ANALISI MOLECOLARE DELLE VIE DI ANGIOGENESI, NEUROGENESI E FUNZIONALITA' SINAPTICA DI SOGGETTI CON PATOLOGIA CEREBROVASCOLARE

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The Role of Vascular Lesion Type on the Extent of Cognitive Impairment

- Vascular lesions may lower the threshold for the clinical manifestation of AD
- Evidence of cholinergic compromise in both AD and VCI
- Do large cortical infarcts, lacunar infarcts, subcortical white matter disease, strategically placed subcortical infarcts and a combination of these lesion types have differing cognitive footprints?

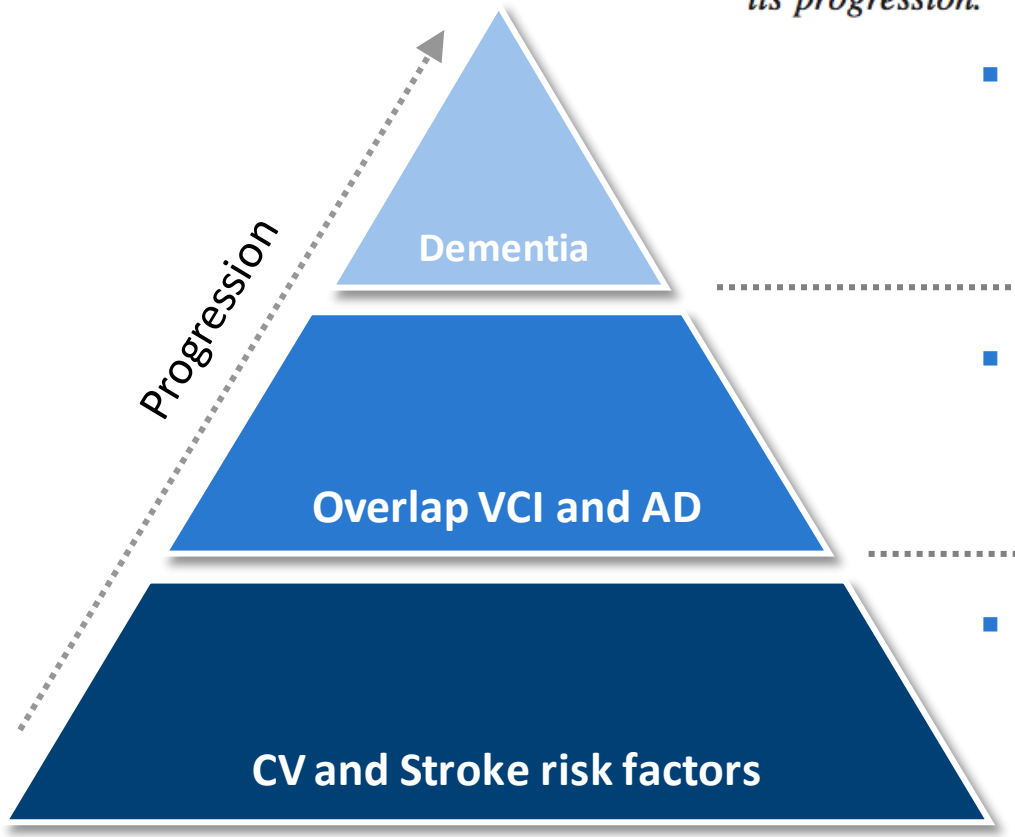
AHA/ASA Scientific Statement

Vascular Contributions to Cognitive Impairment and Dementia

A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association

The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists.

The Alzheimer's Association participated in the development of this statement to advance knowledge and understanding of the causes of dementia and the factors that contribute to its progression. (*Stroke*. 2011;42:2672-2713.)



- it has been proposed that there may be a convergence of pathogenic mechanisms in vascular and neurodegenerative processes that cause dementia
- Cerebral amyloid angiopathy, microinfarction, VCI, microhemorrhage and macrohemorrhage of the brain.
- atrial fibrillation, hypertension, diabetes mellitus, and hypercholesterolemia

Demenza e “fattori vascolari”

Vascular dementia series

International Journal of Stroke © 2011 World Stroke Organization Vol 6, October 2011, 416–424

Can stroke cause neurodegenerative dementia?

Toby B. Cumming* and Amy Brodtmann

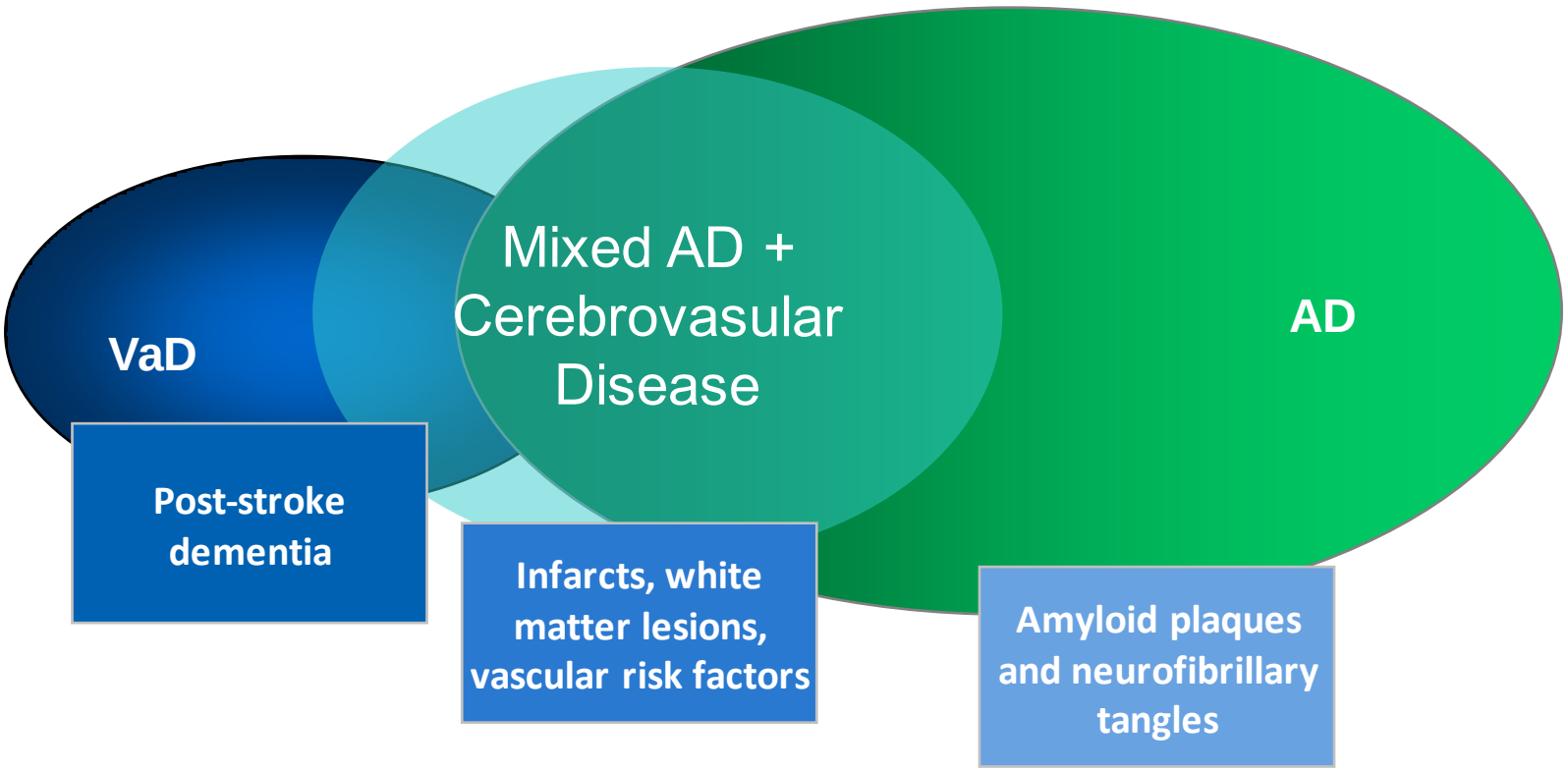
Original Contributions

Carotid Atherosclerosis and Prospective Risk of Dementia

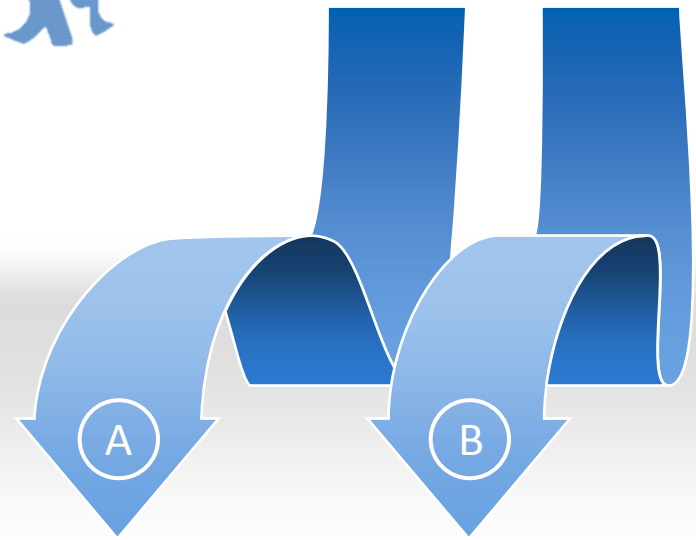
Carrington R. Wendell, PhD; Shari R. Waldstein, PhD; Luigi Ferrucci, MD, PhD;
Richard J. O’Brien, MD, PhD; James B. Strait, MD, PhD; Alan B. Zonderman, PhD

(*Stroke*. 2012;43:00-00.)

The Continuum of Vascular Dementia and Alzheimer's Disease

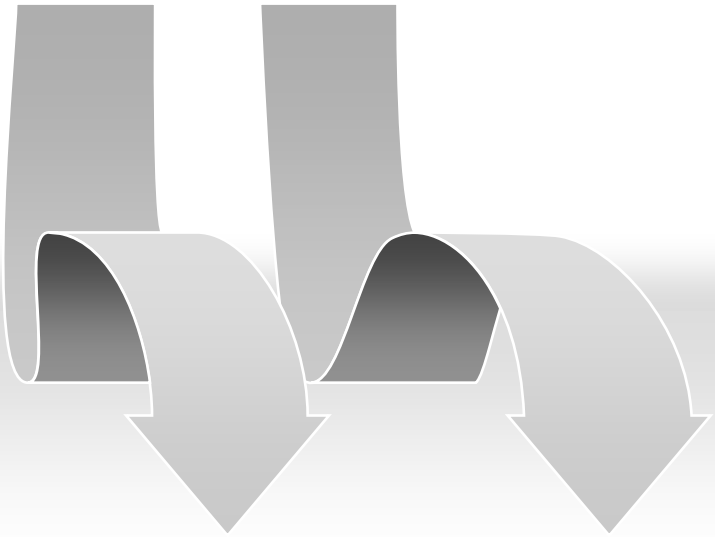


HYPOTHESIS



- We hypothesise that some factors play a key role in developing cognitive decline. Exploring modifications in some key-patways could be useful in identifying a common player which leads to dementia.

AIMS



- To characterize modifications in neurogenesis, angiogenesis and synaptic functions in a animal model of Vascular Dementia;
- To compare animal data with hystopathological findings by the Newcastle Human brain bank.

METHODS

ANIMAL MODEL

- Chronic oligaemia was induced by permanent bilateral common carotid artery occlusion* (2VO); the common carotid artery was doubly bilaterally legated just below the bifurcation with 5–0 silk suture and the artery was cut in between the ligations; 3 months later animal were sacrificed, brain rapidly removed and frozen.

HUMAN SAMPLES

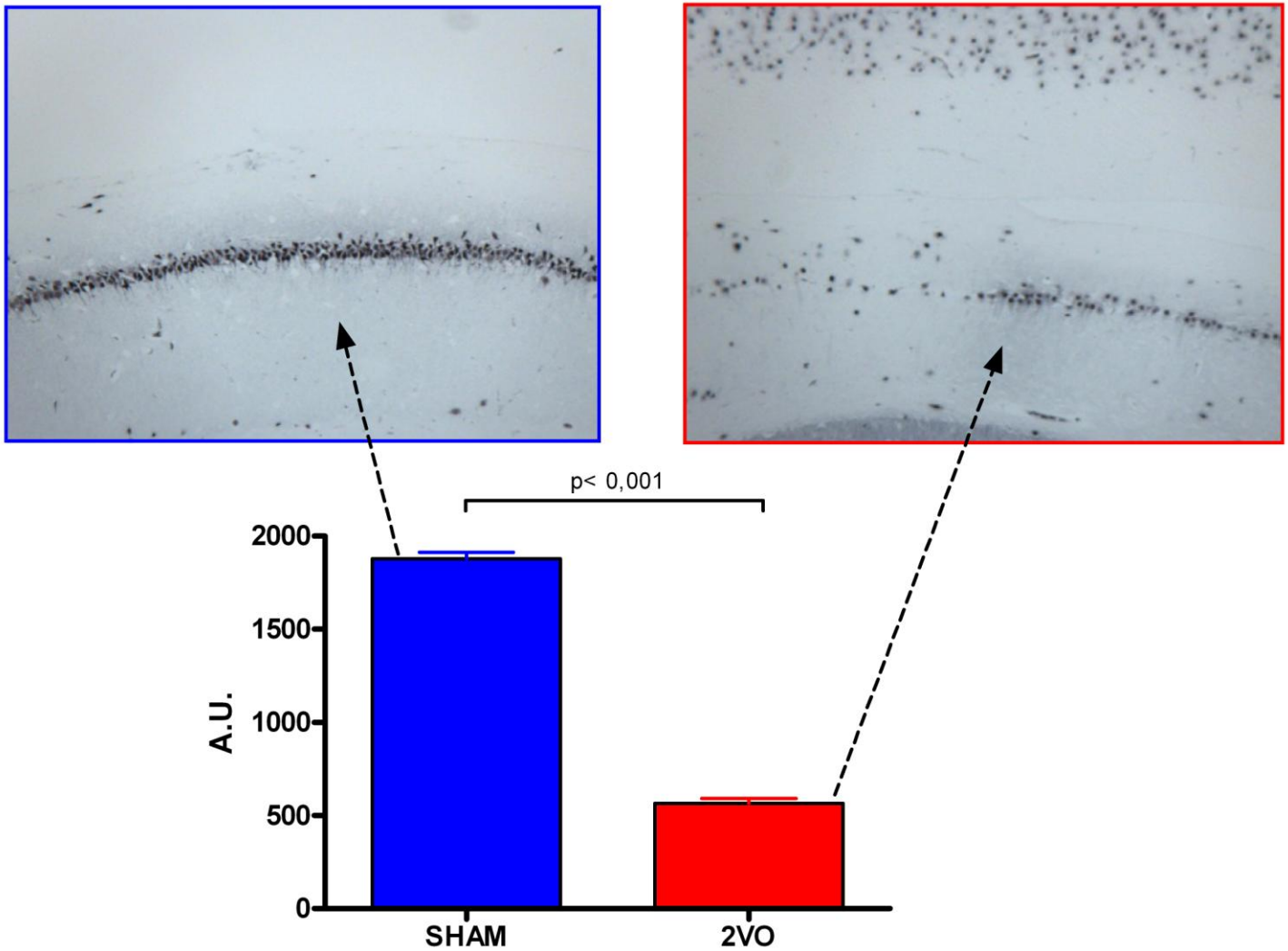
- Postmortem tissue via Brains for Dementia Research (BDR) from the Newcastle Brain Bank;
- 73 patients with Vad, SiVaD, Mixed VaD-AD, SND
- One hemisphere is fixed and one is frozen
- patients (and 'controls') were prospectively followed and clinical data obtained

LABORATORY INVESTIGATIONS

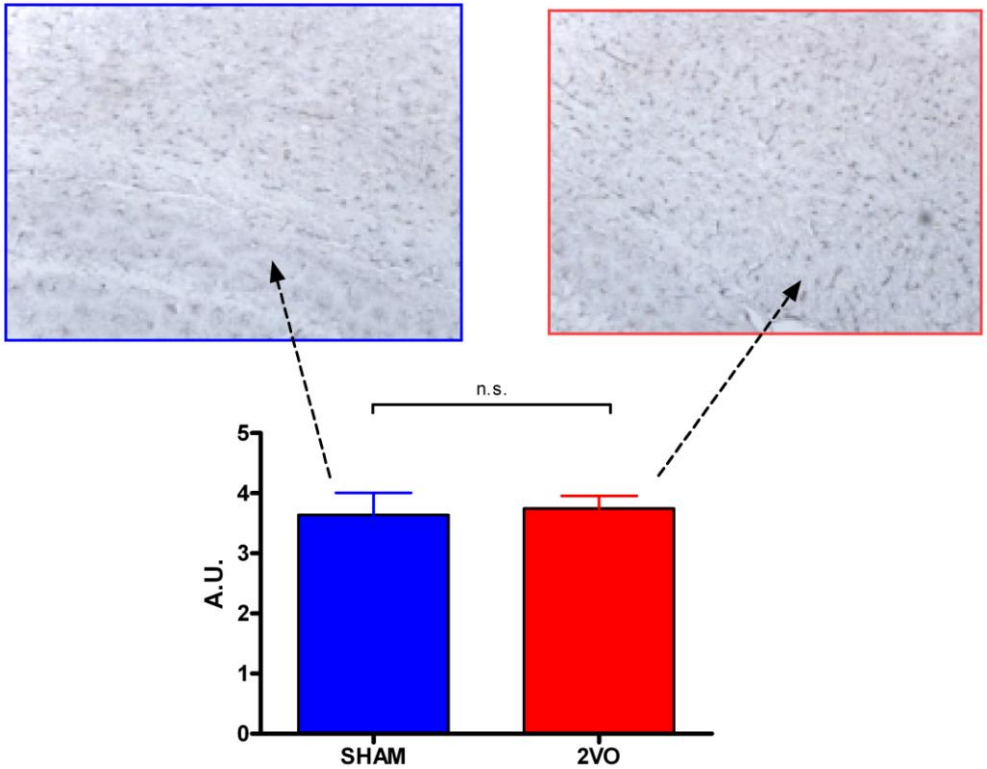
- Western blotting on human and animal samples using antibodies to GFAP, DOUBLECORTIN, SYNAPTOPHYSIN, VEGF.
- Densitometric analysis to quantify expression of proteins
- immunohistochemistry to show patterns of protein expression (DCX, GFAP, VEGF, NeuN)
- Human brain regions:
  - BA 9 dorso-lateral prefrontal cortex → Executive function (motor planning, intellectual function);
  - BA 20-21 mid-temporal cortex →auditory processing and language

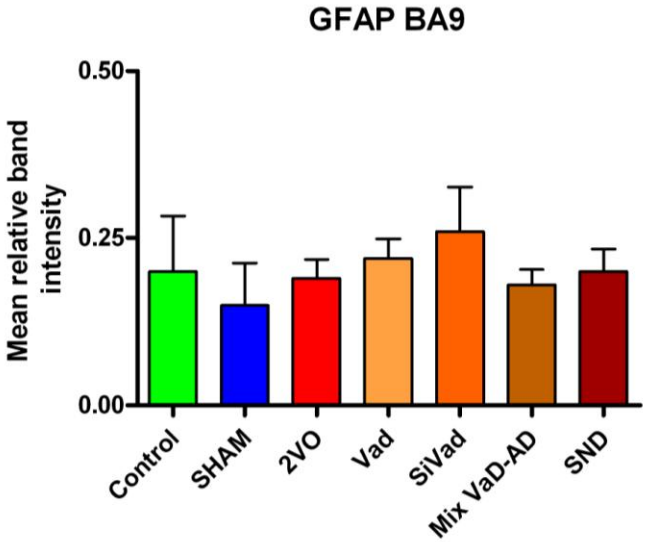
* Farksas et al. Brain Research Reviews 54, 2007, 162-180

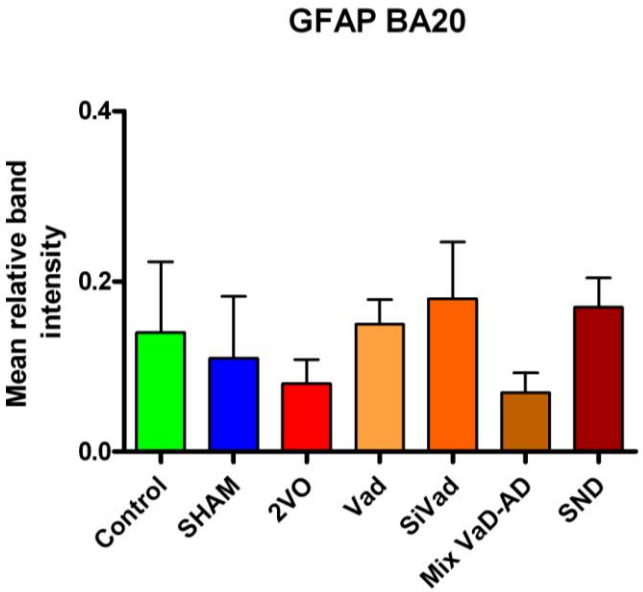
NeuN



GFAP


n.s.
A.U.
0
1
2
3
4
5
SHAM
2VO


GFAP BA9
Mean relative band intensity
0.00
0.25
0.50
Control
SHAM
2VO
Vad
SiVad
Mix VaD-AD
SND


GFAP BA20
Mean relative band intensity
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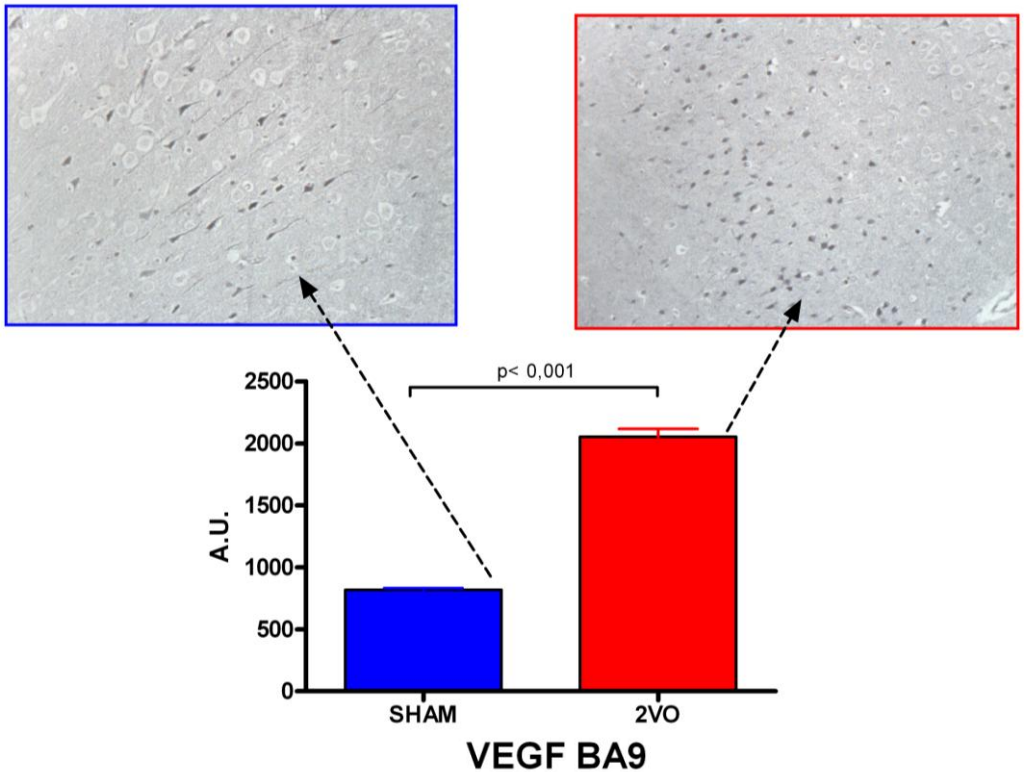
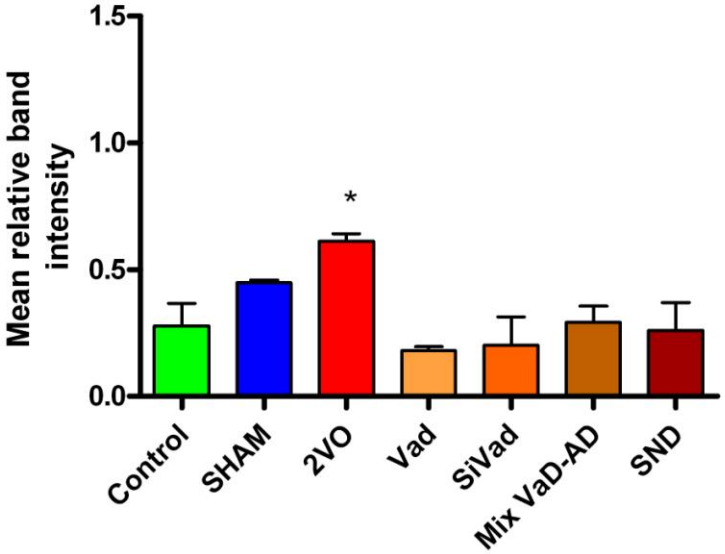
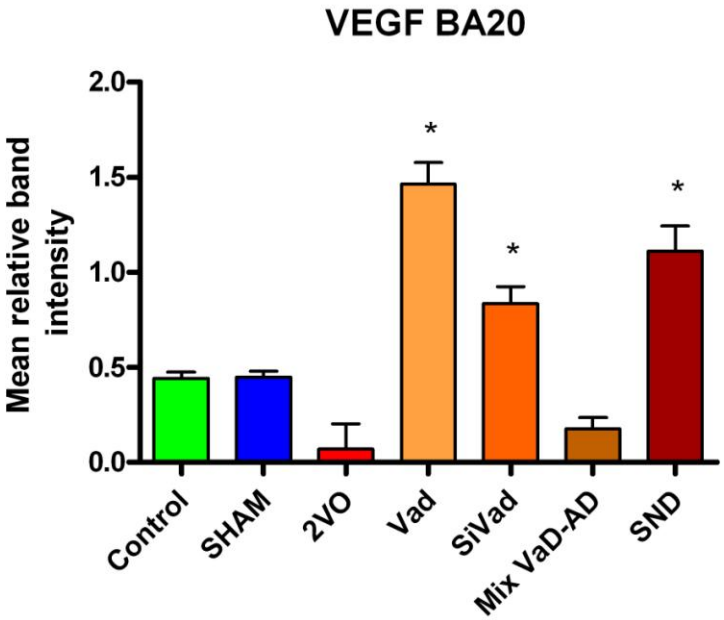
0.2
0.4
Control
SHAM
2VO
Vad
SiVad
Mix VaD-AD
SND

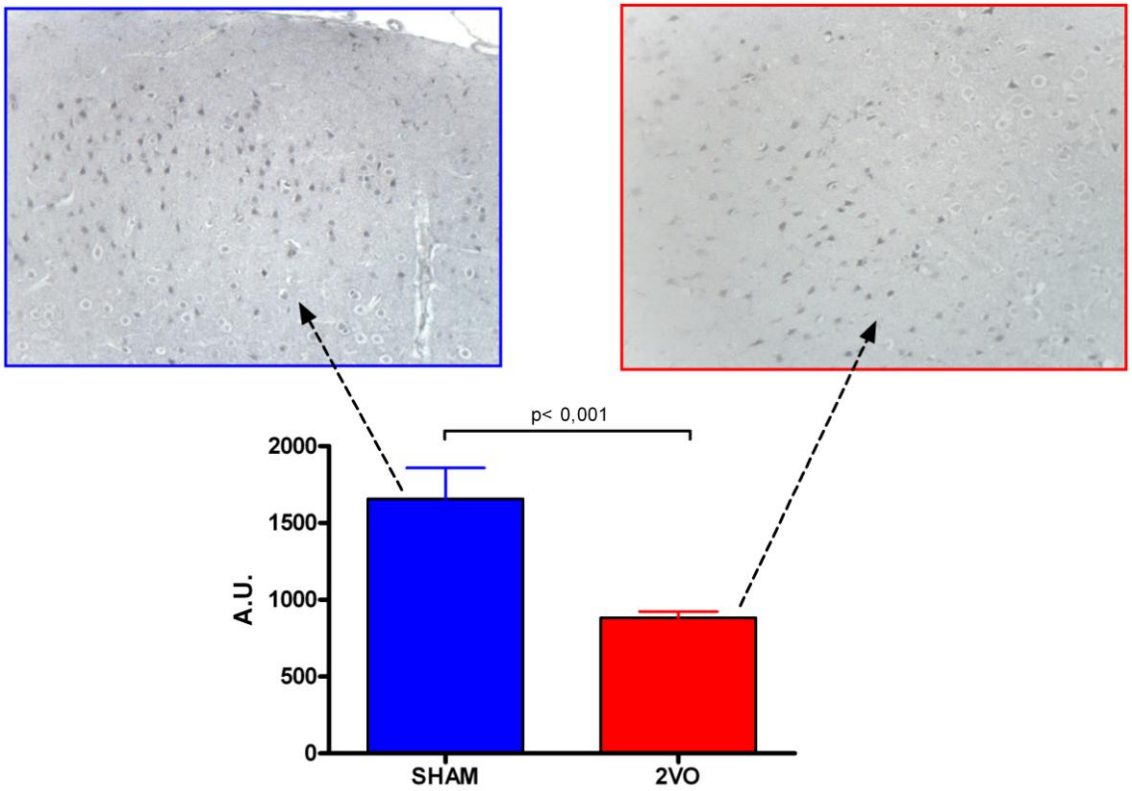
VEGF

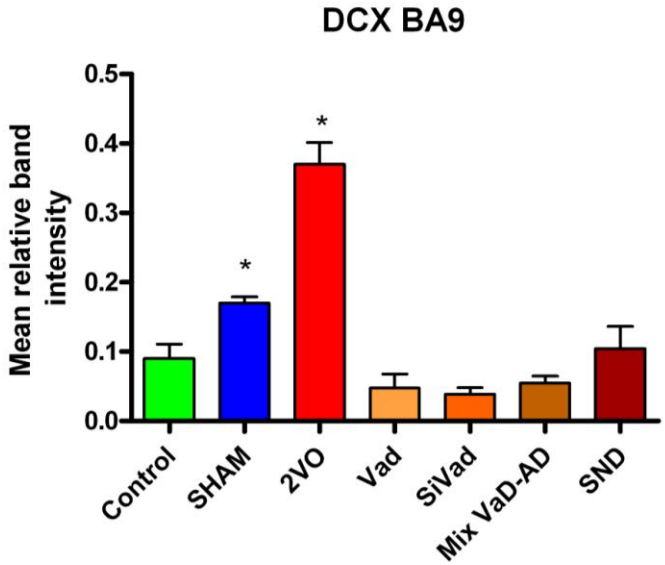

p< 0,001
2500
2000
1500
1000
500
0
A.U.
SHAM
2VO
VEGF BA9

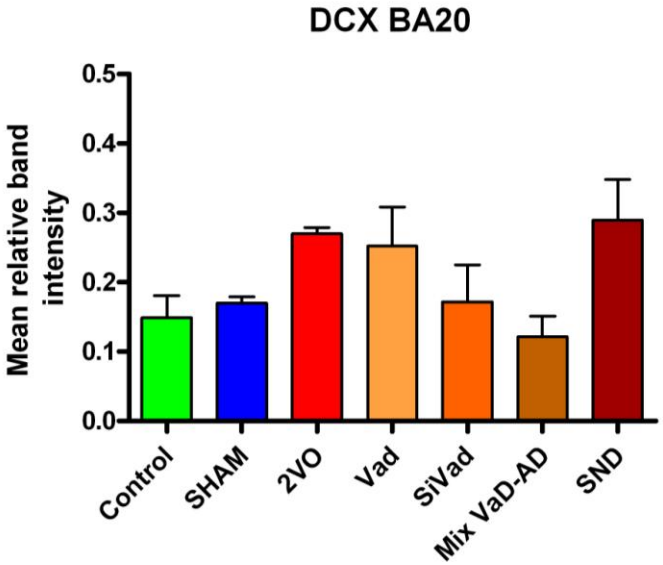

Mean relative band intensity
1.5
1.0
0.5
0.0
*
Control
SHAM
2VO
Vad
SiVad
Mix VaD-AD
SND


VEGF BA20
Mean relative band intensity
2.0
1.5
1.0
0.5
0.0
*
*
*
Control
SHAM
2VO
Vad
SiVad
Mix VaD-AD
SND

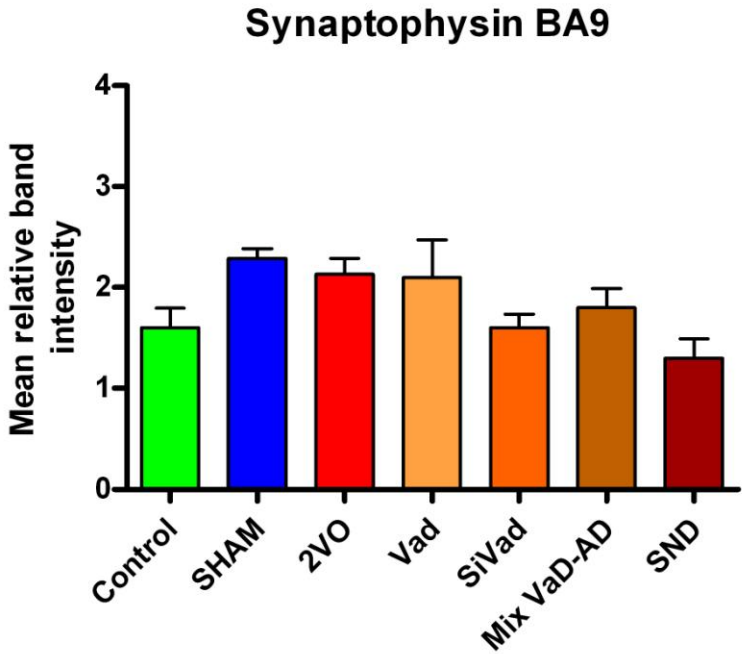
DOUBLECORTIN

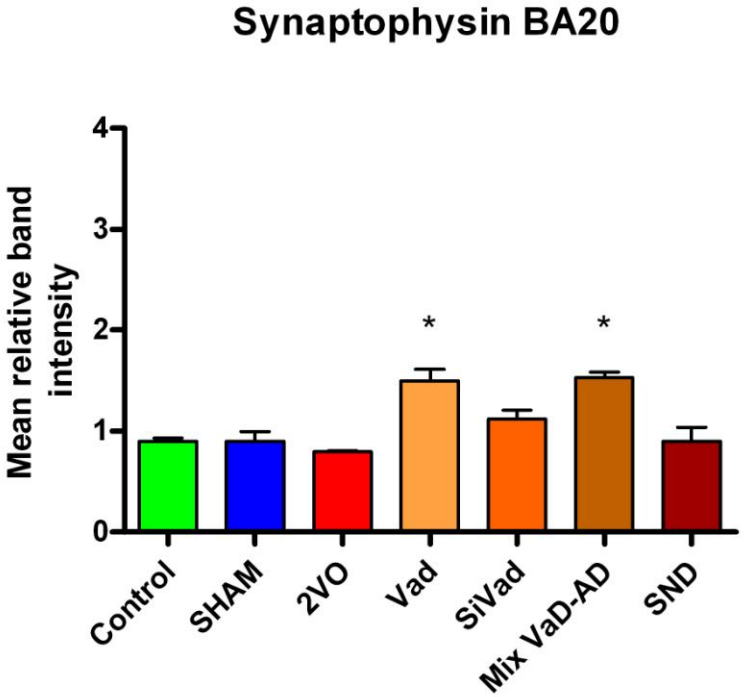






SYNAPTOPHYSIN





CONCLUSIONI

NeuN	▪ Chiara neurodegenerazione a livello dell'area ippocampale CA1, tipicamente vulnerabile all'ischemia;
GFAP	▪ Nessuna risposta gliotica riparativa a tre mesi dall'intervento ▪ Nessuna differenza nei gruppi di demenza vascolare ▪ Dato confermato dalla letteratura: gliosi nei primi giorni post-ischemia
VEGF	▪ Esiste una risposta angiogenetica a livello della corteccia temporale dei pazienti affetti da VaD, SiVaD e SND. ▪ 2VO mostra angiogenesi solo a livello frontale ma non temporale
DCX	▪ Risposta neurogenetica nel 2VO all'analisi di immunoblotting; ▪ Ridotta espressione DCX nei 2VO a livello delle aree sottocorticali ▪ Nessuna differenza nei campioni umani
SYNAPTOPHYSIN	▪ Funzionalità sinaptica invariata nei 2VO e nei campioni umani da corteccia frontale ▪ Aumenta nei campioni umani di VaD e Mix da corteccia temporale

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