University of Iowa
Stead Family
Children's Hospital

Leveraging Neuroimaging To Understand Brain Structure And Function In Pediatric ESKD

Lyndsay Harshman, MD MS

Associate Professor

Medical Director, Pediatric Kidney Transplant

University of Iowa Stead Family Department of Pediatrics: Nephrology, Dialysis, and Transplantation

@HarshmanLyndsay




CURRENT/RECENT SUPPORT – Lyndsay Harshman MD

University of Iowa Stead Family Children's Hospital

Grant/Research Support	NIDDK R01 (R01 DK128835-01, 2021-2026) NIDDK K23 (2016-2021) Children's Miracle Network Grant - University of Iowa (2022) HAWK-IDDRC Grant (2022)

ROADMAP FOR TODAY – buckle up!

University of Iowa
Stead Family
Children's Hospital

- Focus today is largely on hemodialysis populations

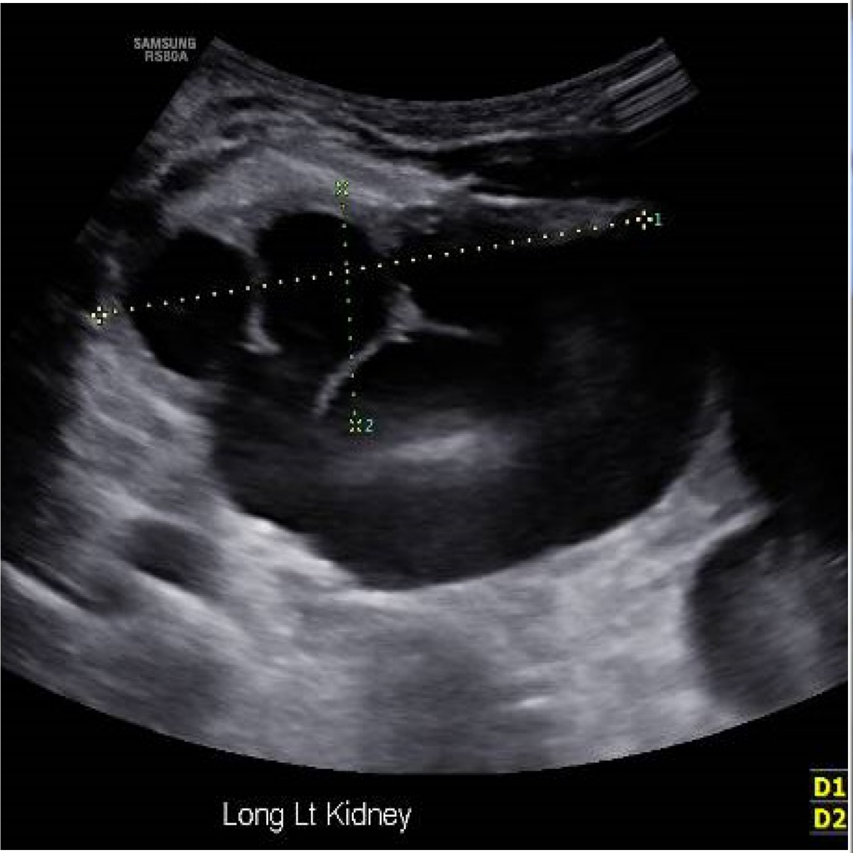
- Much more abundant adult data on the topic of cognition & neuroimaging in ESKD
  - *Where available, high-quality pediatric data will be discussed*

OUTLINE

University of Iowa
Stead Family
Children's Hospital

1. Lifespan approach to pediatric end stage kidney disease (ESKD)
2. Why the brain in a "non-neurological" disease?
3. What is known about brain function (cognition) and structure in the ESKD population?

Etiology of pediatric ESKD – *a lifespan issue*



Harshman LA et al. *Peritoneal dialysis in an extremely low-birth-weight infant with acute kidney injury*. Clin Kidney J. 2014
Images published with permission from family

Today’s talk is RELEVANT

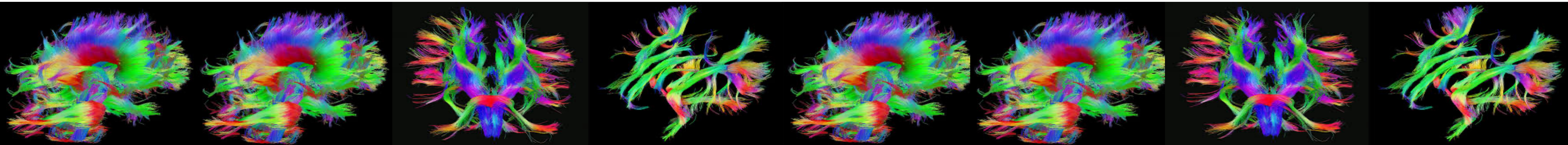
University of Iowa Stead Family Children’s Hospital

CKD is a life-long disease process

- Transition from early-stage CKD to dialysis dependence and subsequent transplant

- Understanding neuroimaging in parallel to CKD/ESKD lends an opportunity to provide critical interventions
  - Medical adherence (*…fluid & nutrition restrictions!*)
  - Educational/career outcomes
  - Health-related quality of life

The Human Connectome Project



OUTLINE

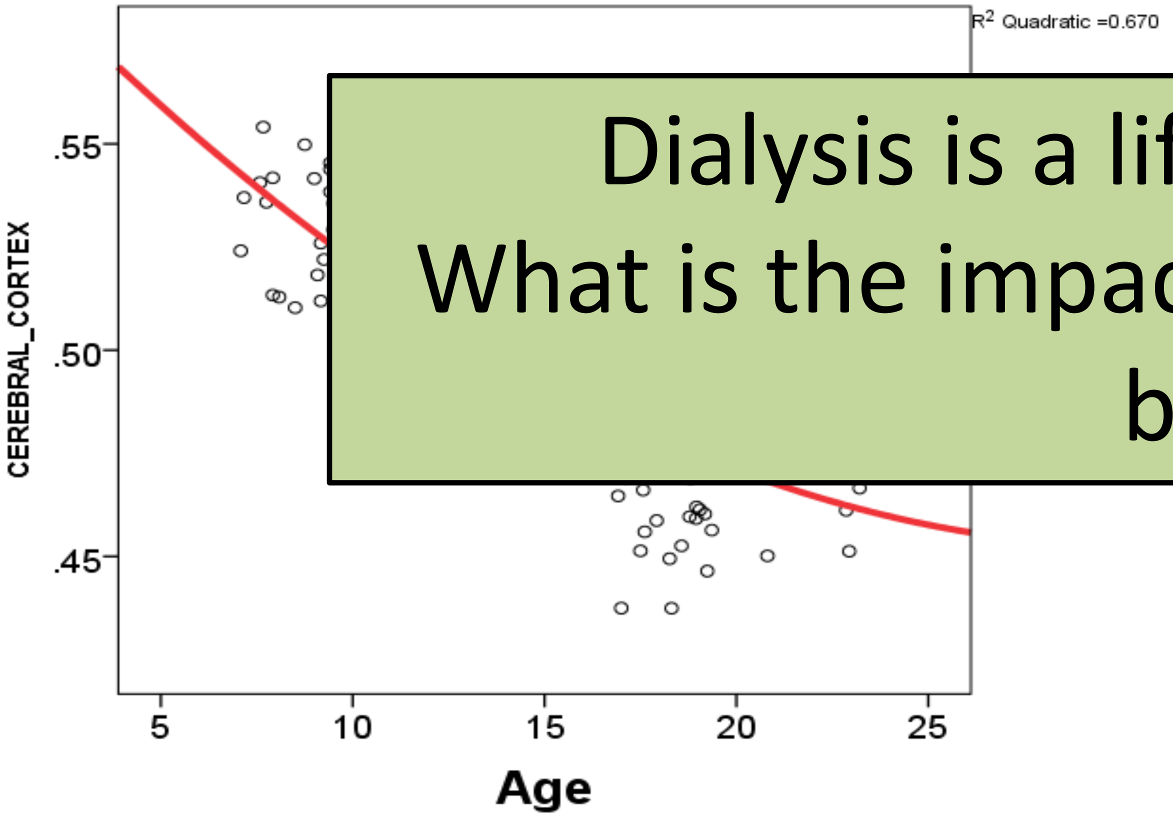
University of Iowa Stead Family Children's Hospital

1. Lifespan approach to pediatric end stage kidney disease (ESKD)
2. Why the brain in a "non-neurological" disease?
3. What is known about brain function (cognition) and structure in the ESKD population?

Brain development is a prolonged process

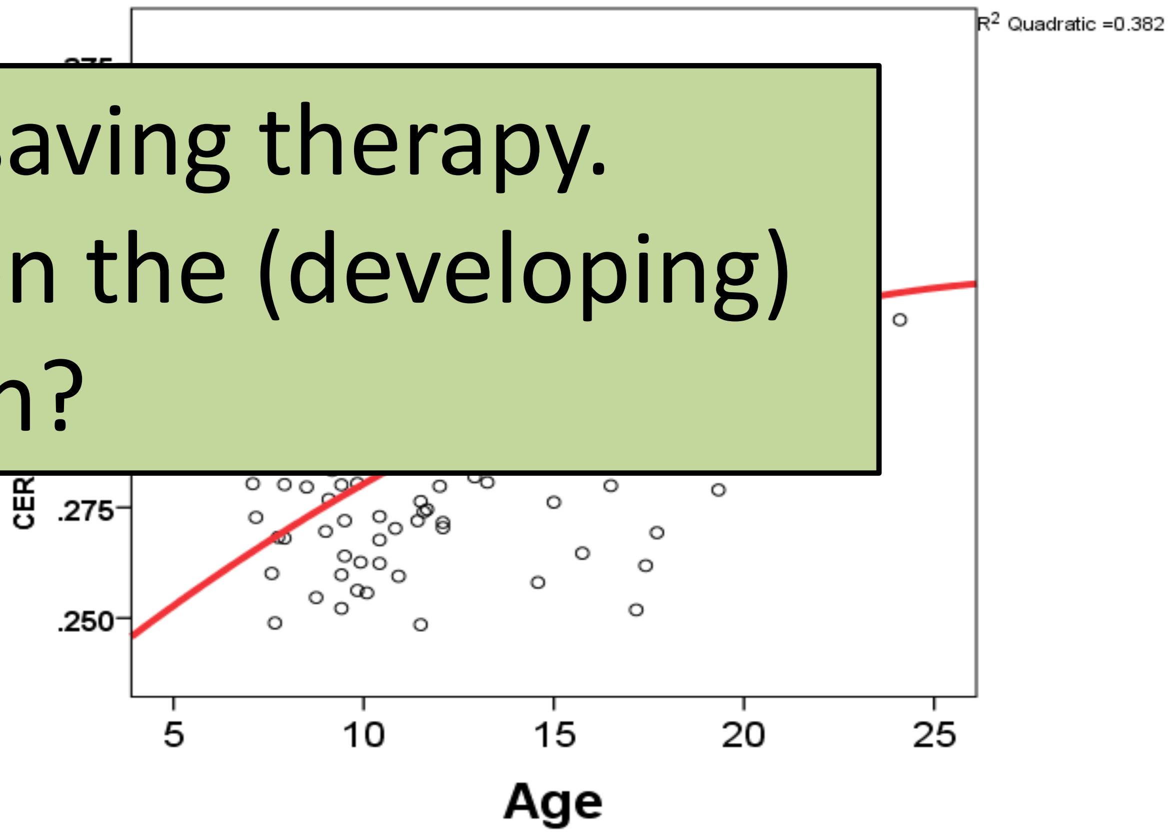
University of Iowa
Stead Family
Children's Hospital

Cerebral Gray Matter (Cortex)



Programmed Synaptic Elimination

Cerebral White Matter



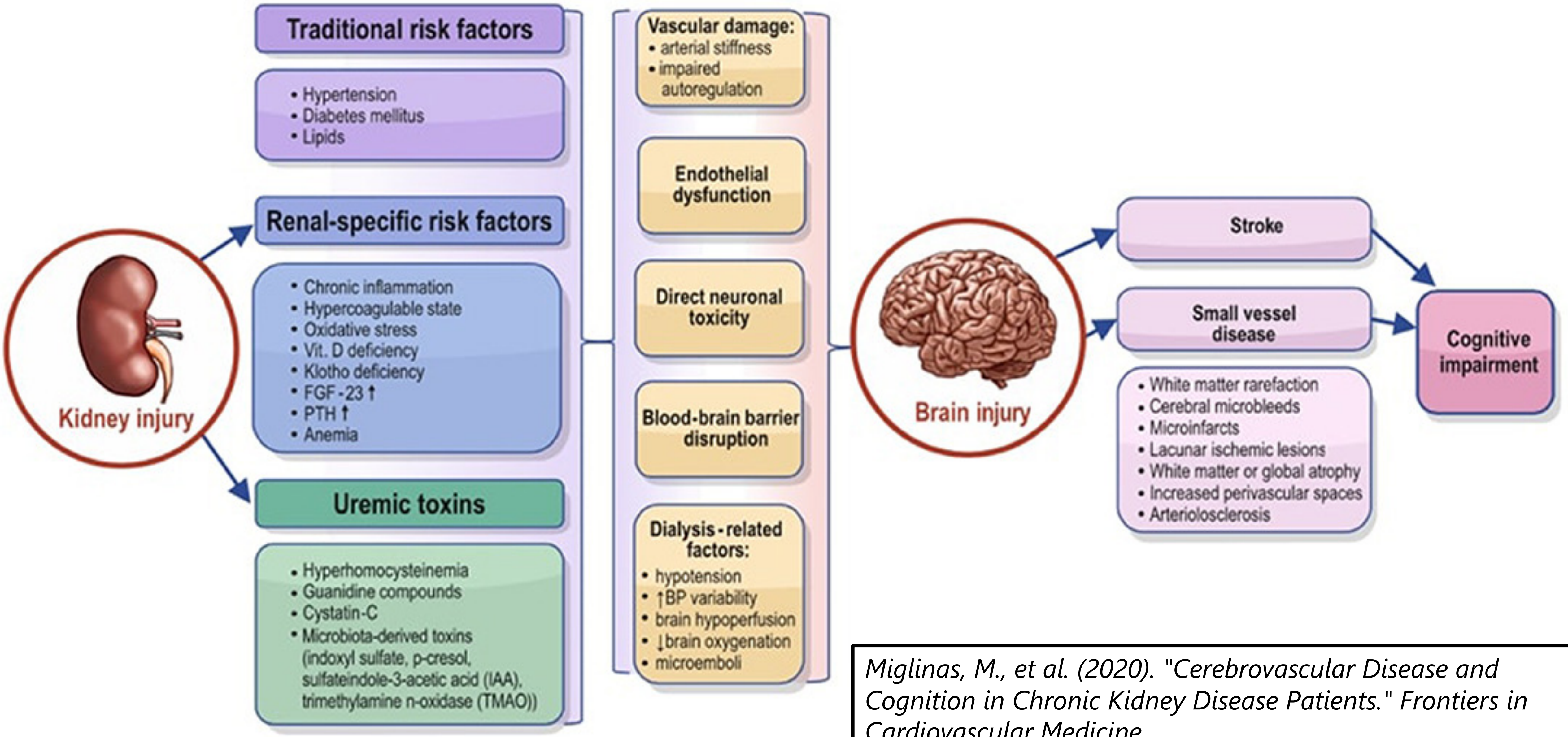
Myelin Deposition

Dialysis is a life-saving therapy.
What is the impact on the (developing) brain?

Nopoulos Lab - Iowa

Why does ESKD status impact the brain?

University of Iowa Stead Family Children's Hospital



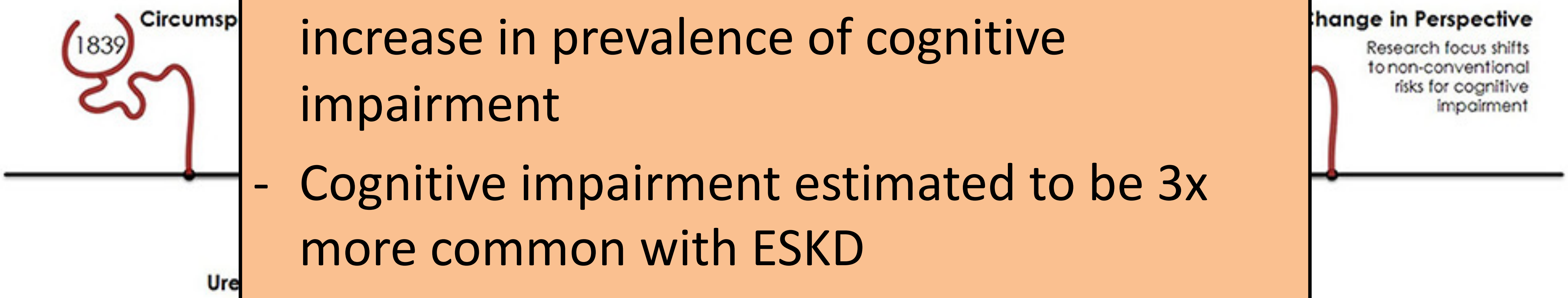
Miglinas, M., et al. (2020). "Cerebrovascular Disease and Cognition in Chronic Kidney Disease Patients." Frontiers in Cardiovascular Medicine

OUTLINE

1. Lifespan approach to ch to pediatric end stage kidney disease (ESKD)
2. Why the brain in a "non-neurological" disease?
3. What is known about brain function (cognition) and structure in the ESKD population?

Brain function (cognition) in ESKD

Is It Removed During Dialysis?



Adult ESKD Data

- Every 10 ml/min/1.73m^2 drop in GFR = 11% increase in prevalence of cognitive impairment
- Cognitive impairment estimated to be 3x more common with ESKD
- Consistent concerns in the literature for memory deficits and executive dysfunction

Crowe K, Quinn TJ, Mark PB, Findlay MD. "Is It Removed During Dialysis?"-Cognitive Dysfunction in Advanced Kidney Failure-A Review Article. Front Neurol. 2021

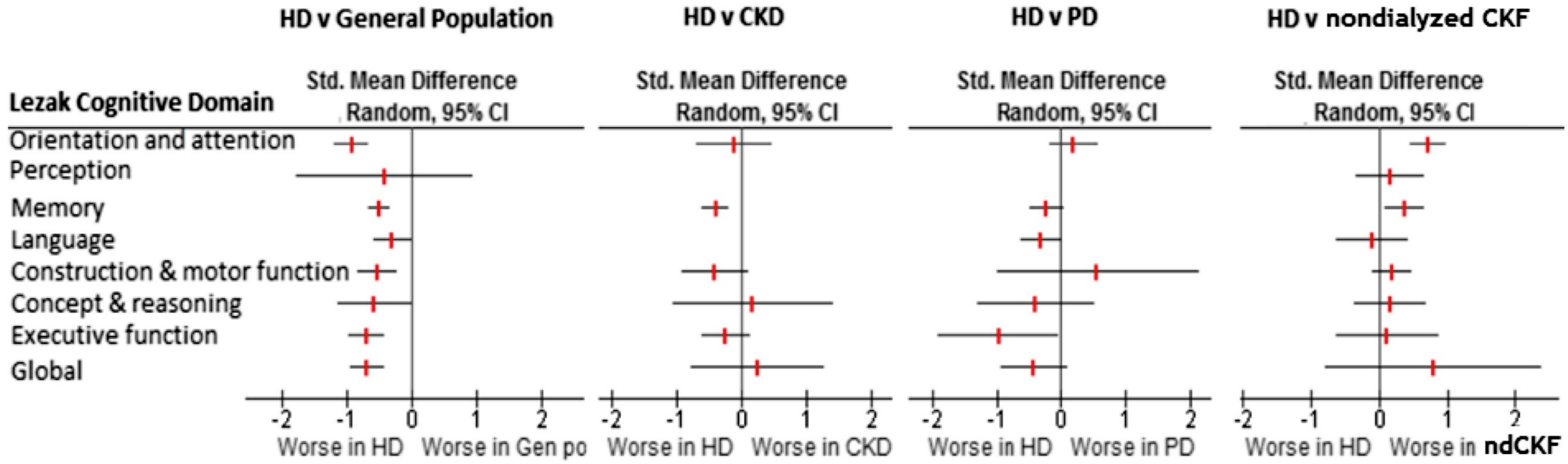
Brain function (cognition) in Adult ESKD

AJKD
Original Investigation

Cognition in People With End-Stage Kidney Disease Treated With Hemodialysis: A Systematic Review and Meta-analysis

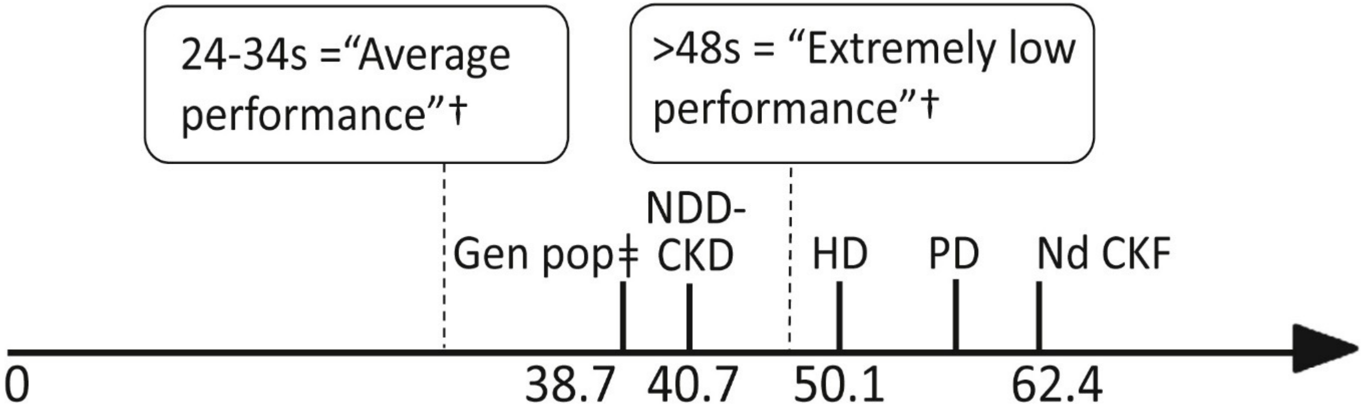
Emma O'Lone, MBChB,[1,2] Michael Connors, PhD,[1,3,4,5] Philip Masson, PhD,[1,2,6] Sunny Wu,[1] Patrick J. Kelly, PhD,[1] David Gillespie, PhD,[6] Daniel Parker, PhD,[7] William Whiteley, PhD,[6] Giovanni F.M. Strippoli, PhD,[1,8,9] Suetonia C. Palmer, PhD,[10] Jonathan C. Craig, PhD,[1,2] and Angela C. Webster, PhD[1,2,11]

- 42 studies
- 3522 participants



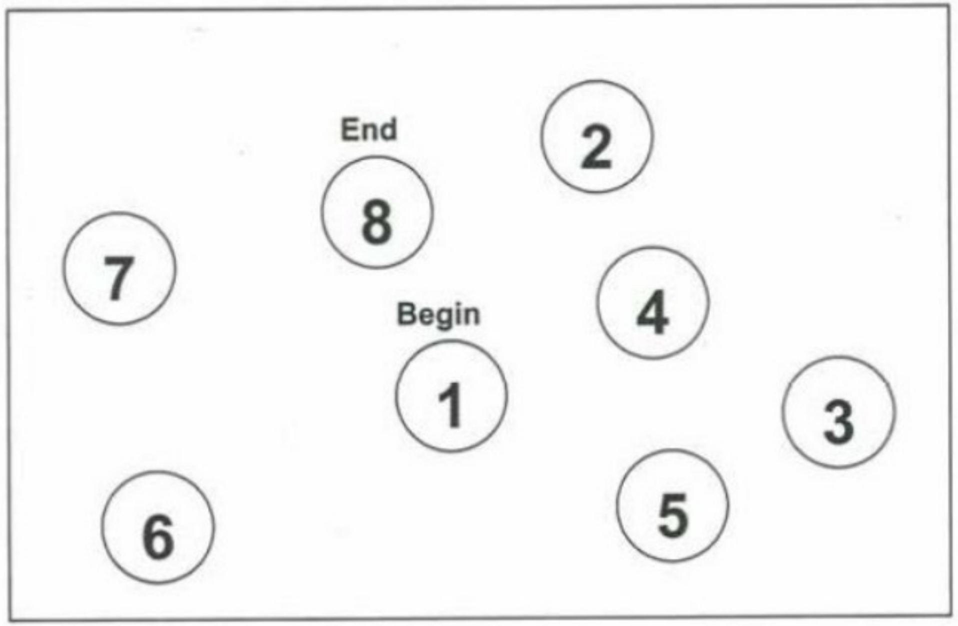
People treated with hemodialysis have impaired general cognitive function compared to the general population and those on PD, particularly in the domains of orientation and attention and executive function.

Estimated difference in "Trail Making Test (A)" representing attention and executive function



Time to completion in seconds
(longer time to completion = poorer orientation and attention)

"TRAILS" Version A - Sample



Adult dialysis patients (both PD & HD) demonstrate "extremely low" performance on the Trail Making Task

Brain function (cognition) in Pediatric ESKD

University of Iowa Stead Family Children's Hospital

Long-term neurocognitive outcomes of patients with end-stage renal disease during infancy

Rebecca J. Johnson · Bradley A. Warady

- 12 patients with history of ESKD requiring chronic dialysis during first 16 months of life
  - Age at neurocognitive assessment was at least 6 years
  - Etiology of disease: renal dysplasia, PUV, congenital nephrotic syndrome, ARPKD

- Patients assessed in parallel with available healthy siblings on measures of intellectual and executive functioning, memory, and academic achievement using paired-samples t tests.

Brain function (cognition) in Pediatric ESKD

University of Iowa Stead Family Children's Hospital

Long-term neurocognitive outcomes of patients with end-stage renal disease during infancy

Rebecca J. Johnson · Bradley A. Warady

Summary Point:
Evidence of neurocognitive impairment or risk for some patients, but a lack of gross neurocognitive impairment overall.

	Patient mean (SD)	Sibling mean (SD)	Paired sample statistics
WISC-IV Verbal Comprehension Index	82.4 (19)	90.8 (16.8)	$t=-1.0$, $p=0.33$
WISC-IV Perceptual Reasoning Index^	83.6 (18.7)	99.7 (19.8)	$t=-2.2$, $p=0.06$
WISC-IV Working Memory Index*	78.8 (11)	92.1 (17.8)	$t=-3.2$, $p=0.01$
WISC-IV Processing Speed Index*	83.4 (14.9)	95.9 (16.5)	$t=-2.3$, $p=0.05$
WISC-IV Full Scale IQ*	77.9 (16.1)	93.9 (19)	$t=-2.7$, $p=0.03$
WIAT-II-A Word Reading*	85.1 (21.8)	99.7 (18)	$t=-3.0$, $p=0.02$
WIAT-II-A Numerical Operations*	84.3 (21.2)	100.1 (24.9)	$t=-3.2$, $p=0.01$
WIAT-II-A Spelling**	86.7 (19)	105.2 (15.9)	$t=-3.6$, $p=0.007$
WIAT-II-A Total Achievement**	84.3 (18.7)	102.8 (20.2)	$t=-4.2$, $p=0.003$
WRAML2 Verbal Memory*	88.8 (11)	100.7 (19.5)	$t=-2.4$, $p=0.04$
WRAML2 Visual Memory	88.7 (8.8)	86.7 (11)	$t=0.36$, $p=0.72$
WRAML2 Screening Memory	86.6 (9.4)	92.7 (14.2)	$t=-1.8$, $p=0.12$

WISC-IV Wechsler Intelligence Scale for Children, Fourth Edition; *WIAT-II-A* Wechsler Individual Achievement Test, Second Edition, Abbreviated; *WRAML2* Wide Range Assessment of Memory and Learning, Second Edition (presented as standard scores with normative M=100, SD=15)

**$p<0.01$, *$p<0.05$, ^$p<0.06$

Pediatric ESKD/CKD Neuroimaging Data – *LIMITED!*

University of Iowa Stead Family Children's Hospital

Pediatric ESKD neuroimaging data LARGELY based on:

– Qualitative ima[...] scans) all from prior to the yea[...] including dialysis participants.

– Imaging in the [...]

– Heterogenous [...] stages

- How do we eva[...] r a child born with CKD versus a [...]
- Mix of "sicker" [...] patients, and transplant recipients.

– Ages spanning childhood and adulthood

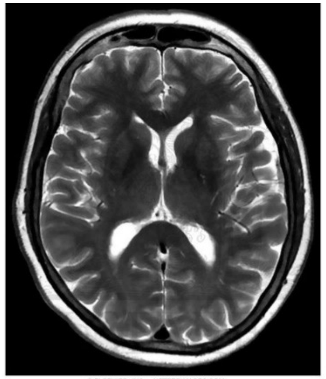
Adult data

- More robust sample sizes
- More consistently performed in parallel with neurocognitive assessment
- Many studies include comprehensive lab & physiological assessment.

Primer on neuroimaging techniques

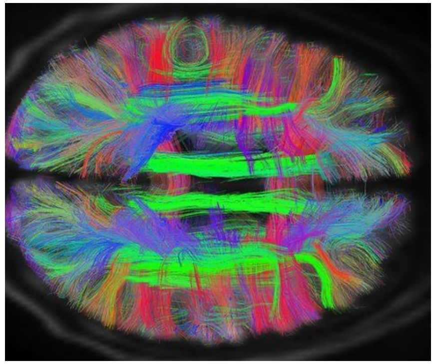
STRUCTURAL IMAGING (MRI)

- Measures discrete volume of gray & white matter
- Measures cortical thickness



WHITE MATTER IMAGING (MRI)

- Measures of the water content of white matter → fractional anisotropy, mean diffusivity
- Can make a 3D reconstruction of DTI images to generate "tractography" maps



The Human Connectome Project

CEREBRAL HEMODYNAMICS

- Uses changes in cerebral blood flow & brain oxygenation through detection of changes in paramagnetic signal from hemoglobin
- Other: functional near infrared spectroscopy (fNIRS)

Photo: University of Iowa fNIRS Core (with permission)

Brain findings

Neuroimaging in ESKD– cortical structure

University of Iowa Stead Family Children's Hospital

Adult Hemodialysis

- Evidence for global, cerebral (cortical) gray matter atrophy
  - *Volume loss may be noted even in pre-dialysis CKD*
  - *Worsens with duration of dialysis*
- Few specific "regional" volumetric differences
  - *Frontotemporal gray matter most notable*
- Higher frequency of cerebral microbleeds within the cortex and deep gray matter
  - *More lesions → lower eGFR*

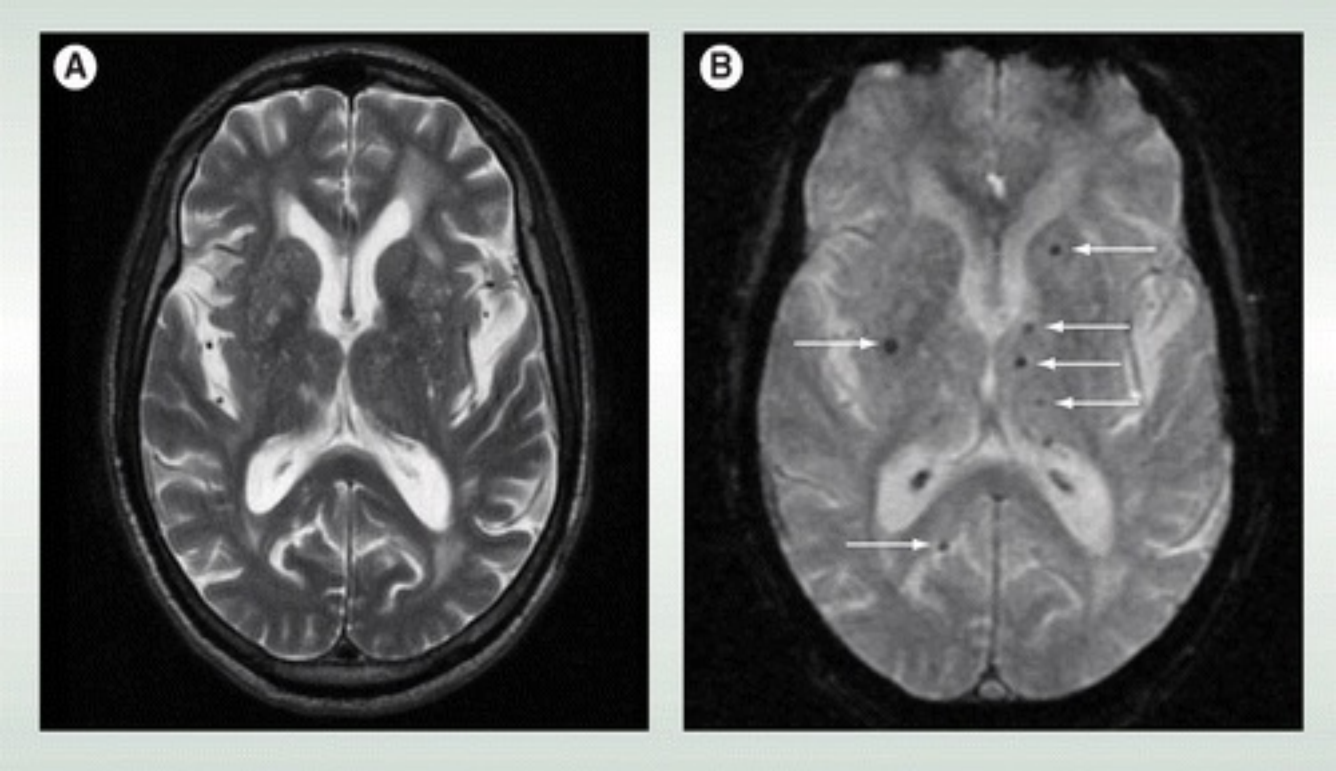


Figure from Charidimou & Werring, 2011

Neuroimaging in ESKD– cortical structure

University of Iowa Stead Family Children's Hospital

Structural brain abnormalities in children and young adults with severe chronic kidney disease *- Lijdsman S et al., 2022 (Ped Neph)*

n	Group		Contrasts		Treatment subgroups			Statistics[a]
	CKD	Healthy control	*p*	*d*	Pre-dialysis	Dialysis	Transplanted	*p*
	24	21			7	7	10	
Brain volume (cm^3)								
Gray matter	875.8.8 (84.7)	866.9 (61.4)	0.690	0.12	916.5 (84.8)	829.4 (60.9)	879.9 (89.8)	0.323
White matter	750.5 (35.9)	752.6 (32.5)	0.839	−0.06	739.3 (24.5)	757.0 (16.7)	753.7 (50.6)	0.777
Subcortical volume (cm^3)								
Thalamus	574.4 (51.3)	546.2 (51.3)	0.072	0.55	576.1 (47.6)	557.2 (46.9)	585.4 (58.1)	0.222
Caudate nucleus	300.9 (40.4)	312.3 (34.5)	0.316	−0.30	293.2 (36.3)	310.5 (32.6)	299.6 (49.6)	0.633
Putamen	431.2 (47.9)	429.5 (33.8)	0.893	0.04	428.4 (33.0)	409.0 (39.2)	448.6 (58.7)	0.289
Pallidum	146.0 (15.8)	150.1 (15.4)	0.388	−0.26	143.0 (9.8)	149.7 (18.4)	145.4 (18.1)	0.710
Hippocampus	329.7 (46.6)	339.3 (31.7)	0.431	−0.24	328.2 (39.7)	348.8 (65.0)	317.4 (35.2)	0.376
Amygdala	78.5 (30.6)	86.7 (27.5)	0.350	−0.28	73.4 (28.9)	71.4 (37.3)	87.0 (27.8)	0.513
Nucleus accumbens	41.3 (13.3)	51.5 (9.5)	**0.005**	−0.87	46.4 (11.3)	40.6 (16.9)	38.2 (12.1)	**0.022**

Neuroimaging in ESKD– white matter

University of Iowa
Stead Family
Children's Hospital

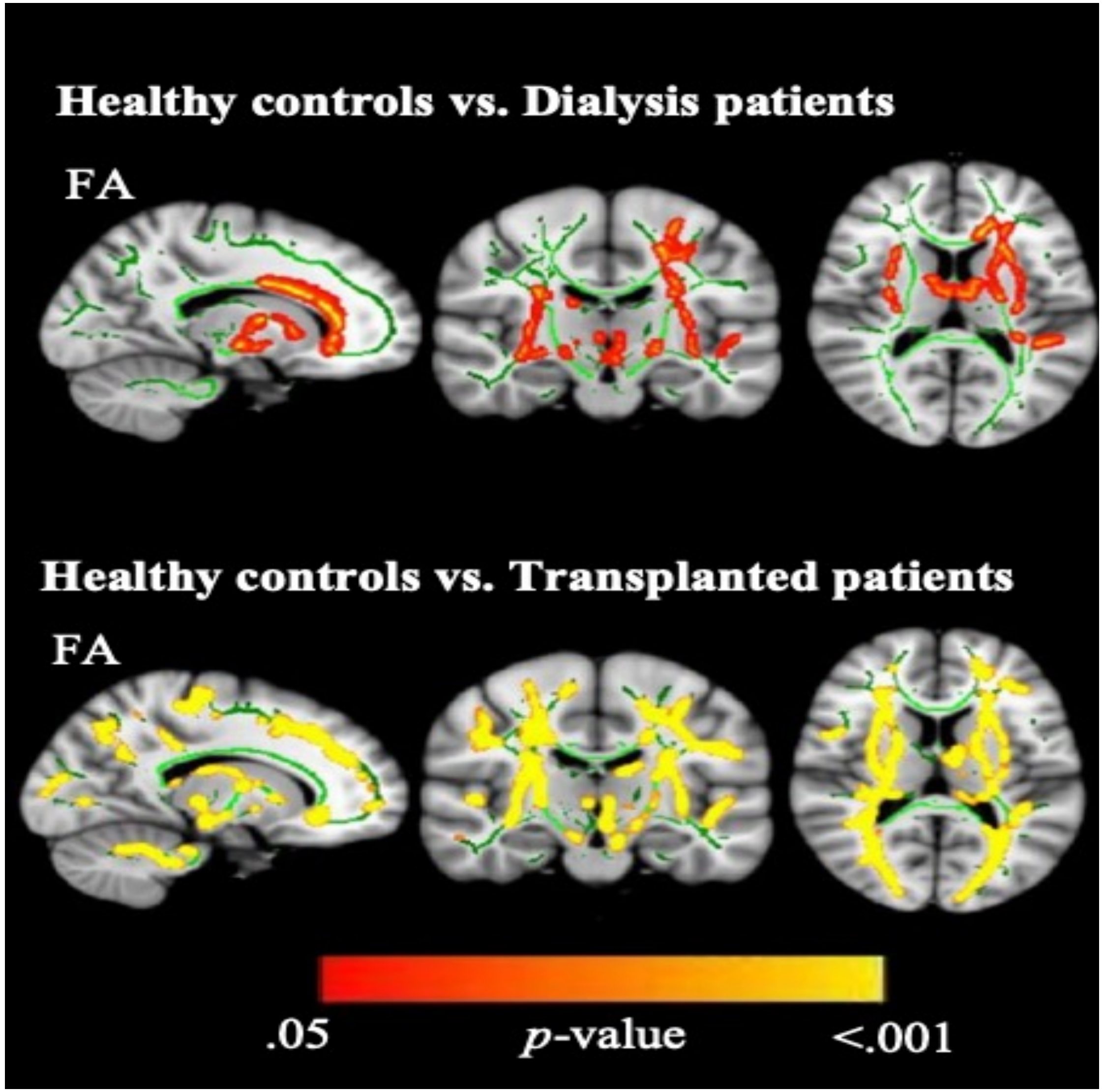
Structural brain abnormalities in children and young adults with severe chronic kidney disease

- Lijdsman S et al., 2022 (Ped Neph)

- Small sample of pediatric ESKD/transplant patients
  - 7 CKD-5, 7 on dialysis, 10 s/p txp

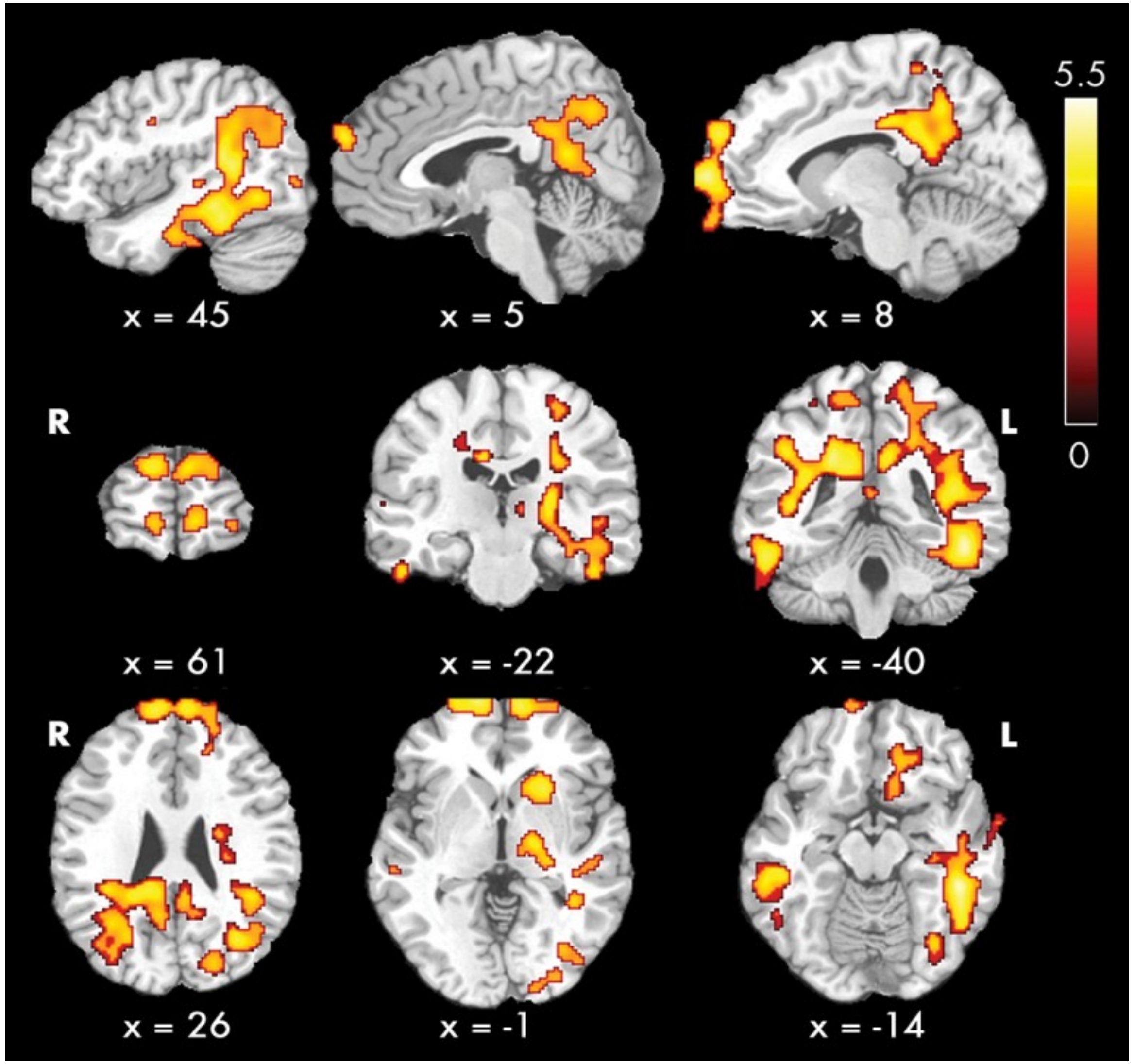
<u>Summary Point</u>

- Lower "fractional anisotropy" is present in major tracts
  - *Suggestive of abnormal white matter integrity*
  - *….That may not improve with transplant*



Neuroimaging in ESKD– cerebral hemodynamics

University of Iowa Stead Family Children's Hospital



Liu HS, et al. Regional Cerebral Blood Flow in Children and Young Adults with Chronic Kidney Disease. Radiology. 2018 Sep;288(3):849-858. doi: 10.1148/radiol.2018171339. Epub 2018 Jun 12.

Neuroimaging in Chronic Kidney Disease (NiCK) Study

73 pediatric CKD/txp patients
57 comparators

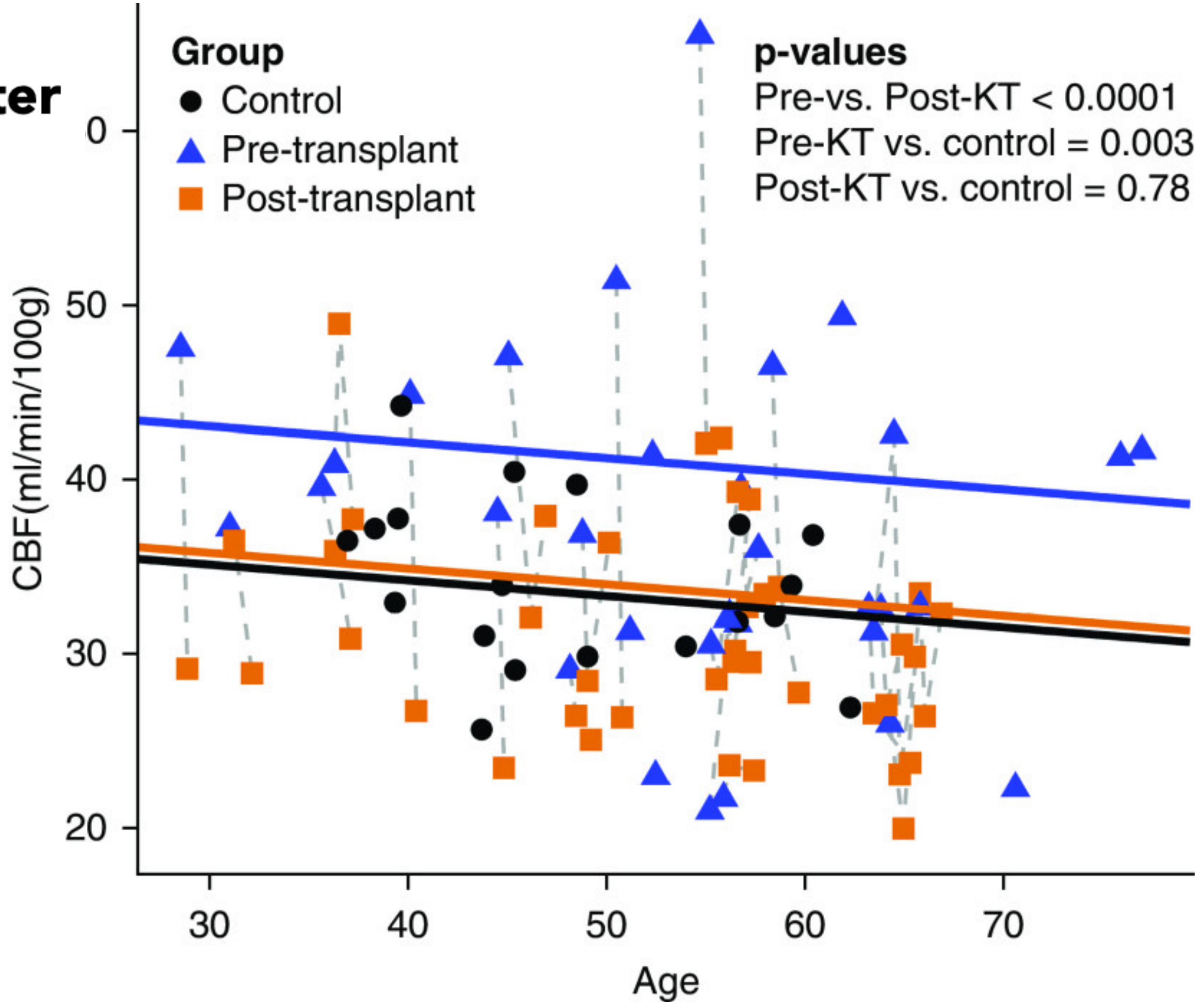
- Patients with CKD showed *higher* (abnormal) global cerebral blood flow compared with control subjects that was attributable to:
  - reduced hematocrit level
  - higher blood pressure
- Regional blood flow was higher in regions encompassing the "default mode network"
  - *Network critical attributable to **executive function***

Neuroimaging in ESKD– cerebral hemodynamics

University of Iowa Stead Family Children's Hospital

Normalization of Cerebral Blood Flow, Neurochemicals, and White Matter Integrity after Kidney Transplantation

- 29 adults with ESKD
  - *22 with follow-up imaging up to 1 year after kidney transplant*
- Adult CKD/ESKD is associated with paradoxically higher cerebral blood flow
  - *Potentially a compensatory mechanism due to altered cerebral hemodynamics*
- Transplant appears to reverse ESKD associated CBF abnormalities



Lepping RJ, Montgomery RN, Sharma P, et al. Normalization of Cerebral Blood Flow, Neurochemicals, and White Matter Integrity after Kidney Transplantation. *J Am Soc Nephrol*. 2021;32(1):177-187. doi:10.1681/ASN.2020050584

Neuroimaging in ESKD– cerebral hemodynamics

University of Iowa
Stead Family
Children's Hospital

Assessment of cerebral oxygenation response to hemodialysis using near-infrared spectroscopy (NIRS): Challenges and solutions.
Wong et al., 2021

- Used NIRS to assess cerebral hemodynamic responses among 95 prevalent HD patients during two consecutive HD treatments

Cerebral ischemia (15% drop from baseline cerebral saturation) for 2+ min or more is a common feature of HD treatments

- Ischemic episodes may be related to volume status
  - Episodes > after a long (weekend) dialytic interval

19.2% of the first weekly treatment is spent in ischemic conditions.

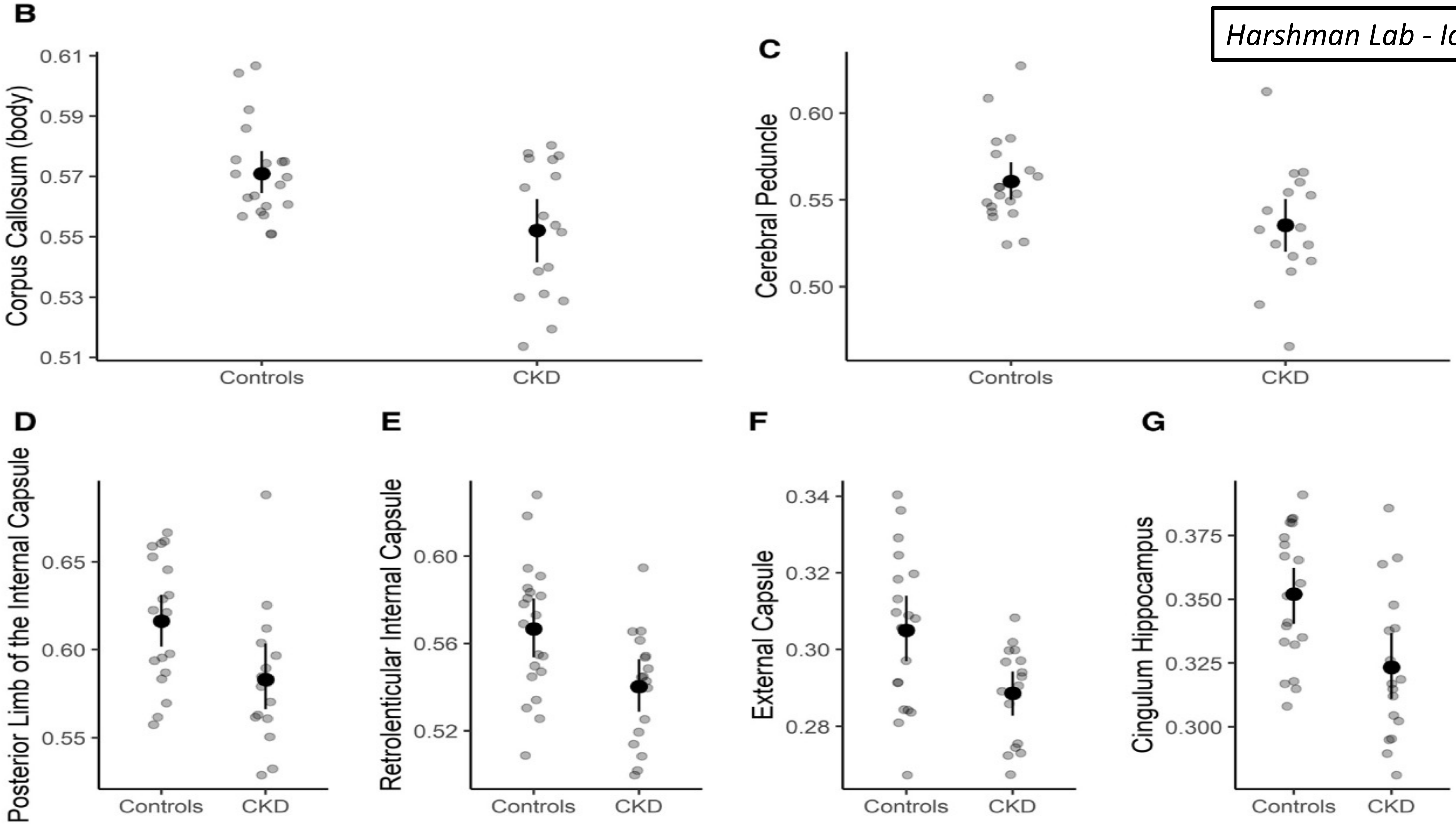
Is this just the tip of the iceberg?

Are there long-standing effects of CKD that predate the impact of ESKD on the brain?

Neuroimaging in CKD 1-3b

University of Iowa Stead Family Children's Hospital

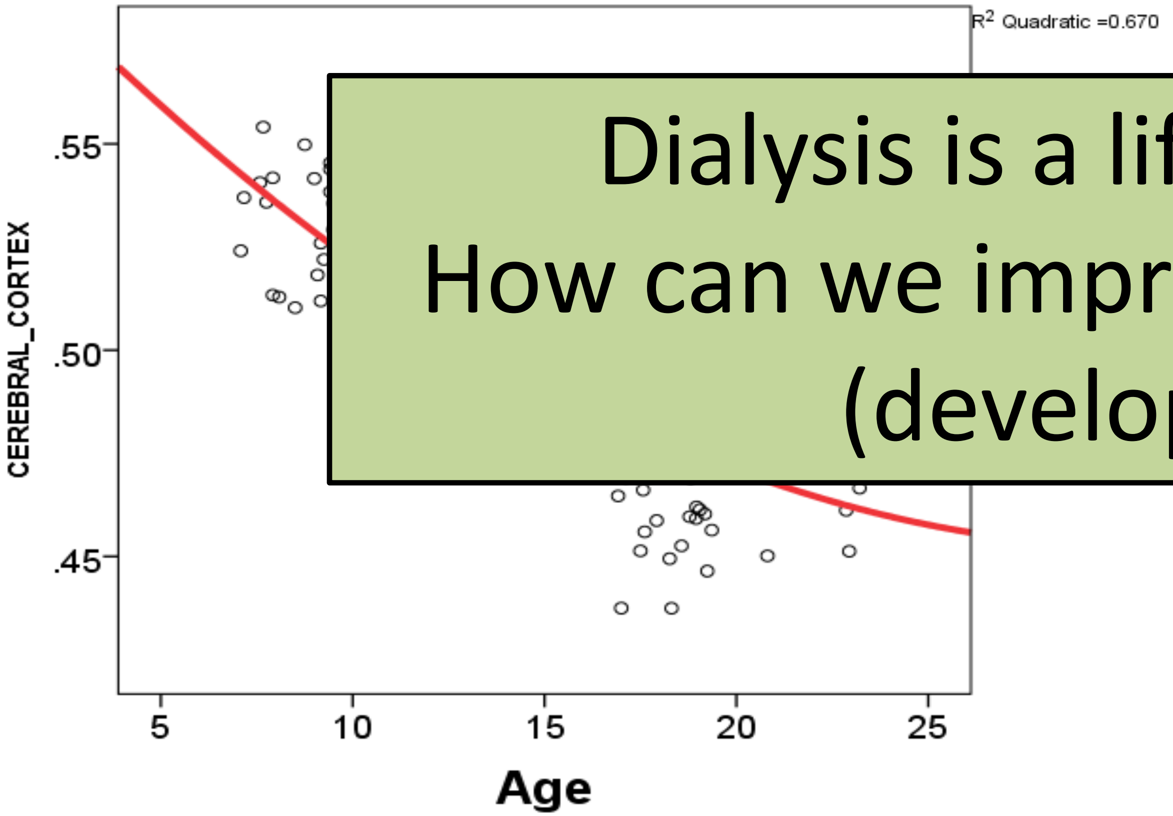
Harshman Lab - Iowa



Remember this slide?

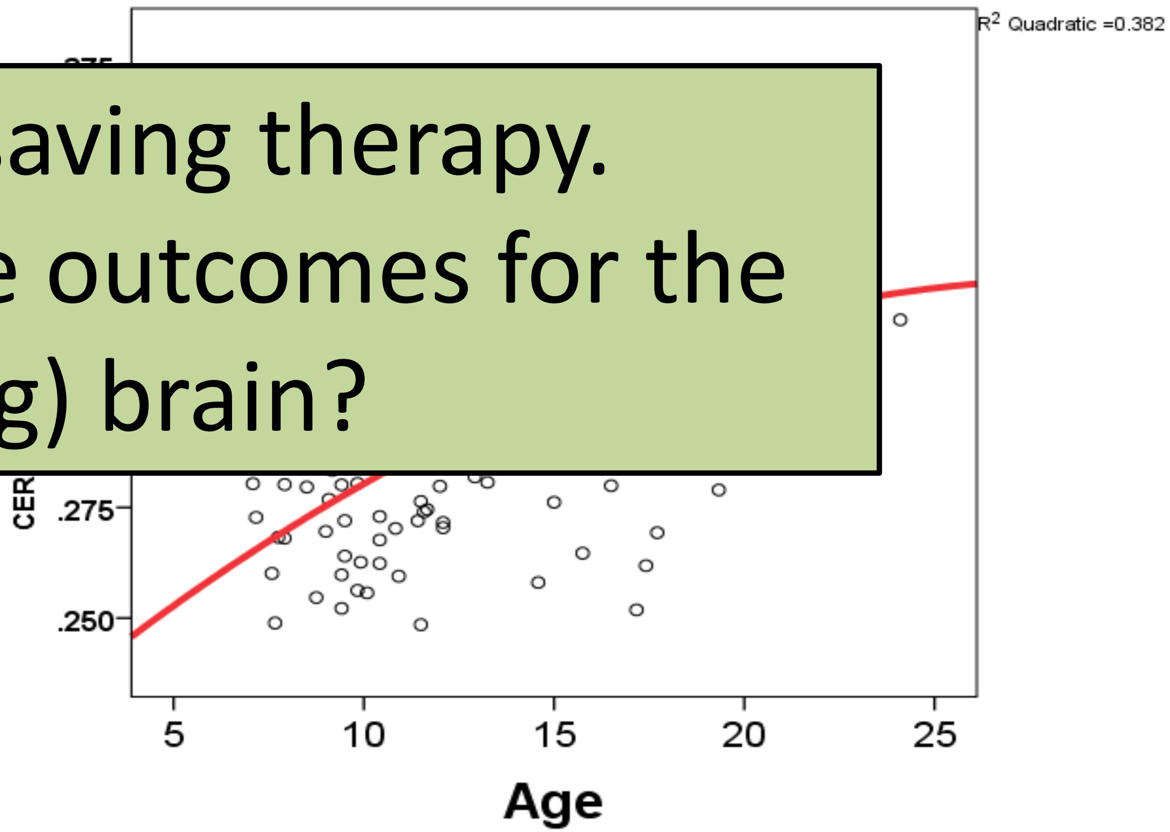
University of Iowa Stead Family Children's Hospital

Cerebral Gray Matter (Cortex)



Programmed Synaptic Elimination

Cerebral White Matter



Myelin Deposition

Dialysis is a life-saving therapy.
How can we improve outcomes for the (developing) brain?

Nopoulos Lab - Iowa

Interventions to optimize the neurophenotype

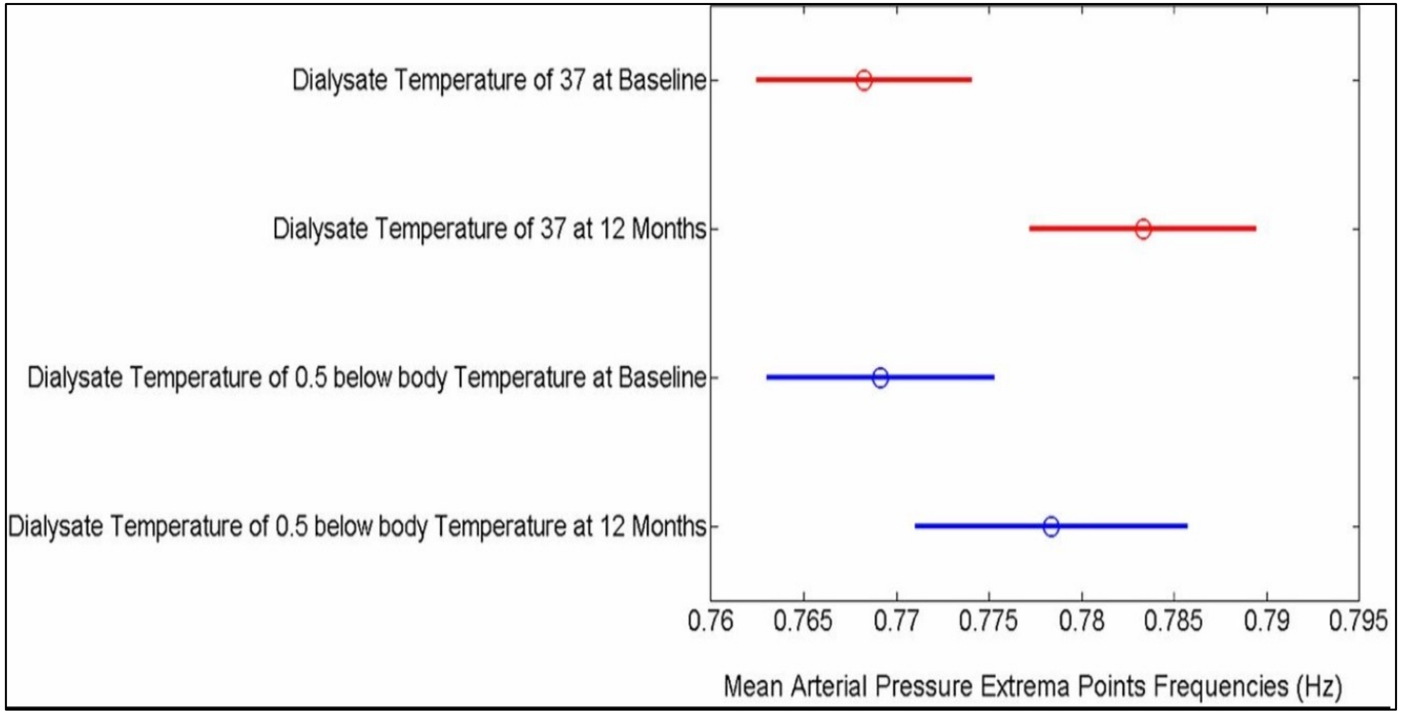
Randomized Clinical Trial of Dialysate Cooling and Effects on Brain White Matter

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

73 patients on incident hemodialysis starting within 6 months

→ Randomized to dialyze with a dialysate temperature of either 37°C or 0.5°C below the core body temperature

→ Neuroimaging at baseline & 1 year



Cooled dialysate minimizes "MAP" extrema

<u>Take home point:</u> Patients who dialyzed at 0.5°C below core body temperature exhibited complete protection against white matter changes at 1 year.

Interventions to optimize the neurophenotype

Practical implications of intra-dialytic weight gain

Impact of blood pressure control

Opportunities for Future Research

- Pediatric ESKD neuroimaging data are limited (…..nearly non-existent)
  - Future research in this field should prioritize opportunities to understand the impact of ESKD on the pediatric brain

- Impact of early life kidney support therapy
  - Critical opportunities exist to evaluate the brain among extremely preterm/low birth weight infants with ESKD on dialysis via novel technology (fNIRS) in the neonatal period and through early childhood.

Standardized approaches to neurocognitive/imaging research

\- and -

multi-center collaboration are critical.

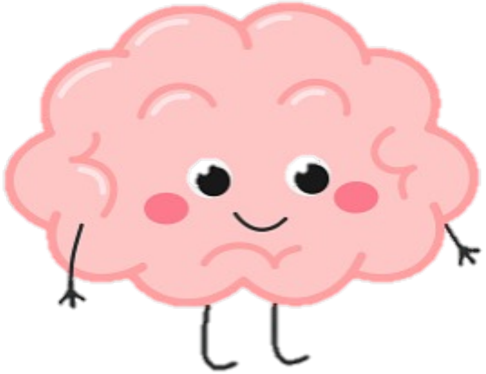
Take Home Message

University of Iowa
Stead Family
Children's Hospital

- **Ischemic events** may be more common than we realize – especially during hemodialysis therapy

- The effects of dialysis on brain structure **may be** influenced by "modifiable" factors such as IDW.

- Adult data support a potential positive role for **dialysate cooling** on white matter integrity.



Images courtesy University of Iowa Marketing

University of Iowa
Stead Family
Children's Hospital

THANK YOU

lyndsay-harshman@uiowa.edu

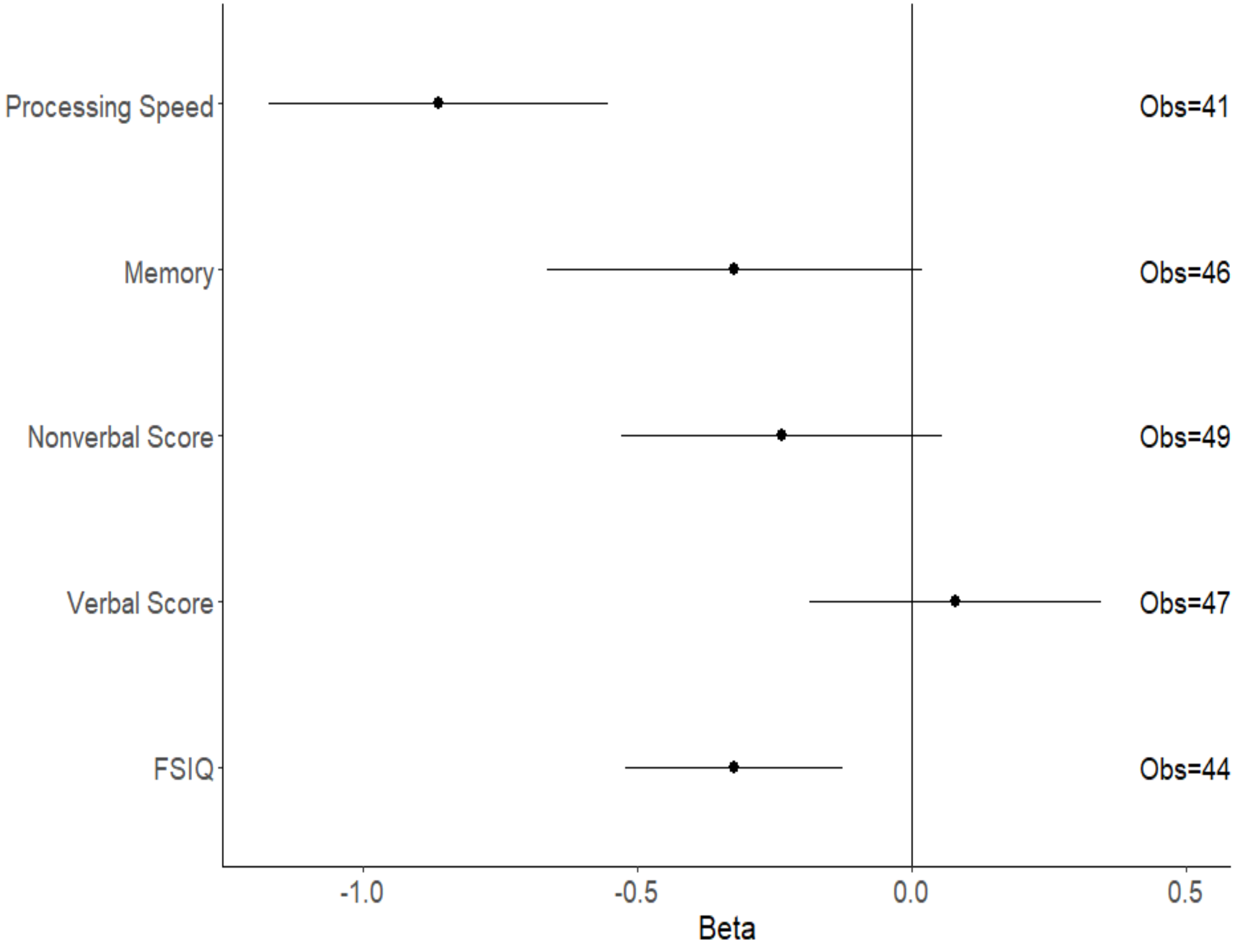
My work family at the University of Iowa

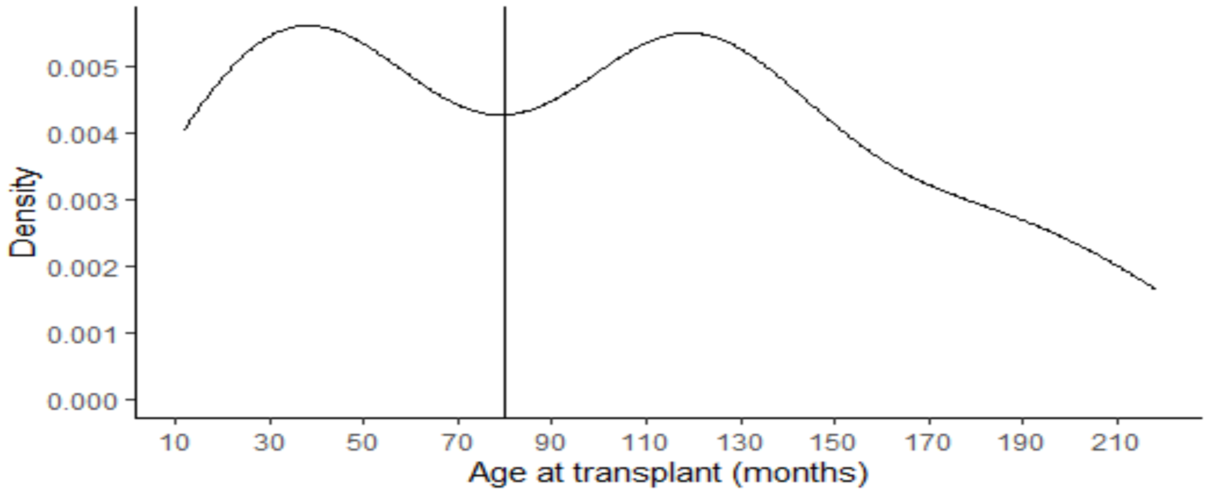
… and my own family

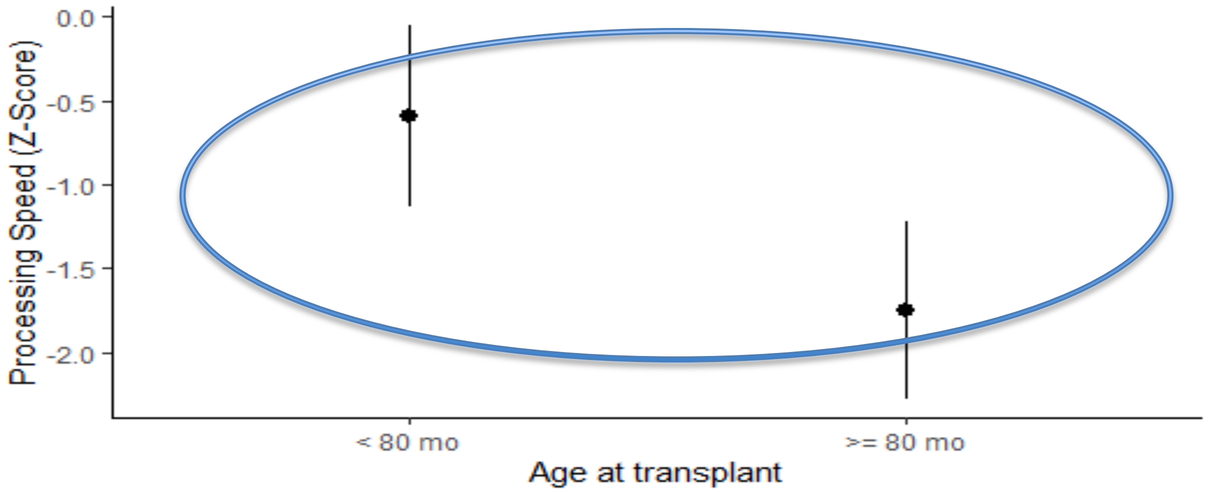
Funding
National Institute of Diabetes and Digestive and Kidney Diseases
K23DK110443 – Harshman
R01DK128835 – Harshman
Stead Family Department of Pediatrics (internal funding) – Harshman

Early age at transplant as an "intervention"?

University of Iowa Stead Family Children's Hospital







Patients s/p kidney txp had lower scores on cognitive tests at 1 year + post transplant compared to normative data for age.

Being older at kidney transplant was associated with substantially lower processing speed scores.

Harshman Lab – Iowa (manuscript accepted)