Spectrum of late, non-stroke manifestations of small vessel disease

Teaching Courses

STROKE TC 2

Hall D Date: SATURDAY, OCTOBER 31, 2015 From: 14:30 To: 18:00

45 min

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XXII World Congress Neurology, Santiago, Chile, Oct31-Nov 5, 2015

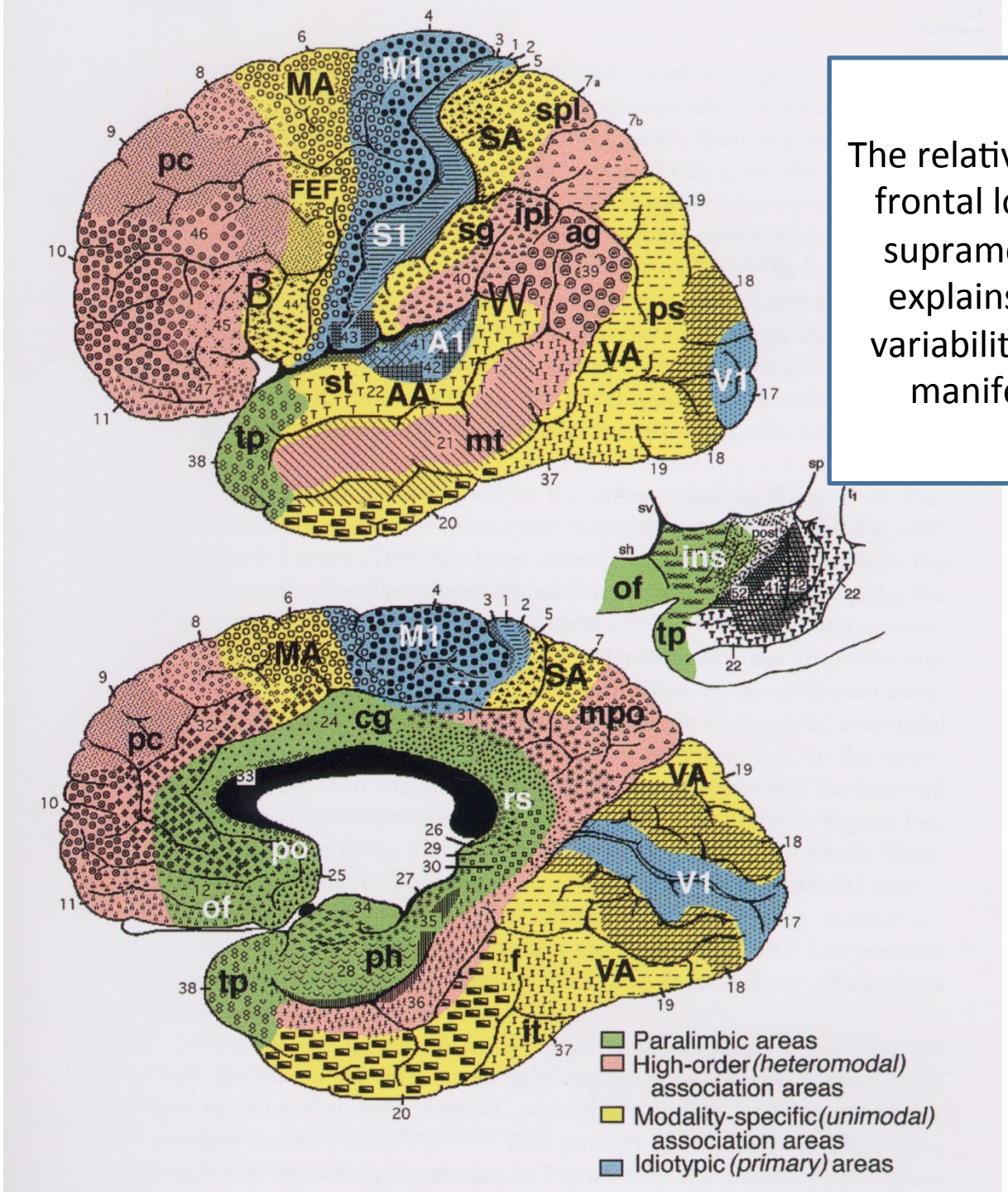
RoI

Consultancy and speakers honoraria	Grants to University and Royalties
• Allergan	• European Commission Public Health
• Boehringer	• European Research Foundation FP7
• Bayer	• Life Science Foundation Krems
• Ever Neuro Pharma	• Ever Neuro Pharma
• Takeda	• Boehringer, Takeda
• Pfizer	• Cambridge Univ Press
• Medtronic	• Wiley Blackwell
• Nestlec	• World Stroke Organsiation
	• European Academy of Neurology

Spectrum of late, non-stroke manifestations of small vessel disease

- In this lecture, the attendee will learn about
- The large variations of frontal lobe syndromes due to SMV
- Apathia, irritability, euphoria are the hall marks (dysexecutive syndrome)
- Neuropsychological assessment
- Some neuropathological facts
- Current trials focusing on prevention

- Due to the differing locations of smd there is a wide spectrum.
- Often the clinical signs become apparent in later stages of the disease
- The main signs are behavioural disoders
- Of these, dysexecutive signs are most frequent



The relative size of the frontal lobe, esp its supramodal parts, explains the large variability of clinical manifestations

Mesulam MM 2000 Distribution of functional zones in relationship to Brodmann's map of th ehuman brain

Table 11.1 Manifestations of Prefrontal Damage (Frontal Lobishness)

Tactlessness	*Irritability
Poorly restrained behavior	Disinhibition
Decreased social concern	Coarseness
Jocularity	Hyperkinetic
Facetiousness	Hypokinetic
Witzelsucht	Flare with anger
Moria	Puerile (silly) attitude
Boastfulness	Disinhibition of social graces
Grandiosity	Inappropriate sexual advances
Decreased intiative	Sexual exhibitionism
Decreased attentiveness	Lewd conversation
Forgetfulness	Erotic behavior
Poor memory	*Euphoria
Indifference	Poor planning ability
*Apathy	Diminished concern for the future
Shallow effect	Capriciousness
Lack of spontaneity	Loss of abstract attitude
Abulia	Loss of esthetic sense
Asthenia	Impulsiveness
Akinesia	Distractability
Deterioration of work quality	Stimulus bound
Depression	Concreteness
Morose discontent	Perseveration
	Restlessness

Delusions: Grandiosity (strength, wealth, intelligence)
Nihilism
Paranoia
Hypochondriasis

*The unholy triad of frontal behavior disorder suggested by Geschwind (1977).

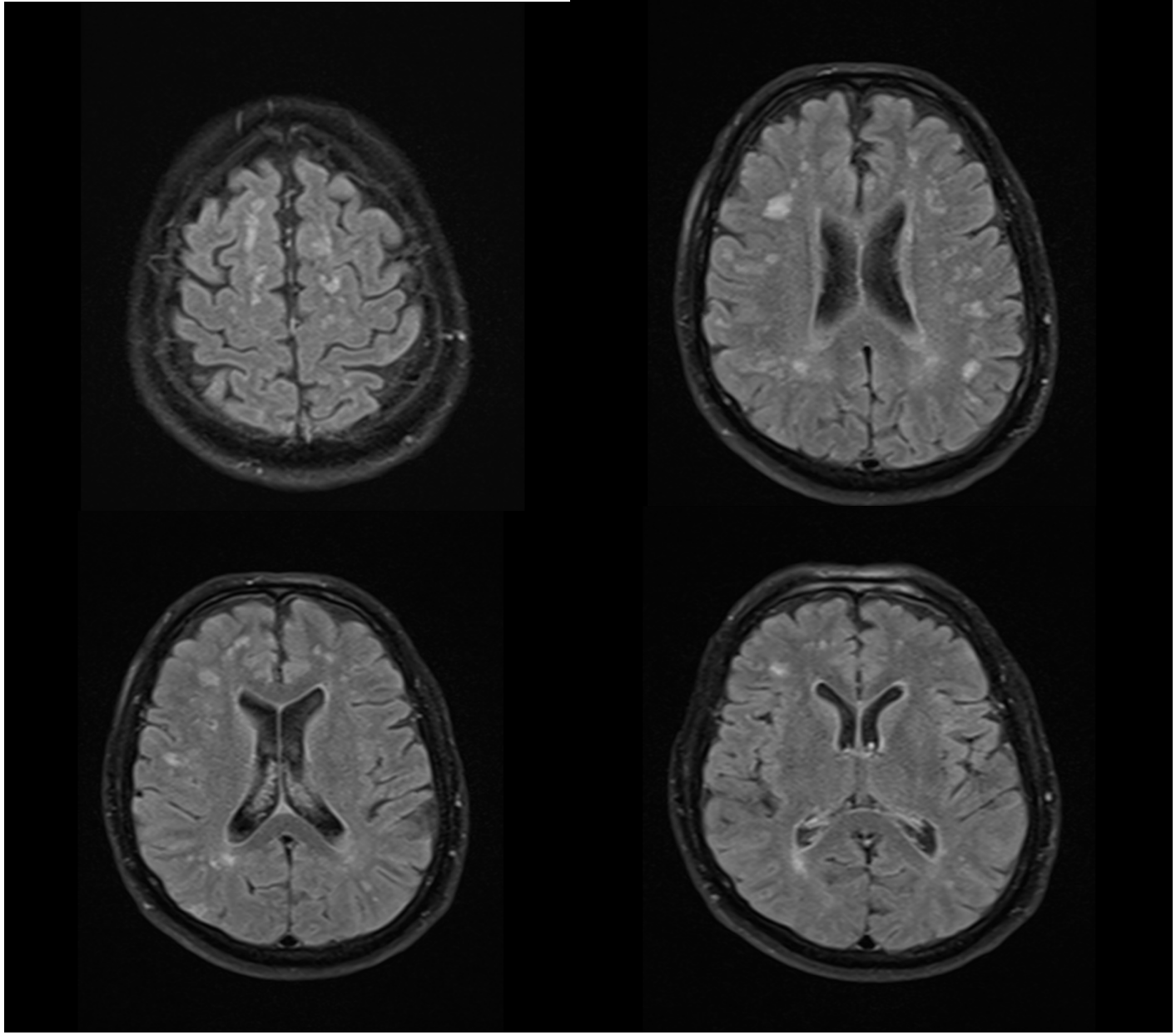
Bensons‘ Neurology of Thinking and ‚frontal lobishness‘

Unholy triad of frontal behaviour disorder (Geschwind, 1977)

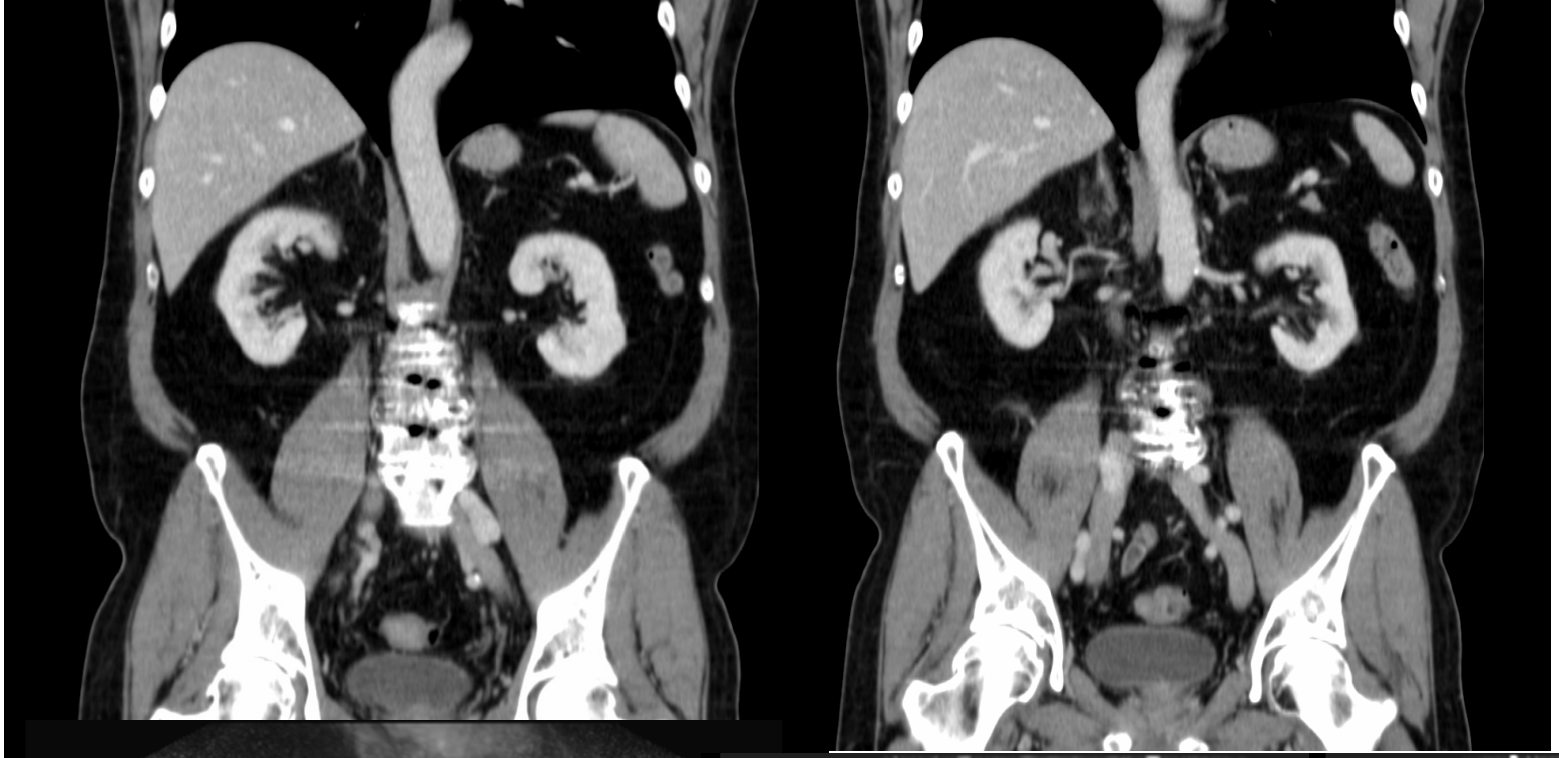
- Apathy
- Irritability
- Euphoria

67 year old sportive motor journalist

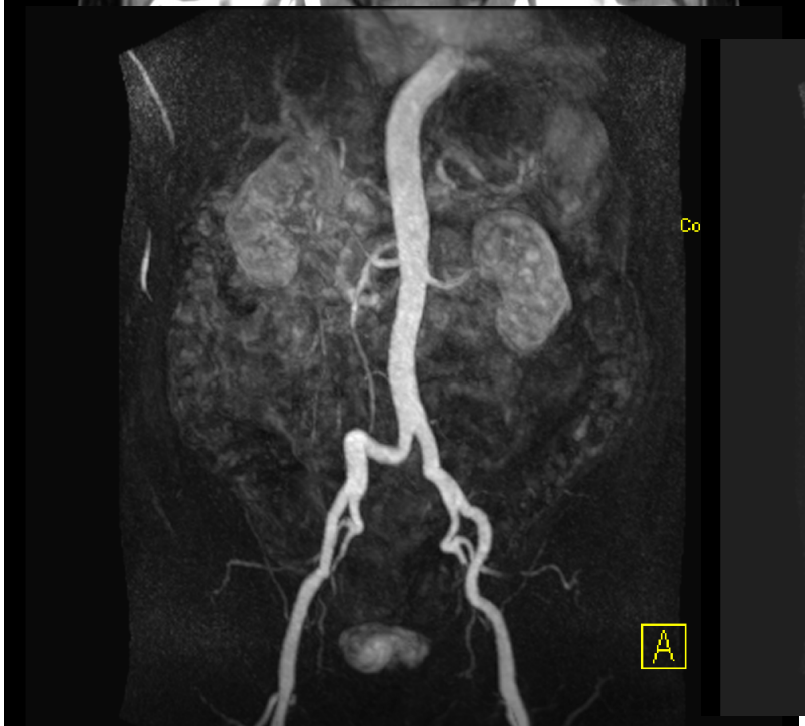
- Compulsive iteration of words/sentences, unaware that he feels he has to comment or iterate sentences with trivial contents, partly not adequate
- Response to the next syndrome *Neurology, 1988; 38:1225-7*
- Agitation, generally in high spirits
- Spreads good mood, jocularity, add times inappropriate charming remarks to nurses
- But highly irritable about changes of lunch/dinner times
- Neuropsychological tests, esp. for memory and attention are normal.

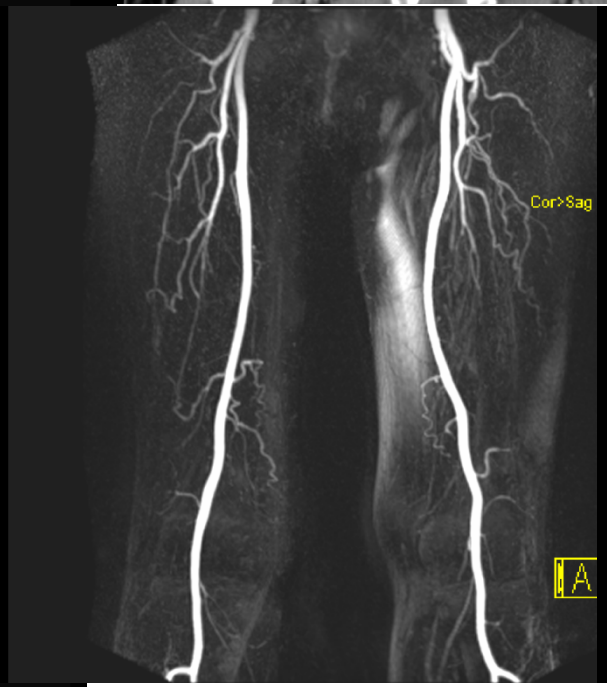


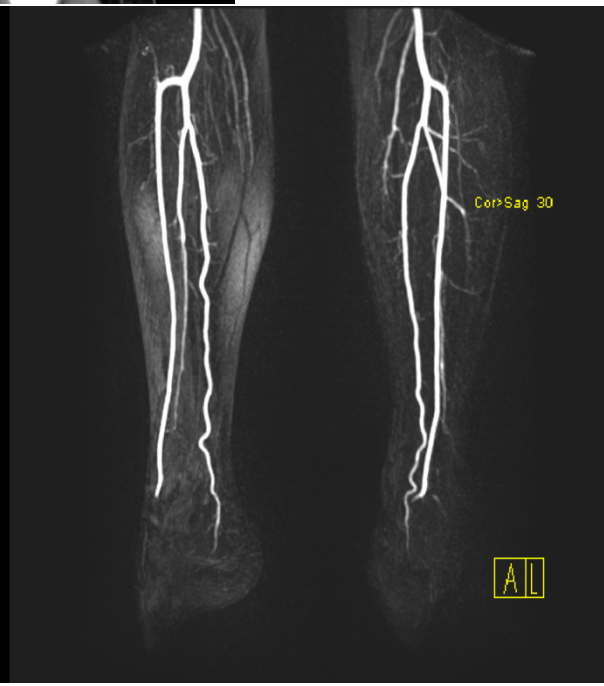
JB, ID 101788754, 67ys, orthostatic syncope, neuro normal



No macrovas-cular involvement







Cognition – test instruments

1) Short neuropsychological test-battery including (20min)

Can be administrated by non-neuropsychologists

- Montreal Cognitive Assessment (MOCA)
- Trail making test A and B
- Digit-Span forward and backward

2) More detailed test-battery (1-1.5h) for centres with neuropsychologists (substudy) to describe in detail the neuropsychological profile of the participants

includes: tests for alertness, reaction time, verbal fluency, verbal memory, visual spatial perception, visual memory...

Teuschl Y, Matz K, Brainin M et al. , submitted

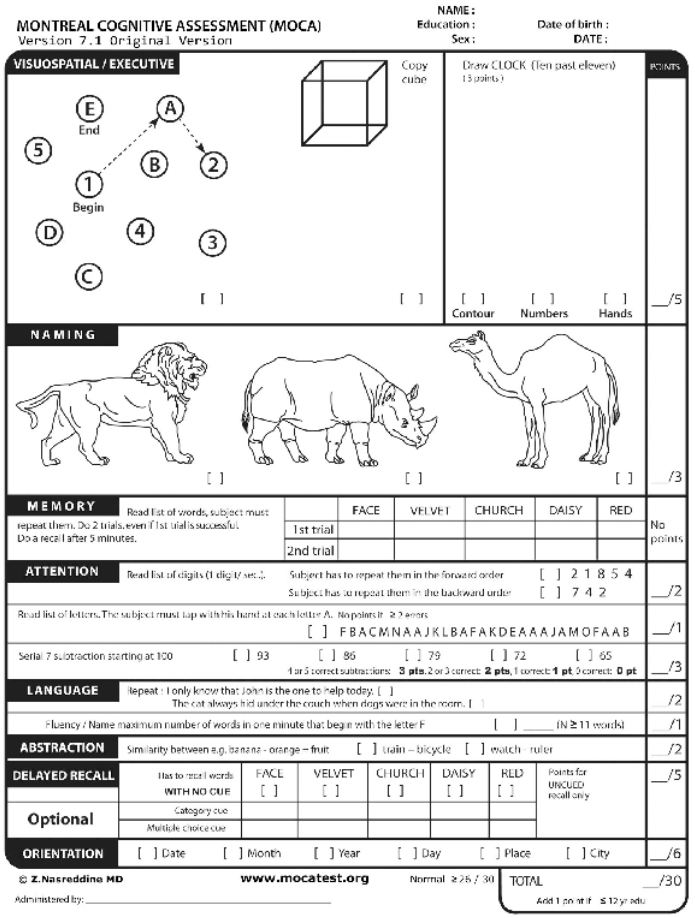
Cognition – test instruments

Montreal Cognitive Assessment (MOCA)

Short screening instrument for mild vascular cognitive impairment

Administration time approximately 10 min

include: - attention and concentration
- executive functions
- memory
- language
- visuoconstructional skills
- conceptual thinking
- calculations
- orientation


MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

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

VISUOSPATIAL / EXECUTIVE — Copy cube — Draw CLOCK (Ten past eleven) (3 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. 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

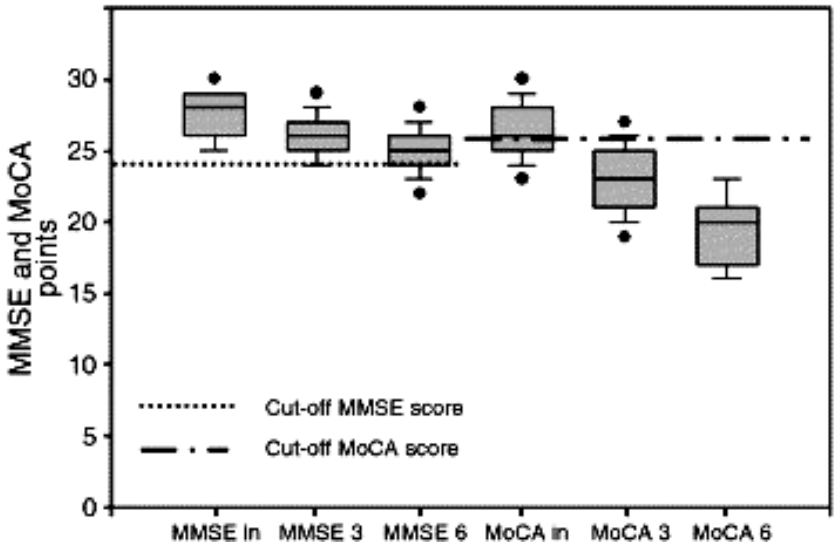
© Z.Nasreddine MD — www.mocatest.org — Normal ≥ 26 / 30 — TOTAL — /30

Administered by: _____ — Add 1 point if ≤ 12 yr edu

Not available in Bulgarian and Lithuanian
No costs, written permission is requested

Cognitive decline

- 0.8-2 points decline on MMSE / year
- 10-32% had cognitively declined after 1 year from baseline (3 months post-stroke)
- cognitive decline increases with recurrent stroke
- detection of cognitive decline depends on the cognitive tests used



Cognitive testing in patients with first ischemic stroke with MMSE and MoCA at baseline, after 3 and 6 months

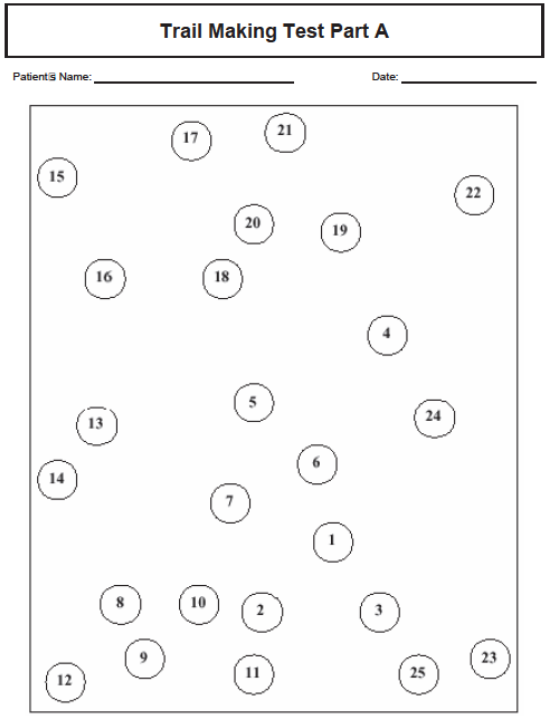
Popovic et al. 2007. J Neurol Sci 257: 185-93

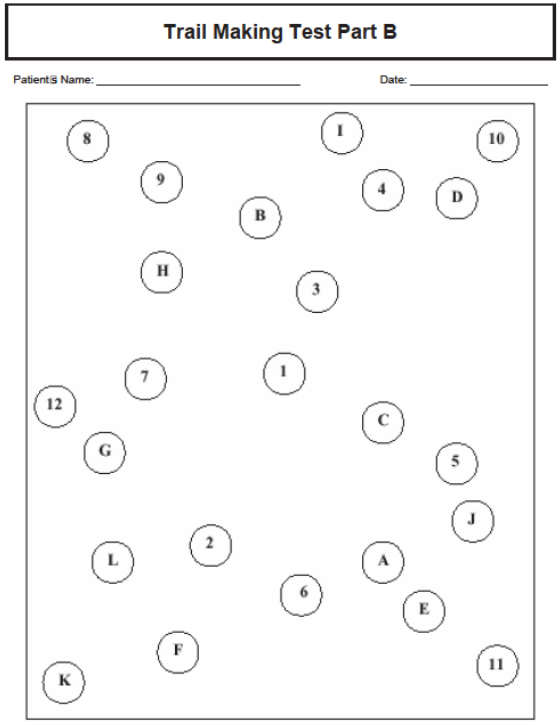
Cognition – test instruments

Trail making test A and B:

Timed paper-and-pencil test, testing the domains: executive functions (cognitive flexibility), speed of processing

Administration time approximately 5 min





Cognition – test instruments

Digit-Span forward and backward:

Subject has to repeat strings of digits of increasing length in same order or reverse order.

Testing the domains: working memory, attention, executive functions

Administration time approximately 5 min

Training for short neuropsychological test battery

Short training (1h) is necessary for standardization and scoring
Best is self-testing and answers to questions afterward (online)

Vascular Cognitive Impairment Harmonization Standards

National Institute of Neurological Disorders and Stroke-Canadian Stroke Network Vascular Cognitive Impairment Harmonization Standards

Hachinski V et al.

Stroke 2006, published 17 August 2006, doi:10.1161/01.STR.0000237236.88823.47

30 minutes

- Semantic fluency (animal naming)
- Phonemic fluency (word association)
- Digital symbol coding (from the WAIS)
- Verbal learning test
- Depression scale (CESDS)
- Neuropsychiatric inventory
- MMSE, Trail making

Hachinski V et al. Stroke 2006

5 minutes

- Montreal Cognitive Assessment subsets:
- 5 word memory task (registration, recall, recognition)
- 6 item orientation
- 1 letter phonemic fluency

Hachinski V et al. Stroke 2006

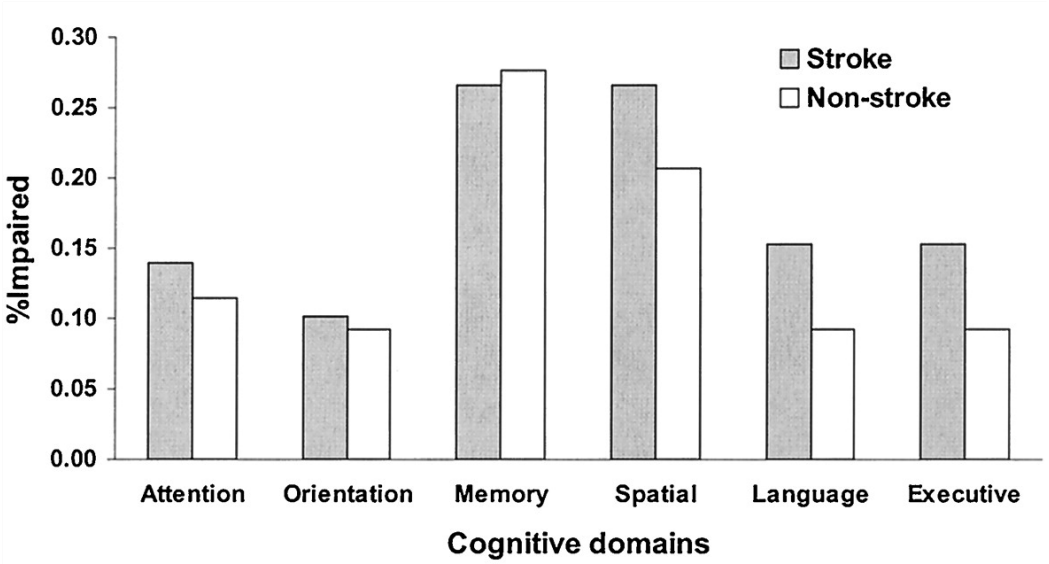
Post-stroke cognitive impairment

- Definitions:
- Lack of consensus on how to operationalize established criteria
- Lack of comparability between studies
- If threshold for inclusion is chosen as 1 SD difference a large number of cases result whereas 2SD difference result in lower numbers
- Plus/minus subjective memory complaints

Pendelbury S et al. CVD 2013

Mild cognitive impairment after stroke spares memory

- Mild cognitive impairment (no dementia) at 3 months varies from 17% - 66% depending on the criteria used.
- RR 1.5 - 2.1 compared to stroke free controls
- more characterized by executive dysfunction, psychomotor speed slowing than by memory problems
- 41% had executive dysfunction at 3 months poststroke



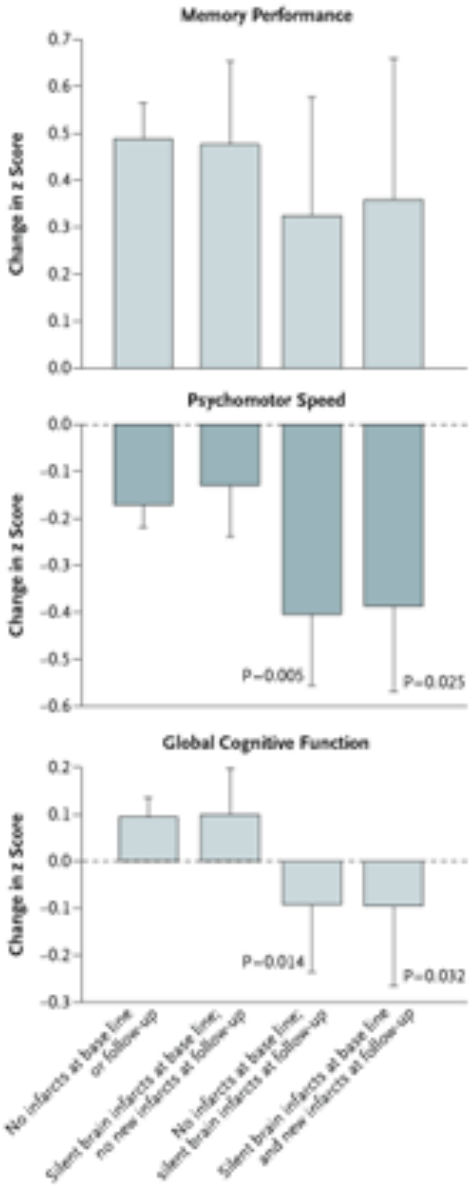
Patterns of cognitive impairment excluding subjects with preexisting cognitive decline (79 strokes, 87 nonstrokes)

Srikanth et al. 2003. Stroke 34:1136-43

Lacunar stroke and cognitive impairment

- 58 - 75% had cognitive deficits within 1 month poststroke; 60% at 2 years
- dementia 11% at 1-3 years poststroke and 15% at 9 years
- leukoaraiosis increases the risk of dementia after lacunar stroke. 16% vs 2% had dementia at 1 month; 22% vs 3% at 25 months; mainly executive functions are affected.
- silent lacunes are associated with poorer executive performance
- silent lacunes in the thalamus and in the basal ganglia are indepent predictors of cognitive decline

Influence of silent brain infarcts on cognitive decline

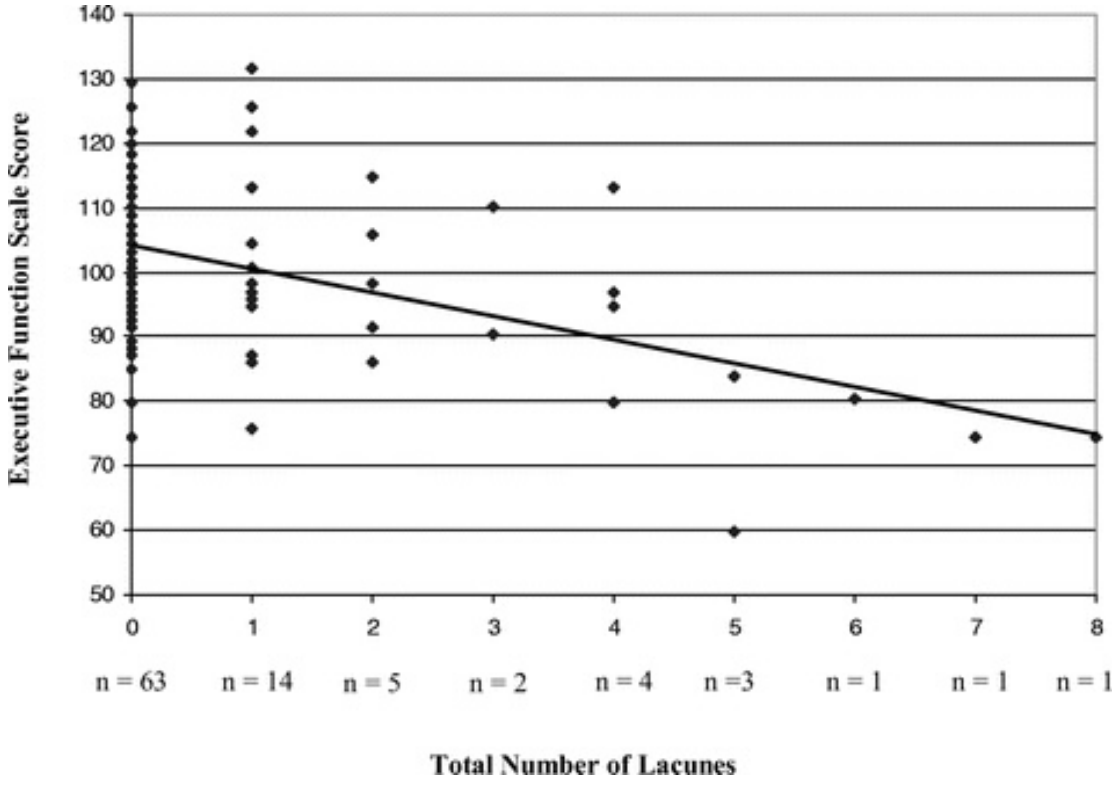


The presence of a new silent brain infarcts more than doubles the risk of dementia; hazard ratio 2.3 (95% CI: 1.1-4.7).

Mean change in memory performance, psychomotor speed, and global cognitive function among participants with and those without silent brain infarcts on MRI at baseline (1995-1996) and at follow-up (1999-2000), after adjustment for age, sex, level of education, and interval between neuropsychological tests

Vermeer S et al 2003. N Engl J Med 348:1215-22

Silent subcortical lacunes are associated with poor executive functions



Correlation between number of lacunes and executive performance (R^2=0.20; P<0.0001)

Carey et al 2008. Stroke 39:397-402

Post-stroke cognitive impairment

- From the Framingham study a significant decline of - 3.7 points (comparable to – 1.3 SD) in the mean MMSE was found in 74 stroke patients tested within 6 months of stroke onset compared to stroke free controls (no change)

Kase C et al. Stroke 1998; 29: 805-812

Post-stroke cognitive impairment

- Americans aged 50+ from the Health and Retiremnt Study 1998-2008
- N=20,567 participants
- N= 1189 strokes, survived
- N= 385 strokes, deceased
- 10 word list delayed recall
- 5-item Likert scale and 16 item version IQ code
- Results: 0.71 SD reduction in similar period than Framingham study

Wang Q et al. Long-term rate of change in memory functioning before and after stroke onset. Stroke 2012

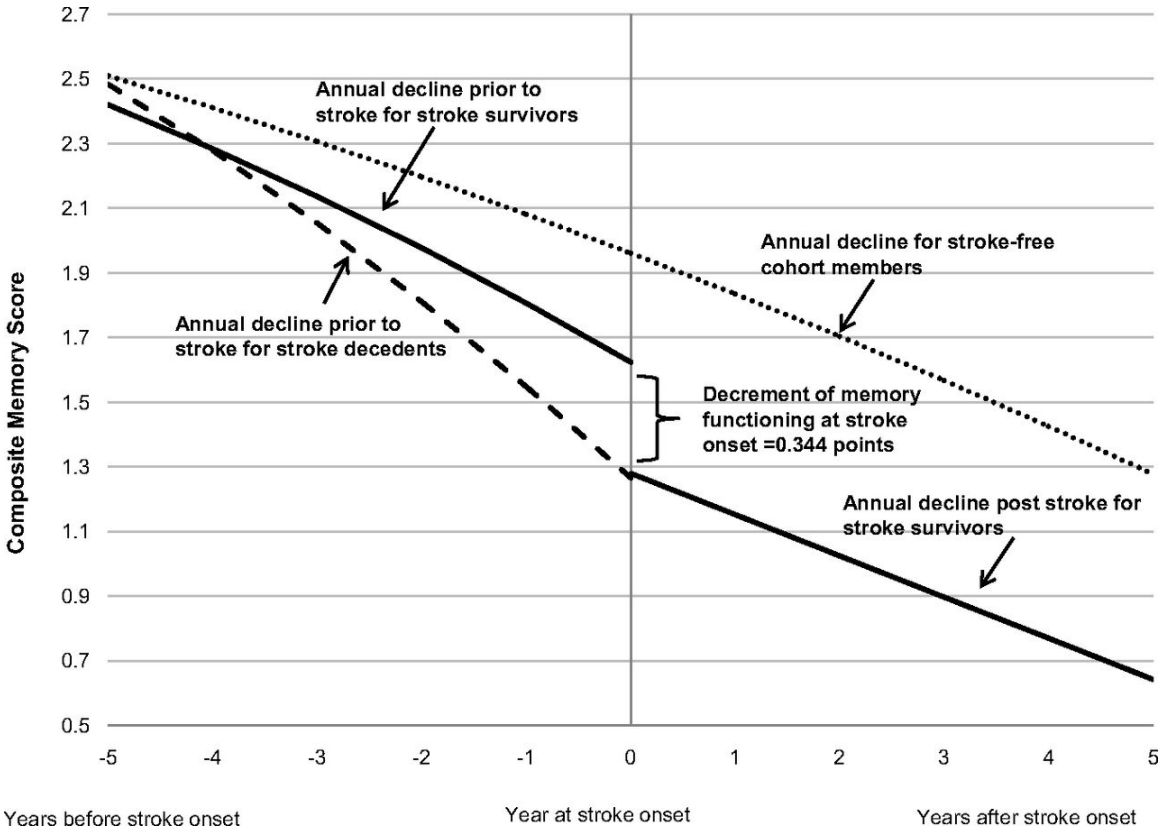
Post-stroke cognitive impairment

- Even prestroke, future stroke pateints experience a long period of memory decline, a decline that continues for years after stroke
- Prestroke memory decline is most likely an early sign of cerebrovascular disease
- Lower memory performance increases vulnerability to clinically manifest stroke
- Individuals with a very high memory scores may have a better cognitive reserve and be able to to sustain an acute ischemic stroke without memory impairment.

Wang Q et al. Stroke 2012;43:2561-66

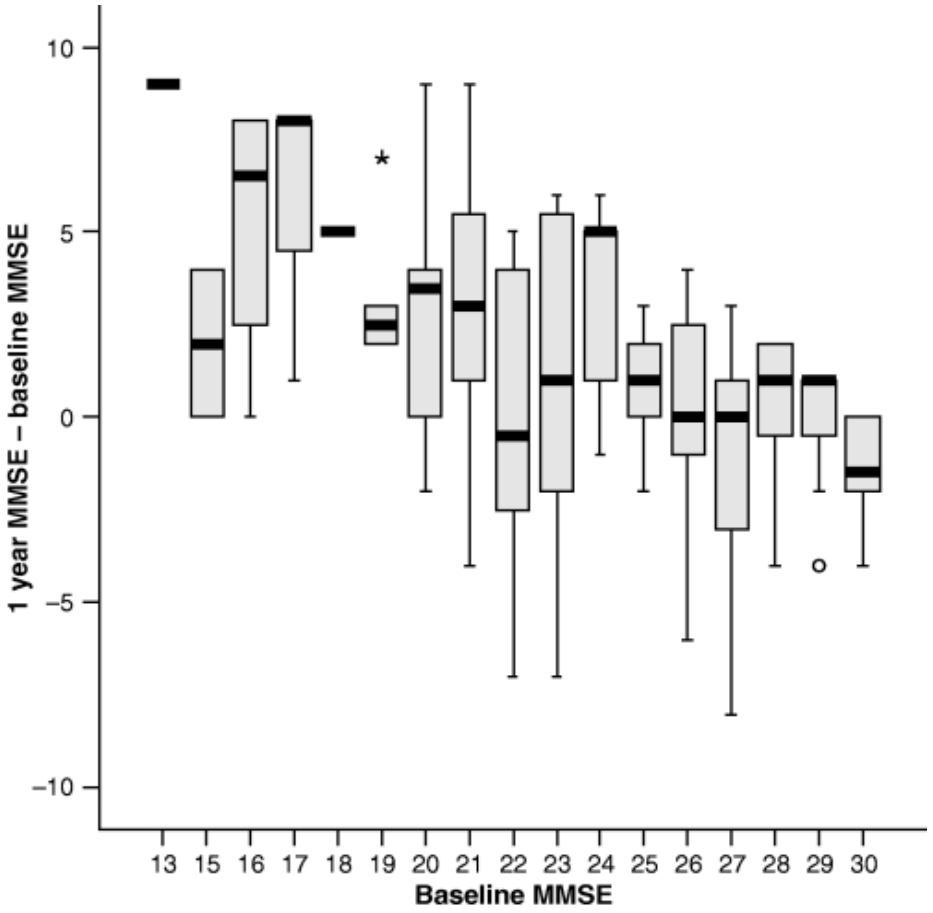
Post-stroke cognitive impairment

Trajectory of memory score for stroke survivors (n=1189) vs stroke decedents (n=385) vs stroke-free cohort members (n=15 766) during entire follow-up.



Wang Q et al. Stroke 2012;43:2561-66

Cognitive impairment prior to stroke correlates with poststroke cognitive decline



Changes in MMSE score between baseline and 1 year after stroke against baseline MMSE

Appelros & Andersson 2006. Eu J Neurol 13:491-5

Factors significantly associated with pre-stroke dementia.

Associated factor	No. of studies	Strength of association
Demographic factors		
Female sex	7	++
Low education	5	++
FH	1	++++
Vascular risk factors		
Diabetes	6	+
AF	5	+
IHD	3	+
Previous TIA	4	+
Hypertension	6	+
Stroke factors		
Previous stroke	6	++
Multiple infarcts	3	+
Brain imaging factors		
MTL atrophy	3	++++
Leukoaraiosis	3	+++

Adapted from Pendlebury and Rothwell [12]. + = OR 1–2; ++ = OR 2–3; +++ = OR 3–4; ++++ = OR >4.

FH = family history; IHD = ischaemic heart disease; TIA = transient ischaemic attack; MTL = medial temporal lobe.

Factors significantly associated with post-stroke dementia.

Associated factor	No. of studies	Strength of association
Demographic factors		
Female sex	24	+
Caucasian	3	—
Low education	11	++
Vascular risk factors		
Diabetes	19	+
AF	13	++
Stroke factors		
Hemorrhagic S.	9	+
Dysphasia	7	+++
Left hemisphere	17	+
Brainstem	9	—
Number of strokes		
Previous stroke	10	+
Multiple strokes	9	++
Recurrent stroke	4	++
Stroke complications		
HI episodes	2	++
Incontinence	7	++++
Acute confusion	2	++
Early seizures	1	++++
Abnormal EEG	1	++
Brain imaging factors		
Leukoaraiosis	7	++
Atrophy	5	++
MTL atrophy	2	++

Adapted from Pendlebury and Rothwell [12]. + = OR 1–2; ++ = OR 2–3; +++ = OR 3–4; ++++ = OR >4; — = OR <1.
Hemorrhagic S. = hemorrhagic stroke; HI = hypoxic ischaemic episodes; EEG = electroencephalogram; MTL = medial temporal lobe.

Brain 2011: 134; 3716–3727

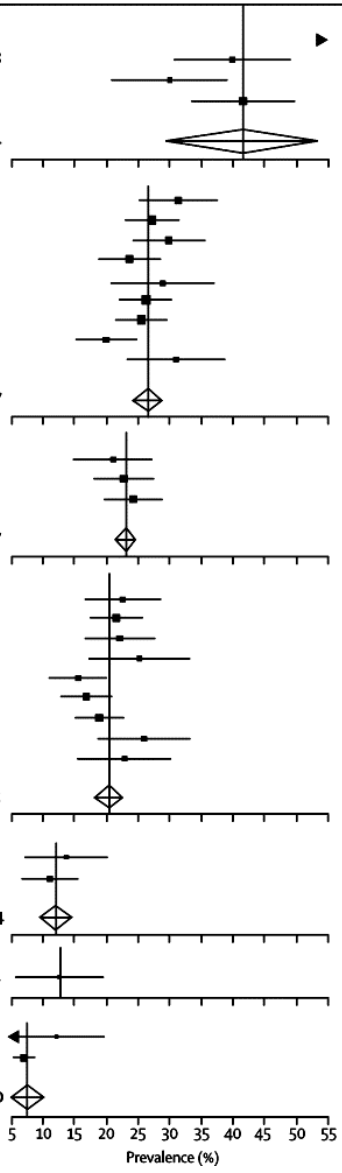
Recurrent stroke and risk of dementia

The rate of dementia is at least twice as high after recurrent stroke.

Hospital-based

Population

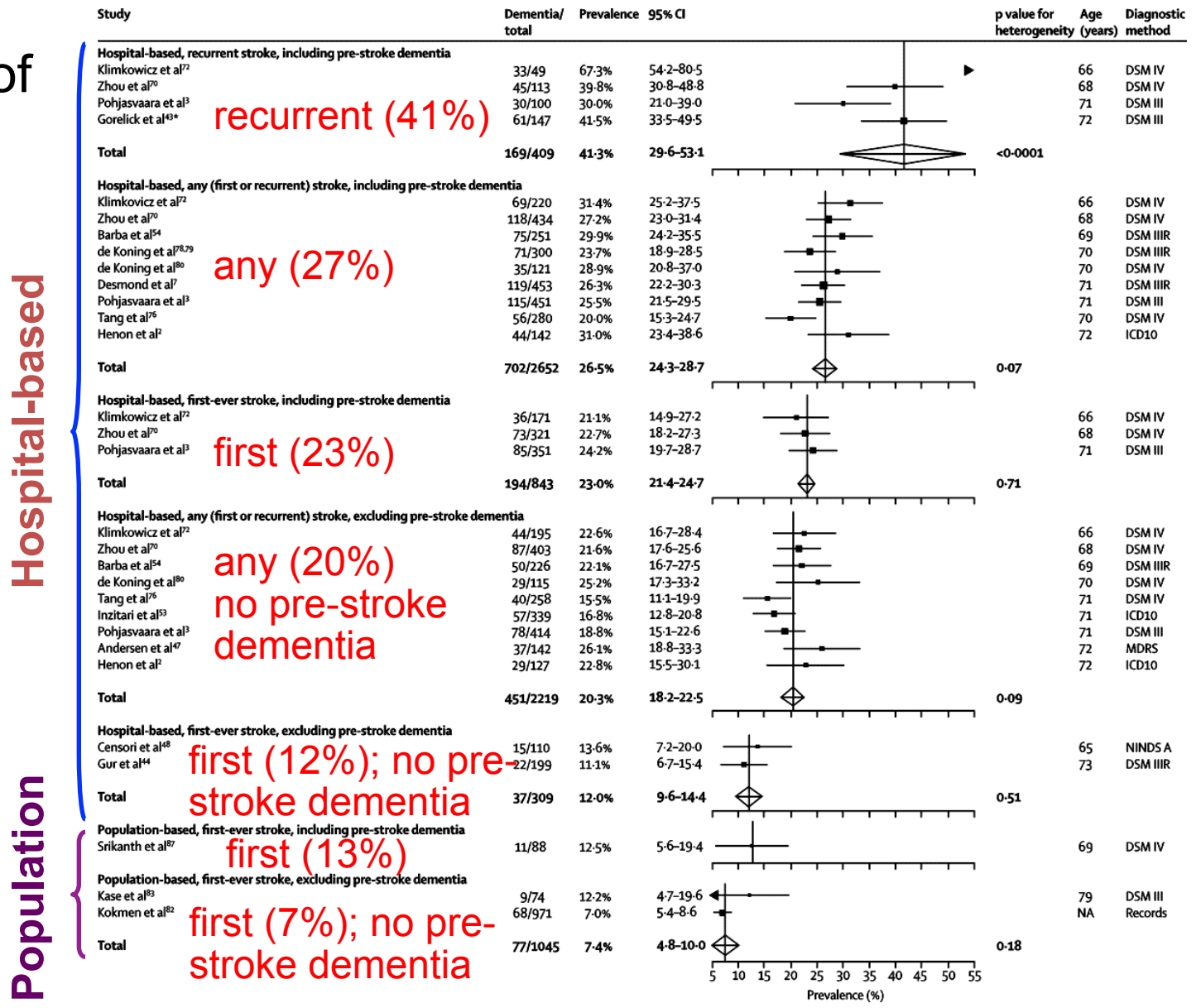
Study	Dementia/ total	Prevalence	95% CI	p value for heterogeneity	Age (years)	Diagnostic method
Hospital-based, recurrent stroke, including pre-stroke dementia						
Klimkowicz et al[72]	33/49	67·3%	54·2–80·5		66	DSM IV
Zhou et al[70]	45/113	39·8%	30·8–48·8		68	DSM IV
Pohjasvaara et al[3]	30/100	30·0%	21·0–39·0		71	DSM III
Gorelick et al[43*]	61/147	41·5%	33·5–49·5		72	DSM III
Total	**169/409**	**41·3%**	**29·6–53·1**	**<0·0001**		
Hospital-based, any (first or recurrent) stroke, including pre-stroke dementia						
Klimkovicz et al[72]	69/220	31·4%	25·2–37·5		66	DSM IV
Zhou et al[70]	118/434	27·2%	23·0–31·4		68	DSM IV
Barba et al[54]	75/251	29·9%	24·2–35·5		69	DSM IIIR
de Koning et al[78,79]	71/300	23·7%	18·9–28·5		70	DSM IIIR
de Koning et al[80]	35/121	28·9%	20·8–37·0		70	DSM IV
Desmond et al[7]	119/453	26·3%	22·2–30·3		71	DSM IIIR
Pohjasvaara et al[3]	115/451	25·5%	21·5–29·5		71	DSM III
Tang et al[76]	56/280	20·0%	15·3–24·7		70	DSM IV
Henon et al[2]	44/142	31·0%	23·4–38·6		72	ICD10
Total	**702/2652**	**26·5%**	**24·3–28·7**	**0·07**		
Hospital-based, first-ever stroke, including pre-stroke dementia						
Klimkowicz et al[72]	36/171	21·1%	14·9–27·2		66	DSM IV
Zhou et al[70]	73/321	22·7%	18·2–27·3		68	DSM IV
Pohjasvaara et al[3]	85/351	24·2%	19·7–28·7		71	DSM III
Total	**194/843**	**23·0%**	**21·4–24·7**	**0·71**		
Hospital-based, any (first or recurrent) stroke, excluding pre-stroke dementia						
Klimkowicz et al[72]	44/195	22·6%	16·7–28·4		66	DSM IV
Zhou et al[70]	87/403	21·6%	17·6–25·6		68	DSM IV
Barba et al[54]	50/226	22·1%	16·7–27·5		69	DSM IIIR
de Koning et al[80]	29/115	25·2%	17·3–33·2		70	DSM IV
Tang et al[76]	40/258	15·5%	11·1–19·9		71	DSM IV
Inzitari et al[53]	57/339	16·8%	12·8–20·8		71	ICD10
Pohjasvaara et al[3]	78/414	18·8%	15·1–22·6		71	DSM III
Andersen et al[47]	37/142	26·1%	18·8–33·3		72	MDRS
Henon et al[2]	29/127	22·8%	15·5–30·1		72	ICD10
Total	**451/2219**	**20·3%**	**18·2–22·5**	**0·09**		
Hospital-based, first-ever stroke, excluding pre-stroke dementia						
Censori et al[48]	15/110	13·6%	7·2–20·0		65	NINDS A
Gur et al[44]	22/199	11·1%	6·7–15·4		73	DSM IIIR
Total	**37/309**	**12·0%**	**9·6–14·4**	**0·51**		
Population-based, first-ever stroke, including pre-stroke dementia						
Srikanth et al[87]	11/88	12·5%	5·6–19·4		69	DSM IV
Population-based, first-ever stroke, excluding pre-stroke dementia						
Kase et al[83]	9/74	12·2%	4·7–19·6		79	DSM III
Kokmen et al[82]	68/971	7·0%	5·4–8·6		NA	Records
Total	**77/1045**	**7·4%**	**4·8–10·0**	**0·18**		



Pendlebury ST, Rothwell PM. 2009. Lancet Neurol 8:1006-18

Recurrent stroke and risk of dementia

The rate of dementia is at least twice as high after recurrent stroke.



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Zhou et al[70]	73/321	22·7%	18·2–27·3		68	DSM IV
Pohjasvaara et al[3]	85/351	24·2%	19·7–28·7		71	DSM III
Total	**194/843**	**23·0%**	**21·4–24·7**	**0·71**		
Hospital-based, any (first or recurrent) stroke, excluding pre-stroke dementia						
Klimkowicz et al[72]	44/195	22·6%	16·7–28·4		66	DSM IV
Zhou et al[70]	87/403	21·6%	17·6–25·6		68	DSM IV
Barba et al[54]	50/226	22·1%	16·7–27·5		69	DSM IIIR
de Koning et al[80]	29/115	25·2%	17·3–33·2		70	DSM IV
Tang et al[76]	40/258	15·5%	11·1–19·9		71	DSM IV
Inzitari et al[53]	57/339	16·8%	12·8–20·8		71	ICD10
Pohjasvaara et al[3]	78/414	18·8%	15·1–22·6		71	DSM III
Andersen et al[47]	37/142	26·1%	18·8–33·3		72	MDRS
Henon et al[2]	29/127	22·8%	15·5–30·1		72	ICD10
Total	**451/2219**	**20·3%**	**18·2–22·5**	**0·09**		
Hospital-based, first-ever stroke, excluding pre-stroke dementia						
Censori et al[48]	15/110	13·6%	7·2–20·0		65	NINDS A
Gur et al[44]	22/199	11·1%	6·7–15·4		73	DSM IIIR
Total	**37/309**	**12·0%**	**9·6–14·4**	**0·51**		
Population-based, first-ever stroke, including pre-stroke dementia						
Srikanth et al[87]	11/88	12·5%	5·6–19·4		69	DSM IV
Population-based, first-ever stroke, excluding pre-stroke dementia						
Kase et al[83]	9/74	12·2%	4·7–19·6		79	DSM III
Kokmen et al[82]	68/971	7·0%	5·4–8·6		NA	Records
Total	**77/1045**	**7·4%**	**4·8–10·0**	**0·18**		

Pendlebury ST, Rothwell PM. 2009. Lancet Neurol 8:1006-18

Stroke and dementia are tightly related

1 patient in 10 already has dementia when stroke occurs,

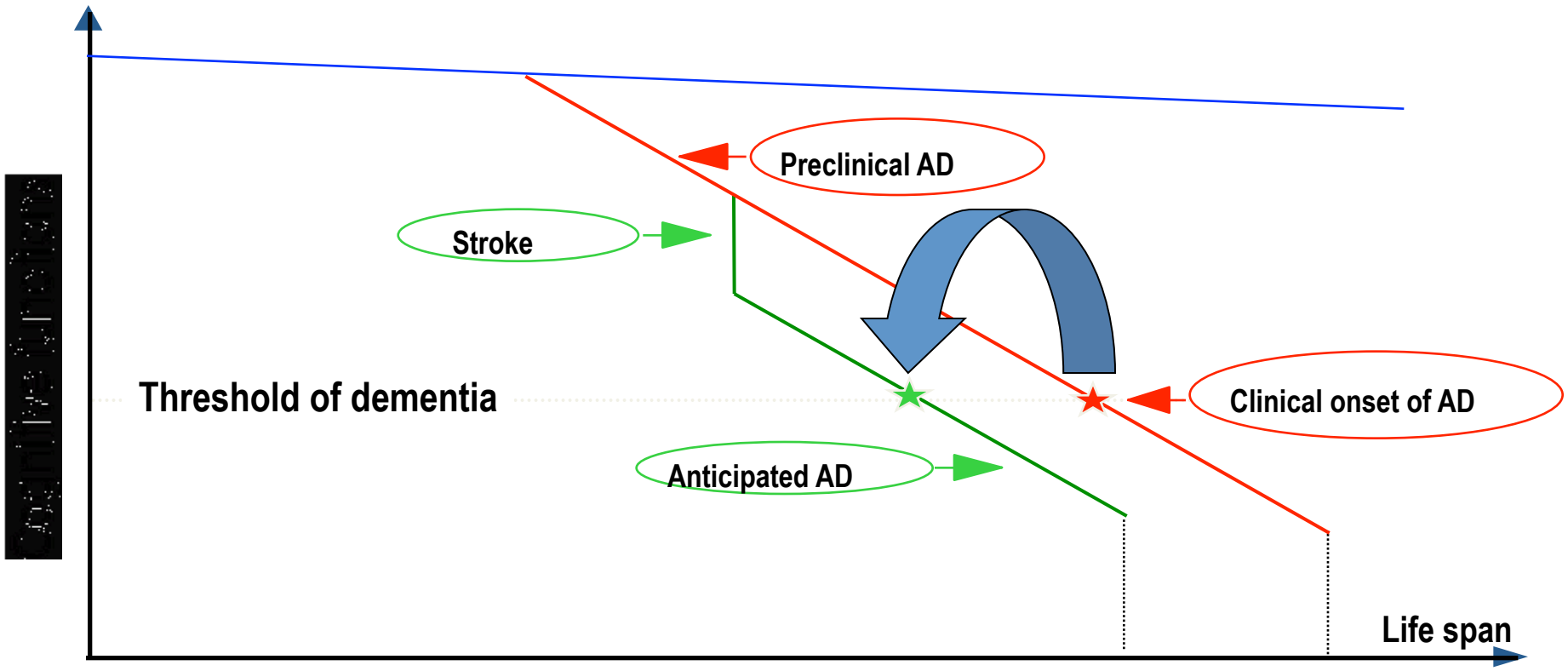
1 patient in 10 will develop dementia after a first-ever stroke

1 in 3 in patients will develop dementia with stroke recurrence.

Leys D et al Dementia and stroke. In: Brainin M and Heiss WD (Eds) Stroke Medicine. Cambridge Univ. Press, 2nd ed. 2014

Interaction: Stroke and Alzheimer

Mechanisms: Alzheimer + stroke



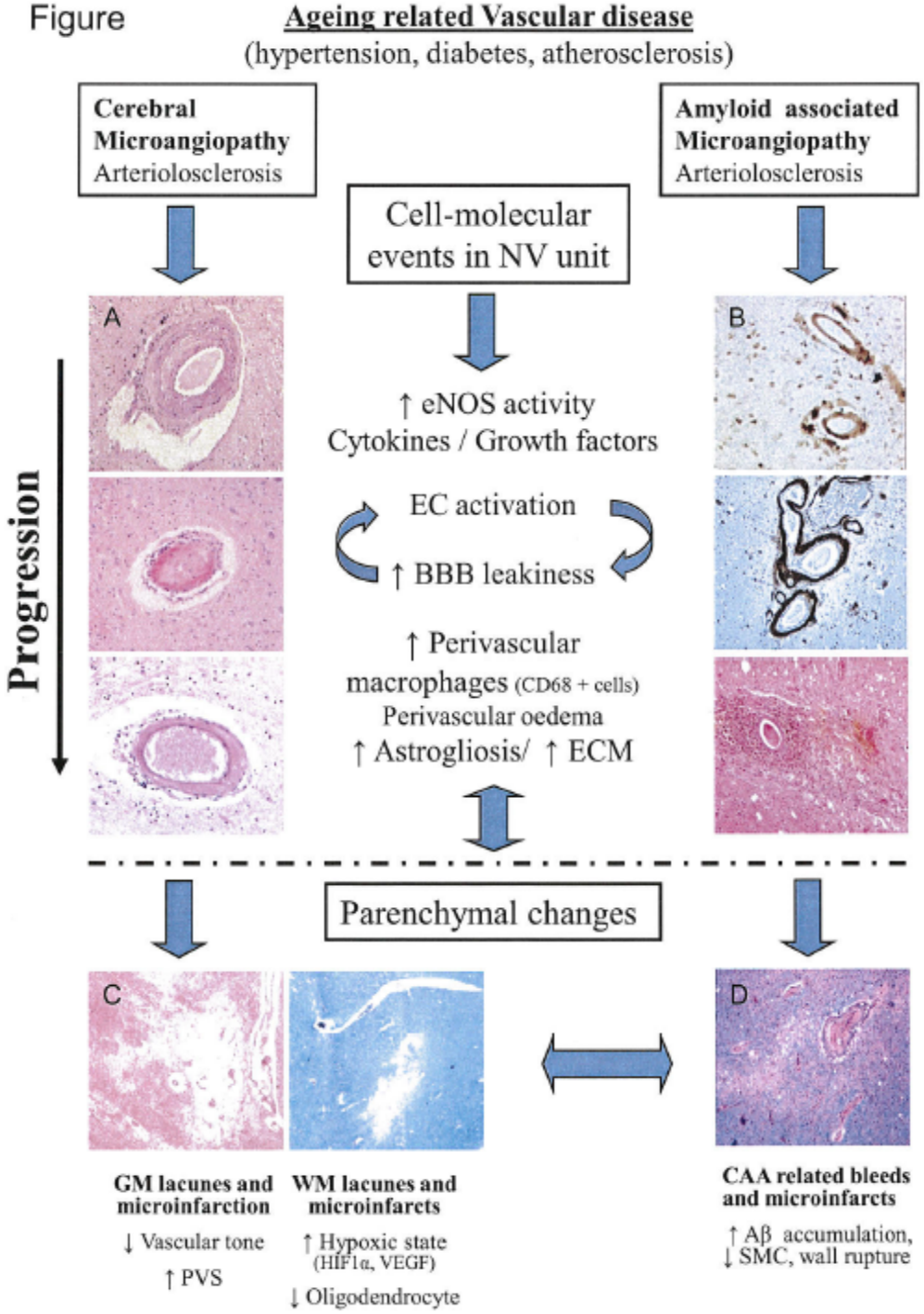
Courtesy Didier Leys and Florence Pasquier, Univ. Lille

Post-stroke cognitive impairment

- **Neuropathological changes in VaD/VCI:**
  - Lacunar infarcts
  - Microinfarcts
  - White matter changes
  - Hippocampal atrophy and sclerosdis
  - Overlap with AD pathology
    - Amyloid plaques
    - Neurofibrillary tangles

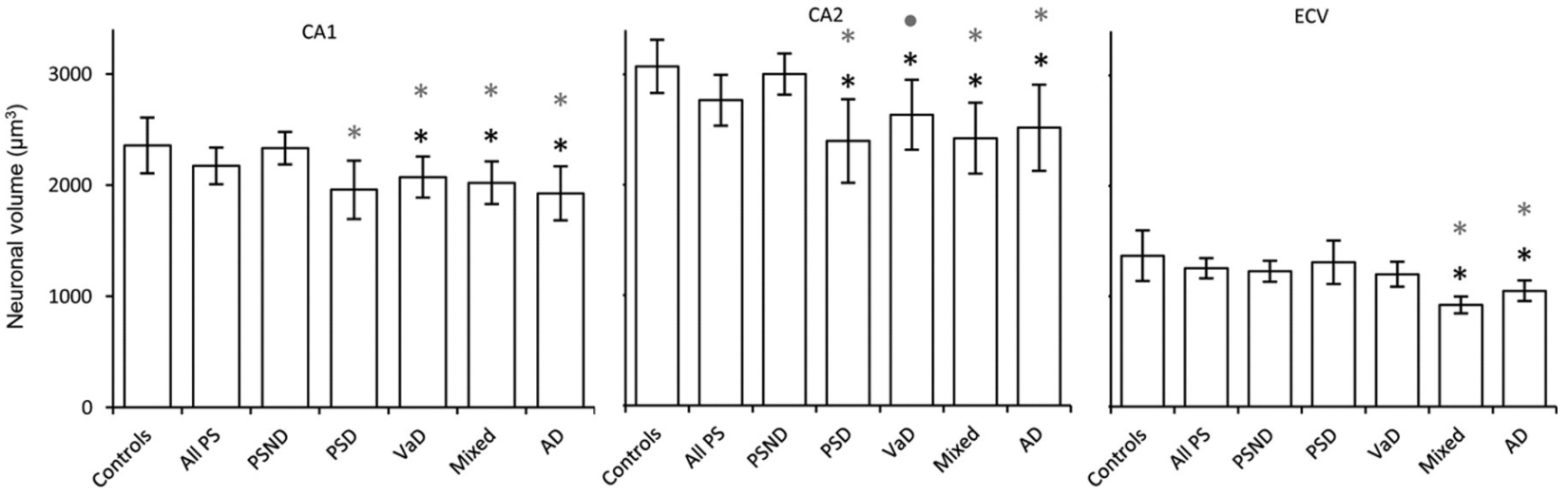
Kalaria Review Stroke 2013

Figure


Ageing related Vascular disease
(hypertension, diabetes, atherosclerosis)
Cerebral Microangiopathy
Arteriolosclerosis
Amyloid associated Microangiopathy
Arteriolosclerosis
Cell-molecular events in NV unit
A
B
Progression
↑ eNOS activity
Cytokines / Growth factors
EC activation
↑ BBB leakiness
↑ Perivascular macrophages (CD68 + cells)
Perivascular oedema
↑ Astrogliosis/ ↑ ECM
Parenchymal changes
C
D
GM lacunes and microinfarction
↓ Vascular tone
↑ PVS
WM lacunes and microinfarcts
↑ Hypoxic state (HIF1α, VEGF)
↓ Oligodendrocyte
CAA related bleeds and microinfarcts
↑ Aβ accumulation,
↓ SMC, wall rupture

Post-stroke cognitive impairment

Neuronal volumes in hippocampal subregions CA1, CA2, and entorhinal cortex Layer V (ECV).



All PS: all poststroke subjects; PSND: poststroke nondemented; PSD: delayed poststroke dementia; VaD: vascular dementia; mixed: mixed Alzheimer, and vascular dementia; AD: Alzheimer disease.

Asterisks indicate significantly different to controls (black) or PSND (gray; $P<0.05$).
Dots indicate trend to significance ($P<0.01$).

Gemmell E et al. Stroke 2012;43:808-814

Post-stroke cognitive impairment

- Neuropathological data show that post-stroke cognitive function correlate with CA-2 neuronal volumes
- CAMCOG total scores and CAMCOG memory scores
- „selective hippocampal neuronal atrophy or shrinkage is an important substrate for dementia afte rstroke in the absence of neurodegenerative pathology“

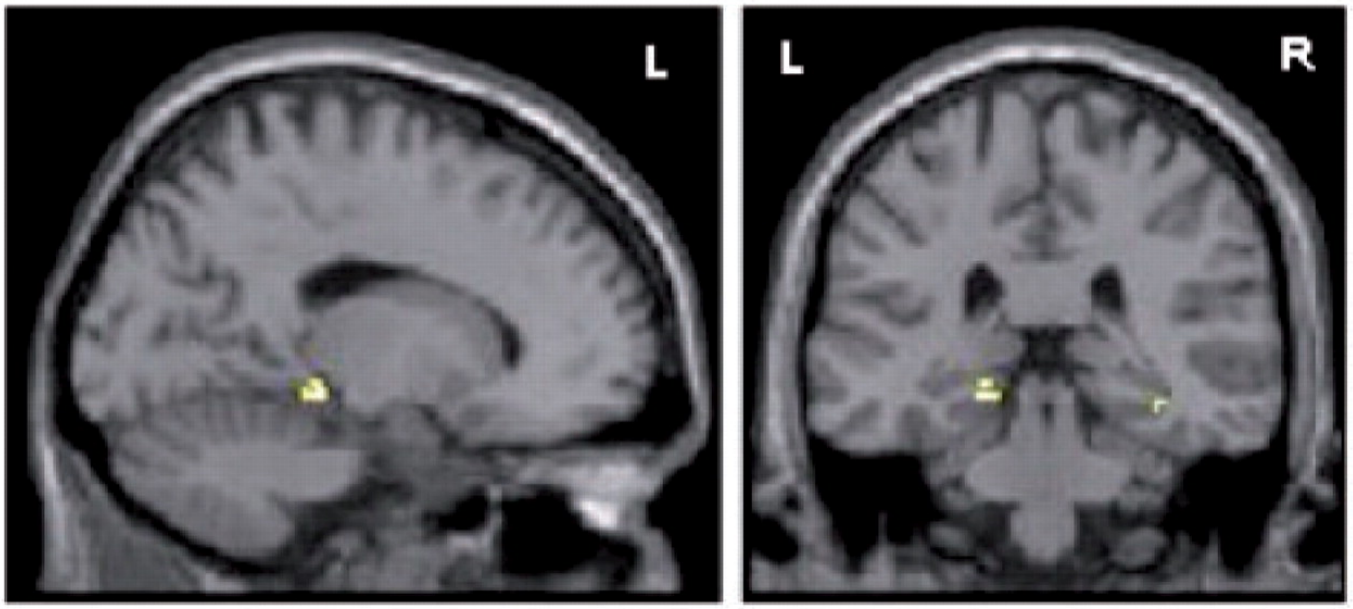
Gemmel E et al. Stroke 2011

Post-stroke cognitive impairment

- „These findings provide evidence of a vascular basis for hippocampal neurodegeneration in delayed PSD and VaD“

Gemmel E et al. Stroke 2011

Post-stroke patients compared to healthy controls: show less MTL activation indicating tertiary, delayed onset mechanisms of vascular neurodegeneration



Difference in MTL activation between healthy controls (*n* = 22) and stroke patients (*n* = 28) during 0-back minus 2-back contrast. Healthy controls showed significantly more MTL activation than patients during the 0-back minus 2-back contrast, thresholded at *P* = 0.001 uncorrected.

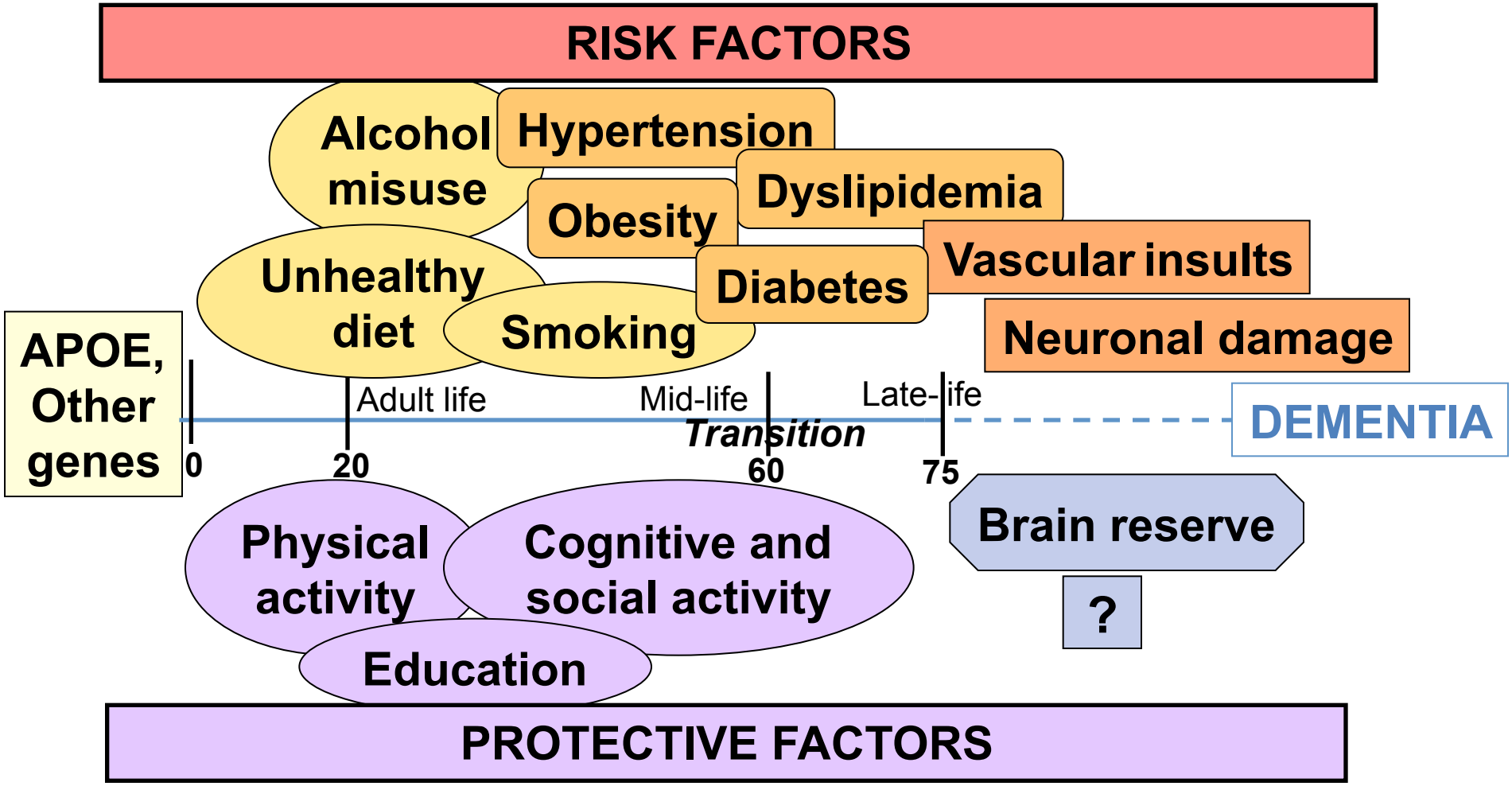
Snaphaan L et al. Brain 2009; 132: 1882

Mofification of life-style factors: prevents post-stroke cognitive decline?

- The FINGER trial has shown that lifestyle modification through multi-domain interventions prevents cogntive decline in persons with a high vascular risk and risk of mild cogntive impairment
- The ASPIS trial used similar interventions in post-stroke patients and was neutral. Perhaps the occurrence of the dysexecutive syndrome was less in the intervention group (n.s.)

Brainin M, Tuomilehto J, Heiss WD et al. Post Stroke Cognition Study Group: Eur. J Neurol. 2015 Feb;22:229-38

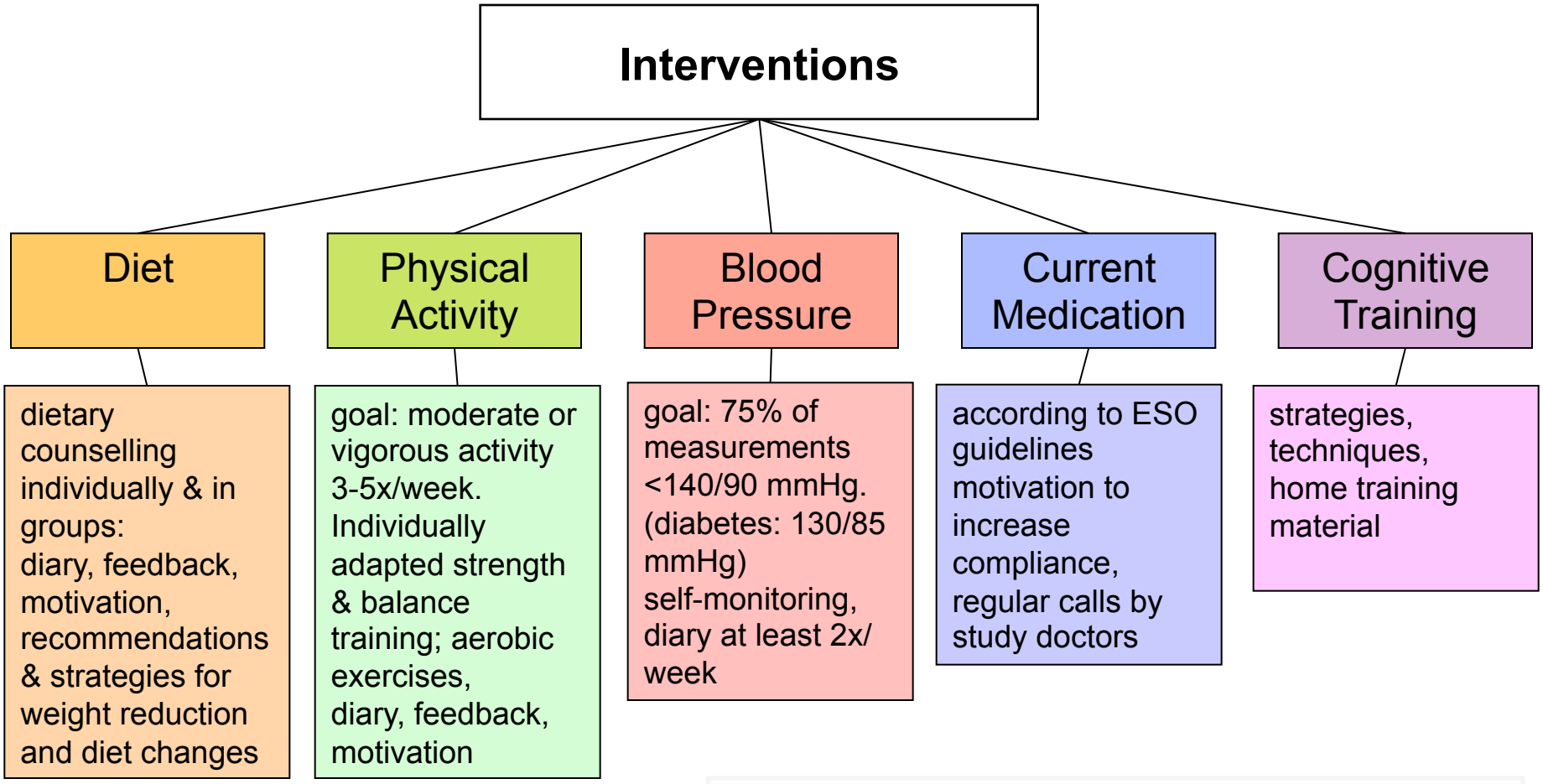
Dementia and AD: importance of life-long exposure to multiple factors



Mangialasche, Kivipelto et al., 2012

ASPIS - Austrian Polyintervention Study to Prevent Cognitive Decline after Ischemic Stroke

Identification number at clinicaltrials.gov: NCT01109836.



Brainin M et al. Int J Stroke. 2013 Nov 10. doi: 10.1111/ijs.12188.

Intervention Goals

Strict blood pressure treatment: Treatment goal BP <140/90mmHg on at least 75% of all measurements, for patients with diabetes 130/85 mmHg.

Physical activity: moderate or vigorous physical activity 3-5 times/ week

Diet: BMI <25, weight reductions and maintenance of at least 5% weight loss during the first year in obese individual. Dietary goals according to nutrient intake and food intake

Smoking cessation in smokers

Pharmacological treatment according to ESO guideline.

Lowering of cholesterol with lipid-lowering drugs (preferably statins). LDL-cholesterol <70 mg/dl

Antithrombotic therapy (ATT): most important is continuous ATT. ATT will be used in all patients except in those eligible for oral anticoagulation.

Patients with diabetes mellitus: optimal pharmacological treatment according to current guidelines of the Austrian Association for Diabetes

Brainin M et al. Int. J. Stroke 2015, Matz et al. Stroke 2015

Definition of Cognitive Decline

Composite z-scores for 5 domains:

- individual test score differences between baseline and 24 month
- Standardization using standard deviations of a control population

Criteria for cognitive decline at 24month:

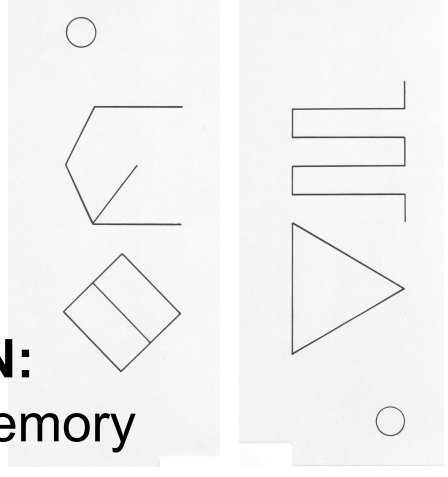
- Significant decline in at least 2 of 5 domains
- Critical level for the decline in a single domain is set using standard normal distribution (alpha level 0.05 and corrected according to binomial function for the probability of a decline in 2 out of 5 domains)

Brainin M et al. Int. J. Stroke 2015, Matz et al. Stroke 2015

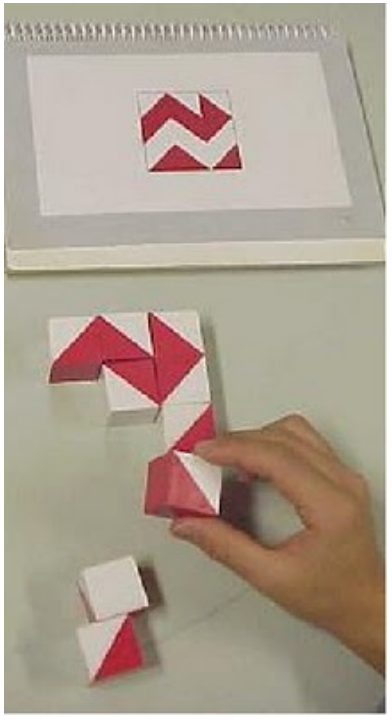
Neuropsychological Test Battery

- Stroop Color Word Interference Test (15 min)
- Trailmaking Test (Parts A and B) (5 min)
- Luria Auditory Verbal Learning Test - immediate recall (6 min)
- Benton Visual Retention Test (reproduction after 10 s) (10 min)
- Letter Fluency Test (semantic and phonemic) (6 min)
- 5-Points Test (Hamasch) – revised (5 min)
- Digit Span (forward and backwards)(6 min)
- Luria Auditory Verbal Learning Test - delayed recall (
- Block Design Test (15 min)
- ADAS-cog

STROOP
executive functions

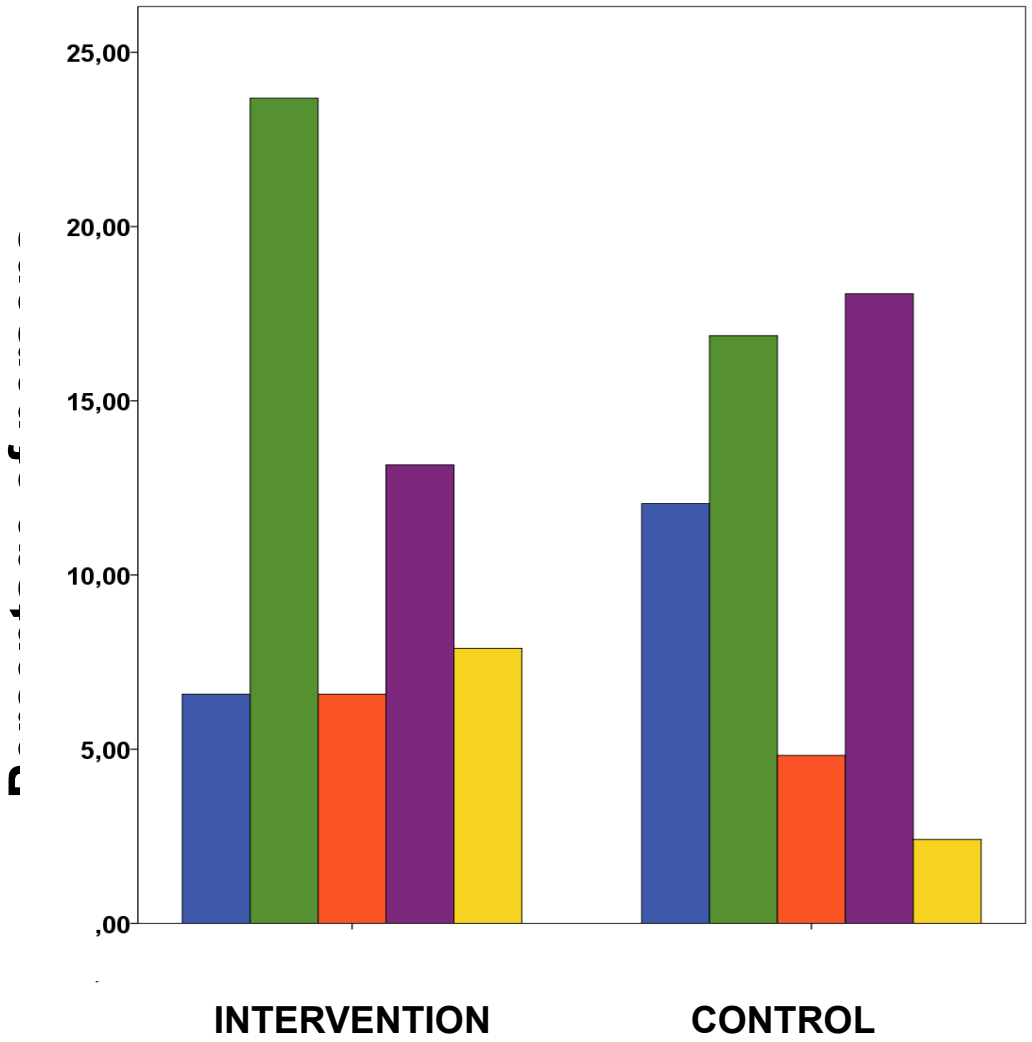


BENTON:
visual memory



MOSAIC:
visual-spatial

Cognitive domains



Executive functions
R 0.546; 95% CI: 0.195-1.526

Speed of mental processing
R 1.404; 95% CI: 0.751-2.624

Visual spatial
RR 1.365; 95% CI: 0.381-4.897

General memory
RR 0.728; 95% CI: 0.348-1.522

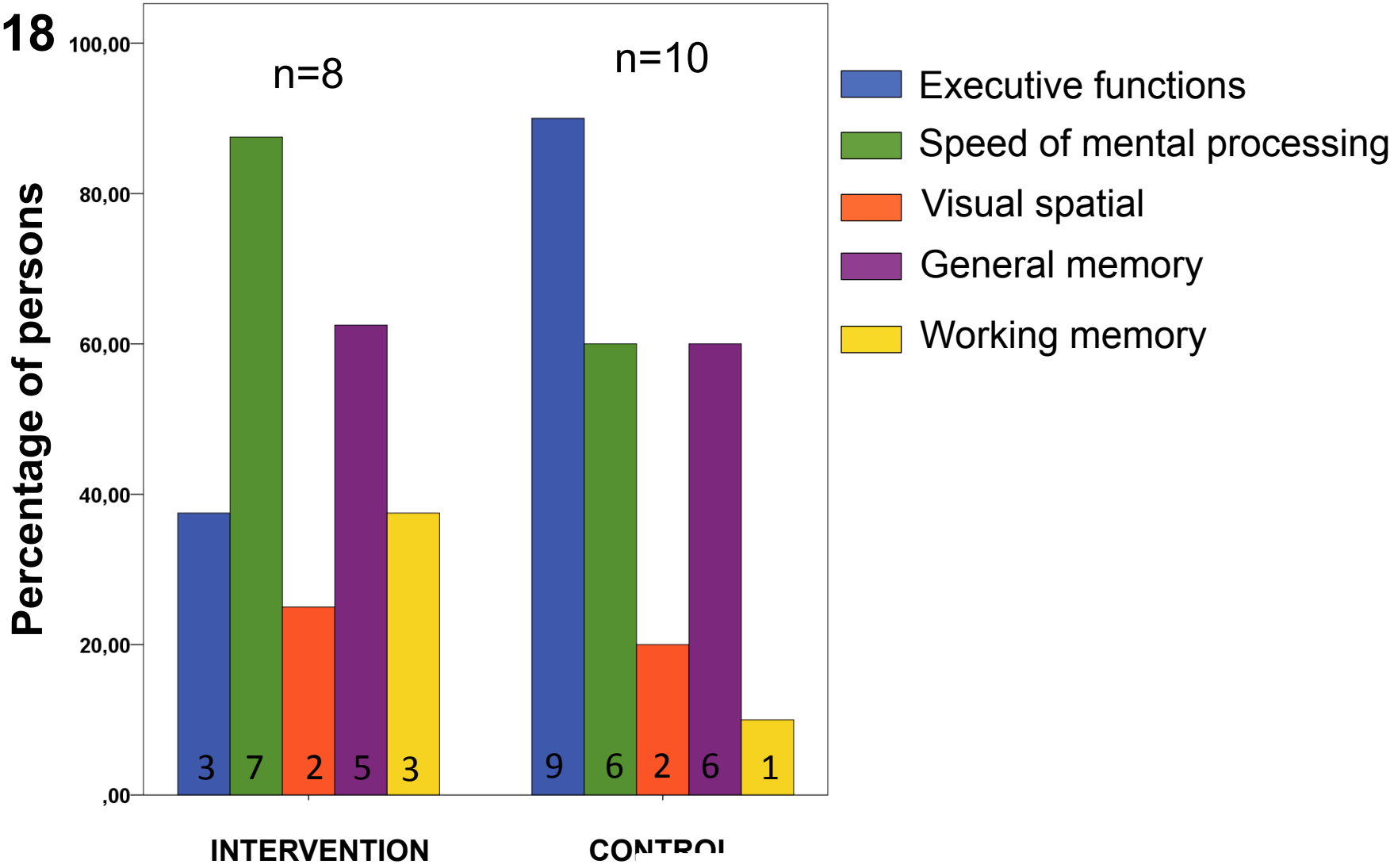
Working memory
RR 3.276; 95% CI: 0.682-15.744

The percentage of persons with cognitive decline according to domains did not differ between groups.

Brainin M et al. Int. J. Stroke 2015, Matz et al. Stroke 2015

Persons with cognitive decline (≥2 domains)

N=18



Brainin M et al. Int. J. Stroke 2015, Matz et al. Stroke 2015

Recommendations for future research.

- Harmonize cognitive outcome measures for RCTs
- Sample size
- High risk population
- Follow up period
- Biomarkers, Imaging
- Interventions that make a difference

Brainin M, Tuomilehto J, Heiss WD et al. Post Stroke Cognition Study Group: Eur. J Neurol. 2015 Feb;22:229-38