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Changes in cerebral volume and white matter integrity in adults on hemodialysis and relationship to cognitive function

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Abstract

Introduction: Patients on hemodialysis (HD) have a significant burden of cognitive impairment. Characterizing the cerebral structural changes in HD patients compared to healthy controls and evaluating the relationship of cerebral structural integrity with cognitive performance in HD patients can help clarify the pathophysiology of the cognitive impairment in HD patients.

Methods: In this cross-sectional study, in-center HD patients ≥50 years of age underwent brain structural and diffusion MRIs and cognitive assessment using NIH toolbox cognition battery. The cerebral imaging measures of the HD participants were compared to imaging from age matched controls. Gray matter volume, white matter volume and white matter integrity determined by diffusion tensor imaging parameters (including Fractional Anisotropy, FA) were measured in both cohorts to determine differences in the cerebral structure between HD participants and healthy controls. The association between cognitive performance on NIH toolbox cognition battery and cerebral structural integrity was evaluated using multiple linear regression models.

Results: We compared imaging measures form 23 HD participants and **15** age-matched controls. The HD participants had decreased gray matter volumes (526.8cm^3 vs 589.5cm^3, p<0.01) and worsened white matter integrity overall (FA values of 0.2864 vs 0.3441, p<0.01) and within major white matter tracts compared to healthy controls. Decreases in white matter integrity in the left superior longitudinal fasciculus was associated with lower executive function scores (r^2=0.24, p=0.02) and inferior longitudinal fasciculus with lower memory scores (r=0.25 and p=0.03 for left and r^2=0.21 and p=0.03 for right).

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Authors' Contributions:

Research idea and study design: DFW, BDS; data acquisition: DFW, WTR; data analysis/interpretation: DFW, WTR, LU and BDS; statistical analysis: WTR; supervision or mentorship: DFW, BDS. Each author contributed important intellectual content during manuscript drafting or revision, accepts personal accountability for the author's own contributions, and agrees to ensure that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Conclusions: HD patients have a pattern of decreased white matter integrity and gray matter atrophy compared to controls. Decreases in white matter integrity were associated with decreased cognitive performance in the HD population.

Keywords

hemodialysis; cognition; white matter integrity; gray matter volume

Introduction

Cognitive impairment in patients with end-stage renal disease (ESRD) treated with hemodialysis (HD) is increasingly apparent and concerning. Cohort studies demonstrate that two thirds of HD patients suffer from cognitive impairment (CI) and half of those have severe impairment that is consistent with dementia.[1-4] Cognitive impairment in the HD population is associated with higher mortality, increased hospitalization rates, and lower functional status and quality of life.[5, 6] In the dialysis population CI can reduce the patients' ability to adhere to medications and dietary restrictions that are complex and central to dialysis care. In addition, it compromises decision-making capacity regarding care. The pathophysiology of cognitive decline in this population is unclear. However the HD population is noted to have generalized cortical atrophy and white matter disease on imaging.[7-10] This indicates that there may be cerebral structural changes that lead to the CI in this population.

Characterizing microstructural cerebral structural changes in HD patients can be used to identify how brain injury might be occurring and inform prevention therapies. **The pathophysiology for CI is likely multifactorial with uremic toxins, inflammation, anemia, electrolytes disturbances and proteinopathies all contributing; however, cerebral ischemia appears to play a key role.** Prior evidence demonstrates an increased risk of cerebrovascular disease after initiation of HD.[11] There is evidence of white matter disease, lacunae and infarcts, and atrophy on brain imaging in HD patients.[1, 12, 8, 13] These ischemic type lesions may be due to the circulatory stress that is induced by HD in the setting of vascular disease.[14] Cerebral hypoperfusion during HD has been demonstrated using a number of methods.[15-17] In addition to infarcts and atrophy, there may also be microstructural changes in white matter integrity that occur. These ischemic lesions, atrophy and loss of integrity of neural pathways and structures may be the link to compromised cognitive function.

To provide further information on cerebral structural and cognitive changes in the HD population, we conducted a cross-sectional analysis using magnetic resonance imaging (MRI) and cognitive testing in an HD cohort with comparison to MRI data from healthy controls. We utilized state of the art image processing methodology to improve accuracy of the measurements of white matter integrity, focusing on parameters of fractional anisotropy (FA, a measure of directional diffusion along neuronal tracts) and mean diffusivity (MD, a measure of dispersion along a tract). We hypothesized that the HD cohort would have decreased gray and white matter volumes and indicators of decreased white matter integrity

compared to healthy controls. Furthermore, we hypothesized that cerebral volumes and white matter integrity would be associated with cognitive performance in the HD cohort.

Methods

Participants

In **this** cross-sectional analysis from an ongoing longitudinal study, we recruited participants with ESRD treated with HD from four Milwaukee, WI area community dialysis units. Each ESRD participant provided informed written consent to the protocol, which was approved by the Institutional Review Board at the Medical College of Wisconsin. Inclusion criteria were age ≥50 years and receiving thrice weekly conventional in-center HD. Participants also had to be on dialysis over one month but less than two years at enrollment. The one month was to avoid the complicating effects of untreated uremia and the less than two years requirement was to capture when cognitive changes may be more commonly occurring as part of the longitudinal study. Exclusion criteria included a history of stroke, traumatic brain injury, brain tumor or surgery within the past year, non-English speaking, hearing or vision impairment enough to preclude the ability to take the cognitive tests, severe CI that would prevent them from completing cognitive testing, or diagnosis of dementia. Healthy control data were used from a previous study.[18] The healthy control group had the same imaging protocol as the HD cohort but did not have the cognitive testing. **Both the HD and control groups' imaging were processed and analyzed using the same processing pipeline described below.**

Cognitive Testing

Each HD participant completed the NIH Toolbox cognition battery, which includes seven assessments that evaluate the following domains: language, attention, processing speed, executive function, working memory, and episodic memory, and three composite scores.[19] Testing was done the day after the participant's 2nd dialysis session of the week. This was to avoid the immediate changes in cognition during and immediately after a dialysis session.[20] All testing was done in a quiet room with a test administrator and completed on an iPad.

MRI

MRI was done on the same day as the cognitive testing, immediately following the cognitive testing. No participant was given anti-anxiety or sedative medications for the scan. Every participant completed an MRI safety screen prior to the scan. T1 weighted anatomical images were acquired using an axial fast spoiled gradient recall 3D sequence (TE=3.2ms, TR=8.16ms, flip angle=12 degrees, prep time=450, bandwidth=22.73, FOV=240mm, 156 1mm slices, Matrix=256x240). The diffusion weighted volumes were acquired using an axial q-ball high angular resolution diffusion imaging (HARDI) sequence using single shot echo planar imaging (TE=72.3ms, TR=5700ms, b-value=1500s/mm^2, 5 b0 images, 150 directions, FOV=256mm, 59 2.5mm slices, Matrix=128x128).

Image Processing—Anatomical morphometry processing included bias correction, skull stripping, spatial normalization and segmentation, completed using cat12 (http://www.neuro.uni-jena.de/cat/). Total volumes of gray matter, white matter, cerebrospinal fluid

and total intracranial volume were calculated with segmented anatomical volumes. Region of interest analysis was done by masking the gray matter segmentation of each participant with the Harvard-Oxford Cortical and Subcortical Atlases and the Probabilistic Cerebellar Atlas.[21, 22] For the diffusion processing, diffusion volumes were skull stripped and corrected for susceptibility in the images, inter- and intra- slice and volume motion, signal dropout, and b vector correction.[23, 24] Diffusion volumes were registered using a rigid transform from diffusion to anatomical space and a combination of affine and non-linear registration were used to obtain the transforms from anatomical to standard MNI 152 Non-Linear 1mm space.

After completing registration, the tensor model was then fit to each voxel in the diffusion volume to get the diffusion tensor imaging (DTI) measures of microstructural integrity (Fractional Anisotropy (FA), Axial Diffusion (AD), Radial Diffusion (RD) and Mean Diffusivity (MD)). FA is a measure of the strength of diffusion in the primary direction relative to the non-primary diffusion directions, MD is the average diffusivity in a certain voxel, AD is the magnitude of diffusion in the primary direction, and RD is the average of the diffusivity in the two non-primary diffusion directions. FA is correlated positively with general white matter integrity. MD is negatively correlated with white matter integrity as more diffusion in all directions would mean less white matter tracts to restrict diffusion. An increase in RD may indicate demyelination as the non-primary diffusion directions are perpendicular to the white matter tracts and any increased diffusion in these directions is a marker of decreased restriction of diffusion in these directions. AD has been previously correlated with axon density as it measures the diffusion along the white matter tracts; a decrease indicates a loss of white matter organization to channel diffusion in the direction of the white matter tract.[25-28]

Identifying Tract Regions of Interest (tROIs)—White matter tract regions of interest (tROIs) were delineated for calculating diffusion parameters for specific tracts. FSL's probabilistic tractography function probtrackx was used to generate white matter tracts.[29] Seed, termination and exclusion masks for 27 white matter tracts were used.[30] For each tract, 5000 streamlines were run per voxel seeded and the resulting tract density images were thresholded at 0.2 to remove noisy tracts from the ROIs. The ROIs were then warped to anatomical space where non-white matter regions identified by FSL's fast segmentation algorithm of the anatomical data were removed from the tROIs for each participant, resulting in 27 tROIs encompassing only white matter. Each measure of white matter microstructural integrity (FA, AD, RD, and MD) was then averaged within each tROI and used for statistical analyses.

Analysis

Cognitive Performance Analysis—Tests **were** scored automatically in the NIH toolbox app. The HD cohort scores were compared to age-corrected standard population means of 100 with SD of 15 using one sided t-tests with a CI of 95%.

Anatomical Statistical Analysis—Total gray matter, white matter and cerebrospinal fluid were compared between the HD and control groups, controlling for total intracranial

volume and age effects, using FSL's PALM software in MATLAB. This comparison was repeated for each gray matter ROI identified using the Harvard-Oxford and Probabilistic Cerebellar Fusion Atlas[31, 21, 32, 33, 22] to identify cortical regions in which the volume was significantly smaller in the HD cohort compared to controls. False discovery rate was used to correct for multiple comparisons.

Diffusion Statistical Analysis—Whole brain white matter DTI measures were compared between the two groups using an ANCOVA with age as a confounding variable. In addition, an ANCOVA analysis was conducted for each tROI identified with tractography using false discovery rate to correct for multiple comparisons (corrected $p<0.05$). Whole brain white matter and tROI results were then used in multiple linear regression models with age and white matter microstructural integrity as two predictors and cognitive scores as the response variable; models were made for each tract and cognitive task. Although we evaluated 27 white matters tracts and 10 cognitive scores, we did not perform multiple comparisons on this specific analysis given the initial small dataset and preliminary nature of this component of the study.

Results

We had 190 HD patients meet age and < 2 years on HD criteria, but of those, 123 were excluded due to exclusion criteria or too sick to complete study procedures. Out of the remaining 67 eligible participants, 32 consented to participate. Subsequently three changed their mind due to having to go off site for MRI, five were unable to get MRI due to MRI screening failure or claustrophobia, and one image was not used due to large strokes that led to DTI parameters and volumes that were statistically noted as outliers. We included 23 HD participants and 15 healthy controls in the analysis. The mean age of the HD cohort was 66.3 vs 62.3 in healthy controls, $p = 0.11$ (see Table 1). Demographics including age, race, and gender as well as **HD duration and** medical comorbidities are noted in Table 1.

Cerebral volumes in HD cohort compared to controls

Global gray matter volume adjusted for age and total intracranial volume was lower in the HD cohort than healthy controls (526.8cm3 vs 589.5cm3, $p <0.01$) (Fig. 1). Regionally, the left putamen, bilateral pallidum, bilateral VIIa cerebellar lobules and right VIIb cerebellar lobule were significantly decreased in HD patients after multiple comparisons correction (Fig. 2). There were no regions with higher gray matter volumes in HD patients compared to controls. Cerebrospinal fluid volume was significantly greater in HD patients (415.4cm3 vs 335.5cm3, $p <0.01$) while white matter volume was not significantly different between the two groups (470.8cm3 vs 490.4cm3, $p =.20$), shown in Figure 1.

White Matter Microstructural Integrity in HD cohort compared to controls

Global white matter FA was significantly lower in HD patients compared to controls (0.2864 vs 0.3441, $p<0.01$) shown in Figure 3, with significantly higher mean AD (0.001 vs 0.00097, $p<0.01$), RD (6.47x10^−4 vs 5.60x10^−4, $p<0.01$), and MD (7.65x10^−4 vs 6.97x10^−4, $p <0.01$) values. The lower FA in HD compared to controls was present in 17 out of the 27 tracts measured (see FA bar plot in Supplementary Fig. 1). The absolute differences in FA

for all significantly different white matter tracts is shown in Figure 3. Additionally, most of the decreased tracts had increased RD (see RD bar plot in Supplementary Fig. 1).

Cognitive performance in HD cohort

NIH Toolbox Cognitive Function scores for the HD cohort are displayed in Table 2, with p values for comparisons with age-corrected standard population scores (mean = 100 and SD = 15 for all scores). The mean (SD) Total Cognition Composite Score in the HD cohort was 92.4 (15.2), significantly less ($p = 0.02$) than the age-corrected population scores. This difference was primarily due to differences in fluid measures. The Fluid Cognition Composite (86.9 (14.3)), and its components of pattern comparison processing speed (83.1 (16.1)) and flanker inhibitory executive function and attention test (84.3 (10.1)) were all significantly less than population scores. The Crystallized Cognition Composite Score (99.1 (14.5)) and all components of it were similar to population scores.

Cognitive function and cerebral imaging parameters in HD cohort

There were no associations between total gray white or total white matter and cognitive scores in the HD cohort. In evaluating the tROI FA values and cognitive function there was a small, but statistically significant, positive relationship between microstructural integrity of the left superior longitudinal fasciculus and scores on the test of executive function and attention ($r^2= 0.24$, $p=0.02$), left inferior longitudinal fasciculus ($r^2=0.25$ and $p =0.03$) and right inferior longitudinal ($r^2=0.21$ and $p=0.03$) with tests of memory, shown in Figure 4.

Discussion

We found evidence of cerebral degeneration with lower gray matter volume, higher cerebrospinal fluid volumes and decreased microstructural integrity of most major white matter tracts (noted by lower FA values and higher MD values) in HD patients relative to healthy age-matched controls. The greatest decreases in white matter integrity were observed in areas of the brain used in executive function and processing speed, cognitive domains in which our HD cohort performed worse than age adjusted standard populations scores. Finally, we found that lower white matter integrity in specific white matter tracts was associated with decreased cognitive performance in our HD patients. **Previous studies have found cerebral structural changes; however, we identify that these changes are present early after dialysis initiation and found new subcortical changes that have not been previously noted. The cerebral structural changes we note and the association with cognitive performance support our framework of an HD associated cerebral injury that has an impact on cognitive function.**

While prior studies of persons with ESRD have documented lower brain matter volumes and global decreases in white matter integrity relative to controls,[7, 10, 35] our study adds information on specific DTI parameters and examines these changes in white matter integrity within specific tracts. In our analysis, 17 of 27 measured tracts had decreased FA in HD patients relative to controls. Many of the tracts affected, including the forceps minor, cingulum, and uncinate fasciculus, project to the frontal cortex and therefore have important roles in cognition and executive function. We also found that, in most tracts, the decreased

tract FA was due to an increase in the RD measurements, which may indicate more demyelination of white matter.[26, 28] These results indicate that there is disruption in the majority of white matter tracts in the HD cohort, with decreased overall white matter integrity, characterized by decreased FA.

An important strength of our approach was to pre-identify the major white matter tracts of the brain. Previous studies have used voxel-wise tract based spatial statistics [10, 35] to characterize changes in white matter integrity. Those methods restrict the area of white matter that is used for quantification to the highest FA regions (rather than the whole tract), which reduces complications of identifying tract boundaries, but is susceptible to systemic misalignment issues.[36, 37] Tract based spatial statistics also requires post hoc assignment of white matter regions to specific tracts. Another method used manual segmentation of white matter into regions based on the cortical location (frontal, parietal, etc) [7], which depends on subjective criteria for tract identification. With our unique processing method, we incorporated individual variation in white matter tract architecture by identifying white matter tract regions using tractography, avoiding potential misalignment issues that can occur in other approaches. The accuracy of this method is demonstrated by the fact that we found differences in white matter integrity despite no difference in white matter volume.

In addition to white matter changes, we found evidence of gray matter atrophy, with lower gray matter volume and higher cerebrospinal fluid volumes in the HD cohort. We found primarily subcortical (putamen and pallidum) and cerebellar gray matter volume differences. This differs from prior studies that found mostly cortical volume changes[9, 34] and provides new information on brain structural changes and CI in HD patients. The lack of significant cortical volume decreases in our study compared to prior studies may also be due to differences in our study demographics. The populations included in prior studies were 30 years younger on average and had minimal or no CI compared to our cohort .[9, 34] Our cohort is more reflective of the current HD population in both age and CI.[38] Cohort age is important since cortical gray matter volume decreases with age.[39, 40] The known age related decreases in cortical gray matter volume might have reduced the differences in cortical gray matter between the HD participants and controls in our older cohort. **Alternatively, our cohort had a lower dialysis vintage compared to prior study cohorts and we may be detecting initial changes that occur before the cortical gray matter changes.** The differences in subcortical gray matter that we observed raise the possibility that changes in subcortical gray matter volume might play a role in CI in older HD patients. The decrease in putamen gray matter volume in the HD cohort may be important as lesions in the putamen have been associated with impairments in memory and processing speed in other neurological disease states and ageing.[41, 42]

To examine the potential effects of the cerebral structural changes we evaluated the relationship between cognitive performance and brain imaging parameters. The pattern of NIH Toolbox scores we noted in our cohort – greatest performance differences in processing speed, executive function and attention domains and less but still notable differences in memory – is consistent with prior literature.[43-46] The relationships between the superior longitudinal fasciculus FA and performance on executive function and attention tasks, and between the inferior longitudinal fasciculus FA and memory tasks are also consistent with

other studies.[47, 48] A study evaluating white matter integrity in 26 HD patients found a similar correlation of lower white matter integrity in superior longitudinal fasciculi with lower performance on executive function and processing speed.[35] Although we did not correct for multiple comparison in our small sample, the trends in our results support the general theory that decreased white matter integrity is associated with worse cognitive performance. Many of the white matter tracts in the HD patients had decreased FA values compared to controls, including the inferior fronto-occipital fasciculus, forceps major and uncinate fasciculus; all of which project to the frontal cortex, a structure important in executive function, an area of deficit in HD patients.[49]

Our study has limitations. Our small sample size may have reduced our ability to identify statistically significant associations between the integrity of specific white matter tracts and cognitive performance. Our controls were healthy volunteers and thus were not matched in rates of comorbidities such as diabetes and hypertension. We cannot determine if the changes in brain matter are due to comorbidities, renal disease versus or HD. However, this does not limit our ability to describe the brain changes in HD patients vs healthy controls and to evaluate **the** relationship between cognitive score and cerebral imaging parameters in HD patients. We relied on comparison to age adjusted population norms to identify the cognitive deficits in the HD cohort. However, using general population norms allowed us to compare our HD cohort to a larger sample rather than just our 15 controls. In terms of imaging processing, the tensor model we used is limited in regions with crossing tracts.[50] We believe the methodology performed better than generic group-defined tract masks by accurately identifying specific tracts in individual participants. We noted misalignment, with tracts going through gray matter or CSF when using generic masks, which were not present when using our tractography method. Finally, our cross-sectional study design only allowed us to look for associations between variables at one point in time. An ongoing longitudinal study will provide further information on how HD may affect the brain over time.

In summary, we found that HD patients had lower white matter integrity and more gray matter atrophy than controls. The changes in white matter integrity in certain tracts were associated with decreased cognitive performance noted in the HD group. Future studies need to replicate our methods in a larger cohort to confirm findings. Additionally, longitudinal studies evaluating changes in the integrity of white matter tracts over time in HD participants are needed to determine if HD-specific factors contribute to white matter changes. Increased focus in this area of research is needed in order to better understand and prevent the cognitive impairment and neurodegeneration in HD patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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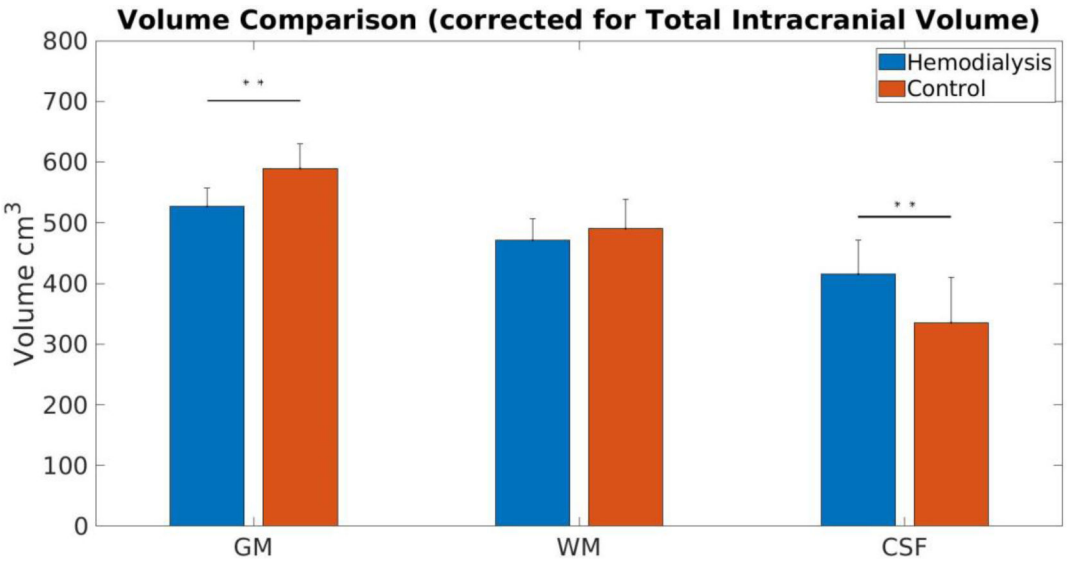

Fig. 1.

Total Gray Matter, White Matter, and Cerebral Spinal Fluid volumes after controlling for age and total intracranial volume as confounding variables. Significance labels represent significance p<.01**.

GM = gray matter, WM = white matter, CSF = cerebral spinal fluid. There is a decrease in gray and white matter volume along with increase in cerebral spinal fluid volume in the hemodialysis cohort compared to healthy control indicating generalized atrophy.

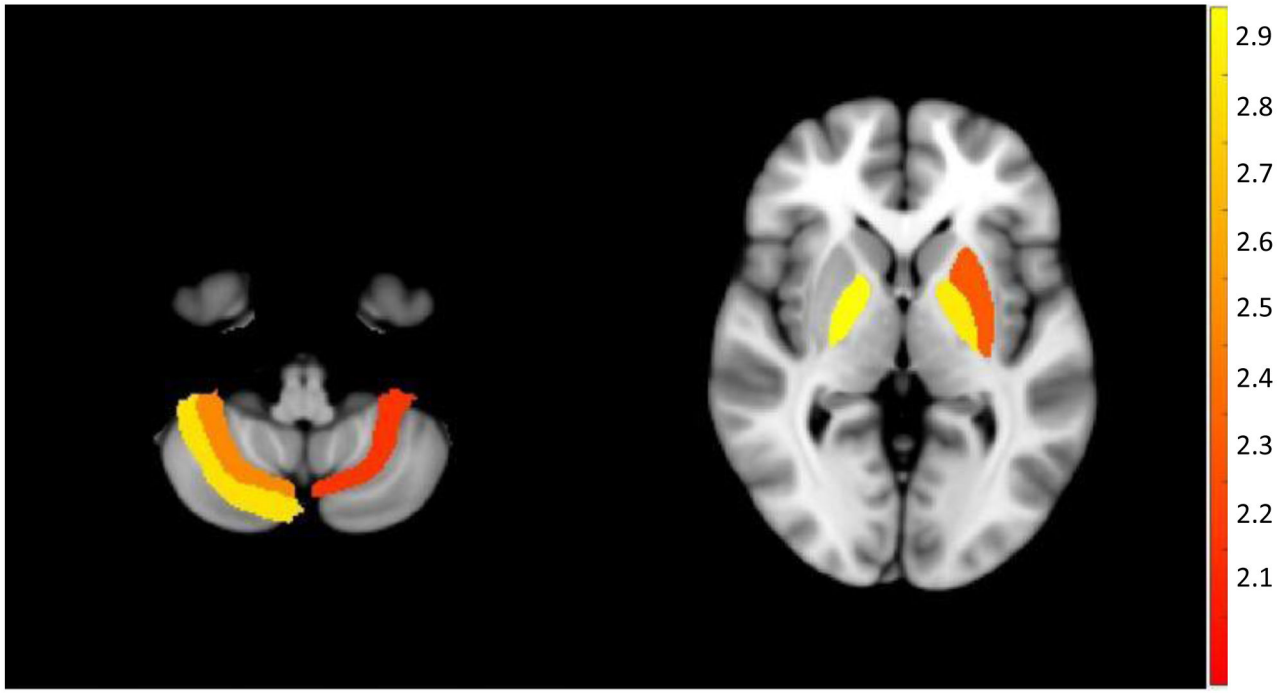

Fig. 2.

T map of significant ($p<.05$) volume differences in individual ROIs derived from the Harvard-Oxford cortical and subcortical atlases and probabilistic cerebellar atlas

Cortical and sub cortical atlases are shown on right and cerebral atlas on left. The color graph on the right indicates the difference in volume in cm^3 with yellow indicating a larger difference. The highlighted subcortical structures include the left putamen and bilateral pallidum.

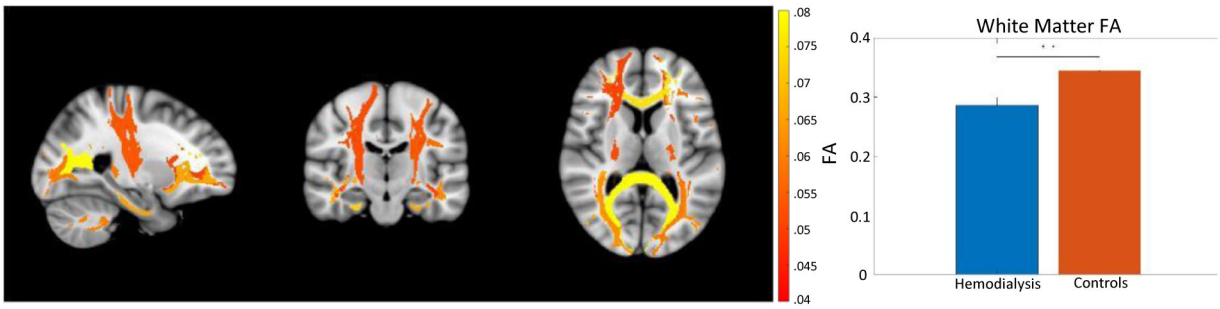

Fig. 3.

Map of significant **Fractional Anisotropy (FA)** differences in tracts identified using tractography and whole white matter difference in FA between the groups.

On left is the FA differences in tracts using tractography, tROIs were summed and mapped as the FA difference between the two groups. Highlighted tracts all have statistically significant differences compared to controls with $p < 0.01$. The degree of differences in FA is shown with the color graph, with yellow indicating a higher difference. On right is the difference in whole white matter FA between the groups, with $p < 0.01$.

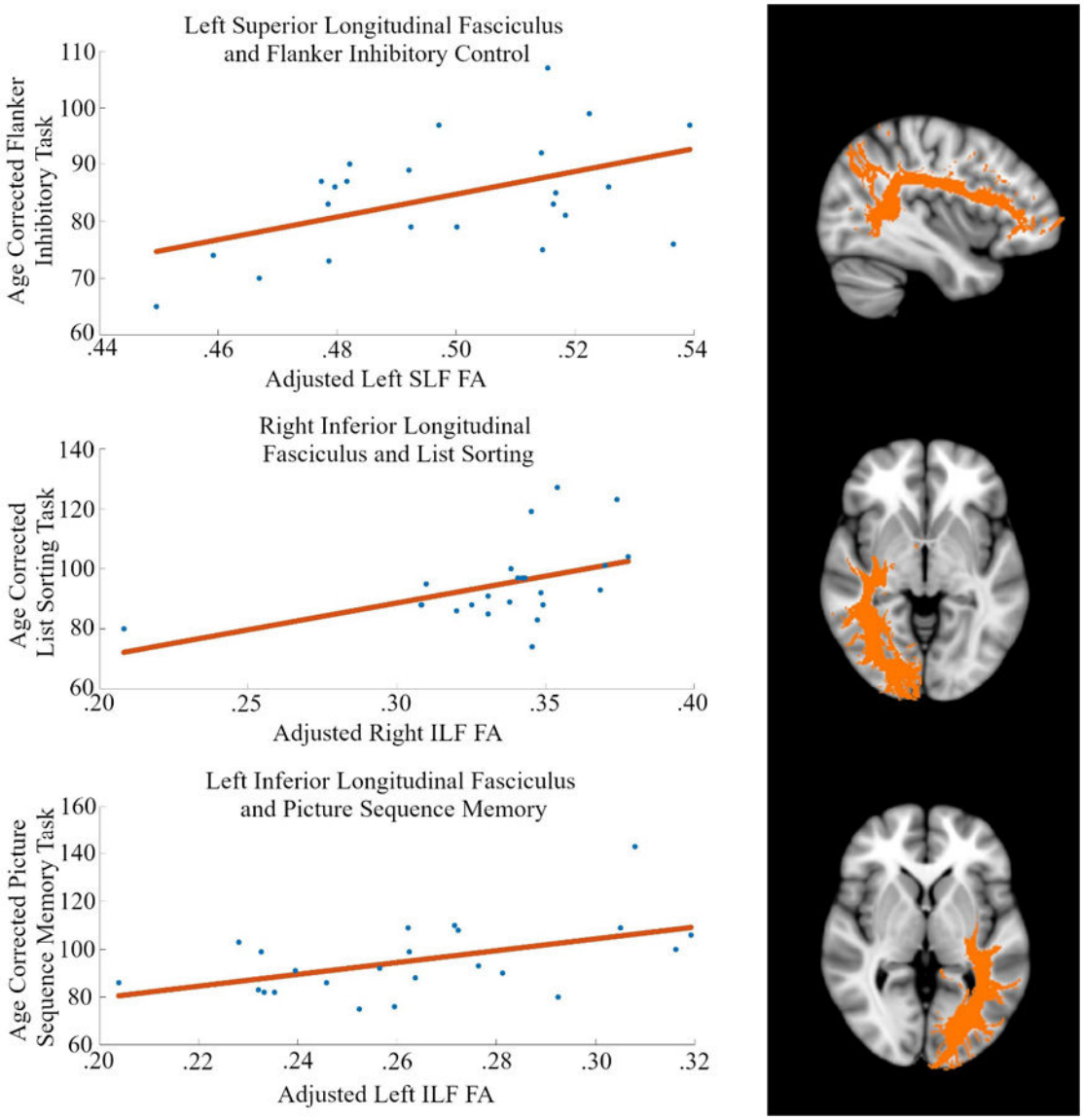

Fig. 4.

Graph of white matter tract FA values with scores on cognitive tasks.

Top panel shows the relationship between the left superior longitudinal fasciculus (SLF) FA values and the age correct score of the flanker inhibitory test, which measures both executive function and attention. The middle and bottom panel shows the relations between the right and left inferior longitudinal fasciculus FA values and tests of working (list sorting) and episodic memory (picture sequence), respectively. The FA values are adjusted for age and a higher FA indicates better white matter integrity. The cortical images on right outline the respective tracts.

Table 1.

Age and Gender Differences between HD participants and healthy controls and HD comorbidities.

	Group		
	Hemodialysis Participants (n=23)	**Healthy Controls (n=15)**	**p value**
Age(SD)	66.3	62.3	0.11
Male N (%)	65.2%	53.3%	0.13
Hemodialysis Duration (months)	**7.8 ± 6.7**	**N/A**	**--**
Comorbidities		N/A	
Hypertension N (%)	18 (78.3)		--
Diabetes N (%)	15 (65.2)		--
CAD N (%)	9 (39.1)		--
PVD N (%)	3 (13.0)		--
CHF N (%)	9 (39.1)		--
Race			
Caucasian	14 (60.9)		
African American	7 (30.4)		
Other	2(8.7)		
Cause of ESRD			
Diabetes	11 (47.8)	N/A	--
Hypertension	6 (26.1)		
Other	6 (26.1)		
Educational level			
High school or less	13 (56.5%)		
Some college/Bachelor's degree	8 (34.8%)		
Advanced degree	2 (8.7%)		

CAD = coronary artery disease, PVD = peripheral vascular disease, CHF = congestive heart failure, ESRD = end stage renal disease. Advanced degree indicates masters', graduate or professional degree.

Table 2.

HD cohort scores on NIH Toolbox tasks with cognitive domain for each test.

Cognitive Tests	Cognitive Domain	Score Mean (SD)	p-value
Picture Vocabulary	Language	97.7 (12.6)	0.20
Oral Reading	Language	99.9 (15.0)	0.49
Crystallized Cognition Composite *	N/A	99.1 (14.5)	0.39
Flanker Inhibitory Control and Attention	**Executive Function and Attention**	**84.3 (10.1)**	**<0.01**
List Sorting	Working Memory	96.3 (12.4)	0.09
Dimension Change Card Sort	Executive Function	96.7 (15.0)	0.15
Pattern Comparison Processing Speed	**Processing Speed**	**83.1 (16.1)**	**<0.01**
Picture Sequence Memory	Episodic Memory	95.4 (15.0)	0.08
Fluid Cognition Composite *	**N/A**	**86.9 (14.3)**	**<0.01**
Total Cognition Composite	**N/A**	**92.4 (15.2)**	**0.02**

The p-value is for comparison with one-sided t-test with 95% CI of HD cohort scores to general population normative scores, mean 100 and SD of 15 for each test. The cognitive tests that are bolded indicate the test that the HD cohort score was significantly below demographic, and age adjusted population means.

* The crystalized cognition composite incudes performance on picture vocabulary and oral reading and is thought to be more resistant to change from pathology. The fluid cognition composite score includes performance on flanker inhibitory, list sorting, dimensional change card sort, pattern comparison, picture sequence memory test and is thought to reflect a measure that changes with pathology.