Cognitive impairment in dialysis patients; The contribution of the CONNECT network.

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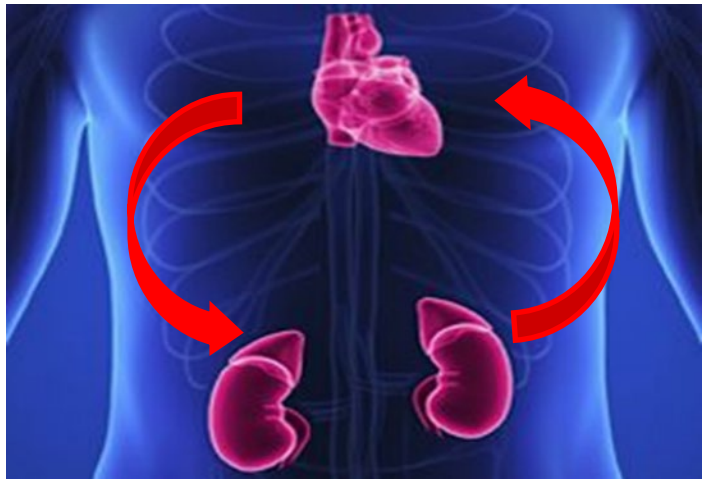
Berliner DialyseSeminar

Potential conflicts of interest declaration

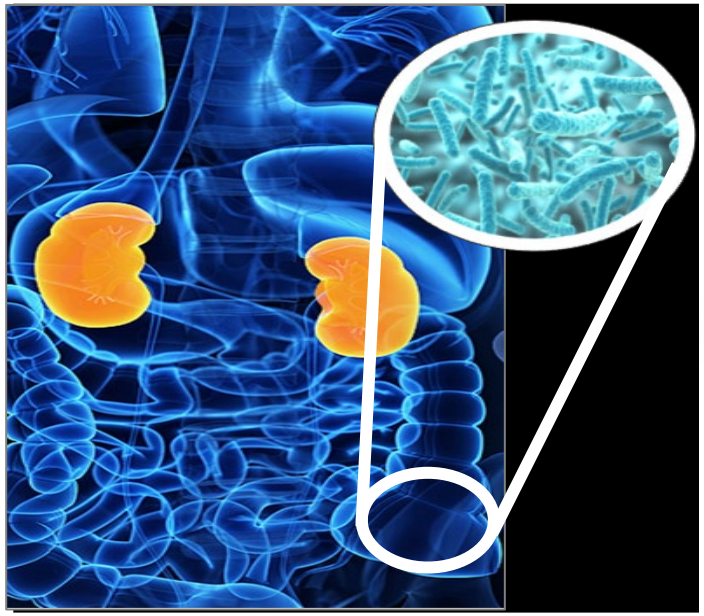
The content of the following speech is the result of efforts to achieve the maximum degree of impartiality and independence.

As a speaker, I hereby affirm that there are **no conflicts of interest** concerning the content of the following speech that are the result of employment, an advisory function or financial contributions for research projects, lectures or any other activity.

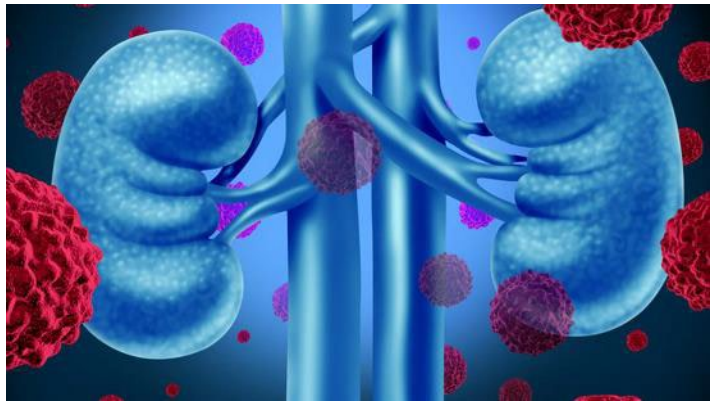
New frontiers of nephrology



Cardio-nephrology



Intestinal microbioma - Kidney interaction

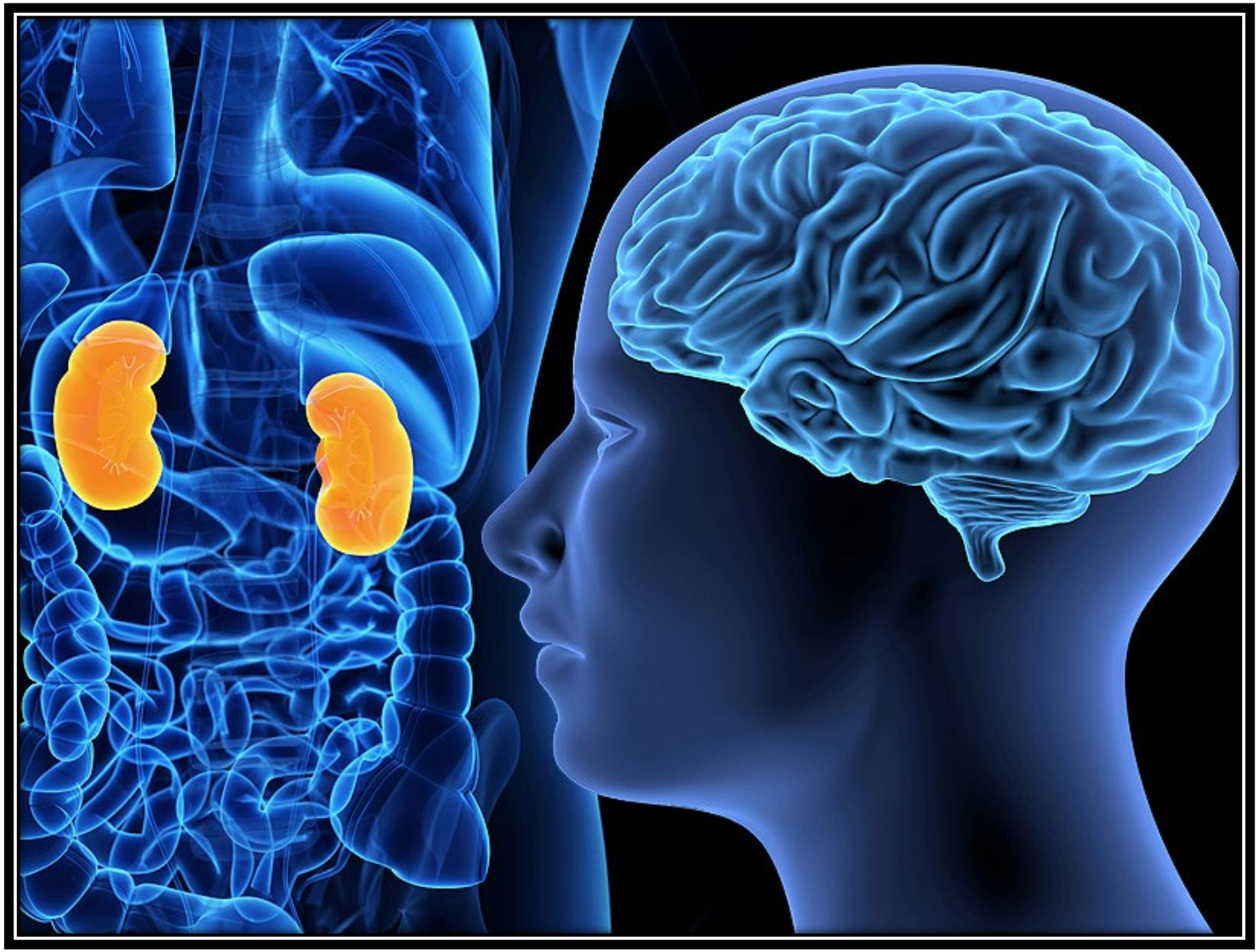


Onco-nephrology

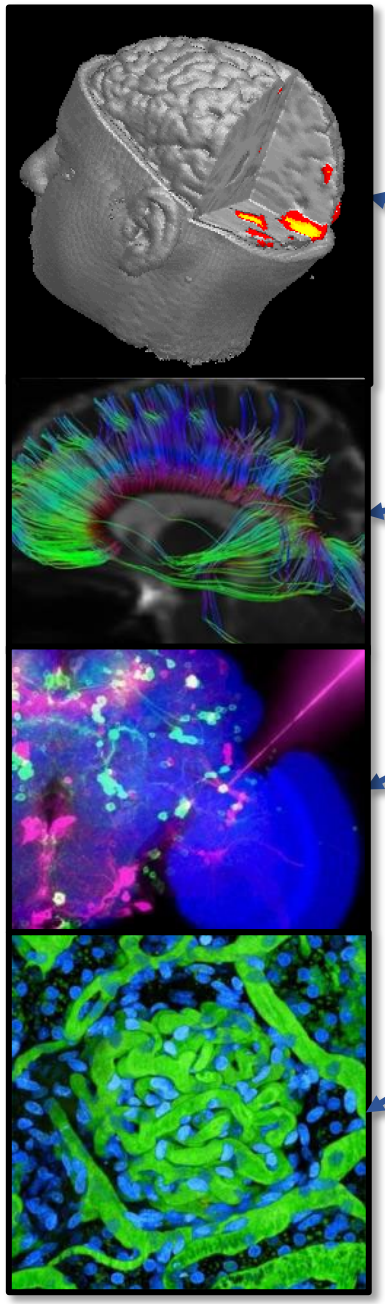
New pharmacological tools

Vaptans,
SGLT2 inhibitors,
biological immunotherapy

Brain-kidney interaction: the new frontier of medicine



WHY NOW?



New tools to study the brain

- Functional Magnetic Resonance (fMRI) to visualize human brain activity
- Tractography to identify brain connections in vivo
- Optogenetics to visualize and activate single neurons in vivo

New tools to study the kidney

- Metabolomics, proteomics, peptidomics to identify kidney-handled substances
- 2-photon microscopy to visualize kidney microcirculation

Big Data Analysis

How the kidney influences the brain?

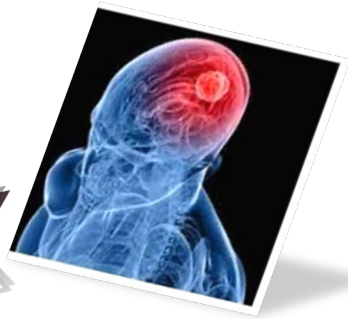
Neurological complications of CKD

Neuropathy

Cognitive/sleep disorders

- MILD COGNITIVE IMPAIRMENT
- Uremic encephalopathy
- Restless leg syndrome
- Sleep apnea

Vascular disorders



- Cortical infarcts (stroke)
- Posterior reversible encephalopathy

Movement disorders

- Tremor
- Myoclonus
- Asterixis
- Seizures
- Dystonia
- Chorea

cost

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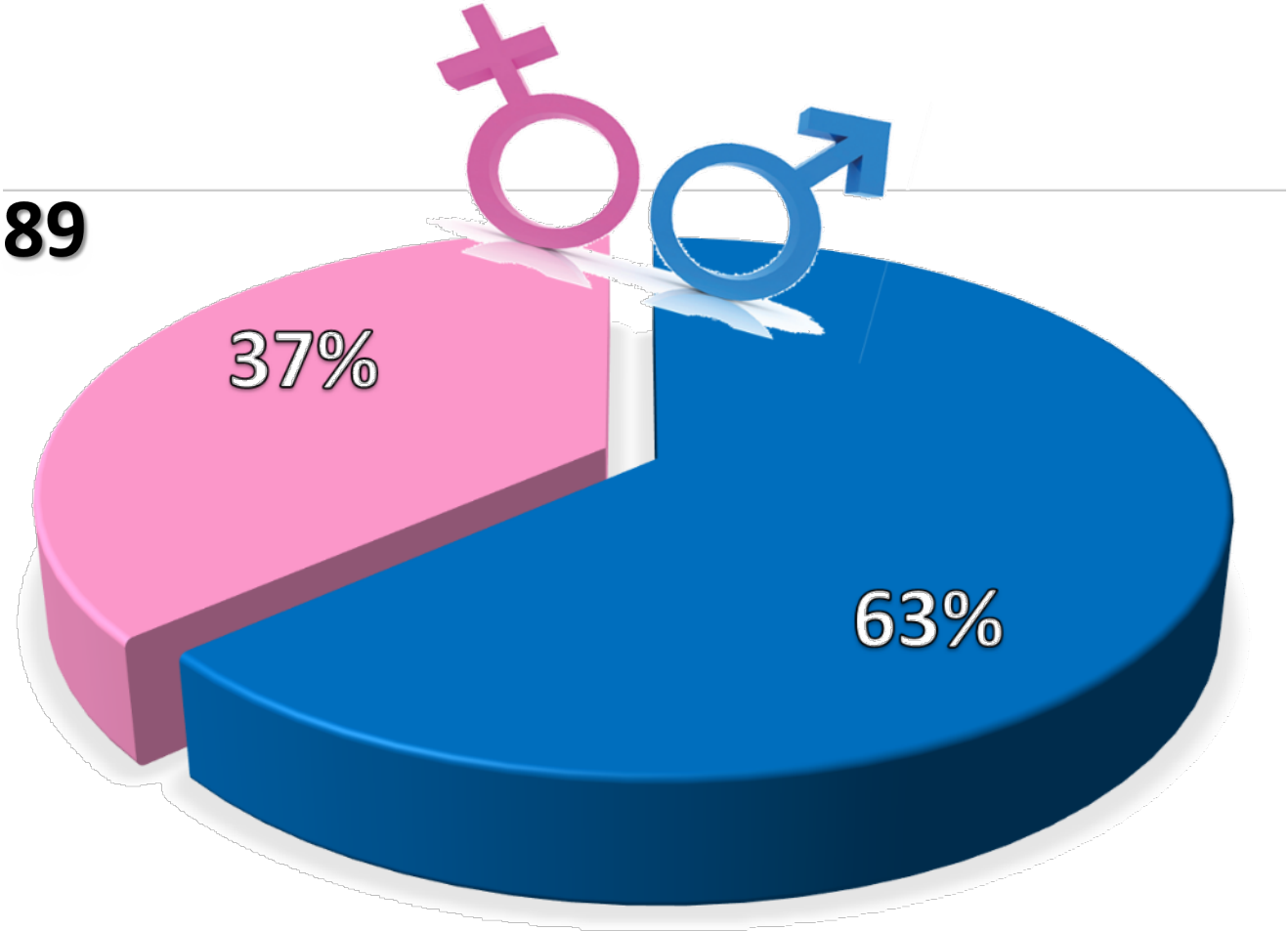
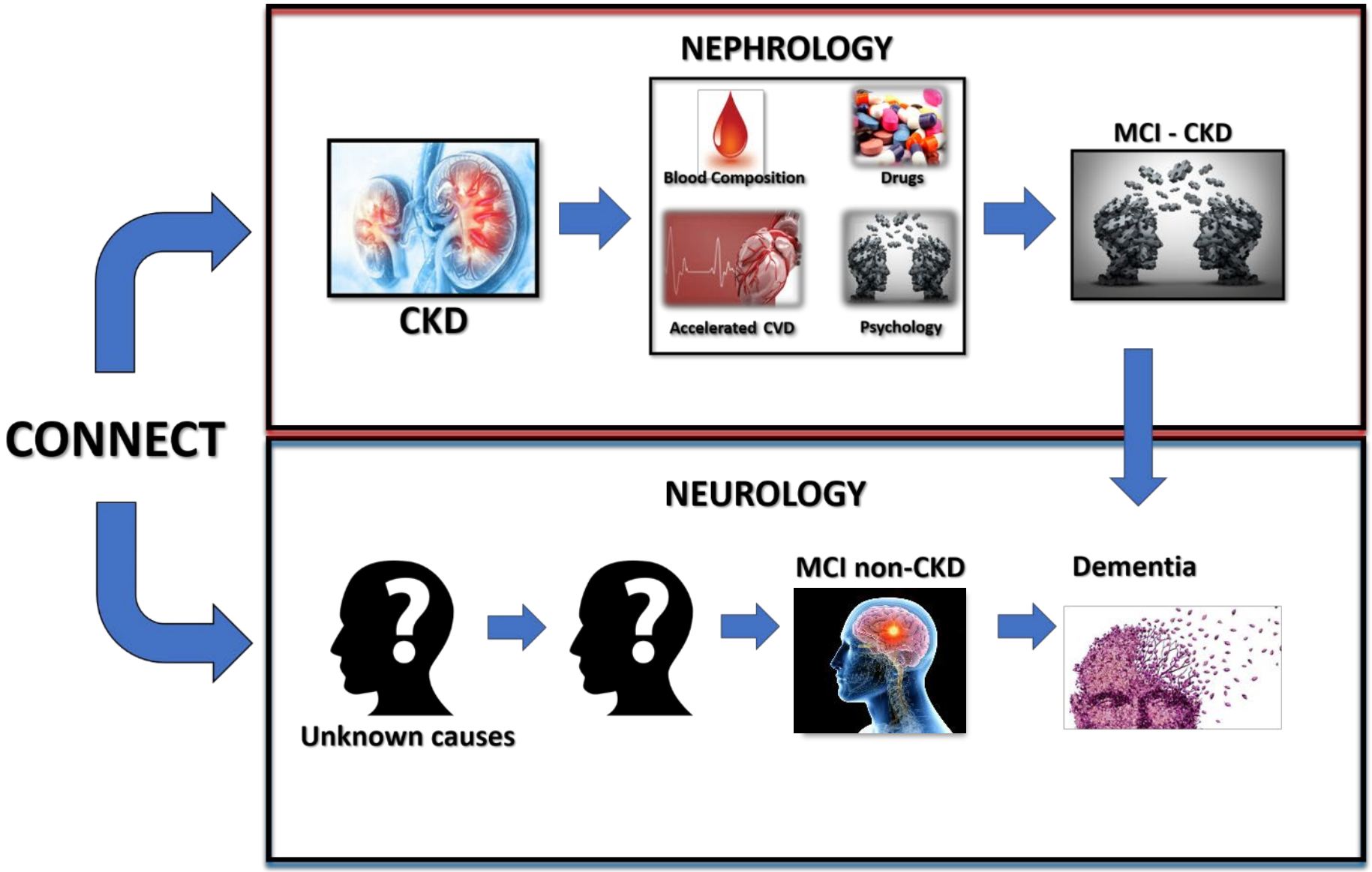


Interdisciplinary:

- Nephrologists
- Neurologists
- Neurophysiologists
- Kidney Physiologists
- Biochemists
- Geriatricians
- Epidemiologists

Brain-kidney interactions in CKD



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NEPHROLOGY DIALYSIS TRANSPLANTATION

AN INTERNATIONAL BASIC SCIENCE AND CLINICAL RENAL JOURNAL

CONNECTing the kidney to brain dysfunction: from animal models to clinical practice

CONNECT
COGNITIVE DECLINE IN NEPHRO-NEUROLOGY

Guest edited by Giovambattista Capasso and Christoph Wanner

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Narrative review

Cognitive disorders in patients with chronic kidney disease: specificities of clinical assessment

Background

Neurocognitive disorders are frequent among chronic kidney disease patients

Screening, identifying and characterizing cognitive impairment is beneficial in chronic kidney patients

Methods

Narrative review of:

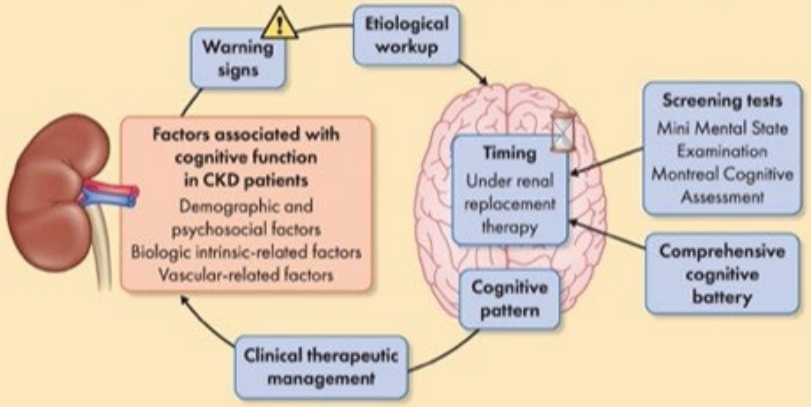
Clinical warning signs of cognitive impairment in CKD patients

Conditions affecting cognitive testing or performance in CKD patients (including dialysis and transplantation)

Available **screening tests**

Results

Collaboration between nephrologists, neurologists, neuropsychologists, geriatricians, and general practitioners



Review

Acidosis, cognitive dysfunction and motor impairments in patients with kidney disease

Background

CKD has recently been associated with cognitive dysfunction, and advanced CKD patients often have reduced motor function

↓HCO_3^-

Recent data point towards the possibility that metabolic acidosis is one modifiable contributor to cognitive dysfunction

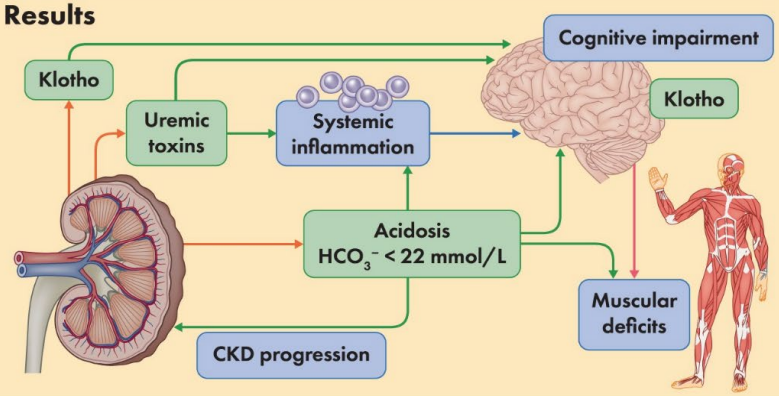
Methods

PubMed

Literature search PubMed for combinations of:

- Cognitive dysfunction
- Brain function
- Motor function
- pH
- Acidosis
- CKD
- AKI

Results



Conclusion

CKD and acidosis are associated with forms of cognitive dysfunction. Further studies are required to test for causality, mechanisms, and therapies.

Review Article

Albuminuria as a risk factor for mild cognitive impairment and dementia – what is the evidence?

Synopsis

This review summarizes the available evidence on increased albuminuria in the development of mild cognitive impairment (MCI) or dementia, points to existing gaps in our knowledge, and suggests actions to overcome them.

Clinical data

Epidemiological studies were conducted in different populations

They demonstrated that the presence of **increased albuminuria is associated with a higher relative risk of MCI or dementia** both in cross-sectional analyses and in studies with long-term follow-up

Pathophysiology

Underlying pathophysiological mechanisms of albuminuria's effect are still under investigation

Available experimental data indicate that elevated albuminuria and low GFR are associated with **significant neuroanatomical declines in hippocampal function and gray matter volume**

Controversies and proposals

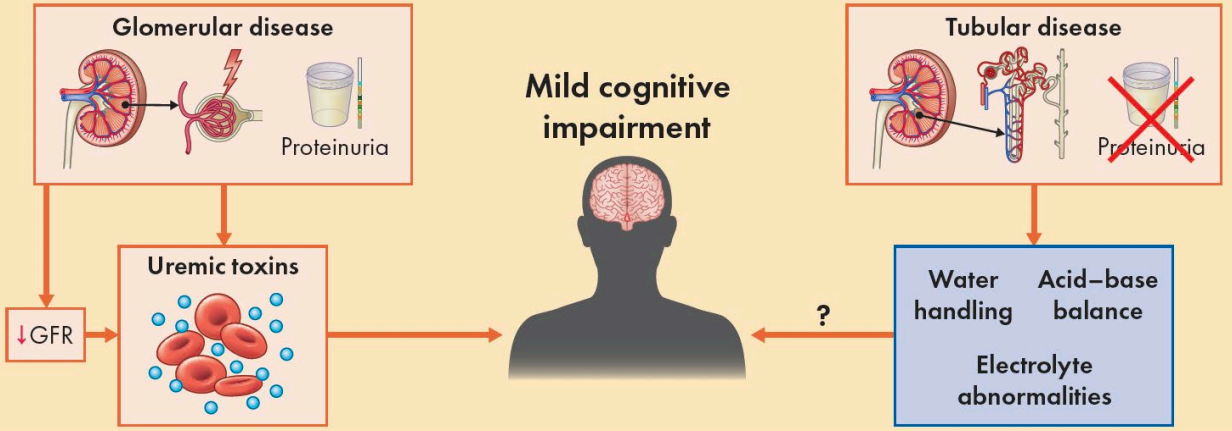
We propose 10 recommendations for further clinical studies on relationship between albuminuria and MCI or dementia that would resolve the major questions about a causal relationship and the effectiveness of interventions targeting albuminuria per se to prevent cognitive decline.

Review

Brain dysfunction in tubular and tubulointerstitial kidney diseases

Background

Tubular and tubulointerstitial disorders are usually characterized by electrolyte and water handling disorders and by a loss of acid–base balance affecting brain activity. CKD has been linked with cognitive impairment, but it is unclear whether this depends on a reduced GFR, altered tubular function or the presence of proteinuria

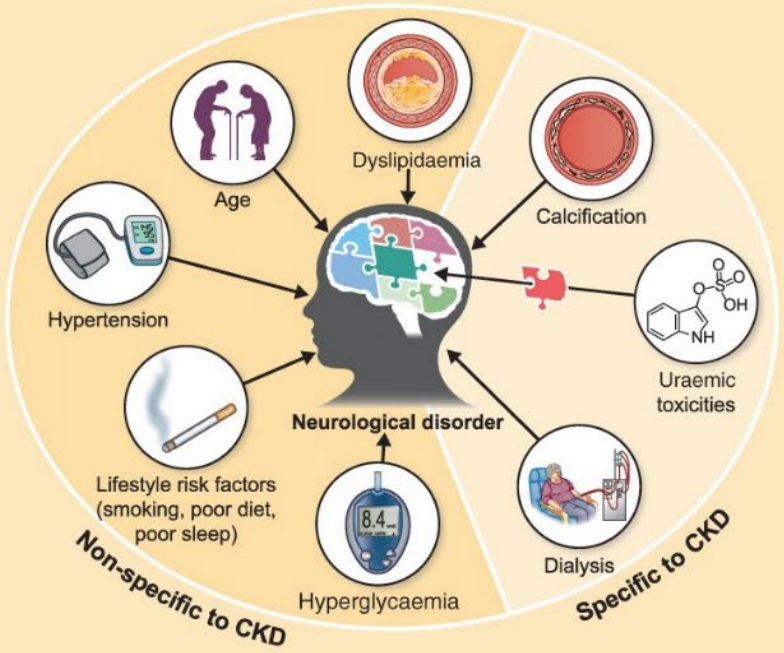


Narrative review

Chronic kidney disease and neurological disorders: are uraemic toxins the missing piece of the puzzle?

Background

Along with traditional cardiovascular risk factors (such as diabetes, inflammation, hypertension and dyslipidaemia), non-traditional risk factors related to kidney damage (such as uraemic toxins) may predispose patients with CKD to neurological disorders.



Aim

Potential clinical impact of CKD on cerebrovascular and neurological complications

Mechanisms underlying the uraemic toxins' putative direct actions (based on preclinical and clinical research)

Potential impact of these findings on patient care, and unmet medical needs

Results

Uraemic toxins that might influence brain function:

Small water-soluble compounds:
Asymmetric dimethylarginine (ADMA)
Symmetric dimethylarginine (SDMA)
Trimethylamine-N-oxide (TMAO)
Uric acid; Urea; Methylguanidine guanidine

Protein-bound compounds
Indoles (Indoxylsulfate (IS), Indoxyl glucuronide, Indole acetic acid (IAA), Kynurenine)
Cresols (p-cresylsulfate (pCS), p-cresyl glucuronide)
Hippurates (Hippuric acid (HA))
3-Carboxy-4-methyl-5-propyl-2-furanpropionate (CMPF)

Middle molecules
ß2 microglobulin (B2M); Interleukin-6; Parathyroid hormone (PTH)

Conclusion

The uraemic toxins that accumulate in the blood in ESRD might explain the association between CKD and cerebrovascular/neurologic complications (at least in part in more advanced CKD stages) and constitute potentially valuable therapeutic targets.

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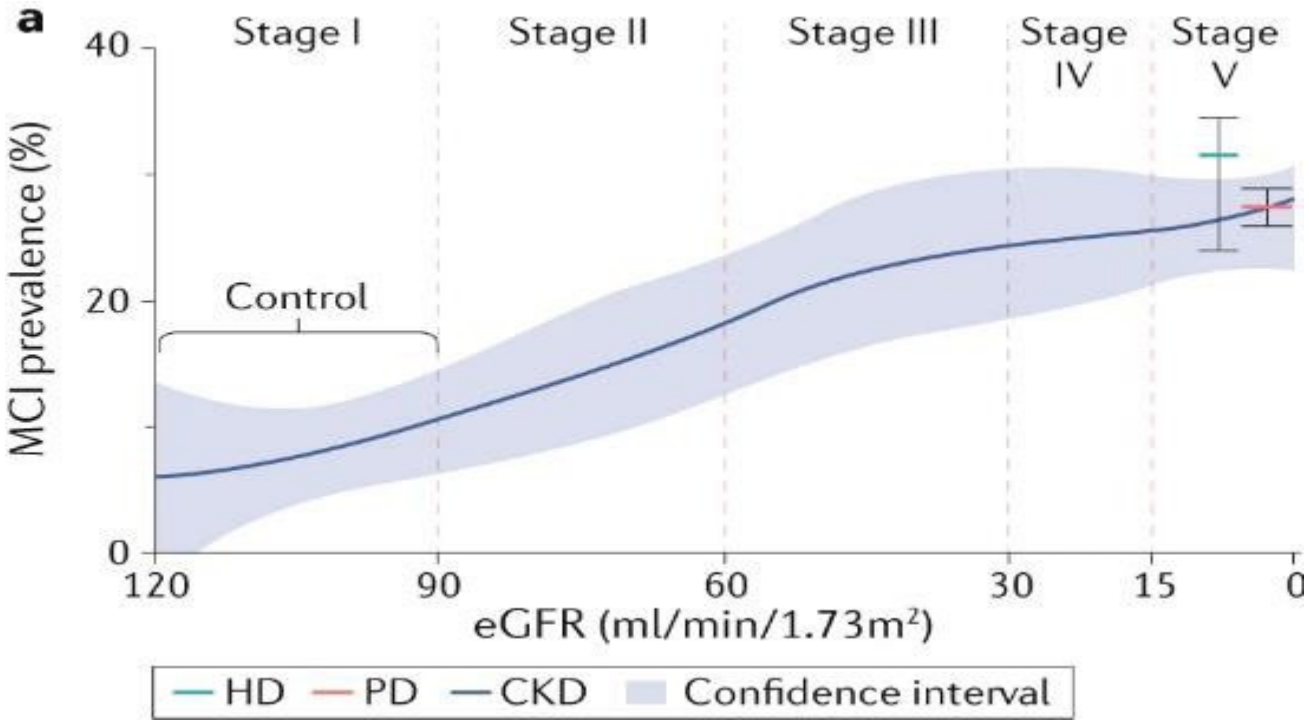
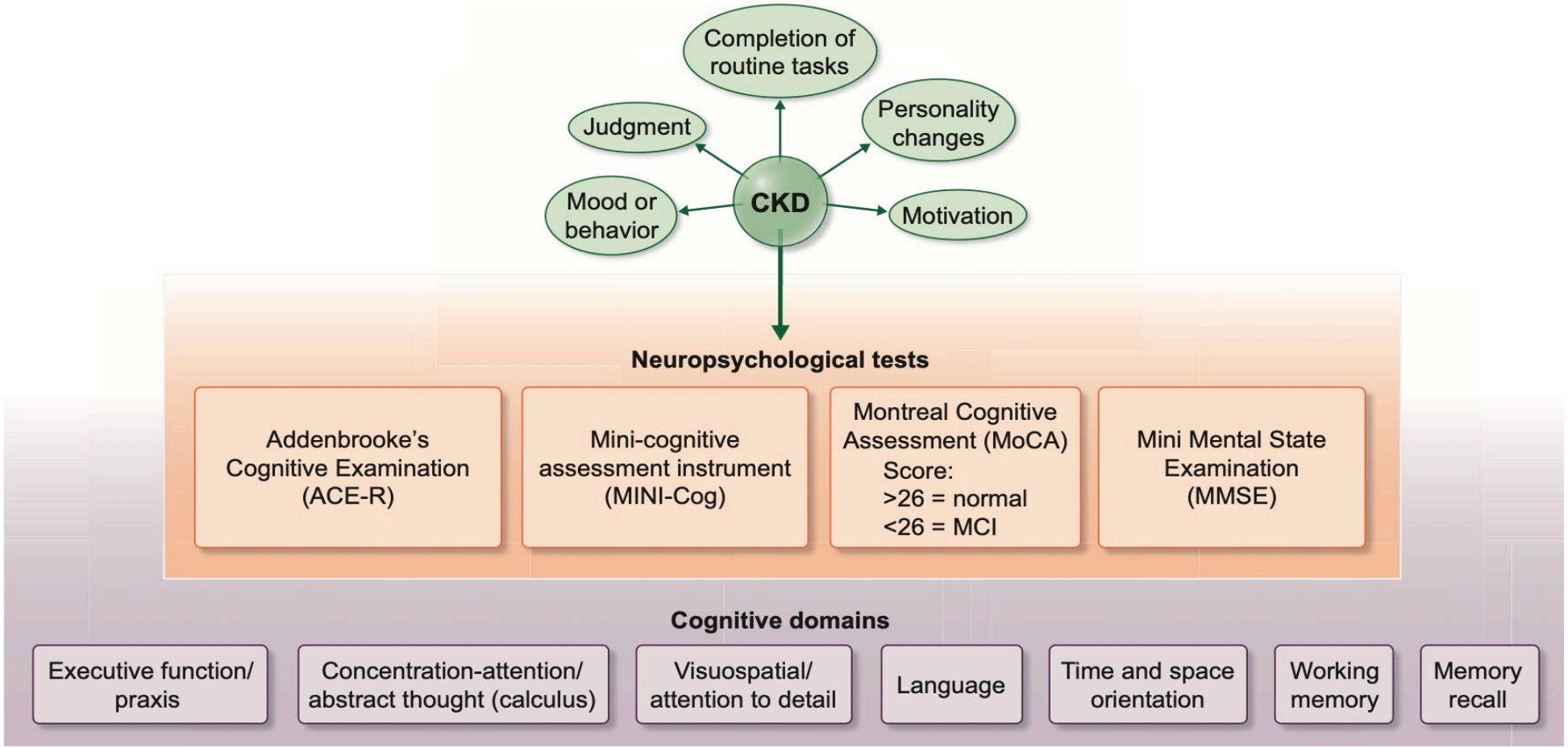
Liabeuf S., et al. NDT (2021)
@NDTSocial

Mild Cognitive Impairment prevalence in patients with CKD



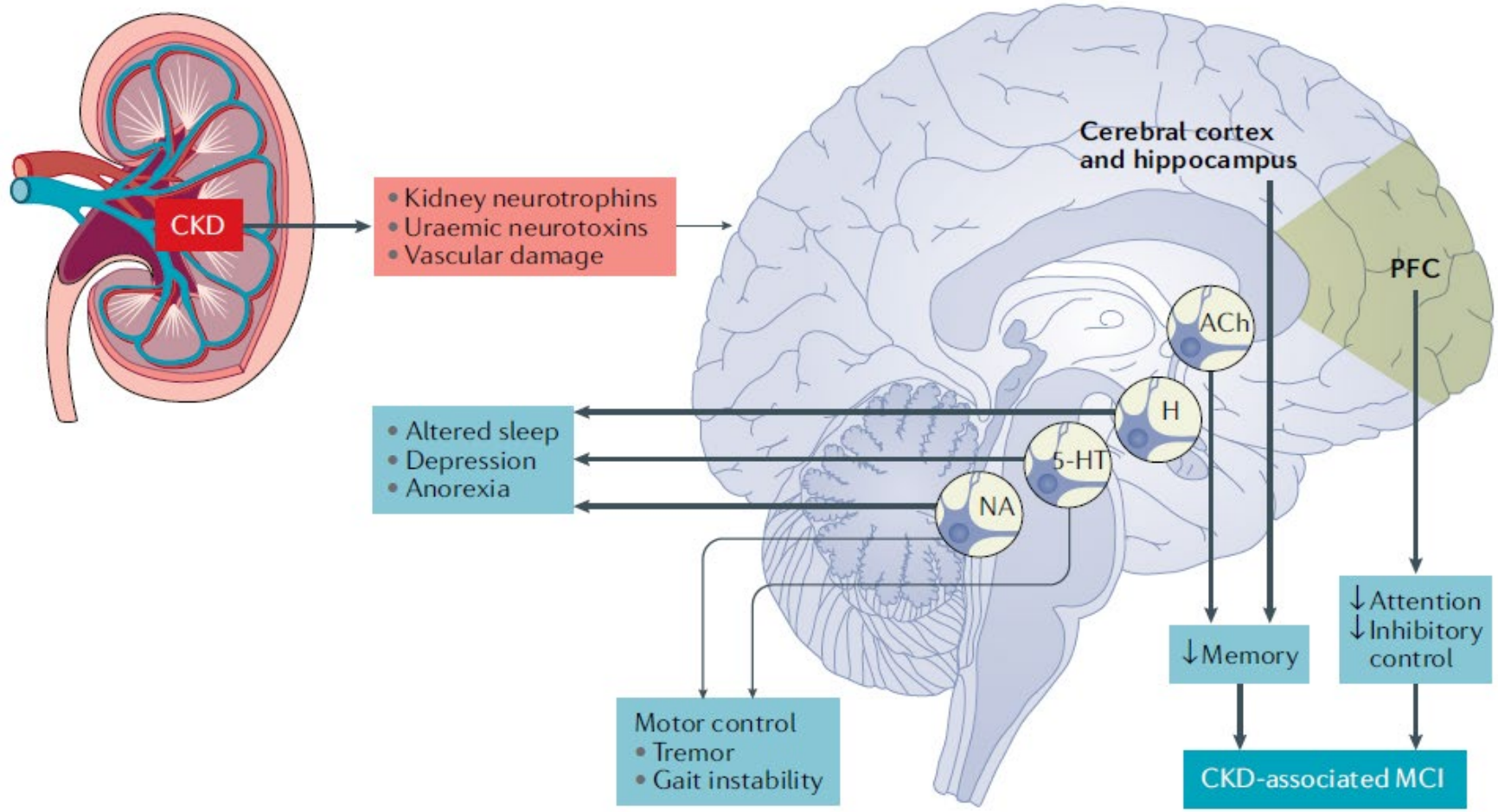
Viggiano & Capasso 2020, Nat Rev Nephrol

Cognitive Impairment Tests



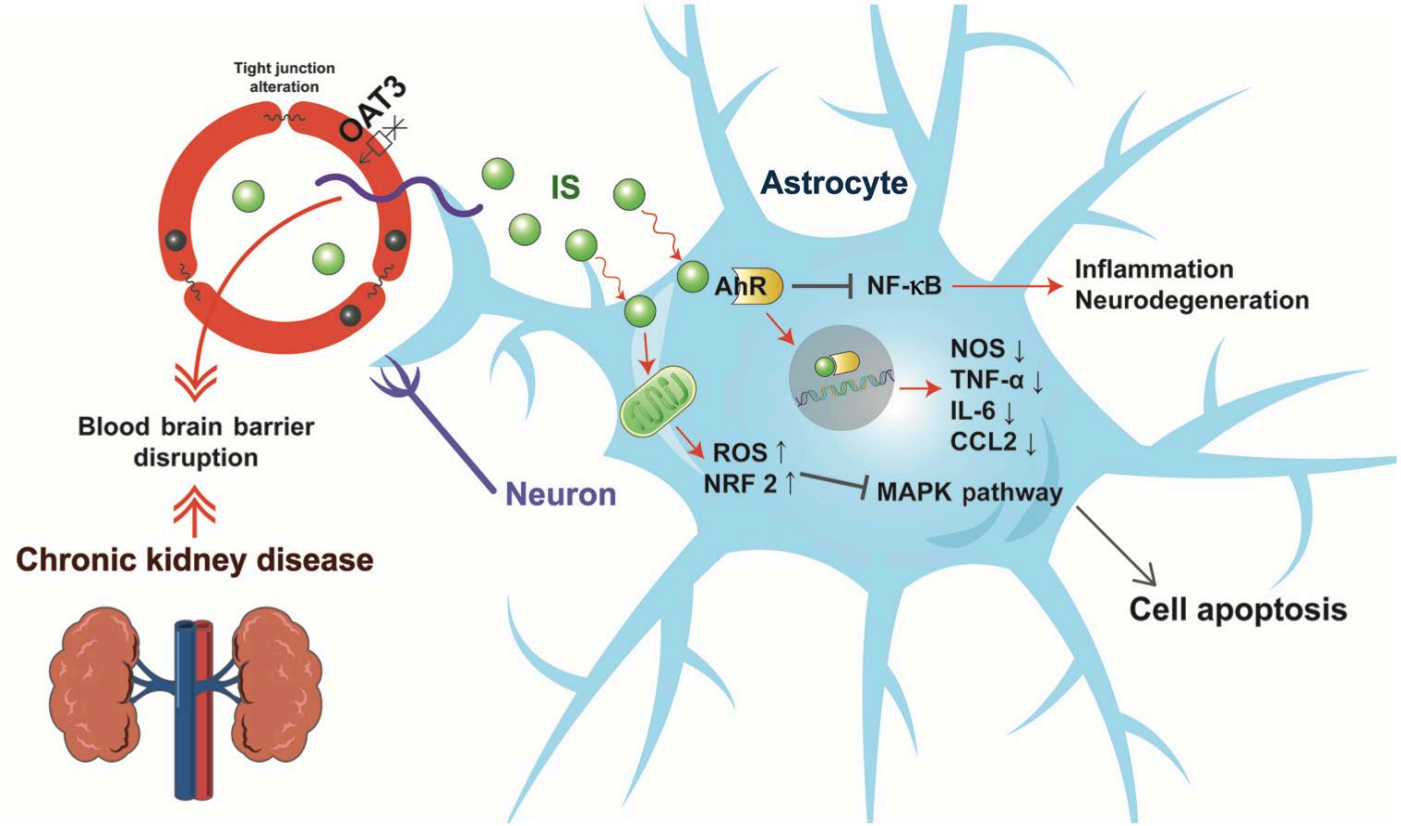
Viggiano D. & Capasso G. **Nephrology Dialysis Transplantation,** ***2019***

Brain modifications in CKD-HD



Viggiano D. & Capasso G. Nature Reviews Nephrol 2020

CI during renal kidney failure

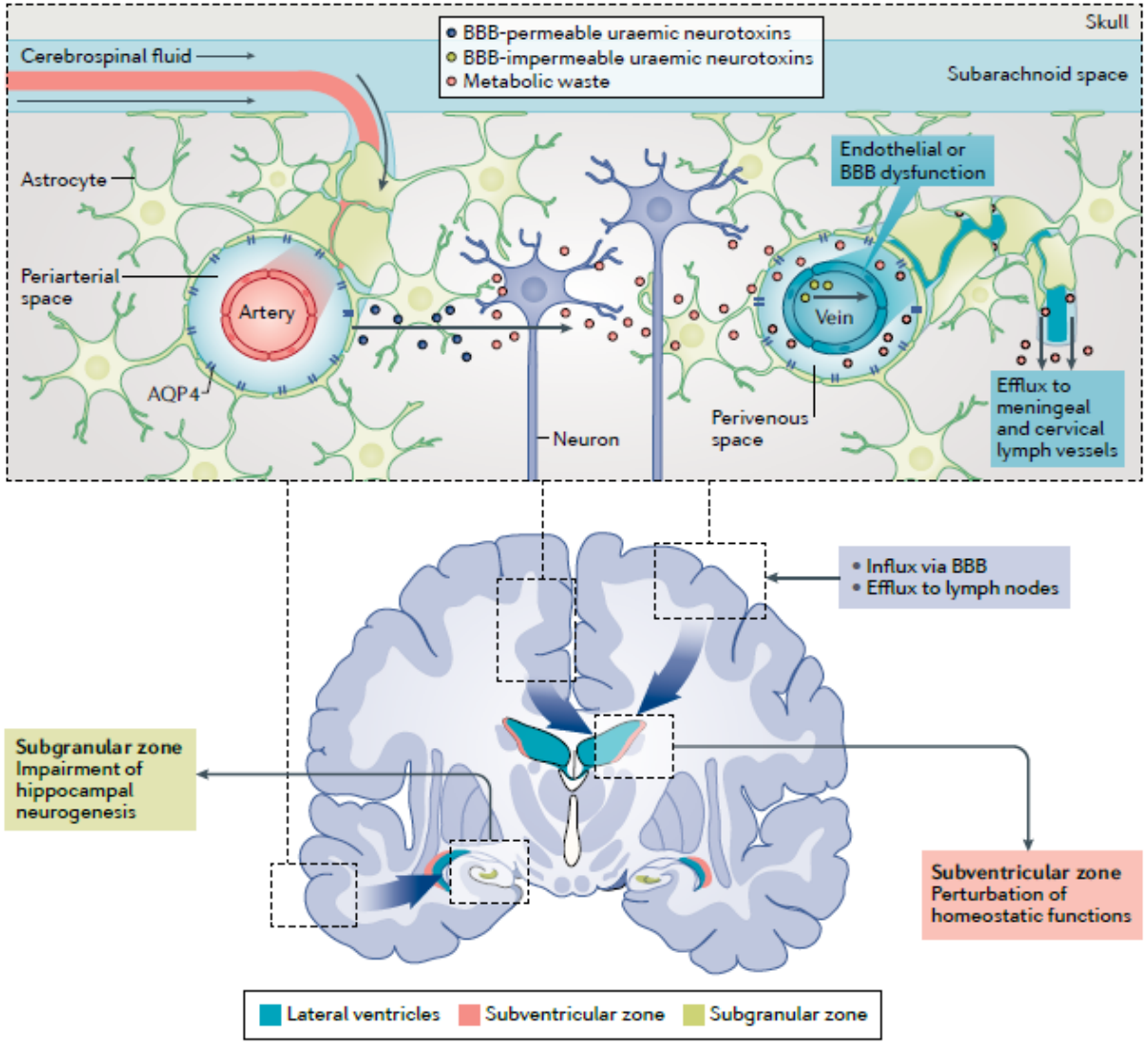


Uremic neurotoxins :

- **Indoxyl sulfate (IS)**
- **P-cresyl sulfate**
- **Guanidine compounds**
- **Excessive phosphates**
- **FGF23**

Kim DS, et al.2022 Kidney–brain crosstalk

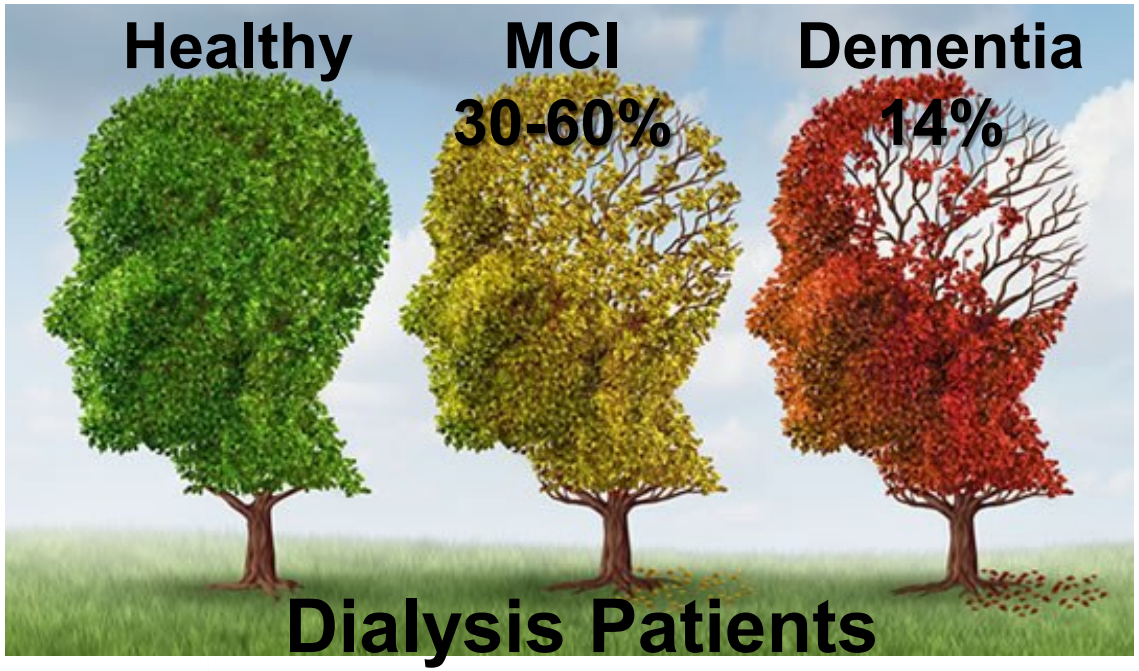
Mechanisms of uremic toxin transport in the brain : the importance of the glymphatic system



Viggiano D. & Capasso G. Nature Reviews Nephrol 2020

High prevalence of CI & damage in HD patients

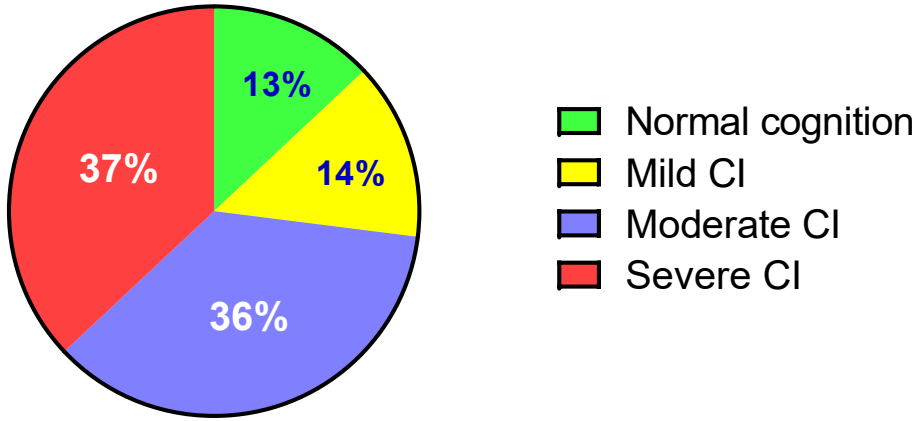
- Persistent cognitive decline and behavioural disturbance
- No interference with independence and daily functioning (in contrast to dementia)
- In HD patients: 30-60% have MCI, 14% have dementia



Tamura et al. Kidney Int 2011 79:14–22; Mc Adams-De Marco CJASN 2018

Murray et al. 2006: 374 HD patients

- Mean age 71 years
- Dialysis vintage 33 months

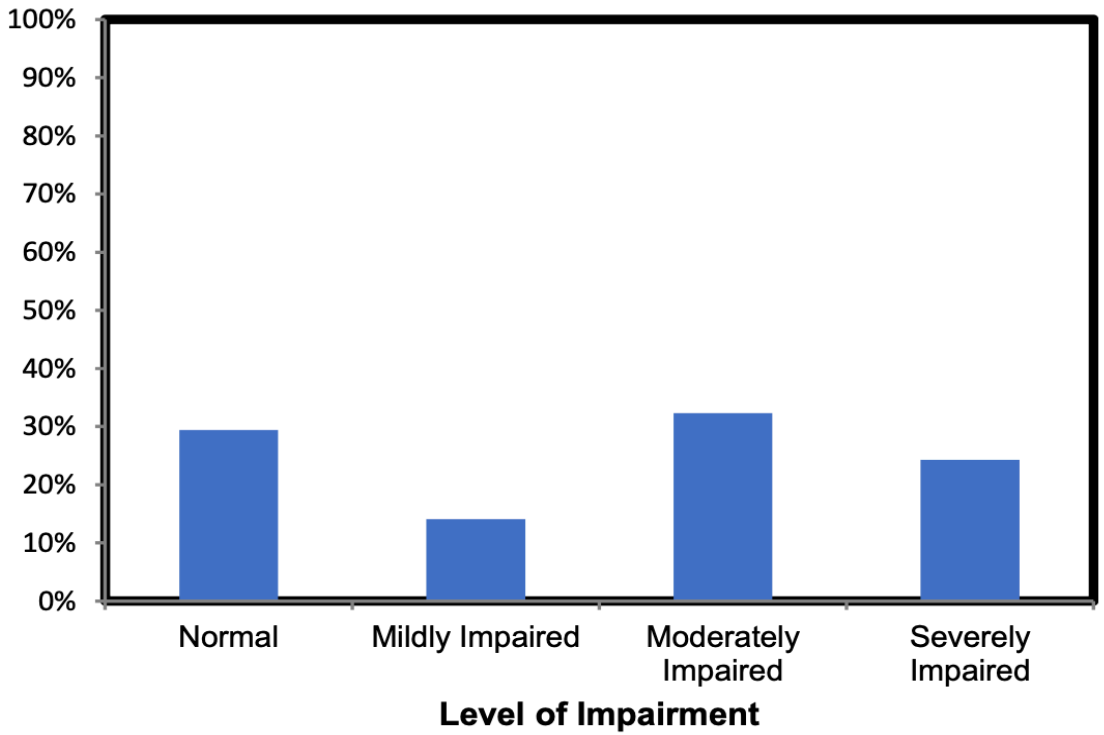


Similar findings by Drew et al. (2020)

Murray et al. Neurology 2006; 67:216-23; Drew et al. JASN 2020;31:855-864

Acceleration of CI & damage after HD initiation

- **314 patients of HD**
- **Only 30% of HD patients had intact cognitive performance**



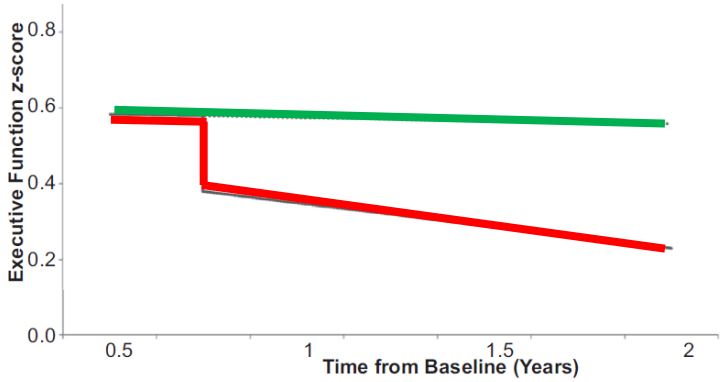
Sernak MJ et al Neurology. 2013;80(5):471-480

Loss of executive function after dialysis initiation in adults with chronic kidney disease

Manjula Kurella Tamura[1,2], Eric Vittinghoff[3], Chi-yuan Hsu[4], Karman Tam[1], Stephen L. Seliger[5], Stephen Sozio[6], Michael Fischer[7], Jing Chen[8], Eva Lustigova[8], Louise Strauss[9], Rajat Deo[10], Alan S. Go[11] and Kristine Yaffe[3,12]; for the CRIC Study Investigators[13]

Prospective study in CKD patients

- 123 patients: no transition to dialysis
- 37 patients: transition to dialysis, 78% HD

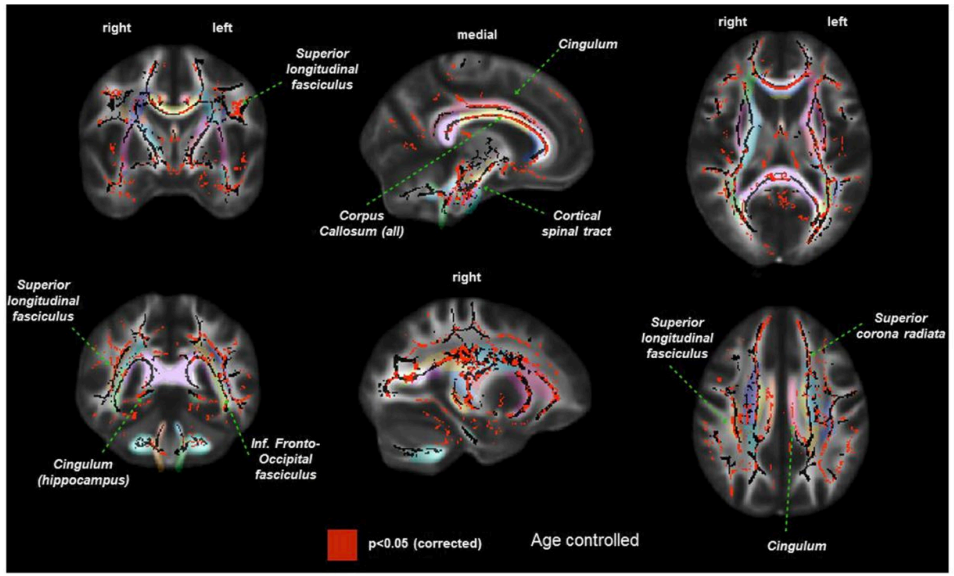


Kurella Tamura et al. Kidney Int 2017;91:948-953

Cerebral damage after HD initiation

White matter damage in maintenance hemodialysis patients: a diffusion tensor imaging study

David A. Drew[1*], Bang-Bon Koo[2], Rafeeque Bhadelia[3], Daniel E. Weiner[1], Sarah Duncan[1], Maria Mendoza-De la Garza[4], Aditi Gupta[5], Hocine Tighiouart[6,7], Tammy Scott[8] and Mark J. Sarnak[1]



Drew et al. BMC Nephrol 2017;18:213, Wesley T. et al. Nephron 2021;145:35-43

Randomized Clinical Trial of Dialysate Cooling and Effects on Brain White Matter

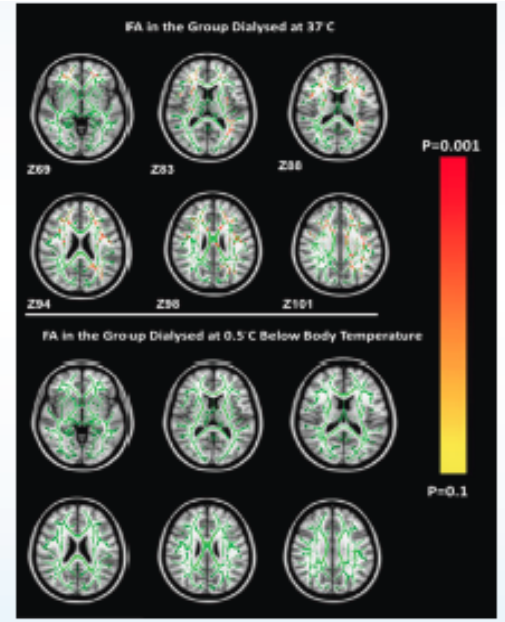
Mohamed T. Eldehni, Aghogho Odudu, and Christopher W. McIntyre

73 incident HD patients were randomised to

- Dialysate temperature 37.0 ℃
- 0.5 ℃ < core temp (min. 36.0 ℃)

Diffusion Tensor Imaging (DTI) to assess brain white matter microstructure at baseline and after 1 year

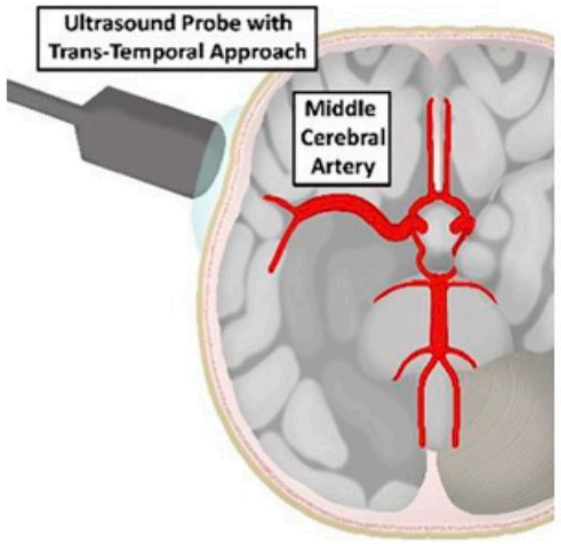
Use of cool dialysate was associated with better hemodynamic stability



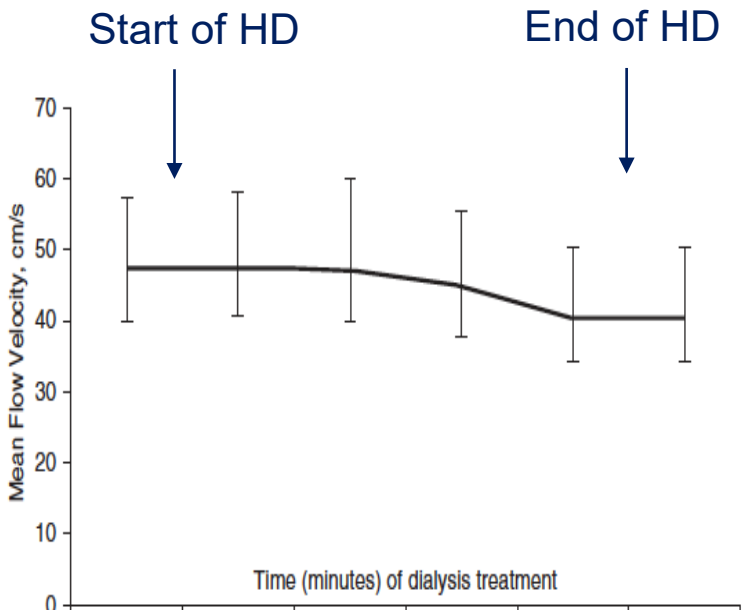
Eldehni et al. JASN 2015;26:957-965

HD related decline in CBF velocity and WM hyperintensities progress

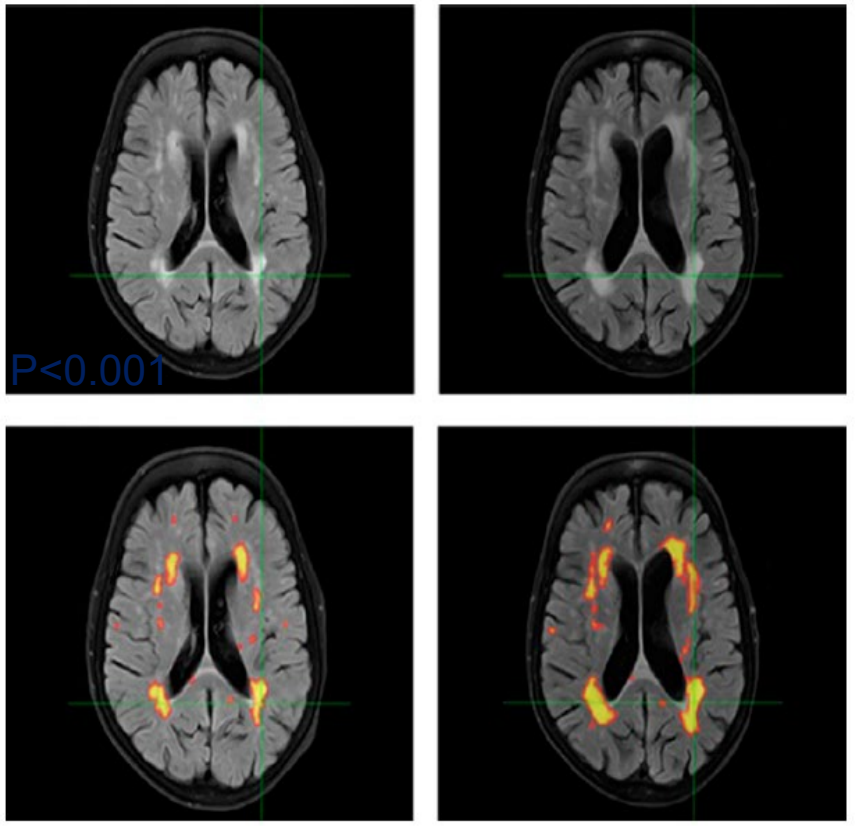
In 82 patients, mean cerebral flow velocity fell from 47 to 40 cm/s (-10%)



Transcranial Doppler ultrasound



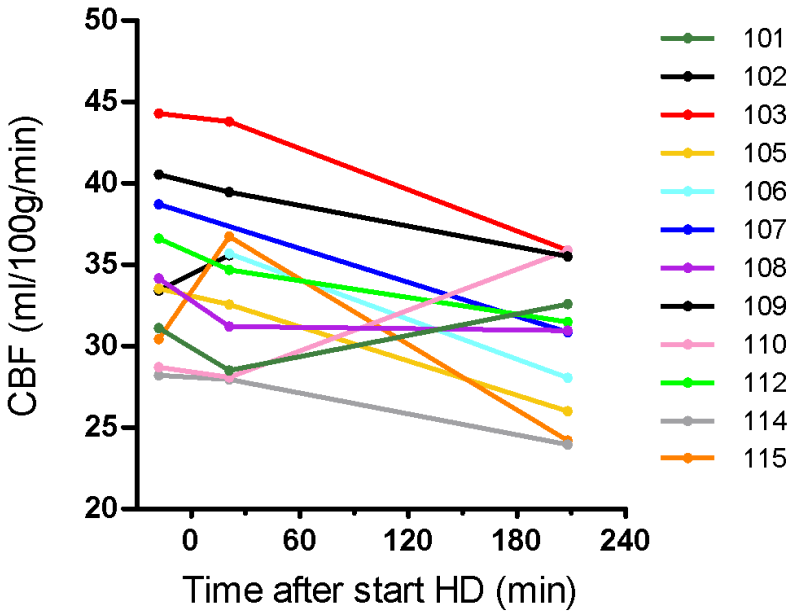
	−15	15	30	90	180	+30
Median MFV, cm/s	47.38	47.38	47.00	45.00	40.25	40.75



Findlay et al. JASN 2019;30:147-158

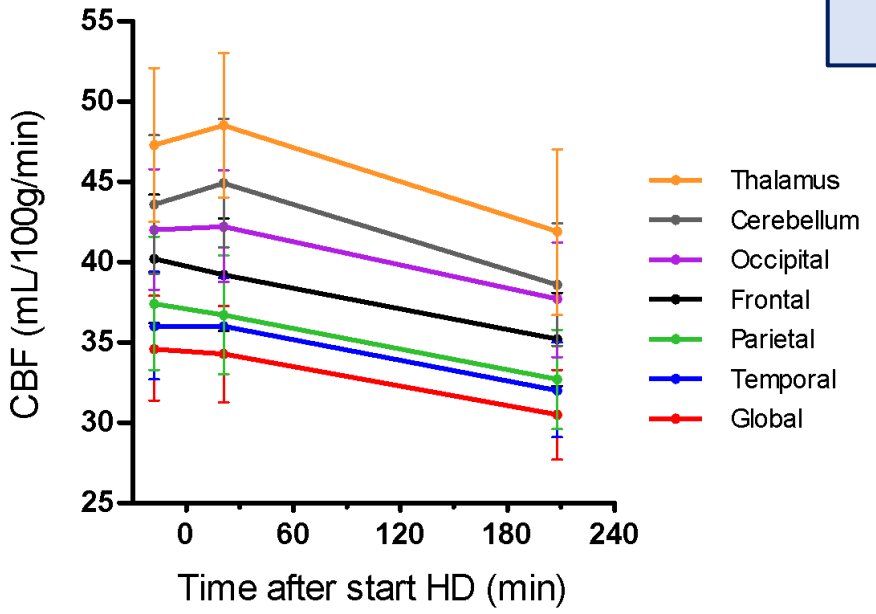
Change in global and regional cerebral blood flow

Global



T1 versus T3: **-4.1** (-7.3 to -0.9) ml/100 g/min
-10.3%; p<0.05

Regional



T1 versus T3: **-9.2** to **-11.3%;** all p<0.05

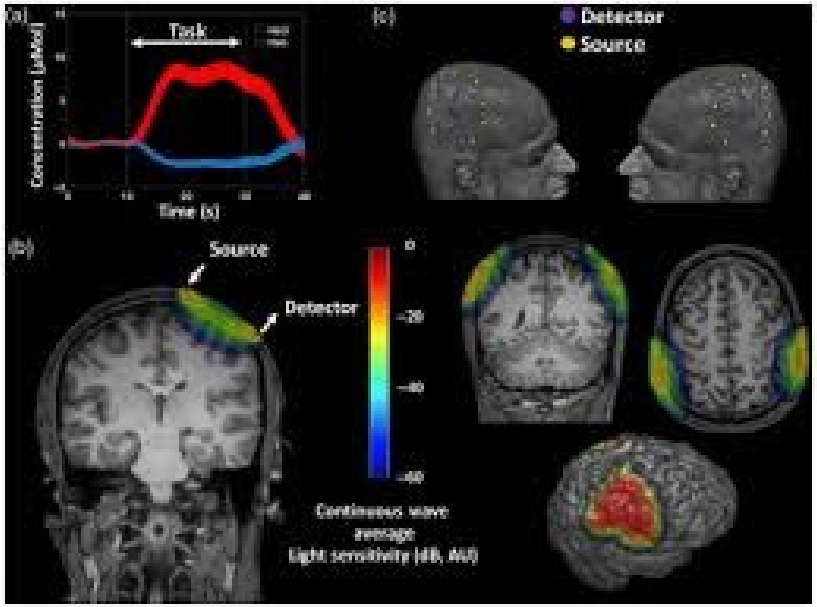
Factors associated with lower CBF:

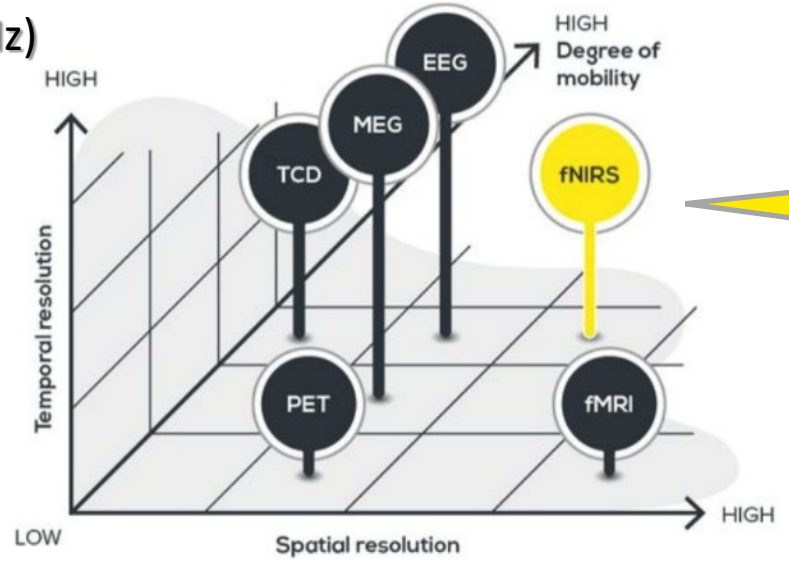
- Higher UF-volume
- Higher tympanic temperature
- Higher blood pH (T2)

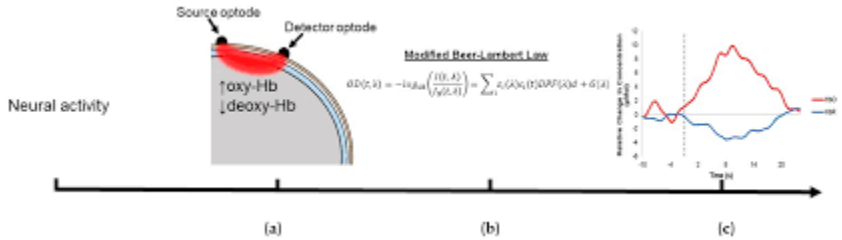
Polinder et al. JASN 2018;29:1317-25

Why use Functional near infrared spectroscopy (fNIRS) on CKD patients ?

- Real time oxygenation evaluation
- Free movement during acquisition
- Handling device and easy to transport
- Low cost and real time neuroimaging
- Good temporal resolution (up to 100Hz)







Non-invasive imaging technology that enables measurement of changes in oxyhemoglobin and deoxyhemoglobin, which reflect local brain activity.

=

- Non-invasive
- Excellent resolution
- Real-time signaling

Ciências ULisboa

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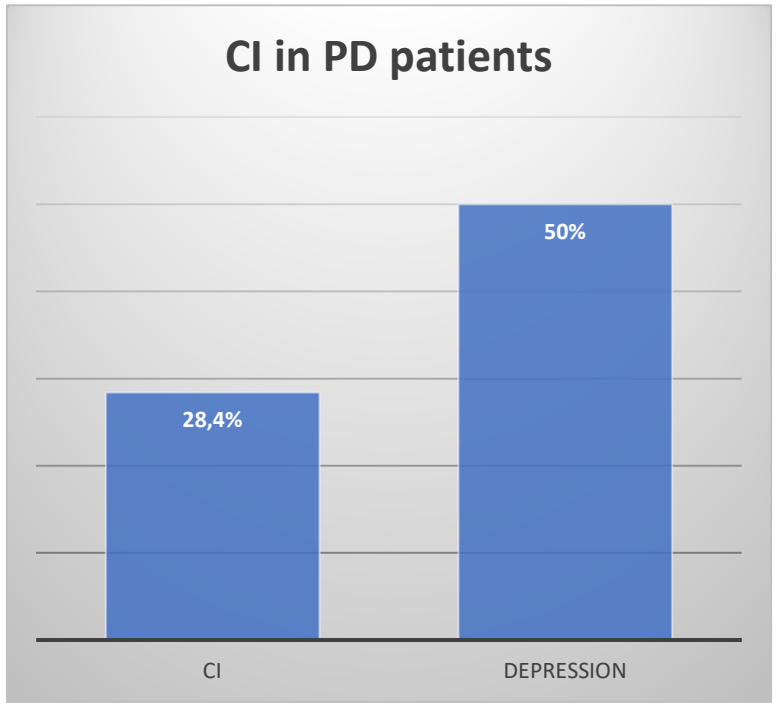
Prof. Alexandre Andrade

CI in Peritoneal Dialysis patients

Meta analysis incuding 8 studies from 1980-2019 of **1736 patients** showed **CI prevalence in 28.7%**

In a multicenter cross-sectional PD researction of **459** patients **28.4% had CI** and 52% with depression

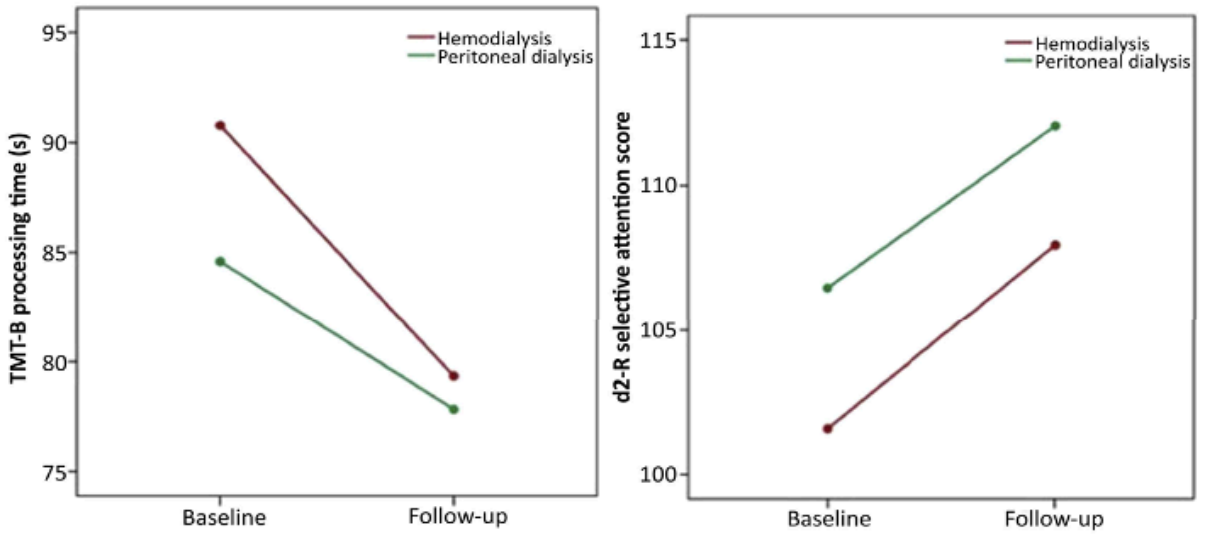


SHEA YF et al. 2019,Springer
SHEA YF et al. 2016 - VOL. 36, NO. 3

Cognitive Function in PD VS HD

- **271** patients at baseline and after **1 year**

- Two of the CI tests done(**TMT-B & D2-R**) showed better cognitive function in PD patients than in HD patients at baseline and after 1 year



TMT-B: lower scores = better CF
d2-R : higher scores = better CF

D Neumann et al. *Kidney International* 2018 93430-438

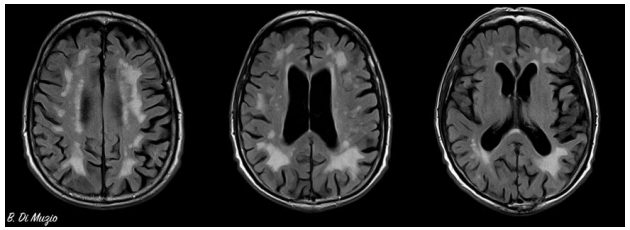
SUMMARY

CI prevalence is extremely high in HD patients

HD initiation seems to accelerate decline in cognitive function & increase progression of damage

Cognitive function declines faster in patients on HD compared with PD

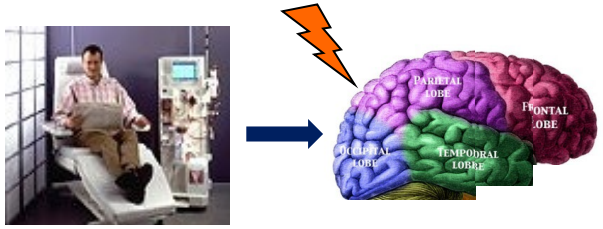
Background damage



Related to:

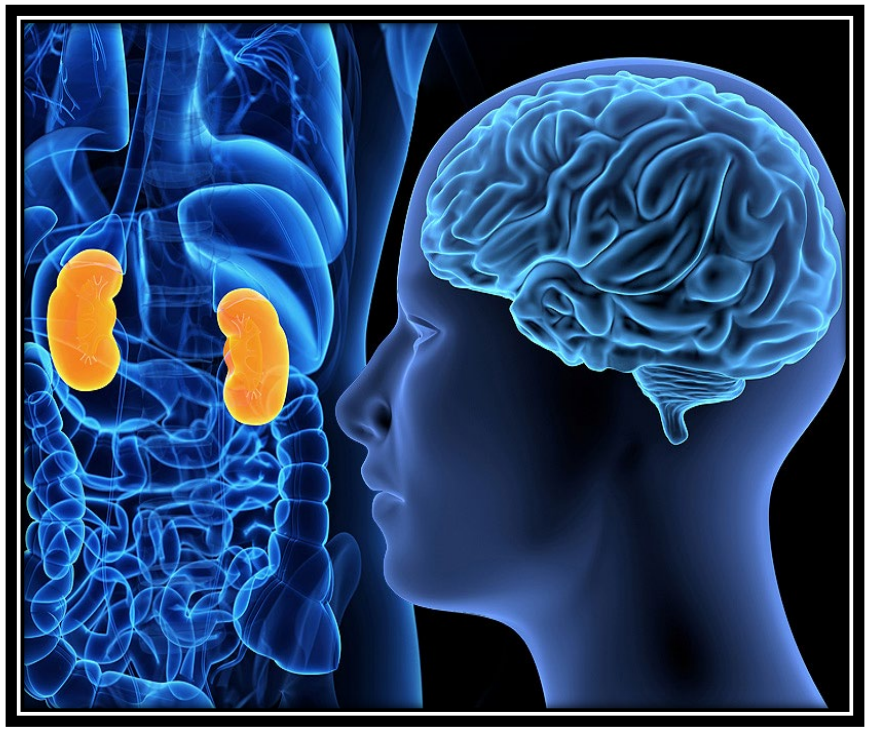
- CV co-morbidity
- Duration & severity of CKD

Hemodialysis-related:



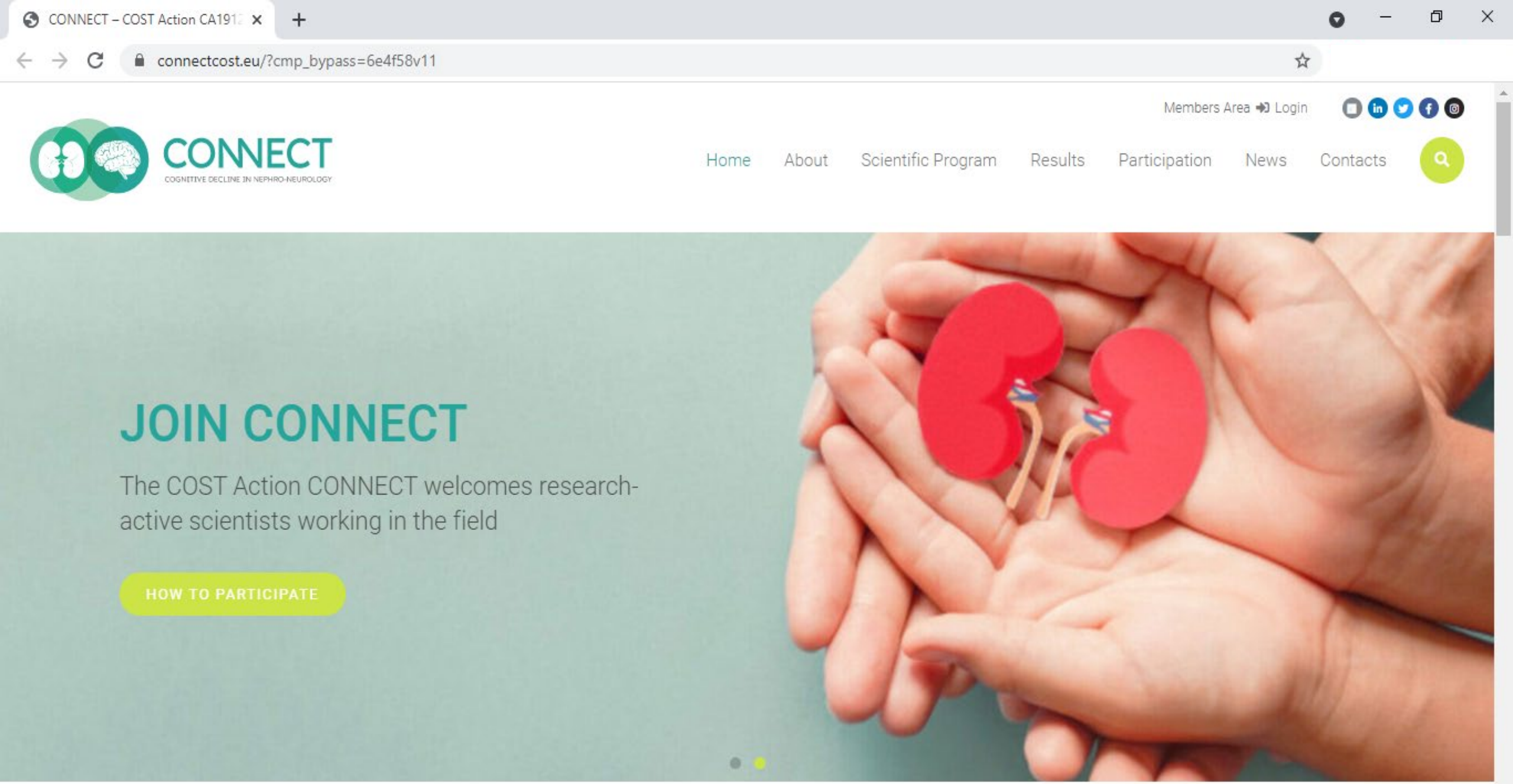
Iyasere et al. Clin Kidney J 2017;10:89-94
Neuman et al. Kidney Int 2018;93:375-89

SUMMARY



1. Significant alteration in white matter integrity is observed in HD patients
2. HD causes change in global and regional cerebral blood flow
3. Cerebral perfusion decreases in patients under HD
4. Conventional HD reduces cerebral perfusion and probably contributes to ischemic damage and CI
5. Cool dialysate, may attenuate cognitive decline

BIOGEM TRANSLATIONAL NEPHROLOGY LABORATORY



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