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Brain Magnetic Resonance Imaging Findings in Children and Young Adults With CKD

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Abstract

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Background: The neuroanatomic basis for cognitive impairment in chronic kidney disease (CKD) is incompletely characterized. We performed advanced quantitative structural magnetic resonance imaging (MRI) to determine whether CKD affects brain structure, and whether poorer neurocognitive performance in CKD is associated with structural brain differences.

Study Design: Cross-sectional.

Setting & Participants: 85 individuals with CKD Stage 2–5 and 63 healthy controls, aged 8–25 years

Predictors: CKD vs. control, estimated glomerular filtration rate (eGFR), and kidney transplant status were analyzed as predictors of MRI findings. MRI volumes in 19 pre-specified regions of gray matter (GM), white matter (WM), and cerebrospinal fluidwere analyzed as predictors of neurocognitive performance (median *z* scores) in 7 pre-specified domains.

Outcomes: Nineteen pre-specified brain regions of interest (ROIs) in 7 pre-specified domains. Neurocognitive performance in 7 pre-specified domains.

Measurements: ROI volumes were compared in CKD vs. controls using unadjusted t-tests and analysis of covariance (ANCOVA). Associations of ROI volumes with eGFR and kidney transplant status in CKD participants were analyzed using ANCOVA and linear regression. Associations of neurocognitive performance and ROI volumes were analyzed by linear regression.

Results: CKD participants had lower whole-brain, cortical, and left parietal GM volumes than controls in unadjusted analyses, but no differences were found in adjusted analysis. In CKD participants, lower eGFR was associated with higher WM volume in whole brain (P=0.05) and frontal (*P*=0.04) ROIs, but differences were not significant after multiple comparisons correction. Kidney transplant recipients had lower GM volumes in whole brain (*P*=0.01, *Q*=0.06), frontal (*P*=0.02, *Q*=0.08), and left and right parietal (*P*=0.01, *Q*=0.06 and *P*=0.03, *Q*=0.1) ROIs, and higher whole-brain WM volume (*P*=0.04, *Q*=0.1). Neurocognitive performance in the CKD group was not associated with ROI volumes.

Limitations: Unable to assess changes in brain structure and kidney function over time; analysis limited to pre-specified ROIs and neurocognitive domains.

Conclusions: CKD in children and young adults may be associated with lower GM volumes and higher WM volumes in some ROIs. Differences were relatively subtle in the CKD group as a whole, but were more prominent in recipients of a kidney transplant. However, neurocognitive performance was not explained by differences in brain ROI volumes, suggesting a functional rather than structural basis for neurocognitive impairment in CKD.

Keywords

Chronic kidney disease (CKD); magnetic resonance imaging (MRI); brain structure; cerebral atrophy; white matter lesions; neurocognitive function; cognitive impairment; pediatric, children; adolescents; region of interest (ROI); ROI volume; neuroanatomy

Introduction

Neurocognitive dysfunction is an important comorbidity in children and adults with chronic kidney disease (CKD). Children with CKD can have reduced performance in attention, memory, executive function, verbal and non-verbal reasoning, and spatial processing.[1–7] Adults with CKD can have reduced global cognitive performance as well as specific cognitive impairments (e.g., attention, memory, executive functioning)[8–11] and dementia.[12–16] Consequences of neurocognitive dysfunction in CKD include lower academic functioning,[17,18] lower employment status[19,20] and decreased adherence to medication regimens.[21,22]

Despite the strong link between CKD and neurocognitive dysfunction, relatively little is known about its neuroanatomic basis. Prior cross-sectional neuroimaging studies in adults with CKD have shown structural abnormalities including cerebral atrophy,[23–28] white matter hyperintensities,[29] cerebral microbleeds,[30] cerebral infarcts,[31] and dialysis-associated cerebral density changes.[32–34] Cross-sectional studies in children with CKD have shown cerebral atrophy,[35–41] cortical infarcts[35,38,39] and periventricular white matter lesions.[38] However, most of these studies have used subjective or non-quantitative imaging methods, limiting the ability to precisely characterize structural brain changes. In addition, most prior pediatric studies have used older imaging methods such as computed tomography.[42]

This study aims to address these gaps in knowledge by using advanced, quantitative structural magnetic resonance imaging (sMRI) methods to obtain a more precise understanding of CKD-associated global and regional differences in brain structure in children and young adults with CKD. Neuroimaging of children with CKD, who have lower rates of pre-existing cardiovascular disease than adults, is of particular value because it allows us to explore CKD-specific brain abnormalities. That is to say, CKD-associated brain abnormalities may be mediated by cerebral small-vessel disease,[8] but in adults with a high prevalence of pre-existing or co-morbid cardiovascular disease, it is difficult to determine which abnormalities are attributable directly to CKD.

The primary objective of this study was to determine whether CKD affects brain structure, and whether CKD-related neurocognitive dysfunction is associated with structural brain differences. In this cross-sectional study, we compared grey matter (GM), white matter (WM), cerebrospinal fluid (CSF), and white matter lesion (WML) volumes in key brain regions of interest (ROIs) in children and young adults with CKD, with those of healthy controls. Within the CKD group, we explored how estimated glomerular filtration rate (eGFR) and kidney transplant status affected brain structure. Given prior literature describing cerebral atrophy in patients with CKD[23–26,35,36,38–40,43], we hypothesized that children and young adults with CKD would have lower total brain GM volumes and higher CSF volumes compared to controls. We further hypothesized that the frontal, temporal, and parietal cortices would be particularly affected, given prior findings in this cohort and others showing deficits in executive function, language, memory, and other complex cognitive functions in children with CKD.[1–7] We also hypothesized that these structural brain findings would be more prominent in patients with more severe CKD (i.e. lower eGFR or history of

kidney transplant), and that neurocognitive performance would be associated with brain ROI volumes.

Materials and Methods

Study Design and Population

This investigation was conducted as part of the cross-sectional NiCK Study (Neurocognitive Assessment and Magnetic Resonance Imaging Analysis of Children and Young Adults with Chronic Kidney Disease). Detailed design and methods of this study have been published previously.[44] Eligible participants were aged 8–25 years, without history of traumatic brain injury, significant neurological disorder, or psychiatric disorder. CKD participants had Stage 2 to 5 CKD (eGFR < 90 mL/min/1.73m^2, including dialysis and post-transplant). Healthy controls were siblings or individuals recruited from Children's Hospital of Philadelphia (CHOP) general pediatrics practices, with similar age, sex, race, and socioeconomic status (using insurance status as a proxy) to the CKD participants. Recruitment of controls was intentionally initially lagged in order to collect demographic data on CKD participants. Proportions of CKD participants in each 2-year age group (8–10 years, 11–13 years, etc.) and of each sex and race (African American vs. non-African American) were tracked. Using a database of several thousand healthy controls maintained by the CHOP Pediatric Research Consortium (PeRC), recruitment postcards were targeted to the appropriate demographic group to keep the CKD and control groups as similar as possible. Although demographic criteria for control recruitment were updated frequently, both groups were recruited simultaneously after the initial lag. Therefore, the healthy controls were not strictly matched one-on-one with CKD participants.[5] Participants who were currently receiving dialysis were excluded from the current analysis in order to eliminate possible effects of dialysis therapy.[32–34] eGFR was calculated using the bedside CKiD equation[45] for subjects aged 8–18 years, and the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation[46] for those >18 years of age. The Institutional Review Board at CHOP approved this study (IRB 10–007919), and informed consent was obtained from all participants.

Study Procedures

Data collected included demographic information (age at visit, age at CKD diagnosis, sex, maternal education, insurance status, and race), medical and family history, and current medications. Prematurity was defined based on participant/caregiver response to the question, "Was the participant considered premature at the time of his/her birth?" Duration of CKD was calculated based on parent/caregiver report of the date of diagnosis.

Imaging Measurements

After MRI safety screening, participants underwent non-sedated, non-contrast brain MRI, acquired on a single Siemens Verio 3T scanner equipped with a 32-channel head coil. Complete FDA- and manufacturer-approved sequences for this study have been published previously.[44] A 3D T1 MPRAGE sequence was used to calculate brain masks and ROIs (TR=1.79 s, TE=3.06 ms, TI=1.050 s, FoV=250×250 mm^2, flip angle=10°, voxel size=1×1×1 mm ^{3}).

sMRI analysis

An automated processing pipeline consisting of extensively validated methods was applied for processing sMRI images, including: extraction of the brain parenchymal tissue using multi-atlas skull-stripping[47]; inhomogeneity correction and tissue segmentation into GM, WM and CSF[48]; segmentation of WMLs using a multi-modal supervised learning method[49]; and segmentation into a set of expert-defined anatomic ROIs using a multi-atlas label fusion method.[50,51] Although age-specific brain atlases are not available, deformable registration procedures adapt the templates to each individual to account for differences in shape and size. The segmentation included 148 ROIs, including 98 cortical regions, WM regions partitioned into brain lobes, as well as important deep structures such as hippocampus, thalamus and amygdala. The ROIs were organized within a hierarchical structure to allow derivation of volumetric measurements in larger structures.

A strict quality control (QC) protocol including both automated and manual control steps was applied on initial, intermediate, and final data. All brain masks were visually verified by overlaying them on corresponding T1 scans. On final volumetric data, subjects with values that significantly deviated from the distribution of the sample were automatically detected and their final image maps were verified for quality. WMLs with volumes smaller than 9 mm^3 were considered noise and were discarded.

Nineteen ROIs were chosen for analysis *a priori* based on available CKD imaging literature: whole-brain GM, whole-brain WM, cortical GM, frontal GM (left, right, and total), frontal WM, temporal GM (left and right), parietal GM (left and right), occipital GM (left and right), limbic GM (left and right; includes cingulate gyrus, entorhinal area, and parahippocampal gyrus), amygdala, hippocampus, thalamus, and lateral ventricles (CSF).

ROI volumes were calculated in cubic millimeters (mm^3). Raw ROI volumes were normalized for intracranial volume (ICV) by dividing ROI volumes by ICV, and then multiplying by 1,500,000 mm^3 (a constant representing the approximate average ICV) to scale them to a larger value.

Neurocognitive Assessments

A battery of age-specific standardized neurocognitive assessments included tests of intelligence (Wechsler Abbreviated Scales of Intelligence [WASI]), attention regulation (Conners' Continuous Performance Test-II [CPT-II]), working memory (Wechsler Intelligence Scale for Children Fourth Edition Integrated [WISC-IV-I] and Wechsler Memory Scale Third Edition [WMS-III]), and executive functioning (Behavior Rating Inventory of Executive Function [BRIEF] and Delis-Kaplan Executive Function System [D-KEFS]).[44] All tests were administered by a trained examiner supervised by a licensed psychologist.

Statistical Analysis

Baseline demographic and clinical characteristics of CKD and control participants were reported as mean and standard deviation (SD) for continuous variables, or frequencies and percentages for binary or categorical variables. Distributions of all variables were examined

before conducting statistical analyses to ensure that assumptions required to utilize parametric tests such as t-tests, analysis of covariance (ANCOVA) and linear regression analysis were met. Group differences were compared using t-tests or the Wilcoxon rank sum test as appropriate for continuous variables, Fisher's exact test for binary variables, and Chi squared for categorical variables.

Volumes of the 19 selected ROIs were first compared between CKD and control groups using a two-sample t-test with Satterthwaite approximation, without adjustment for other covariates. CKD and control groups were then compared using ANCOVA (Type III sums of squares), with each ROI volume as the dependent variable and CKD vs. control group status as the independent variable, controlling for age (years) and sex (female vs. male). Sensitivity analyses excluding kidney transplant recipients were also performed for each analysis.

WML burden was then compared between CKD and control groups. Since overall WML volumes in both groups were very low and distributions were extremely skewed even after log transformation, WMLs were examined as a binary variable (presence vs. absence of WMLs >300 mm^3) using Fisher's exact test.

Further analyses were then performed within the CKD group to explore how eGFR and kidney transplant status affected ROI volumes. Participants with eGFR <45 versus ≥45 mL/min/1.73m^2 were compared using ANCOVA, with each ROI volume as the dependent variable and eGFR group as the independent variable, adjusting for age and sex. The impact of eGFR on ROI volumes was then examined using linear regression, with ROI volume as the dependent variable, and the following variables as predictors: eGFR (in increments of 10 mL/min/1.73m^2), age, sex, race, prematurity, hematocrit, and whether the participant started renal replacement therapy (RRT) at age ≤ 5 years. Sensitivity analyses excluding transplant recipients were also performed for each analysis. ROI volumes were then compared between CKD participants with and without kidney transplant, using ANCOVA, with each ROI volume as the dependent variable and kidney transplant status as the independent variable, adjusting for age and sex.

Finally, the association between neurocognitive performance and ROI volume was analyzed. Our pre-specified analysis plan was to select the subset of ROIs that showed CKD-related differences in the above analyses, and examine their relationship with neurocognitive performance in the 7 domains that have previously been shown in this cohort to have lower performance in CKD:[5] attention, language, verbal memory, verbal working memory, visual memory, visual spatial, inhibitory control. As described previously,[5] results of tests are reported as age-normalized *z* scores. If domains were defined by multiple tests, the median *z* score of tests within that domain was used. Multiple linear regression was performed with neurocognitive domain median z score as the dependent variable and ROI volume as the main explanatory variable, adjusted for age and sex.

To assess for the potential presence of multi-collinearity that could impact regression analysis results, we examined the variance inflation factor (VIF) to measure correlations between variables. All VIFs were <3, indicating no significant multi-collinearity of predictor variables.[52]

For all analyses, *P* values are reported with a significance threshold of $P=0.05$. We also computed corrected *P* values for multiple comparisons using the false discovery rate (FDR) correction method.[53] The resulting *Q* values (FDR-adjusted *P* values) are reported with a significance threshold of $Q=0.05$

Results

Clinical and demographic features

The NiCK study enrolled 92 participants with CKD and 70 control participants, of whom 88 CKD and 66 control participants completed brain MRI. Following QC procedures, six subjects were excluded: three due to extreme motion and three due to moderate-to-high motion on the T1 scan. Evaluable sMRI data were therefore available for 85 CKD and 63 control participants; three current dialysis participants were excluded from this analysis, leaving 82 CKD participants.

Baseline clinical and demographic characteristics of the CKD and control groups are shown in Table 1. CKD and control participants were similar with respect to age, sex, race, income level, insurance status, and maternal education. CKD participants had a mean duration of kidney disease of 9.9 years and mean eGFR of 48 mL/min/1.73m^2. Fifteen CKD participants (18.5%) had ever received dialysis, and 21 (26%) had received a kidney transplant. Six CKD participants (7%) had received their first RRT at age ≤ 5 years. Prematurity was more prevalent in CKD participants than controls (34% vs. 16%, $P=0.01$).

Within the CKD group, participants with eGFR < 45 mL/min/1.73m^2 were similar in age, gender distribution, rates of prematurity, and need for RRT at age ≤ 5 years to those with eGFR ≥ 45 mL/min/1.73m^2. Participants with eGFR < 45 mL/min/1.73m^2 had lower hematocrit and a lower proportion of African-Americans compared to the higher eGFR group (Table 2). Comparisons of CKD subjects with (N=21) and without (N=61) kidney transplant showed similar age [mean of 17.5 +/− 3.6 (SD) vs. 15.9 +/− 3.8 years, $P=0.09$] and eGFR [mean of 48 +/− 21 vs. 48 +/− 25 mL/min/1.73m^2, $P=0.9$] in both groups. However, transplant recipients had lower hematocrit than non-transplant CKD participants [mean of 35.7% +/− 3.3% vs. 39.0% +/− 5.0%, $P=0.001$].

Analysis of brain ROI volumes

ROI volumes in CKD versus control groups—Unadjusted comparisons of ROI volumes showed that CKD participants had lower GM volumes in the whole brain ($P=0.04$), cortex ($P=0.04$), and left parietal ($P=0.04$) ROIs compared to healthy controls (Table S1). None of these differences remained statistically significant after FDR correction for multiple comparisons. Sensitivity analysis excluding kidney transplant recipients showed no significant group differences in ROI volumes between non-transplant CKD participants and controls (Table S2). After adjusting for age and sex, there were nominally lower GM volumes in the whole brain, cortex, and left parietal ROIs in the CKD group compared to controls, but this did not reach statistical significance ($P=0.08$) (Table S3). Sensitivity analysis excluding kidney transplant recipients again showed no significant differences between non-transplant CKD participants and controls (Table S4).

WMLs in CKD versus control groups

Overall WML volumes were very low in both CKD and control groups, with median WML volume of 25 [interquartile range (IQR), 0–106] mm^3 in the CKD group and 14 [IQR, 0–70] mm^3 in controls. Distributions were extremely right skewed even after log transformation (not shown), precluding statistical comparison of medians. We therefore compared the proportions of participants with WML volumes of >300 mm^3 in CKD and control groups. WMLs > 300 mm^3 were present in 6 of 82 (7%) of CKD participants and in 2 of 63 (3%) of healthy controls (P=0.5).

ROI volumes and eGFR within CKD group

Comparisons of CKD participants with eGFR <45 versus ≥45 mL/min/1.73m^2, adjusted for age and sex, showed that the lower eGFR group had higher frontal WM volume than the higher eGFR group (P=0.04) (Table 3). Sensitivity analysis excluding transplant recipients showed no significant differences between the two eGFR groups (Table S5). In analyses of ROI volumes with eGFR as a continuous variable (adjusting for age, sex, race, prematurity, hematocrit, and whether the participant had RRT at age ≤ 5 years), lower eGFR was associated with higher WM volumes in the whole brain (P=0.05) and frontal (P=0.04) ROIs. (Table S6). However, in both analyses, FDR-adjusted P values (Q values) were not significant (Tables 3 and S6).

ROI volumes and kidney transplant status within CKD group

Comparisons between non-transplant CKD subjects and kidney transplant recipients, adjusted for age and sex, showed that kidney transplant recipients had lower GM volumes in the whole brain (P=0.01), frontal (total: P=0.02; left: P=0.02; right: P=0.01), and parietal (left: P=0.01; right: P=0.03) ROIs. In addition, transplant recipients had higher whole brain WM volumes (P=0.04). Although none of these differences remained statistically significant following FDR correction for multiple comparisons, Q values were borderline (Q=0.06) for whole brain GM, right frontal GM, and left parietal GM (Table 3).

ROI volumes and neurocognitive performance

Based on the above results, the following subset of ROIs showing CKD-related differences were selected for analysis as predictors for the outcome of neurocognitive performance: whole brain GM, whole brain WM, frontal GM, frontal WM, and left and right parietal GM. The pre-specified neurocognitive outcomes included in this analysis were the 7 domains that have previously been shown in this cohort to have lower performance in CKD:[5] attention, language, verbal memory, verbal working memory, visual memory, visual spatial, inhibitory control (Table 1). Multiple linear regression analyses within the CKD group, adjusted for age and sex, showed that performance in these 7 neurocognitive domains was not associated with volumes of these selected ROIs (Table 4).

Discussion

The overarching objective of the NiCK study is to help define the biological basis of neurocognitive deficits in CKD using multimodal MRI along with detailed clinical and neurocognitive phenotyping. In this study, we sought to characterize structural brain

abnormalities in children and young adults with CKD using advanced quantitative sMRI methods, and to explore whether CKD-related neurocognitive dysfunction is explained by structural brain differences.

In unadjusted comparisons, we found that CKD participants had lower whole-brain, cortical, and left parietal GM volumes than healthy controls. Although these findings are consistent with prior reports describing cerebral atrophy in CKD patients,23–26,35,36,38–40,43 these differences did not remain statistically significant following FDR correction for multiple comparisons, and did not persist in analyses adjusted for age and sex. In contrast to much of the existing CKD literature, this study showed a very low burden of WMLs in CKD participants, likely due to the relatively early stage of CKD in this cohort (52% had eGFR ≥ 45 mL/min/1.73m2). This large proportion of early stage CKD participants likely also reduced our ability to detect differences in ROI volumes when comparing the CKD and control groups.

We then performed further analyses within the CKD group to analyze the effect of clinical factors including eGFR and kidney transplant status on ROI volumes. These analyses showed that lower eGFR was associated with higher whole-brain and frontal WM volume, but these findings did not remain statistically significant after FDR correction. Kidney transplant recipients had lower GM volumes in whole-brain, bilateral frontal, and bilateral parietal ROIs, and higher whole-brain WM volumes compared to non-transplant CKD participants. After FDR correction, several GM ROIs approached but did not reach statistical significance. Structural brain differences between transplant recipients and non-transplant CKD participants are particularly interesting considering that eGFR was similar in the two groups, making it likely that other clinical factors contribute to brain structural changes. Transplant recipients had lower hematocrit, which has been associated with lower brain volume in prior reports.54 Many of the transplant recipients had previous exposure to dialysis (15 of 21, 71%), and 6 of 21 (29%) had received RRT at age ≤ 5 years, a critical window of neurodevelopment. These past exposures may have contributed to structural brain differences, either due to direct effects of dialysis treatment,32–34,36 prior exposure to periods of high acuity illness or severely reduced kidney function, or perhaps due to prenatal disruption of the neurodevelopmental process. In addition, calcineurin inhibitor therapy, a mainstay of transplant immunosuppression, has been associated with neurotoxicity.55

Somewhat surprisingly, neurocognitive performance in the CKD group was not associated with ROI volumes in our analyses. In functional brain imaging studies, the frontal and parietal lobes have been associated with specific neurocognitive functions including verbal reasoning (left temporo-parietal), spatial processing (right temporo-parietal), and attention (frontal-parietal network).[56–58] Despite our observed CKD-related differences in frontal and parietal ROI volumes, and the lower neurocognitive performance in this cohort in domains historically related to those ROIs, differences in brain structure did not appear to explain poorer neurocognitive performance. This suggests that neurocognitive impairment in CKD may have a functional rather than structural basis, possibly due to changes in functional connectivity and/or blood flow. Further analyses of other MRI modalities in the NiCK study, including resting state blood oxygenation level dependent functional MRI and arterial spin labeled MRI, may help to address this question.

Overall, our findings are relatively reassuring for individuals with early-stage CKD, where we found relatively few structural brain differences and a very low burden of WMLs. However, kidney transplant appeared to be associated with some structural brain changes including global and regional cerebral atrophy.

A major strength of this study is that it is one of the largest prospective neuroimaging studies in children and young adults with CKD. Our analysis of sMRI data using an advanced, validated, automated processing pipeline with strict QC methods provided high-data quality while minimizing bias. Our precise, quantitative methods of measuring regional brain structures are an important addition to the neuroimaging literature in children with CKD, which has previously consisted of mostly qualitative studies. There are, however, limitations to this study. Although our sample size was relatively large for a study of pediatric/young adult CKD, it is possible that we did not have adequate power to detect structural brain differences between CKD and control groups. However, we note that other similar-sized studies were able to detect group differences in brain structure based on premature birth history or sex.[59,60] We found nominal differences in brain structure between individuals with and without kidney transplant, but these differences did not reach statistical significance after correcting for multiple comparisons. It is possible that the relatively small number of transplant recipients in this study reduced our power to detect such differences. Larger studies will therefore be needed to evaluate how kidney transplant status affects brain structure. The cross-sectional nature of the study does not allow us to assess changes in brain structure over time, or to identify whether the associations we found between sMRI characteristics and kidney disease severity would apply to an individual experiencing a decline in kidney function over time. Although we accounted for a number of co-variates in our analyses, it is possible that other confounders could affect brain structure in this population. Although our analyses adjusted for age and sex, it is possible that other factors (such as pubertal stage) may have affected brain maturation and regional brain volumes in this age group.[60]

As part of our hypothesis-driven analysis, we selected 19 ROIs *a priori* from the list of 148 ROIs following tissue segmentation. This approach to data reduction means we did not examine CKD-related findings in other brain ROIs that were ascertained in our imaging. Due to our analyses of multiple ROIs, we performed FDR correction to adjust for multiple comparisons. Although FDR is less conservative than Bonferroni correction, we must note that there are concerns that FDR correction can also increase the rate of Type II errors, particularly in neuroimaging research.[61] We therefore chose to report and discuss our findings from both uncorrected and FDR-corrected analyses. We also limited our neurocognitive analyses to those domains and ROIs in which we found CKD-related differences in this cohort. We therefore cannot assess whether brain structure and neurocognitive functioning may be related in other domains and ROIs.

In summary, we found that early stage CKD in children and young adults is associated with relatively subtle differences in brain structure, but these differences are more prominent in kidney transplant recipients, including global and regional cerebral atrophy and increased global white matter volume. However, these differences in brain structure were not associated with neurocognitive performance, suggesting a functional rather than structural

basis for neurocognitive impairment in CKD. Further studies using other imaging modalities may help to elucidate the functional basis for CKD-related neurocognitive dysfunction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1:

Baseline demographic and clinical characteristics of CKD and control groups

Characteristic	CKD (n=82)	Control (n=63)	*P*
Age, years	**16.3 +/− 3.8**	**15.9 +/− 4.0**	**0.5**
Male sex	54 (66%)	33 (52%)	0.1
African-American race	20 (24%)	23 (37%)	0.1
Annual income ≤$36,000 $36,000-$75,000 >$75,000	 32 (40%) 15 (19%) 33 (41%)	 21 (34%) 15 (24%) 26 (42%)	0.6
Private insurance	55 (68%)	43 (69%)	0.9
Maternal education High school or less College Post-graduate	 38 (46%) 33 (40%) 11 (14%)	 22 (35%) 24 (38%) 17 (27%)	0.1
Premature birth	28 (34%)	10 (16%)	**0.01**
Hematocrit	38.2 +/− 4.8	41.4 +/− 3.4	**<0.001**
Duration of CKD, years	9.9 +/− 6.2	-	-
eGFR, mL/min/1.73m^2	48 +/− 24	99 +/− 20	**<0.001**
eGFR category			
≥ 45 mL/min/1.73m^2	43 (52%)		
<45 mL/min/1.73m^2	39 (48%)		
Glomerular diagnosis[a]	27 (33%)		
Urinary protein-creatinine ratio (mg/mg) Median Mean	 0.4 [0.1–1.4] 1.3 +/− 2.4		
Ever on dialysis	15 (18.5%)		
Current functioning kidney transplant	21 (26%)		
First RRT at age ≤ 5 years	6 (7%)		
Neurocognitive performance[b]			
Attention	−0.32 [−0.13, −0.52]		
Language	−0.24 [0.00, −0.50]		
Verbal Memory	−0.96 [−0.50, −1.41]		
Verbal Working Memory	−0.72 [−0.29, −1.15]		
Visual Memory	− 0.44 [−0.13, −0.76]		
Visual Spatial	−0.47 [−0.22, −0.73]		
Inhibitory Control	−0.28 [−0.11, −0.45]		

Continuous variables given as mean +/− standard deviation or median [interquartile range]; categorical variables as count (percentage).

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; RRT, renal replacement therapy

[a]Out of N=81; N=1 missing

[b]difference in *z* scores between CKD and control groups; values in parentheses are 95% confidence intervals. Adjusted for age, race, sex, and maternal education; N=92 CKD and 70 controls. Data previously published in Ref. 5.

Table 2:

Baseline demographic and clinical characteristics of the CKD group, stratified by level of eGFR

Characteristic	eGFR <45 (n=39)	eGFR ≥ 45 (n=43)	*P*
Age, years	**16.5 +/− 4.1**	**16.2 +/− 3.5**	**0.7**
Male sex	**28 (72%)**	**26 (60%)**	**0.4**
African-American race	5 (13%)	15 (35%)	**0.02**
Premature birth	12 (31%)	16 (37%)	0.6
Hematocrit	36.7 +/− 5.1	39.6 +/− 4.2	**0.006**
First RRT at age ≤ 5 years	4 (10%)	2 (5%)	0.4

Continuous variables given as mean +/− standard deviation; categorical variables as count (percentage). CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate (given in mL/min/1.73m^2); RRT, renal replacement therapy

Table 3:

Comparisons of brain ROI volumes within the CKD group, between individuals with eGFR <45 versus ≥45 mL/min/1.73m^2, and individuals with and without kidney transplant.

ROI	Normalized ROI volume, mm^3*				F value‡	*P*	*Q*‡	Normalized ROI volume, mm^3*				F value‡	*P*	*Q*‡
	eGFR <45 (n=39)		eGFR ≥45 (n=43)					CKD Tx (n=21)		CKD non-Tx (n=61)				
	LSM	SE	LSM	SE				LSM	SE	LSM	SE			
Whole brain GM	815,015	5,823	821,488	5,544	0.64	0.4	0.9	800,936	7,714	824,424	4,485	6.83	**0.01**	0.06
Whole brain WM	517,252	2,627	510,815	2,501	3.12	0.08	0.8	520,463	3,584	511,609	2,084	4.50	**0.04**	0.1
Cortex GM	636,690	5,546	638,844	5,280	0.08	0.8	0.9	626,691	7,495	641,651	4,358	2.94	0.09	0.2
Frontal GM, total	241,134	2,599	241,762	2,475	0.03	0.9	0.9	234,160	3,447	243,978	2,005	5.98	**0.02**	0.08
Frontal GM, left	120,502	1,329	120,897	1,265	0.05	0.8	0.9	117,143	1,769	121,937	1,028	5.41	**0.02**	0.08
Frontal GM, right	120,632	1,304	120,865	1,241	0.02	0.9	0.9	117,017	1,726	122,041	1,004	6.24	**0.01**	0.06
Frontal WM	200,658	1,345	196,819	1,280	4.24	**0.04**	0.8	201,010	1,874	197,830	1,090	2.12	0.1	0.2
Temporal GM, left	67,375	575	66,857	547	0.42	0.5	0.9	67,968	785	66,806	456	1.61	0.2	0.3
Temporal GM, right	67,929	635	67,304	604	0.51	0.5	0.9	68,443	869	67,311	505	1.25	0.3	0.4
Parietal GM, left	61,185	816	61,830	777	0.33	0.6	0.9	59,139	1081	62,344	629	6.48	**0.01**	0.06
Parietal GM, right	60,964	833	62,147	793	1.05	0.3	0.9	59,473	1,121	62,312	652	4.73	**0.03**	0.1
Occipital GM, left	45,842	494	46,313	470	0.47	0.5	0.9	45,641	679	46,243	395	0.58	0.4	0.5
Occipital GM, right	46,222	503	46,167	479	0.01	0.9	0.9	46,346	692	46,141	402	0.06	0.8	0.9
Limbic GM, left	23,451	303	23,499	288	0.01	0.9	0.9	23,218	415	23,565	241	0.52	0.5	0.6
Limbic GM, right	22,587	279	22,965	266	0.95	0.3	0.9	22,304	381	22,951	222	2.13	0.1	0.2
Amygdala	2,340	37	2,319	36	0.17	0.7	0.9	2,355	52	2,320	30	0.33	0.6	0.7
Hippocampus	8,410	118	8,260	113	0.83	0.4	0.9	8,474	163	8,282	95	1.02	0.3	0.4
Thalamus Proper	16,855	154	17,107	147	1.39	0.2	0.9	16,986	214	16,988	125	0.00	0.9	0.9
Lateral Ventricles	11,998	855	11,384	814	0.27	0.6	0.9	11,706	1,179	11,665	685	0.00	0.9	0.9

Analyses adjusted for age and sex.

*Raw ROI volumes normalized for intracranial volume (ICV) by dividing ROI volume by ICV, then multiplying by 1,500,000 mm3 (a constant representing the approximate average ICV) to scale to a larger value.

[≠]Degrees of freedom = 81

[≠]False discovery rate-adjusted P values

GM: Gray matter; WM: White matter; SE: standard error; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate (given in mL/min/1.73m^2); RRT, renal replacement therapy; LSM, least squares mean; Tx, transplant recipient

Table 4:

Multiple linear regression analysis, with neurocognitive domain *z* score as the dependent variable and ROI volume as the independent variable

Neurocognitive domain	ROI β coefficient[a] (95% CI) *P* value					
	Whole brain GM	Whole brain WM	Frontal GM, total	Frontal WM	Parietal GM, left	Parietal GM, right
Attention	**0.0013 (−0.043, 0.045) *P*=0.9**	**0.0098 (−0.084, 0.10) *P*=0.8**	**−0.02 (−0.12, 0.079) P=0.7**	**0.053 (−0.13, 0.23) *P*=0.6**	**0.17 (−0.14, 0.47) *P*=0.3**	**0.075 (−0.23, 0.38) *P*=0.6**
Language	**−0.018 (−0.068, 0.033) *P*=0.5**	**−0.027 (−0.14, 0.083) *P*=0.6**	**−0.078 (−0.19, 0.036) *P*=0.2**	**−0.062 (−0.27, 0.15) *P*=0.6**	**−0.10 (−0.46, 0.26) *P*=0.6**	**−0.044 (−0.40, 0.31) *P*=0.8**
Verbal memory	**0.046 (−0.034, 0.12) *P*=0.3**	**0.040 (−0.13, 0.21) *P*=0.6**	**0.15 (−0.024, 0.33) *P*=0.09**	**0.12 (−0.21, 0.45) *P*=0.5**	**0.45 (−0.11, 1.0) *P*=0.1**	**0.32 (−0.23, 0.87) *P*=0.2**
Verbal working memory	**0.032 (−0.046, 0.11) *P*=0.4**	**−0.086 (−0.25, 0.082) *P*=0.3**	**0.058 (−0.12, 0.23) *P*=0.5**	**−0.019 (−0.34, 0.30) *P*=0.9**	**0.23 (−0.32, 0.78) *P*=0.4**	**0.21 (−0.33, 0.75) *P*=0.4**
Visual memory	**−0.0069 (−0.066, 0.05) *P*=0.8**	**0.0042 (−0.12, 0.13) *P*=0.9**	**−0.011 (−0.15, 0.12) *P*=0.9**	**−0.011 (−0.25, 0.23) *P*=0.9**	**−0.025 (−0.44, 0.40) *P*=0.9**	**0.046 (−0.37, 0.46) *P*=0.8**
Visual spatial	**0.0038 (−0.049, 0.057) *P*=0.9**	**−0.012 (−0.13, 0.10) *P*=0.8**	**0.016 (−0.10, 0.14) *P*=0.8**	**−0.071 (−0.29, 0.15) *P*=0.5**	**0.090 (−0.29, 0.47) *P*=0.6**	**0.075 (−0.29, 0.44) *P*=0.7**
Inhibitory control	0.0092 (−0.026, 0.044) *P*=0.6	−0.0076 (−0.084, 0.069) *P*=0.8	−0.030 (−0.11, 0.050) *P*=0.5	−0.059 (−0.21, 0.088) *P*=0.4	0.027 (−0.22, 0.28) *P*=0.8	0.029 (−0.22, 0.27) *P*=0.8

N=82 subjects with chronic kidney disease, adjusted for age and sex.

[a] β coefficient indicates difference in domain *z* score per 10,000 mm^3 higher ROI volume

GM: Gray matter; WM: White matter; SE: standard error; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate (given in $mL/min/1.73m^2$); RRT, renal replacement therapy; LSM, least squares mean; ROI, region of interest; CI, confidence interval