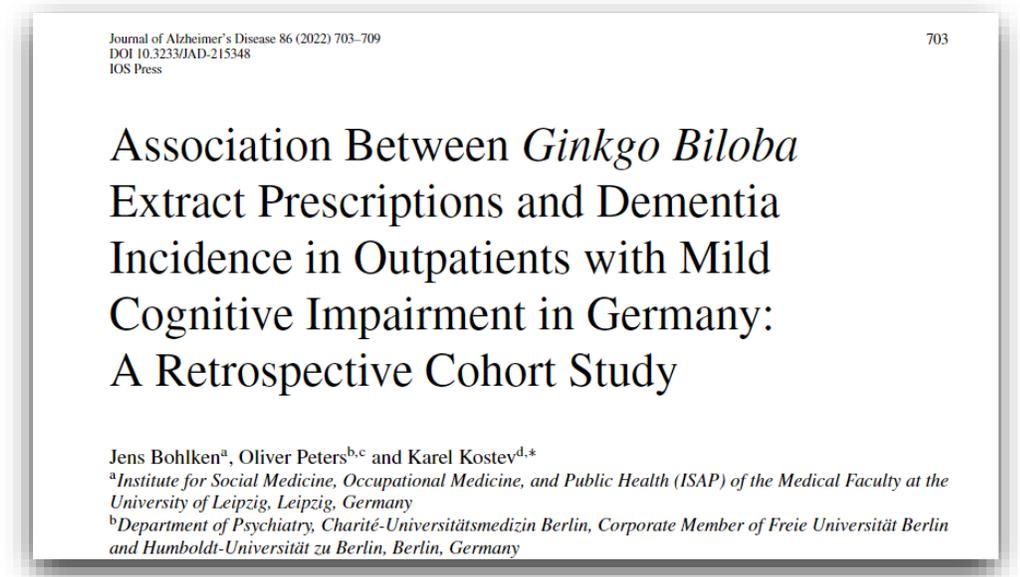
^aInstitute for Social Medicine, Occupational Medicine, and Public Health (ISAP) of the Medical Faculty at the University of Leipzig, Leipzig, Germany

^bDepartment of Psychiatry, Charité-Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany

EGb 761[®] prescriptions and cognitive outcome

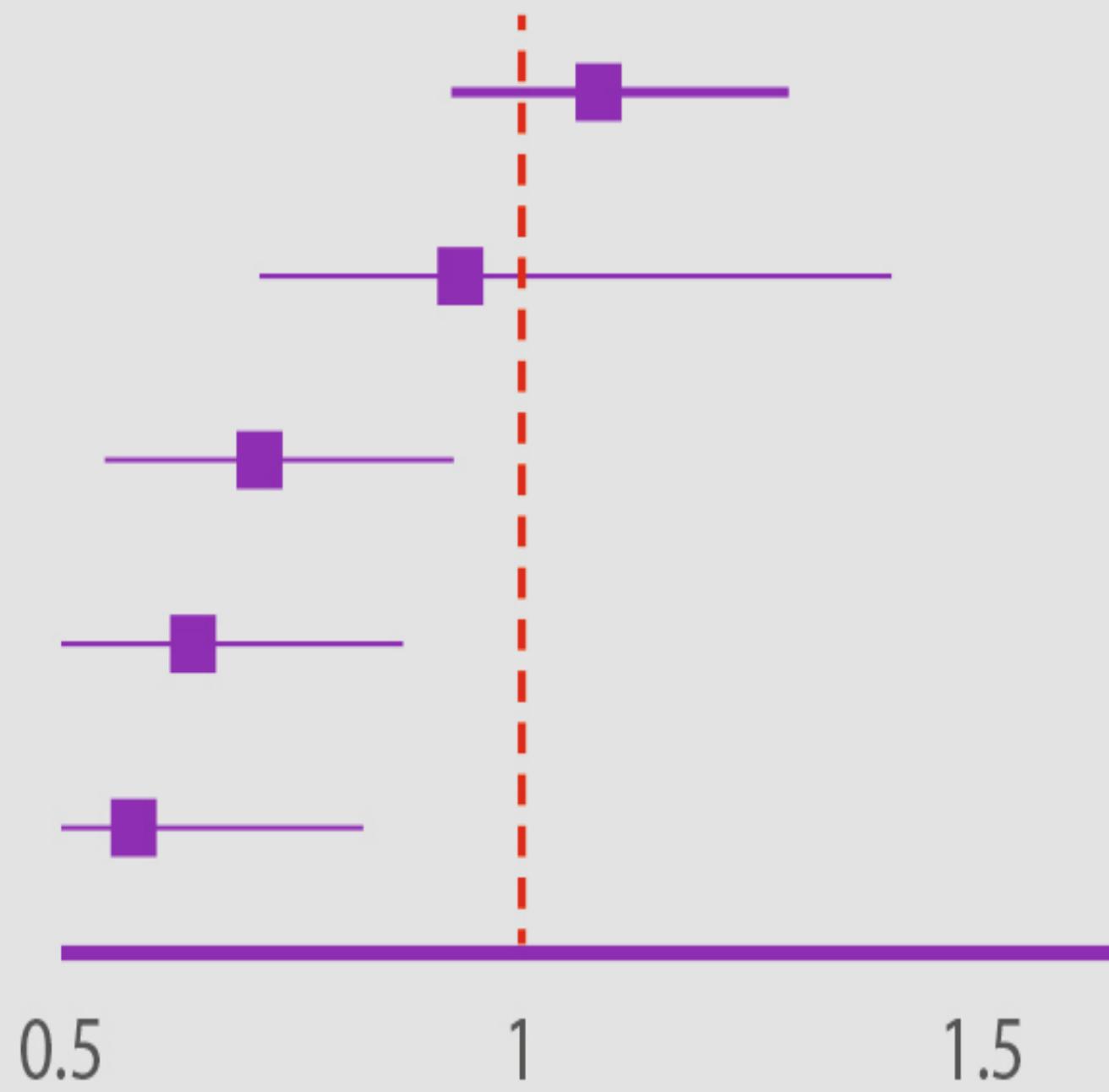


Graphic adapted from Bohlken et al. 2022



>2 Ginkgo-extract prescriptions: substantially lower dementia risk

1 Gbe prescriptions
2 Gbe prescriptions
>2 Gbe prescriptions
>3 Gbe prescriptions
>4 Gbe prescriptions



REVIEW

Treatment effects of *Ginkgo biloba* extract EGb 761[®] on the spectrum of behavioral and psychological symptoms of dementia: meta-analysis of randomized controlled trials

Egemen Savaskan,¹ Heiko Mueller,² Robert Hoerr,² Armin von Gunten³
and Serge Gauthier⁴

¹Department of Geriatric Psychiatry, University Hospital of Psychiatry, Zurich, Switzerland

²Clinical Research Department, Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany

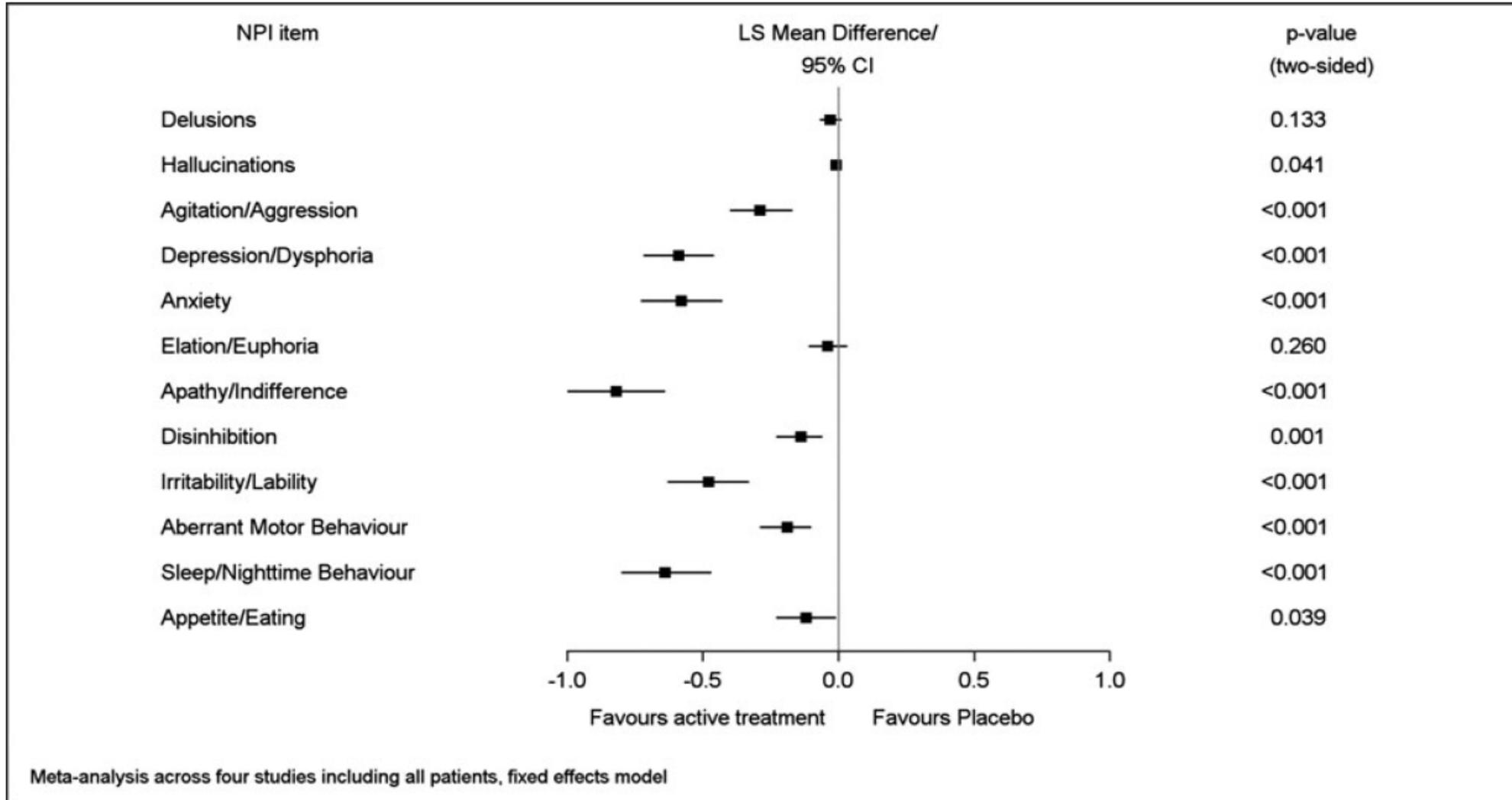
³Department of Psychiatry, Service Universitaire de Psychiatrie de l'Age Avancé (SUPAA), Centre Hospitalier Universitaire Vaudois, Prilly, Switzerland

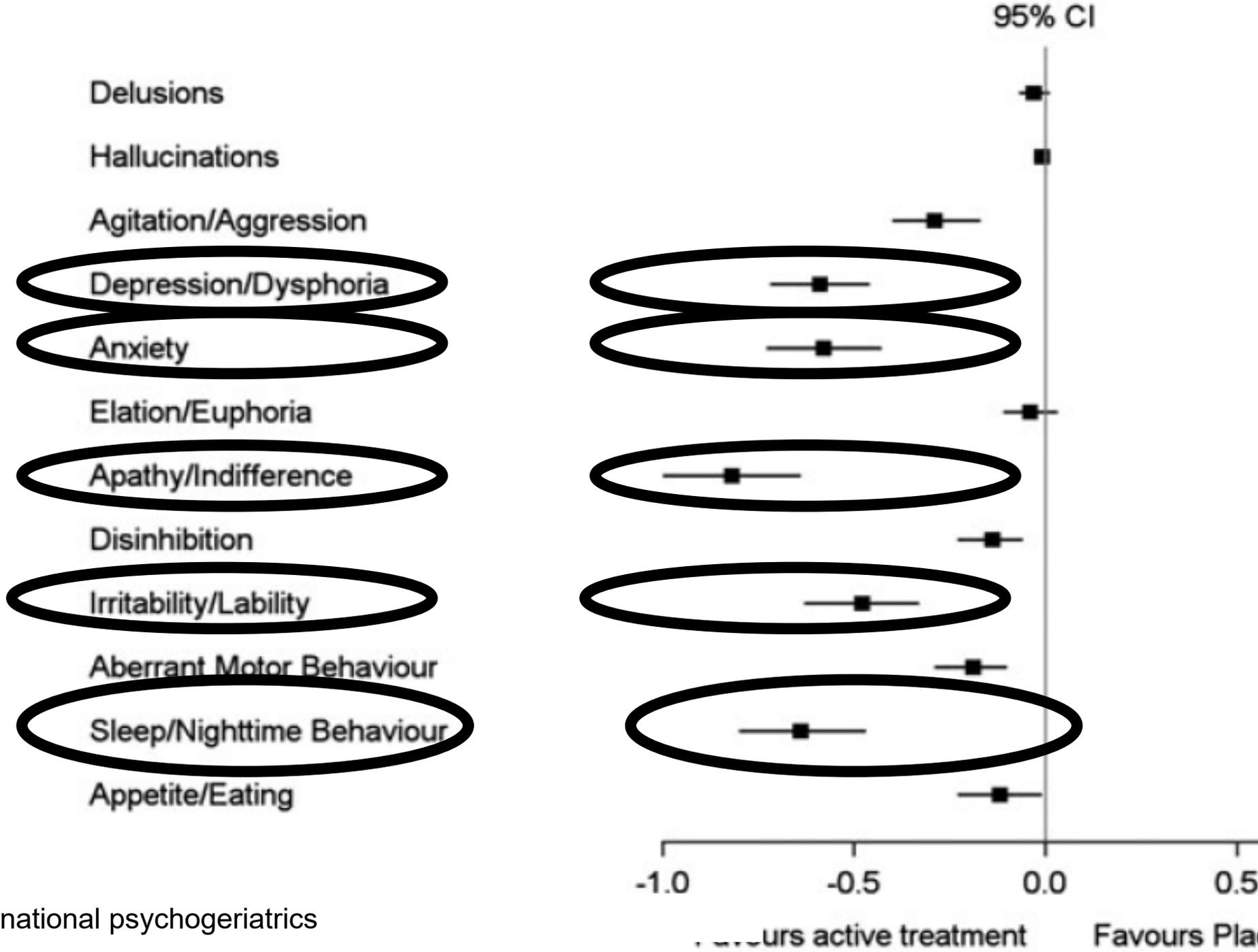
⁴Alzheimer Disease Research Unit, Memory Clinic, McGill Centre for Studies in Aging, McGill University, Verdun, Quebec, Canada

ABSTRACT

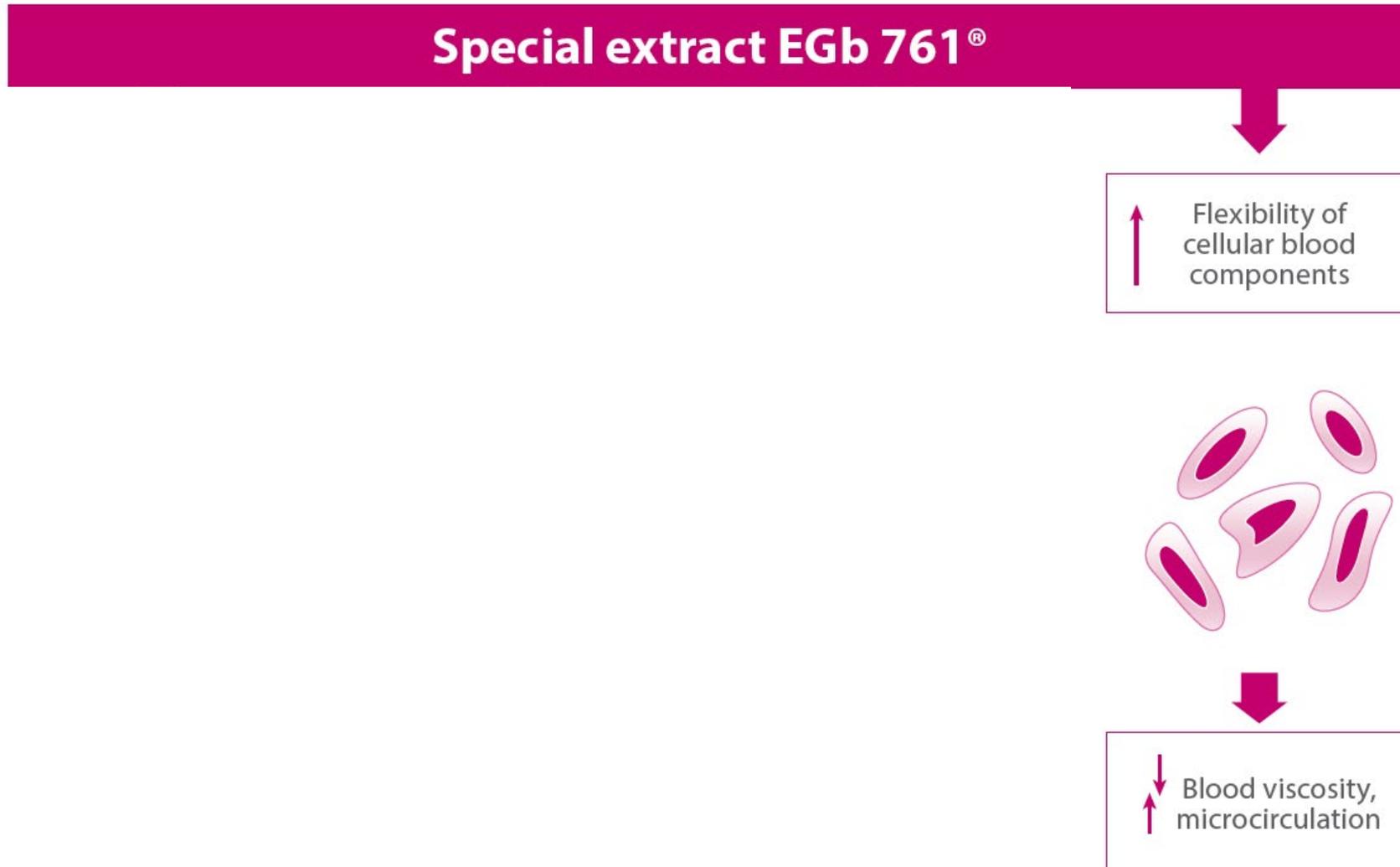
Background: In randomized controlled trials, *Ginkgo biloba* extract EGb 761[®] has been found to be effective in the treatment of behavioral and psychological symptoms of dementia (BPSD).

EGb 761[®] – psychiatric effects

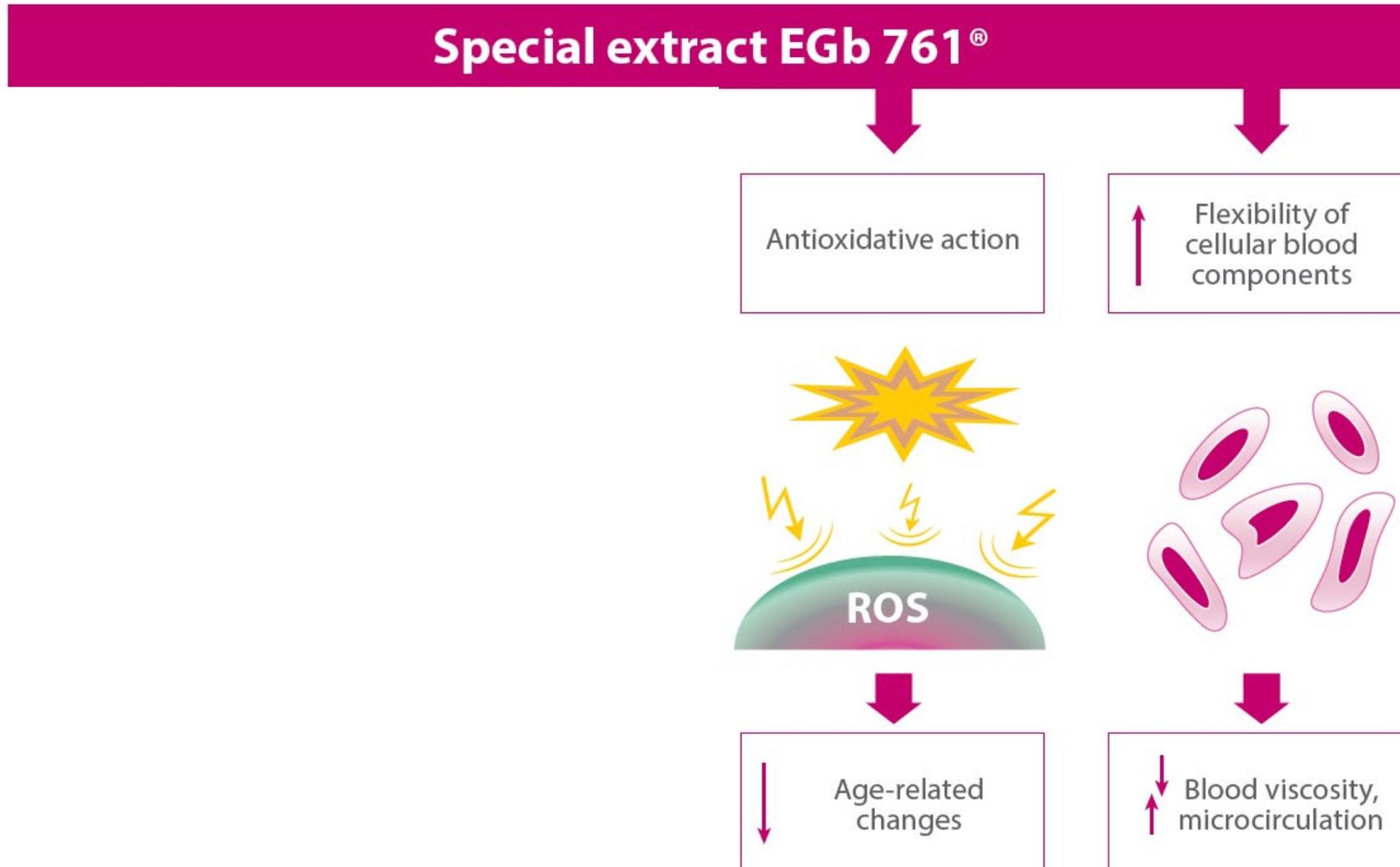




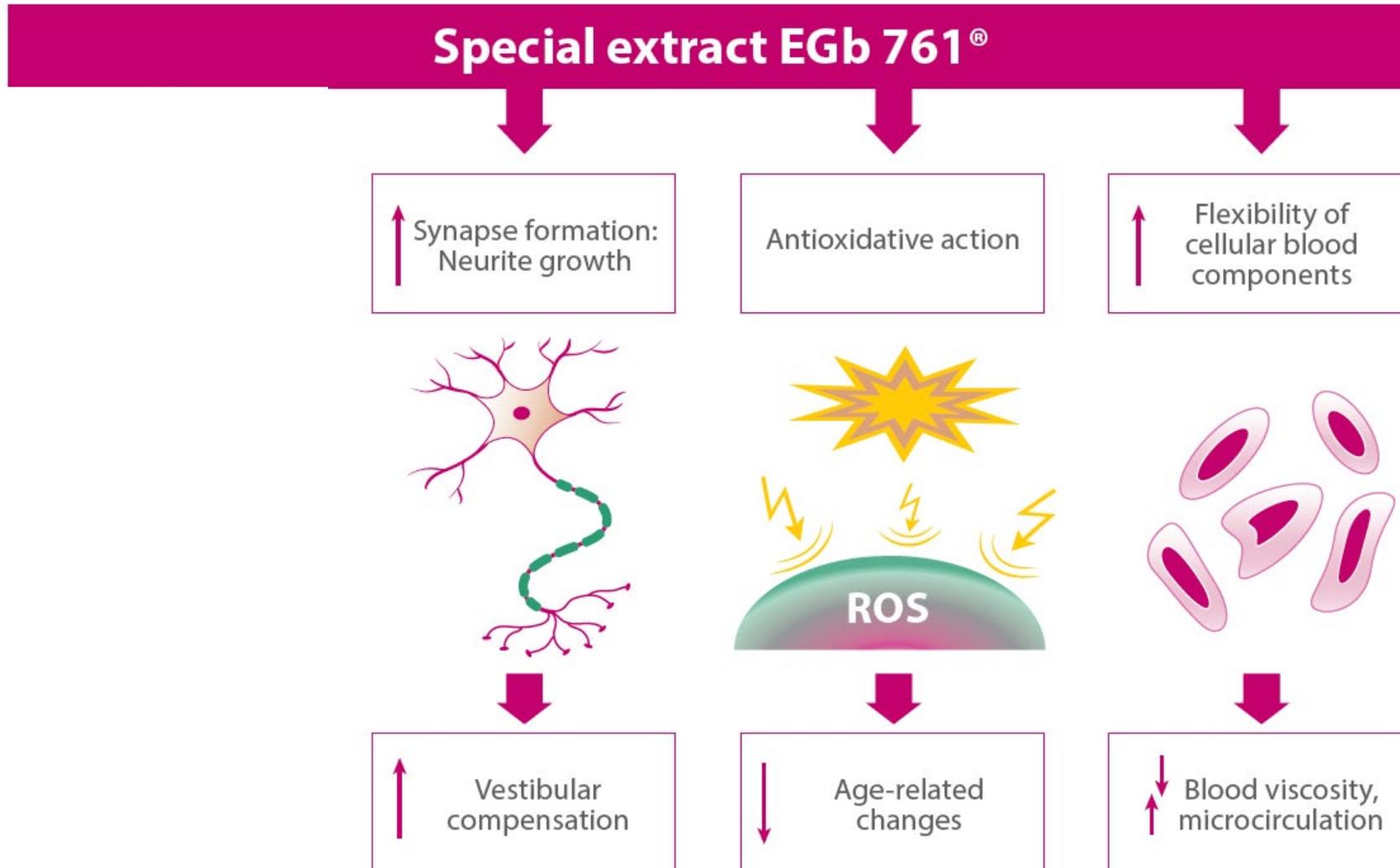
EGb 761[®] – proposed mode of action



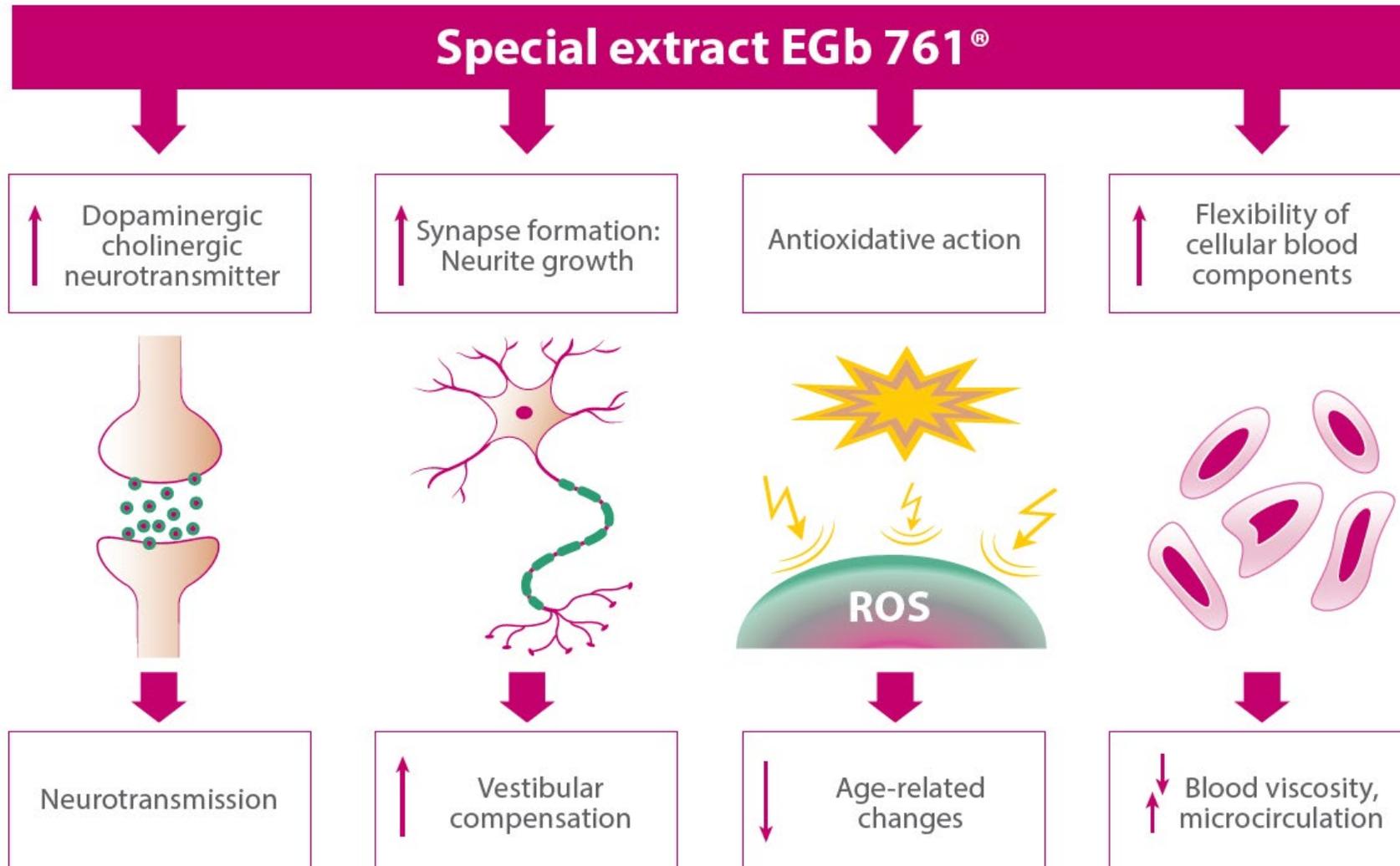
EGb 761[®] – proposed mode of action



EGb 761[®] – proposed mode of action



EGb 761[®] – proposed mode of action



EGb 761[®] – side effects

- No safety risk in long-term trials
- Mild gastrointestinal disturbances
- Headache
- Dizziness or enhancement of already existing dizziness

(Pharmacotherapy 2011;31(5):490–502)

Is There a Risk of Bleeding Associated with Standardized *Ginkgo biloba* Extract Therapy? A Systematic Review and Meta-analysis

Andrea J. Kellermann, Dipl. Pharm., and Charlotte Kloft, Ph.D.

Study Objective. To determine the effect of standardized *Ginkgo biloba* leaf extracts (GBE) on outcome parameters of hemostasis associated with risk

Conclusion. Based on meta-analysis of hemostasis outcomes, comparison of mean difference or baseline change between treatment and placebo groups did not indicate a higher bleeding risk associated with standardized GBE.

Measurements and Main Results. The MEDLINE, EMBASE, Cochrane Library, and SciSearch databases were searched from inception through 2009. The following outcome parameters of hemostasis were assessed: blood flow, blood viscosity, adenosine 5'-diphosphate (ADP)-induced platelet aggregation, fibrinogen concentration, activated partial thromboplastin time (aPTT), and prothrombin time (PT). Reference parameter values were taken into account when assessing clinical relevance

Clinical trials of EGb 761[®] in thousands of patients did not demonstrate any risk of bleeding, either when administered alone or together with ASA or warfarin.

EGb 761[®] as a Treatment Option in MCI / Prodromal AD

- **Czech Consensus** (Jirák 2014/2017):

EGb 761[®] recommended in "incipient dementia" (MMSE > 25)

- **European Medicines Agency / Committee on Herbal Medicinal Products: Monograph 2015, well established use:** for the improvement of (age-associated) cognitive decline and of quality of life in mild dementia

- **Swiss Expert Recommendation** (Kressig 2015):

start of **EGb 761[®] treatment recommended at MCI** stage

- **China Dementia & MCI Diagnosis & Treatment Guidelines** (Jia 2015):

EGb 761[®] is effective in the treatment of AD, multi-infarct dementia and MCI

- **Spanish Consensus** (López Trigo et al. 2017):
EGb 761[®] is the only approved drug treatment for MCI
- **European Experts Review** on the Management of MCI (Kasper et al. 2020):
EGb 761[®] is recommended for the symptomatic treatment of cognitive impairment and associated NPS
- **Thailand Dementia & MCI Treatment Guidelines 2020:**
EGb 761[®] is the 1st and only drug approved by Thailand FDA for the treatment of MCI
- **ASCEND2 Asian Expert Consensus** (Kandiah et al. 2021):
EGb 761[®] is currently the only pharmacological agent recommended for treatment of MCI. EGb 761[®] has a role in the multidomain intervention strategy for MCI management.

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Check for updates

CLINICAL GUIDELINES

CNS Neuroscience & Therapeutics WILEY

Strategies for the use of *Ginkgo biloba* extract, EGb 761[®], in the treatment and management of mild cognitive impairment in Asia: Expert consensus

Nagaendran Kandiah^{1,2,3} | Yee Fai Chan⁴ | Christopher Chen⁵ | Darwin Dasig⁶ | Jacqueline Dominguez⁷ | Seol-Heui Han⁸ | Jianping Jia⁹ | SangYun Kim¹⁰ | Panita Limpawattana¹¹ | Li-Ling Ng¹² | Dinh Toan Nguyen¹³ | Paulus Anam Ong¹⁴ | Encarnita Raya-Ampil¹⁵ | Nor'izzati Saedon¹⁶ | Vorapun Senanarong¹⁷ | Siti Setiati¹⁸ | Harjot Singh¹⁹ | Chuthamane Suthisisang²⁰ | Tong Mai Trang²¹ | Yuda Turana²² | Narayanaswamy Venketasubramanian²³ | Fee Mann Yong²⁴ | Yong Chul Youn²⁵ | Ralf Ihl²⁶

Strategies for the use of *Ginkgo biloba* extract, EGb 761[®], in the treatment and management of mild cognitive impairment in Asia: Expert consensus

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ASCEND2 Consensus (Asian Clinical Expert Group):



At least four randomized trials have shown improvement in MCI symptoms with **EGb 761[®]**



EGb 761[®] may be incorporated into a multidomain intervention for MCI



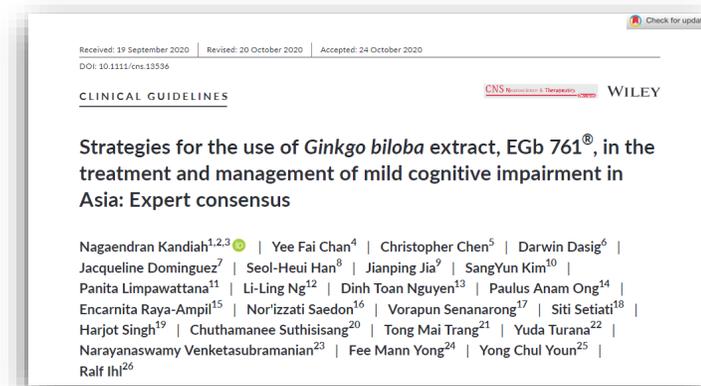
There is evidence suggesting **EGb[®] 761** may help delay progression from MCI to dementia in some individuals



EGb[®] 761 is currently the **only** pharmacological agent recommended for treatment of MCI



EGb 761[®] may improve cognitive performance and NPS in MCI patients





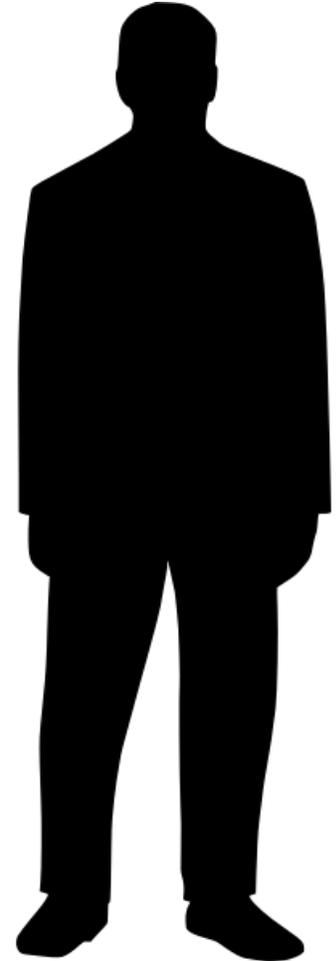
ASCEND2 Consensus (Asian Clinical Expert Group):



**EGb 761[®] is currently the only
pharmacological agent
recommended for treatment of MCI**

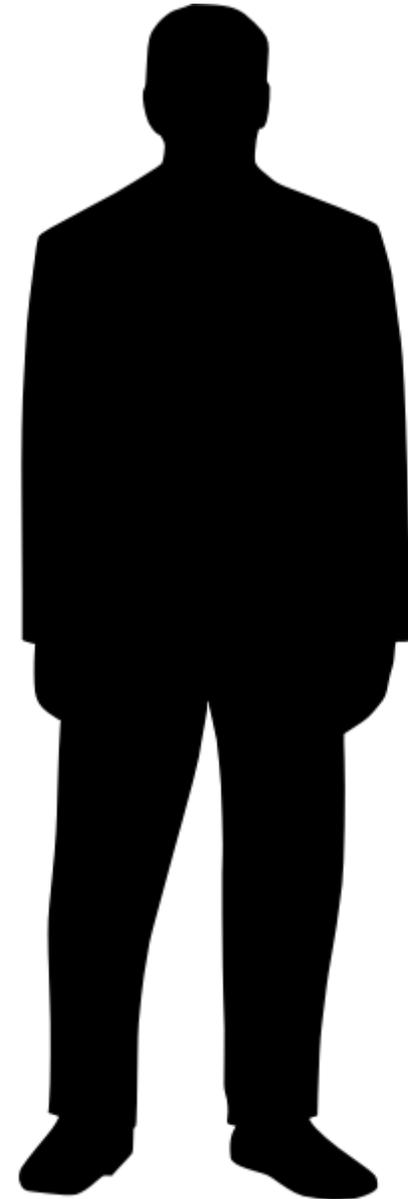


Again - what about our patients?



Mr. M

- 74, “apathetic”
- Probable MCI
- Was started on EGb 761[®] 120 mg twice daily
- Improved hedonia, renewed visits to his grandkids





Mrs. T

- 78, anxious and depressed for the 1st time in her life
- Cognitively intact
- Workup revealed metastatic pancreatic cancer
- Was given an SSRI



Mr. S

- 79 Started “talking dirty”
- Major NCD
- Started choline-esterase inhibitor
- Was institutionalized upon follow up

