Somatic depression in the picture

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Chapter 4

Gray matter volume and white matter lesions in chronic kidney disease: exploring the association with depressive symptoms

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Abstract

Objective: Chronic kidney disease (CKD) is associated with structural brain damage and with a high prevalence of depression. We therefore investigated structural brain alterations in both gray and white matter in CKD patients, focusing on depression-related (frontal-subcortical) regions.
Methods: This cross-sectional MRI study in 24 CKD patients and 24 age- and sex-matched controls first tested whether CKD was associated with regionally lower gray matter (GM) volumes and more severe white matter lesions (WMLs). In exploratory sub-analyses it was examined whether differences were more pronounced in CKD patients with depressive symptoms.
Results: CKD patients showed lower global GM volume (p=0.04) and more severe WMLs (p=0.04) compared to controls. In addition, we found substantial clusters of lower GM in the bilateral orbitofrontal-cortex for CKD patients, which were however non-significant after proper multiple-comparison-correction. In exploratory analyses for depressed CKD patients, reduced GM-clusters were mainly detected within the frontal lobe. WML severity was unrelated to depression.
Conclusions: CKD was characterized by differences in brain structure. Although subthreshold, lower GM volumes were observed in depression-related brain areas, and were more pronounced for depressed patients. There is a need for replication in larger and longitudinal studies, as our data suggests WMLs and regional GM reductions may render CKD patients more susceptible for depression.

Introduction

Depression is common in patients with chronic kidney disease (CKD). More than a quarter of patients with CKD have elevated depressive symptoms, which is as much as 40% in the most advanced stage of CKD (stage 5).[1] CKD is associated with a high burden of somatic symptoms, disability, and reduced quality of life,[2,3] predisposing patients to depression.[4]

CKD is also an established risk factor for cerebrovascular disease and subclinical brain changes visualized on MRI, such as white matter lesions (WMLs), reduced white matter integrity, gray matter (GM) atrophy, and hypoperfusion.[5-7] These abnormalities can be caused by toxic processes and ischemia resulting from a range of underlying processes associated with CKD, such as chronic hypertension, uremia, inflammation, and vascular calcification.[8-10] Furthermore, hemodialysis (HD) treatment can alter tissue hydration and/or perfusion, which could have additional damaging effects on the brain.[10,11] Brain alterations associated with CKD may be partly responsible for the high prevalence of depression in patients with CKD.[6,7,12,13]

The vascular depression hypothesis proposes that disruption of frontal-subcortical networks, due to cerebrovascular disease, may lead to depressive symptoms.[14,15] A late age at onset of depression, the presence of cardiovascular risk factors, and cerebrovascular abnormalities are proposed characteristics of this vascular depression subtype. Some recent meta-analyses including longitudinal and cross-sectional studies in the elderly and in patients with a recent stroke showed that the presence of WMLs was associated with depressive symptoms.[16,17] In addition, reduced gray matter volumes within the frontal and limbic areas are suggested to play a role in the pathophysiology of depression later in life.[18]

Although both depression and structural brain alterations are common in patients with CKD, very few studies have evaluated whether brain changes in patients with CKD are related to depressive symptoms. Nevertheless, some studies that focused on *perfusion* in patients with CKD stage 4 and 5 (no dialysis), observed perfusion changes in depression-related brain areas (e.g. the orbitofrontal cortex (OFC)), which were associated with depressive symptoms.[19] To our knowledge, no studies so far focused on the relation between *brain structure* and depression in the context of CKD. Volumetric neuroimaging studies in CKD patients most consistently reported lower GM volumes in structures within the frontal and temporal lobes, such as in the hippocampus, OFC, and the cingulate cortex.[5,12,20,21] Interestingly, these regions have also been found to be reduced in depressed patients.[18] Abnormalities in these regions may therefore play a role in the association between CKD and depression. Of note, CKD has been associated with diffusely reduced GM volumes, including regions that have not specifically been associated with depression as well.[12] As much as 30-70%

of CKD patients are reported to have WMLs.[22-24] Some studies suggested that lesion severity (number and size) and lesion localization (frontal-subcortical) are of importance in the association between WMLs and depression in late life.[25-27] To date, none of the existing studies that reported on the presence and severity of WMLs in CKD patients examined the localization of WMLs.[22-24,28,29]

The aim of the present study was to compare GM volumes and the presence and severity of WMLs in patients with CKD to persons without CKD. We specifically examined whether depression related areas (i.e. frontal-subcortical) were affected. We hypothesize that differences will be more pronounced in patients with depressive symptoms; this was examined in exploratory sub-analyses.

Methods

Participants

MRI data of 24 patients with CKD stages 4 and 5 (mean age 59 years; 21% female), and 24 age- and sex-matched control participants (mean age 57 years; 29% female) were derived from the Depression In the Picture (DIP) study. CKD patients were recruited at the University Medical Center Groningen, Martini Hospital Groningen and Dialysis Center Groningen. Healthy control participants were recruited by means of advertisements at public places and in local newspapers.

Participants of the DIP study had to be older than 18 years. CKD patients had to be in stage 4 or 5 (GFR<30 mL/min/1.73 m^2); either pre-dialysis or receiving hemodialysis or peritoneal dialysis (stage 5D). General exclusion criteria were MRI incompatibility, cerebrovascular accidents (CVA), and past or current psychiatric diagnoses other than depressive and anxiety disorders, as these potentially confound results. Specific exclusion criteria for the control group were: a diagnosis of CKD or cardiovascular disease (myocardial infarction, heart failure, CVA, serious stenosis of a major vessel); BDI score ≥10; past or current diagnosis of depressive or anxiety disorder. Furthermore, depressed CKD patients with concrete suicidal plans and currently non-depressed CKD patients with a history of depressive or anxiety disorders were excluded. The study protocol was approved by the local Medical Ethics Committee and all participants gave written informed consent before entering the study.

Measurements

All participants were screened for depressive symptoms using the Beck depression inventory-II (BDI-II).[30] When CKD patients had at least mild symptoms of depression (BDI>13) at screening, they were considered to have elevated depressive symptoms (N=10).[31] The reason for setting different BDI thresholds for CKD and healthy controls, is that CKD patients generally have

higher BDI scores due to somatic symptoms. Excluding patients with a BDI≥10 may therefore result in a selection bias towards relatively healthy patients in the non-depressed group. In addition, psychiatric diagnoses were established using the semi-structured psychiatric interview Mini-Schedules for Clinical Assessment in Neuropsychiatry (Mini-SCAN) according to the Diagnostic and Statistical Manual of mental disorders, fourth edition (DSM-IV) criteria,[32] administered by trained interviewers. Demographic variables and the presence of hypertension and diabetes were assessed by a self-report inventory. For CKD patients, presence of hypertension and diabetes, and laboratory values were also obtained from medical records.

Data acquisition

Participants underwent a MRI scan in a 3-Tesla MRI scanner, with a SENSE 32-channel head coil (Philips Intera, Best, NL). A three-dimensional gradient-echo T1-weighted sequence was used to acquire anatomical images (170 slices; TR=9 ms; TE=3.6 ms; matrix=256x231; voxel size=1x1x1 mm; scan duration=4:11 min). In addition, T2-weighted FLAIR scans were used (180 slices; TR=8000 ms; TE=355 ms; matrix=256x255; voxel size=1x1x1 mm; scan duration=4:56 min).

Data preprocessing Voxel Based Morphometry (VBM) analyses

Statistical Parametric Mapping software (SPM12), implemented in Matlab 7.8.0, was used to preprocess and analyze the MRI data. First, the images were manually reoriented to the anterior commissure. Then, the standard segmentation option in SPM 12, with the 'light clean-up' setting was used to segment the images into GM, white matter (WM), cerebrospinal fluid, skull, and soft tissue outside the brain. Diffeomorphic Anatomical Registration Trough Exponentiated Lie algebra (DARTEL) was used for normalization and modulation of the images. All individual deformation fields were registered to a DARTEL template, created based on the deformation fields produced during the segmentation procedure. After this, the obtained deformed images were used to generate smoothed, spatially normalized, and Jacobian scaled gray and white images in MNI space. To increase the signal to noise ratio, the GM and WM images were smoothed using an 8 mm full-width-half-maximum Gaussian kernel. Voxels were resampled into 1.5x1.5x1.5 mm.

White matter lesions rating scale

Periventricular and subcortical WMLs were counted if visible as hyperintense on T2-weighted images, and isointense on T1-weighted images. We used the same scoring method as de Groot et al. used previously.[33] When the WML was adjacent to the lateral ventricle it was considered as periventricular, otherwise as subcortical. Periventricular WMLs (pvWML) were scored for three separate

regions: adjacent to the frontal horns (frontal caps); lateral walls (bands); and occipital horns (occipital caps). The severity for each region was determined based on a scale ranging from 0 to 3 (0=none; 1=pencil thin; 2=moderate; 3=large confluent), with a total periventricular score ranging from 0-9. The number of subcortical WMLs (scWML) was rated for the frontal, temporal, parietal, and occipital lobe, and the insula and cerebellum. Distinction between lobes was according to anatomical landmarks, using http://headneckbrainspine.com. The size of the scWMLs were based on their largest diameter and were counted for four categories: small (<3mm), medium (3-10mm), large (>10mm), and confluent. A total scWML volume (in ml) was approximated by considering scWMLs spherical with a fixed diameter of 2 (small), 6 (medium), or 12mm (large) and adding these volumes. The WMLs were scored by a neuro-radiologist (HL). A consensus reading took place by experienced neuro-radiologist (JCG); no discrepancies were found.

Statistical analyses

With SPSS 20.0, demographic and clinical data were analyzed, using chi-square tests and ANOVA. For the *gray matter volume analyses*, Voxel Based Morphometry (VBM) analyses were masked using a study specific explicit mask to optimize sensitivity and to exclusively select true positive GM voxels for analysis, created with the Masking toolbox of Ridgeway et al.[34] We compared total GM volumes between participants with CKD and controls, and subsequently between depressed and non-depressed CKD patients, using ANOVA with a significance level of $p<.05$. We calculated the relative difference of total GM volume between CKD and controls by considering the total GM volume of controls 100%.

Next, two 2x1 ANOVA analyses were performed in SPM12 to compare GM volumes between 1) CKD patients and age- and sex-matched controls, and 2) in a subsequent exploratory analysis, depressed (BDI>13) and non-depressed patients with CKD (age- and sex-matched). For the whole sample, we first tested for effects occurring in a-priori regions of interest that were chosen based on analogue regions found in previous meta-analyses on volumetric differences in (late-life) depression,[18] and in neuroimaging of CKD.[5,12,20,21,35] These ROIs included the anterior cingulate cortex (ACC), the orbitofrontal cortex (OFC), and the hippocampus. A composite mask was created using the WFU pickatlas (http://fmri.wfubmc.edu), based on the automated anatomical labeling (AAL) system. All analyses were performed with a one-sided t-test, as we expected to find lower GM volumes for CKD patients.[20,36] In addition a whole-brain analysis was performed for the whole sample and for depressed versus non-depressed CKD patients (exploratory analyses). Results of the CKD vs. HC comparison were considered significant after family-wise-error (FWE) cluster-correction ($p<.05$), with the initial voxel threshold at $p<.005$ and a spatial cluster extent threshold of

k>50. For effects occurring in our a priori specified ROIs, the area for multiple comparisons control was restricted to the spatial extent of the composite mask. The exploratory analysis was undertaken at the uncorrected threshold of p<.005 and k>50, as this was an underpowered and exploratory analysis. Non-stationarity correction was applied to correct for non-uniformity in image smoothness (http://fmri.wfubmc.edu/cms/software#NS) in all VBM analyses. Furthermore, analyses were corrected for total gray and white matter volume (i.e. Total Brain Volume (TBV)), by using the global values to proportionally scale the original voxel values.

For all *WML analyses*, we used SPSS. First, we compared the pvWML total scores between CKD patients and controls, using ANOVA. In addition, we compared the presence of scWMLs between CKD patients and controls, using Chi-square. As the presence of only one or two scWMLs is easily confused with blood vessels on a T2-weighted scan, scWMLs were considered present if the total count was at least 3 small scWMLs. Furthermore, we analyzed whether the total lesion load differed between CKD patients and controls using the non-parametric Mann-Whitney U test, as lesion load was not normally distributed. Because localization of WMLs in the frontal lobe may be specifically associated with depressive symptoms, we additionally tested whether CKD was associated with a higher (periventricular and subcortical) lesion load in the frontal lobe compared to controls. All analyses were repeated for depressed versus non-depressed CKD patients, in order to explore whether alterations were more pronounced for depressed patients. All analyses were performed using a threshold of p<.05.

Results

Baseline characteristics

The total sample consisted of 48 participants (mean age: 58; SD:13): 24 CKD patients and 24 age- and sex-matched controls. Causes of CKD were diverse: hypertension (N=2), diabetes (N=4), vascular disease (N=2), polycystic kidney disease (N=4), tubulo-interstitial nephritis (N=2), other or unknown (N=10). Eleven CKD patients received hemodialysis treatment (mean vintage: 23 months) and 1 patient peritoneal dialysis (vintage: 2 months) (for details of hemodialysis settings see Supplementary table 1). Mean creatinine was 814 µmol/l for patients with stage 5D and 391 µmol/l for patients with CKD stage 4 and 5. Mean estimated Glomerular Filtration Rate (eGFR) was 16 mL/min/1.73m^2 for patients with CKD stage 4 and 5. Patients with CKD had a significantly lower education level, were more often past or current smokers, and had more often diabetes and hypertension compared with control participants (Table 1). Ten CKD patients with current elevated depressive symptoms were included, of which 7 met the DSM-IV criteria for depression and 2 used anti-depressive medication.

Table 1: Baseline characteristics

			CKD	
	Controls	**CKD (all)**	**DEP-**	**DEP+**
	(N=24)	(N=24)	(N=12)[a]	(N=10)
Age (SD)	57 (12)	59 (14)	56.4 (10)	56.9 (13)
Female	7 (29%)	5 (21%)	3 (25%)	2 (20%)
Right-handed	24 (100%)	24 (100%)	12(100%)	10 (100%)
Education level:				
Low	2 (8%)	11 (46%)*	3 (25%)	6 (60%)
Middle	10 (42%)	7 (29%)	5 (42%)	2 (20%)
High	12 (50%)	6 (25%)	4 (33%)	2 (20%)
Smoking status:				
Never	12 (50%)	3 (13%)**	1 (9%)	2 (20%)
current	1 (4%)	7 (29%)	6 (50%)	1 (10%)
Past	11 (46%)	14 (61%)	5 (45.5%)	7 (70%)
Hypertension	3 (13%)	20(83%)***	10 (83%)	9 (90%)
Diabetes	0 (0%)	7 (29%)**	4 (33%)	3 (30%)
BDI (SD)	1.5 (2)	11.7 (14)**	2.5 (2.4)	23.7 (14.6)
Dialysis treatment	-	12 (50%)	6 (50%)	4 (40%)

SD = standard deviation; CKD = chronic kidney disease; DEP- = no elevated depressive symptoms; DEP+ = elevated depressive symptoms; BDI = Beck Depression Inventory; eGFR = estimated Glomular Filtration Rate
*aTwo participants aged >80 were excluded from the analyses because they were not age matched to the comparison group. * p<.05; ** p<.01 ***p<.001*

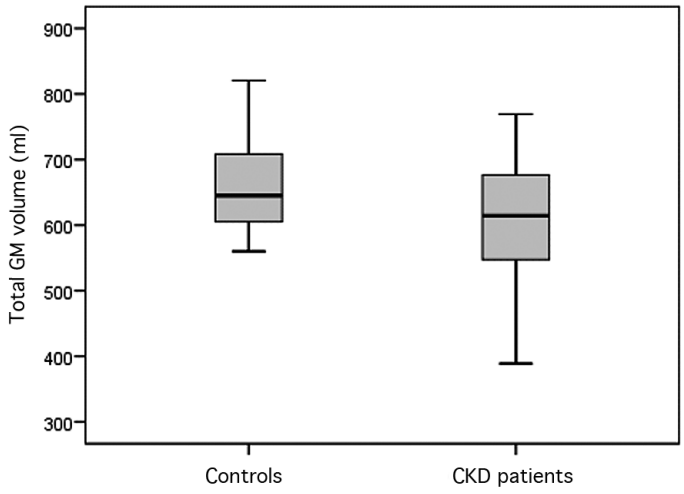

Figure 1: Boxplots of total gray matter (GM) volume for controls and CKD patients (in ml).

Table 2: Results for patients with CKD versus controls: SV-corrected (p<.05) and uncorrected ROI analyses, with an initial threshold of p<.005 and k>50.

Region	k	*p* SV-cluster corrected	MNI-coordinate x	y	z	T	Z	*p* peak uncorrected
Orbitofrontal cortex	384	.31	39	60	-12	3.37	3.17	.001
	355	.34	-14	62	-17	3.55	3.32	<.001
	141	.59	39	34	-18	3.30	3.11	.001
	114	.63	20	64	-17	3.75	3.49	<.001

ROI = region of interest; GM = gray matter; k = cluster size (based on voxels of 1.5 x 1.5 x 1.5mm); MNI-coordinate = coordinates of the voxel showing peak significance in mean Montreal Neurological Institute (MNI)-space; SV = small volume. Bilateral ROIs included in the analyses: orbitofrontal cortex, hippocampus, and anterior cingulate cortex based on the corresponding Automated Anatomical Labeling (AAL) Labels.

Table 1 also shows baseline characteristics separately for CKD patients with and without elevated depressive symptoms. There were no significant demographic and clinical differences between these groups.

Total gray matter volumes

Participants with CKD had a significant 8% lower total GM volume (in ml) compared to controls: 610 (SD=90); 660 (SD=80); p=.04) (figure 1). Depressed and non-depressed participants with CKD did not differ with respect to their total GM volumes (GM volumes: 610 (SD=0.07); 630 (SD=0.10); p=0.63. respectively).

VBM: CKD versus controls

In the ROI analyses, four clusters located in the bilateral OFC were observed at the initial voxel threshold at p<.005 and the spatial cluster extent threshold of k>50 (k=384; k=355; k=141; k=114), but these did not survive small volume (SV) correction (Table 2). There were no clusters in the hippocampus and the ACC. Whole-brain VBM analyses did not reveal significant FWE-corrected clusters of reduced GM volume for CKD. However, 12 clusters were observed at the initial uncorrected voxel threshold, most of these were located in the bilateral precuneus and bilateral OFC (supplementary table 1; figure 2A).

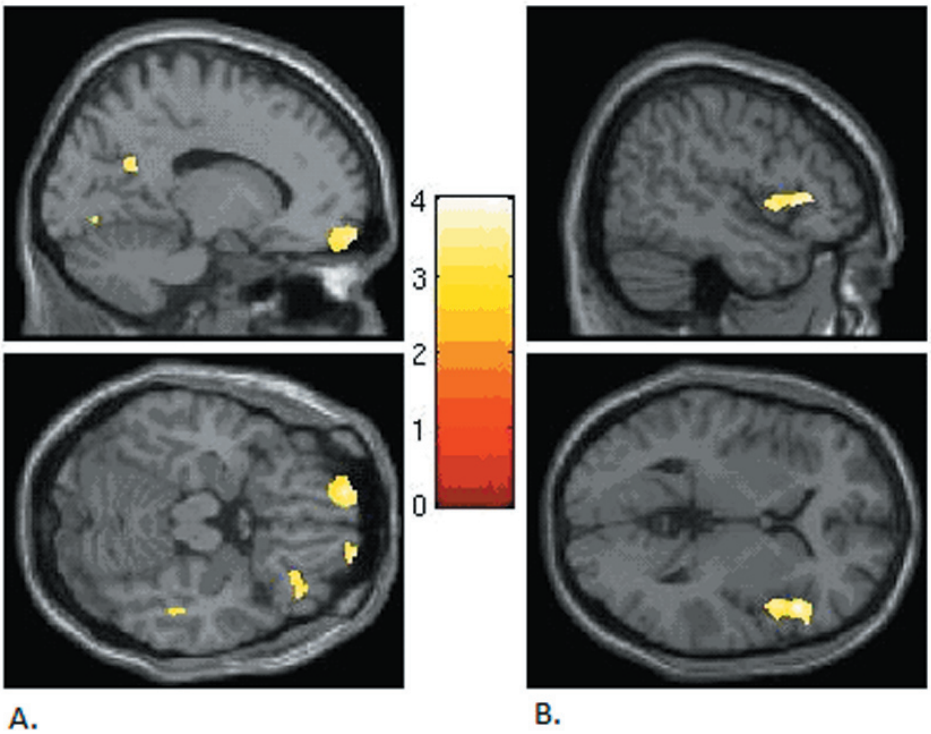

Figure 2: A. Bilateral clusters in the OFC for CKD compared to controls (N=48; MNI coordinates: -14 62 -18). B. Cluster in the left IFG for depressed versus non depressed CKD patients (N=24; MNI coordinates: 48 11 3). Images are presented in neurological convention.

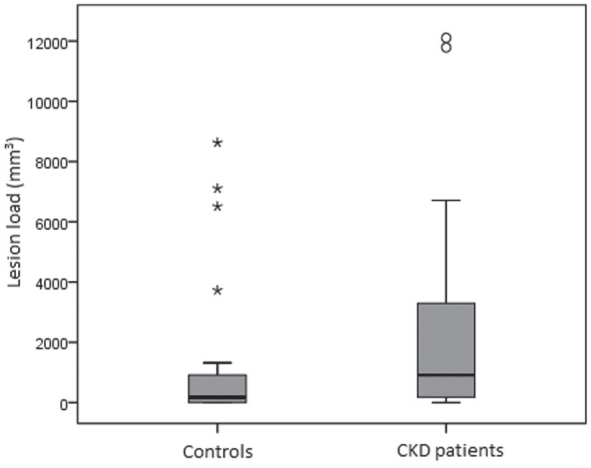

Figure 3: Boxplots of lesion load for controls and CKD patients. Circles depict mild outliers and asterisks depict extreme outliers (whiskers and boxes represent the four quartiles without outliers).

Table 3: Results for depressed (N=10) versus non-depressed (N=12) CKD patients: uncorrected whole brain analyses, at p<.005, uncorrected; k>50.

		MNI-coordinate					*p* peak uncorrected
Region	**k**	**x**	**y**	**z**	**T**	**Z**	
Inferior frontal gyrus	429	48	21	3	4.09	3.45	<.001
Orbitofrontal cortex	92	30	50	-3	4.07	3.43	<.001
	55	-44	36	-5	3.73	3.21	.001
Precuneus	110	10	-73	22	3.74	3.22	.001
Inferior temporal gyrus	61	56	-21	-35	3.61	3.13	.001

k = cluster size (based on voxels of 1.5 x 1.5 x 1.5mm); MNI-coordinate = coordinates of the voxel showing peak significance in mean MNI-space (defined by Montreal Neurological Institute).

VBM exploratory analysis: depressed versus non-depressed CKD patients

In the whole-brain VBM analyses examining depression in CKD patients (Table 3), five clusters were observed at the initial threshold (p<.005, k>50). The largest cluster (k=429) was located in the right inferior frontal gyrus (Figure 2B). Two smaller clusters were located in the bilateral OFC (k=92 and k=55). Furthermore, one cluster was located in the inferior temporal gyrus (k=61) and one in the precuneus (k=110). The cluster overlay function of MRIcron showed that clusters found for depressed versus non-depressed CKD patients did not spatially overlap with the clusters found for CKD versus controls.

WMLs: CKD versus controls

CKD patients had more severe pvWMLs than controls (mean: 3.6 [SD:1.9] versus 2.6 [SD:1.3], respectively; F=4.4; p=.04), as shown in Table 4. This was also significant for pvWMLs of the frontal caps (mean: 1.38 [SD:0.71] versus 0.96 [SD:0.69], respectively; F=4.2; p<.05). The presence of scWMLs did not differ between CKD patients and controls (79% versus 63%; p=.20). However, CKD patients had a higher lesion load than controls (mean rank 29 versus 20, respectively; U=183; Z=-2.18; p=.03) (Figure 3). Of note, the boxplot of Figure 3 shows four outliers in the control group, which represent relatively old hypertensive participants. In addition, the two outliers of the CKD group represent relatively old hypertensive patients on hemodialysis. Furthermore, lesion load in the frontal lobe tended to be higher for patients with CKD compared with controls (mean rank 28 versus 21, respectively; U=195; Z=-1.92; p=.05).

WMLs exploratory analyses: depressed versus non-depressed CKD patients

As shown in table 4, the presence and severity of periventricular and subcortical WMLs was unrelated to the presence of depression.

Table 4: WML results for CKD patients vs. controls and depressed vs. non-depressed CKD patients

	Controls	CKD	*p*	CKD: DEP-	CKD: DEP+	*p*
pvWMLs severity (M)	2.6	3.6	.04	3.3	3.5	.73
pvWMLs severity: frontal caps (M)	.96	1.4	<.05	1.2	1.4	.40
Presence of >2 scWMLs (%)	63%	79%	.20	47%	53%	.78
scWML severity (M rank)	20	29	.03	11.5	11.5	1.0
scWML severity: frontal lobe (M rank)	21	28	.05	12	11	.60

CKD = chronic kidney disease; DEP+ = depressed; DEP- = non-depressed; pvWML = periventricular white matter lesion; scWML = subcortical white matter lesion; M = mean.

Discussion

This structural neuroimaging study found significantly reduced global GM volume and more severe WMLs in CKD patients compared to age- and sex-matched controls. Moreover, lower regional GM was observed in frontal areas previously associated with CKD, and important for emotion regulation: Robust bilateral clusters were found in the OFC for CKD patients, though effects did not survive proper correction for multiple comparisons. Furthermore, CKD patients had a marginally higher WM lesion load in the frontal lobe compared to controls. In subsequent exploratory analyses comparing depressed versus non-depressed CKD patients, reduced GM clusters were indeed detected in depression-related structures within the frontal lobe. Therefore, the results suggest that frontal lobe pathology in CKD might mediate the increased risk for depressive pathology. Results indicate the need for studies with larger sample sizes in order to objectify the potential role of regional atrophy and WMLs in the relation between CKD and depression.

VBM findings

In line with a previous VBM study comparing dialysis patients with controls,[12] we observed that CKD patients had 8% lower total GM volume compared to age- and sex-matched controls. Although all VBM findings were only observed in FWE-uncorrected analyses, we observed relatively large clusters of reduced GM in the bilateral OFC and precuneus for CKD patients compared to controls. Studies of comparable sample sizes reported volumetric reductions of comparable or even smaller magnitude by using less stringent thresholds.[20,37,38] Previous studies in CKD patients showed reduced GM clusters in both the precuneus and OFC.[12,20] However, the precuneus was not included in our ROI analyses and has not

consistently been associated with depression.[39] In contrast, reduced GM volume in the OFC has been consistently found in patients with late-life depression.[18]

The exploratory VBM analyses showed reduced GM clusters mainly located in frontal brain areas for depressed compared to non-depressed CKD patients. This is in line with the vascular depression hypothesis, which proposes that abnormalities would occur specifically in frontal brain regions.[14,15] We found reduced GM in the OFC, which is thought to be an important part of networks involved in emotional and cognitive processing.[40] It is proposed to play a role in decision making and experiencing pleasure and reward, with especially the last function likely to be impaired in depression.[41] Thus, the observed trends for the bilateral OFC are in line with our initial hypothesis regarding this region as a potential link in CKD and depression. In addition, these observations are in consonance with findings from a previous PET study that found that higher scores on the Hamilton Depression Rating Scale (HDRS) were associated with decreased cerebral glucose metabolism of the OFC in pre-dialysis CKD patients[35] Furthermore, GM reductions in the OFC were observed for depressed cardiac patients compared to depressed patients without cardiac disease.[42] Perhaps, GM abnormalities in the OFC is particularly associated with depression in the context of vascular disease.

The largest and therefore the most compelling cluster of the exploratory analyses was located in the right inferior frontal gyrus (IFG). Previous neuroimaging studies in depression showed GM reductions and abnormal functional activation in the IFG for depressed patients.[43,44] The right IFG is found to be particularly involved in inhibitory processes.[45] Although we cannot draw definite conclusions from the exploratory analyses, the observed trends are in line with the suggestion that CKD patients with reduced GM in frontal areas might be more vulnerable for depressive symptoms. This would be interesting to replicate in a larger sample.

WML findings

CKD patients had a higher severity of both periventricular and subcortical WMLs than controls, which is consistent with previous studies in CKD patients.[22-24,28,29] The presence of WMLs was not significantly different between patients and controls (79% vs. 63% respectively). This is probably due to the age of the current sample.[46] We also tested whether periventricular and subcortical WML severity was larger in the frontal lobe for CKD patients compared to controls, as this potentially poses a vulnerability for the onset of depressive symptoms.[14,25-27] CKD patients had a (borderline) significant larger frontal lesion load compared to controls.

In the subsequent explorations, depressed CKD patients did not differ from non-depressed patients with respect to the presence/absence and severity of WMLs. One explanation may be that WMLs arising in different anatomic locations may relate differently to depression.[25-27] In the current study we were

unable to examine WMLs with more regional specificity. Instead of quantifying WMLs within the frontal lobe, it would be more specific and sensitive to investigate tract-based WM pathology.[27,47] Diffusion Tensor Imaging (DTI) for instance, is a method that can detect more subtle impairments to WM tracts and provides the opportunity to study white matter with more regional specificity.[48]

Strengths, limitations, and implications for future research

The strength of this exploratory study is that -to the best of our knowledge- it is the first to assess structural brain abnormalities as a potential factor in the relation between CKD and depressive symptoms. The main limitation of this study is the small sample size, especially for the sub-analyses comparing depressed and non-depressed CKD patients. Consequently, power was limited to detect only relatively large effect sizes. Future research is therefore needed to confirm whether our trends of regional reduced GM in depression-related areas could be replicated in a larger sample. In addition, a larger sample makes it possible to adjust for factors which could potentially confound the results (e.g. educational level and smoking status). However, it is a challenging task to include a sufficient number of CKD patients for MRI research, because of the poor physical condition of many patients and the related MRI-contraindications. Alternatively, meta-analysis of the few existing studies would be valuable in order to examine the relation between CKD and regional brain alterations with sufficient power. Further, as this was a cross-sectional study, we could not infer causality. In order to examine whether there is a causal pathway from CKD leading to atrophy and WMLs leading to depressive symptoms, or whether brain morphology poses a pre-existing vulnerability, a longitudinal study design is required. Another limitation is that patients with most severe CKD and vascular pathology were possibly under-represented in the sample, due to MRI incompatibilities. In addition, we included both pre-dialysis and dialysis patients, which potentially hampers the comparison of our results with other studies using more homogeneous patient groups, but which increases generalizability across CKD patients. Of note, whether patients were on dialysis or not, was not associated with differences in brain structure (GM: p=0.33; pvWML: p=0.29; scWML: p=0.77). Finally, total scWML volume was approximated based on a visual rating scale instead of a more objective semi-automated segmentation method to measure WML volume.

Clinical implications

If brain alterations would play a role in causing depressive symptoms in CKD patients, this may have important clinical implications. Because of a different depression etiology, patients may be less responsive to traditional depression treatments.[49] Instead, focusing on the prevention of development and progression of brain damage might be more effective in these patients. Clinicians

should particularly monitor modifiable cerebrovascular risk factors such as smoking, cholesterol levels, and hypertension. Cerebrovascular drugs might slow the progression of brain damage.[50] In addition, anti-inflammatory drugs might be effective to reduce CKD- and dialysis-induced inflammation, thereby preventing the progression of cerebrovascular damage and depressive symptoms.[9] Furthermore, exercise is a promising non-pharmacological intervention that has shown to improve brain structure and function -particularly subcortical-frontal brain areas-, as well as cognitive function and depression in older adults.[51] Finally, patients on dialysis should be treated with cooled dialysate, as this provides protection against dialysis-associated brain injury.[11]

Summary and conclusion

We examined whether structural brain alterations in CKD patients were located in depression-related areas, and whether these were more pronounced for patients with elevated depressive symptoms. We found that CKD was associated with globally lower GM volumes and higher WML severity. In addition, CKD patients had a marginally higher lesion load in the frontal lobe and we found trends of lower GM volumes in depression-related brain areas, which were more pronounced for patients with elevated depressive symptoms. WMLs were not associated with depressive symptoms, possibly because of the lack of anatomic specificity in the WML ratings.

To conclude, besides the psychological burden of CKD, brain changes may make patients more susceptible for the onset of depressive symptoms. The results imply the need for future (longitudinal) studies with larger samples to objectify whether and which structural brain abnormalities could possibly underlie the relation between CKD and depressive symptoms, as this might have important clinical implications.

References

1. Palmer S, Vecchio M, Craig JC, et al. Prevalence of depression in chronic kidney disease: Systematic review and meta-analysis of observational studies. Kidney Int. 2013;84(1):179-191.

2. Murtagh FE, Addington-Hall J, Higginson IJ. The prevalence of symptoms in end-stage renal disease: A systematic review. *Adv Chronic Kidney Dis*. 2007;14(1):82-99.

3. Soni RK, Weisbord SD, Unruh ML. Health-related quality of life outcomes in chronic kidney disease. *Curr Opin Nephrol Hypertens*. 2010;19(2):153-159.

4. Chan R, Steel Z, Brooks R, et al. Psychosocial risk and protective factors for depression in the dialysis population: A systematic review and meta-regression analysis. *J Psychosom Res*. 2011;71(5):300-310.

5. Drew DA, Bhadelia R, Tighiouart H, et al. Anatomic brain disease in hemodialysis patients: A cross-sectional study. *Am J Kidney Dis*. 2013;61(2):271-278.

6. Toyoda K, Ninomiya T. Stroke and cerebrovascular diseases in patients with chronic kidney disease. *Lancet Neurol*. 2014;13(8):823-833.

7. Moodalbail DG, Reiser KA, Detre JA, et al. Systematic review of structural and functional neuroimaging findings in children and adults with CKD. *Clin J Am Soc Nephrol*. 2013;8(8):1429-1448.

8. Agildere AM, Kurt A, Yildirim T, Benli S, Altinors N. MRI of neurologic complications in end-stage renal failure patients on hemodialysis: Pictorial review. *Eur Radiol*. 2001;11(6):1063-1069.

9. Brouns R, De Deyn PP. Neurological complications in renal failure: A review. *Clin Neurol Neurosurg*. 2004;107(1):1-16.

10. Lakadamyali H, Ergun T. MRI for acute neurologic complications in end-stage renal disease patients on hemodialysis. *Diagn Interv Radiol*. 2011;17(2):112-117.

11. Eldehni MT, Odudu A, McIntyre CW. Randomized clinical trial of dialysate cooling and effects on brain white matter. *J Am Soc Nephrol*. 2014.

12. Zhang LJ, Wen J, Ni L, et al. Predominant gray matter volume loss in patients with end-stage renal disease: A voxel-based morphometry study. *Metab Brain Dis*. 2013;28(4):647-654.

13. Vu NQ, Aizenstein HJ. Depression in the elderly: Brain correlates, neuropsychological findings, and role of vascular lesion load. *Curr Opin Neurol*. 2013;26(6):656-661.

14. Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charlson M. 'Vascular depression' hypothesis. *Arch Gen Psychiatry*. 1997;54(10):915-922.

15. Krishnan KR, Taylor WD, McQuoid DR, et al. Clinical characteristics of magnetic resonance imaging-defined subcortical ischemic depression. *Biol Psychiatry*. 2004;55(4):390-397.

16. Herrmann LL, Le Masurier M, Ebmeier KP. White matter hyperintensities in late life depression: A systematic review. *J Neurol Neurosurg Psychiatry*. 2008;79(6):619-624.

17. Wang L, Leonards CO, Sterzer P, Ebinger M. White matter lesions and depression: A systematic review and meta-analysis. *J Psychiatr Res*. 2014;56:56-64.

18. Sexton CE, Mackay CE, Ebmeier KP. A systematic review and meta-analysis of magnetic resonance imaging studies in late-life depression. *Am J Geriatr Psychiatry*. 2013;21(2):184-195.

19. Song SH, Kwak IS, Kim SJ, Kim YK, Kim IJ. Depressive mood in pre-dialytic chronic kidney disease: Statistical parametric mapping analysis of tc-99m ECD brain SPECT. *Psychiatry Res*. 2009;173(3):243-247.

20. Qiu Y, Lv X, Su H, Jiang G, Li C, Tian J. Structural and functional brain alterations in end stage renal disease patients on routine hemodialysis: A voxel-based morphometry and resting state functional connectivity study. *PLoS One*. 2014;9(5):e98346.

21. Chiu ML, Li CW, Chang JM, et al. Cerebral metabolic changes in neurologically presymptomatic patients undergoing haemodialysis: In vivo proton MR spectroscopic findings. *Eur Radiol*. 2010;20(6):1502-1507.

22. Martinez-Vea A, Salvado E, Bardaji A, et al. Silent cerebral white matter lesions and their relationship with vascular risk factors in middle-aged predialysis patients with CKD. *Am J Kidney Dis*. 2006;47(2):241-250.

23. Fazekas G, Fazekas F, Schmidt R, Kapeller P, Offenbacher H, Krejs GJ. Brain MRI findings and cognitive impairment in patients undergoing chronic hemodialysis treatment. *J Neurol Sci*. 1995;134(1-2):83-88.

24. Kim CD, Lee HJ, Kim DJ, et al. High prevalence of leukoaraiosis in cerebral magnetic resonance images of patients on peritoneal dialysis. *Am J Kidney Dis*. 2007;50(1):98-107.

25. Taylor WD, Aizenstein HJ, Alexopoulos GS. The vascular depression hypothesis: Mechanisms linking vascular disease with depression. *Mol Psychiatry*. 2013;18(9):963-974.

26. Dalby RB, Chakravarty MM, Ahdidan J, et al. Localization of white-matter lesions and effect of vascular risk factors in late-onset major depression. *Psychol Med*. 2010;40(8):1389-1399.

27. Sheline YI, Price JL, Vaishnavi SN, et al. Regional white matter hyperintensity burden in automated segmentation distinguishes late-life depressed subjects from comparison subjects matched for vascular risk factors. *Am J Psychiatry*. 2008;165(4):524-532.

28. Khatri M, Wright CB, Nickolas TL, et al. Chronic kidney disease is associated with white matter hyperintensity volume: The northern manhattan study (NOMAS). *Stroke*. 2007;38(12):3121-3126.

29. Wada M, Nagasawa H, Iseki C, et al. Cerebral small vessel disease and chronic kidney disease (CKD): Results of a cross-sectional study in community-based japanese elderly. *J Neurol Sci*. 2008;272(1-2):36-42.

30. Beck AT, Steer RA, Ball R, Ranieri W. Comparison of beck depression inventories -IA and -II in psychiatric outpatients. *J Pers Assess*. 1996;67(3):588-597.

31. Beck AT, Steer RA, Brown GK. *Beck depression inventory manual.* 2 ed. ed. ; 1996.

32. Nienhuis FJ, van de Willige G, Rijnders CA, de Jonge P, Wiersma D. Validity of a short clinical interview for psychiatric diagnosis: The mini-SCAN. *Br J Psychiatry*. 2010;196(1):64-68.

33. de Groot JC, de Leeuw FE, Oudkerk M, et al. Cerebral white matter lesions and cognitive function: The rotterdam scan study. *Ann Neurol*. 2000;47(2):145-151.

34. Ridgway GR, Omar R, Ourselin S, Hill DL, Warren JD, Fox NC. Issues with threshold masking in voxel-based morphometry of atrophied brains. *Neuroimage*. 2009;44(1):99-111.

35. Song SH, Kim IJ, Kim SJ, Kwak IS, Kim YK. Cerebral glucose metabolism abnormalities in patients with major depressive symptoms in pre-dialytic chronic kidney disease: Statistical parametric mapping analysis of F-18-FDG PET, a preliminary study. *Psychiatry Clin Neurosci*. 2008;62(5):554-561.

36. Prohovnik I, Post J, Uribarri J, Lee H, Sandu O, Langhoff E. Cerebrovascular effects of hemodialysis in chronic kidney disease. *J Cereb Blood Flow Metab*. 2007;27(11):1861-1869.

37. Egger K, Schocke M, Weiss E, et al. Pattern of brain atrophy in elderly patients with depression revealed by voxel-based morphometry. *Psychiatry Res*. 2008;164(3):237-244.

38. Yuan Y, Zhu W, Zhang Z, et al. Regional gray matter changes are associated with cognitive deficits in remitted geriatric depression: An optimized voxel-based morphometry study. *Biol Psychiatry*. 2008;64(6):541-544.

39. Cavanna AE, Trimble MR. The precuneus: A review of its functional anatomy and behavioural correlates. *Brain*. 2006;129(Pt 3):564-583.

40. Phillips ML, Drevets WC, Rauch SL, Lane R. Neurobiology of emotion perception I: The neural basis of normal emotion perception. *Biol Psychiatry*. 2003;54(5):504-514.

41. Kringelbach ML. The human orbitofrontal cortex: Linking reward to hedonic experience. *Nat Rev Neurosci*. 2005;6(9):691-702.

42. Gilbert AM, Prasad K, Goradia D, Nutche J, Keshavan M, Frank E. Grey matter volume reductions in the emotion network of patients with depression and coronary artery disease. *Psychiatry Res*. 2010;181(1):9-14.

43. Du MY, Wu QZ, Yue Q, et al. Voxelwise meta-analysis of gray matter reduction in major depressive disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2012;36(1):11-16.

44. Fitzgerald PB, Srithiran A, Benitez J, et al. An fMRI study of prefrontal brain activation during multiple tasks in patients with major depressive disorder. *Hum Brain Mapp*. 2008;29(4):490-501.

45. Aron AR, Robbins TW, Poldrack RA. Inhibition and the right inferior frontal cortex. *Trends Cogn Sci*. 2004;8(4):170-177.

46. Galluzzi S, Lanni C, Pantoni L, Filippi M, Frisoni GB. White matter lesions in the elderly: Pathophysiological hypothesis on the effect on brain plasticity and reserve. *J Neurol Sci*. 2008;273(1-2):3-9.

47. Taylor WD, Zhao Z, Ashley-Koch A, et al. Fiber tract-specific white matter lesion severity findings in late-life depression and by AGTR1 A1166C genotype. *Hum Brain Mapp*. 2013;34(2):295-303.

48. Sexton CE, Le Masurier M, Allan CL, et al. Magnetic resonance imaging in late-life depression: Vascular and glucocorticoid cascade hypotheses. *Br J Psychiatry*. 2012;201(1):46-51.

49. Sheline YI, Pieper CF, Barch DM, et al. Support for the vascular depression hypothesis in late-life depression: Results of a 2-site, prospective, antidepressant treatment trial. *Arch Gen Psychiatry*. 2010;67(3):277-285.

50. Brunoni AR, Bensenor IM, Alves TC. Therapeutic interventions for vascular depression: A systematic review. *Rev Bras Psiquiatr*. 2011;33(4):400-409.

51. Erickson KI, Gildengers AG, Butters MA. Physical activity and brain plasticity in late adulthood. *Dialogues Clin Neurosci*. 2013;15(1):99-108.

Supplementary

Hemodialysis settings

Patients were on conventional bicarbonate dialysis with a low-flux polysulfone (F8, Fresenius Medical Care, Bad Hamburg, Germany) or polyamide (Gambro-Hospal, Lund, Sweden) hollow-fiber dialyser. Blood flow and dialysate flow rates were 250-350 ml/min and 500 ml/min, respectively. Dialysate temperature was 36.0°C or 36.5°C. Dialysate composition was as follows: sodium 139 mmol/l, calcium 1.5 mmol/l, magnesium 0.5 mmol/l, chloride 108 mmol/l, bicarbonate 34 mmol/l, acetate 3.0 mmol/l, and glucose 1.0 g/l. The concentration of potassium was 1.0 or 2.0 mmol/l, depending on prevailing plasma potassium concentrations.

Supplementary table 1: Sub-threshold results for patients with CKD versus controls significant at the initial threshold of p<.005.

Whole-brain region	k	*p*	MNI-coordinate					*p*
		FWE-cluster corrected	x	y	z	T	Z	Uncorrected peak
OFC	477	.87	-14	62	-17	3.55	3.32	<.001
	450	.89	39	62	-12	3.41	3.21	<.001
	153	1.0	20	64	-17	3.75	3.49	<.001
	145	1.0	39	34	-18	3.30	3.11	.001
	149	1.0	-33	-73	-11	3.25	3.07	.001
	72	1.0	-32	63	-3	3.11	2.95	.002
Cuneus/post cing cx	838	.56	-14	-55	22	3.57	3.33	<.001
	652	.73	-24	-72	37	3.78	3.51	<.001
	561	.81	24	-60	24	4.03	3.71	<.001
Inferior parietal cx	223	1.0	-62	-48	39	3.72	3.46	<.001
Inferior occipital cx	143	1.0	-24	-88	-12	3.54	3.32	<.001
Lingual gyrus	85	1.0	14	-73	-2	3.17	3.00	.002

OFC = orbitofrontal cortex; post cing = posterior cingulate; cx = cortex; k = cluster size (based on voxels of 1.5 x 1.5 x 1.5mm); MNI-coordinate = coordinates of the voxel showing peak significance in mean Montreal Neurological Institute (MNI)-space; FWE= family wise error.