OPEN

Cognitive Improvement After Kidney Transplantation Is Associated With Structural and Functional Changes on MRI

Marit S. van Sandwijk, MD,[1,2] Ineke J. M. ten Berge, MD, PhD,[1] Matthan W. A. Caan, PhD,[3] Marco Düring, MD,[4] Willem A. van Gool, MD, PhD,[5] Charles B. L. M. Majoie, MD, PhD,[3] Henk-Jan M. M. Mutsaerts, MD, PhD,[3] Ben A. Schmand, MD, PhD,[6,7] Anouk Schrantee, PhD,[3] Leo M. J. de Sonneville, MSc, PhD,[8] and Frederike J. Bemelman, MD, PhD[1]

Downloaded from http://journals.lww.com/transplantationdirect by BhDMf5ePHKbH4TTImqenVCtwyQk6f6gqtEDCq7fOnVnhg0prGw7K9tfIs58euxTD7lRg73dJEg= on 06/08/2020

Background. Several studies have reported improved cognitive outcomes after kidney transplantation, but most studies either did not include controls or lacked extensive neuroimaging. In addition, there is uncertainty whether kidney donation is a safe procedure in terms of cognitive outcomes. **Methods.** We prospectively studied neurocognitive function in kidney transplant recipients. The primary outcome was change in neurocognitive function after 1 year compared with baseline, which was evaluated using the Amsterdam Neuropsychological Task battery and verbal fluency tests. Secondary outcomes included changes in depression and anxiety (measured by the Hospital Anxiety and Depression scale) and changes in fatigue (measured by the Checklist for Individual Strength). We included kidney donors to control for learning effects, socioeconomic status, and surgery. In addition, kidney transplant recipients were evaluated with MRI scans at baseline and at year 1. The MRI protocol included conventional MRI, automated volumetric measurement, diffusion tensor imaging, magnetic resonance spectroscopy, arterial spin labeling, and a resting state functional MRI. **Results.** Twenty-seven recipients and 24 donors were included. For both recipients and donors, neuropsychologic testing scores improved 1 year after transplantation (donation). Recipient improvement significantly exceeded donor improvement on tasks measuring attention and working memory. These improvements were associated with increases in white matter volume and *N*-acetylaspartate/creatine (a marker for neuronal integrity). **Conclusions.** Attention and working memory improve significantly 1 year after kidney transplantation. Learning effects do not account for these improvements because recipient improvement in these areas exceeds donor improvement and correlates with an improvement in white matter integrity after transplantation. Kidney donation appears to be a safe procedure in terms of cognitive outcomes.(Transplantation Direct 2020;6: e531; doi: 10.1097/TXD.0000000000000976. Published online 10 February, 2020.)

Cognitive impairment in chronic kidney disease (CKD) severely impacts quality of life in patients and caregivers and is strongly associated with an increased mortality.[1] It also affects treatment in CKD because it diminishes medication adherence, hinders the capacity to oversee implications of different types of renal replacement therapy (RRT), and results in more frequent hospital admissions. Compared with age-matched controls, the prevalence of cognitive impairment is

Received 3 July 2019. Revision received 19 November 2019.

Accepted 8 December 2019.

[1] Department of Nephrology, Amsterdam University Medical Centers, Location Academic Medical Center, Amsterdam, the Netherlands.

[2] Dianet Dialysis Center, Amsterdam, the Netherlands.

[3] Department of Radiology and Nuclear Medicine, Amsterdam University Medical Centers, Location Academic Medical Center, Amsterdam, the Netherlands.

[4] Institute for Stroke and Dementia Research, University Hospital, LMU Munich, Munich, Germany.

[5] Department of Neurology, Amsterdam University Medical Centers, Location Academic Medical Center, Amsterdam, the Netherlands.

[6] Department of Medical Psychology, Amsterdam University Medical Centers, Location Academic Medical Center, Amsterdam, the Netherlands.

[7] Department of Psychology, University of Amsterdam, Amsterdam, the Netherlands.

[8] Department of Clinical Child and Adolescent Studies, Faculty of Social and Behavioral Sciences, Leiden University, Leiden, the Netherlands.

The authors declare no funding.

M.W.A.C. and C.B.L.M.M. are shareholders of Nico-lab BV.

M.S.v.S., W.A.v.G., C.B.L.M.M., B.A.S., L.M.J.d.S., and F.J.B. designed the study. M.S.v.S., M.W.A.C., M.D., H.-J.M.M.M., and A.S. did the MRI analyses. M.S.v.S. and L.M.J.d.S. did the Amsterdam Neuropsychological Tasks analyses. M.S.v.S. wrote the initial draft of the article. All other authors reviewed the draft of the article, provided expertise for revisions, and approved the final version of the article.

Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.transplantationdirect.com).

Correspondence: Marit S. van Sandwijk, MD, Department of Nephrology, Amsterdam University Medical Centers, Location Academic Medical Center, Amsterdam, the Netherlands. (m.s.vansandwijk@amsterdamumc.nl).

Copyright © 2020 The Author(s). Transplantation Direct. Published by Wolters Kluwer Health, Inc.This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

ISSN: 2373-8731

DOI: 10.1097/TXD.0000000000000976

increased 3-fold in end-stage renal disease (ESRD).[2] Uremic toxins, an abnormal calcium phosphate homeostasis, and an increased burden of cerebrovascular disease are possible contributing factors; this is discussed in more detail elsewhere.[3]

RRT protects against cognitive impairment by removing uremic toxins and improving calcium phosphate homeostasis, but each form of RRT has its drawbacks. Long-term hemodialysis (HD) contributes to cognitive impairment due to intradialytic cerebral hypoperfusion,[4] whereas kidney transplant recipients are at risk for neurotoxicity induced by infections and immunosuppressive medications.[3]

Several studies have investigated whether kidney transplantation can improve cognitive function[5] and these generally report improved cognitive outcomes after transplantation. However, all these studies have their specific limitations. Some are cross-sectional only,[6-12] which by design cannot assess whether kidney transplantation can improve cognitive function in individual patients. Of the prospective studies, some lack a control group,[13-15] implying that learning effects cannot be ruled out. Four prospective studies with a suitable control group remain, of which 3 studies reported improvement after transplantation,[16-18] and 1 study did not find significant differences.[19] Unfortunately, these studies did not include neuroimaging, implying that the underlying anatomic and/or functional substrate of the observed cognitive changes remains unclear. To our knowledge, there are only 6 studies in kidney transplant recipients that combine neuropsychologic testing with limited neuroimaging,[20-25] of which 3 were prospective and included a control group.[23-25] Two of these used resting state functional MRIs and found that functional connectivity improved after transplantation, in some networks to normal levels. This was positively correlated with improved performance on neurocognitive tests. The third study[25] used diffusion tensor imaging (DTI) and found an association between an increased fractional anisotropy (FA) (indicating improved white matter [WM] integrity) and improved executive function in a subgroup of 15 HD patients who received a kidney transplant during 1-year follow-up. There are no prospective studies with more extensive neuroimaging so that many uncertainties regarding the underlying anatomic and/or functional substrate of observed cognitive changes remain. Possible mechanisms include changes in gray matter (GM) and WM volume, WM quality, metabolically important compounds, cerebral blood flow, and connectivity of neuronal networks.

We designed a prospective observational cohort study to assess the cognitive improvement in renal transplant patients before transplantation and at 1 year after transplantation and relate this functional improvement to changes in neuroimaging. The primary outcome was change in neurocognitive function after 1 year in recipients compared with baseline, which was evaluated using the Amsterdam Neuropsychological Task (ANT) battery and verbal fluency tests. We included kidney donors to control for learning effects, socioeconomic status, and surgery. Secondary outcomes included changes in fatigue, depression, and anxiety scores in both recipients and donors. Finally, recipients were evaluated with advanced neuroimaging techniques measuring changes in GM and WM volume, WM quality, metabolically important compounds, cerebral blood flow, and connectivity of neuronal networks.

MATERIALS AND METHODS

We conducted a prospective observational cohort study in kidney transplant recipients and kidney donors. The study was approved by the Academic Medical Center (AMC) Medical Ethics Committee beforehand. All participants provided informed consent, had to be at least 18 years of age, have sufficient visual and hearing acuity, and had to be fluent in either Dutch or English. Kidney transplant recipients had to be scheduled for an ABO-compatible, HLA-nonidentical living kidney donor transplantation before having started dialysis or within 1 year after starting dialysis. Exclusion criteria were pre-existing documented cognitive impairment, uncontrolled psychiatric illness, substance abuse, diabetes mellitus, a history of cerebrovascular disease, other types of brain injury, epilepsy, and contraindications for MRI. These inclusion and exclusion criteria were defined to obtain a relatively homogeneous group of kidney transplant recipients, that is, patients on identical immunosuppression with mostly preterminal kidney insufficiency and without any background cerebral abnormalities associated with neurologic or psychiatric disease, diabetes mellitus, or long-term dialysis.

Kidney transplantation and donation were performed according to standard clinical practice, with kidney transplant recipients receiving standard quadruple immunosuppressive therapy consisting of basiliximab, prednisolone, mycophenolate mofetil, and tacrolimus. Cellular rejections were treated with methylprednisolone; humoral rejections with plasmapheresis, and immunoglobulins.

Kidney transplant recipients were evaluated using neuropsychologic tests, questionnaires, and MRI scans just before and 1 year after transplantation. Kidney donors were evaluated using neuropsychologic tests and questionnaires just before and 1 year after kidney donation. Figure 1 provides an overview of all investigations.

ANT Battery

All participants performed 8 tasks from the ANT battery.[26] This battery consists of computerized tasks measuring speed, stability, and accuracy of the participants' responses. Using visual stimuli, these tasks measure the basic processes that underlie more complex neurocognitive functioning, such as alertness, sustained attention, and major aspects of executive function, that is, working memory, cognitive flexibility, inhibition, and executive visuomotor control. The ANT has been validated to assess neurocognitive performance in many domains associated with a diffuse impact on the brain, such as metabolic disorders, malignancies, psychiatric disorders, and developmental disorders.[27-30] Table S1, SDC, http://links.lww.com/TXD/A241 in the Supplementary Data lists the tasks that were performed. To ensure proper understanding and execution of the tests, all participants were allowed to practice 2 weeks before taking the actual test.

Verbal Fluency

Both letter and categorical verbal fluency were tested. Letter fluency was tested by asking the participants to list as many words as possible within 1 minute beginning with a specific letter: D/A/T at baseline and K/O/M at year 1. Categorical fluency was tested by asking the participant to list as many words as possible within 1 minute within a specific category: supermarket articles and professions at baseline, and animals

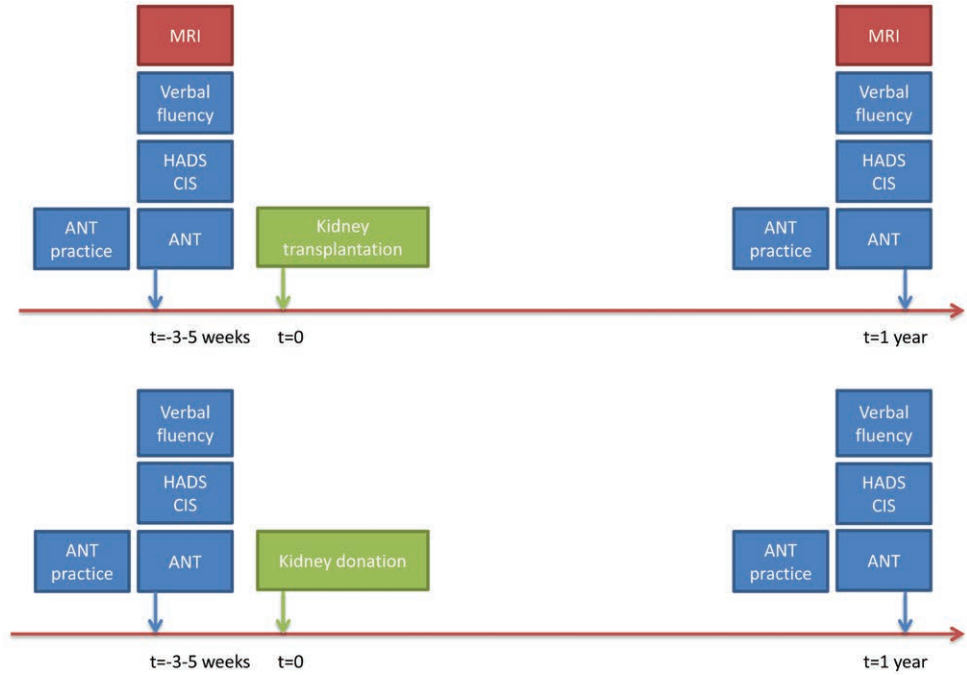

FIGURE 1. Overview of investigations. All investigations were performed 3–5 weeks before and 1 year after transplantation/donation. An Amsterdam Neuropsychological Tasks (ANT) practice session was scheduled 2 weeks before the actual session, to ensure proper understanding and execution of the tasks. CIS, Checklist for Individual Strength; HADS, Hospital and Anxiety Scale.

and kitchen utensils at year 1. These letters and category combinations have been extensively validated previously.[31,32]

Questionnaires

All participants filled out the Hospital Anxiety and Depression Scale (HADS) and Checklist for Individual Strength (CIS) questionnaire. The HADS is an extensively validated scale to assess states of anxiety and depression.[33] It contains 2 7-item scales: 1 for anxiety and 1 for depression, both with a score range of 0–21. A score of 6 or higher on either anxiety or depression indicates a probable anxiety or depressive disorder. The CIS is a validated 20-item self-report questionnaire that captures 4 dimensions of fatigue: subjective experience of fatigue, reduction in motivation, reduction in activity, and reduction in concentration.[34] Each item is scored on a 7-point Likert scale. A score of 35 or higher on the CIS subjective experience of fatigue scale defines severe fatigue.

MRI Acquisition

Patients were scanned using a 3T Philips Ingenia MRI scanner at the Academic Medical Center, Amsterdam. Conventional MRI (3D [three dimensional]-T1, T2, FLAIR [Fluid Attenuated Inversion Recovery], 3D-FLASH [Fast Low Angle Shot]) was used to determine GM and WM atrophy, parenchymal lesion load including leukoencephalopathy, and cerebrovascular disease burden. Furthermore, the 3D-T1 scan was used for automated volumetric measurement (based on voxel-based morphometry) of GM and WM volume to control for subtle volumetric changes. DTI was used to measure FA and mean diffusivity (MD), which are both parameters that can be used to study WM diffusion and microstructural properties. Magnetic resonance spectroscopy (MRS) was performed to measure concentrations of *N*-acetylaspartate, choline, glutamine, and creatine in the frontal WM and the basal ganglia. Arterial spin labeling analysis, an MRI technique that uses labeled blood as an endogenous contrast agent, was used to measure cerebral blood flow. Finally, a resting state functional MRI was obtained to obtain functional connectivity in brain networks. The full scan protocol, as well as image processing details, can be found in the Supplementary Data (Table S2, SDC, http://links.lww.com/TXD/A241).

Outcomes

The primary outcome of this study was defined as the change in neurocognitive performance in kidney transplant recipients at 1 year after transplantation compared with pretransplantation. This was compared with the change in neurocognitive performance in kidney donors at 1 year after donation compared with predonation. Secondary outcomes were changes in fatigue, depression, and anxiety scores, and changes in MRI parameters.

Statistical Analysis

Baseline characteristics were analyzed using *t* tests, Mann-Whitney *U* tests, and chi-square tests, where applicable. CIS, HADS, verbal fluency, and ANT outcomes were compared using repeated-measure ANOVA analysis, with time as a within-subject factor and group as a between-subject factor. The interaction term of (time × group) was used to determine whether the change in neurocognitive performance over time was significantly different between both groups. The MRI results pretransplantation and posttransplantation were compared using multivariate general linear modeling, with the change in the MRI variables as dependent variables under the null hypothesis that change equaled zero. The relationship between MRI and ANT results was explored using linear regression analyses, with changes in ANT outcomes as dependent variables and changes in MRI outcomes as independent variables.

On the primary endpoint, the difference between neurocognitive performance pretransplantation and at 1 year after

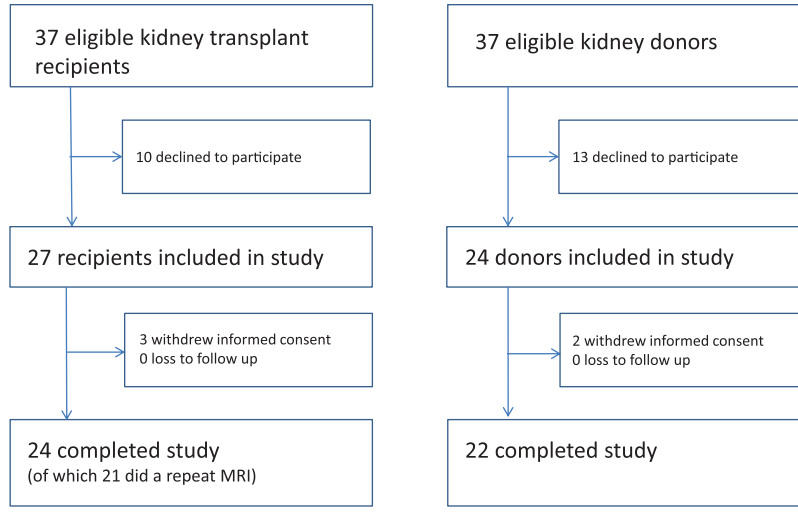

FIGURE 2. Study flow chart.

transplantation was estimated to be >0.8 SD, implying that we needed 25 patients to achieve a power of 0.8, with an α of 0.05. To correct for a 10% dropout rate, we aimed to include 28 patients in both groups.

RESULTS

From November 2013 to October 2015, we approached all eligible patients scheduled for a living donor kidney transplantation or kidney donation who fulfilled the inclusion criteria at the Academic Medical Center in Amsterdam and included 27 recipients and 24 donors (Figure 2). Twenty-four of 27 recipients completed their neuropsychologic evaluation at year 1, and 21 also did a repeat MRI at year 1. Twenty-two of 24 donors completed their neuropsychologic evaluation at year 1.

Table 1 lists the baseline characteristics of both kidney transplant recipients and donors. The groups were well-matched demographically, except for a higher percentage of used participants in the donor group, which was expected beforehand. There was also a trend toward a higher percentage of smokers (55% compared with 27% current or former smokers; $P = 0.087$) and toward a lower amount of alcohol usage in the recipient group ($P = 0.076$).

In Table 2, the renal characteristics of all recipients are summarized. The majority of patients (67%) received a preemptive transplantation, whereas the rest underwent dialysis for an average period of 0.6 years, mostly HD. Because all recipients received a kidney from a living donor, the rate of postoperative complications was low and renal function at 1 year was good, with an average modification of diet in renal disease of 51 mL/min/1.73 m^2. Table 2 also includes a selection of laboratory parameters for which an effect on cognitive function has been described. Not surprisingly, hemoglobin increased (7.1–8.0 mmol/L; $P = 0.002$) and parathyroid hormone decreased (26.2–10.4 pmol/L; $P = 0.028$) after transplantation. Thyroid-stimulating hormone also increased significantly (0.98–1.78 mU/L; $P = 0.028$), but the magnitude of the increase was small and is probably not relevant. All other laboratory values (vitamin D, B1, B6, B12, and folic acid) were within normal range and did not change significantly after transplantation.

Figure 3A–C shows the results of selected representative ANT tasks (memory search letters, pursuit, tracking, and sustained attention). From Figure 3A, it is evident that recipient scores on the memory search letters task improved significantly after transplantation, whereas donor scores remained unchanged. This indicates improved working memory capacity and reduced distractibility in recipients. Pursuit and tracking scores (Figure 3B), which measure executive visuomotor

TABLE 1.
Baseline characteristics

	Recipients (n = 27)	Donors (n = 24)	*P*
Age at transplantation/donation (y), mean ± SD	53 ± 13	55 ± 13	0.53
Gender (% male)	63	50	0.36
Ethnicity (%)			0.22
Caucasian	85	91	
Afro-Caribbean	11	0	
Other	4	9	
Marital status (%)			0.98
Married or long-term relationship	81	82	
Single, divorced, or widower	19	18	
Level of education (%)			0.76
Primary school	14	5	
High school	41	41	
Vocational training	30	32	
Higher vocational training or university	15	23	
Employment status (%)			**<0.001**
Working fulltime	0	46	
Working part-time	37	23	
Unemployed	48	18	
Retired	4	14	
Studying	11	0	
Working less due to illness	48	N/A	
Smoking (%)			0.09
Never	45	72	
Current	7	9	
Former	48	18	
Alcohol use (no. of units per wk), median (interquartile range)	2.0 (0–6)	2.5 (2–8)	0.08

All values as percentages, mean and SD, or median and interquartile range. *P* calculated with *t* test, Mann-Whitney *U* test, or chi-square test where applicable.
N/A, not applicable; SD, standard deviation.

TABLE 2.

Disease characteristics of kidney transplant recipients

	Baseline	At 1 y	*P*
Donor characteristics			—
Donor age, mean ± SD	59 ± 13	—	
Donor gender (% male)	56	—	
Related/unrelated donor (% related)	33	—	
Donor creatinine clearance, mean ± SD	117 ± 27	—	
HLA mismatches, mean ± SD	3.9 ± 1.7	—	
Underlying renal disease (%)			—
Glomerulonephritis	44	—	
Hypertensive nephropathy	19	—	
Polycystic kidney disease	26	—	
Urologic disease	7	—	
Other	4	—	
Previous renal replacement therapy (%)			—
Pre-emptive	67	—	
Hemodialysis	29	—	
Peritoneal dialysis	4	—	
Duration of RRT (y)	0.6	—	
Comorbidity (%)			—
Heart disease	11	—	
Peripheral vascular disease	4	—	
Vital signs, mean ± SD			
Blood pressure (mm Hg)	138/81 ± 17/13	129/81 ± 10/10	**0.03**/0.97
BMI (kg/m^2)	22 ± 4	22 ± 4	0.46
Transplantation characteristics			—
Cold ischemia time (min), mean ± SD	158 ± 28	—	
Second warm ischemia time (min), mean ± SD	31 ± 10	—	
Delayed graft function (%)	0	—	
Postoperative complications (%)			—
Death	—	0	
Graft loss	—	0	
Cellular rejection	—	11	
Humoral rejection	—	4	
Surgical complications	—	7	
Infectious complications	—	59	
Malignancy	—	0	
Kidney function at year 1, mean ± SD			—
MDRD (mL/min/1.73 m2)	—	51 ± 18	
Creatinine clearance (mL/min)	—	63 ± 23	
Proteinuria (g/24 h)	—	0.23 ± 0.19	
Selected laboratory values, mean ± SD			
Hemoglobin (mmol/L)	7.1 ± 0.8	8.0 ± 1.3	**0.002**
25OH-vitamin D2,3 (nmol/L)	59 ± 20	57 ± 23	0.81
Vitamin B1 (pmol/L)	140 ± 34	141 ± 29	0.93
Vitamin B6 (nmol/L)	140 ± 104	126 ± 89	0.62
Vitamin B12 (pmol/L)	562 ± 294	451 ± 292	0.16
Folic acid (nmol/L)	27 ± 15	20 ± 10	0.12
PTH (pmol/L)	26 ± 21	10 ± 7	**<0.001**
TSH (mU/L)	1.0 ± 0.6	1.8 ± 1.4	**0.03**

All values as percentages or mean and SD or median and interquartile range. *P* calculated with *t* tests.

Bold values indicate statistically significant (P < 0.05) values.

BMI, body mass index; MDRD, modification of diet in renal disease; OH, hydroxy; PTH, parathyroid hormone; RRT, renal replacement therapy; SD, standard deviation; TSH, thyroid-stimulating hormone.

control, remained unchanged for both recipients and donors. Pursuit and tracking SDs, because they indicate average distance from the target at each time point, can also be interpreted as measuring tremors. Figure 3B (b and d) shows that pretransplantation and posttransplantation SD scores were not significantly different when compared with healthy donors, which suggests that there were no significant uremic- or tacrolimus-induced tremors. Figure 3C shows the results of the sustained attention task. Both recipients and donors improved, and recipients appeared to improve somewhat more than donors, but the differences between both groups were not significant.

Figure 3D summarizes all ANT tasks. It shows that most test results are within the right upper quadrant, implying improvement in both donors and recipients. Within this quadrant, for tasks below the dotted line, improvement of recipients exceeds improvement of donors. Recipient improvement significantly exceeded donor improvement for the memory search letter task only.

Figure 4A indicates that fatigue decreased significantly in recipients compared with donors ($P < 0.001$). Anxiety scores (Figure 4B) were higher in recipients than in donors and did not change significantly after transplantation ($P = 0.787$). Depression scores (Figure 4C) were higher at baseline but decreased significantly in recipients compared with donors ($P = 0.025$). Figure 4D shows the results of the verbal fluency tests. Both categorical and semantic verbal fluency improved in donors and recipients.

MRI Results

Details of the qualitative MRI analysis can be found in the Supplementary Data (Figure S2, SDC, http://links.lww.com/TXD/A241). To summarize, atrophy scores and WM hyperintensity scores were both low and not significantly different between baseline and at 1-year posttransplantation. There were 4 patients with a lacunar infarction at baseline; this did not increase after 1 year. There were no microbleeds or other abnormalities.

Quantitative MRI results can be found in Figure 5. Volumetric measurements revealed that GM and WM volume increased after transplantation (Figure 5A), at the expense of cerebrospinal fluid volume (as total intracranial volume must always remain constant). Using free water imaging analysis (described in the Supplementary Data, Figure S2, SDC, http://links.lww.com/TXD/A241), we were able to show that these volume changes were caused by a water shift from the extracellular to the intracellular compartment.

As shown in Figure 5B, cerebral blood flow decreased after transplantation. This was a whole brain effect and was strongly correlated ($P = 0.005$) with an increased hemoglobin after transplantation, suggesting a physiologic response, which has also been reported in a study by Jiang et al.[35] Tacrolimus trough levels were not significantly related to cerebral blood flow changes in multivariate analysis; neither were changes in blood pressure. Figure 5C shows the MRS results. *N*-acetylasparate/creatine (NAA/Cr), a marker for neuronal integrity, increased after transplantation, whereas choline/creatine, a marker for neurodegeneration/inflammation, and glutamine/creatine, a marker for metabolic activity, decreased. Figure 5D displays DTI results. FA was unchanged after transplantation, but MD significantly decreased after transplantation ($P = 0.004$). A decrease in MD essentially means

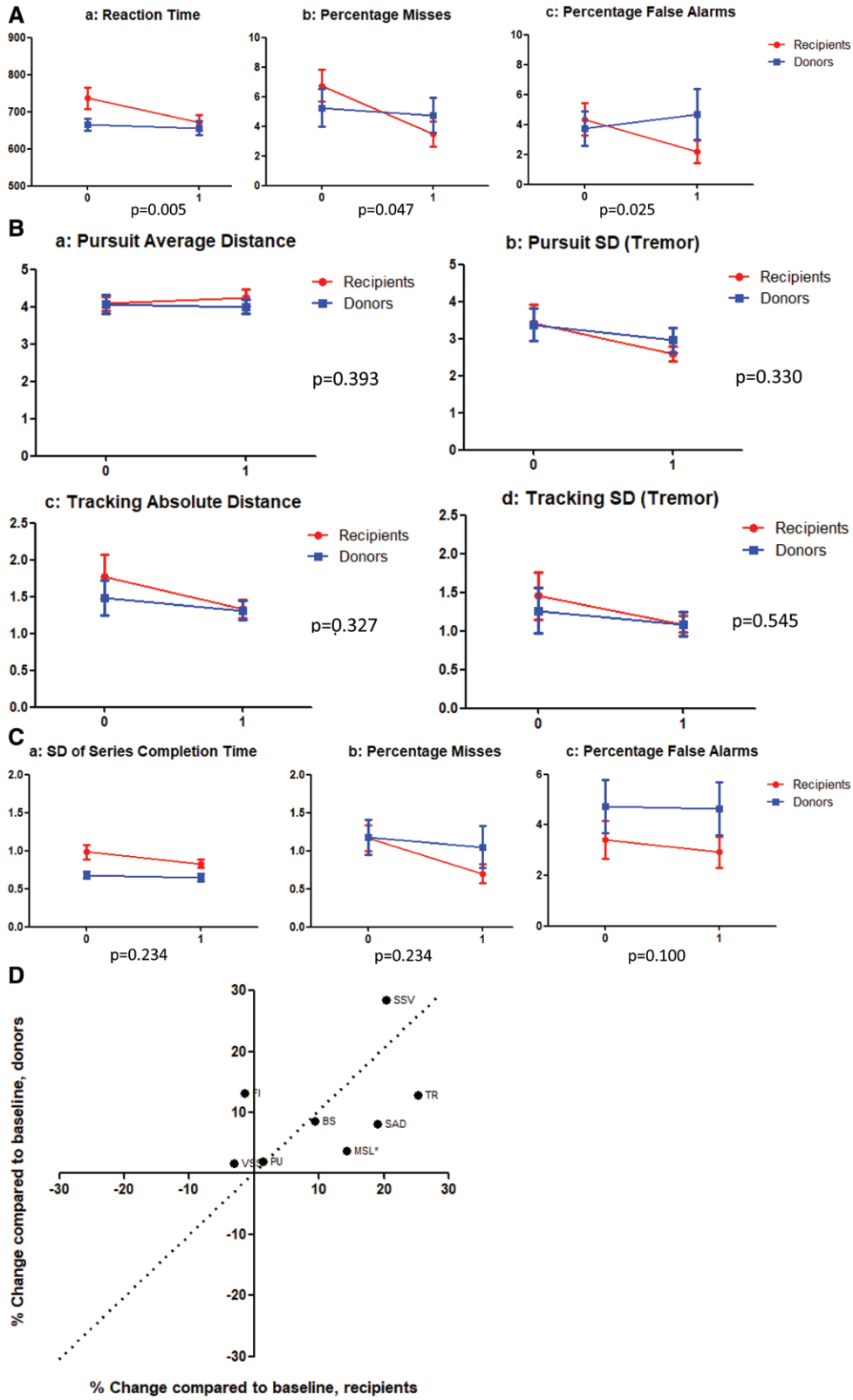

FIGURE 3. Amsterdam Neuropsychological Task (ANT) results. A, Memory search letters (a, mean reaction time for hits at level 1 in milliseconds; b, percentage misses [ie, target present but not detected by subject] at level 1; c, percentage false alarms at level 3 [ie, target not present but subject thinks it is]). B, Pursuit (PU) and tracking (TR) (a, PU average distance from target in centimeters; b, PU SD; c, TR absolute distance from target in centimeters; d, TR SD). C, Sustained attention dots (SADs) (a, SD from mean series completion time in seconds; b, percentage misses [ie, target signal of 4 dots present but not detected by subject]; c, percentage false alarms [ie, target signal of 4 dots not present but subject thinks it is]). Plotted lines show mean and SEM at baseline and 1 year. *P* values test group interactions, that is, whether the differences between the groups change over time. D, Summary of ANT test results. *Improvement of recipients exceeds improvement of donors, $P < 0.05$. BS, baseline speed; FI, feature integration; MSL, memory search letter; SD, standard deviation; SEM, standard error of the mean; SSV, shifting attentional set visual; VSS, visuospatial sequencing.

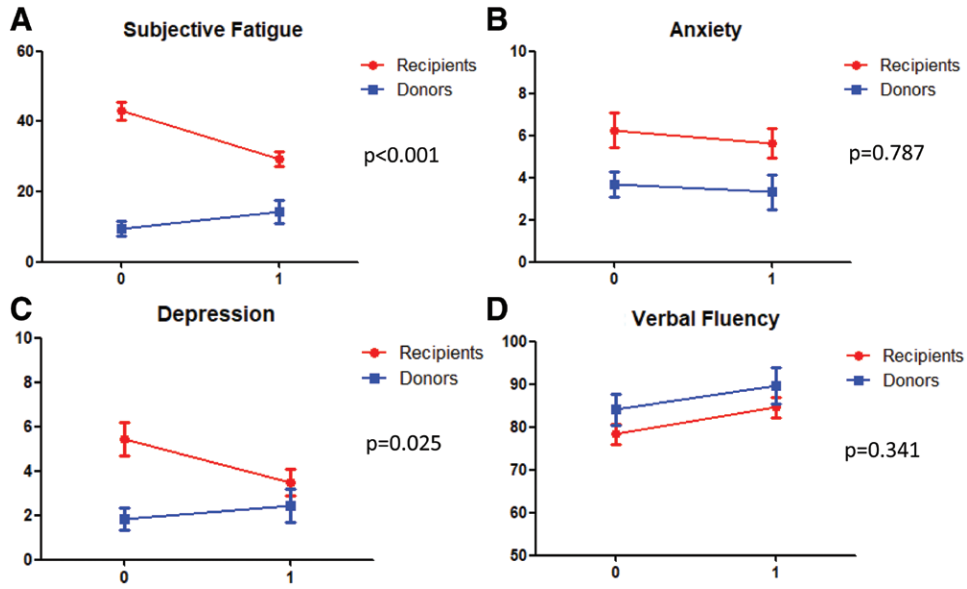

FIGURE 4. Fatigue, depression, and anxiety scores. A, Subjective fatigue scores, as measured by the Checklist for Individual Strength (CIS). Anxiety (B) and depression scores (C), as measured by the Hospital Anxiety and Depression Scale (HADS). A CIS subjective fatigue score >35 indicates severe fatigue. A HADS score >6 indicates a probable depressive or anxiety disorder. Plotted lines show mean and SEM at baseline and 1 year. *P* values test group interactions, that is, whether the differences between the groups change over time. SEM, standard error of the mean.

that water movement within cells becomes more organized. Figure 5E reports resting state functional MRI results. Ten standard networks[36] were tested; in 3 of these networks, highlighted areas depict a significant increase in connectivity with the default mode network posttransplantation after correction for changes in cerebral blood flow; in the other networks, no significant changes were found. The default mode network is active when the mind is wandering at random, and improved connectivity with the default network is thought to represent improved brain functionality. However, the effects are quite small, especially in the depicted executive control network so that one can question the clinical relevance of these results.

Exploratory Analysis of the Relationship Between Neuropsychologic Tasks and MRI Results

As described before, on the memory search letters task, measuring attention, and working memory, recipient scores improved more than donor scores. We, therefore, analyzed whether improvements on this task were associated with changes in several MRI parameters. For task accuracy, there were no significant correlations, but improved reaction times were significantly correlated with an increase in WM volume and NAA/Cr. The same was true for other ANT task reaction times (Table 3). As depression scores also improved after transplantation, we included this variable in our analysis, but it was not significantly correlated with reaction times.

DISCUSSION

This is the first study in kidney transplantation recipients to prospectively analyze neurocognitive function and combine this with extensive neuroimaging. It is also the first study to include kidney donors to control for learning effects, socioeconomic status, and surgery. Both kidney donors and kidney transplant recipients had higher neuropsychologic testing scores 1 year after transplantation (donation). Recipient improvement on tasks measuring attention and working memory exceeded donor improvement and was significantly correlated with an increase in WM volume and NAA/Cr.

We showed that the WM volume increase was caused by a water shift from the extracellular to the intracellular compartment. The pathophysiology behind this water shift is not completely understood. ESRD results in osmotic changes due to the accumulation of uremic toxins and water retention. Under normal circumstances, the brain is able to keep intracellular volume constant by adapting its intracellular osmolytes. However, this ability may be impaired by uremic toxin-induced chronic inflammation resulting in cell dysfunction and increased cellular permeability, causing an intracellular volume decrease in patients with ESRD, which normalizes after transplantation.

The NAA/Cr increase we found could also be related to the normalization of osmotic and volume status after transplantation, as NAA is a major brain osmolyte, providing about 7% of total brain osmolarity.[37] In addition, NAA is hypothesized to have several other functions, including myelination of the central nervous system (most critically during postnatal brain development), and facilitation of energy metabolism in neuronal mitochondria.[38] It is, therefore, not surprising that NAA is considered a marker of neuronal integrity. On MRS, NAA concentration decreases are invariably associated with diseases where neuronal loss and dysfunction are involved, such as brain ischemia, Alzheimer's disease, amyotrophic lateral sclerosis, and multiple sclerosis.[38]

Our study also has some limitations. First of all, the sample size is relatively small, but we believe that this is justified because this is an exploratory study by nature. We tried to limit the risk of underpowering by defining a number of inclusion and exclusion criteria, designed to make the kidney transplant recipient group relatively homogenous, that is, mostly pre-emptive ABO-compatible, HLA-nonidentical living kidney transplant recipients using similar immunosuppressive drug therapy without extensive comorbidity that could potentially affect their cognitive function.

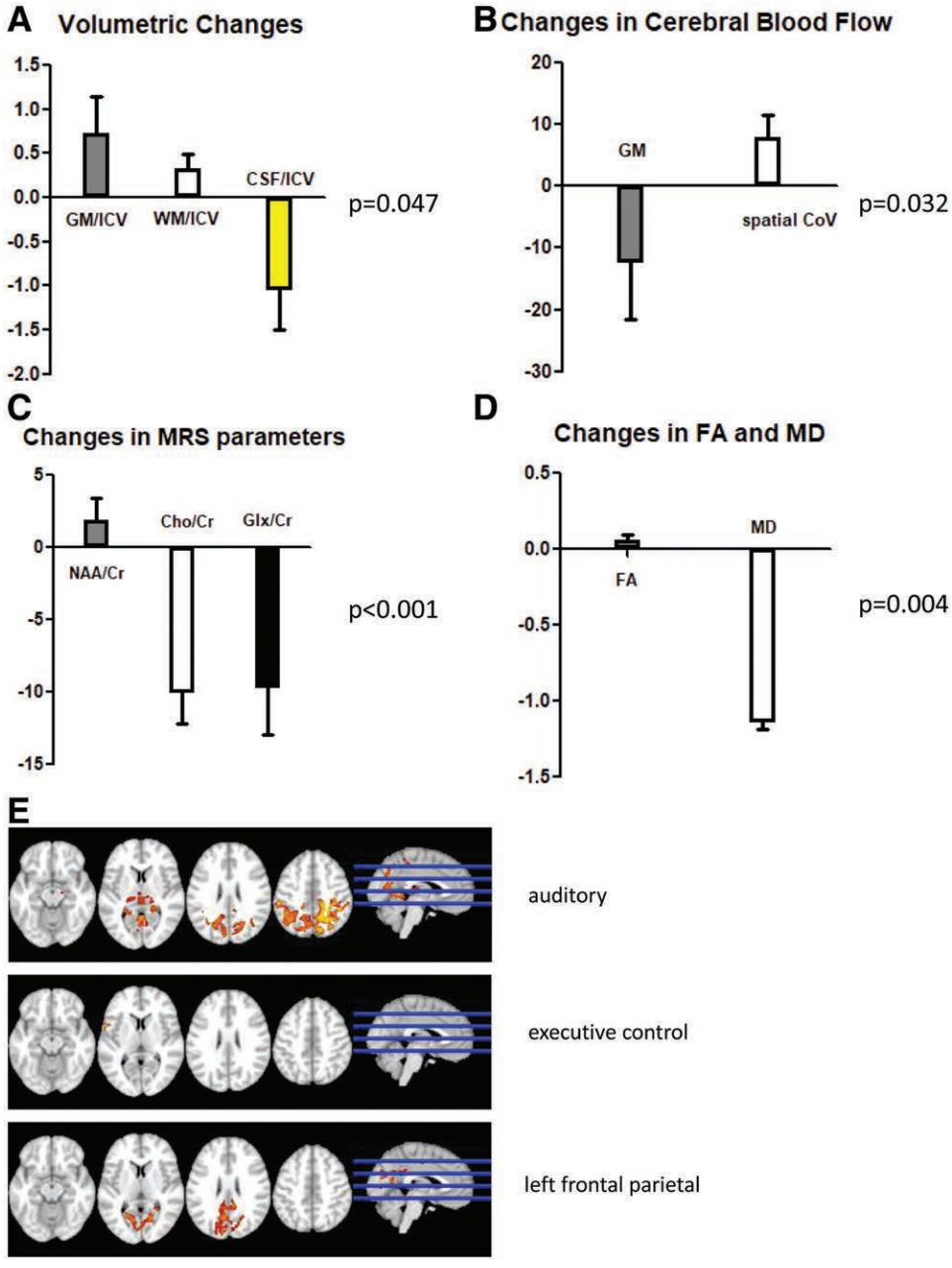

FIGURE 5. Quantitative MRI results. A, Volumetric changes (in %). B, Changes in cerebral blood flow (in %). Gray matter (GM) cerebral blood flow is the most robust parameter in arterial spin labeling (ASL) analysis; white matter (WM) cerebral blood flow estimates are generally considered not robust enough. Spatial coefficient of variation is an ASL parameter measuring the difference in signal between large and small vessels and is therefore a proxy for arrival time. C, Changes in magnetic resonance spectroscopy (MRS) parameters (in %). All MRS results are represented with creatine (Cr) in the denominator because this compound is generally considered to be constant. We verified whether this assumption was accurate in our population by comparing pretransplantation and posttransplantation Cr values: they did not significantly change (average Cr pretransplantation 6.6, and posttransplantation 6.9 mmol/kg wet weight; $P = 0.262$). Reporting results with Cr in the denominator has the added benefit that changes in water content (Figure 5A) do not affect the results. D, Changes in fractional anisotropy (FA) and mean diffusivity (MD) (in %). Bars indicate mean and SEM percentage change over time. E, Resting state functional MRI (RS fMRI): Networks with a significant increase in connectivity with the default network posttransplantation (highlighted areas, family-wise error corrected $P < 0.05$). All analyses were corrected for changes in cerebral blood flow. Cho, choline; CSF, cerebrospinal fluid; Glx, glutamine; ICV, intracranial volume; NAA, *N*-acetylaspartate; SEM, standard error of the mean.

Second, we included kidney donors to control for surgery, socioeconomic status, and learning effects. Learning effects occur when testing scores improve as participants become more familiar with the testing procedure. In the ANT, learning effects are mostly present when time between different sessions is short, generally below 2 or 3 months, and mostly between the first and the second session, with most participants reaching a plateau in successive sessions.[26] We have tried to minimize the disturbing effect of learning effects in our study design by setting the time period between study sessions at 1 year and by including a practice session before each study session. However, small learning effects do remain, which is why a control group remains necessary.

TABLE 3.

Regression analysis of selected neuropsychologic tasks and MRI parameters

	% Change in reaction time (MSL)		% Change in reaction time (Overall)	
% Change in	Univariate	Multivariate	Univariate	Multivariate
WM/ICV	−10.847 (−18.375; −3.319)[a]	−8.952 (−16.213; −1.690)[b]	−9.281 (−15.148; −3.414)[a]	−7.486 (−12.764; −2.209)[a]
GM/ICV	−2.260 (−5.545; 1.025)	—	−1.823 (−4.502; 0.856)	—
FA	−1.813 (−3.626; 0.001)	—	−1.313 (−2.902; 0.276)	—
MD	1.305 (−2.222; 4.833)	—	1.672 (−1.131; 4.475)	—
NAA/Cr	−0.971 (−1.798; −0.145)[b]	−0.719 (−1.470; 0.032)	−0.914 (−1.566; −0.263)[a]	−0.696 (−1.257; −0.136)[b]
Cho/Cr	0.300 (−0.378; 0.978)	—	0.256 (−0.308; 0.820)	—
Glx/Cr	0.242 (−0.187; 0.670')	—	0.108 (−0.251; 0.467)	—
Depression score	−0.021 (−0.049; 0.007)	—	−0.021 (−0.039; 0.007)	—

[a]Significant at $P < 0.01$ level.
[b]Significant at $P < 0.05$ level.
The table shows the results of regression analyses with changes in ANT reaction times as dependent variables and changes in several MRI parameters as independent variables. From all available ANT results, we included only MSL results because this was the only task in which recipient improvement exceeded donor improvement, implying genuine improvement posttransplantation. The MSL task measures attention and memory, which are both complex cognitive functions that require the collaboration of multiple brain areas so that we could not exclude any MRI variables beforehand based on theoretical considerations. However, because we did not find any relevant posttransplantation changes in the ASL and fMRI analyses, we decided to exclude these parameters and include all relevant parameters from the volumetric, DTI, and MRS analyses. We started with univariate analysis and used $P < 0.20$ as a backward elimination criterion for the multivariate analysis until we found the model with the highest adjusted R^2. Reported values are mean and 95% confidence interval.
ANT, Amsterdam Neuropsychological Tasks; ASL, arterial spin labeling; Cho, choline; Cr, creatine; DTI, diffusion tensor imaging; FA, fractional anisotropy; fMRI, functional MRI; Glx, glutamine; GM, gray matter; ICV, intracranial volume; MD, mean diffusivity; MRS, magnetic resonance spectroscopy; MSL, memory search letter; NAA, *N*-acetylaspartate; WM, white matter.

We realize that there are reasons to argue against the inclusion of kidney donors instead of actual healthy controls. The advantages of using kidney donors are that they are well-matched in terms of socioeconomic status, have both undergone extensive screening to rule out occult disease, and have undergone a similar surgical procedure so that the main difference between both groups is the underlying kidney disease and subsequent presence of a kidney transplant.

Our results in kidney donors suggest that kidney donation is a safe procedure in terms of cognitive outcomes. As kidney donation is a medically unnecessary procedure, this is an important new finding that can be used when counseling potential kidney donors.

To summarize, this study shows that kidney transplantation results in improved neurocognitive function, possibly related to an improved WM integrity due to the normalization of volume and osmotic status, without negatively affecting neurocognitive function in kidney donors. In addition to improved cognitive function, fatigue and depression scores also improved, all of which are important contributors of quality of life of CKD patients and their caregivers, providing them with another reason to opt for transplantation as their preferred mode of RRT.

ACKNOWLEDGMENTS

The authors thank Jan Willem van Dalen (Department of Neurology, Amsterdam University Medical Centers, Location AMC) for his helpful comments and Gerrie Nieuwenhuizen, Dorien Standaar, Ingrid Bunck, Tessa de Jong, and Janneke Vervelde (Department of Nephrology, Amsterdam University Medical Centers, location AMC) for their help in performing the neuropsychologic tests.

REFERENCES

1. Griva K, Stygall J, Hankins M, et al. Cognitive impairment and 7-year mortality in dialysis patients. *Am J Kidney Dis.* 2010;56:693–703.
2. Murray AM, Tupper DE, Knopman DS, et al. Cognitive impairment in hemodialysis patients is common. *Neurology.* 2006;67:216–223.
3. Van Sandwijk MS, Ten Berge IJ, Majoie CB, et al. Cognitive changes in chronic kidney disease and after transplantation. *Transplantation.* 2016;100:734–742.
4. Wolfgram DM. Intradialytic cerebral hypoperfusion as mechanism for cognitive impairment in patients on hemodialysis. *J Am Soc Nephrol*. 2019;30:2052–2058.
5. Joshee P, Wood AG, Wood ER, et al. Meta-analysis of cognitive functioning in patients following kidney transplantation. *Nephrol Dial Transplant.* 2018;33:1268–1277.
6. Griva K, Hansraj S, Thompson D, et al. Neuropsychological performance after kidney transplantation: a comparison between transplant types and in relation to dialysis and normative data. *Nephrol Dial Transplant.* 2004;19:1866–1874.
7. Gelb S, Shapiro RJ, Hill A, et al. Cognitive outcome following kidney transplantation. *Nephrol Dial Transplant.* 2008;23:1032–1038.
8. Troen AM, Scott TM, D'Anci KE, et al; FACT Study Investigators. Cognitive dysfunction and depression in adult kidney transplant recipients: baseline findings from the FAVORIT Ancillary Cognitive Trial (FACT). *J Ren Nutr.* 2012;22:268–276.e1.
9. Anwar W, Ezzat H, Mohab A. Comparative study of impact of hemodialysis and renal transplantation on cognitive functions in ESRD patients. *Nefrologia.* 2015;35:567–571.
10. Ozcan H, Yucel A, Avşar UZ, et al. Kidney transplantation is superior to hemodialysis and peritoneal dialysis in terms of cognitive function, anxiety, and depression symptoms in chronic kidney disease. *Transplant Proc.* 2015;47:1348–1351.
11. Lambert K, Mullan J, Mansfield K, et al. Comparison of the extent and pattern of cognitive impairment among predialysis, dialysis and transplant patients: a cross-sectional study from Australia. *Nephrology (Carlton).* 2017;22:899–906.
12. Gupta A, Mahnken JD, Johnson DK, et al. Prevalence and correlates of cognitive impairment in kidney transplant recipients. *BMC Nephrol.* 2017;18:158.
13. Griva K, Thompson D, Jayasena D, et al. Cognitive functioning pre-to post-kidney transplantation–a prospective study. *Nephrol Dial Transplant.* 2006;21:3275–3282.
14. Radić J, Ljutić D, Radić M, et al. Kidney transplantation improves cognitive and psychomotor functions in adult hemodialysis patients. *Am J Nephrol.* 2011;34:399–406.
15. Kaya Y, Ozturkeri OA, Benli US, et al. Evaluation of the cognitive functions in patients with chronic renal failure before and after renal transplantation. *Acta Neurol Belg.* 2013;113:147–155.
16. Kramer L, Madl C, Stockenhuber F, et al. Beneficial effect of renal transplantation on cognitive brain function. *Kidney Int.* 1996;49:833–838.
17. Harciarek M, Biedunkiewicz B, Lichodziejewska-Niemierko M, et al. Continuous cognitive improvement 1 year following successful kidney transplant. *Kidney Int.* 2011;79:1353–1360.

18. Dixon BS, VanBuren JM, Rodrigue JR, et al; FHN study. Cognitive changes associated with switching to frequent nocturnal hemodialysis or renal transplantation. *BMC Nephrol.* 2016;17:12.
19. Sharma A, Yabes J, Al Mawed S, et al. Impact of cognitive function change on mortality in renal transplant and end-stage renal disease patients. *Am J Nephrol.* 2016;44:462–472.
20. Michaelis T, Videen JS, Linsey MS, et al. Dialysis and transplantation affect cerebral abnormalities of end-stage renal disease. *J Magn Reson Imaging.* 1996;6:341–347.
21. Fiorina P, Vezzulli P, Bassi R, et al. Near normalization of metabolic and functional features of the central nervous system in type 1 diabetic patients with end-stage renal disease after kidney-pancreas transplantation. *Diabetes Care.* 2012;35:367–374.
22. Gupta A, Lepping RJ, Yu AS, et al. Cognitive function and white matter changes associated with renal transplantation. *Am J Nephrol.* 2016;43:50–57.
23. Zhang LJ, Wen J, Liang X, et al. Brain default mode network changes after renal transplantation: a diffusion-tensor imaging and resting-state functional MR imaging study. *Radiology.* 2016;278:485–495.
24. Chen HJ, Wen J, Qi R, et al. Re-establishing brain networks in patients with ESRD after successful kidney transplantation. *Clin J Am Soc Nephrol.* 2018;13:109–117.
25. Findlay MD, Dawson J, Dickie DA, et al. Investigating the relationship between cerebral blood flow and cognitive function in hemodialysis patients. *J Am Soc Nephrol.* 2019;30:147–158.
26. De Sonneville LMJ. *Handbook Amsterdam Neuropsychological Tasks*. Amsterdam, The Netherlands: Publishers uitgevers; 2014:347–399.
27. Christ SE, Huijbregts SC, de Sonneville LM, et al. Executive function in early-treated phenylketonuria: profile and underlying mechanisms. *Mol Genet Metab.* 2010;99(Suppl 1):S22–S32.
28. Buizer AI, de Sonneville LM, van den Heuvel-Eibrink MM, et al. Chemotherapy and attentional dysfunction in survivors of childhood acute lymphoblastic leukemia: effect of treatment intensity. *Pediatr Blood Cancer.* 2005;45:281–290.
29. Lazeron RH, de Sonneville LM, Scheltens P, et al. Cognitive slowing in multiple sclerosis is strongly associated with brain volume reduction. *Mult Scler.* 2006;12:760–768.
30. Daams M, Schuitema I, van Dijk BW, et al. Long-term effects of cranial irradiation and intrathecal chemotherapy in treatment of childhood leukemia: a MEG study of power spectrum and correlated cognitive dysfunction. *BMC Neurol.* 2012;12:84.
31. Schmand B, Groenink SC, van den Dungen M. Letter fluency: psychometric properties and Dutch normative data. *Tijdschr Gerontol Geriatr.* 2008;39:64–76.
32. Van Overschelde JP, Rawson KA, Dunlosky J. Category norms: an updated and expanded version of the Battig and Montague (1969) norms. *J Memory Lang*. 2004;50:289–335.
33. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand.* 1983;67:361–370.
34. Vercoulen JH, Swanink CM, Fennis JF, et al. Dimensional assessment of chronic fatigue syndrome. *J Psychosom Res.* 1994;38:383–392.
35. Jiang XL, Wen JQ, Zhang LJ, et al. Cerebral blood flow changes in hemodialysis and peritoneal dialysis patients: an arterial-spin labeling MR imaging. *Metab Brain Dis.* 2016;31:929–936.
36. Smith SM, Fox PT, Miller KL, et al. Correspondence of the brain's functional architecture during activation and rest. *Proc Natl Acad Sci U S A.* 2009;106:13040–13045.
37. Rae CD. A guide to the metabolic pathways and function of metabolites observed in human brain 1H magnetic resonance spectra. *Neurochem Res*. 2014;39:1–36.
38. Moffett JR, Ross B, Arun P, et al. N-acetylaspartate in the CNS: from neurodiagnostics to neurobiology. *Prog Neurobiol.* 2007;81:89–131.