„Dementia”

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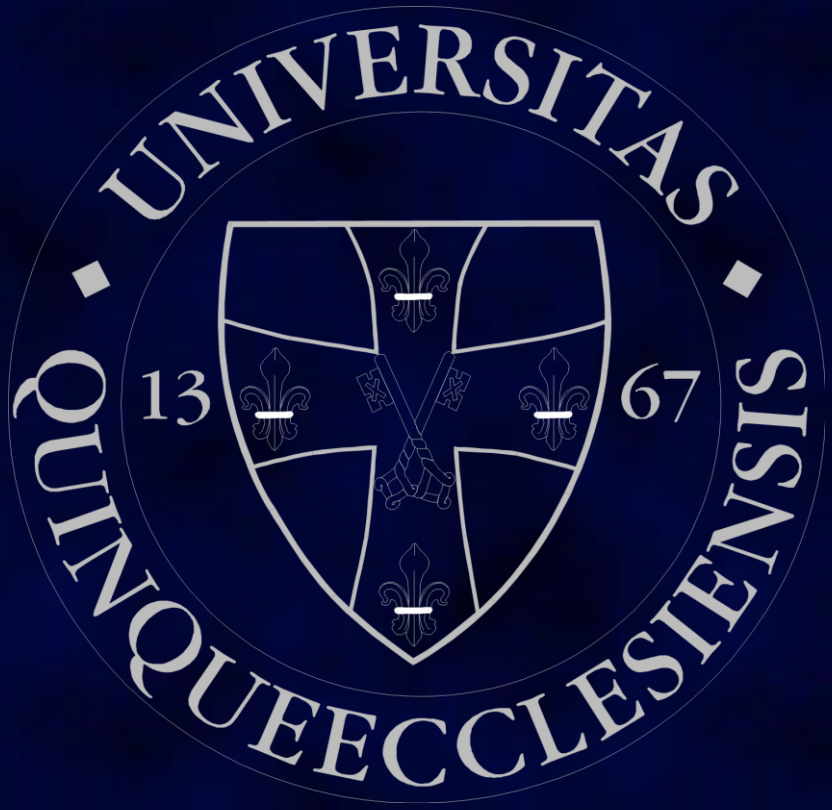

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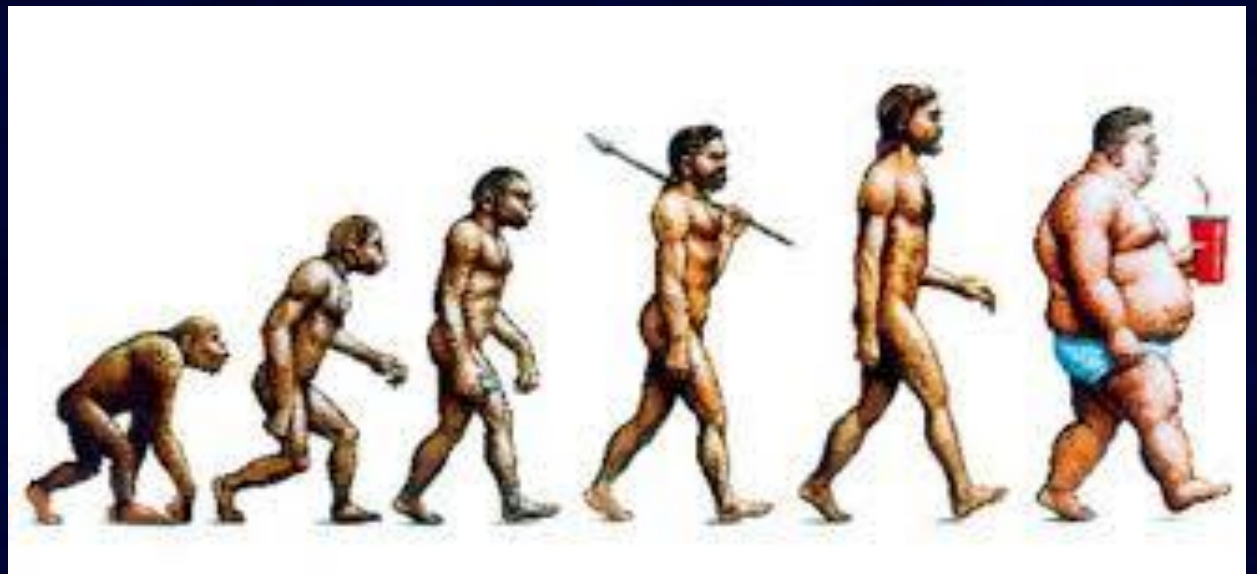
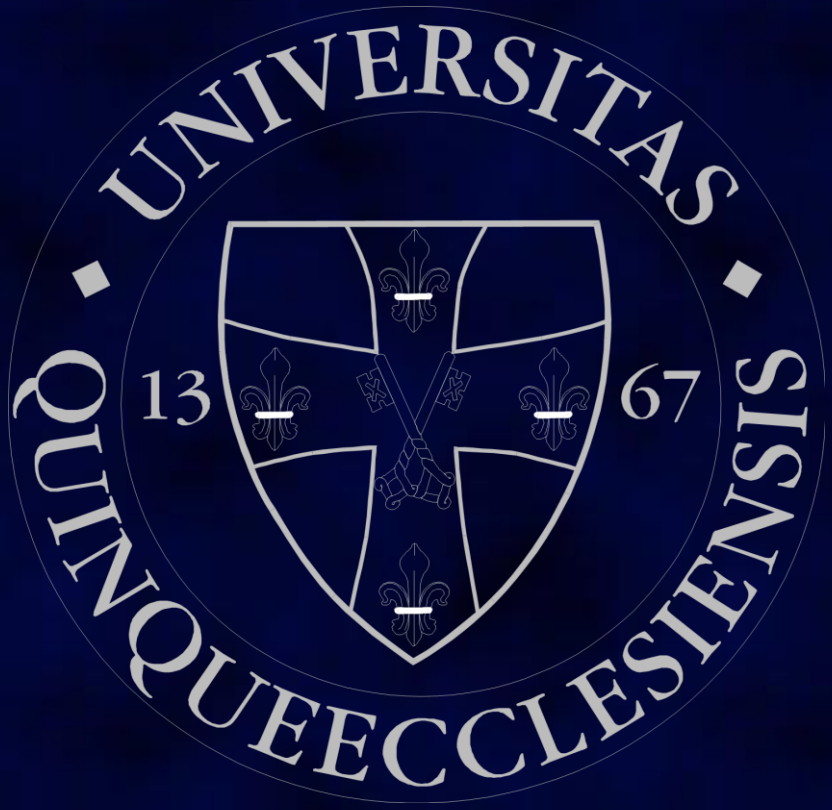
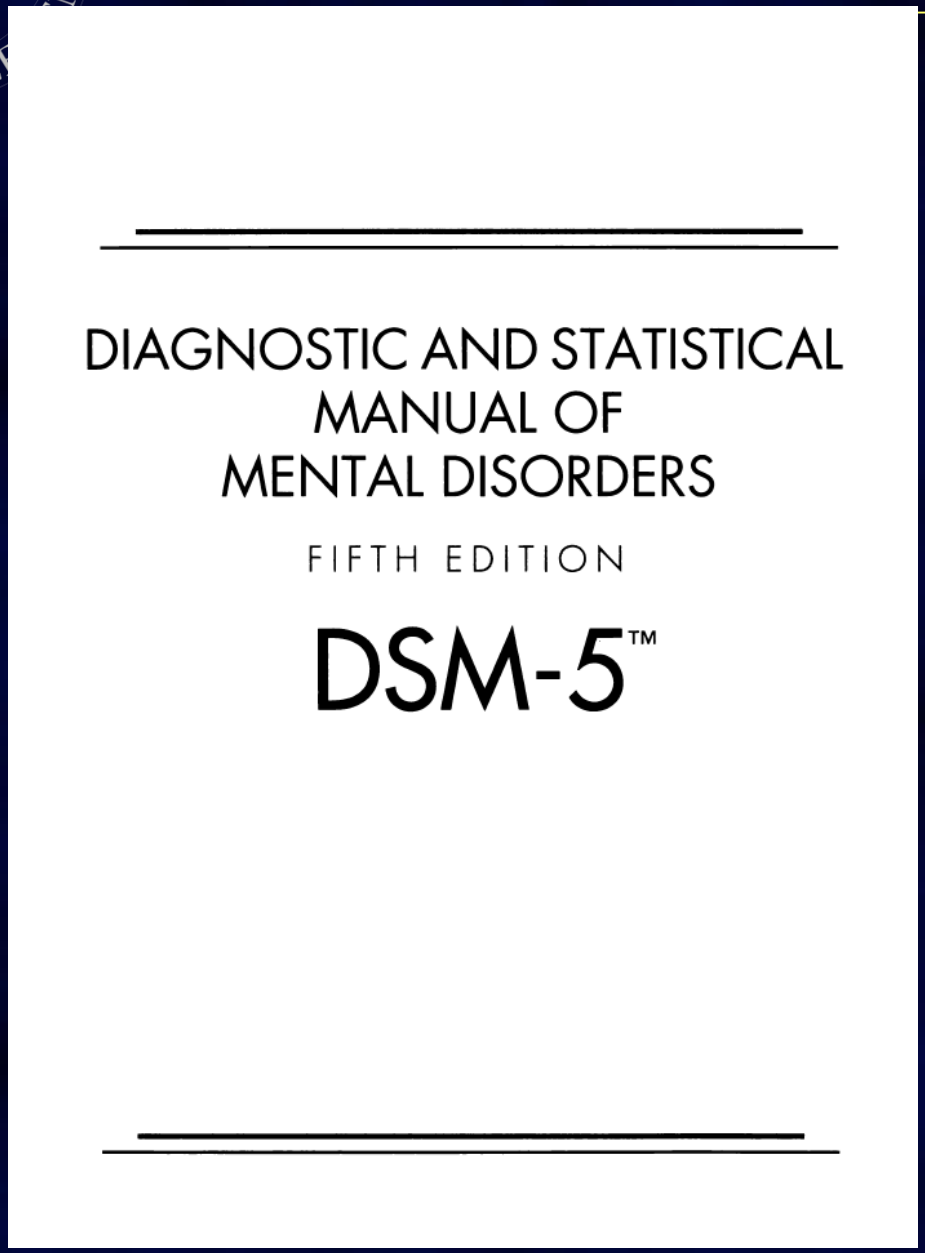
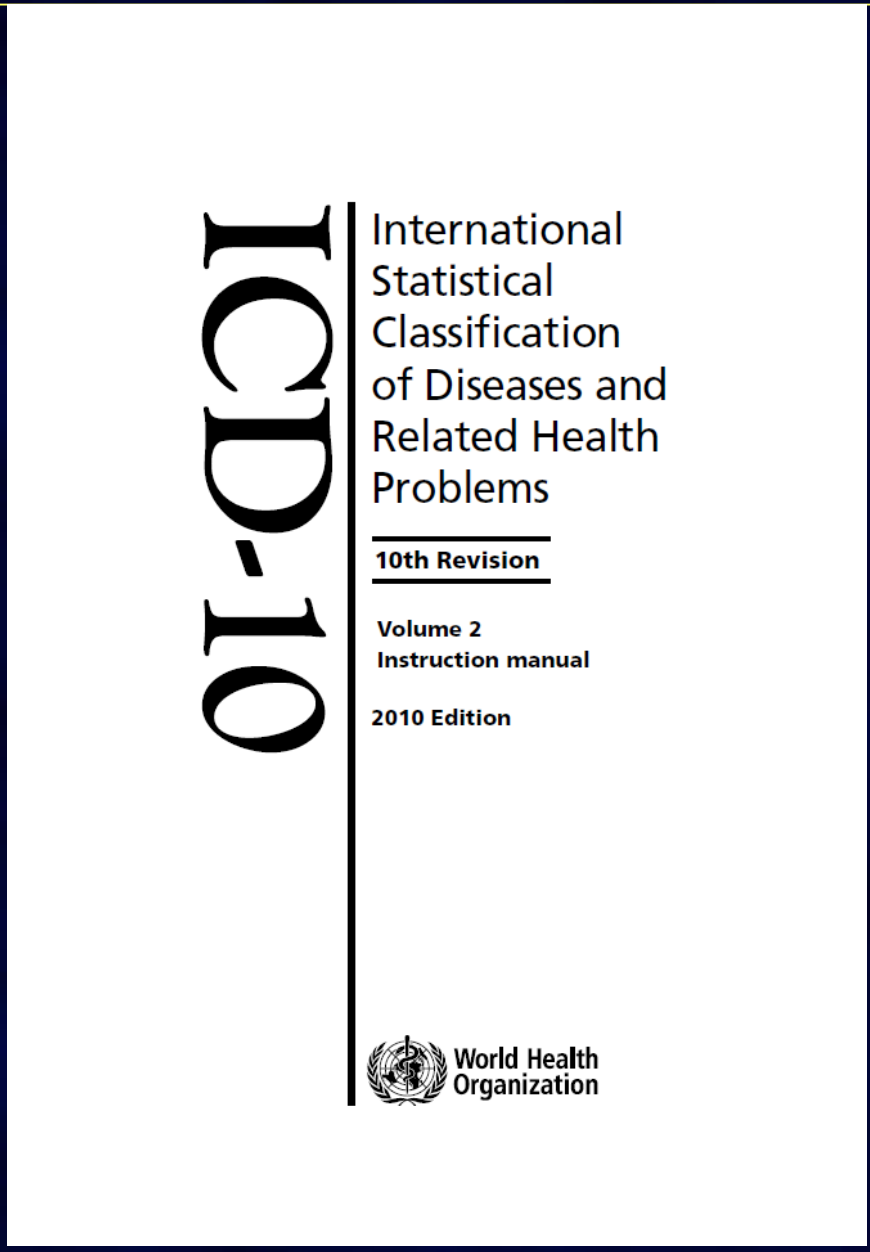


1. Definitions



Definitions





American Psychiatric Association: 2013 WHO: 1990

Definitions

SMI: Subjective memory impairment

- There is no consensus definition
- Patient subjectively feel worsening in cognitive performance
- No objective symptoms, do not fulfil MCI or dementia
- Mixture of syndromes, etiologies
- May be secondary to other problems (e.g. depression)

MCI: Mild cognitive impairment

- the changes in cognition exceeds the normal, expected changes related to age, but not fulfills the criteria for dementia
- In one classification of MCI, the amnestic form is distinguished from the nonamnestic form.
- 1 domain vs. multiple domains

Dementia

Definitions: DSM-V

Neurocognitive disorders (NCDs)

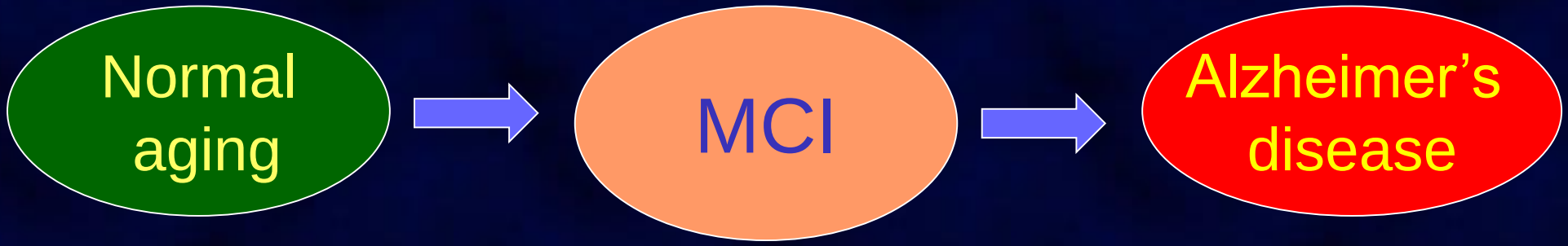
- New definition introduced by DSM-V
- Encompasses the group of disorders in which the primary clinical deficit is in cognitive function,
- and that are acquired rather than developmental
- impaired cognition has not been present since birth or very early life, and thus represents a decline from a previously attained level of functioning

- Dementia → **major neurocognitive disorder**
- MCI→ **minor neurocognitive disorder**

Definitions: DSM-V

Minimal cognitive impairment - MCI:

- Introduced by DSM-IV and DSM-IVTR
- Thought to be the pre-phase of the AD (>40-60% of cases convert to AD)



Minor NCDs (DSM-V):

- Each major NCD now has its minor NCD form
- E.g. Major NCD in PD and minor NCD in PD

Definitions: DSM-V

Term of „Dementia" is outdated

- Dementia is subsumed under the newly named entity **major neurocognitive disorder**, although the term dementia is not precluded from use in the etiological subtypes in which that term is standard.
- Dementia is a „negative term" with negative associations
- Dementia is associated with older persons
- NCDs do not have negative stigma and may be a broader category (including younger persons)

mild neurocognitive disorder:

- less severe level of cognitive impairment,
- It can be (should be) both diagnosed and treated

Neurocognitive domains -1

Complex attention:

- sustained attention *(pressing buttons over a period of time)*,
- divided attention *(two tasks: e.g. tapping while learning a story being read)*
- selective attention *(hearing numbers and letters, but count one type)*
- processing speed *(time to match symbols, counting speed)*

Major: Has increased difficulty in environments with multiple stimuli (TV, radio, conversation); is easily distracted by competing events in the environment. Is unable to attend unless input is restricted and simplified. Has difficulty holding new information in mind, such as recalling phone numbers or addresses just given, or reporting what was just said. Is unable to perform mental calculations. All thinking takes longer than usual, and components to be processed must be simplified to one or a few.

Mild: Normal tasks take longer than previously. Begins to find errors in routine tasks; finds work needs more double-checking than previously. Thinking is easier when not competing with other things (radio, TV, other conversations, cell phone, driving).

Neurocognitive domains -2

Executive function:

- Planning *(ability to find exit, object arrangement, interpret sequential picture)*,
- decision making *(e.g. stimulated gambling)*
- working memory *(adding up a list of numbers, repeating a list of numbers, words backwards)*
- feedback/error correction *(ability to benefit from feedback)*
- overriding habits/inhibition *(e.g. Stroop test: naming the color of a words font)*
- mental flexibility: *ability to shift between two concepts, tasks, or response rules*

Major: Abandons complex projects. Needs to focus on one task at a time. Needs to rely on others to plan instrumental activities of daily living or make decisions.

Mild: Increased effort required to complete multistage projects. Has increased difficulty multitasking or difficulty resuming a task interrupted by a visitor or phone call. May complain of increased fatigue from the extra effort required to organize, plan, and make decisions. May report that large social gatherings are more taxing or less enjoyable because of increased effort required to follow shifting conversations.

Neurocognitive domains -3

Learning and memory:

- immediate memory *(ability to repeat a list of words or digits)*,
- recent memory *(learn word list, short story or diagrams)*
- very-long-term memory *(semantic –memory for facts- and autobiographical)*
- implicit memory *(unconscious learning of skills)*

Major: Repeats self in conversation, often within the same conversation. Cannot keep track of short list of items when shopping or of plans for the day. Requires frequent reminders to orient to task at hand.

Mild: Has difficulty recalling recent events, and relies increasingly on list making or calendar. Needs occasional reminders or re-reading to keep track of characters in a movie or novel. Occasionally may repeat self over a few weeks to the same person. Loses track of whether bills have already been paid.

Note: Except in severe forms of major neurocognitive disorder, semantic, autobiographical, and implicit memory are relatively preserved, compared with recent memory.

Neurocognitive domains -4

Language

- expressive language: *naming, fluency, phonemic*
- grammar and syntax:
- receptive language: *word definition, performance of actions by verbal command*

Major: Has significant difficulties with expressive or receptive language. Often uses general-use phrases such as "that thing" and "you know what I mean," and prefers general pronouns rather than names. With severe impairment, may not even recall names of closer friends and family. Idiosyncratic word usage, grammatical errors, and spontaneity of output and economy of utterances occur. Stereotypy of speech occurs; echolalia and automatic speech typically precede mutism.

Mild: Has noticeable word-finding difficulty. May substitute general for specific terms. May avoid use of specific names of acquaintances. Grammatical errors involve subtle omission or incorrect use of articles, prepositions, auxiliary verbs, etc.

Neurocognitive domains -5

Perceptual-motor

- visual perception: *line bisection tasks for defects or neglect, facial recognition*
- Visuoconstructional: *drawing, copying or block assembly*
- perceptual-motor: *inserting blocks into a form board*
- Praxis: *imitate gestures or pantomime use of objects (e.g. a hammer)*
- Gnosis: *integrity of recognition, e.g. faces and colors*

Major: Has significant difficulties with previously familiar activities (using tools, driving motor vehicle), navigating in familiar environments; is often more confused at dusk, when shadows and lowering levels of light change perceptions.

Mild: May need to rely more on maps or others for directions. Uses notes and follows others to get to a new place. May find self lost or turned around when not concentrating on task. Is less precise in parking. Needs to expend greater effort for spatial tasks such as carpentry, assembly, sewing, or knitting.

Neurocognitive domains -6

Social cognition

- recognition of emotions
- theory of mind: *ability to consider another person's mental state*

Major: Behavior clearly out of acceptable social range; shows insensitivity to social standards of modesty in dress or of political, religious, or sexual topics of conversation. Focuses excessively on a topic despite group's disinterest or direct feedback. Behavioral intention without regard to family or friends. Makes decisions without regard to safety (e.g., inappropriate clothing for weather or social setting). Typically, has little insight into these changes.

Mild: Has subtle changes in behavior or attitude, often described as a change in personality, such as less ability to recognize social cues or read facial expressions, decreased empathy, increased extraversion or introversion, decreased inhibition, or subtle or episodic apathy or restlessness.

Major Neurocognitive Disorder

- A. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains based on:
  - 1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function; and
  - 2. A substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.
- B. The cognitive deficits interfere with independence in everyday activities (i.e., at a minimum, requiring assistance with complex instrumental activities of daily living such as paying bills or managing medications).
- C. The cognitive deficits do not occur exclusively in the context of a delirium.
- D. The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia).

Mild Neurocognitive Disorder

- A. Evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains based on:
  - 1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a mild decline in cognitive function; and
  - 2. A modest impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.
- B. The cognitive deficits do not interfere with capacity for independence in everyday activities (i.e., complex instrumental activities of daily living such as paying bills or managing medications are preserved, but greater effort, compensatory strategies, or accommodation may be required).
- C. The cognitive deficits do not occur exclusively in the context of a delirium.
- D. The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia).

Major subtypes of NCDs

According to DSM-V

- Alzheimer's disease (AD)
- Frontotemporal lobar degeneration (FTLD)
- Lewy body disease (DLBD)
- Vascular disease (VD)
- Traumatic brain injury (TBI)
- Substance/medication use
- HIV infection
- Prion disease
- Parkinson's disease (PD)
- Huntington's disease (HD)
- Another medical condition
- Multiple etiologies
- Unspecified

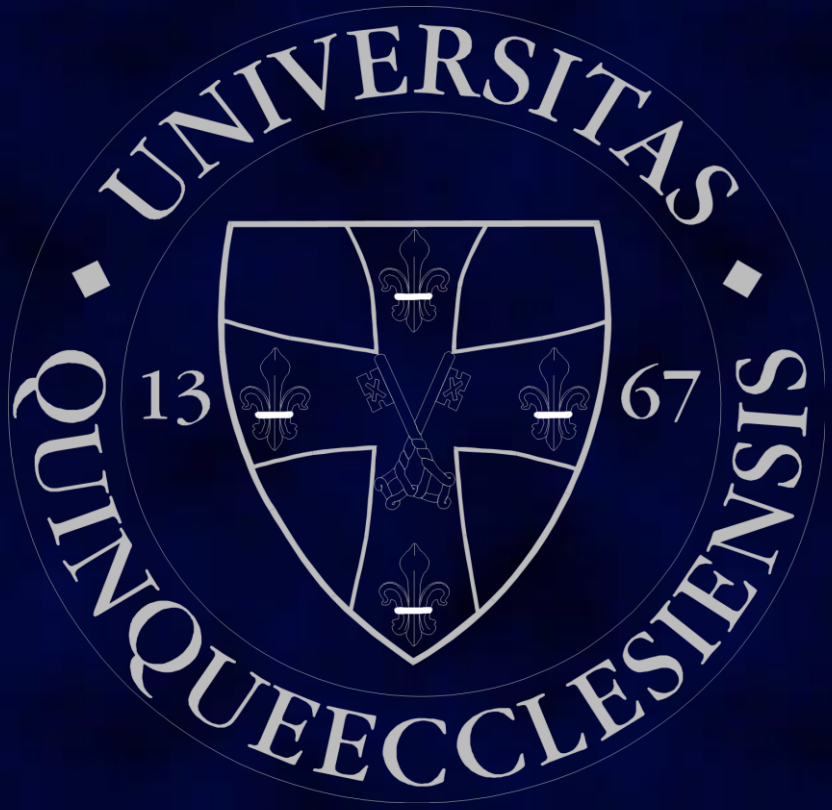
Major subtypes of NCDs

Suggestive features

- NCDs are primarily subtyped according to the known or presumed etiological/pathological entity
- distinguished on the basis of a combination of time course, characteristic domains affected, and associated symptoms

- Etiologies: PD, HD, TBI, stroke
- Psychotic features are common in AD, DLBD and FTLD
- Depression: AD, PD
- Elation: FTLD

2. Diagnostic workup



Diagnostic workup

Basic steps

1. Evaluation of mental status

2. Examination for the presence of potential causative comorbid conditions

3. Examination for the presence of sensory and/or motor deficits as potential causes or exacerbating factors

Diagnostic workup

For defining NCDs:

- 1) a concern about cognition on the part of the individual, a knowledgeable informant, or the clinician, and
- **2**) performance on an objective assessment that falls below the expected level or that has been observed to decline over time.

- *Why do we require both of them?*
  - Both a concern and objective evidence are required because they are complementary.
  - *A highly qualified person may reach normal values on tests, but may perform worse then s/he used to or experienced a decline.*
  - *Low performance may be „normal" for a person with low baseline without any worsening*

Diagnostic workup

Major NCDs (formerly known as dementia):

- individual's level of independence in everyday functioning.
- have impairment of sufficient severity so as to interfere with independence, such that others will have to take over tasks that the individuals were previously able to complete on their own.

Minor NCDs (formerly known as minimal cognitive impairment - MCI):

- have preserved independence
- there may be subtle interference with function or a report that tasks require more effort or take more time than previously.

Screening tests

To diagnose minor or major NCDs we require

- Concern about cognitive worsening
- Objective measurements

Recommended scales

- **MINI-COG**
- **MEMORY IMPAIRMENT SCREEN (MIS)**
- **GPCog**
- Mini-Mental Status Examination
- Montreal Cognitive Assessment
- Addenbrooke Cognitive Examination
- Mattis Dementia Rating Scale

Recommended for GPs
5 minutes

GPs and non-psychologists
10-15 minutes

Neuropsychologists
>20 minutes

MEMORY IMPAIRMENT SCREEN

Buschke H, Kuslansky G, Katz M, et al. Screening for dementia with the memory impairment screen. Neurology. 1999;52(2):231–238.

Memorization 4 Words

Word	Cue	Free recall (2 pts.)	Cued Recall (1 pts)
Checkers	Game		
Saucer	Dish		
Telegram	Message		
Red Cross	Organization		

Scoring

The maximum score for the MIS is 8.

- 5-8 No cognitive impairment
- ≤ 4 Possible cognitive impairment

Mini-Cog

Memorization of 3 Words
+
Clock drawing

Borson et al., 2000

ADMINISTRATION	SPECIAL INSTRUCTIONS
1. Get patient's attention and ask him or her to remember three unrelated words. Ask patient to repeat the words to ensure the learning was correct.	• Allow patient three tries, then go to next item. • The following word lists have been validated in a clinical study:[1–3] **Version 1**: • Banana • Sunrise • Chair **Version 2**: • Daughter • Heaven • Mountain **Version 3**: • Village • Kitchen • Baby **Version 4**: • River • Nation • Finger **Version 5**: • Captain • Garden • Picture **Version 6**: • Leader • Season • Table
2. Ask patient to draw the face of a clock. After numbers are on the face, ask patient to draw hands to read 10 minutes after 11:00 (or 20 minutes after 8:00).	• Either a blank piece of paper or a preprinted circle (other side) may be used. • A correct response is all numbers placed in approximately the correct positions AND the hands pointing to the 11 and 2 (or the 4 and 8). • These two specific times are more sensitive than others. • A clock should not be visible to the patient during this task. • Refusal to draw a clock is scored abnormal. • Move to next step if clock not complete within three minutes.
3. Ask the patient to recall the three words from Step 1.	Ask the patient to recall the three words you stated in Step 1.

Scoring

3 recalled words	Negative for cognitive impairment
1-2 recalled words + normal CDT	Negative for cognitive impairment
1-2 recalled words + abnormal CDT	Positive for cognitive impairment
0 recalled words	Positive for cognitive impairment

GPCog

Brodaty H, Pond D, Kemp NM, Luscombe G, Harding L, Berman K, Huppert FA. The GPCOG: a new screening test for dementia designed for general practice. J Am Geriatr Soc. 2002 Mar;50(3):530-4.

1. Memorization of a name and address
2. Time orientation
3. Clock drawing
4. Information
5. Recall

GPCOG Screening Test

Step 1: Patient Examination

Unless specified, each question should only be asked once

Name and Address for subsequent recall test

1. "*I am going to give you a name and address. After I have said it, I want you to repeat it. Remember this name and address because I am going to ask you to tell it to me again in a few minutes: John Brown, 42 West Street, Kensington.*" (Allow a maximum of 4 attempts).

Time Orientation	Correct	Incorrect
2. *What is the date?* (exact only)	☐	☐
Clock Drawing – use blank page		
3. *Please mark in all the numbers to indicate the hours of a clock* (correct spacing required)	☐	☐
4. *Please mark in hands to show 10 minutes past eleven o'clock* (11.10)	☐	☐
Information		
5. *Can you tell me something that happened in the news recently?* (Recently = in the last week. If a general answer is given, eg "war", "lot of rain", ask for details. Only specific answer scores).	☐	☐
Recall		
6. *What was the name and address I asked you to remember*		
John	☐	☐
Brown	☐	☐
42	☐	☐
West (St)	☐	☐
Kensington	☐	☐

(*To get a total score, add the number of items answered correctly*
Total correct (score out of 9) /9

If patient scores 9, no significant cognitive impairment and further testing not necessary.
If patient scores 5-8, more information required. Proceed with Step 2, informant section.
If patient scores 0-4, cognitive impairment is indicated. Conduct standard investigations.

GPCog

Brodaty H, Pond D, Kemp NM, Luscombe G, Harding L, Berman K, Huppert FA. The GPCOG: a new screening test for dementia designed for general practice. J Am Geriatr Soc. 2002 Mar;50(3):530-4.

6 questions on decline in daily functioning

Date: _____

Informant's name: _____

Informant's relationship to patient, i.e. informant is the patient's: _____

These six questions ask how the patient is compared to when s/he was well, say 5 – 10 years ago

Compared to a few years ago:

	Yes	No	Don't Know	N/A
▪ Does the patient have more trouble remembering things that have happened recently than s/he used to?	☐	☐	☐	
▪ Does he or she have more trouble recalling conversations a few days later?	☐	☐	☐	
▪ When speaking, does the patient have more difficulty in finding the right word or tend to use the wrong words more often?	☐	☐	☐	
▪ Is the patient less able to manage money and financial affairs (e.g. paying bills, budgeting)?	☐	☐	☐	☐
▪ Is the patient less able to manage his or her medication independently?	☐	☐	☐	☐
▪ Does the patient need more assistance with transport (either private or public)? (If the patient has difficulties due only to physical problems, e.g bad leg, tick 'no')	☐	☐	☐	☐

(To get a total score, add the number of items answered 'no', 'don't know' or 'N/A')

Total score (out of 6) ☐

If patient scores 0-3, cognitive impairment is indicated. Conduct standard investigations.

MMSE

"Mini-mental state". A practical method for grading the cognitive state of patients for the clinician.

Folstein MF, Folstein SE, McHugh PR.

J Psychiatr Res. 1975 Nov;12(3):189-98

Mini-Mental State Examination (MMSE)

Patient name:

Date: Visit 1: Visit 2: Visit 3: Visit 4:

Maximum score	Visit 1	Visit 2	Visit 3	Visit 4	
					ORIENTATION
5	( )	( )	( )	( )	What (year) (season) (date) (day) (month) is it? *(1 point for each correct answer.)*
5	( )	( )	( )	( )	Where are we: (province) (country) (town or city) (hospital or clinic) (floor)? *(1 point for each correct answer.)*
					REGISTRATION
3	( )	( )	( )	( )	Listen to the following: "apple," "table," "penny." Repeat all 3. *(1 point for each correct answer.)*
# Trials:	( )	( )	( )	( )	(Repeat the objects until the patient learns all 3. Make a maximum of 6 trials. Record the number of trials.)
					ATTENTION AND CALCULATION
5	( )	( )	( )	( )	Spell "world" backwards. *(1 point for each letter in correct order.)* **Alternate:** Subtract 7 from 100. Take the result and subtract 7 from that. Continue until I ask you to stop. *(Continue for 5 subtractions. 1 point for each correct subtraction.)*
					RECALL
3	( )	( )	( )	( )	What were the 3 objects we repeated earlier? *(1 point for each correct answer.)* (Note: Recall cannot be tested if all 3 objects were not remembered during registration.)
					LANGUAGE
2	( )	( )	( )	( )	What are these? (pencil) (watch).
1	( )	( )	( )	( )	Repeat the following: "No ifs, ands, or buts."
3	( )	( )	( )	( )	Take a piece of paper in your right hand, fold it in half and put it on the floor. *(1 point for each section of the command performed.)*
					READ AND OBEY
1	( )	( )	( )	( )	Read the following ("Close your eyes.") and do as it says.
1	( )	( )	( )	( )	Write a sentence.
1	( )	( )	( )	( )	Copy the following design on the back of this page:  No construction problem
Total score (max. score 30)					

MMSE

					ORIENTATION
5	( )	( )	( )	( )	What (year) (season) (date) (day) (month) is it? *(1 point for each correct answer.)*
5	( )	( )	( )	( )	Where are we: (province) (country) (town or city) (hospital or clinic) (floor)? *(1 point for each correct answer.)*
					REGISTRATION
3	( )	( )	( )	( )	Listen to the following: "apple," "table," "penny." Repeat all 3. *(1 point for each correct answer.)*
# Trials:	( )	( )	( )	( )	(Repeat the objects until the patient learns all 3. Make a maximum of 6 trials. Record the number of trials.)
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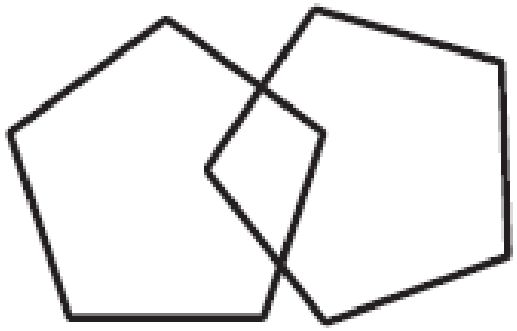
					RECALL
3	( )	( )	( )	( )	What were the 3 objects we repeated earlier? *(1 point for each correct answer.)* (Note: Recall cannot be tested if all 3 objects were not remembered during registration.)

MMSE

					LANGUAGE
2	( )	( )	( )	( )	What are these? (pencil) (watch).
1	( )	( )	( )	( )	Repeat the following: "No ifs, ands, or buts."
3	( )	( )	( )	( )	Take a piece of paper in your right hand, fold it in half and put it on the floor. *(1 point for each section of the command performed.)*
					READ AND OBEY
1	( )	( )	( )	( )	Read the following ("Close your eyes.") and do as it says.
1	( )	( )	( )	( )	Write a sentence.
1	( )	( )	( )	( )	Copy the following design on the back of this page:



No construction problem

MMSE cut-off: 27 points

From: Arch Neurol. Author manuscript; available in PMC Jul 1, 2009.
Published in final edited form as:
Arch Neurol. Jul 2008; 65(7): 963–967.
doi: 10.1001/archneur.65.7.963

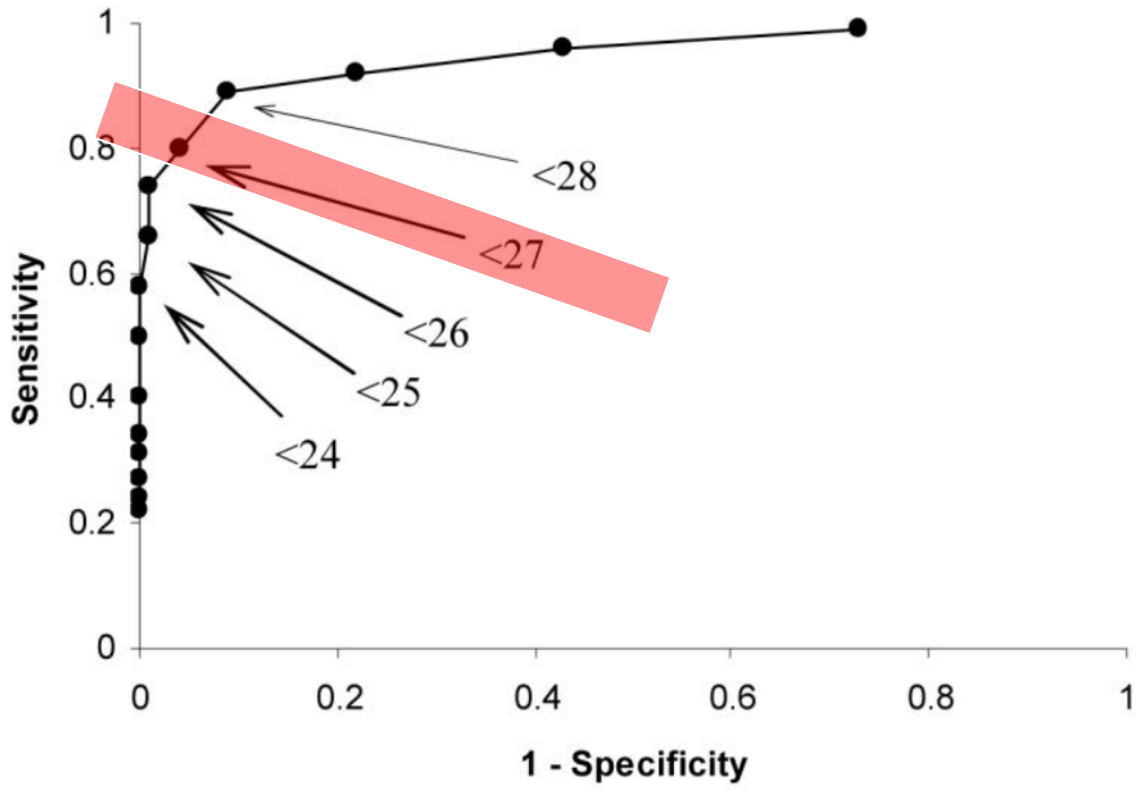
General cut-off value is 27 points

Table 1

Sensitivity and Specificity Estimates for Detecting Dementia using the MMSE

Cut score	Sensitivity (CIs)	Specificity (CIs)
< 16	0.22 (0.17-0.27)	1.00 (0.99-1.00)
< 17	0.24 (0.19-0.29)	1.00 (0.99-1.00)
< 18	0.27 (0.22-0.32)	1.00 (0.99-1.00)
< 19	0.31 (0.26-0.36)	1.00 (0.99-1.00)
< 20	0.34 (0.29-0.40)	1.00 (0.99-1.00)
< 21	0.40 (0.35-0.47)	1.00 (0.99-1.00)
< 22	0.50 (0.44-0.55)	1.00 (0.99-1.00)
< 23	0.58 (0.52-0.63)	1.00 (0.99-1.00)
< 24	0.66 (0.61-0.71)	0.99 (0.99-1.00)
< 25	0.74 (0.67-0.79)	0.99 (0.97-0.99)
< 26	0.80 (0.75-0.84)	0.96 (0.95-0.98)
< 27	0.89 (0.85-0.92)	0.91 (0.88-0.93)
< 28	0.92 (0.88-0.95)	0.78 (0.74-0.81)
< 29	0.96 (0.93-0.98)	0.57 (0.53-0.61)
< 30	0.99 (0.97-1.00)	0.27 (0.23-0.30)

Figure 1



Receiver operating characteristic curve for Mini-Mental State Examination scores (indicated by numbers within figure) in detecting dementia.

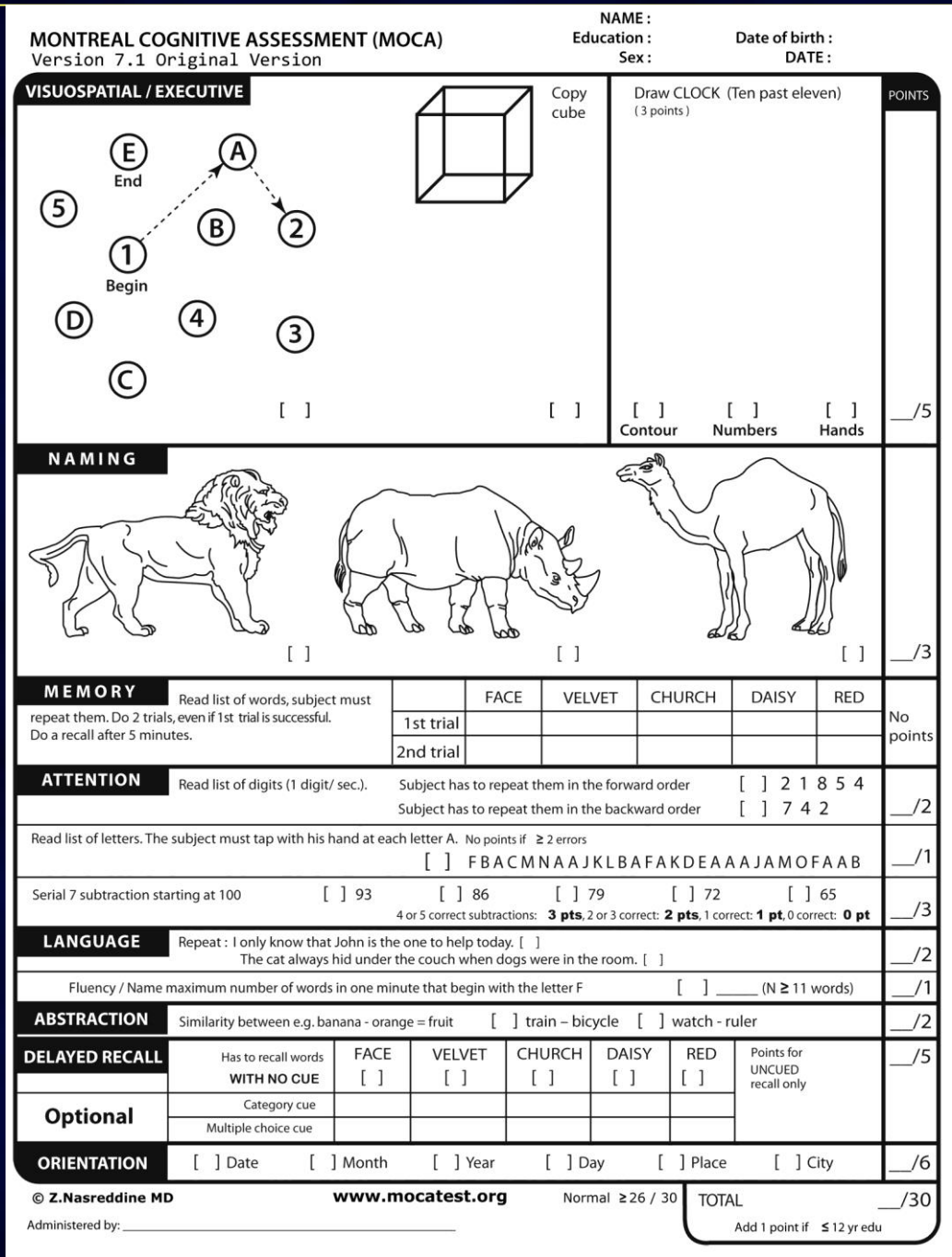
Montreal Cognitive Assessment

Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H.
The Montreal Cognitive Assessment (MoCA©): A Brief Screening Tool For Mild Cognitive Impairment.
J Am Geriatr Soc 53:695–699, 2005.

It evaluates 5 domains out of the 6 neurocognitive domains

It was designed to assess MCI

Clinicians can use it without any psychological training



MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

NAME :
Education : Date of birth :
Sex : 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, even if 1st trial is successful. 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
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B __/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** __/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ] __/2

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

	FACE	VELVET	CHURCH	DAISY	RED	
Has to recall words WITH NO CUE	[ ]	[ ]	[ ]	[ ]	[ ]	Points for UNCUED recall only
Optional Category cue						
Optional Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City __/6

© Z.Nasreddine MD www.mocatest.org Normal ≥ 26 / 30

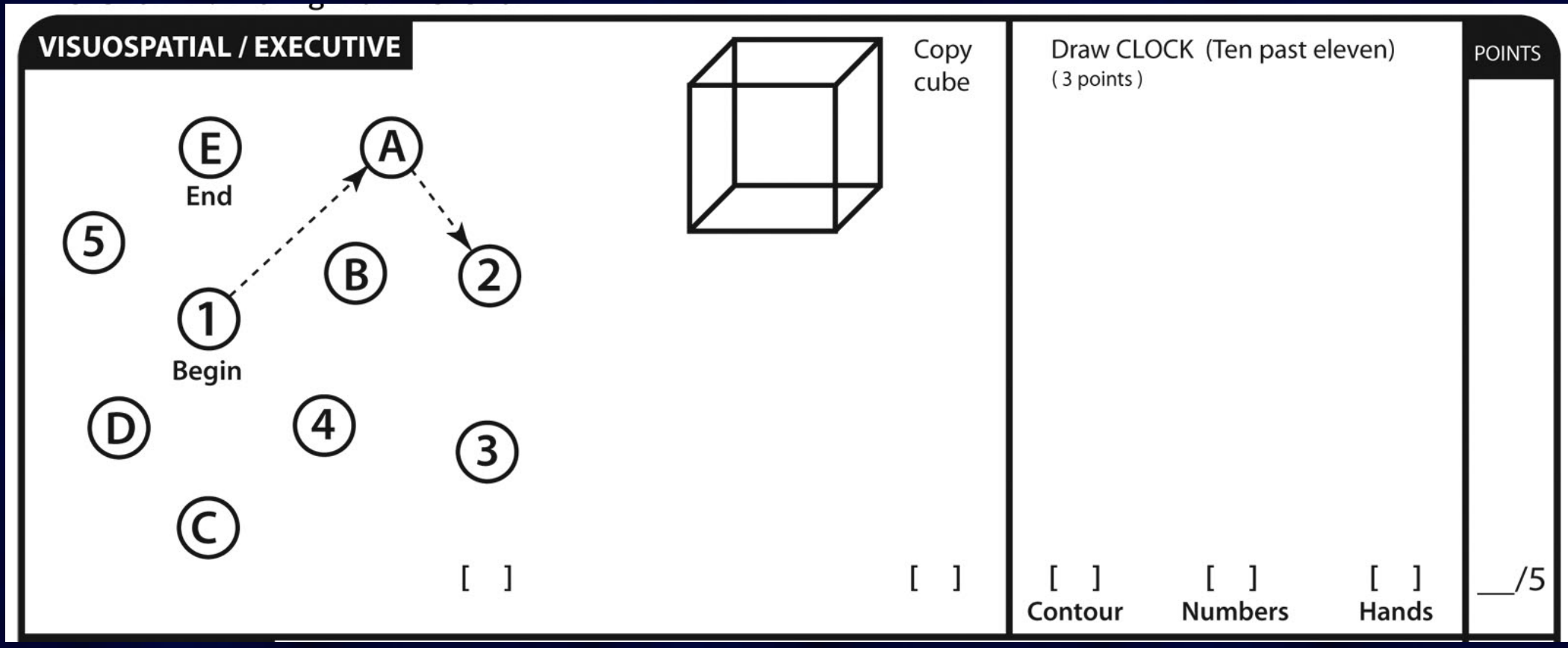
TOTAL __/30
Add 1 point if ≤ 12 yr edu

Administered by: _____

Montreal Cognitive Assessment

MOCA evaluates more neurocognitive domains

1. Visuospatial:
    1. Alternating Trail Making
    2. Visuoconstructional Skills (Cube, cylinder, rectangle)
    3. Visuoconstructional Skills (Clock)

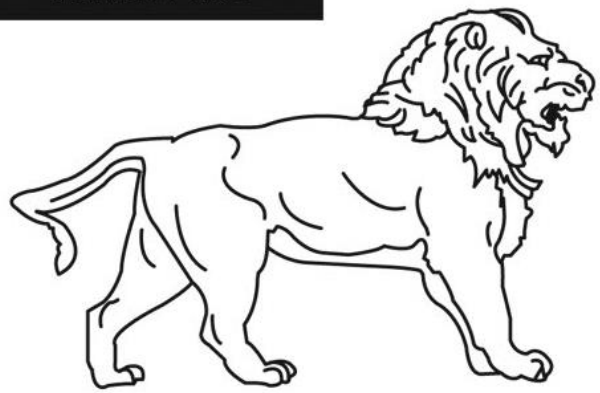


Montreal Cognitive Assessment

MOCA evaluates more neurocognitive domains

1. Naming
2. Memory
    1. Immediate recall – not scored

NAMING



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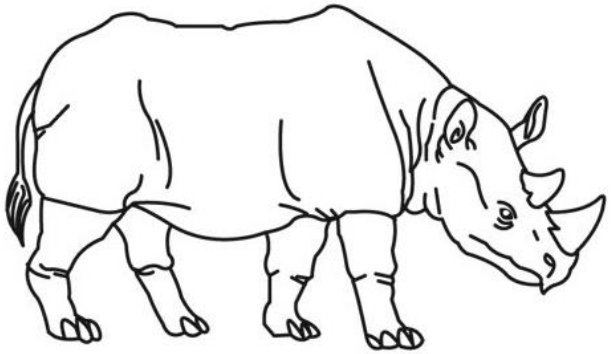
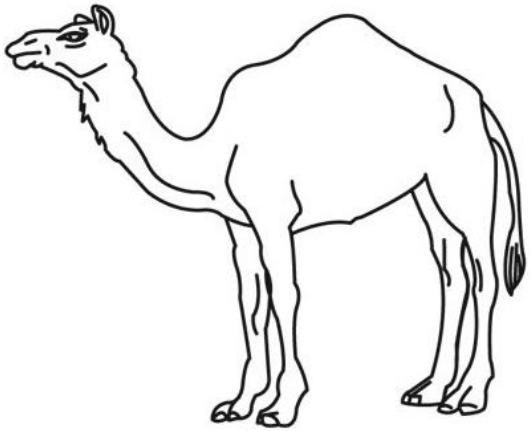


[ ]



[ ]

__/3

MEMORY

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

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

Montreal Cognitive Assessment

MOCA evaluates more neurocognitive domains

- Attention: Forward Digit Span, Backward Digit Span, Vigilance, Serial 7s
- Language: Sentence repetition, **Verbal fluency**
- Abstraction
- Delayed recall: without cues, category cue and multiple choice cue
- Orientation

ATTENTION	Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order [ ] 2 1 8 5 4 Subject has to repeat them in the backward order [ ] 7 4 2	___/2
	Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors [ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B	___/1
	Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65 4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**	___/3
LANGUAGE	Repeat : I only know that John is the one to help today. [ ] The cat always hid under the couch when dogs were in the room. [ ]	___/2
	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

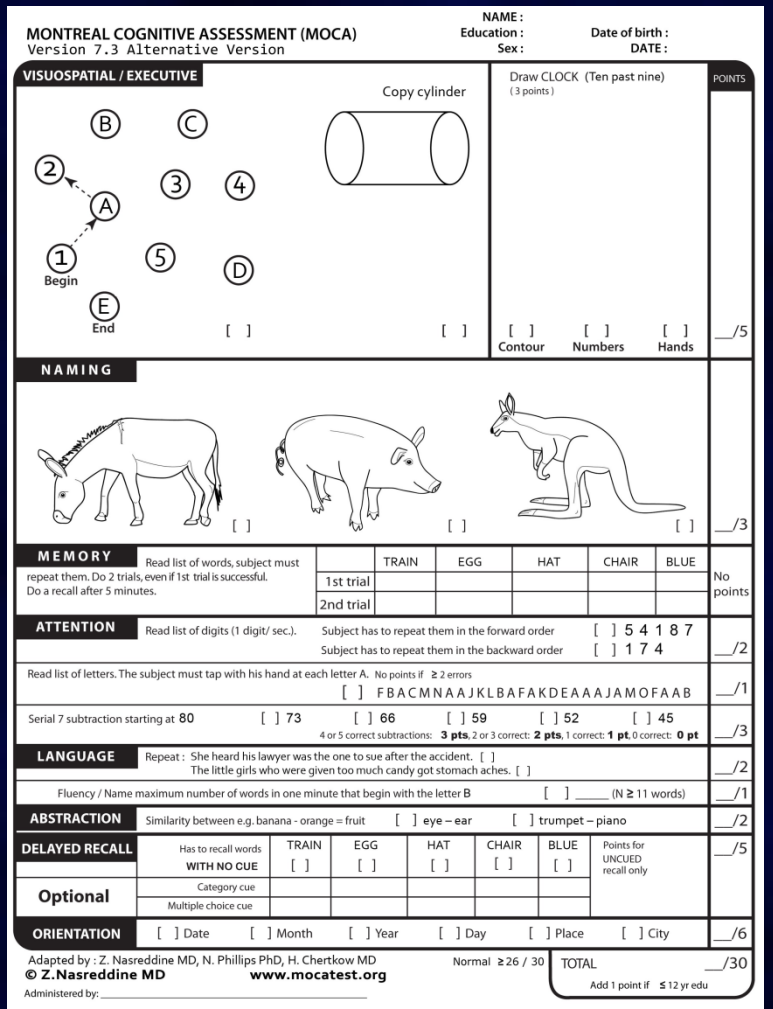
DELAYED RECALL								
	Has to recall words **WITH NO CUE**	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only	___/5
Optional	Category cue							
	Multiple choice cue							

ORIENTATION	[ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City	___/6

MoCA (www.mocatest.org)

Advantages:

- 100+ countries, 30+ language validations
- 3 different, but equivalent versions available
- Freely available for clinical use
- GPs can use, 10 minutes


MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.3 Alternative Version

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

VISUOSPATIAL / EXECUTIVE — Copy cylinder — Draw CLOCK (Ten past nine) (3 points) — Contour — Numbers — Hands — POINTS /5

NAMING /3

MEMORY — Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes. — TRAIN EGG HAT CHAIR BLUE — 1st trial / 2nd trial — No points

ATTENTION — Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order [ ] 5 4 1 8 7. Subject has to repeat them in the backward order [ ] 1 7 4 /2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors [ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B /1

Serial 7 subtraction starting at 80 [ ] 73 [ ] 66 [ ] 59 [ ] 52 [ ] 45 — 4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** /3

LANGUAGE — Repeat : She heard his lawyer was the one to sue after the accident. [ ] The little girls who were given too much candy got stomach aches. [ ] /2

Fluency / Name maximum number of words in one minute that begin with the letter B [ ] ____ (N ≥ 11 words) /1

ABSTRACTION — Similarity between e.g. banana - orange = fruit [ ] eye – ear [ ] trumpet – piano /2

DELAYED RECALL — Has to recall words WITH NO CUE — TRAIN [ ] EGG [ ] HAT [ ] CHAIR [ ] BLUE [ ] — Points for UNCUED recall only /5

Optional — Category cue / Multiple choice cue

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City /6

Adapted by : Z. Nasreddine MD, N. Phillips PhD, H. Chertkow MD
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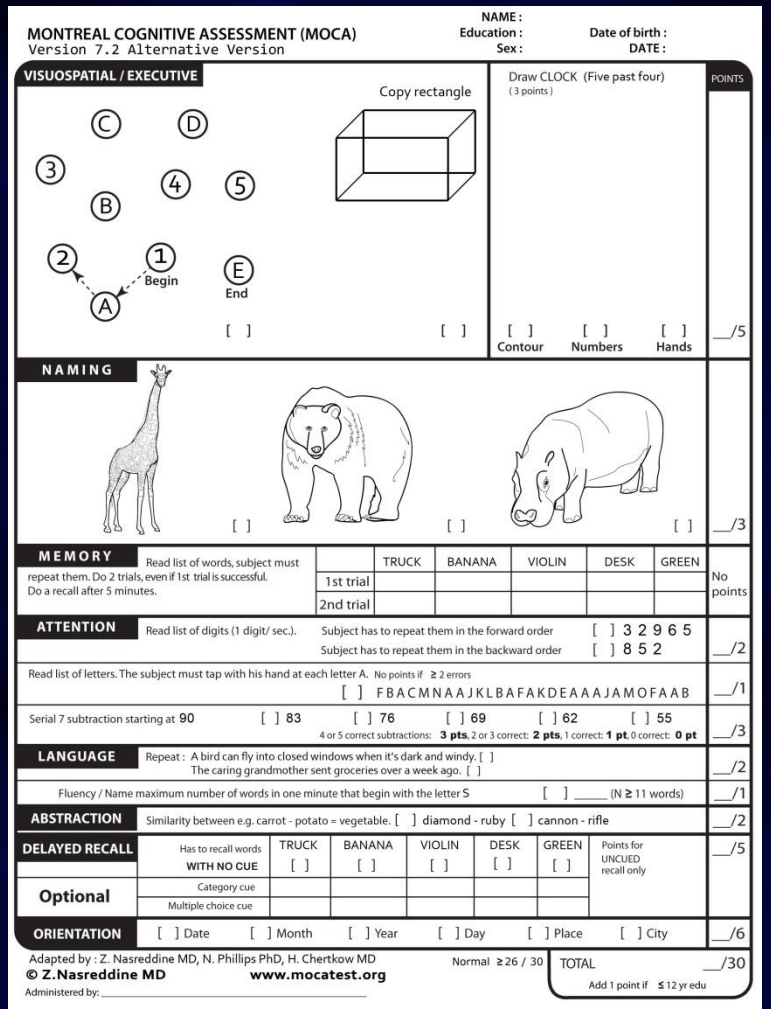
Normal ≥ 26 / 30
TOTAL /30
Add 1 point if ≤ 12 yr edu
Administered by: _____


MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.2 Alternative Version

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

VISUOSPATIAL / EXECUTIVE — Copy rectangle — Draw CLOCK (Five past four) (3 points) — Contour — Numbers — Hands — POINTS /5

NAMING /3

MEMORY — Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes. — TRUCK BANANA VIOLIN DESK GREEN — 1st trial / 2nd trial — No points

ATTENTION — Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order [ ] 3 2 9 6 5. Subject has to repeat them in the backward order [ ] 8 5 2 /2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors [ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B /1

Serial 7 subtraction starting at 90 [ ] 83 [ ] 76 [ ] 69 [ ] 62 [ ] 55 — 4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** /3

LANGUAGE — Repeat : A bird can fly into closed windows when it's dark and windy. [ ] The caring grandmother sent groceries over a week ago. [ ] /2

Fluency / Name maximum number of words in one minute that begin with the letter S [ ] ____ (N ≥ 11 words) /1

ABSTRACTION — Similarity between e.g. carrot - potato = vegetable. [ ] diamond - ruby [ ] cannon - rifle /2

DELAYED RECALL — Has to recall words WITH NO CUE — TRUCK [ ] BANANA [ ] VIOLIN [ ] DESK [ ] GREEN [ ] — Points for UNCUED recall only /5

Optional — Category cue / Multiple choice cue

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City /6

Adapted by : Z. Nasreddine MD, N. Phillips PhD, H. Chertkow MD
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Normal ≥ 26 / 30
TOTAL /30
Add 1 point if ≤ 12 yr edu
Administered by: _____

SELECT TEST LANGUAGE (PgDown/PgUp)
English (Original)
English (Additional version 2)
English (Additional version 3)
English (MoCA-BLIND)
Arabic
Afrikaans
Bulgarian
Chinese (Beijing)
Chinese (Cantonese)
Chinese (Changsha)
Chinese (Hong Kong)
Chinese (Taiwan)
Czech
Croatian
Danish
Dutch
Dutch (Additional version 7.2)
Dutch (Additional version 7.3)
Estonian
Filipino
Finnish
French
German
German (Additional version 2)
German (Additional version 3)
Greek
Hebrew
Hindi
Hungarian (Addtional version 7.2)
Hungarian (Addtional version 7.3)
Italian
Japanese
Korean
Korean-K2
Malayalan
Malay (Bahasa-Malaysia)
Norwegian
Persian
Polish
Polish (Alternate version)
Portuguese
Portuguese (Additional version 7.2)
Portuguese (Additional version 7.3
Portuguese (Brazil)
Romanian
Russian
Serbian
Sinhalese
Slovak
Slovenian
Spanish
Spanish (Additional version 7.2)
Spanish (Additional version 7.3)
Swedish
Thai
Turkish
Ukrainian

MoCA is superior to MMSE

Advantages:

- MoCA is superior to MMSE in detection of MCI
- Hungarian cut-off: 24 points (Psych Hung. 2013;28:370-392

MOCA SCORES

	Normal Controls (NC)	Mild Cognitive Impairment (MCI)	Alzheimer's Disease (AD)
Number of subjects	90	94	93
MoCA average score	**27.4**	**22.1**	**16.2**
MoCA standard deviation	2.2	3.1	4.8
MoCA score range	25.2 – 29.6	19.0 – 25.2	21.0 – 11.4
Suggested cut-off score	≥26	<26	<26ψ

ψ Although the average MoCA score for the AD group is much lower than the MCI group, there is overlap between them. The suggested MoCA cut-off score is thus the same for both. The distinction between AD and MCI is mostly dependent on the presence of associated functional impairment and not on a specific score on the MoCA test.

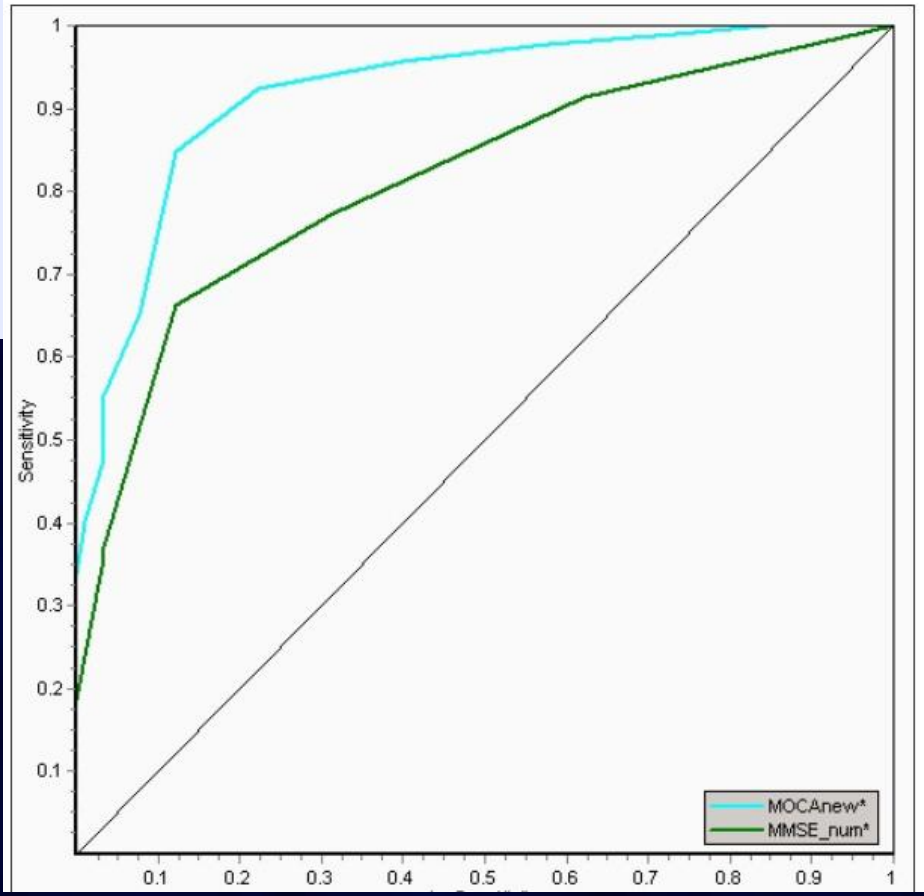
MoCA is superior to MMSE

Advantages:

- MoCA is superior to MMSE in detection of MCI

Sensitivity and Specificity (%) MoCA and MMSE

Cut-off	≥ 26	< 26	< 26
Group (n)	Normal controls (90)	Mild Cognitive Impairment (94)	Alzheimer Disease (93)
MoCA	87	90	100
MMSE	100	18	78



MoCA is superior to MMSE

Advantages:

- MoCA is superior to MMSE in detection of MCI

MoCA Items Average scores

	NC		MCI		AD	
	AVG	SD	AVG	SD	AVG	SD
Trails	0.87	0.34	0.56	0.50	0.27	0.45
Cube	0.71	0.46	0.46	0.50	0.25	0.43
Clock	2.65	0.65	2.16	0.82	1.56	0.98
Naming	2.88	0.36	2.64	0.58	2.19	0.82
Memory	3.73	1.27	1.17	1.47	0.52	1.03
Digit span	1.82	0.44	1.83	0.43	1.49	0.62
Letter A	0.97	0.18	0.93	0.26	0.67	0.47
Serial 7	2.89	0.41	2.65	0.65	1.82	1.12
Sentence rep	1.83	0.37	1.49	0.71	1.37	0.80
Fluency F	0.87	0.34	0.71	0.45	0.32	0.47
Abstraction	1.83	0.43	1.43	0.68	0.99	0.80
Orientation	5.99	0.11	5.52	0.84	3.92	1.73
Total *	27.37	2.20	22.12	3.11	16.16	4.81

SD=Standard Deviation. AVG=Average
*Total is adjusted for education

Alternate trail making, cube, clock drawing and memory items are the most sensitive for MCI

MoCA is superior to MMSE

MONTREAL KOGNITÍV FELMÉRÉS (MOCA) 7.2

7.2 verzió. Alternatív verzió

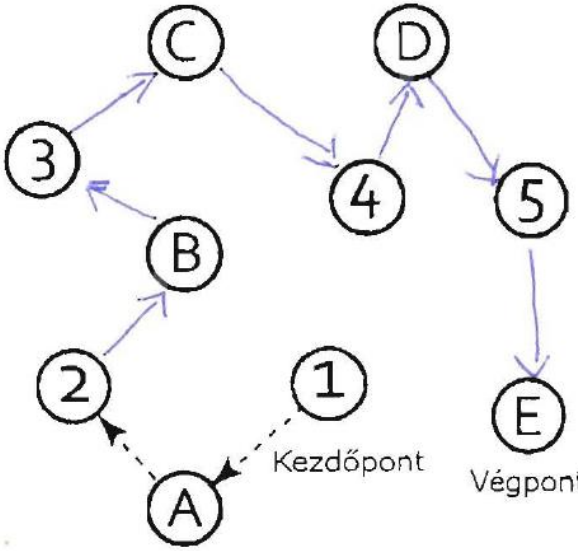
NÉV : [redacted]

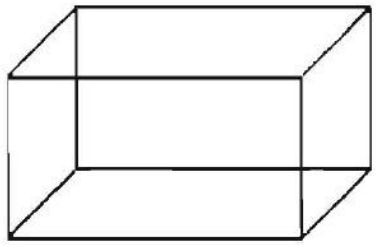
Iskolázottság : 15 Születési idő : 1948

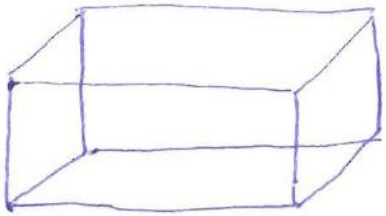
Nem : NŐ Dátum : 2013.10.02

TÉRI-VIZUÁLIS / VÉGREHAJTÓ

Másolja le a téglalapot!

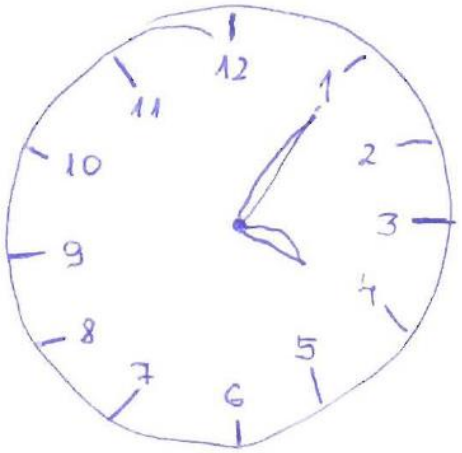






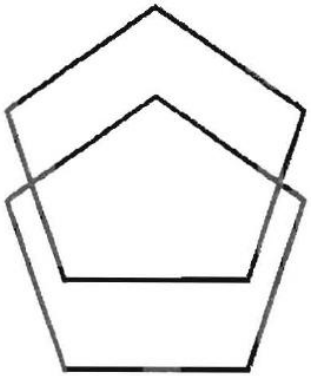
[1] [1]

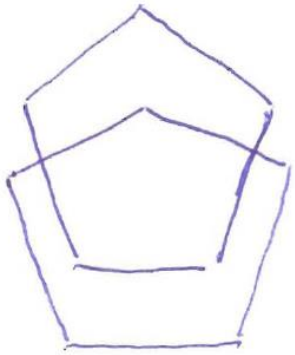
Rajzoljon egy ÓRÁT! (Négy óra öt perc) (3 pont)



[1] Körvonal [1] Számok [1] Mutatók

Pontszám 5/5

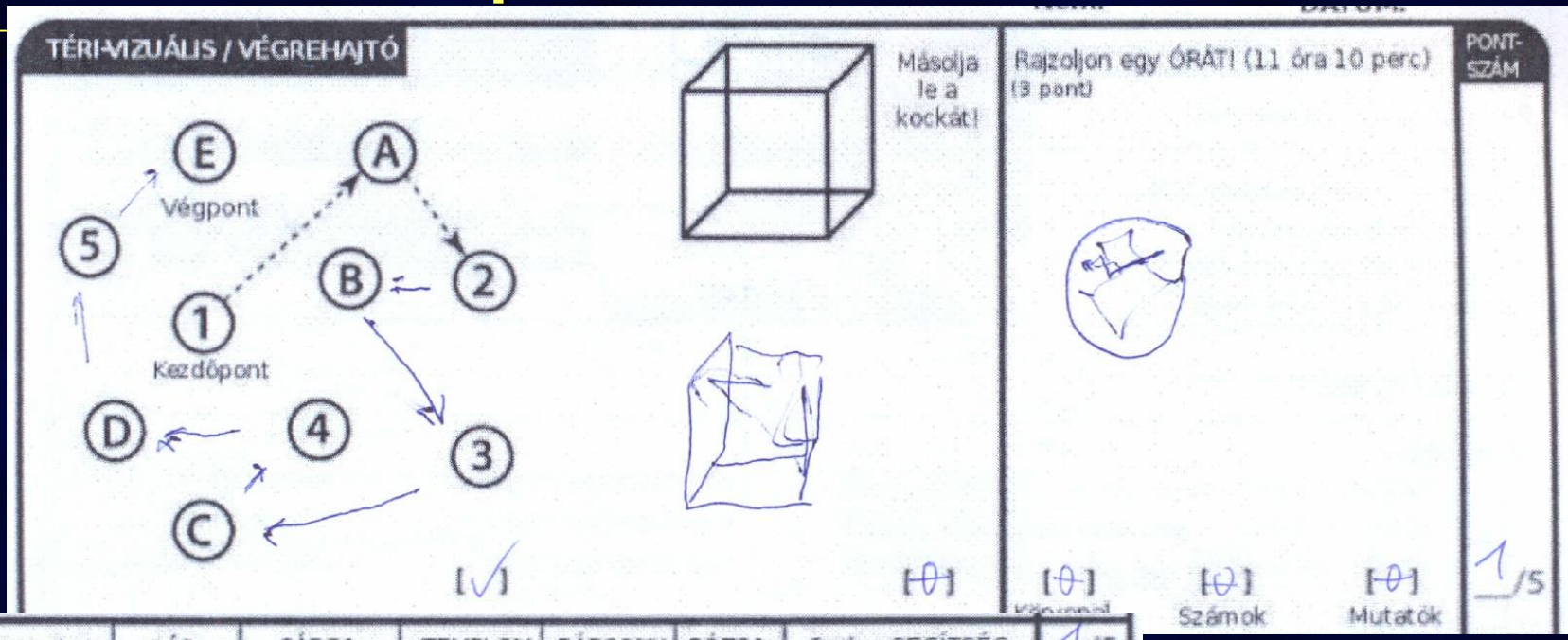




Ha végre nem esik az eső!

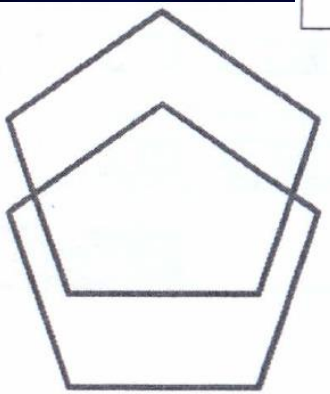
65 years old female patient achieved 29/30 points on MMSE and 28/30 points on MoCA. Clinically normal cognition.

MoCA is superior to MMSE



KÉSLELTETETT FEL-IDÉZÉS	Idézze fel a szavakat SEGÍTSÉG NÉLKÜL!	LÁB [0]	SÁRGA [1]	TEMPLOM [0]	BÁRSONY [0]	RÓZSA [0]	Csak a SEGÍTSÉG NÉLKÜL felidézett szavakért adunk pontot!	1/5
VÁLASZHATÓ	Kategória megadása	0		0	0	0		
	Feleletválasztás	✓		✓	✓	✓		

4. **Felidéző emlékezés**
Kérje meg a beteget, hogy a korábban elismételtetett 3 szót idézze fel hangosan. 3/3



65 years old male patient achieved 29/30 points on MMSE and 19/30 points on MoCA. Clinically minor NCD-AD (MCI).

Diagnostic workup

Lab tests:

1. Blood count
2. TSH level (hypothyreodism)
3. B12 and folic acid
4. Creatinine and electrolytes (kidney failure)
5. Liver function tests
6. VDRL (syphilis)
7. Antinuclear antibodies (CNS vasculitis)
8. HIV (HIV-dementia)
9. CSF analysis (paraneoplastic)
10. Toxic (metals, poisons, druges)

All cases

Individually

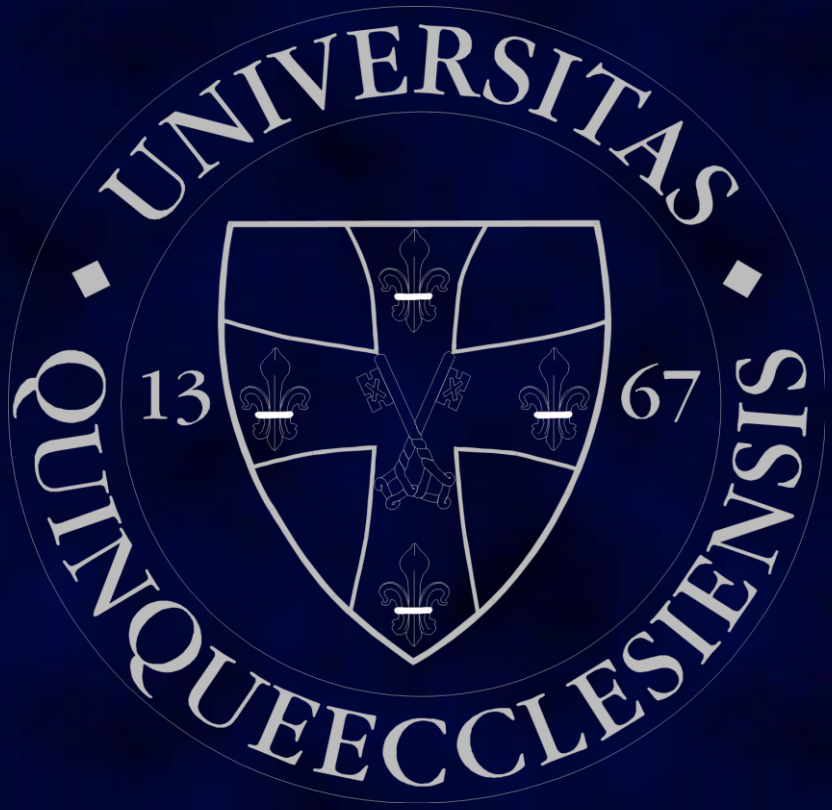
Diagnostic workup

Other examinations:

1. Screening for depression, anxiety (Beck Depression Inventory)
2. Structural brain imaging
    1. CT: cheaper, less sensitive
    2. MRI:
        1. Other factors: hydrocephalus, tumors, brain damage (e.g. traumatic)
        2. White matter (vascular lesions, adrenoleukodystrophy)
        3. Atrophy (degree of atrophy and the localization)
        4. Predicting factors, biomarkers (e.g. not the size of hippocampus, both the fornix and mammillary body determines the transformation from MCI to AD)
        5. Special sequences (e.g. SWI to detect Wilson's disease or NBIA)
3. ECG (e.g. atrial fibrillation)
4. EEG: epilepsy, prion
5. Functional neuroimaging
    1. PET (amyloid imaging)
    2. SPECT
6. Genetic testing
    1. Huntington's disease
    2. Risk factors and/or predicting factors for AD
    3. Risk factors and/or predicting factors for Frontotemporal NCD

Individually

3. Major NCD syndromes



Differential diagnosis: Top 10

(commonly used mnemonic device: AVDEMENTIA

1. **A**lzheimer Disease (pure ~40%, + mixed~70%)
2. **V**ascular Disease, MID (5-20%)
3. **D**rugs, **D**epression, **D**elirium
4. **E**thanol (5-15%)
5. **M**etabolic Systems
6. **E**ndocrine (thyroid, diabetes), **E**ars, **E**yes, **E**nviron.
7. **N**eurologic (other primary degenerations, etc.)
8. **T**umor, **T**oxin, **T**rauma
9. **I**nfection, **I**diopathic, **I**mmunologic
10. **A**mnesia, **A**utoimmune, **A**pnea, **A**AMI

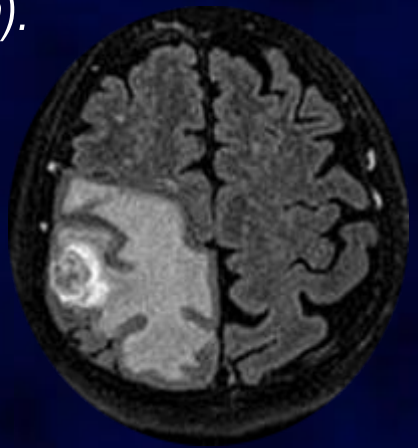
NCD due to Another Medical Condition

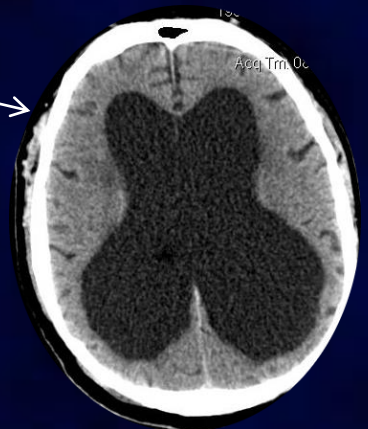
Definition

- *A. The criteria are met for major or mild neurocognitive disorder.*
- *B. There is evidence from the history, physical examination, or laboratory findings that the neurocognitive disorder is the pathophysiological consequence of another medical condition.*
- *C. The cognitive deficits are not better explained by another mental disorder or another specific neurocognitive disorder (e.g., Alzheimer's disease, HIV infection).*

Differential-diagnosis
(potentially reversible causes have green color)

- *structural lesions*
  - *primary or secondary brain tumors,*
  - *subdural hematoma (treated by surgery)*
  - *slowly progressive or normal-pressure hydrocephalus (treatable by shunt surgery)*
- *hypoxia*
  - *related to hypoperfusion from heart failure,*
  - *OSAS: treatable by CPAP/BiPAP therapy*





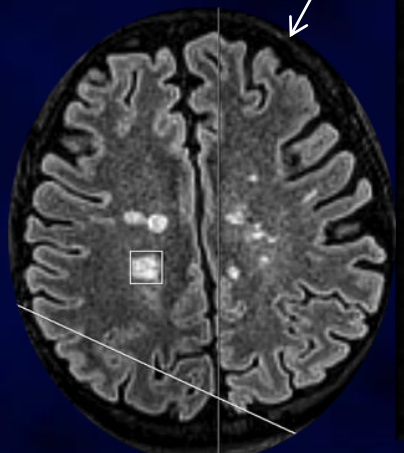
NCD due to Another Medical Condition

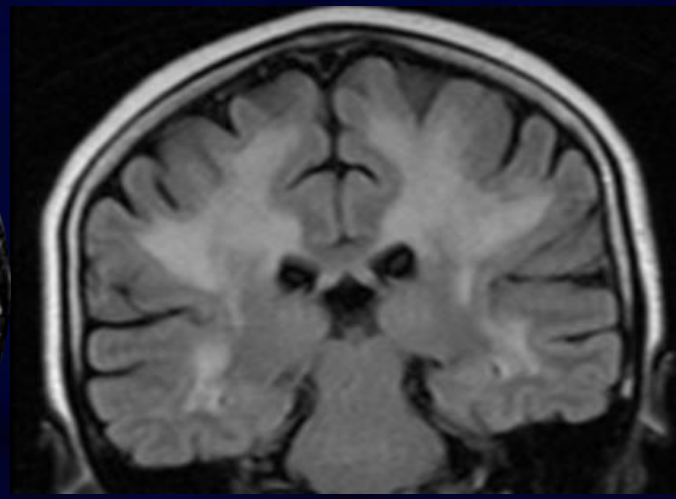
Differential-diagnosis
(potentially reversible causes have green color)

- *endocrine conditions*
  - *hypothyroidism,*
  - *hypercalcemia,*
  - *hypoglycemia*
- *nutritional conditions:*
  - *deficiencies of thiamine or niacin*
- *infectious conditions*
  - *neurosyphilis,*
  - *cryptococcosis,*
- *immune disorders*
  - *temporal arteritis,*
  - *systemic lupus erythematosus),*
- *hepatic or renal failure,*
- *Major depression*

Diagnostic features

- *metabolic conditions*
  - *Kufs' disease,*
  - *adrenoleukodystrophy,*
  - *metachromatic leukodystrophy,*
  - *other storage diseases of adulthood and childhood),*
- *other neurological conditions*
  - *epilepsy,*
  - *multiple sclerosis).*





Alzheimer's disease

- A. The criteria are met for major or mild neurocognitive disorder.
- B. There is insidious onset and gradual progression of impairment in one or more cognitive domains (for major neurocognitive disorder, at least two domains must be impaired).
- C. Criteria are met for either probable or possible Alzheimer's disease as follows:
- *For major neurocognitive disorder:* Probable Alzheimer's disease is diagnosed if either of the following is present; otherwise, possible Alzheimer's disease should be diagnosed.
  - 1. Evidence of a causative Alzheimer's disease genetic mutation from family history or genetic testing.
  - 2. All three of the following are present:
    - a. Clear evidence of decline in memory and learning and at least one other cognitive domain (based on detailed history or serial neuropsychological testing).
    - b. Steadily progressive, gradual decline in cognition, without extended plateaus.
    - c. No evidence of mixed etiology (i.e., absence of other neurodegenerative or cerebrovascular disease, or another neurological, mental, or systemic disease or condition likely contributing to cognitive decline).
- *For mild neurocognitive disorder:* Probable Alzheimer's disease is diagnosed if there is evidence of a causative Alzheimer's disease genetic mutation from either genetic testing or family history. Possible Alzheimer's disease is diagnosed if there is no evidence of a causative Alzheimer's disease genetic mutation from either genetic testing or family history, and all three of the following are present:
  - 1. Clear evidence of decline in memory and learning.
  - 2. Steadily progressive, gradual decline in cognition, without extended plateaus.
  - 3. No evidence of mixed etiology
- D. The disturbance is not better explained by cerebrovascular disease, another neurodegenerative disease, the effects of a substance, or another mental, neurological, or systemic disorder

Alzheimer's disease

- *The most common neurodegenerative disease of the brain!*
- ***Definite Alzheimer's disease***: Clinical features + histopathologic confirmation

	Probable AD	***Possible AD***
Minor NCD	Typical features (3) + causative genetic positivity	Typical clinical features (3)
Major NCD	Typical clinical features (3)	Not all the 3 typical features are observed

Impaired neurocognitive domains

- The typical presentation is amnestic (i.e., with impairment in memory and learning).
- At the mild NCD phase, Alzheimer's disease manifests typically with impairment in memory and learning, sometimes accompanied by deficits in executive function.
- At the major NCD phase, visuoconstructional/perceptual motor ability and language will also be impaired. Social cognition tends to be preserved until late in the course of the disease.

Alzheimer's disease

Associated features

- have behavioral and psychological manifestations
- these features are also frequent at the mild NCD stage of impairment
- These symptoms are as or more distressing than cognitive manifestations

Mild stage:

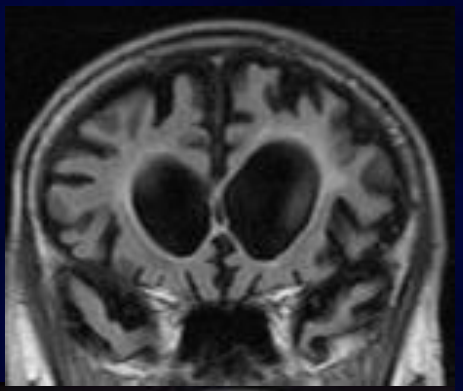
- depression and/or apathy

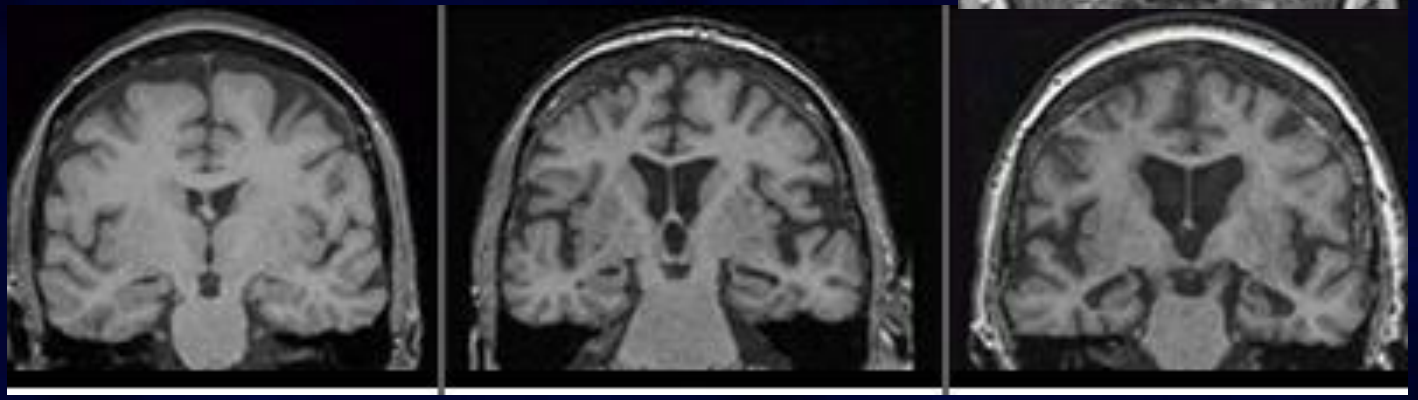
With moderately severe major NCD,

- psychotic features,
- irritability,
- agitation,
- combativeness, and
- wandering

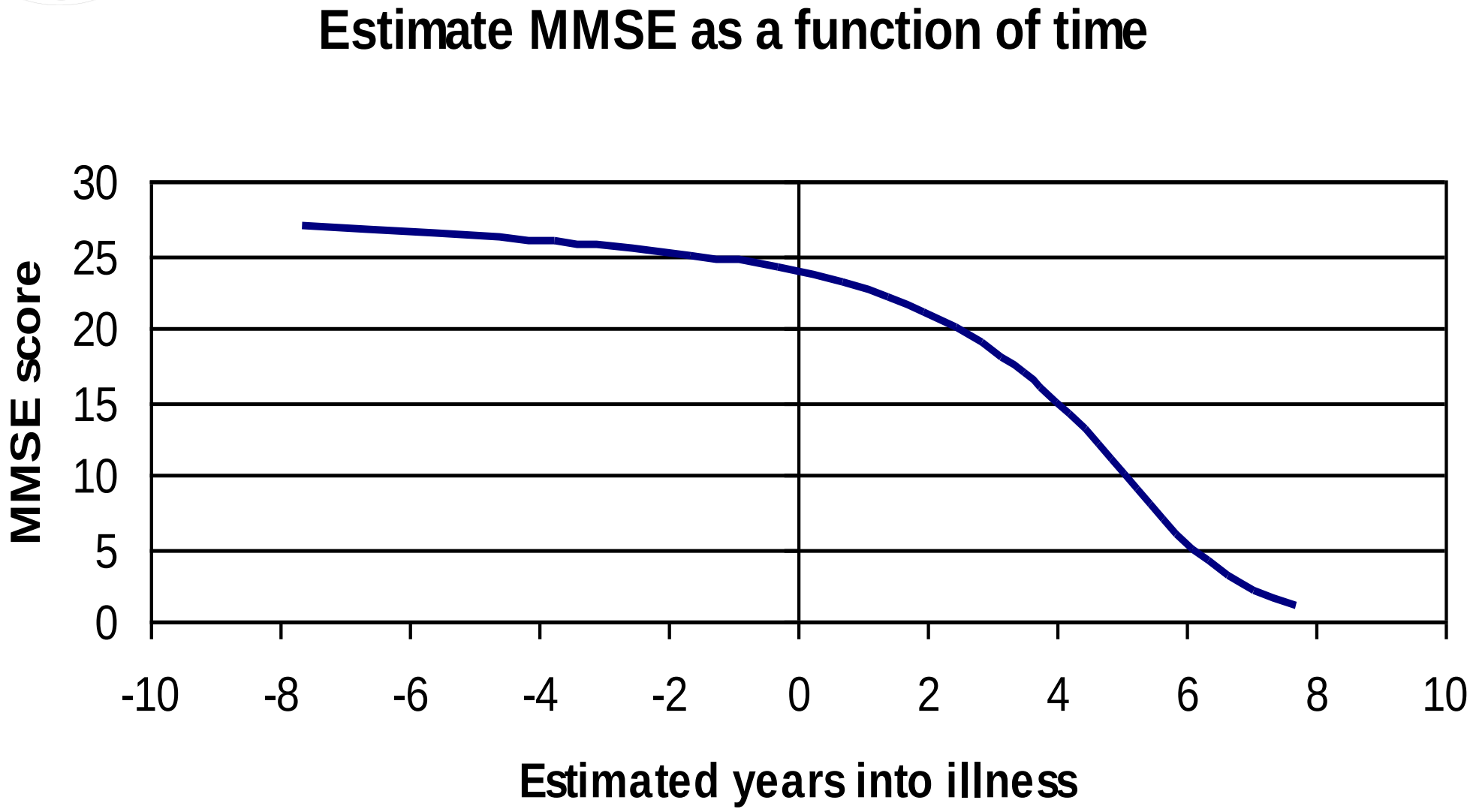
Late in the illness,

- gait disturbance,
- dysphagia,
- incontinence,
- myoclonus, and
- seizures





Alzheimer's disease



MCI → DEMENTIA

Economic impact of AD

- Ageing society: increasing prevalence
  - Overall prevalence estimates for dementia are approximately 1%-2% at age 65 years and as high as 30% by age 85 years.
  - MCI ranges from 2% to 10% at age 65 and 5% to 25% by age 85
- Survival: 8-10 years (up to 20 years)
- Direct costs (medication, hospitalization, nursing)
  - 2 million AD patients in nursing homes in USA
  - Nursing homes cost - $120 to $160 per daycare of AD patients costs $80 billion per year
- Indirect costs:
  - With lost wages of patients and families plus costs for non-nursing home patients:
- Total costs: $120 billion annually (*Am J Publ Hlth*)

Alzheimer's disease: etiology

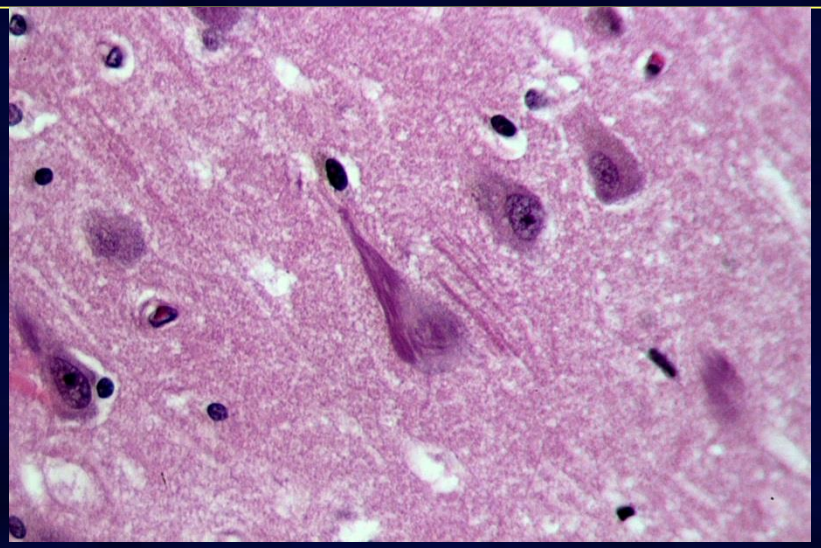
- Age (initial genesis vs response to stress)
  - This factor has the biggest impact
  - Stressor response (adequate repair mechanisms)
- Trauma (head injury),
- vascular (stroke risk factors)
- Genetics (amyloid related)
  - Familial, early onset: APP (21), PS (14, 1) (less than 5%)
  - Late onset: APOE e4 (ch19) (?50% of AD)
    - relation to brain cholesterol metabolism?
  - many other candidate genes
- Relation to vascular factors, cholesterol, BP
- Higher education
- Environment - diet, exercise, smoking
- Estrogens, statins, NSAIDs,
- APOE e2 may be most protective

Risk factors for AD

Family history of dementia	3.5 (2.6 - 4.6)
Family history - Downs	2.7 (1.2 - 5.7)
Family history - Parkinson's	2.4 (1.0 - 5.8)
Maternal age > 40 years	1.7 (1.0 - 2.9)
Head trauma (with LOC)	1.8 (1.3 - 2.7)
History of depression	1.8 (1.3 - 2.7)
History of hypothyroidism	2.3 (1.0 - 5.4)
NSAID use or statin use	0.2 (0.05 – 0.83)

Roca, 1994, t'Veldt, 2002

Neuropathology of AD



- Senile plaques
  - beta-amyloid protein
- Neurofibrillary tangles
  - hyper-phosphorylated tau (loss of synapses, dementia)
- Neurotransmitter losses
  - Acetylcholine (Ach) – major loss of nicotinic receptors
  - Norepinephrine, serotonin, glutamate, GABAss
- Inflammatory responses

Diagnostic markers for AD

Genetic factors/markers

- Familial AD (onset < 60 y/o) (<5%)
  - Presenilin I, II (ch 14, 1) and APP (amyloid precursor protein, ch 21)
  - They are diagnostic markers!!!
- Non-familial (late onset)
  - APOE, only risk factor and not diagnostic marker!

Other factors/markers (orange colored items have higher specificity)

- CSF: reduced levels of amyloid beta-42, elevated total tau and phospho-tau levels
- PET: amyloid imaging and temporoparietal hypometabolism on a fluorodeoxyglucose PET
- MRI: hippocampal and temporoparietal cortical atrophy

Why should we diagnose AD early?

- Safety (driving, compliance, cooking, etc.)
- Family stress and misunderstanding (blame, denial)
- Early education of caregivers of how to handle patient (choices, getting started)
- Advance planning while patient is competent (will, proxy, power of attorney, advance directives)
- Patient's and Family's right to know
- Specific treatments now available, may delay nursing home placement longer if started earlier

Consensus statement of Alzheimer's Association

- AD continues to be missed as diagnosis
- AD is unrecognized and under-reported
  - patients do not realized
  - families tend to compensate
- Effective treatment and management techniques are available

Small et al., JAMA, 1997

Frontotemporal Neurocognitive Disorder

- *A. The criteria are met for major or mild neurocognitive disorder.*
- *B. The disturbance has insidious onset and gradual progression.*
- *C. Either (1) or (2);*
  - *1. Behavioral variant;*
    - *a. Three or more of the following behavioral symptoms:*
      - *i. Behavioral disinhibition.*
      - *ii. Apathy or inertia.*
      - *iii. Loss of sympathy or empathy.*
      - *iv. Perseverative, stereotyped or compulsive/ritualistic behavior.*
      - *v. Hyperorality and dietary changes.*
    - *b. Prominent decline in social cognition and/or executive abilities.*
  - *2. Language variant:*
    - *a. Prominent decline in language ability, in the form of speech production, word finding, object naming, grammar, or word comprehension.*
- *D. Relative sparing of learning and memory and perceptual-motor function.*
- *E. The disturbance is not better explained by cerebrovascular disease, another neurodegenerative disease, the effects of a substance, or another mental, neurological, or systemic disorder.*

Frontotemporal Neurocognitive Disorder

Definite FTNCD:

- *Features of possible FTNCD + histopathologic confirmation*

Probable FTNCD:

- *Clinical features + if either of the following*
- *1. Evidence of a causative frontotemporal neurocognitive disorder genetic mutation, from either family history or genetic testing (mutations in the gene coding for microtubule-associated protein tau.*
- *2. Evidence of disproportionate frontal and/or temporal lobe involvement from neuroimaging.*

Possible FTNCD:

- *Clinical features if there is no evidence of a genetic mutation, and neuroimaging has not been performed.*

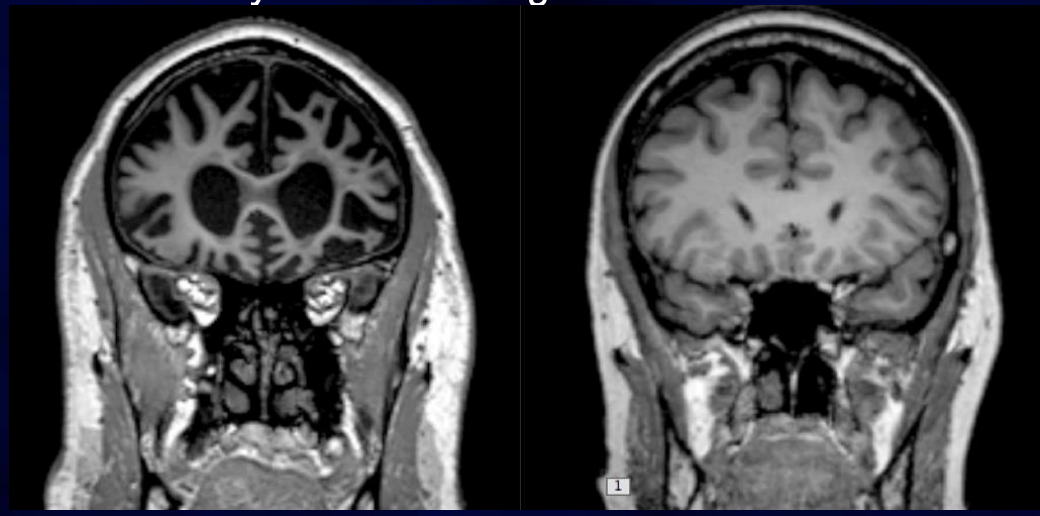
Clinical features

- *progressive development of behavioral and personality change and/or language impairment.*
- *The behavioral variant and three language variants (semantic, agrammatic/nonfluent, and logopenic) exhibit distinct patterns of brain atrophy*
- *apathy or disinhibition.*
- *lose interest in socialization, self-care, and personal responsibilities,*
- *display socially inappropriate behaviors.*
- *lack of planning and organization, distractibility, and poor judgment*
- *Insight is usually impaired*
- *Cognitive decline is less prominent*
- *3 language variants (semantic, agrammatic/nonfluent, and logopenic, primary progressive aphasia*

Frontotemporal Neurocognitive Disorder

Prevalence

- FTNCD is a common cause of early-onset NCD in individuals younger than 65 years
- Population prevalence: 2-10 per 100,000
- 80% of cases <65 years old
- median survival being 6-11 years after symptom onset and 3-4 years after diagnosis



Associated features

- May overlap with
  - progressive supranuclear palsy
  - corticobasal degeneration
  - Motoneuron disease (ALS-like disorders)

Risk factors

- Approximately 40% of individuals have a family history

Diagnostic markers

- MRI: distinct patterns of atrophy (In behavioral-variant, both frontal lobes, especially the medial frontal lobes) and the anterior temporal lobes are atrophic)
- Genetic: microtubule associated protein tau (MAPT), granulin gene (CRN), C90RF72 gene, transactive response DNA-binding protein of 43 kDa (TDP-43, or TARDBP), valosin-containing protein (VCP), chromatin modifying protein 2B (CHMP2B), and fused in sarcoma protein (FUS)

Neurocognitive Disorder With Lewy Bodies

- *A. The criteria are met for major or mild neurocognitive disorder.*
- *B. The disorder has an insidious onset and gradual progression.*
- *C. The disorder meets a combination of core diagnostic features and suggestive diagnostic features for either probable or possible neurocognitive disorder with Lewy bodies.*
  - *For probable major or mild neurocognitive disorder with Lewy bodies, the individual has two core features, or one suggestive feature with one or more core features.*
  - *For possible major or mild neurocognitive disorder with Lewy bodies, the individual has only one core feature, or one or more suggestive features.*
  - *1. Core diagnostic features:*
    - *a. Fluctuating cognition with pronounced variations in attention and alertness.*
    - *b. Recurrent visual hallucinations that are well formed and detailed.*
    - *c. Spontaneous features of parkinsonism, with onset subsequent to the development of cognitive decline.*
  - *2. Suggestive diagnostic features;*
    - *a. Meets criteria for rapid eye movement sleep behavior disorder.*
    - *b. Severe neuroleptic sensitivity.*
- *D. The disturbance is not better explained by cerebrovascular disease, another neurodegenerative disease, the effects of a substance, or another mental, neurological, or systemic disorder.*

Neurocognitive Disorder With Lewy Bodies

Previous name:

- *dementia with Lewy bodies (DLB)*

Prevalence:

- *1.7% to 30.5% of all dementia cases, in brain banks: 20%-35% of cases of dementia*
- *2nd most common degenerative dementia*

Clinical features

- *The symptoms fluctuate in a pattern that can resemble a delirium, but no adequate underlying cause can be found.*
- *spontaneous parkinsonism, which must begin after the onset of cognitive decline; by convention, major cognitive deficits are observed at least 1 year before the motor symptoms.*
- *repeated falls and syncope*
- *transient episodes of unexplained loss of consciousness*
- *Autonomic dysfunction*
- *REM sleep behavior disorder*
- *low striatal dopamine transporter uptake on single photon emission computed tomography*

Vascular Neurocognitive Disorder

- *A. The criteria are met for major or mild neurocognitive disorder.*
- *B. The clinical features are consistent with a vascular etiology, as suggested by either of the following:*
  - *1. Onset of the cognitive deficits is temporally related to one or more cerebrovascular events.*
  - *2. Evidence for decline is prominent in complex attention (including processing speed) and frontal-executive function.*
- *C. There is evidence of the presence of cerebrovascular disease from history, physical examination, and/or neuroimaging considered sufficient to account for the neurocognitive deficits.*
- *D. The symptoms are not better explained by another brain disease or systemic disorder.*

Probable vascular neurocognitive disorder is diagnosed if one of the following is present; otherwise possible vascular neurocognitive disorder should be diagnosed:

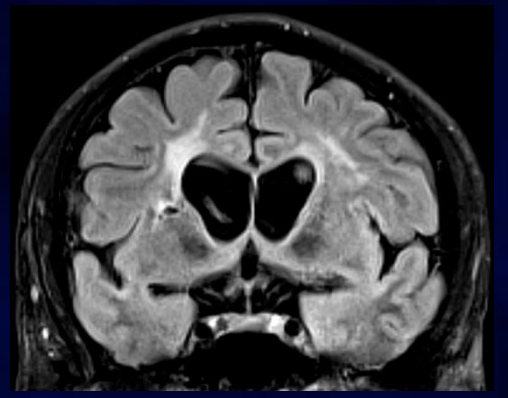
- *1. Clinical criteria are supported by neuroimaging evidence of significant parenchymal injury attributed to cerebrovascular disease (neuroimaging-supported).*
- *2. The neurocognitive syndrome is temporally related to one or more documented cerebrovascular events.*
- *3. Both clinical and genetic (e.g., cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) evidence of cerebrovascular disease is present.*

Possible vascular neurocognitive disorder is diagnosed if the clinical criteria are met but neuroimaging is not available and the temporal relationship of the neurocognitive syndrome with one or more cerebrovascular events is not established.

Vascular Neurocognitive Disorder

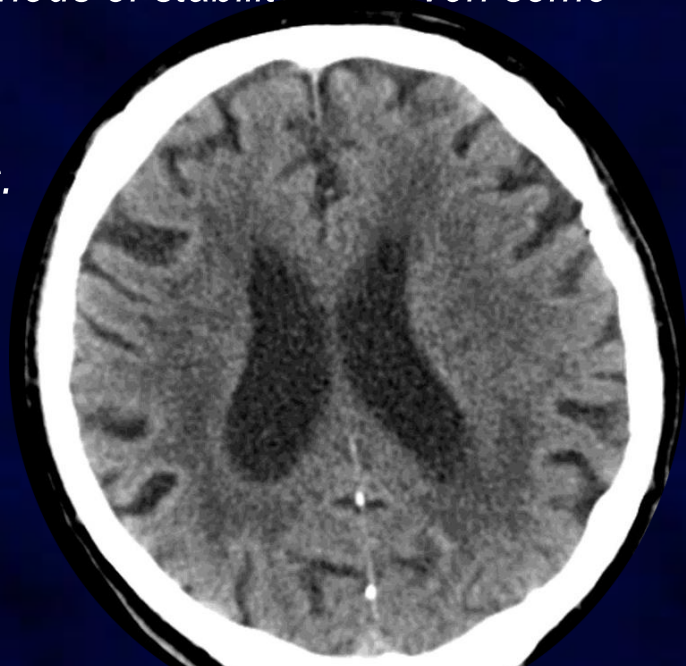
Clinical features

- *commonly associated are personality and mood changes, abulia, depression, and emotional lability.*
- *second most common cause of NCD after Alzheimer's*
- *prevalence increases exponentially after age 65 years.*
- *0.2% in the 65-70 years age group to 16% in individuals 80 years and older*
- *commonly co-occurs with Alzheimer's disease*



Vascular etiology may range from large vessel stroke to microvascular disease

- *presentation is therefore very heterogeneous*
- *acute stepwise or fluctuating decline in cognition, and intervening periods of stability and even some improvement.*
- *slow progression is generally due to small vessel disease leading to lesions in the white matter, basal ganglia, and/or thalamus.*

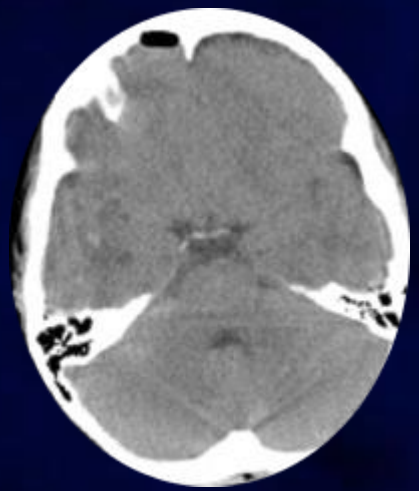


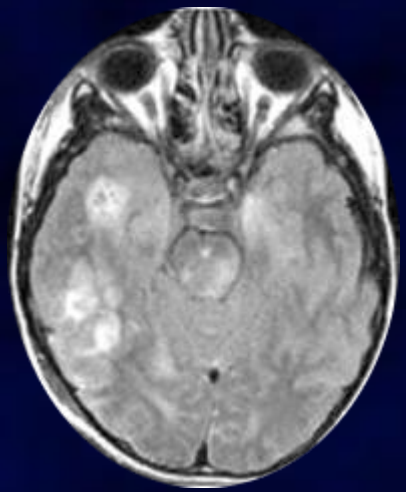
MRI depends on either of the following

- *one or more large vessel infarcts or hemorrhages,*
- *a strategically placed single infarct or hemorrhage (e.g., in angular gyrus, thalamus, basal forebrain),*
- *two or more lacunar infarcts outside the brain stem, or*
- *extensive and confluent white matter lesions*

NCD due to Traumatic Brain Injury

- *A. The criteria are met for major or mild neurocognitive disorder.*
- *B. There is evidence of a traumatic brain injury—that is, an impact to the head or other mechanisms of rapid movement or displacement of the brain within the skull, with one or more of the following:*
  - *1. Loss of consciousness.*
  - *2. Posttraumatic amnesia.*
  - *3. Disorientation and confusion.*
  - *4. Neurological signs (e.g., neuroimaging demonstrating injury; a new onset of seizures; a marked worsening of a preexisting seizure disorder; visual field cuts; anosmia; hemiparesis).*
- *C. The neurocognitive disorder presents immediately after the occurrence of the traumatic brain injury or immediately after recovery of consciousness and persists past the acute post-injury period.*





NCD due to Traumatic Brain Injury

Clinical features

- *Difficulties in the domains of complex attention, executive ability, learning, and memory are common as well as slowing in speed of information processing and disturbances in social cognition*
- *disturbances in emotional function (e.g., irritability, easy frustration, tension and anxiety, affective liability);*
- *Personality changes (e.g., disinhibition, apathy, suspiciousness, aggression);*
- *physical disturbances (e.g., headache, fatigue, sleep disorders, vertigo or dizziness, tinnitus or hyperacusis, photosensitivity, anosmia, reduced tolerance to psychotropic medications);*
- *neurological symptoms and signs (e.g., seizures, hemiparesis, visual disturbances, cranial nerve deficits) and aphasia, neglect, and constructional dyspraxia*
- *severe incoordination, ataxia, and motor slowing, may be present in major NCD due to TBI and may add to functional difficulties*
- *evidence of orthopedic injuries.*

Prevalence

- *In the United States, 1.7 million TBIs occur annually, resulting in 1.4 million emergency department visits, 275,000 hospitalizations, and 52,000 deaths.*
- *About 2% of the population lives with TBI-associated disability.*

Substance/Medication-induced NCD

- *Alcohol: executive-function and memory and learning domains,*
  - *alcohol-induced amnestic confabulatory (Korsakoff's) NCD, the features include prominent amnesia (severe difficulty learning new information with rapid forgetting)and a tendency to confabulate.*
  - *co-occur with signs of thiamine encephalopathy (Wernicke's encephalopathy) with associated features such as nystagmus, ataxia and ophthalmoplegia*

- *sedative, hypnotic, or anxiolytic drugs (e.g., benzodiazepines, barbiturates) may show greater disturbances in memory than in other cognitive functions*

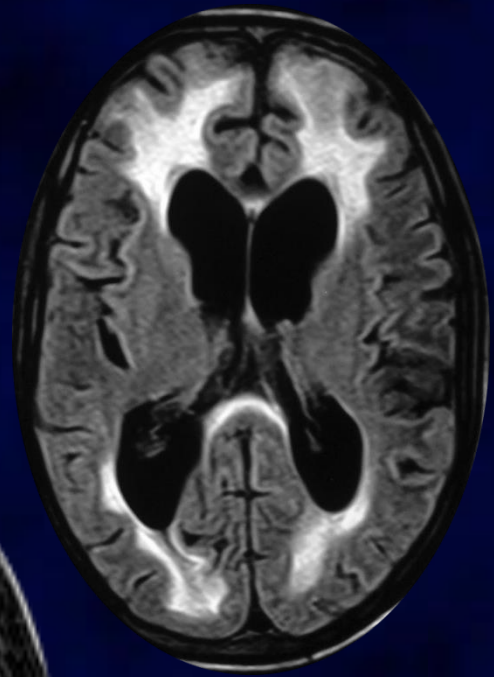
- *Anticholinergic medications*

- *Drugs: methamphetamine, opioids, phencyclidine, inhalants, methamphetamine, cocaine (can also elicit vascular damage!)*
- *Role of cannabis is controversial.*

NCD due to HIV infection

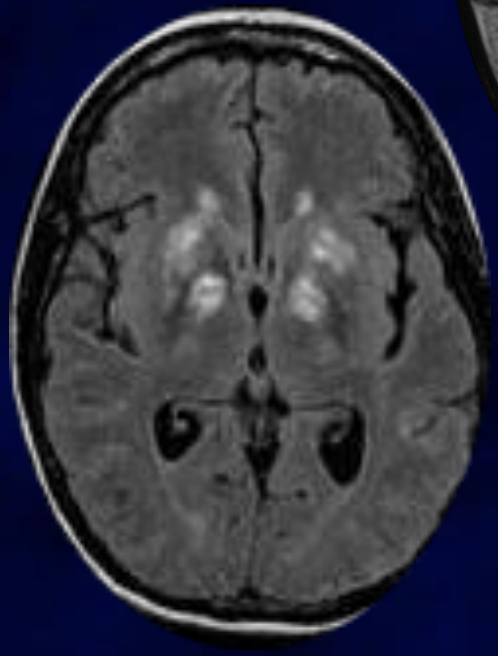
Clinical features

- *prominently impaired executive function, slowing of processing speed, problems with more demanding attentional tasks, and difficulty in learning new information, but fewer problems with recall of learned information.*
- *Slowing may be prominent*
- *Language difficulties, such as aphasia, are uncommon*
- *may experience prominent neuromotor features such as severe incoordination, ataxia*
- *can resolve, improve, slowly worsen, or have a fluctuating course*



Risk factors for developing NCD

- *prior episodes of severe immunosuppression*
- *high viral loads in the cerebrospinal fluid,*
- *and indicators of advanced HIV disease such as anemia and hypoalbuminemia.*



Prevalence

- *one-third to over one-half of HIV-infected individuals have at least mild neurocognitive disturbance*
- *5% have major NCD*

NCD due to prion disease

Definition

- *A. The criteria are met for major or mild neurocognitive disorder.*
- *B. There is insidious onset, and rapid progression of impairment is common.*
- *C. There are motor features of prion disease, such as myoclonus or ataxia, or biomarker evidence.*
- *D. The neurocognitive disorder is not attributable to another medical condition and is not better expiated by another mental disorder.*

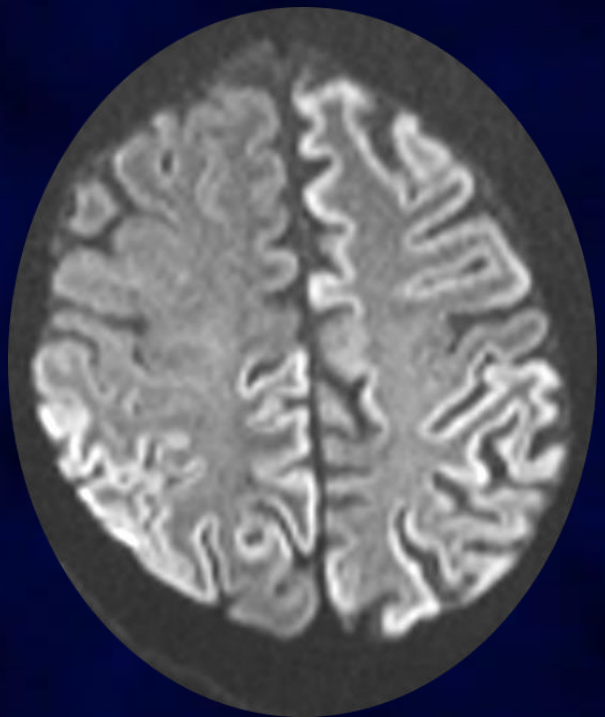
Clinical features

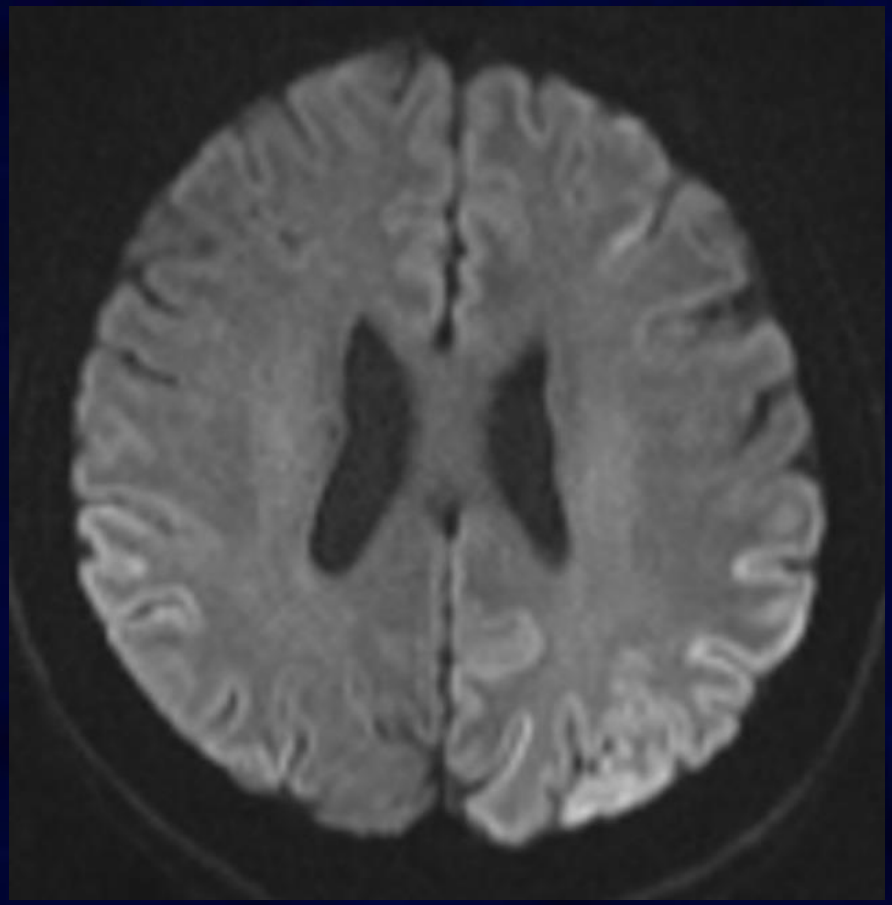
- *Creutzfeldt- Jakob disease, variant Creutzfeldt-Jakob disease, kuru, Gerstmann-Sträussler-Scheinker syndrome, and fatal insomnia*
- *neurocognitive deficits, ataxia, and abnormal movements such as myoclonus, chorea, or dystonia; a startle reflex is also common.*
- *Typically, the history reveals rapid progression to major NCD over as little as 6 months*
- *psychiatric symptoms, characterized a by low mood, withdrawal, and anxiety*

NCD due to prion disease

Diagnostic features

- *recognized lesions on magnetic resonance imaging with DWI (diffusion-weighted imaging) or FLAIR (fluid-attenuated inversion recovery)*
  - *Multifocal gray matter hyperintensities in subcortical and cortical regions*
- *tau or 14-3-3 protein in cerebrospinal fluid,*
- *characteristic triphasic waves on electroencephalogram,*
- *for rare familial forms, family history or genetic testing*
- *Definite diagnosis: only by biopsy or at autopsy*





NCD due to Parkinson's disease

Prevalence

- *0.5% between ages 65 and 69 to 3% at age 85 years and older*
- *75% will develop a major NCD sometime in the course of their disease*
- *mild NCD in Parkinson's disease has been estimated at 27%.*
- *Parkinson's disease may coexist with Alzheimer's disease and cerebrovascular disease*

Clinical features

- *apathy,*
- *depressed mood,*
- *anxious mood,*
- *hallucinations,*
- *delusions,*
- *personality changes,*
- *rapid eye movement sleep behavior disorder, and*
- *excessive daytime sleepiness*

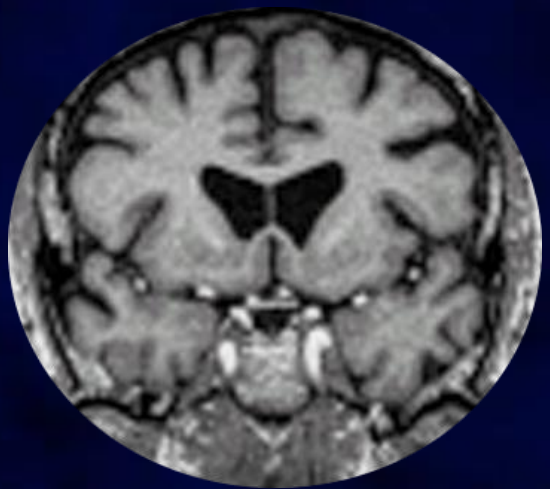
NCD due to Huntington's Disease

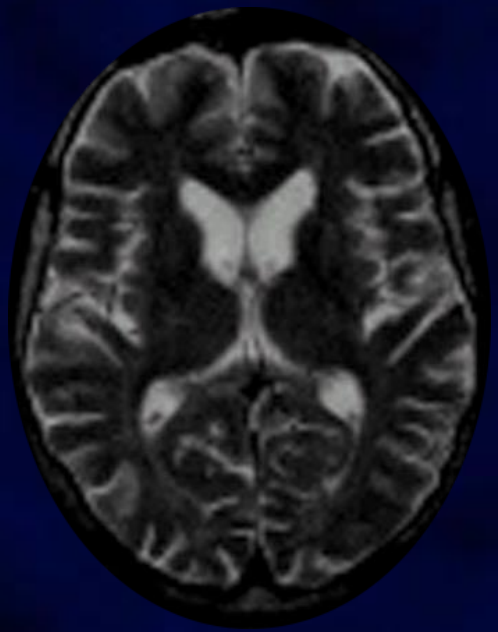
Prevalence

- *2.7 per 100,000*
- *CAG trinucleotide repeat expansion in the HIT gene, located on chromosome 4*
- *average age at diagnosis of Huntington's disease is approximately 40 years*
- *Age at onset is inversely correlated with CAG expansion length*

Features

- *Psychiatric and cognitive abnormalities can predate the motor abnormality by at least 15 years.*
- *Progressive cognitive impairment is a core feature of Huntington's disease*
- *early changes in executive function (i.e., processing speed, organization, and planning) rather than learning and memory*
- *Chorea, ballism*
- *Depression, irritability, anxiety, obsessive-compulsive symptoms, and apathy are frequently,*



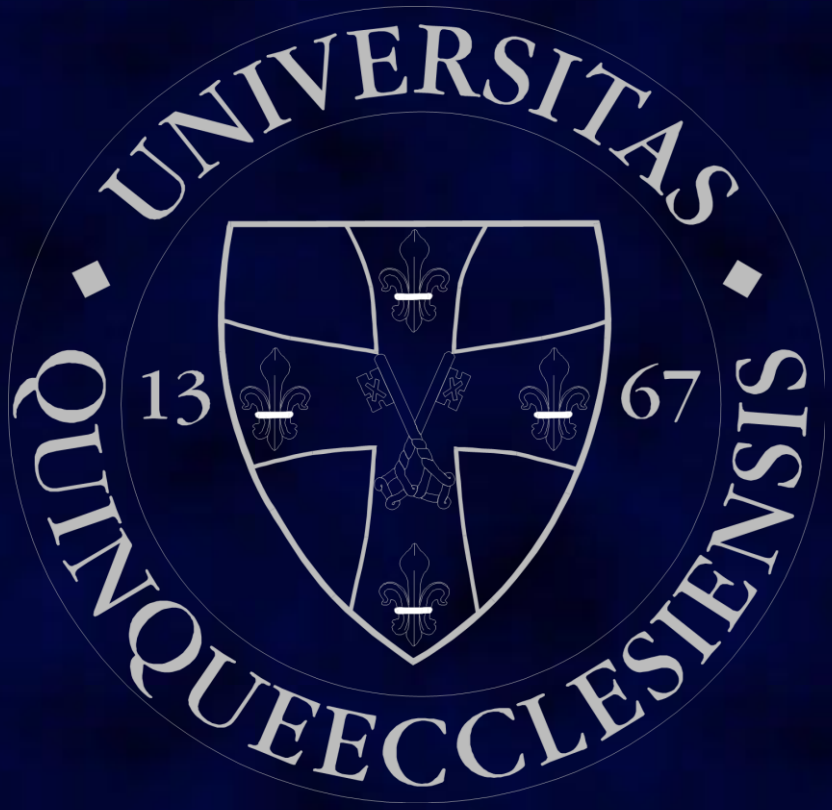


NCD due to Multiple Etiologies

Definition

- *A. The criteria are met for major or mild neurocognitive disorder.*
- *B. There is evidence from the history, physical examination, or laboratory findings that the neurocognitive disorder is the pathophysiological consequence of more than one etiological process, excluding substances (e.g., neurocognitive disorder due to Alzheimer's disease with subsequent development of vascular neurocognitive disorder)..*
- *C. The cognitive deficits are not better explained by another mental disorder and do not occur exclusively during the course of a delirium.*

4. Treatment options



Treatment of minor NCDs (MCI)

- *MCI should be identified and monitored because of their increased risk for AD*

- *At present, no established treatment exists*
- *donepezil has been found to delay the progression to AD in MCI patients with depression*
- *centrally acting angiotensin-converting enzyme inhibitors (CACE-Is) may reduce the rate of cognitive decline*
- *consume a Mediterranean diet*
- *social and mental activity are often recommended*
- *A prospective study suggested that engaging in moderate exercise of any frequency in midlife or late life was associated with reduced odds of having MCI*

Cholinesterase inhibition (ChEIs)

Definition

- *Numerous lines of evidence suggest that cholinergic systems that modulate information processing in the hippocampus and neocortex are impaired early in the course of AD.*
- *All ChEIs have shown modest benefit on measures of cognitive function and activities of daily living.*
- *Patients on ChEIs have shown slower declines on cognitive and functional measures than patients on placebo.*
- *However, ChEIs do not address the underlying cause of the degeneration of cholinergic neurons, which continues during the disease.*
- *The ChEIs may also alleviate the noncognitive manifestations of AD, such as agitation, wandering, and socially inappropriate behavior*
- *The ChEIs share a common profile of adverse effects, the most frequent of which are nausea, vomiting, diarrhea, and dizziness. These are typically dose related and can be mitigated with slow up-titration*
- *can provoke symptomatic bradycardia and syncope and precipitate fall-related injuries, including hip fracture*

Cholinesterase inhibition: mild to moderate severity

	Tacrine	Donepezil	Rivastigmine	Galantamine
Year available	1993	1996	2000	2001
Brain selectivity	No	Yes	Yes	Yes
Reversibility	Yes	Yes	Yes/slow	Yes
Chemical class	Acridine	Piperidine	Carbamate	Phenanthrene alkaloid
Enzymes inhibited:				
Acetylcholinesterase	Yes	Yes	Yes	Yes
Butyrylcholinesterase	Yes	Negligible	Yes	Negligible
Nicotinic receptor modulation	No	No	No	Yes
Doses per day	4	1	2	2
Initial dose (mg/day)	40	5	3	8
Maximum dose (mg/day)	160	10	12	24
Given with food	No, unless nausea occurs	No	Yes	Yes
Plasma half-life (hrs)	2–4	~70	~1	~6
Elimination pathway	Liver	Liver	Kidney	50% Kidney 50% Liver
Metabolism by cyto-chrome P450	Yes	Yes	Minimal	Yes

Treatment of severe NCD

Memantine

- *partial N -methyl-D-aspartate (NMDA) antagonist memantine*
- *believed to work by improving the signal-to-noise ratio of glutamatergic transmission at the NMDA receptor*
- *Several studies have demonstrated that memantine can be safely used in combination with ChEIs*

rivastigmine transdermal for severe AD

- *In June 2013, the FDA approved*
- *a higher dose of the drug (13.3 mg/24 hours) demonstrated statistically significant improvement in overall cognition and function compared with a lower dose (4.6 mg/24 hours)*

Treatment of other symptoms

First treat medical problems

Second environmental interventions

Third neuropsychiatric medications

- *Cognitive impairment*
- *Psychotic symptoms*
- *Depressive symptoms*
- *Insomnia symptoms*
- *Anorexia symptoms*
- *Parkinsonian symptoms*

Other treatment options

- *Antidepressants*
- *Anxiolytics*
- *Beta-blockers*
- *Antiepileptic drugs (for their effects on behavior)*
- *Neuroleptics (They can be associated with increased cardiovascular and cerebrovascular risk!!!!)*

Experimental therapeutic options

Vaccination with amyloid species

- *Administration of monoclonal antiamyloid antibodies*
- *Administration of intravenous immune globulin that may contain amyloid-binding antibodies*
- *Selective amyloid-lowering agents*
- *Chelating agents to prevent amyloid polymerization*
- *Brain shunting to improve removal of amyloid*
- *Beta-secretase inhibitors to prevent generation of the A-beta amyloid fragment*
- *Transcranial magnetic stimulation (TMS)*
- *Estrogen*
- *statins*
- *vitamin E supplementation*
- *Deep brain stimulation (fornix)*
- *Routine physical activity and exercise may have an impact on AD progression*

	Tacrine	Donepezil	Rivastigmine	Galantamine
Year available	1993	1996	2000	2001
Brain selectivity	No	Yes	Yes	Yes
Reversibility	Yes	Yes	Yes/slow	Yes