Brain function in young patients with chronic kidney disease

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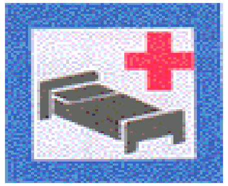
History of V, age 34 – a life with ESKD

- 1987 
- 1989   -> FSGS
- 1990 
- 1992 

-> rejection- > 
- 1993 

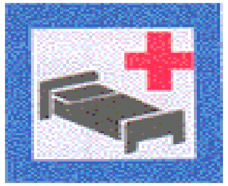
-> FSGS -> 
- 1997 

History of V, age 34 – a life with ESKD

- **1997**    HD 4x3 hrs

History of V, age 34 – a life with ESKD

- **1997**



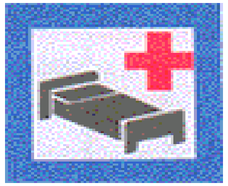
HD 4x3 hrs

- **1999**

HD 6x2.5 hrs

History of V, age 34 – a life with ESKD

- **1997**


HD 4x3 hrs

- **1999**



HD 6x2.5 hrs

- **2004**



HD 6x8 hrs


V>2004: “Continuous brainfog”

- V: nocturnal home dialysis ->" **as if the fog disappeared"**:
    - better concentration
    - better memory
    - more clear view on what is happening
    - less fatigue

- upgrade school level -> nursing school -> psychiatry nurse, practices as nurse & gives education courses

- 2018 3rd tx -> FSGS -> PE

The problem:
cognitive performance in CKD at childhood

- SA: IQ 73 vs. 95 in 30 ESKD children[1]
- CKiD[2-6] studies on large population, mainly mild CKD
  - CKD 1-4: normal IQ, subtle abnormalities executive functioning (mathematics)
  - CKD4+: problems **working memory, attention and executive function**
  - Factors:
    - Young age onset?
    - Anemia?, high blood pressure? High FGF-23[6]?
    - unsuspected genomic disorders->most significant in high educated mothers[4]

Al Shahawy ea Saudi J Kidney Dis Transpl. 2020[1], Solomon[2] ea, Ped Research 2021, Harsman[3] ea Ped Neph 2019, Verbitsky[4] ea JASN 2017, Harsman/Hooper[5] Ped Neph 2020, Yokoyama[6] ea, Kidney Med 2020, Harting ea AJKD 2018

The problem: late outcome (LERIC study)

IQ 140 patients 20-40y with ESKD at age<15y (2000)

	Difference patients-controls	*95% CI*
Verbal IQ	**-9.7**	**-6.4;-14.7***
Performal IQ	**-9.2**	**-5.0;-13.4***
Full Scale IQ	**-10.4**	**-6.4;-14.5***

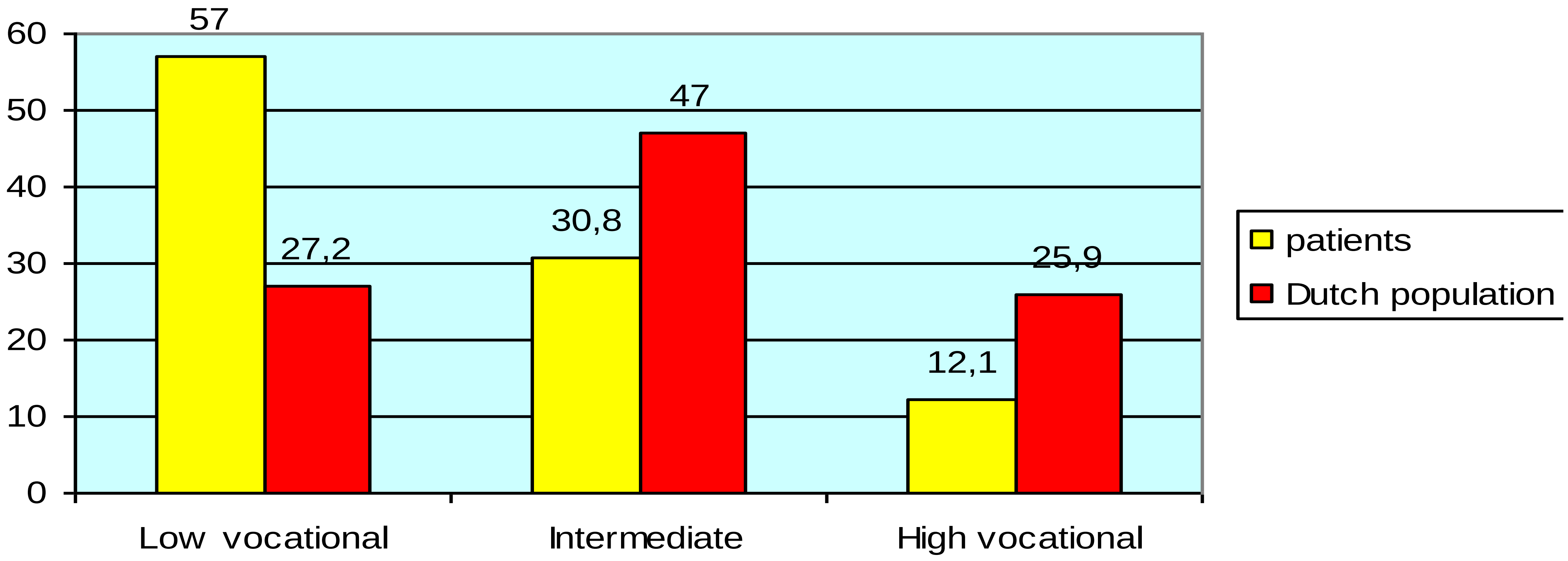
**p<0.0001*

Duration dialysis ≥4 y: Odds 3.0 (1.3;6.6) p<0.01*

Worst scores on tasks that require ***memory, education or general knowledge***

Groothoff ea Arch Dis Child 2001

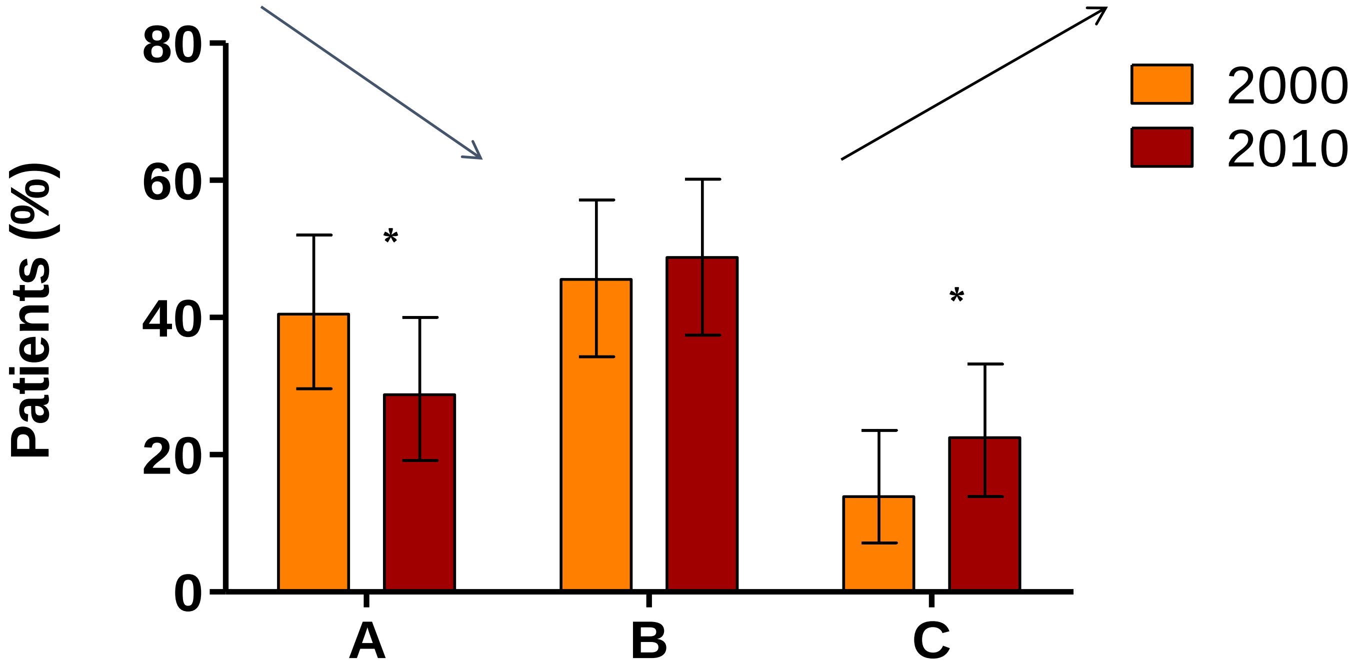
LERIC patients:
Low educational attainment compared to Dutch population



High: HBO, University   *Intermediate: HAVO,VWO, MBO;*   *Low: basic, VMBO, LBO*

Groothoff ea J Pediatrics 2002

Over time (2000-2010): increase in Educational Attainment



A: Low level or primary school

B:Intermediate level vocational training

C:High level educational training/ university

* *P*<0.05

Tjaden et al J Pediatrics 2016

Summary data on cognition in young CKD

- Lower IQ in severe CKD at childhood, persistent in adulthood

- School problems in children with severe CKD: disorders in
  - Global intellectual abilities, **attention, working memory, executive function,**
  - ‘like living mentally in a fog’ (patient comment’s)

- After transplantation, better but for some persistent cognitive dysfunction
- Association with duration dialysis?

Harting ea AJKD 2018

Summary data on cognition in young CKD

- Inconsistent findings
- Unclear nature of brain abnormalities
- Pathophysiology?:
  - “Uremic toxins”
  - Vascular problem?
  - Medication after tx?

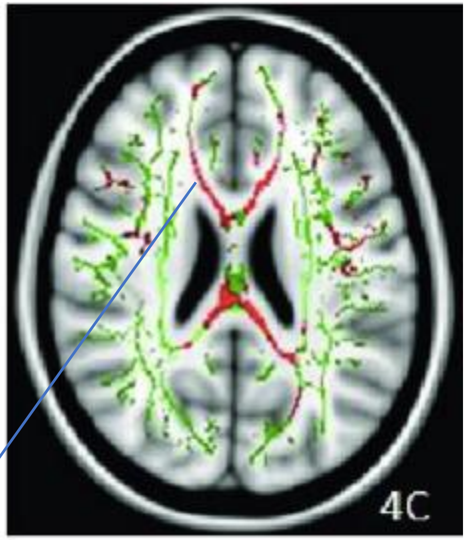
Brain damage in CKD:
Is it a matter of loss of brain volume or network disturbances?

Network function of the brain depends on **organisation of the white matter: <u>depicted by DTI</u>**

Fractional anisotropy (FA) = value 0-1 -> degree of anisotropy of a diffusion process
-> measure of organisation of fiber arrangements, degree of myelination, and axonal integrity

0 = unrestricted to all directions = total dysorganisation

1= diffusion occurs only along one axis = normal



In red area's with decreased FA

White matter organisation predicts good network function brain

- Healthy persons (n=1187)[1]: white matter organisation (FA) is associated with **cognitive performance in all domains** - especially on executive functions & attention (beta 0,155& 0.171) **and with** endurance, measured by walking endurance test

- Low FA predicts cognitive disturbances in patients with white matter lesions[2]

- Lower FA in elderly related to **worse information processing speed and motor speed**[3]

- Low FA in diseases associated with severely impaired cognition (overall IQ Ischemic Moyamoya disease[4]), **processing speed defect & working memory defect** in Schizophrenia[5] & Pyschosis[6]

[1]Opel ea Scientific Reports 2019, [2]Soriano-Raya J Cereb Blood Flow Met 2014, [3]Vernooij JAMA Psychiatry 2009, [4]Lie ea BMC Neurology 2020, [5]Kuchinov ea JAMA Psychiatry, [6] Kristensen Human Brain Mapping 2019

Brain abnormalities in CKD children

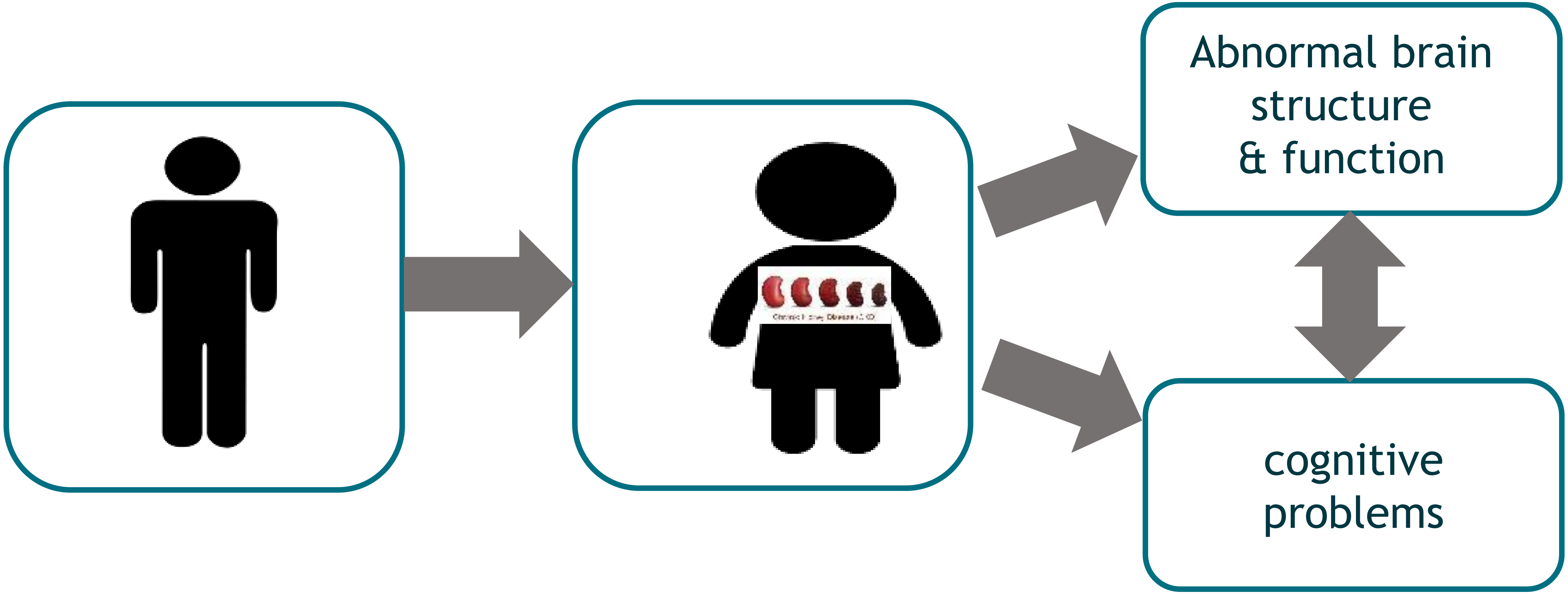
- [1]MRI, n= 85, age 8-25 ,CKD2-5 (tx), no dx ->
  - Lower grey matter volumes & higher White Matter, especially after tx.
  - No association neurocognitive tests N=73, age 9-25, 57 controls, eGFR 45
- [2]DTI n =29, age 14, 19 CKD 1-5, 10 tx -> lower FA CKD & TX group compared to controls, no cognitive tests, no dx patients

[1]Harting ea AJKD 2018, [2]Matsuda-Abedini Ped Research 2018

Questions INPACT study

- To what extent have children and young adults with severe CKD brain anatomic brain abnormalities, related to volume and network function
- Association with cognitive functioning
- Assocation with adaptive functioning & HRQOL
- Impact dialysis & transplantation

INPACT study:
pilot study association brain abnormalities & EEG vs. cognitive functioning in CKD4+



Investigative tools

- MRI
  - brain volumes
  - DTI: White matter integrity = fibre & axon integrity –
- EEG: abnormal patterns consistent with brain damage & dysfunction
- cognitive tests: ANT

Tools cognitive assessment

Cognitive assessment with standard paper-pencil tasks

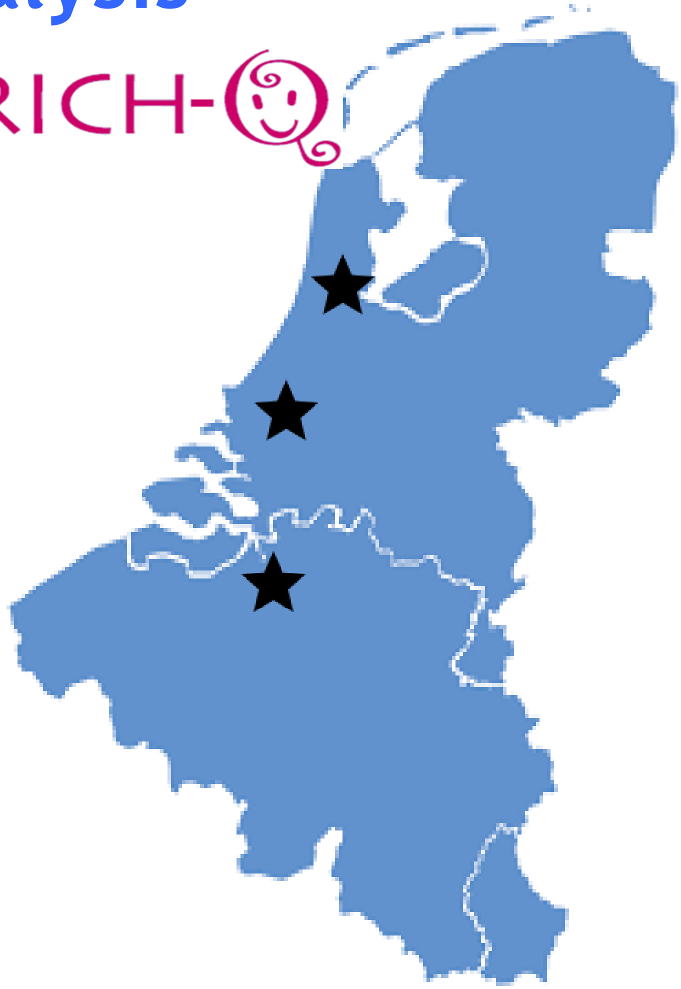
Attentional Network Task (ANT): tests alerting, orienting and executive control

Neurocognitive variables:

- Estimated full-scale IQ (eFSIQ)
- 8 neurocognitive components (created with PCA):
    1. Basic speed and working memory
    2. Fluency
    3. Verbal memory,
    4. Processing speed and control
    5. Switching
    6. processing speed and variability
    7. attention efficiency
    8. interference control

Patients 12 Tx, 8 dx, 8 predialysis

Patients (n = 28)	
	Median (range)
Age	9.1 - 30.5y
Female / Male	N = 9 / 19
Educational level of parents	2.0 (2.0-3.0)
eGFR	26.6 (10.0-90.0)
Duration severe CKD (% of life)	12% (0-81%)
Age at CKD 4-5 diagnosis (years)	14.3 (0.0 – 24.7)
Currently on dialysis	N = 8
Ever treated by dialysis	N = 16 HD = 8; PD = 7; both = 1
Duration dialysis (% of life)	1% (0-49%)
Renal transplantation ▪ Preemptive ▪ Non-preemptive	N = 12 N = 4 N = 4
Time since renal transplantation (% of life)	6% (0-75%)



CKD treatment groups

	Predialysis (GFR < 30)	Currently on dialysis	Transplanted (GFR > 30)
N (total = 28)	8	8	12
Age (median, range)	16.5 (10.1-26.6)	23.0 (9.6 – 27.1)	18.7 (9.1 – 30.5)
Female / male	2 / 6	4 / 4	4/8
Educational level parents	4.5 (3.5 - 7.0)	4.0 (3.0 – 5.0)	5.5 (3.0 – 6.0)
GFR (ml/min/1.73 m^2) *	22.4 (11.3 – 29.0)	<15**	51.2 (31.0 – 90.0)
Total duration CKD4-5* (months)	6.5 (1.0 – 99.0)	31.5 (3.0 – 145.0)	45.0 (8.0 – 270)
Age diagnosis (years)*	16..0 (1.9 – 24.7)	19.9 (9.1 – 24.0)	7.7 (0.0 – 22.8)

*P < 0.01

[a]*GFR of dialysis patients is set on 10 for calculations

Brain volumes:
CKD lower white matter volumes & of several subcortical structures: putamen, hippocampus, N accumbens, pallidum

	Group		Contrasts		CKD treatment subgroup			
	CKD	Healthy control	*p*	*d*	Pre-dialysis	Dialysis	Transplanted	*p*
n	24	21			7	7	10	
Brain volume (cm³)								
Grey Matter [b c]	631.8 (78.4)	667.0 (51.2)	.087	-.52	697.3 (40.6)	588.5 (76.7)	616.4 (75.0)	**.032**
White Matter [d]	542.0 (59.0)	580.7 (55.8)	**.029**	-.67	565.8 (54.0)	536.8 (56.4)	528.9 (64.6)	.056
Subcortical volume (cm³)								

Lijdsman ea, submitted for publication

Brain volumes: treatment effects

Brain volumes:

- **Longer dialysis** duration → 🡻 **grey matter** volume

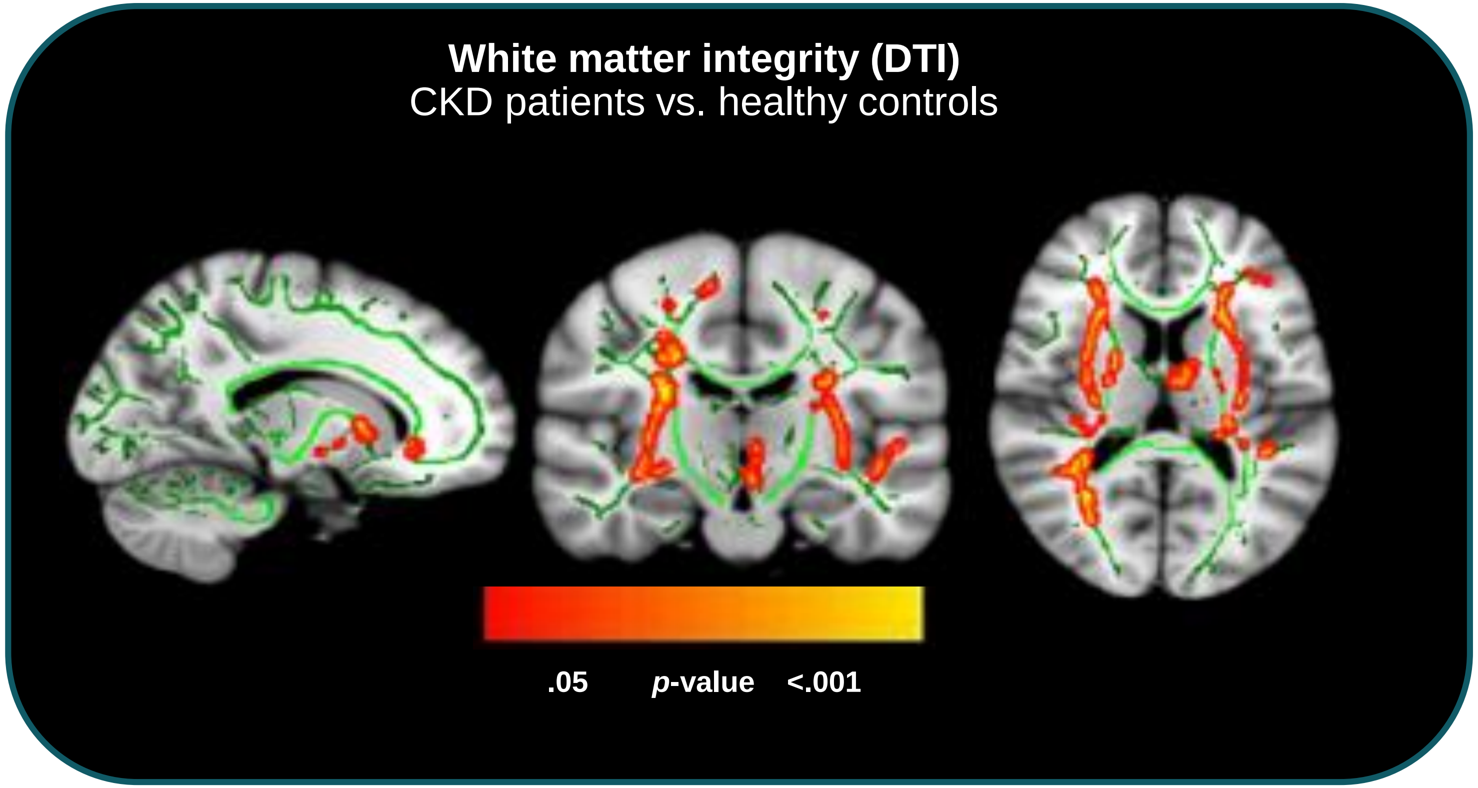
- **Tx & dx** group **smaller volumes of grey matter** and subcortical volumes
  Healthy controls

- Trend for subgroup effect on white matter volume

Lijdsman ea, submitted for publication

DTI outcomes:
lower FA CKD patients vs. healthy controls

Red = areas with decreased FA white matter $p<0.05$ compared to normals



Lijdsman ea, submitted for publication

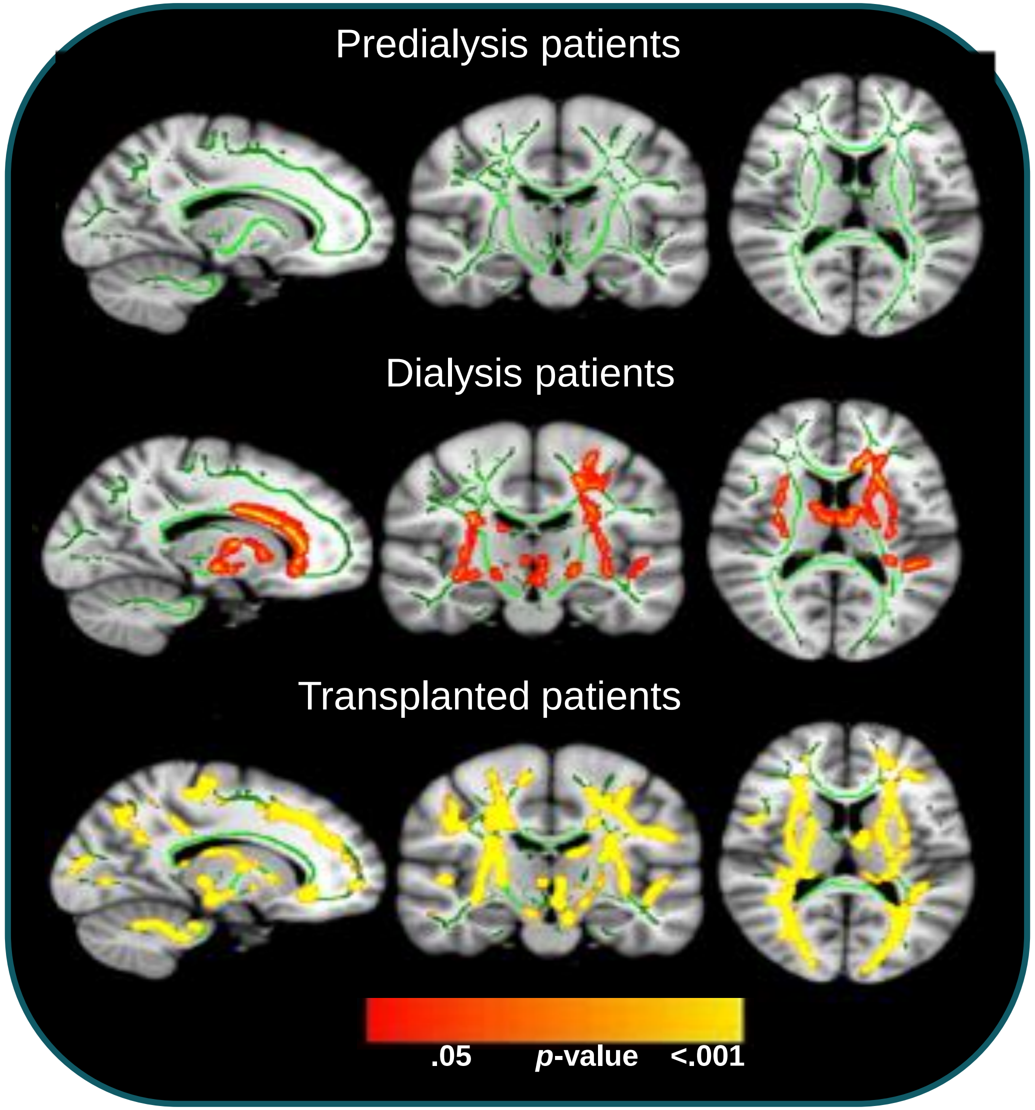
DTI: treatment effects

Longer time since transplantation associated with decreased white matter integrity (lower FA)

Red = areas with decreased FA white matter $p<0.05$ compared to normals

Yellow = areas with decreased FA white matter $p<0.001$ compared to normals

-> tx & dx patients abnormal low FA



Cognitive functioning: results

Lower eFSIQ and worse Basic Speed & Working Memory performance:

- Longer dialysis duration
- Longer time since transplantation
- Older age at diagnosis

No effects of CKD parameters on other neurocognitive components

No significant main effect of type of treatment, but:

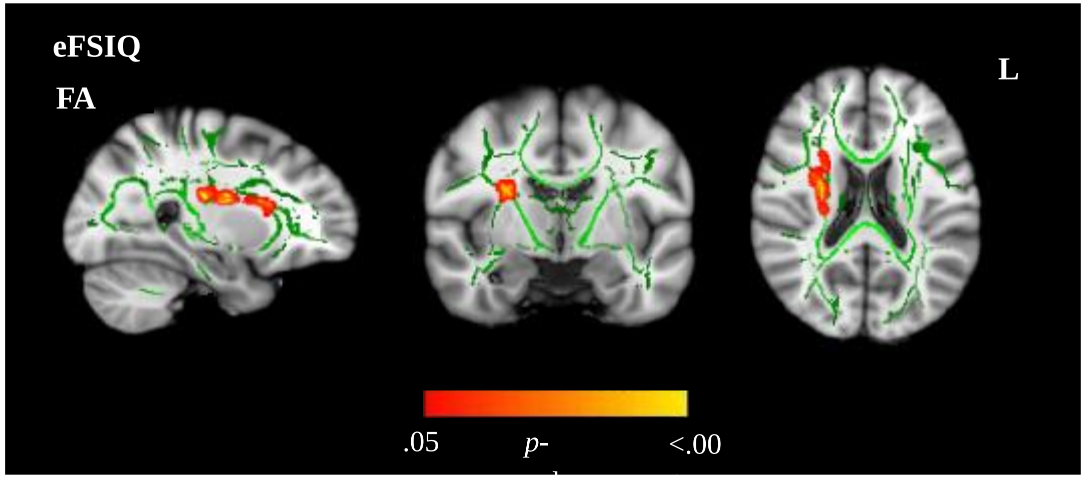
- Trend: eFSIQ of predialysis (eFSIQ=112) > transplanted (95) & Dialysis group (92)
- Trend: Basic speed & Working memory of predialysis group > dialysis group

Lijdsman ea, in preparation

MRI & neurocognition: associations

Lower eFSIQ predicted by:

- lower FA associated with lower eFSIQ in certain regions: superior longitudinal fasciculus, corticospinal tract, anterior thalamic radiation & inferior fronto-occipital fasciculus



Worse performance of Basic Speed & Working memory predicted by Lower grey matter volume in CKD

MRI & Neurocognition: conclusion

Young CKD patients have structural brain abnormalities:

- **Smaller volumes of grey matter and subcortical volumes**
- **Lower white matter integrity**

Longer time on dialysis and since transplantation related to:

- More structural brain abnormalities
- More cognitive impairments

Smaller grey matter volume and CKD-induced white matter abnormalities related to cognitive problems

EEG connectivity:
more direct information on how the brain functions
(preliminary results)

Background

- Different EEG frequency bands:
  - Delta frequency (1-4 Hz) } slow wave frequencies
  - Theta frequency (4-8 Hz) }
  - Alpha frequency (8-12 Hz)
  - Beta frequency (12-30Hz)

EEG analyses methods:

- Clinical assessment
- Power (%): the contribution of a frequency band to the overall power of the signal
- Power correlations (R2): measure of functional connectivity of brain

EEG Literature in CKD: Qualitative analyses

Patients with CKD and other metabolic diseases show:

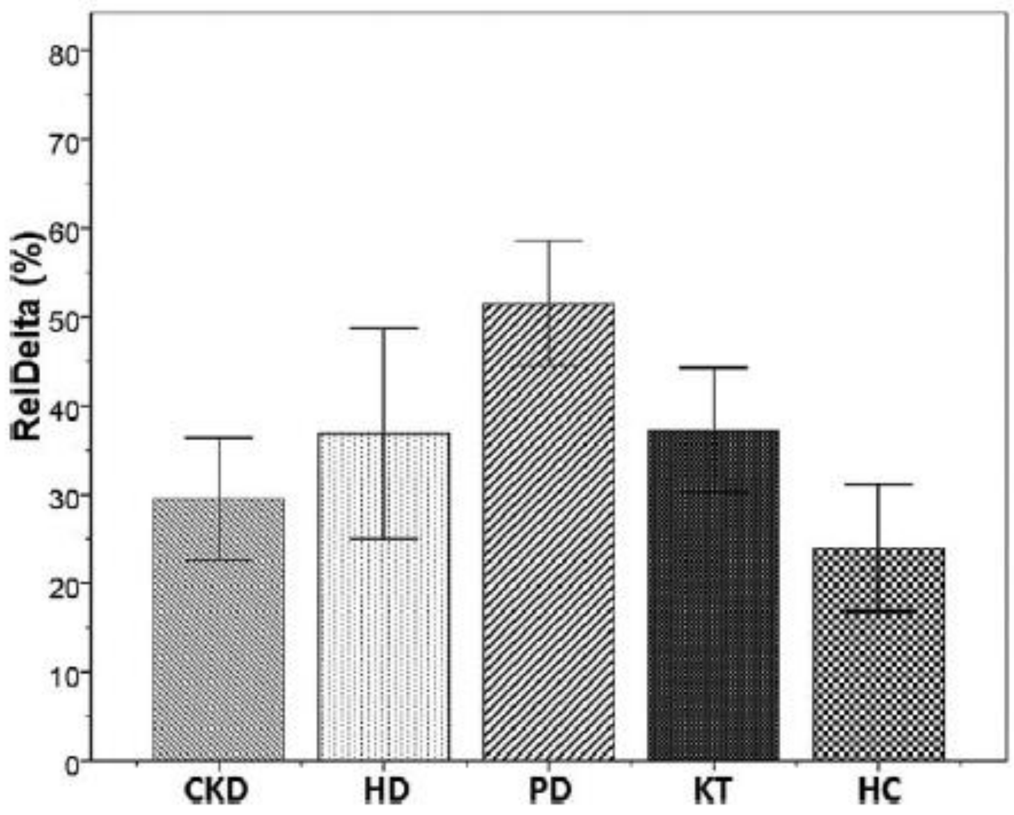
- Generalized slowing of EEG background activity, **specifically increase in slower frequencies (delta and theta)**
- Frontal intermittent rhythmic delta activity **(FIRDA) -> often seen in stroke patients - association with vascular impairment**

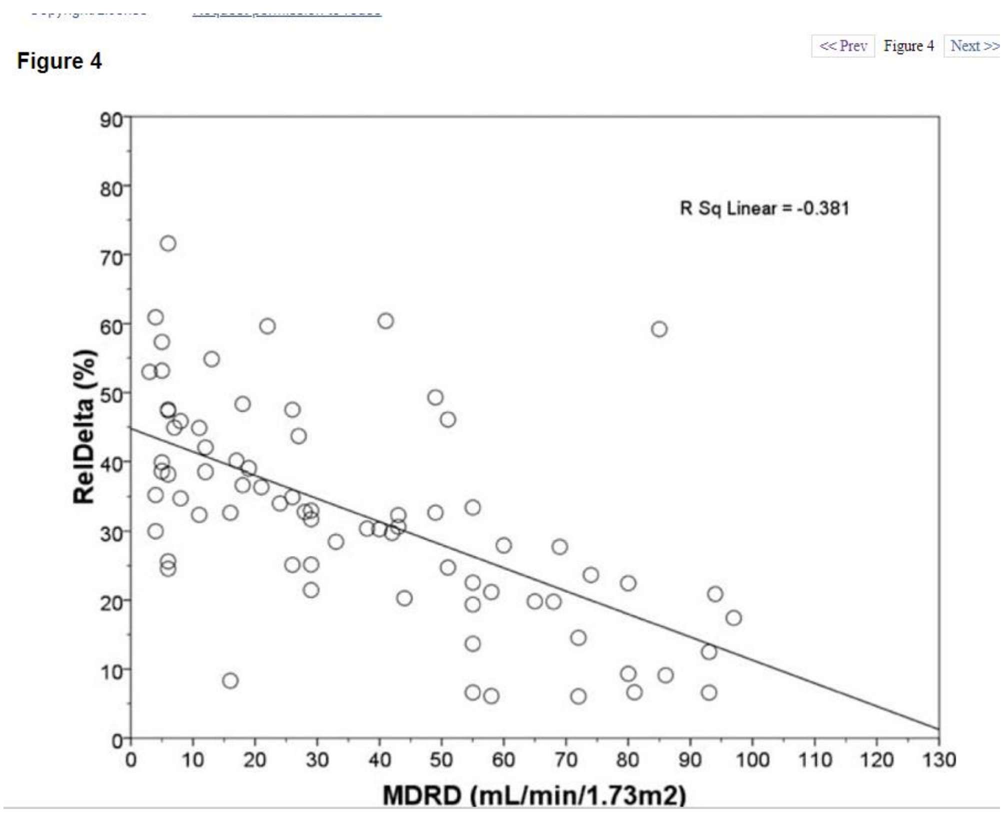
- 1 pediatric study* -> CKD 5 -> **high power slow waves** (theta)

- **No functional connectivity analyses performed in CKD so far.**

Lai et al. Medicine (Baltimore) 2016 ; Rohl et al. 2007; Gadewar P J Clin Diagn Res. 2015 , Abd El Naby Front Paed 2020*

High delta power in PD patients & association with low eGFR





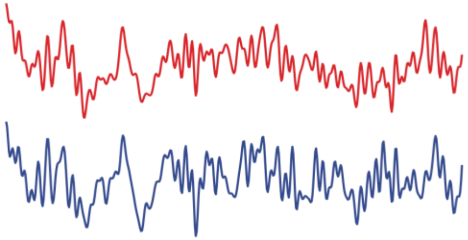
Lai et al. 2016 Medicine (Baltimore) 2016

Methods: Power Correlations, a measure of functional connectivity

Fourier-based Analyses

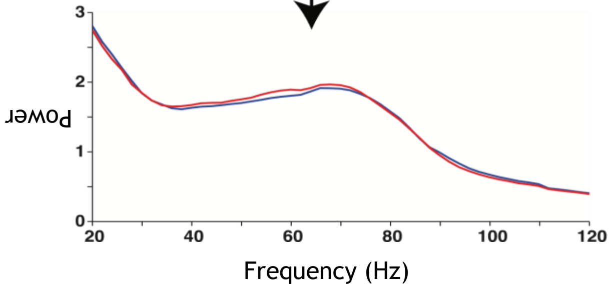
Jean Fourier (1767-1830)

EEG Recordings

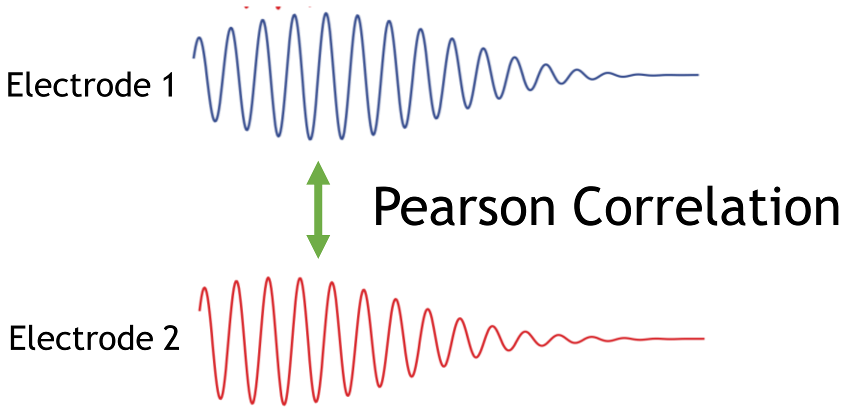


Fourier Analysis

Power Spectrum

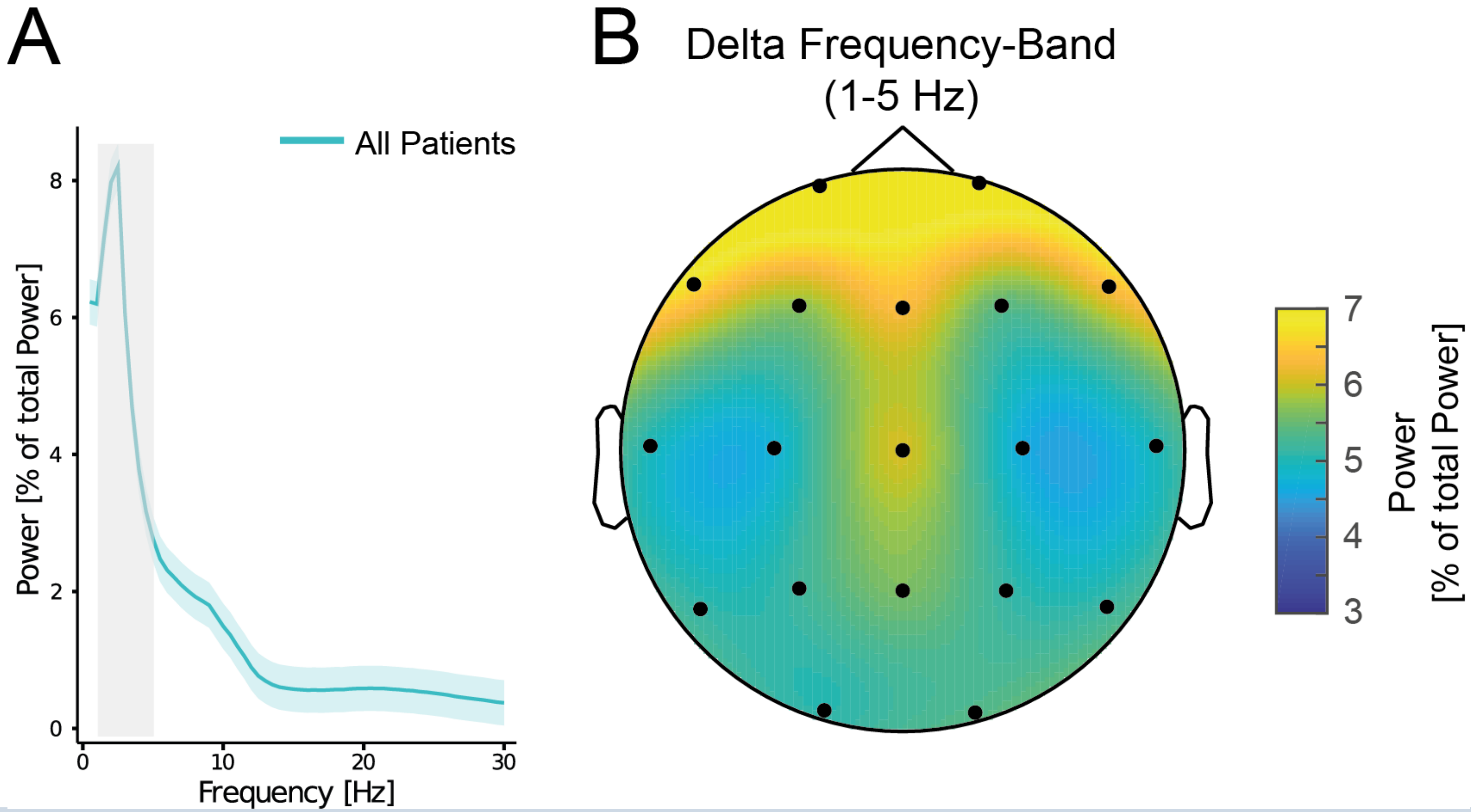


Power (% of total power)



Power Correlation (R2)

EEG outcomes: Power of all frequency bands



EEG: Power correlation (PC)

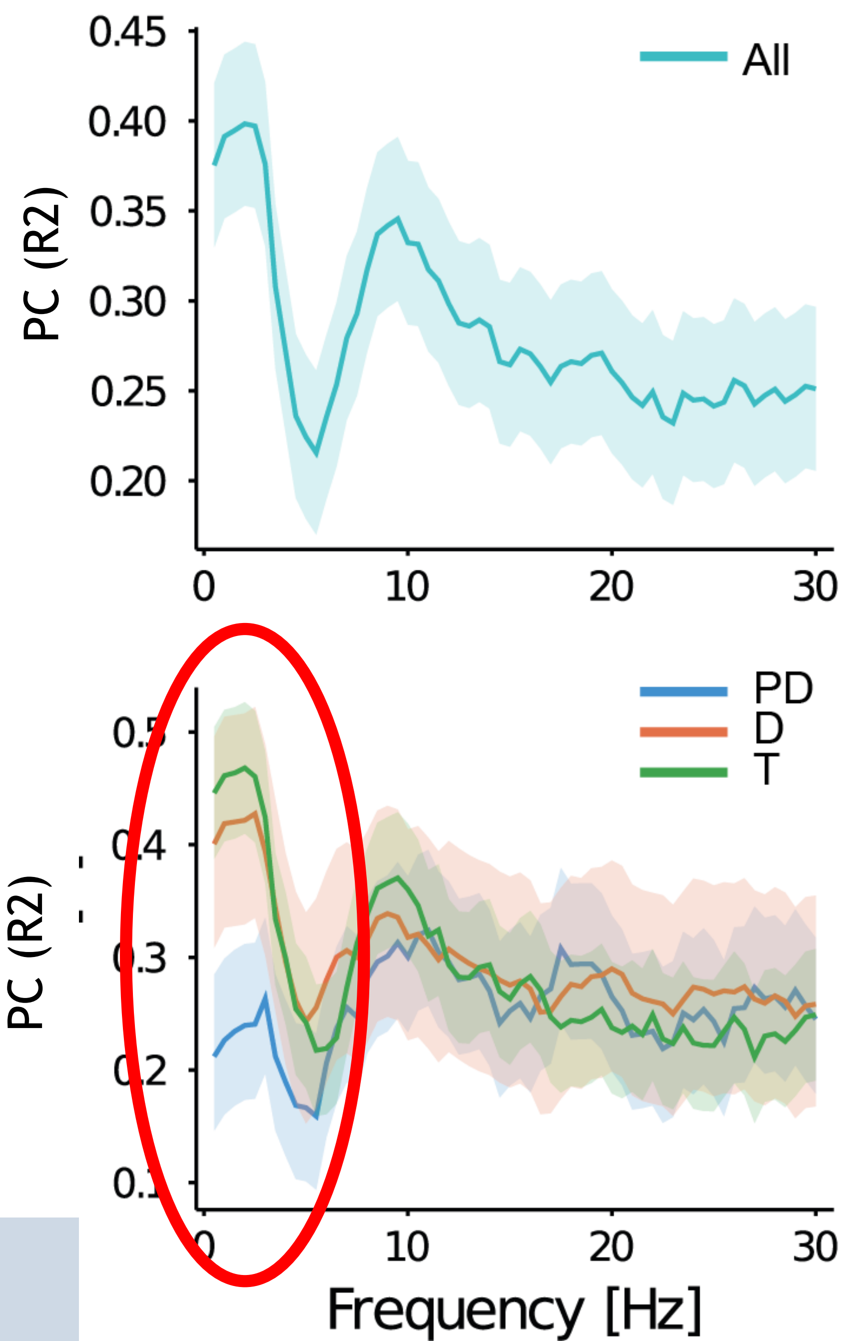
focus on delta frequency

- All electrodes referenced to **frontal** electrodes

Next mixed models: alows to correct for variability between patients and channels**.**

-> increased activity delta waves tx and dx group

- > more Frontal intermittent rhythmic delta activity (FIRDA)



Work in progress: to be assessed coming months

- Association delta EEG activity – cognitive performance, especially attention
- Assocation HRQOL & adaptive functioning

High delta rest activity:
what could it mean for brain function?

- Non-rapid eye movement sleep, sleep walking
- Associated with metbolic derangement (uremia? inhibition of GABAA receptor)
- Adult CKD patients: associated with adverse scores on **hysteria, cynical responses & paranoia, emotional alienation & depression** (*P*=0.016)

Conclusions on brain function in young CKD patients

- Severe CKD -> high risk for **attention disorder, overall lower IQ, working memory disorder & problems executive functioning**

- Brain volume abnormalities & white matter integrity disorder **in both tx & dx patients**, associated with cognitive dysfunctioning to a certain extent

- **High frontal delta activity** & Frontal intermittent rhythmic delta activity **(FIRDA)** in **tx and dx patients -> impact?**

Brain damage in CKD: Uremic or vascular?

- **Association low FA and vascular damage:**
  - Aortic Stiffness by PWV & White Matter Microstructural Integrity assessed by DTI: The ARIC-NCS

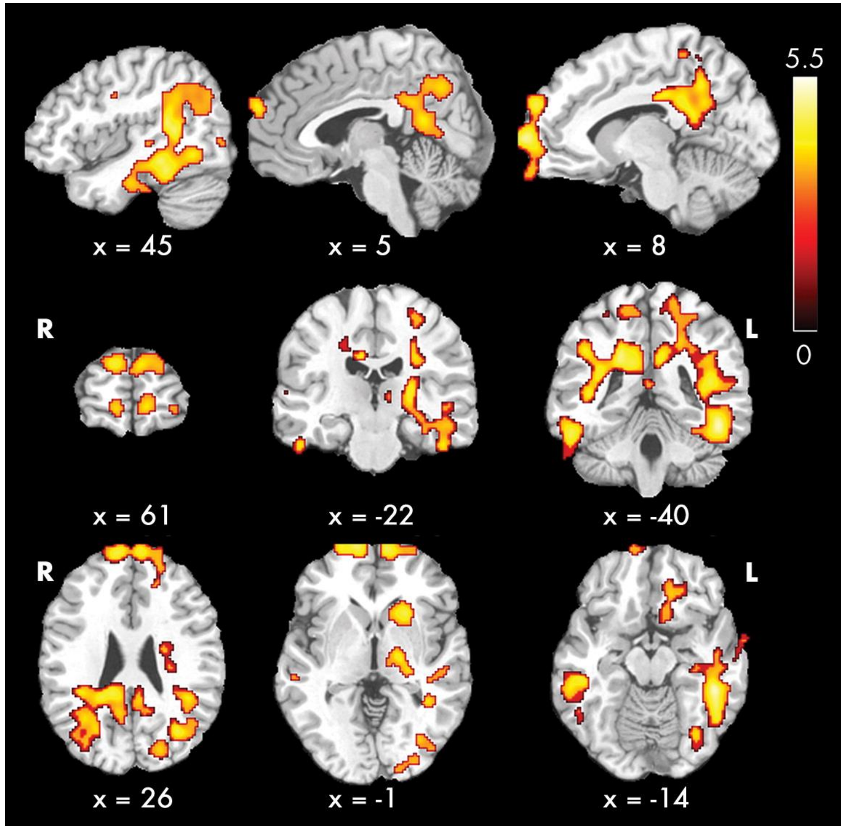
  -> **vascular stiffness strongly associated wit low FA white matter** in 1484 seniors (age 76)[1]

- Frontal intermittent rhythmic delta activity (FIRDA) -> often seen in stroke patients - association with vascular impairment[2]

- **Equal DTI abnormalities in tx and dx, also in pre-emptive tx**

-> All outcomes seem **more related to vascular impairment than uremic toxins**

Regional Cerebral Blood Flow in Children & Young Adults with CKD



- 73 CKD, age 9-25, eGFR 40 & 57 controls
- MRI arterial spin labeling
- cognitive performances assessed
- **Altered White matter CBF related to blood pressure** -> altered cerebrovascular auto regulation

Voxel-wise group comparison of cerebral blood flow (CBF) after removal of effects of hematocrit level, age, and sex.
Contrast shown demonstrates regions where CBF in patients with CKD is greater than that in control. There were no regions where control subjects showed greater CBF than patients with CKD. Color bar indicates *t* scores. *x, y, z* = coordinates in Montreal Neurological Institute (MNI) space.

Liu H et al Radiology 2018

Radiology

Association altered CBF in CKD children & loss of executive functioning

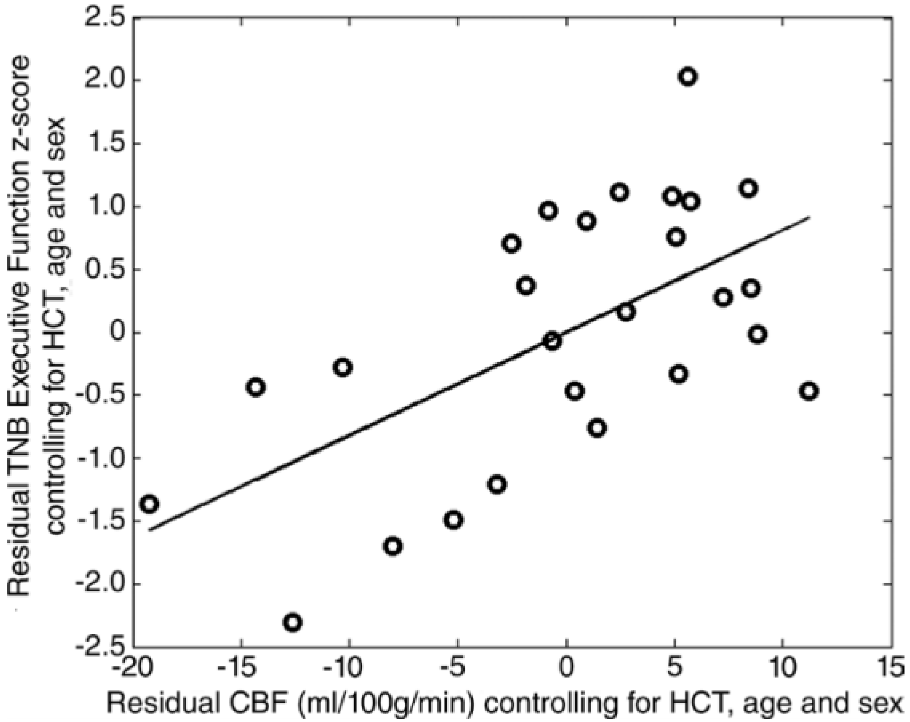
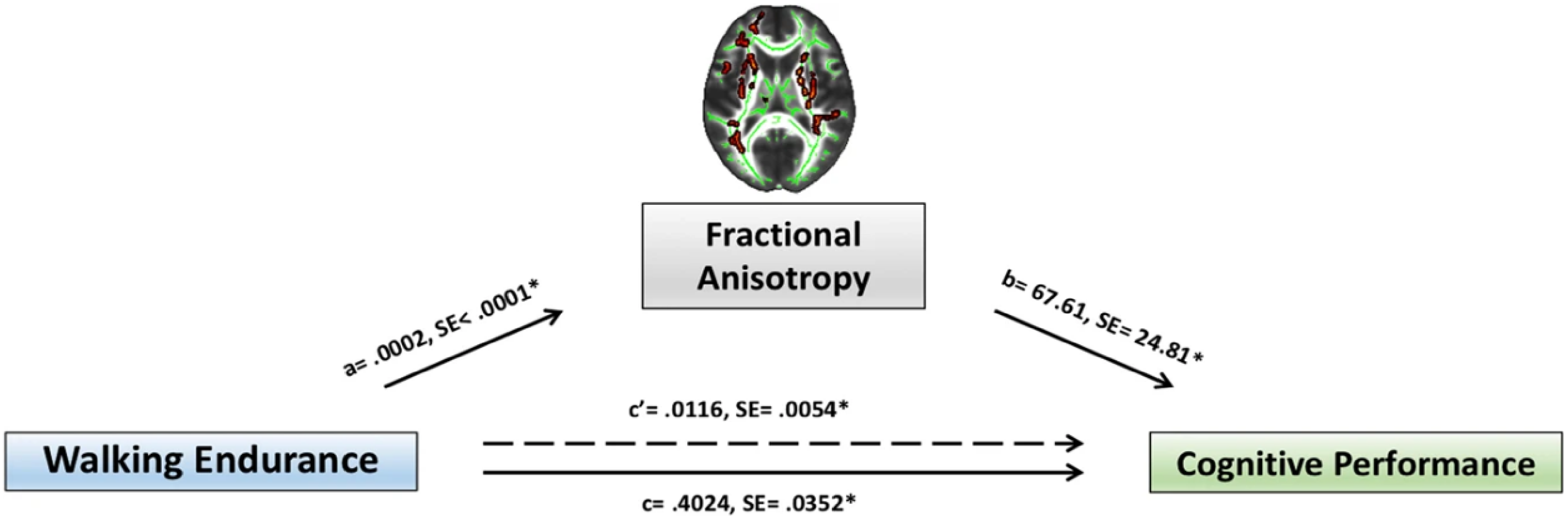


Figure 3: Scatter plot shows partial residual values of precuneus cerebral blood flow (CBF) and executive function in patients with chronic kidney disease with presence of positive extrema CBF, indicating significant correlation between precuneus CBF and executive function after controlling for hematocrit (*HCT*), age, and sex ($\rho = 0.608$, $P = .001$). *TNB* = traditional neurocognitive battery.

Liu H et al Radiology 2018

Sport intervention?

White matter microstructure mediated the association between physical fitness and cognition in healthy young adults[1]



Fractional anisotropy mediates the association between walking endurance and cognitive performance. Depiction of the applied mediation model: Unstandardized coefficients and standard errors for each path of the mediation model are presented. Note that c represents the direct effect and c' the indirect effect. * indicates significance at $p < 0.05$.

[1]Opel ea Scientific Reports 2019

Research agenda

- Reproducibility in large CKD 4+ & tx group
- Impact of calcineurine inhibitors and hypertension on outcomes in tx
- Impact of pre-emptive vs. non-pre-emptive transplantation
- Impact of exercise programs on improvement of cognitive function

Session 10
Neurocognitive dysfunction in pediatric kidney disease
Chairs: **Rukshana Shroff, Marsch Konigs**
State of the Art
Brain structure and function in children and adolescents with kidney failure **Sophie Lijdsman**
State of the Art
Learning from disease models **Marsh Konigs**
Invited Lecture
Kidney Fog: a patient's perspective **Vincent Moolenaar**
oral communications
oral communications
State of the Art
Are my kidneys bad for the brain? **Stephan Hooper**

Questions?

Amsterdam UMC
Universitair Medische Centra

Work in progress: Mixed Models

- allows to correct for variability between patients and channels