Cognition deteriorating after stroke- a major disability

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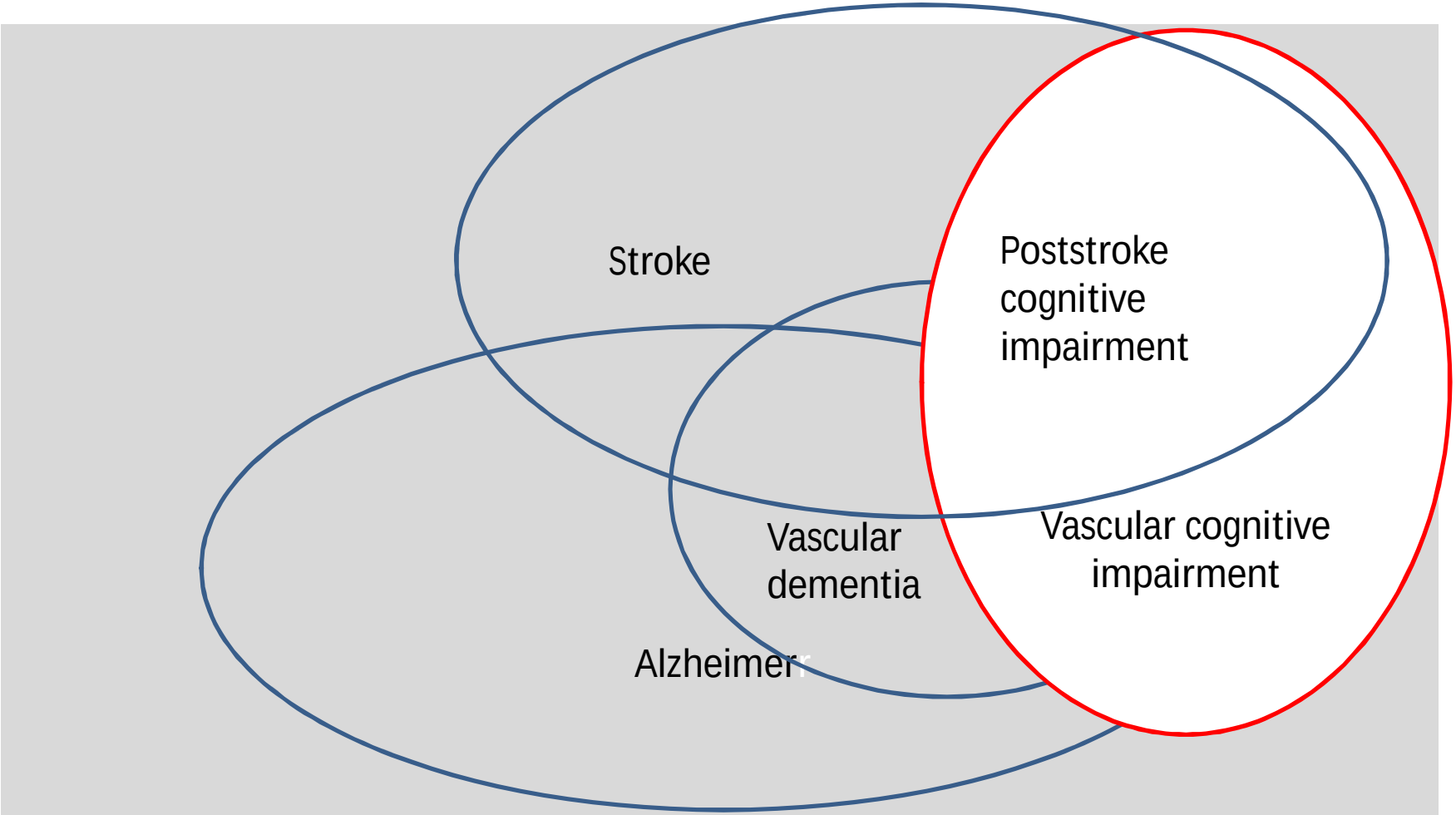
RoI

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, BMS	• Cambridge Univ Press
• AstraZeneca	• Wiley Blackwell
	• World Stroke Organisation, ESO
	• Europ. Federation of Neurol Societies

Post-stroke cognitive impairment



Global burden of disabilities

PAPF, population-attributable prevalence fractions

	YLD (×10⁶) (contribution to total chronic-disease YLDs [%])	Rank order (by YLD)	PAPF*	Rank order (by PAPF)
Dementia	8·3 (10·2%)	3	25·1%	1
Cerebrovascular diseases	3·5 (4·3%)	8	11·4%	2
Musculoskeletal diseases	7·2 (8·9%)	4	9·9%†	3
Neuropsychiatric diseases (other than dementia)	5·9 (7·3%)	6	8·3%	4
Eye diseases	27·5 (33·9%)	1	6·8%	5
Digestive diseases	1·6 (1·9%)	11	6·5%	6
Diabetes mellitus	2·1 (2·6%)	10	4·1%	7
Respiratory conditions	4·3 (5·3%)	7	3·3%‡	8
Hearing loss	9·2 (11·3%)	2	2·2%	9
Skin conditions	0·5 (0·6%)	15	2·1%	10
Heart disease	6·1 (7·6%)	5	0·8%§	11
Oral conditions	2·6 (3·3%)	9	Not assessed	..
Malignant neoplasm	0·9 (1·1%)	12	Not assessed	..
Endocrine disorders	0·8 (1·0%)	13	Not assessed	..
Genitourinary diseases	0·6 (0·7%)	14	Not assessed	..
Total chronic disease burden	81·1 (100%)	..	..	..

Sousa et al. Lancet 2009;374:1821-30

Post-stroke cognitive impairment

- What is it?
  - Definitions
- How frequent is it?
  - Prevalence rates
- Correlates in the brain
  - Neuropathology
- Indicators, markers
  - Laboratory, associated factors
- Prevention, interventions, cure?
  - Life-style, drugs

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Post-stroke cognitive impairment

„Vascular cognitive impairment represents the spectrum of cognitive impairment associated with frank stroke, vascular brain injury, or subclinical disease ranging from the least severe to most severe clinical manifestations“

Gorelick et al. Stroke 2011; 42: 2672-2713

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

Post-stroke cognitive impairment

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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

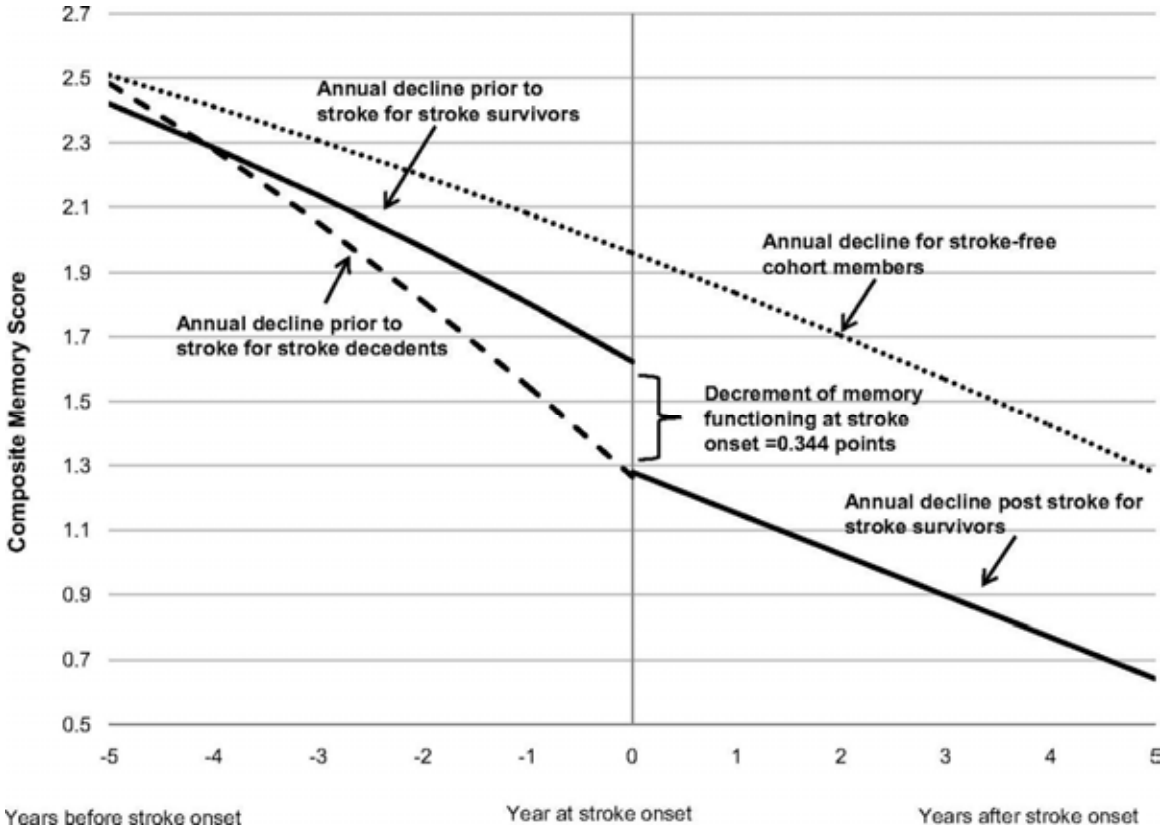
Post-stroke cognitive impairment

- 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. Stroke 2012;43:2561-66

Post-stroke cognitive impairment

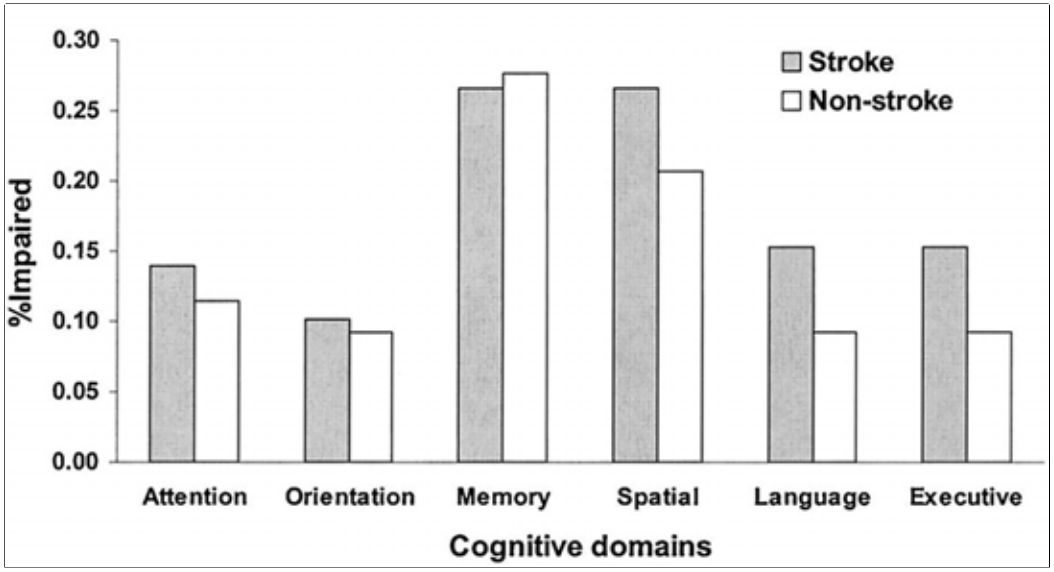
Trajectory of memory score for stroke survivors (n=1189) vs stroke decedents (n=385) vs stroke-free cohort members (n=15 766) during entire follow-up.



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

Mild cognitive impairment after stroke

- 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

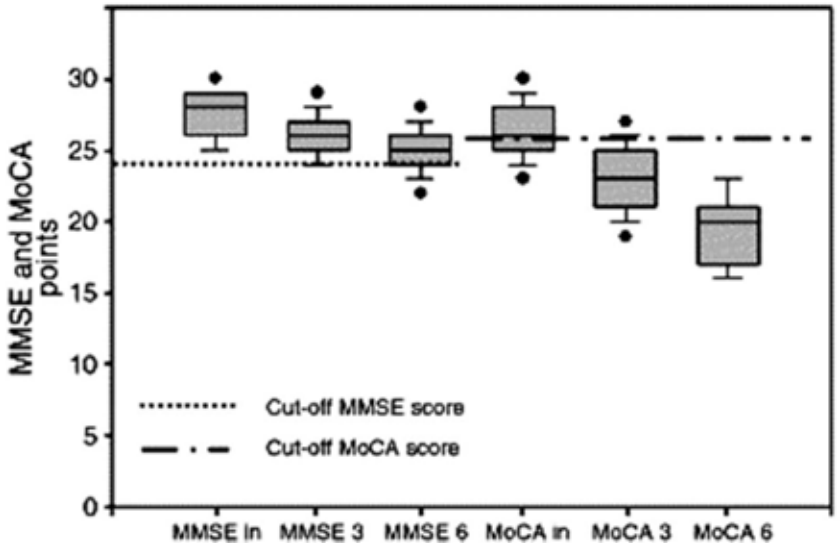


Patterns of cognitive impairment excluding subjects with preexisting cognitive decline (79 strokes, 87 nonstrokes)

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

Cognitive decline

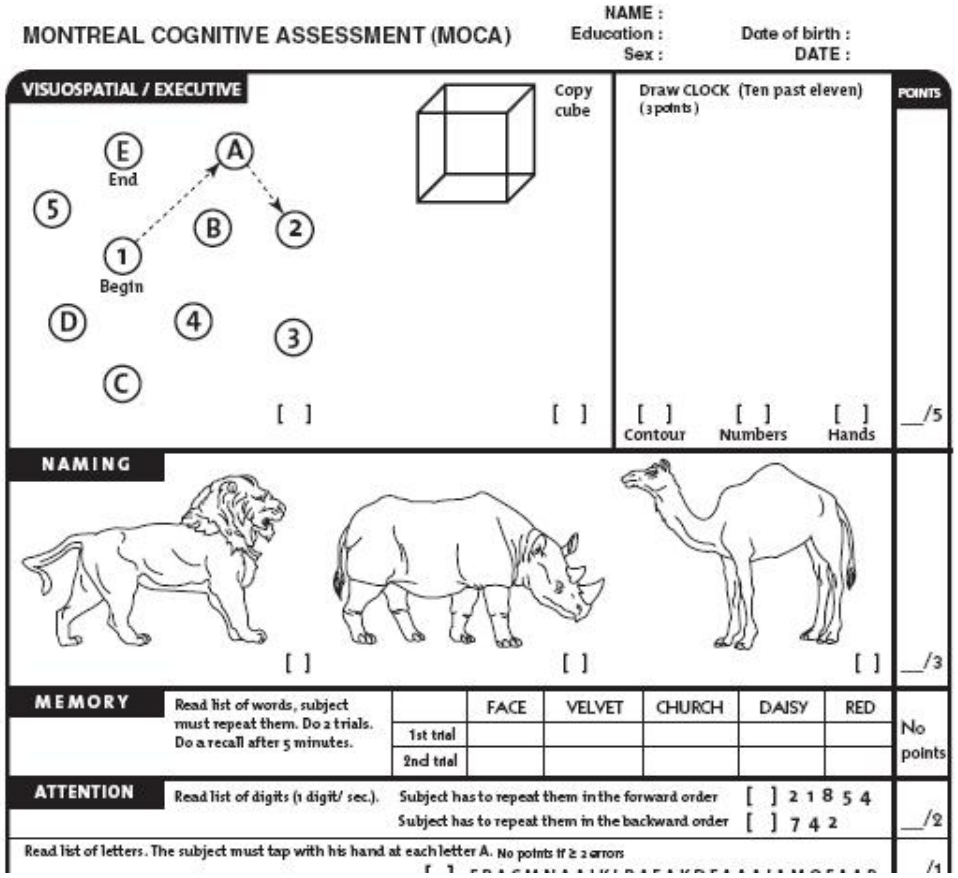
- 0.8-2 points decline on MMSE / year
- 10-32% had cognitively declined after 1 year from baseline (3 months post-stroke)
- cognitive decline increases with recurrent stroke
- detection of cognitive decline depends on the cognitive tests used



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

http://www.mocatest.org/pdf_files/MOCA-Test-English.pdf



MONTREAL COGNITIVE ASSESSMENT (MOCA)

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

VISUOSPATIAL / EXECUTIVE

Copy cube

E End, A, 5, B, 2, 1 Begin, D, 4, 3, C

[ ] [ ]

Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands

POINTS __/5

NAMING

[ ] [ ] [ ]

__/3

MEMORY

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

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION

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

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

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...

Brainin et al. Int J Stroke , in press

Post-stroke cognitive impairment

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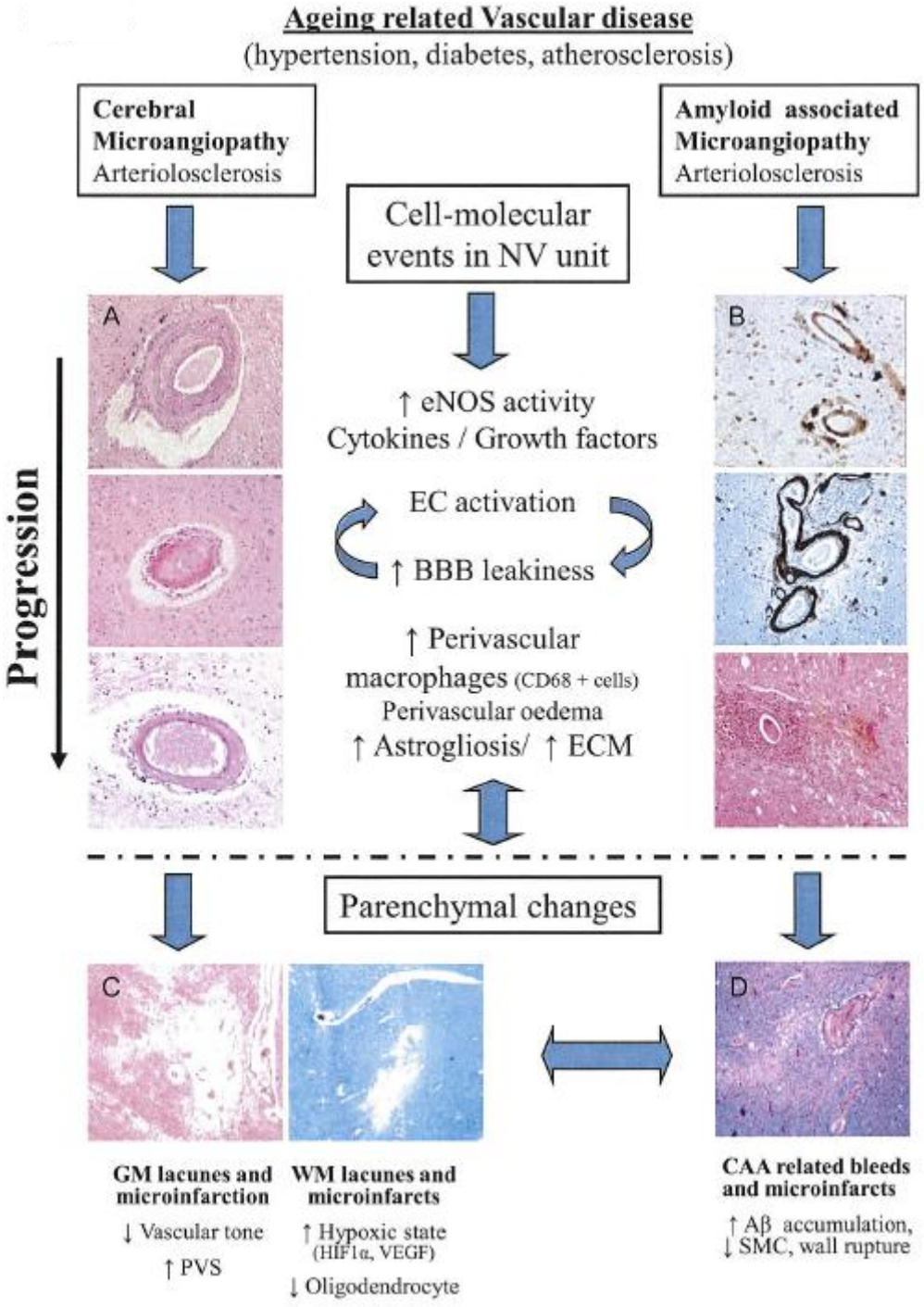
Post-stroke cognitive impairment

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

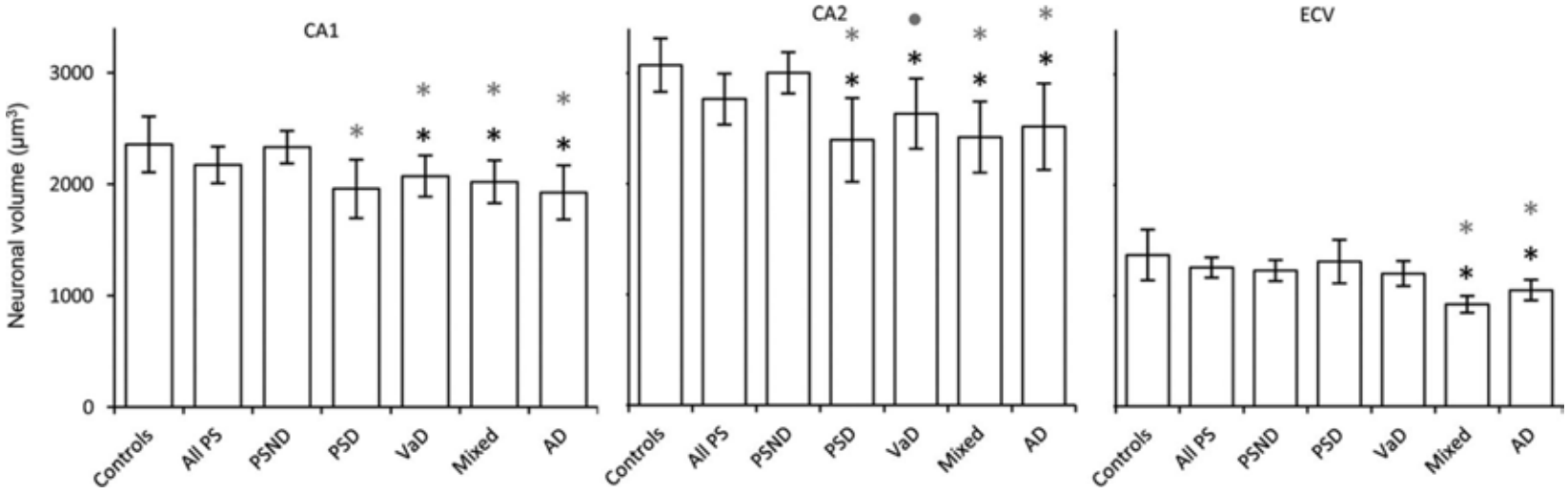
Kalaria RN Stroke 2012; 43 :2526-34



Kalaria RN Stroke 2012; 43 :2526-34

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 ($P<0.01$).

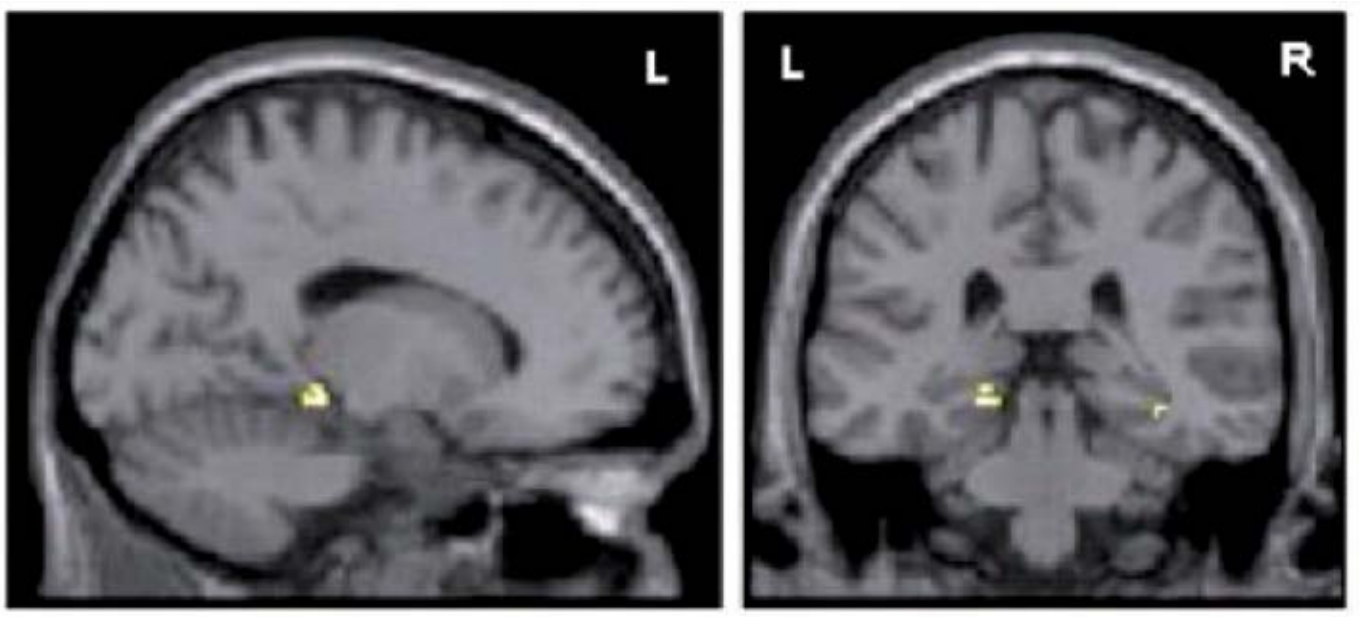
Gemmell E et al. Stroke 2012;43:808-814

Post-stroke cognitive impairment

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

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

Difference in MTL activation between healthy controls and stroke patients



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

Risk factors for post-stroke cognitive impairment –delayed onset

1. Not the infarct itself is the cause but the disturbance of cross talk between endothelium, astrocytes, and neurons
2. Tertiary (epigenetic) mechanisms play a role resulting in degeneration of brain structures remote from the infarct

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Patient-related variables associated with an increased risk of dementia after stroke

increasing age, low education level, dependency before stroke, pre-stroke cognitive decline without dementia, diabetes mellitus, atrial fibrillation, myocardial infarction, epileptic seizures, sepsis, cardiac arrhythmias, congestive heart failure, silent cerebral infarcts, global and medial temporal lobe atrophy, and white matter changes.

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

Stroke-related variables associated with an increased risk of dementia after stroke

severity, volume, location, and recurrence of stroke. Dementia in stroke patients may be due to vascular lesions, Alzheimer pathology, or summation of these lesions.

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

Post-stroke cognitive impairment

- Biomarkers:
- N=368 consecutive stroke patients (mild to moderate): high level of C-reactive protein and elevated ESR was associated with worse performance in cognitive tests, particularly memory scores.
- In addition, ESR values correlated with hippocampal atrophy

Kliper et al. Stroke 2013

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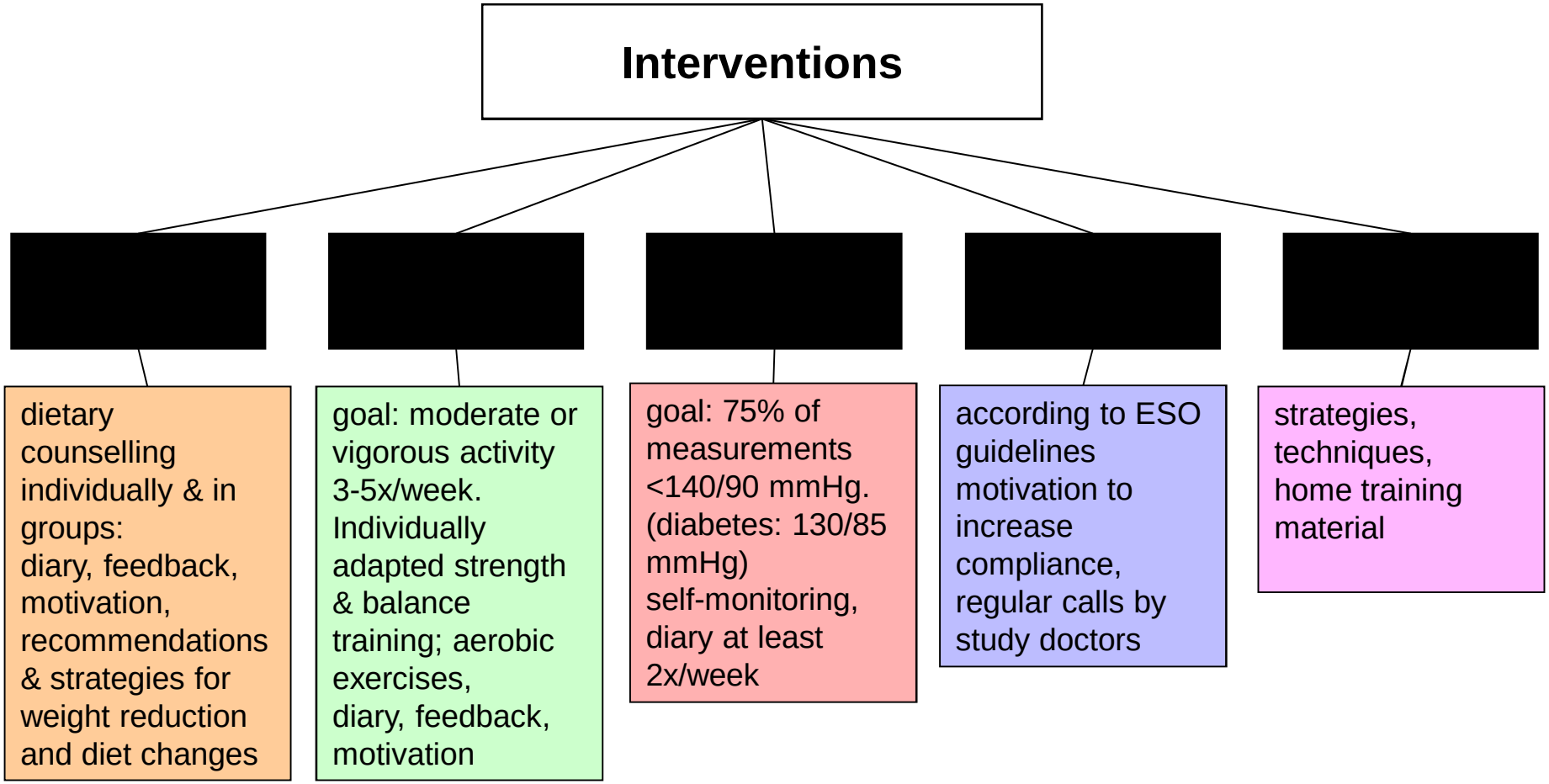
Post-stroke cognitive impairment

- Pharmacological treatment:
  - Donezepil
  - Galantamine
  - Rivastigmine
  - Memantine
- Modest benefit, if any, on standard cogntive measures. Small samples of executive dysfunctions, inconsistent benefit in global and daily function, not distinguishable from Alzheimer disease

Gorelick et al. Stroke 2011; 42: 2672-2713

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



Brainin M et al. Int. J. Stroke (in press)

Post-stroke cognitive impairment

- Time-delayed onset of cognitive impairment following stroke needs to be better understood in its dynamic properties and molecular development.
- Prestroke markers (epigenetic, imaging and laboratory) need to be studied.
- Most likely, multimodal interventions aiming at early restoration and recovery stand the best chance of becoming an effective preventive strategy.