Dementia

Part I: Clinical manifestation and neurocognitive assessment of different types of dementia

Part II (Heide Baumann-Vogel):
classification, epidemiology, pathophysiology, neuroimaging, prognosis & therapy, selected types of dementia; case presentation

Peter Brugger, PhD, Heide Baumann-Vogel, MD
Neuropsychology Unit, Dept. of Neurology
University Hospital Zurich
peter.brugger@usz.ch

Overview

* What is dementia?
* Why neuropsychology? Biomarkers and cognitive markers
* Principles of cognitive testing
* Clinical picture of three different types of dementia….:
  … with an assessment focus on different functional domains:

A case with AD (Alzheimer Dementia):	learning and memory
A «posterior variant of AD»:	visual-spatial functions
A case with frontotemporal dementia :	(pre)frontal functions

What is dementia?

Dementia ≠ Alzheimer's disease

Alois Alzheimer
1864 - 1915
«Über eine eigenartige Erkrankung der Hirnrinde» 1907
(Patient, 56 yrs., with «Fibrillen in Zellen der Hirnrinde»)

Alheimer Dementia (AD) is just one type of many dementias!

What is dementia? Clinical definition according to statistical manuals of diseases (DSM, ICD)

Acquired cognitive decline involving memory plus….

…. at least one more deficit in either:
ORIENTATION
ATTENTION
LANGUAGE
PERCEPTION
PRAXIS
PLANNING
FLEXIBILITY
AFFECT CONTROL
SOCIAL COGNITION

Unimpaired consciousness

NOT due to one isolated focal cerebral lesion (vascular, space-occupying)

NOT due to depression

Decline has been present for at least 6 months

Decline is not just measurable psychometrically, but affects daily living

Decline is progressive

Why neuropsychology?

«behavioral neurology»,
«cognitive neurology»

Neuropsychological testing important for…

* early diagnosis of dementia (dementia yes or no)
* differential diagnosis / exclusion of treatable cause(s)
* severity (and quality) of cognitive impairment
* documentation of decline in repeated exams
* documentation of spared functions

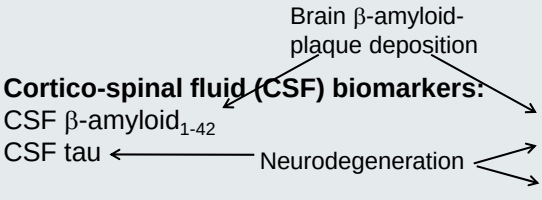
Biomarkers and neuropsychology

- Clinical symptoms do not always correlate with biomarker status!

Large «Over-90» study reveals that some patients with dementia (AD) do not have plaques nor tangles, whereas in some high functio-ning old-aged (3/8) lots of both markers were discovered post mortem

Fluid vs. imaging biomarkers: different association with cognition!

Biomarkers and neuropsychology



- Most proximate pathological substrate of clinical symptoms in AD is neurodegeneration (synapse loss), reflected in gross cerebral atrophy
- Clinical symptoms are more closely related to neurofibrillary tangles than to plaques
- Fluid vs. imaging biomarkers are differently correlated to cognition!
  CSF β-amyloid$_{1-42}$ may be more useful during presymptomatic stages, PET a more sensitive marker of later progression.

Collecting biomarkers without neuropsycho-logical testing does not make sense

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Not only biomarkers precede dementia:

Major genetic risk factors associated with BETTER memory performance at age 22 and with decreased neural recruitment (fMRI) in repeated learning

Cerebral Cortex August 2007;17:1934–1947
doi:10.1093/cercor/bhl103
Advance Access publication October 31, 2006

Better Memory and Neural Efficiency in Young Apolipoprotein E ε4 Carriers

Christian R.A. Mondadori[1], Dominique J.-F. de Quervain[1], Andreas Buchmann[1], Henrietta Mustovic[1], M. Axel Wollmer[1], Conny F. Schmidt[2], Peter Boesiger[2], Christoph Hock[1], Roger M. Nitsch[1], Andreas Papassotiropoulos[1] and Katharina Henke[3]

ANN NEUROL 2010;68:865–875 (same in 20 presenilin I mutation carriers vs. 19 non-carriers)

Hippocampal Hyperactivation in Presymptomatic Familial Alzheimer's Disease

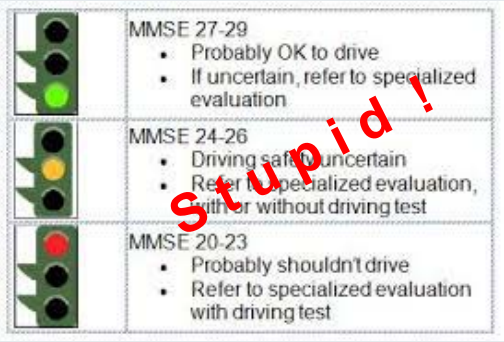
Yakeel T. Quiroz, MA,[1,2] Andrew E. Budson, MD,[3,4] Kim Celone, MA,[1] Adriana Ruiz, BA,[2] Randall Newmark, BA,[1] Gabriel Castrillón, BS,[5] Francisco Lopera, MD,[2] and Chantal E. Stern, PhD[1]

Assessment principles

age education gender

Standardized psychometric testing with normative values

No MMSE (mini-mental state examination, 10-20 minutes)!



MMSE asks for orientation, ability to recall 3 words, calculation ability, reading, writing and drawing
-> score from 0 to 30
DOES NOT CAPTURE FRONTAL LOBE FUNC-TIONING, ATTENTION

Assessment principles

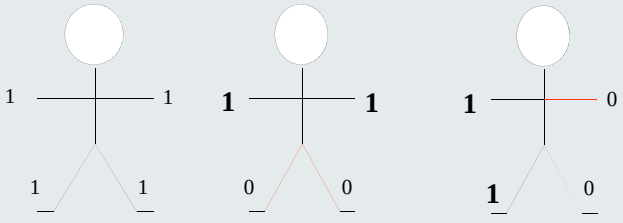
age education gender

Standardized psychometric testing with normative values

No MMSE (mini-mental state examination, 10-20 minutes)!

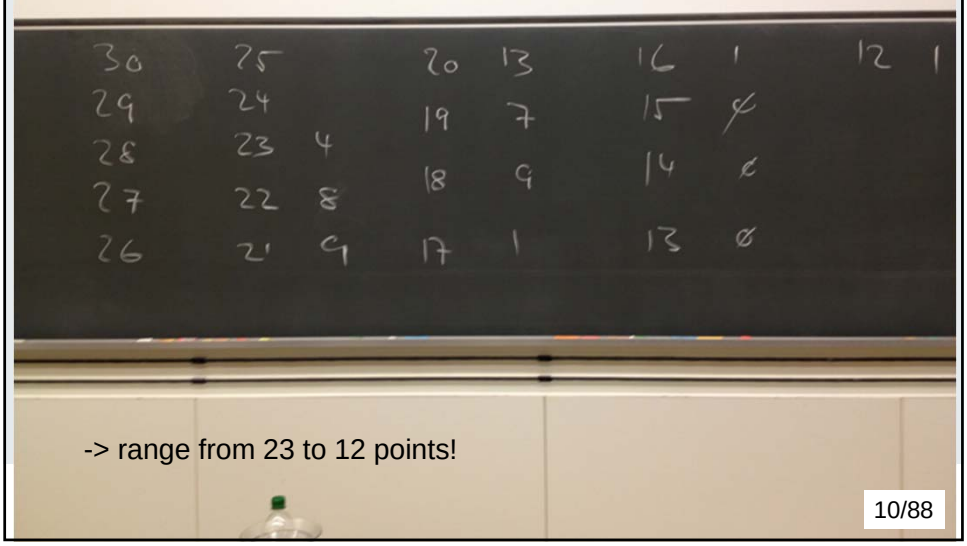
Describing a cognitive status with a score from 0 to 30 is like….

… describing a neurological status in one numerical score:



normal = 4 paraplegic = hemiplegic = **2**

53 assistant doctors scoring a fake patient aiming for 21 points:



-> range from 23 to 12 points!

Assessment principles

age education gender

Standardized psychometric testing with normative values

Use of MMSE:

Eat sh.. - ten billion flies can't be wrong!

Assessment principles

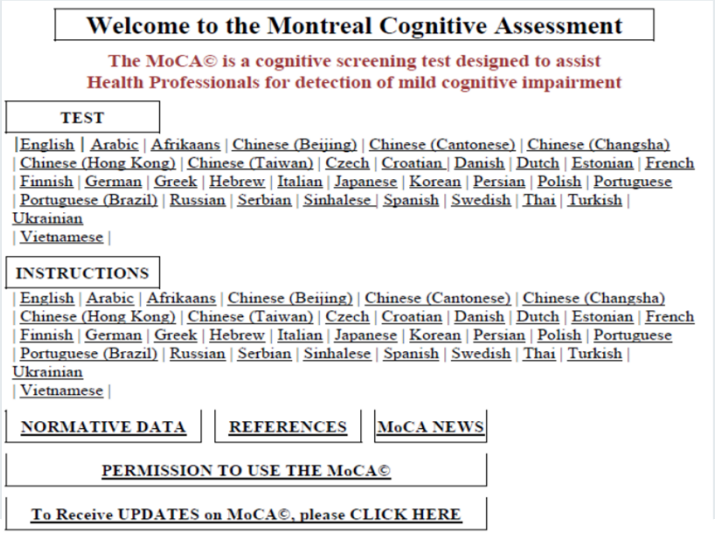
age education gender

Standardized psychometric testing with normative values; ideally in a regular neuropsychological examination, assessing language+, learning & memory, motor planning and praxia, perception and visuo-construction, frontal executive functions (2 hours, approx.)

If brief screening instrument desired/needed….

> ***MoCA-test: Mo****ntreal* ***C****ognitive* ***A****ssessment*
> approx. 30 minutes;
> *does* address frontal lobe functions;
> has several parallel versions;
> normative data provided

www.mocatest.org



Welcome to the Montreal Cognitive Assessment

The MoCA© is a cognitive screening test designed to assist Health Professionals for detection of mild cognitive impairment

TEST

English | Arabic | Afrikaans | Chinese (Beijing) | Chinese (Cantonese) | Chinese (Changsha) | Chinese (Hong Kong) | Chinese (Taiwan) | Czech | Croatian | Danish | Dutch | Estonian | French | Finnish | German | Greek | Hebrew | Italian | Japanese | Korean | Persian | Polish | Portuguese | Portuguese (Brazil) | Russian | Serbian | Sinhalese | Spanish | Swedish | Thai | Turkish | Ukrainian | Vietnamese |

INSTRUCTIONS

English | Arabic | Afrikaans | Chinese (Beijing) | Chinese (Cantonese) | Chinese (Changsha) | Chinese (Hong Kong) | Chinese (Taiwan) | Czech | Croatian | Danish | Dutch | Estonian | French | Finnish | German | Greek | Hebrew | Italian | Japanese | Korean | Persian | Polish | Portuguese | Portuguese (Brazil) | Russian | Serbian | Sinhalese | Spanish | Swedish | Thai | Turkish | Ukrainian | Vietnamese |

NORMATIVE DATA | REFERENCES | MoCA NEWS

PERMISSION TO USE THE MoCA©

To Receive UPDATES on MoCA©, please CLICK HERE

Assessment principles

age education gender

Standardized psychometric testing with normative values; ideally in a regular neuropsychological examination, assessing language+, learning & memory, motor planning and praxia, perception and visuo-construction, frontal executive functions

If brief screening instrument desired/needed….

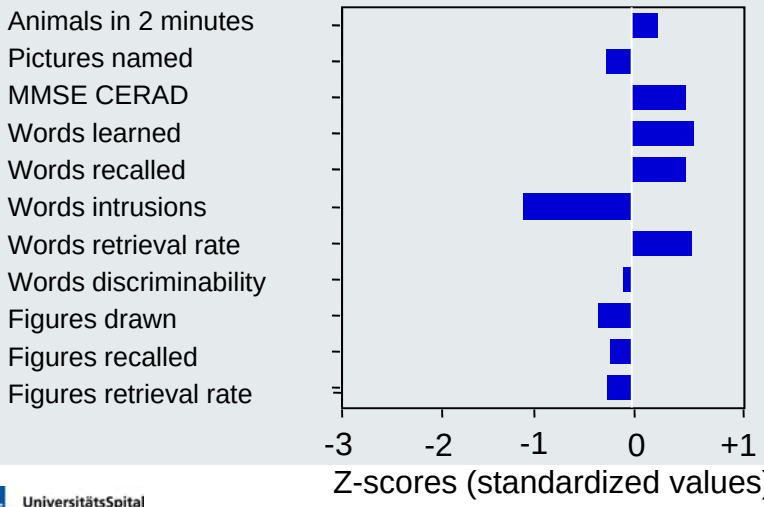
C **onsortium to**
E **stablish a**
R **egistry for**
A **lzheimer's**
D **isease**

CERAD neuropsychological assessment; US registry, German translation mid-90ies, well-validated in multicenter study

…or MoCA: Montreal Cognitive Assessment

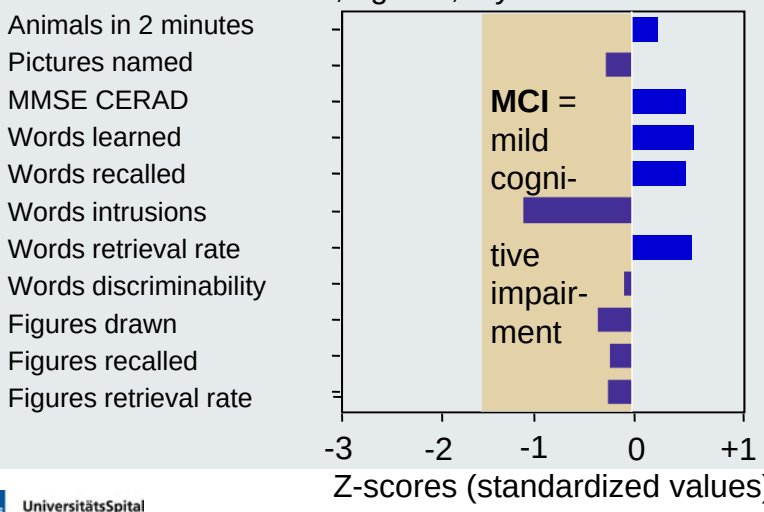
CERAD test battery for dementia screening

Performance expressed relative to normative values



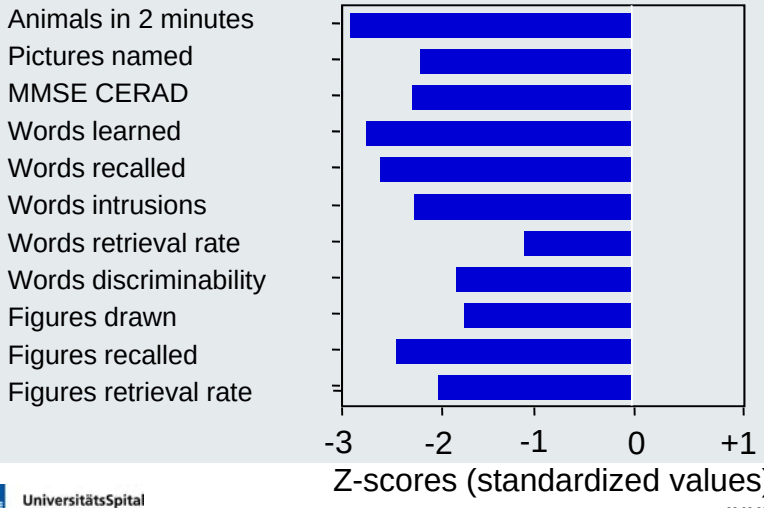
CERAD test battery for dementia screening

Two patients with identical overall scores:
Patient 1: man, age 90, 9 years of education



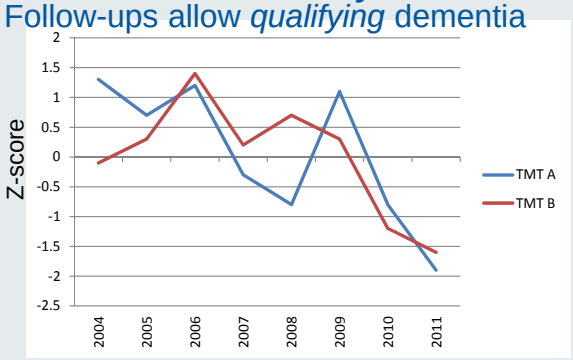
CERAD test battery for dementia screening

Two patients with identical overall scores:
Patient 2: woman, age 55, 20 years of education

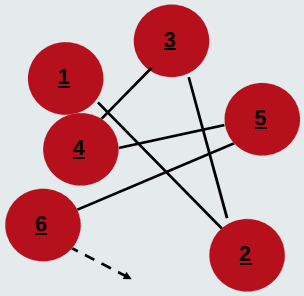


CERAD test battery for dementia screening

Follow-ups allow *qualifying* dementia



TMT: Trail Making Test: A:



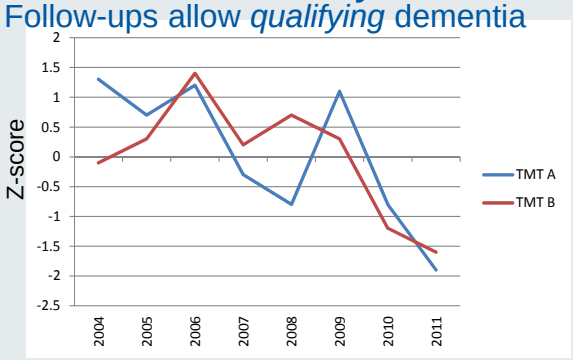
motor speed

If captured early, slope of decline for different functions can be informative about type of dementia.

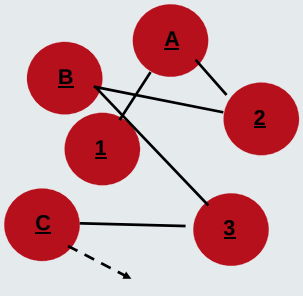
(In this case of a person ultimately diagnosed with DAT, there is a comparable decline in motor speed and cognitive flexibility)

CERAD test battery for dementia screening

Follow-ups allow *qualifying* dementia



TMT: Trail Making Test: B:



Cognitive speed

If captured early, slope of decline for different functions can be informative about type of dementia.

(In this case of a person ultimately diagnosed with DAT, there is a comparable decline in motor speed and cognitive flexibility)

Behavioral / neuropsychological assessment
in 3 different types of dementia

Dementia type:	points to illustrate:
AD, regular form	mnestic functions, planning. discrepancy everyday life / exam
AD, «posterior variant»	visual-perceptual functions, face processing, way-finding
FTD (fronto-temporal d.)	behavioral observation, executive functions, social cognition. language functions in a case of PPA (primary progressive aphasia)

Alzheimer Dementia (AD): typical features

A patient with AD typically

- gives impression of physical health
- is unconcerned about decline in mental abilities

BUT: initial hyper-concern: «de-mentia phobia»

- On very first formal examination, deficits are often more pronounced than one would expect from the patient's appearance and from his/her report and complaints
  The more concern the confrontation elicits, the milder the dementia
  -> «facade» <-> anosognosia

Typical features of DAT: lack of concern, «facade»

58 year old man,
referred to by the USZ interdisciplinary center for vertigo and balance disorders, where he had referred himself for a check of *peripheral* vestibular functions

Surgeon in a medium-size hospital, works 100%; healthy up to episode of vertigo with vomiting; normal MRI. No family hx for degenerative or psychiatric diseases

On further questioning «problems in the planning of non-routine movements», word finding difficulties (sister's name; thread type during surgery), slight progression. No changes in personality, no hallucinations, no motor system complaints.

Neuropsychological evaluation
Patient shows up the day before the appointment (to guarantee finding the location). Spared are: Orientation to time and place, perceptual functions, motor speed and focused attention.

Typical features of DAT: deficient mnestic functions: learning, recall, recognition

LÖWE
SMARAGD
PFERD
ZELT
SAPHIR
HOTEL
HÖHLE
OPAL
TIGER
PERLE
KUH
HÜTTE

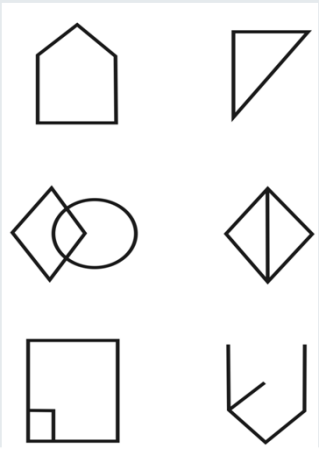
4 animals
4 precious stones
4 'housings'

1) recalled after 1st reading 4
2) recalled after 2nd reading 4
3) recalled after 3rd reading 7
4) late recall (20 minutes) 0

5) Recognition: was «Pferd» in the list? 9/12
Rubin? Katze? Fahrrad? Opal?
confabulations and repetitions! 2 c., 0 rep.

Typical features of DAT: deficient mnestic functions: learning, recall, recognition (nonverbal)

(correctly recalled figure scores 1, at correct place plus 1)



1) recalled after 1st reading 1
2) recalled after 2nd reading 1
3) recalled after 3rd reading 1
4) late recall (20 minutes) 1

5) Recognition: 12/12

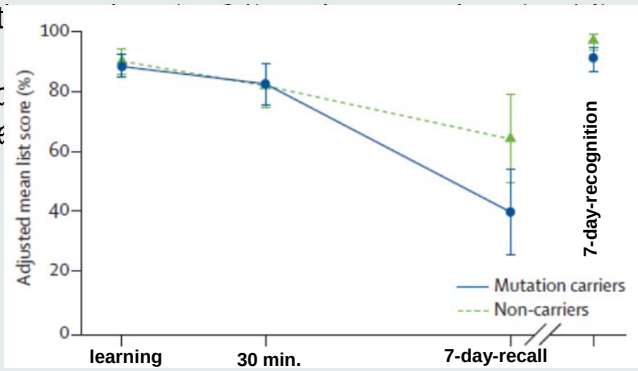
(confabulations and repetitions!) none

Typical features of DAT: deficient recall more long-term than session duration?

presenilin 1 or 2 or amyloid precursor protein

Symptom-free mutat
tested at age 38-39.
to 10 trials), asked fo
AFTER 7 DAYS (tele

Presymptomatic cognitive testing may be promising/ indispensable



Interpretation Accelerated long-term forgetting is an early presymptomatic feature of autosomal dominant Alzheimer's disease, which appears to pre-date other amnestic deficits and might underpin subjective memory complaints in Alzheimer's disease. Accelerated long-term forgetting testing might be useful in presymptomatic Alzheimer's disease trials.

Between attention and memory:

«attention span» = digit repetition (increasing sequence length):

4,7; 3,8,1; 4,2,7,3; etc.

5

«working memory» = digit repetition backwards (increasing sequence length):

1,4; 8,2,5; 7,2,1,3; etc.

2

Attention span can be spared in early stages of DAT. Working memory declines more rapidly

Between attention and memory:

Biology of the attention span

Chimpanzee Ai
(Inoue & Matsuzawa, 2007)

Precondition:

Chimps know single digits and can order them according to their magnitude.

This may not be self-evident, as we underestimate animal cognition…..

Numerical cognition:
From humans to chimps to chicks…

New-born chicks know that 5 < 8, and 8 < 20, and they place 5 to the left of 8, 8 to the left of 20, etc.
The chick's mind contains a number line that extends from left to right in number space!

(Rugani et al., 2015, *Science* 347)

Far from bird-brained. Rugani *et al.* report elegant experiments investigating the sense of numerical order in 3-day-old domestic chicks.

ANIMAL BEHAVIOR

Chicks with a number sense

Chicks and humans map numbers to space in a similar way

… and back to humans: P.Brugger, *Science* 347/2015:477-478

Between attention and memory:

Biology of the attention span

If digits are immediately masked, Ai still «remembers» their location!

(better than medical students…)

Current Biology Vol 17 No 23
R1004

2007

Working memory of numerals in chimpanzees

Sana Inoue and Tetsuro Matsuzawa

Chimpanzee memory has been extensively studied [1,2]. The general assumption is that, as with many other cognitive functions, it is inferior to that of humans [3]; some data, however, suggest that, in some circumstances, chimpanzee memory may indeed be superior to human memory [4]. Here we report that young chimpanzees have an extraordinary working memory capability for numerical recollection — better even than that of human adults tested in the same apparatus following the same procedure.

Impact of memory loss on language:
(mild) amnestic amnesia

Confrontation naming:

language disorder
CONSECUTIVE
to memory disorder!

Composites, rare words:
Long hesitations or no response (HÄNGEMATTE, MAULKORB), occasional semantic («Blumen-strauss» for KRANZ) or phone-matic paraphasias («Roller» for ROLLSTUHL)

Almost always impaired in addition to memory loss: «executive functions»

Planning, monitoring and modifying behavioral sequences.

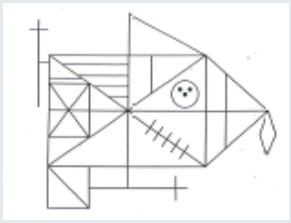
Flexible adaptation of automatized programs to situationally specific affordances («flexibility»)

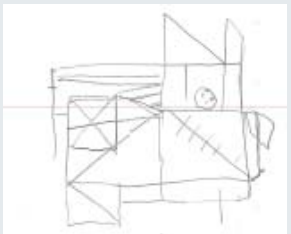
Inhibition of inappropriate routines

Innovative generation of items according to certain criteria («fluency» tasks)

Concept finding and conceptual shifting

Almost always impaired in addition to memory loss: «executive functions»

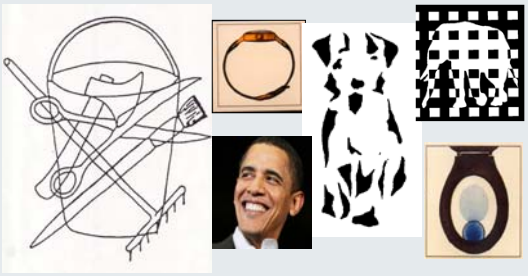




present case: 21/36; 5 min. 56 s.

Planning deficits as revealed in copying a complex figure:

Notably: spared elementary visual functions, intact motor behavior in present case!



Almost always impaired in addition to memory loss: «executive functions»

Other executive functions impaired in present case:

Increased susceptibility to interferences: naming the color of (incompatibly colored) color words (BLUE, RED, GREEN, …)

Reduced flexibility / set shifting: connecting 1-A-2-B-3-… relative to 1-2-3-4-… or A-B-C-D-…

Quantitatively only minimal impairment of «fluency»: generating words starting with S, any animals, nonverbal configurations (but: many perseverations as *qualitative* signs!)

In addition, in present case:

Severe calculation deficits, especially written.

Writing of numerals on dictation: «778» first 70078, then 787

Addition problems:

413
787
?

«Seven plus three…, but I don't know where to write the «ten»!

Thus, we document in this case:

Severe anterograde memory deficit with difficulties in word retrieval, impaired executive functions and dyscalculia. Spared motor speed, no agnosia, no aphasia, no apraxia. The patient is relatively unconcerned, but can be persuaded to prospectively organize his affairs with the assisstance of his wife

To sum up:

This early-onset case (age 58) illustrates:

Surprising discrepancy between integration in everyday life and actual test performance.
Typical for patients with DAT to downplay their symptoms, also for themselves («facade» <-> anosodiaphoria <-> anosognosia)

Out-of-routine event can initiate consultation of a specialist (flu with severe vertigo; general anaesthesia; loss of a close relative, «moving to dementia» (i.e., change of address, new environment): Sudden breakdown in «cognitive reserve»?

«Posterior cortical atrophy» («posterior cortical dementia»): a posterior variant of AD

61 year old man,
referred to by GP after patient's complaints about a gradual decline of memory over the past 5 years and, according to a close relative, difficulties in spatial orientation. «Seeing has changed» Question: allowed to drive?

Healthy, apart from TGA for a few hours some months before first symptoms. Five years ago fall w'out loss of consciousness, but signs of frontal concussion. No family history of psychiatric or neurodegenerative diseases. Brain MRI unremarkable.
Office worker, 100%, «adapted»

Neuropsychological evaluation
Fully oriented right-hander. Affectively and behaviorally normal. Speech/language, praxis, executive functions normal. Normal learning, but mild retrieval deficit (both verbally and nonverbally).
Visual-spatial functions: difficulties in recognizing degraded images, subjective contours, faces. Constructional apraxia. Slowed RTs to visual field stimulation.

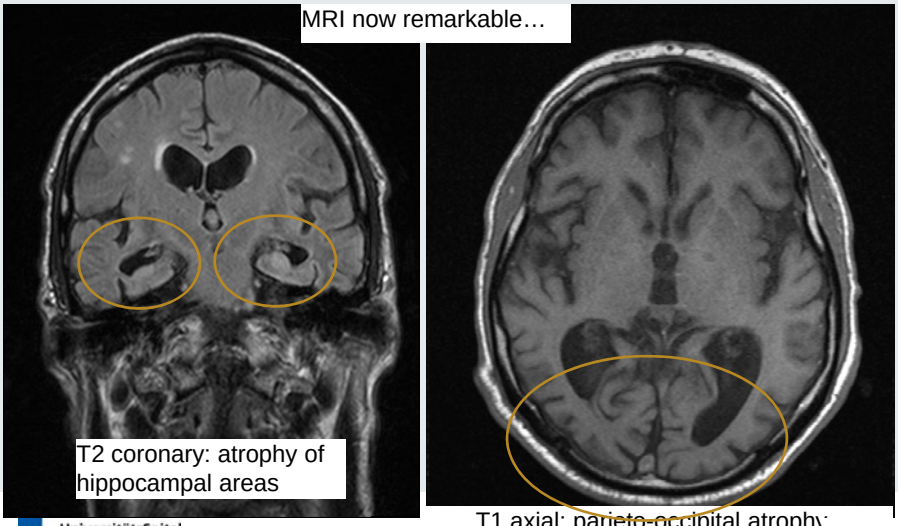
-> Ability to drive no longer given

«Posterior cortical atrophy» («posterior cortical dementia»): a posterior variant of AD

Second referral, 4 years later (now 65 years old)
referred by GP to neurology after patient's complaints about increasing «difficulties with vision». Has a hard time to recognize objects and faces, gets lost within own house.

Neurological status: slight hyposmia, signs of hemianopia (finger perimetry), slow and slightly saccadic (etchy) ocular pursuit, saltations left leg unsecure, walking on a line unsecure (both blind and seeing), finger movements clumsy – otherwise unremarkable

«Posterior cortical atrophy» («posterior cortical dementia»): a posterior variant of AD



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«Posterior cortical atrophy» («posterior cortical dementia»): a posterior variant of AD

65-year-old gentleman, second neuropsychological examination

Disoriented to time (knows month). Fully cooperative. Full insight into dysfunctions. No apraxia. Severely impaired verbal and abolished figural learning with no recall and no figural recognition (verbally borderline). Digit span normal, block span severely impaired (2). Dyscalculia. *Visual-spatial functions: see below*

In all aspects spared speech and language, except reading (writing non-fluent):

no problem:	*marked difficulties:*
HAUSWART	
FUSSBALL	

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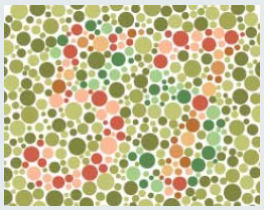
23.03.2018 39/88

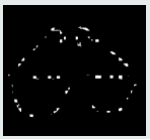
«Posterior cortical atrophy» («posterior cortical dementia»): a posterior variant of AD

visual acuity

Spared visual functions:

Recognizes colors, contrast, orientation, drawings of canonical objects (delayed):

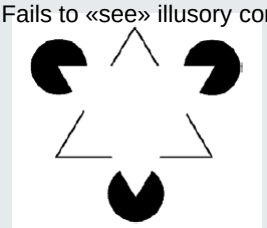




noncanonical views impossible to decode

«Posterior cortical atrophy» («posterior cortical dementia»): a posterior variant of AD

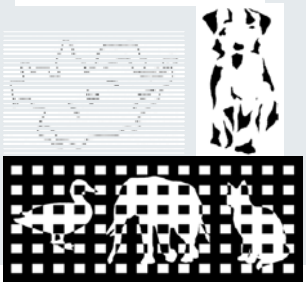
Fails to «see» illusory contours…



… overlapping drawings…

… analogue times …(digital no problem)

16:40

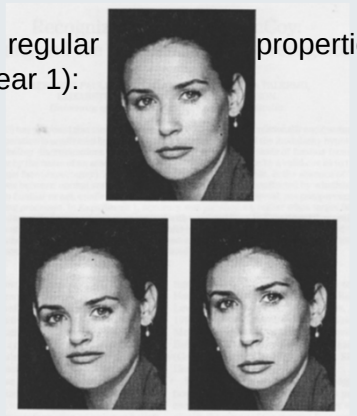


… rotated or degraded images…

…faces and emotional facial expressions

«Posterior cortical atrophy» («posterior cortical dementia»): a posterior variant of AD

Loss of sense for regular properties of a face (already during year 1):

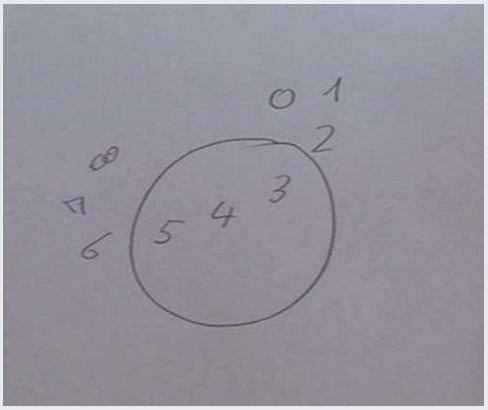


.. but could spot faces in trees, differentiate gender, old/young, animal and human faces

«Posterior cortical atrophy» («posterior cortical dementia»): a posterior variant of AD

Loss of ability to judge emotional facial expressions (discretely compromized already during year 1):

«Posterior cortical atrophy» («posterior cortical dementia»): a posterior variant of AD



Drawing of a clock-face (2dn attempt):

difficulties in orientation on the sheet («simultan-agnosia») despite having learned a trick: 'begin with drawing a circle'

«Posterior cortical atrophy» («posterior cortical dementia»): a posterior variant of AD

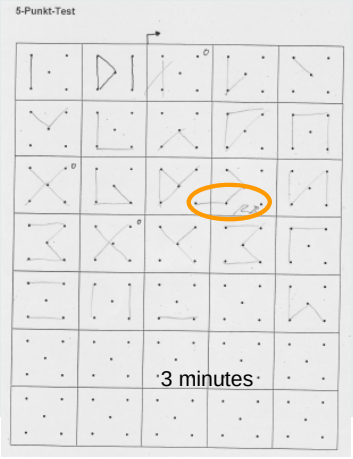
Drawing of a clock-face (2dn attempt):

difficulties in orientation on the sheet («simultan-agnosia») despite having learned a trick: 'begin with drawing a circle'

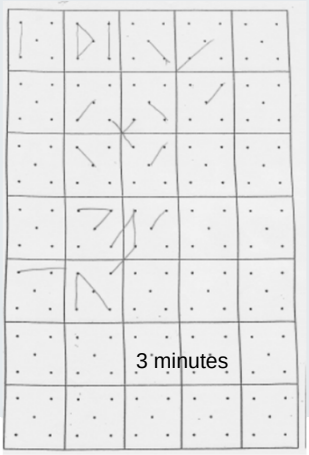
(copying comparable)

«Posterior cortical atrophy» («posterior cortical dementia»): a posterior variant of AD

Nonverbal fluency: disorganized because of a breakdown in scene organization



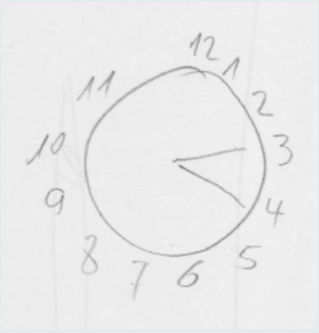
first exam



follow-up

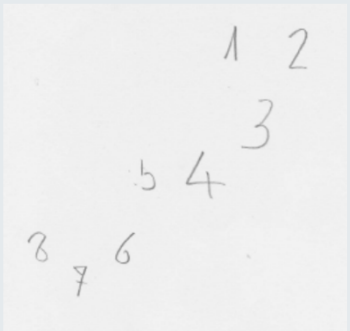
«Posterior cortical atrophy» («posterior cortical dementia»): a posterior variant of AD

Decline of clock-face drawing over 4 years



first exam

«20 past 3»

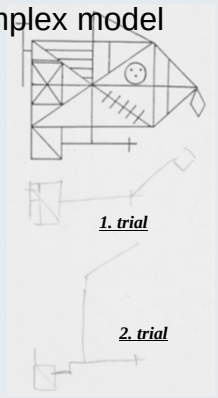


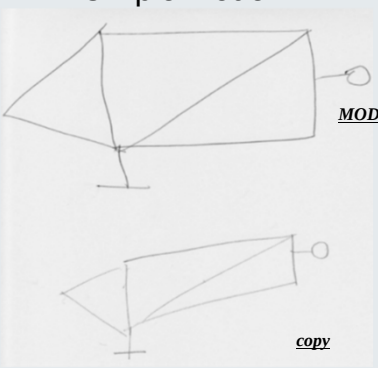
follow-up

(first attempt, but similar after drawing a circle)

«Posterior cortical atrophy» («posterior cortical dementia»): a posterior variant of AD

Constructional ability («copying») at year 1:
complex model vs. simple model

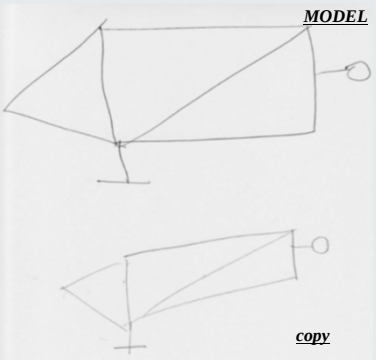


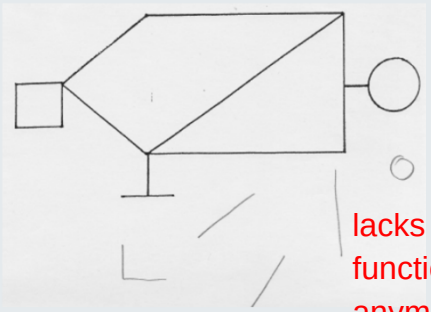


«constructional apraxia»

«Posterior cortical atrophy» («posterior cortical dementia»): a posterior variant of AD

Decline of constructional ability («copying») over 4 years



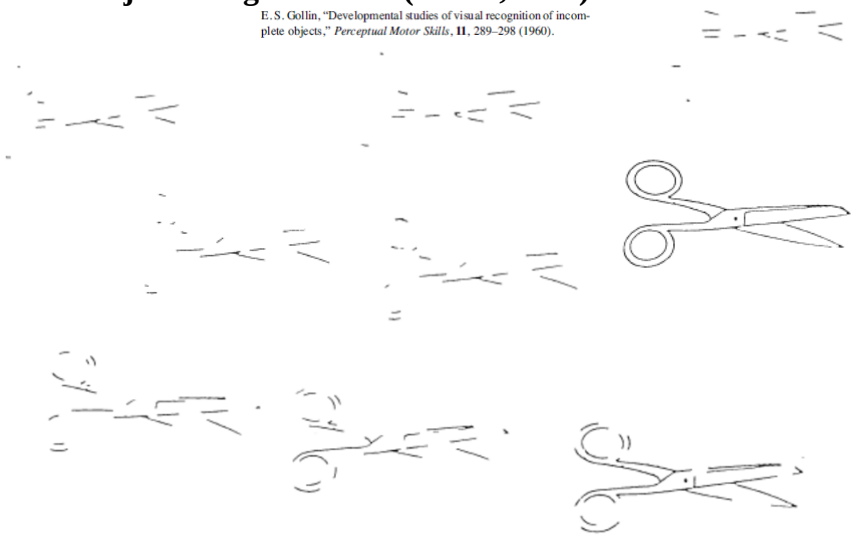


lacks integral part of visual function, cant integrate info anymore

first exam follow-up

Graded objekt recognition test (Gollin, 1960)

E. S. Gollin, "Developmental studies of visual recognition of incomplete objects," *Perceptual Motor Skills*, **11**, 289–298 (1960).



First exploration: 5.7, 4 years later: 8.2

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«Posterior cortical atrophy» («posterior cortical dementia»): a posterior variant of AD

Face agnosia and prosopagnosia:

Scores low on Mooney faces

C. M. Mooney, "Age in the development of closure ability in children," *Can. J. Psychol.*, **2**, 219–226 (1957).

Does not automatically spot the face:

UniversitätsSpital Zürich

(slight difficulties already 4 years ago)

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«Posterior cortical atrophy» («posterior cortical dementia»): a posterior variant of AD

Face agnosia and prosopagnosia:

very poor at differentiating animal from human faces (preserved ability 4 years ago)

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«Posterior cortical atrophy» («posterior cortical dementia»): a posterior variant of AD

Prosopagnosia: loss of facial familiarity (only at second exploration)

Partner, children, grand children

«Posterior cortical atrophy» («posterior cortical dementia»): a posterior variant of AD

Face perception:

difficulties in differentiating between animal and human faces

«Posterior cortical atrophy» («posterior cortical dementia»): a posterior variant of AD

Face perception:

difficulties in differentiating between animal and human faces
(is not surprised when told that it's an animal's face)

«Posterior cortical atrophy» («posterior cortical dementia»): a posterior variant of AD

Topographagnosia:

Description of way-finding during walks (asks other people; relies on memory)

(not shown/recorded: reliance on odor perception; «where it smells of rotten plants, I turn left, […] the gas station is a prominent land mark; it smells of…»)

«Posterior cortical atrophy» («posterior cortical dementia»): a posterior variant of AD

No agnosias in other modalities:

auditory:

tactile: recognizes (also uncommon) objects by haptic exploration

To sum up:

This case of a «posterior variant of AD» illustrates:

First signs of dementia can be changes in how a patient «sees» the world. Visual-perceptual problems can be very serious even in the absence of visual cortex atrophy («posterior cortical atrophy» ≠ «posterior cortical dementia»)

Agnosias are modality-specific

Unlike in the presence of memory deficits as the primary symptom, there is spared insight into difficulties in visual perception and cognition

«Posterior cortical atrophy» («posterior cortical dementia»): a posterior variant of AD

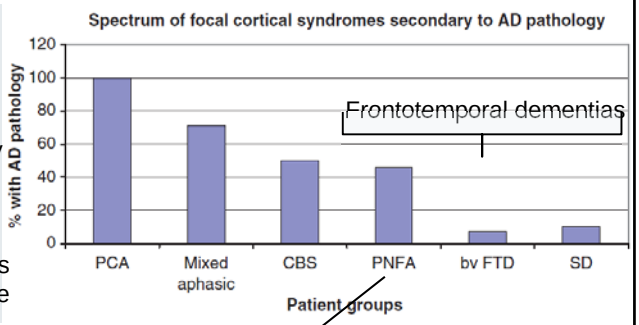
doi:10.1093/brain/awm213 *Brain* (2007), **130**, 2636–2645

Focal cortical presentations of Alzheimer's disease

S. Alladi,[1] J. Xuereb,[2] T. Bak,[1] P. Nestor,[1] J. Knibb,[1] K. Patterson[3] and J. R. Hodges[1,3]

Total 100 patients with focal signs of aphasia, apraxia or agnosia that are progressive. -> post mortem pathology; neuritic plaques, neurofibrillary tangles.

All «posterior cortical dementia» and 45% – 70% of patients with other dementia types have AD pathology!



«Progressive nonfluent aphasia» = primary progressive aphasia