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慢性腎臟病人認知功能缺損與海馬迴萎縮之關聯研究

The Association of Cognitive Impairment and Hippocampal Atrophy in Chronic Kidney Disease

張峻源

Chun-Yuan Chang

指導教授：林發暄 博士

Advisor: Fa-Hsuan Lin, Ph.D.

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序言

失智症是全球面對人口老化一項嚴重的課題，對國家社會乃至於家庭個人的衝擊影響尤為深遠。在電機所時就對人腦神經影像有特別的興趣，博班時便選擇在醫工所林發暄教授實驗室中進行失智症人腦影像的相關研究。過去文獻已經發現慢性腎臟病人的認知功能缺損是比正常腎功能人來的顯著，本篇論文藉由核磁共振人腦影像配合臨床腎功能及心智功能評估，分析影像與臨床症狀相關性。

這篇研究的完成首先要感謝台北榮總傅中玲教授的指導，從臨床收集到文章寫作對我助益良多。林發暄指導教授，自我研究生時期選修其人腦映像方法，對神經影像研究目的及方法給予我莫大的啟蒙。

感謝口試委員張楊全教授、郭文瑞教授以及吳文超教授在我論文口試時的指導，以不同專業領域的觀點給予寶貴和實用的建議，使我的論文內容更為充實。

感謝Eva、義程，這幾年相關的程式及實驗設計跟問題，給我很多的協助。已畢業的若寧，謝謝她在陽明MRI實驗室的幫忙。謝謝若芙，對統計分析方法給我很多寶貴的意見。感謝實驗室大管家彥如，舉凡出國開會、實驗經驗申請等，幫我大大減少行政上的繁瑣時間。還有許多實驗室來來往往的夥伴，kevin、僕射、tasso等等，讓我在實驗室的生活裡留下豐富的回憶；感謝我醫院的同事：林逸昇以及簡仲賢醫師，在我課業繁忙之餘能幫我分擔臨床的工作。

最後要感謝我體貼美麗的太太彥吟及可愛懂事的女兒淮柔，讓我在工作學業兩忙之際，沒有後顧之憂，不僅放鬆了自己更是充滿甜美的記憶，成全我在過不惑之年完成博士學位的心願，最後辛苦甜美的果實願與你們一起分享。

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摘要

長久以來慢性腎臟病人的認知功能缺損已經廣為注意，也有不少文獻提及，但是腦部結構變化以及認知表現和腎臟功能的關聯則很少被提及，到本論文旨在探討這三者之間的關聯性。本研究共納入了性別年齡相似的慢性腎臟病人(CKD)實驗組及正常腎功能對照組，每位受試者皆有接受腎功能檢查、完整的神經心知功能評估以及腦部核磁共振檢查(MRI)，腦部影像資料藉由軟體 FreeSurfer 分析可以獲得腦部結構的各項參數，並藉此與臨床腎功能與心智功能量表進行統計分析，結果發現相較於對照組，實驗組(CKD)有較低的簡單心智功能評估分數(Mini-Mental State Examination, MMSE)，較小的腦部灰質體積、海馬迴大小及皮質厚度。而估算腎絲球過濾率(eGFR)則與前述四項有明顯相關性，進一步校正干擾因子(confounding factors)線性分析發現，eGFR 對於認知功能、灰質體積及皮質厚度有明顯負相關。結論在本研究中發現腎功能缺損在心智認知功能以及大腦結構之灰質體積，海馬迴體積以及皮質厚度有明顯相關。

關鍵字:慢性腎臟病，心血管疾病、認知、核磁共振影像、灰質體積、海馬迴、皮質厚度

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ABSTRACT

Cognition impairment is well known in patients with chronic kidney disease (CKD). The relationship between brain structure and cognitive performance in CKD patients is still under investigation. The study aimed to quantitatively assessment the relationship between brain structure and cognitive performance in patients with CKD. Thirty-nine patients with CKD and thirty-nine age- and sex-matched control participants were recruited from a tertiary medical center. All participants underwent 3-T MRI scan neuropsychological assessments, and renal function tests. FreeSurfer software was used for imaging processing and analysis, including measurement of cortical thickness and gray matter (GM) and white matter volumes. As a result, compared with control subjects (73.1 ± 7.5 years old), patients with CKD (76.4 ± 8.4 years old) had significantly lower scores on the Mini-Mental State Examination, and forward digit span test ($p < 0.01$). Patients with CKD had smaller cerebral GM volume, hippocampus and decreased cortical thickness ($p < 0.01$**)** relative to the control group. Estimated glomerular filtration rate (eGFR) was correlated with cognitive performance, cortical thickness, GM volume, and hippocampal volume ($p <$

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0.001). Linear regression analysis revealed that eGFR and GM volume were independently negatively associated with cognitive performance ($p < 0.001$), while eGFR and age were negatively associated with cortical thinning and GM volume after controlling for confounding factors. In conclusion**,** this study demonstrated that impaired kidney function is associated not only with poor cognitive performance, but also with small cerebral GM volume and reduced cortical thickness.

Index words: Chronic kidney disease, cardiovascular disease, cognition, magnetic resonance imaging, gray matter volume, Hippocampus, cortical thickness

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1. INTRODUCTION

Chronic kidney disease (CKD) is a major health issue worldwide due to its progressive course and the risk of adverse outcomes. Cognitive impairment has long been recognized in patients with end-stage renal disease (ESRD). The prevalence of cognitive impairment in patients with kidney failure is approximately 30–60% (1-3), more than twice that found in an age-matched general population (4). The previous study demonstrated that middle-aged women with moderate CKD had significantly worse cognitive performance in delayed recalls and backward digit span tests than the control subjects (5). Other studies have also suggested that general cognitive dysfunction or specific cognitive impairments are already present in early stages of CKD (6, 7).

About one-third of middle-aged patients with CKD were found to have silent cerebral white matter (WM) lesions associated closely with vascular nephropathy (8). Some study showed that more white matter hyperintensity (WMH) were noted in the brains of patients with CKD (9) and a study conducted in Japan using indirect semiquantitative measurement determined that the estimated glomerular filtration rate

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(eGFR) was strongly associated with cerebral atrophy (10). Little is known about the relationships between cognitive performance and brain structure features, as characterized by detailed quantitative evaluation, in patients with CKD. Thus, the aim of this study was to analyze the correlation between brain structure and cognitive dysfunction by quantitative measurement of gray matter (GM),WM parameters, and the cognitive performance in patients with CKD.

2. METHODS

2.1 Participants

We recruited patients with CKD and age- and sex-matched control participants from the nephrology and general outpatient clinics, respectively, of Taipei Veterans General Hospital (TVGH). The control subjects are those patients, or their spouses, who visit the clinics without memory complaints and with normal renal function. All patients with CKD have independent activities of daily living despite of various cognitive performances. Among these patients with CKD, 2 patients had stage 2 (mild), 18 patients had stage 3 (moderate), 11 patients had stage 4 (severe), and 8

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patients had stage 5 (kidney failure) CKD. We classified subjects according to eGFR, determined using the abbreviated Modification of Diet in Renal Disease (MDRD) formula (11) :

$eGFR = 186 \times (\text{serum creatinine [mg/dL]}^{-1.154}) \times age^{(-0.203)} \times (0.742 \text{ for women})$.

CKD was categorized according to the criteria of the U.S. National Kidney Foundation Kidney Disease Outcomes Quality Initiative (12). Staging was based on the presence of kidney damage and level of kidney function, defined by eGFR. Kidney damage was defined as pathologic abnormalities or markers of damage, including abnormalities detected by blood or urine test (e.g., hematuria, proteinuria, or pyuria) or imaging studies (e.g., renal cyst or collecting system abnormality), for more than 3 months. Stage 1 was defined as eGFR > 90, stage 2 (mild function reduction) as eGFR of 60–89 mL/min/1.73 m^2, stage 3 (moderate reduction) as eGFR of 30–59 mL/min/1.73 m^2, stage 4 (severe reduction) as eGFR of 15–29 mL/min/1.73 m^2), and stage 5 (kidney failure) as eGFR < 15 mL/min/1.73 m^2.

Exclusion criteria were: current dialysis therapy, including peritoneal dialysis and hemodialysis; pregnancy or breast feeding; history of chemotherapy or radiation

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therapy for any cancer; psychiatric disorder; hearing or visual disability that could affect cognitive tests; clinical evidence of prior stroke; and prior diagnosis of dementia and abnormal activity of daily function.

2.2 Data collection and assessments

We recorded demographic and medical history data for each participant, and measured blood pressure, body weight, and height. The body mass index (BMI) was calculated as body weight divided by body height squared (kg/m^2). All study participants underwent neuropsychological testing and brain magnetic resonance imaging (MRI). Blood samples were collected for the laboratory measurement of serum creatinine level, eGFR, and lipid profile.

2.2.1 Neuropsychological tests

The following tests were administered:

a. Mini-Mental State Examination (MMSE) (13): this 11-item questionnaire, which evaluates subjects' memory, orientation, attention, calculation, and language, was used to screen for cognitive impairment. The highest possible

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score is 30 points, and lower scores reflect poorer cognition.

b. Forward and backward digit span subtests of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (14): these tests require the participant to repeat digits in forward and reverse orders, respectively. The forward digit span test was used to evaluate attention and concentration, and the backward digit span test was used to evaluate attention and working memory.

c. Verbal fluency test (15): this test requires the subject to name as many animals as possible in 1 min. The score is the number of different animals correctly named (one point for each correct response). This test can be used to evaluate language and executive function.

2.2.2 MRI data acquisition & Imaging processing

Brain MRI series were performed using a 3T MRI scanner (Discovery 750; General Electric, Milwaukee, PA, USA) with a T_1-weighted pulse sequence. Imaging parameters were: repetition time/echo time/inversion time ([TR/TE/TI]) = 2,530/3.49/1,100 ms, flip angle = 7°, partition thickness = 1.33 mm, image matrix = 256 × 256, 128 partitions, and field of view = 21 × 21 cm. A fluid attenuation

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inversion recovery (FLAIR) turbo spin-echo sequence was also performed using the following parameters: TR/TE/TI = 6,000/127.7/1,864 ms, slice thickness = 1 mm, image matrix = 256 × 256, 180 slices, and field of view = 26 × 26 cm.

Structural T_1 MRI reconstruction was performed used FreeSurfer, version 5.1.0, which is a set of software tools for the study of neuroanatomy from brain MRI data (16-18). In the cortical surface stream, the tools construct models of the boundary between WM and GM, as well as the pial surface boundary between GM and cerebrospinal fluid (CSF). The GM/WM boundary was further processed to yield two triangulated mesh models with optimally 10242 vertices for each hemispheres (19-21). This cortical surface model was then used to facilitate visualization after "inflation" (19, 20).

After reconstruction of these surfaces, an array of anatomical measures was generated, including cortical thickness, surface area, cortex curvature, surface normal direction at each point on the cortex, and volumes of major subcortical and ventricular structures. Procedures for the measurement of cortical thickness have been previously validated with histological analysis (22) and manual processing (23, 24). In addition, FreeSurfer

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defined a cortical surfaced-based atlas based on average folding patterns mapped to a sphere. Surfaces from individuals were aligned with this atlas with a high-dimensional nonlinear registration algorithm. The registration is based on aligning the cortical folding patterns and so directly aligns the anatomy instead of image intensities. The spherical atlas naturally forms a coordinate system in which point-to-point correspondence between subjects can be achieved. This coordinate system can then be used to morph between an individual subject and standard brain template and to create group maps (similar to how Talairach space is used for volumetric measurements (17)). Moreover, an array of noncortical structures, including the hippocampus, amygdala, lateral ventricles, and thalamus, were also automatically labeled. The total intracranial volume (TIV) is used to normalize volumes by simple division.

WMH was defined as hyperintense changes on intermediate-intensity FLAIR and T_2-weighted images with no corresponding T_1 abnormality. WMH volumes were determined using FLAIR images and by automated WM lesion segmentation, the Lesion Segmentation Toolbox (LST)(25); it was an extension toolbox of Statistical

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Parametric Mapping (SPM8), which is written in Matlab (MathWorks, Natick, Massachusetts). Previous study had showed good validity for determining WMH volume compared with subjective WM lesion rating scale(26).

2.2.3 Statistical analysis

All statistical analyses were carried out using SPSS (IBM SPSS statistics, version 22.0). Demographic and other health-related variables were compared between the moderate to severe CKD and control groups using *t*-tests or chi-squares tests, respectively. All results are presented as means ± standard deviation (SD), unless otherwise noted. Moreover, the brain volumetric measurements were corrected for age and neuropsychological tests were corrected for age and education by multiple linear regression. The t-statistics and associated p values were used in testing whether a given coefficient in regression equation is significantly different from zero. To test the hypothesis that CKD diagnosis was associated with neuropsychological test performance (outcome variable), Pearson correlation analyses and multivariate regression analyses adjusted for potential confounding variables, which were eGFR, age, education, diabetes, hypertensions, and hyperlipidemia, were performed. To

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balance type I and type II errors in multiple comparisons, we defined a significance level of $p < 0.01$. Statistical maps of the difference in cortical thickness were thresholded at a false discovery rate (FDR) of 0.05(27).

3. RESULTS

3.1 Characteristics of the study population

In total, 39 (31M/8F) patients with CKD (mean age, 76.4 ± 8.4 [range, 54–85] years) and 39 (32M/7F) subjects with normal renal function (mean age, 73.1 ± 7.5 [range, 61–85] years) participated in this study. No difference in age, sex, education level, or BMI was observed between groups. Table 1 displays demographic and medical characteristics of the study sample. eGFR values were lower among patients with CKD than among control subjects (35.0 ± 17.3 *vs*. 79.3 ± 13.4, $p < 0.001$). The rates of diabetes, and dyslipidemia were higher among patients with CKD than among control subjects ($p < 0.01$).

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Table 1 Demographic and clinical characteristics of the study population

	CKD (***n*** = 39)	Control (***n*** = 39)	*p*
Sex (male)	31 (79.4%)	32 (82.5%)	0.78
Age (years)	76.4 ± 8.4 (54–85)	73.1 ± 7.5 (61–85)	0.07
Education (years)	10.9 ± 4.9 (0–16)	12.9 ± 4.5 (0–16)	0.07
Body mass index	24.6 ± 3.0	24.0 ± 2.7	0.52
Diabetes mellitus	29 (74.4%)	8 (20.1%)	0.008
Hypertension	34 (85.0%)	24 (61.5%)	0.02
Dyslipidemia	24 (60.0%)	15 (38.5%)	0.035
Serum creatinine (mg/dL)	2.50 ± 1.50	0.93 ± 0.16	<0.001
eGFR (mL/min/1.73 m^2)	35.0 ± 17.3	79.3 ± 13.4	<0.001
Mini-Mental Status Examination	25.0 ± 4.2	28.4 ± 1.4	<0.001

Data are presented as *n* (%), mean ± standard deviation, or mean ± standard deviation (range). CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

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3.2 Results of neuropsychological testing

Table 2 shows neuropsychological test results. Compared with the control group, patients with CKD had significantly lower scores on the MMSE (28.4 ± 1.4 *vs.* 25.0 ± 4.2) and forward digit span test (11.0 ± 2.1 *vs*. 9.1 ± 2.2; both corrected $p < 0.01$). No difference in the backward digit span test and verbal fluency were observed between groups after correcting for age and education by multiple linear regression model (Table3).

Table 2 Neuropsychological test scores and white matter and gray matter parameters

	CKD (***n*** **= 39)**	**Control** (***n*** **= 39)**	*p*
Verbal fluency	11.7 ± 3.2	10.8 ± 3.1	0.04
Forward digit span	9.1 ± 2.2	11.0 ± 2.1	0.03
Backward digit span	5.8± 2.6	7.0 ± 2.1	0.35
WMH volume (mm^3)	18.8 ± 19.0	12.0 ± 15.1	0.09
Gray matter volume (10^4 mm^3)	45.1 ± 4.3	48.1 ± 3.6	0.004

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White matter volume (10^4 mm^3)	34.7 ± 5.4	38.1 ± 4.4	0.007
Hippocampus (10^3 mm^3)	6.7 ± 0.8	7.5 ± 0.8	<0.001
Total intracranial volume (10^4 mm^3)*	146.0±17.4	149.9±14.3	0.29
Cortical thickness (mm)	2.49 ± 0.15	2.59 ± 0.12	<0.001**

CKD, chronic kidney disease; WMH, white matter hyperintensity. *estimated total intracranial volume; ** Corrected *p* using FDR=0.05

Table 3. Estimates of multiple linear regression models with neuropsychological test scores and brain volume parameters as dependent variables and age, education and CKD as independent variables, showing effects by standardized coefficients (beta value)

	Variables control in the models		
Dependent variable	Age	CKD[a]	Education
MMSE	-0.03	-0.42**	0.25
Verbal fluency	-0.37*	0.24	0.18
Forward Digit span	-0.11	-0.35*	0.15
Backward Digit span	-0.21	-0.10	-0.41**
WMH volume	0.19	0.15	
Gray matter volume	-0.19	-0.32*	
White matter volume	-0.12	-0.31*	
Hippocampus volume	-0.30*	-0.38**	
Total intracranial volume	0.09	-0.14	
Cortical thickness	-0.28*	-0.33*	

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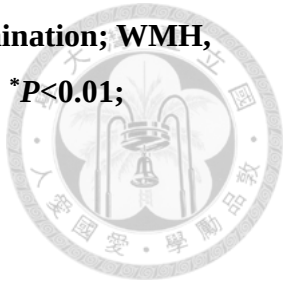
CKD, Chronic kidney disease; MMSE, Mini-Mental State Examination; WMH, White matter hyperintensity; CKD[a], 0=normal control, 1=CKD; *P<0.01; **P<0.0001



3.3 Hippocampus, Gray matter volume and cortical thickness

Brain morphometric values are presented in Table 2 .The effect of CKD status on brain volume after corrected for age by multiple linear regression are shown in Table 3. Detailed regression analyses are listed in supplemental table S1. Cerebral GM , WM and hippocampus volumes are smaller in patients with CKD than in control subjects by 6.2%,8.9% and 10.7% respectively (p < 0.01)(Figure 1). There is no significant difference in WMH volume between two groups. Average cortical thickness was lower among patients with CKD than among control subjects (2.49 ± 0.15 *vs*. 2.59 ± 0.12 mm, p =0.003). Using an FDR of 0.05, we found that 2.7% and 3.5% of brain surface vertices in the right and left hemispheres (n = 10,242 each), respectively, were smaller in the CKD group than in the control group. Figure 2 shows the main differences in cortical thickness between two groups. There are in the bilateral occipito-temporal medial lingual gyri, left frontal pole, bilateral superior

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temporal sulci, left calcarine sulci, left inferior temporal sulcus, right superior circular insula and right parieto-occipital sulcus (Table S2).

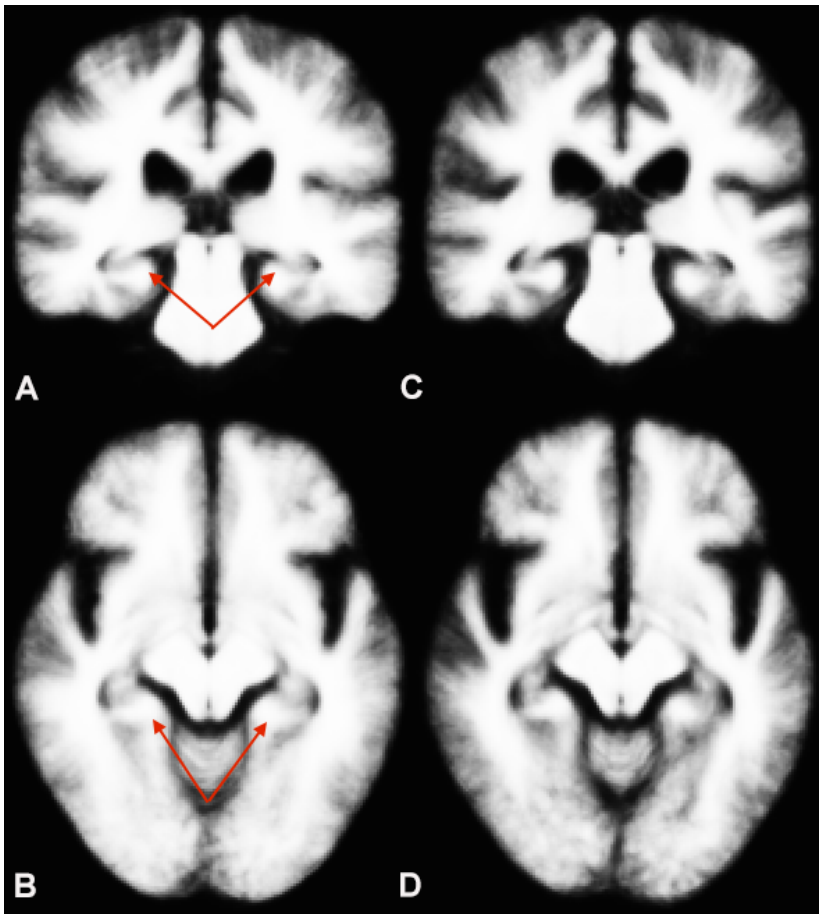

Figure 1 The average brain volume image of control subjects is shown on A(coronal view) and B(axial view) whereas the brain average volume image of patients with CKD is shown on C and D. Red arrow indicates the hippocampus which is located according to Talairach coordinates. Dilated ventricle and perisylvian space and reduced hippocampal volume are noted in CKD group

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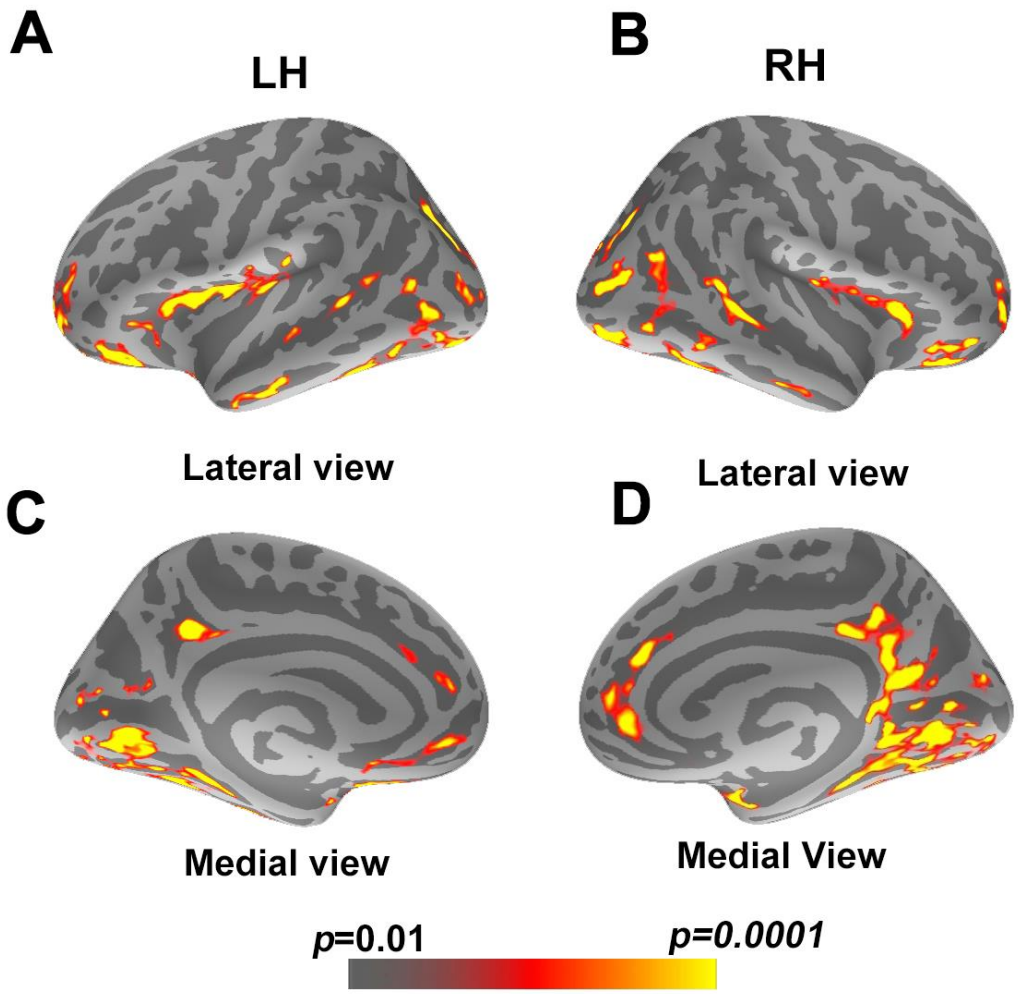

Figure 2 **Maps identifying regions of lesser cortical thickness (highlighted) in patients with CKD relative to control subjects. Main affected regions were the lateral temporal, orbital frontal, and occipital lobes. (A, C) lateral and medial sides of the left hemisphere, respectively; (B, D) lateral and medial sides of the right hemisphere, respectively. Scale for false discovery rate (FDR) *p* values is 0.01–0.0001. LH, left hemisphere; RH, right hemisphere**

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3.4 Correlation analysis of renal function , cognition and brain measurement

eGFR was moderately correlated with MMSE score, cortical thickness, and GM and hippocampal volumes (r = 0.48, 0.43, 0.35, and 0.37, respectively; all $p < 0.001$), but not with WM or WMH volume (r = 0.27 and -0.07, respectively; p =0.02 and p =0.58)(Figure 3). In addition, MMSE score was correlated with GM and hipoccampal volumes (r = 0.42 and 0.31, respectively; both $p < 0.001$;).

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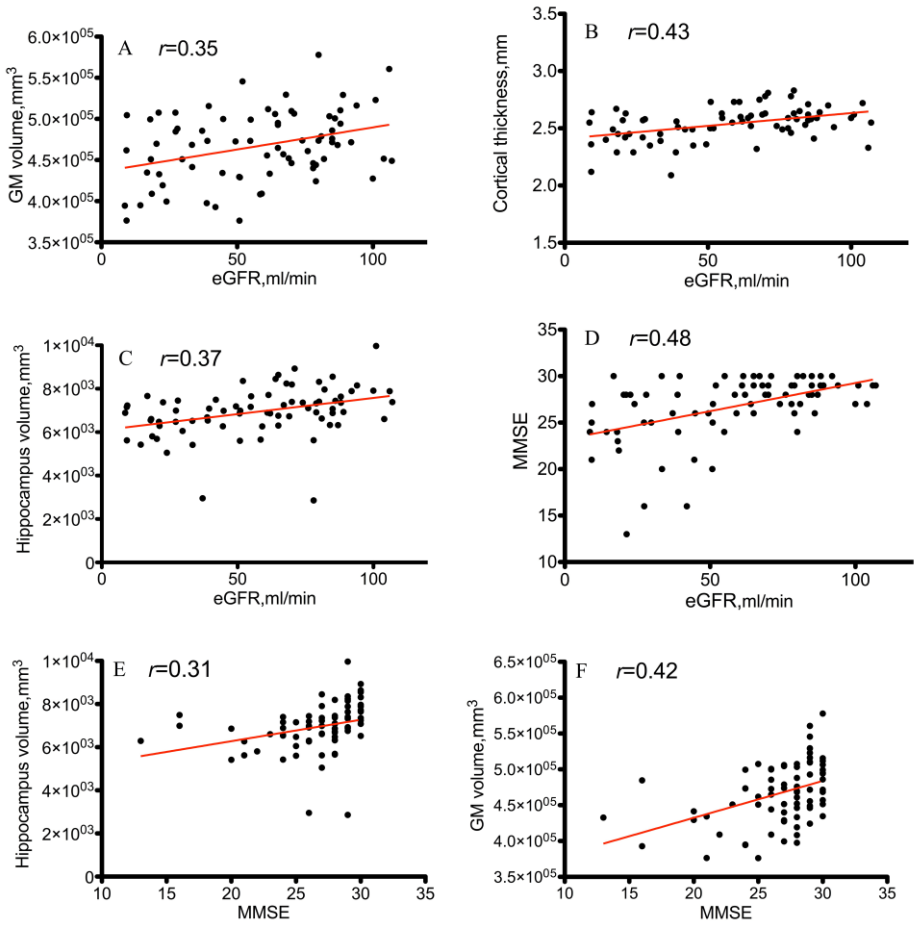

Figure 3 Correlations among eGFR, gray matter volume, and MMSE score

eGFR was correlated with brain structure measurement and cognitive performance. (A-D) while cogntion was correlated with global and hippocampal volume(E,F)

***r* = correlation coefficient. MMSE, Mini-Mental State Examination; eGFR, estimated glomerular filtration rate (mL/min/1.73 m^2)**

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A multiple linear regression model was created for each neuropsychological test to assess the significance of the effects of moderate to severe CKD diagnosis and brain morphometric measurement. GM volume, hippocampal volume and cortical thickness were set as dependent variables while independent variables were eGFR, age, years of education, diabetes, hypertension and dyslipidemia. Table 4 showed eGFR and age significantly predicted hippocampal volume, cortical thickness and GM volume ($p <$ 0.01).

Table 4 Results of multiple linear regression analyzing renal function and age as predictors of brain structure

	eGFR (Standardized coefficient)	Age (Standardized coefficient)	Adjusted $\boldsymbol{R}^2$	*p*
Hippocampal volume	0.41	-0.35	0.30	0.001
Cortical thickness	0.36	-0.33	0.25	<0.001
Gray matter volume	0.32	-0.22	0.15	0.001

Data are $\boldsymbol{R}^2$ = coefficient of determination. eGFR, estimated glomerular filtration rate

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4. DISCUSSION

In this study, we found that eGFR was moderately correlated with cognitive function, cortical thickness, and GM volume. Study participants with reduced kidney function, had impaired cognitive performance, less cortical thickness, and smaller hippocampal volume and GM volume than did subjects with normal renal function. In further regression analysis, we found that renal function and age were major contributing factors for cortical thickness, GM and hippocampal volume after controlling for confounding factors.

A few studies have reported brain atrophy and WMH burden in patients with CKD or renal failure (9, 10, 28-31). A meta-analysis of numerous structural and functional neuroimaging studies that examined children and adults with CKD identified several clear trends, including cerebral atrophy, WMH, cerebral infarction, microbleeding, and cerebral blood flow pattern with affective disorders (31). In the retrospective population-based Rotterdam Scan Study, subjects with low eGFR had smaller brain and deep WM volumes and more WMH (30). No close relationship was

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found between eGFR and GM or WM volume, which is not fully consistent with our results (30). The demographic characteristics of participants in the Rotterdam Scan Study differed from those in the present study subjects, such as lower percentage of diabetes and hypertension, and the higher ratio of male patients to female patients than those in the present population. Nevertheless, the Rotterdam Scan Study lacked neuropsychological assessment, which precluded correlation of brain measurements with cognitive performance. Most previous imaging analyses were focus on grading of WMH and detection of ischemic infarction, which were based on qualitative visual rating, rather than objective quantitative measurement. However, little about quantitative measurement of brain structure in patients with CKD was reported. Furthermore, the present study quantitatively showed the GM, WM and hippocampus volumes decreased by 6.2%, 8.9% and 10.7%, respectively, in patients with CKD compared with control subjects. The hippocampal volume seems to be more affected by eGFR and age than global GM and WM volume.

In present study, significant cortical thinning in bilateral superior temporal sulci and medial lingual gyri was found in these patients with CKD and they showed

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lower global cognition scores and poorer performance in working memory (forward digit span) than those in the control group. In patients with mild cognitive impairment or dementia, cortical thinning has been found in association with cardiovascular risk factors, such as hypertension and diabetes (32). However, eGFR and age were independently related to GM volume and cortical thickness in analyses controlling for the vascular component in the present study. The CKD group also had a significant reduction in hippocampal volume. Hippocampal atrophy has been shown to be an effective marker differentiating people with normal and impaired cognition, regardless of WMH and lacunar infarcts (33). Thus, renal function seems to be an independent factor affecting cortical atrophy and thinning *via* an uncertain mechanism rather than cerebrovascular risk factors. Nevertheless, the difference in WMH between patients with CKD and control subjects didn't reach significant level in this study. This result may be explained by the more frequent occurrence of WMH in patients with advanced CKD and those receiving hemodialysis, whereas about half of patients in our study had moderate CKD.

In line with previous studies (2, 5, 34), the present study also showed that

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patients with CKD had poorer global cognitive function, executive function, verbal and working memory than the control subjects. A recent meta-analysis found that both cross-sectional and longitudinal studies have demonstrated a significantly increased risk of cognitive impairment in patients with CKD (35). Furthermore, another longitudinal cohort study conducted in Japan found that CKD was associated with the risk of dementia in patients with v independent of vascular components (36). These results are consistent with the hypothesis of a connection between renal impairment and dementia risk.

The close relationship between cardiovascular risk factors and dementia with small vessel disease is well established (37). Recently, CKD was found to be related to neurological disorders and this brain–renal connection is thought to involve small vessel disease in kidney and brain, based on hemodynamic similarities (38). The main pathologic vascular feature of CKD and albuminuria, implied impaired kidney vascular integrity, which might also be found in other organs with similar vascular bed. Recent study showed lower eGFR was independently associated with lower cerebral blood flow. The impaired cerebral autoregulation, probably leading to

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hypoperfusion, was thought to increased risk of dementia (39). Furthermore it has been suggested that various toxins have been involved in the pathogenesis of cognitive impairment in uremic patients(40). Oxidative radicals, elevated serum homocysteine level and inflammation have also been related to cognitive impairment in dialysis patients. These toxic substance could lead to vascular endothelial dysfunction and thus aggravate atherosclerosis and increase risk of dementia(41). These studies implied that impaired renal function, as measured by decreased eGFR, with alterations in water and electrolytes balance, accumulation of vasoactive species, and chronic inflammation is related to cerebral small vessel disease, independent of cardiovascular risk factors (30). Such findings are consistent with our study results: impaired eGFR is correlated with reduced GM volume and global cognitive performance, independent of other cardiovascular disease. In contrast, some study showed that mild CKD was associated with an increased risk of Alzheimer disease (AD) (36). The longitudinal BRain IN Kidney disease (BRINK) study found smaller GM volume in region of interests (ROIs) associated with both AD (tempo-parietal areas) and vascular cognitive impairment (VCI)(frontal lobes), worse cognition

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function than patients without CKD(42, 43). Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS) reported both Alzheimer type and vascular pathology were found in most elder sample with cognitive decline by necropsy(44). Thus the possibilities of mixed AD and VCI in CKD group should be also taken into account.

The strengths of this study include the examination of patients with moderate CKD and the use of automated MRI analysis, which make it possible to accurately quantify cortical thinning and GM and WM atrophy and to investigate subcortical WM lesions. The associations between CKD and cognitive performance, cortical GM volume, cortical thickness, as well as eGFR were clearly demonstrated. To my knowledge, this study is the first study on cognitive impairment in patients with CKD based on comprehensive quantitative measurement of brain structure and renal function.

This study has some limitations. First, diabetes was more prevalent among patients with CKD than among the control subjects, reflecting a similar difference in the Taiwanese population (the prevalence of diabetes is about 15% in individuals with

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and 4% in those without CKD) (45). To eliminate the effect of this difference, analysis with multiple linear regression model adjusted for age, education, diabetes, and other comorbidities was applied. Second, patients in the present study were recruited from a tertiary medical center, rather than from a community-based hospital, which may have led to selection bias. Third, smoking is indeed a major cardiovascular factor and it was not controlled in the present study. This might cause some bias. Forth, the present study did not perform CSF markers check-up and PET isotope study, the possibilities of prodrome of AD in CKD group cannot be excluded. Finally, though cortical thickness, GM volume, and MMSE score were lower in the CKD group than in the control subjects, the cause–effect relationships between renal function, brain morphometric features and cognitive performance remain uncertain because of the cross-sectional study design and lack of longitudinal follow-up.

5. Conclusion

In conclusion, the results of this study show that impaired kidney function is independently related to cerebral hippocampal volume, GM volume, cortical thickness, and cognitive performance after adjusting the confounding vascular risk

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factors. The mechanism of cognitive impairment in patients with CKD may not only be related to small vessel disease but also involved the neurodegenerative process. The results further emphasize the importance of identifying those with subclinical CKD, in whom impaired renal function might play a crucial role in cognitive decline and brain morphometric changes. These patients might benefit from early and appropriate therapy. Clinicians' monitoring of cognitive performance in patients with CKD using brain structure surveys is important. However, more studies are needed to investigate the extent to which any intervention can be beneficial.

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7. Appendix

Supporting information

Table S1 Multiple linear regression analyses of neuropsychological test scores and brain volume parameters

Predictor	β	Standard error	t	*p*	Lower Bound	Upper Bound
Model 1 Neuropsychological test scores						
Test / Predictor	**MMSE**					
Age	-0.001	0.05	-0.25	0.80	-0.10	0.08
CKD[a]	-2.98	0.73	-4.11	**0.00**	-4.43	-1.54
Education	0.18	0.07	2.48	0.02	0.04	0.33
			Verbal Fluency			
Age	-0.15	0.05	-3.26	0.002	-0.25	-0.06
CKD	1.51	0.74	2.06	**0.04**	0.04	2.99
Education	0.12	0.08	1.55	0.13	-0.03	0.27
			Digit span forward			
Age	-0.03	0.03	-1.00	0.32	-0.10	0.03
CKD	-1.65	0.53	-3.10	**0.003**	-2.71	-0.59
Education	0.08	0.06	1.35	0.18	-0.04	0.19
			Digit span backward			
Age	-0.06	0.03	-1.99	0.05	-0.13	0.00
CKD	-0.50	0.53	-0.94	0.35	-1.56	0.56
Education	0.21	0.06	3.83	0.00	0.10	0.32
Model 2 Brain structure volume						
			WMH			
Age	0.40	0.25	1.62	0.11	-0.09	0.90
CKD	5.32	3.99	1.33	0.19	-2.63	13.27
			Gray matter			

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Age	-994.42	566.34	-1.76	0.08	-2122.63	133.78
CKD	-26868.31	9066.69	-2.96	**0.004**	-44930.09	-8806.53
White matter volume						
Age	-784.00	713.88	-1.10	0.28	-2206.13	638.13
CKD	-31897.83	11428.82	-2.79	**0.007**	-54665.20	-9130.45
Hippocampus volume						
Age	-33.90	11.10	-3.05	0.003	-56.00	-11.79
CKD	-681.31	177.66	-3.84	**0.00**	-1035.22	-327.39
Total intracranial volume						
Age	1846.17	2311.67	0.80	0.43	-2758.92	6451.25
CKD	-44870.76	37008.38	-1.21	0.23	-118595.23	28853.71
Cortical thickness						
Age	-0.005	0.002	-2.66	0.01	-0.01	-0.001
CKD	-0.09	0.030	-3.13	**0.003**	-0.15	-0.03

Note:β=unstandardized beta coefficient, t=test statistics, CKD[a]: 0=normal control, 1=CKD, CKD, Chronic kidney disease; MMSE, Mini-Mental State Examination,; WMH, White matter hyperintensity

Table S2 Distribution of decreased cortical thickness in both hemispheres

Left hemisphere	Right hermispehre
G_and_S_transv_frontopol	G_oc-temp_med-Lingual
G_oc-temp_med-Lingual	Lat_Fis-posterior
S_calcarine	S_circular_insula_superior
S_occipital_ant	S_oc_sup_and_transversal
S_temporal_inferior	S_parieto_occipital
S_temporal_superior	S_temporal_superior

G: Gyrus; S: Sulcus. Correct *p* value was set to 0.01 by FDR of 0.05.

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