Neuropsychological performance after kidney transplantation: a comparison between transplant types and in relation to dialysis and normative data

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Abstract

Background. Neuropsychological (NP) performance after kidney transplantation (TX) has received little attention. This study compared NP functioning between dialysis and transplant patients and between living-related donor (LRD) and cadaver (CAD) transplant recipients. The association between immunosuppressive medication and NP outcomes was also examined.

Methods. One hundred and seventeen transplant recipients (25 LRD and 92 CAD patients) and 145 dialysis patients (77 haemodialysis and 68 peritoneal dialysis) were administered an NP test battery to assess learning and verbal recall, attention and concentration, and psychomotor abilities/speed. Biochemical markers of renal function were also assessed.

Results. Overall, transplant patients showed normal cognitive functioning in all domains assessed. NP performance was found to be equivalent in both transplant groups and in patients on cyclosporin and those on tacrolimus. ANCOVAs showed that TX patients performed significantly better than dialysis patients on selective NP tests, i.e. the two memory tasks and two out of the four tests of attention. No differences were found in motor tasks.

Conclusions. Our results reveal no evidence of NP deficits in TX patients. The NP advantage of TX relative to dialysis is evident mainly in verbal memory.

Keywords: cadaver; dialysis, functioning; living-related donor; neuropsychological; renal transplantation

Introduction

Kidney transplantation (TX) is the preferred form of treatment for most end-stage renal disease (ESRD) patients. Although quality of life [1] and clinical outcomes [2] have been studied extensively in kidney transplant recipients, there is relative paucity of data on neuropsychological (NP) outcomes post-transplantation. This is an important question as cognitive capacity is intimately connected to outcomes such as social and vocational adjustment [3].

Most of the existing research on the NP aspects of kidney function has focused on the effects of dialysis treatment [4,5] or the cognitive functioning in paediatric transplant populations [6]. There have been only a few studies that have examined NP aspects of TX in adults. Teschan et al. [7] studied eight patients repeatedly during dialysis treatment and 4–23 months following TX. They found a significant improvement in choice reaction times and memory test scores following TX. Teschan et al. [8] assessed non-dialysed, dialysed and transplanted ESRD patients and compared their performance with that of normal controls. They found renal transplant patients to perform at levels comparable with those of normal controls on attention and memory tasks but did not present comparisons between the dialysis and transplant groups. Kramer et al. [9] reported improved cognitive functioning as measured by the Trail Making Tests and Minimental State Examination (MMSE) in a group of 16 haemodialysis (HD) patients before and after transplantation compared with age-matched healthy subjects. Prior to transplantation, HD patients performed significantly worse than controls in both NP tests, but performance between groups did not differ significantly following TX. There are important limitations to these studies. These include the very small sample sizes, limitations in the NP tests used and insufficient adjustment for case mix and other confounding factors likely to impinge upon NP performance. The measures used did not
assess cognitive domains found to be particularly impaired in ESRD patients such as complex attention and mental processing or are not considered to be sensitive enough to determine subtle cognitive deficits [4].

Given these shortcomings, a reinvestigation of this area with improved methodology was performed to ascertain how the NP performance of TX patients compares with that of patients on dialysis and to examine TX patients’ NP performance in relation to normative data. In line with the previous small studies, it may be expected that if NP performance is associated with renal biochemistry such as clearance of metabolic wastes and toxins, cognitive functioning would be more efficient in TX patients compared with patients maintained on chronic dialysis treatments, since TX has the potential to improve renal function. Further questions that have not been addressed in previous research were also assessed in this study. These included a comparison of the NP functioning between cadaver (CAD) transplant recipients and living-related donor (LRD) transplant patients. It has been demonstrated that these two types of transplant show different clinical outcomes regarding patients and graft survival. One question addressed in this study was whether these differences are reflected in NP performance. Another question in TX relates to the NP consequences of anti-rejection medication. The clinical benefits of TX are achieved at the cost of lifelong therapy with immunosuppressive drugs such as glucocorticoids and cyclosporin or tacrolimus. While the neurological complications of these treatments are well documented [10] and there is evidence on neurotoxic effects and brain imaging changes with both cyclosporin and tacrolimus [11], no studies have examined their impact on NP functioning. Finally, the association between biochemical and other medical markers of kidney function and NP outcomes has not been explored in TX patients and is considered in this study.

The aims of the present study were therefore: (i) to examine NP functioning in TX recipients in relation to normative data and a concurrently assessed group of dialysis patients on the waiting list for a kidney transplant; (ii) to examine the association between transplant type and immunosuppressive medication with NP outcomes; and (iii) to identify socio-demographic and medical factors associated with NP performance in TX patients.

Subjects and methods

Participants

The study was conducted at the Middlesex Hospital in London, UK from October 1997 to October 1999. Following ethical approval and signed consent, transplant and dialysis patients treated in the renal units were invited to participate. Eligible participants were approached if they met the following inclusion criteria: (i) aged ≥18 years; (ii) no history or clinically evident cerebrovascular disease as reflected by new, transient or fixed neurological deficits; (iii) no major visual or hearing impairments, or other sensory or motor impairments that prohibit them from completing the scheduled assessments; (iv) absence of acute or chronic psychosis, evident depression, severe learning disabilities and/or dementia; (v) currently stable, defined as not being acutely ill or hospitalized at the time of the assessments; (vi) fluency in written and spoken English; and (vii) a minimum of 3 months on their respective mode of treatment (TX or dialysis) and dialysis techniques (e.g. the same dialysate or dialyser if on HD).

Out of 123 TX patients contacted, 117 consented to the protocol (response rate = 95.1%). The recruited sample consisted of 54.4% males, with a mean age 46.8 (13.95) years and a mean of 8.6 (6.55) years since their transplant. Approximately 21% (n = 25) had received their transplant from an LRD. Of the eligible 167 dialysis patients who were approached, a total of 145 agreed to the full research protocol (response rate = 88.4%). The dialysis sample comprised 68 patients on peritoneal dialysis (PD) and 77 patients on HD treatments.

Socio-demographic characteristics

Demographic information including age, gender, ethnicity, education, marital and employment status, perceived work ability and household income were collected by questionnaire.

Medical measures

A nephrologist familiar with the patient completed the End Stage Renal Disease Severity Index (ESRD-SI) [12] for each patient. This provided a measure of co-morbid illnesses and other complications of renal failure. The ESRD-SI measures severity of illness as a function of 11 organic conditions.

Medical notes were also reviewed, and information regarding dialysis and TX history (e.g. time on dialysis, duration of functioning graft, TX failure, infection, rejection episodes) was recorded. The most recent glomerular filtration rate (GFR) levels were also documented. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) recordings were performed in a standardized manner in the clinic by a transplant sister, with measurements made in both supine and sitting positions before the NP assessments. Pulse pressure ratings expressed as the difference between DBP and SBP (taken when standing and lying) were also computed. Finally, blood samples were taken after the completion of each NP testing session so as to avoid interference of any venopuncture pain with participants’ NP performance. All blood samples were delivered to the respective laboratories within 2 h of collection. Laboratory analyses consisted of the measurements of blood concentration of urea (BUN), creatinine (Cr), sodium (Na⁺), potassium (K⁺), phosphate (PO₄), calcium (Ca²⁺), alkaline phosphatase, haemoglobin (Hb) and albumin (Alb).

GFR was measured following the intravenous administration of 13 MBq of 51Cr-EDTA diluted to 10 ml on 0.1% (w/v) excess EDTA solution [13]. Venous blood samples are taken from the opposite arm at 2, 3 and 4 h after injection. Following centrifugation, 3 ml aliquots are counted with standards and blanks in an automated γ counter. GFR was calculated from the slow exponential of the bi-exponential plasma clearance curve and multiplied by a correlation factor.
of 0.87 because of underestimation of the plasma integral by this method.

Dialysis adequacy was assessed by a calculated kinetic transfer/volume urea measurement (Kt/V) in both HD (single pool single pool determination) and PD patients (total weekly Kt/Vurea). Only measurements of adequacy made within 6 months of the study assessment were used for analysis purposes. Treatment was considered adequate when Kt/V met or exceeded the UK Renal Association Guidelines [14] as follows: for CAPD, a Kt/V of 1.70; for APD (without a daytime dwell) a Kt/V of 2.0; for HD, a Kt/V of 1.20.

Neuropsychological assessment

The NP tests were selected on the basis of previous reports of their sensitivity and their acceptance and extensive use in the general medical and renal literature [15].

Trail Making Test Forms A and B (TMT) [16]. This is a two-part measure of attention, visual scanning, motor speed and planning ability. Part A (TMT-A) requires participants to connect 25 randomly arranged numbers in the proper order. Part B (TMT-B) requires participants to connect a series of number and letters in sequence (i.e. 1–A–2–B–3–C...13–L) as quickly as possible. Both parts of the test are timed (number of seconds) to completion, with lower scores indicating better cognitive function.

Symbol Digit Modalities Test (SDMT) [17]. This is a visual perception task that require visual attention–concentration, scanning and visual shifting for successful completion. Oculomotor abilities and hand–eye co-ordination are also involved. It consists of matching numbers and symbols as quickly as possible within a time frame of 90 s, with the number of correct matches being the score. Both the written (SDMT-W) and oral (SDMT-O) administrations were used in this study.

Rey Auditory Verbal Learning Test (RAVLT) [18]. This widely used auditory verbal memory task assesses immediate memory as well as retrieval from verbal short-term memory storage. It consists of five presentations with a recall of a list of 15 words that are read out to the participants by the examiner, one presentation of a second 15-word list and a sixth recall trial of the original word list. Alternative forms were used for the repeat assessments [19]. The score used in this study was the total verbal recall from trials 1–5 (RAVLT-T) as it enabled comparison to be made with normative samples.

Grooved Pegboard (GP) [20]. This test of fine motor co-ordination and manual dexterity involves placing 25 pegs as rapidly as possible into an equivalent number of similarly shaped holes, but varying in their orientation to the vertical. The GP is a timed test so the score is time to completion, with higher scores demonstrating a slower and thus worse performance. Both dominant (GP-D) and non-dominant (GP-ND) hands were tested.

Procedure

The NP assessments were conducted by a trained psychologist and were administered in the order as listed above. This was determined primarily by their cognitive domain focus with all attention or memory tasks administered together, and secondarily by their degree of difficulty, with the relatively easier tasks within each cognitive domain preceding the more difficult ones so as to optimize patients’ co-operation, boost motivation and a sense of achievement, and thus assess patients’ best performance. Where available as part of the administration procedure, practice trials were also administered (TMT, SDMT and GP). NP testing took ~30–45 min and was conducted in the same specially designated room in the research unit.

Dialysis patients were assessed twice within a 24-h interval to ascertain acute NP changes from pre- to 24 h post-dialysis. PD patients were also assessed twice as they served, in part, as a control group against which to examine the acute changes in NP functioning of the HD group. Results of these acute changes have been reported [5]. In this analysis, only pre-dialysis NP scores are presented for the dialysis group to avoid the effect of learning when the same NP test is administered more than once [21].

Data analysis

Independent t-tests or Mann–Whitney tests (for continuous data) and χ² tests (for categorical data) were performed to compare groups (dialysis vs TX; CAD vs LRD; tacrolimus-vs cyclosporin-treated TX patients) on socio-demographic and clinical characteristics. If any of these variables differed significantly between groups and were significantly associated with the outcome in question, they were statistically controlled in subsequent comparative analyses. A series of analyses of covariance (ANCOVA) were used to compare NP performance among the subgroups, with P-values, uncorrected for multiple comparisons, considered significant if P < 0.05.

Correlations and hierarchical multiple regressions were performed to examine the associations between socio-demographic factors, medical factors and NP scores. Predictors were entered in blocks in the multiple regressions as follows: socio-demographic and clinical variables in the first two steps, followed by biochemical measures in the last step. To determine entry into the models, the stepwise method was used within blocks to avoid the problem of multi-collinearity among variables [22].

In order to judge the TX patients’ performance on NP tests relative to normative performance, individual raw scores were standardized, i.e. converted to z-scores which relate the difference between an individual score and the normative group mean to the SD for the normative reference group. A negative z-score indicates that the individual’s performance lies below the mean for the reference group, a positive z-score represents higher performance than the mean for the reference group, and a z-score of 0 indicates that the raw score is equal to the mean of the reference group. Standardization of scores also allowed comparisons of the relative standing of individuals across the different tests despite the differences in the measurement scales or the means and SDs of these tests. z-scores (which are expressed as SDs from the mean) in the range of ±1 lie within 1 SD on the norm mean, which is set to 0. NP performance was considered as impaired if >1 SD below the group mean.
Results

Sample demographic and clinical characteristics

Socio-demographic and medical characteristics of the TX and dialysis patients are shown in Table 1. PD and HD patients were collapsed to form one group (n = 145) as there were no significant group differences in any of the NP scores. Previous research has demonstrated no differences between these groups at post-dialysis assessments for HD and at an equivalent time for PD [5].

Significantly more TX patients rated themselves as able to work full or part time ($\chi^2 = 21.11$, $P < 0.000$) and reported an annual income in the higher brackets ($\chi^2 = 25.878$, $P < 0.000$) than dialysis patients. TX patients also had lower ESRD severity scores [$F(1,260) = 8.515$, $P = 0.004$], lower incidence of diabetes ($\chi^2 = 9.107$, $P = 0.0025$) and ischaemic heart disease ($\chi^2 = 5.265$, $P = 0.021$) and had been in the renal replacement therapy (RRT) programme [$F(1,260) = 23.436$, $P < 0.000$] and in their respective current form of treatment for longer relative to dialysis patients [$F(1,260) = 24.559$, $P < 0.000$]. The lack of homogeneity of the dialysis and transplant groups was anticipated, as access to TX tends to favour younger and fitter patients. The better clinical status of TX patients may also at least partially explain the different employment rates and the resulting annual income disparities between dialysis and transplant groups. In subsequent comparisons between the two groups, these differences were controlled for statistically.

NP performance in TX relative to norms and dialysis patients

The NP performance is reported in Table 2. Inspection of the standardized scores showed no evidence of NP deficits for the TX patients compared with norms. The mean $z$-scores of both the combined TX sample as well as the CAD and LRD TX groups separately were clearly within the normal range (within 1 SD of the population mean) on all NP tests, thereby indicating normal cognitive functioning. The observed SDs did, however, indicate large individual differences in NP performance. The percentage of TX patients performing $>1$ SD below norms was, however, only a little higher than anticipated in a normal distribution of performance (i.e., $>15.86\%$).

A series of ANCOVAs (covarying for ESRD severity, diabetes, ischaemic heart disease and time on RRT) was performed to compare absolute NP performance between transplant and dialysis patients.

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**Table 1. Socio-demographic and clinical characteristics of study samples: dialysis, transplant, CAD and LRD TX patients (mean±SD)**

<table>
<thead>
<tr>
<th></th>
<th>Dialysis</th>
<th>Transplant</th>
<th>P-value</th>
<th>CAD TX</th>
<th>LRD TX</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>50.12 (14.26)</td>
<td>50.26 (12.33)</td>
<td>0.933</td>
<td>52.43 (12.11)</td>
<td>41.91 (9.41)</td>
<td>0.001</td>
</tr>
<tr>
<td>Age (years at diagnosis)</td>
<td>41.23 (17.32)</td>
<td>35.08 (15.93)</td>
<td>0.061</td>
<td>37.44 (15.90)</td>
<td>26.10 (12.70)</td>
<td>0.002</td>
</tr>
<tr>
<td>Age (years at RRT onset)</td>
<td>44.63 (15.78)</td>
<td>41.05 (13.28)</td>
<td>0.225</td>
<td>43.67 (12.52)</td>
<td>30.59 (11.03)</td>
<td>0.000</td>
</tr>
<tr>
<td>Education (years)</td>
<td>12.37 (5.41)</td>
<td>11.19 (3.84)</td>
<td>0.087</td>
<td>10.7 (3.86)</td>
<td>13.04 (3.20)</td>
<td>0.01</td>
</tr>
<tr>
<td>Gender (% female)</td>
<td>35.2%</td>
<td>40.2%</td>
<td>0.406</td>
<td>62%</td>
<td>52%</td>
<td>0.368</td>
</tr>
<tr>
<td>Ethnicity (% white)</td>
<td>64.1%</td>
<td>83.7%</td>
<td>0.053</td>
<td>82.4%</td>
<td>87.7%</td>
<td>0.723</td>
</tr>
<tr>
<td>% married</td>
<td>60%</td>
<td>66.1%</td>
<td>0.473</td>
<td>65.9%</td>
<td>66.7%</td>
<td>0.946</td>
</tr>
<tr>
<td>% employed</td>
<td>35.9%</td>
<td>48.7%</td>
<td>0.022</td>
<td>41.3%</td>
<td>76%</td>
<td>0.001</td>
</tr>
<tr>
<td>% able to work</td>
<td>43.4%</td>
<td>71.1%</td>
<td>0.001</td>
<td>66.7%</td>
<td>87.5%</td>
<td>0.046</td>
</tr>
<tr>
<td>Income</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0138</td>
</tr>
<tr>
<td>£0–10000</td>
<td>58.6%</td>
<td>23.4%</td>
<td></td>
<td>28.2%</td>
<td>4.5%</td>
<td></td>
</tr>
<tr>
<td>£10001–20000</td>
<td>24.8%</td>
<td>21.5%</td>
<td></td>
<td>24.7%</td>
<td>9.1%</td>
<td></td>
</tr>
<tr>
<td>£20001–30000</td>
<td>9.7%</td>
<td>19.6%</td>
<td></td>
<td>18.8%</td>
<td>22.7%</td>
<td></td>
</tr>
<tr>
<td>£30 001</td>
<td>6.9%</td>
<td>27.1%</td>
<td></td>
<td>18.8%</td>
<td>59.1%</td>
<td></td>
</tr>
<tr>
<td>ESRD-SI</td>
<td>11.16 (9.47)</td>
<td>7.94 (8.06)</td>
<td>0.008</td>
<td>9.21 (8.51)</td>
<td>3.29 (3.25)</td>
<td>0.001</td>
</tr>
<tr>
<td>GFR</td>
<td>40.32 (17.92)</td>
<td>38.96 (17.59)</td>
<td>0.001</td>
<td>45.16 (18.62)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb</td>
<td>11.03 (1.46)</td>
<td>12.88 (1.70)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time on DL prior to TX</td>
<td>37.57 (45.64)</td>
<td>31.67 (31.89)</td>
<td></td>
<td>36.67 (33.24)</td>
<td>12.75 (15.67)</td>
<td>0.001</td>
</tr>
<tr>
<td>Time on RRT</td>
<td>65.36 (74.31)</td>
<td>110.9 (77.37)</td>
<td>0.001</td>
<td>104.4 (70.66)</td>
<td>134.86 (96.1)</td>
<td></td>
</tr>
<tr>
<td>% diabetes</td>
<td>17.2%</td>
<td>5.1%</td>
<td>0.003</td>
<td>6.5%</td>
<td>0%</td>
<td>0.424</td>
</tr>
<tr>
<td>% heart disease</td>
<td>40%</td>
<td>26.5%</td>
<td>0.022</td>
<td>30.4%</td>
<td>16.7%</td>
<td>0.064</td>
</tr>
<tr>
<td>% hypertension</td>
<td>91.7%</td>
<td>88.9%</td>
<td>0.437</td>
<td>92.4%</td>
<td>68%</td>
<td>0.051</td>
</tr>
<tr>
<td>% on cyclosporin</td>
<td>59.8%</td>
<td>57.6%</td>
<td></td>
<td>77.3%</td>
<td>0.137</td>
<td></td>
</tr>
<tr>
<td>% on tacrolimus</td>
<td>36.4%</td>
<td>38%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cause of ESRD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% GN</td>
<td>13.8%</td>
<td>17.1%</td>
<td>0.460</td>
<td>13%</td>
<td>32%</td>
<td>0.053</td>
</tr>
<tr>
<td>% APKD</td>
<td>10.3%</td>
<td>12%</td>
<td>0.662</td>
<td>15.2%</td>
<td>0%</td>
<td>0.083</td>
</tr>
<tr>
<td>% Diabetes</td>
<td>11%</td>
<td>4.3%</td>
<td>0.045</td>
<td>5.4%</td>
<td>0%</td>
<td>0.526</td>
</tr>
<tr>
<td>% Hypertension</td>
<td>10.3%</td>
<td>8.5%</td>
<td>0.622</td>
<td>10.9%</td>
<td>0%</td>
<td>0.187</td>
</tr>
<tr>
<td>% Other</td>
<td>54.6%</td>
<td>58.1%</td>
<td></td>
<td>55.5%</td>
<td>68%</td>
<td></td>
</tr>
</tbody>
</table>

ESRD-SI = end-stage renal disease severity index; GFR = glomerular filtration rate; Hb = haemoglobin; DL = dialysis; TX = kidney transplantation; RRT = renal replacement therapy; ESRD = end-stage renal disease; GN = glomerulonephritis; APKD = adult polycystic kidney disease; CAD TX = cadaver transplant patients; LRD TX = living-related donor transplant patients.
The time on current treatment modality was not used as a covariate as it was highly correlated with time on RRT and the latter had stronger correlations with NP scores (data not shown). The results demonstrated that transplant patients performed significantly better in four NP tests: TMT-A \( F(5,249) = 6.147, P = 0.014 \); SDMT-O \( F(5,244) = 4.385, P = 0.037 \); RAVLT-T \( F(5,246) = 21.024, P < 0.000 \); and RAVLT-D \( F(5,246) = 8.37, P = 0.003 \). Trends in the same direction were also noted in SDMT-W \( F(5,248) = 3.137, P = 0.078 \) and GP-D \( F(5,245) = 3.548, P = 0.061 \), but these did not reach significance.

**NP functioning in CAD and LRD patients**

Socio-demographic and medical characteristics of the two TX groups are reported in Table 1. Age, education, work status, annual income, ESRD severity, time elapsed since TX and time spent on dialysis differed significantly between the two TX groups (see Table 1).

LRD transplant recipients were younger \( t(114) = 3.95, P < 0.000 \), were more likely to be employed \( \chi^2 = 10.34, P < 0.000 \), reported higher annual income \( \chi^2 = 6.054, P = 0.014 \) and had a higher education level than CAD patients \( t(107) = -2.68, P = 0.009 \). They also had lower ESRD severity scores \( t(115) = 3.401, P = 0.001 \), had their TX for longer (Mann–Whitney \( U = 477, P < 0.000 \) and had spent significantly less time on dialysis prior to their transplant than CAD transplant patients (Mann–Whitney \( U = 632.5, P < 0.000 \). The difference in time on dialysis was anticipated given the elective nature of LRD transplantation that allows shorter delay between dialysis and transplantation.

Comparisons of absolute NP test scores between the two transplant groups were performed using a series of ANCOVAs controlling for the following case mix differences: age, education and ESRD severity. No control for RRT duration, dialysis duration and time with TX was applied as these were not significantly associated with NP scores \( P > 0.05 \). Employment status was not included despite significant univariate associations as it was regarded more of an outcome of cognitive functioning rather than a predictor. Results indicated that there were no significant differences between LRD and CAD transplant recipients in any of the observed absolute NP scores (see Table 2).

**NP functioning and immunosuppression**

The association between immunosuppressive medication and cognitive functioning was examined by comparing NP scores between patients on cyclosporin \( n = 70 \) and those on tacrolimus \( n = 40 \) as well as by correlating serum drug levels and NP scores.

Significant case mix differences were found between the two groups requiring statistical control in subsequent analyses. These indicated that patients on tacrolimus were significantly younger \( t(107) = 2.164, P = 0.033 \), and have been on RRT (Mann–Whitney \( U = 843, P < 0.000 \) and with their transplant (Mann–Whitney \( U = 206.5, P < 0.000 \) for less time compared with patients on cyclosporin. Results also showed that significantly more diabetic patients were managed on tacrolimus than on cyclosporin \( \chi^2 = 4.094, P = 0.043 \). The differences in age and duration of RRT and of functioning graft (i.e. time with transplant) were anticipated, as tacrolimus only recently became available for the management of TX patients.

ANCOVAs (covarying only for age and diabetes, as neither TX duration nor RRT duration were significantly associated with any of the NP scores) were performed to compare cyclosporin-treated with...
tacrolimus-treated TX patients. There were no significant differences in any of the NP scores, indicating that different types of immunosuppressive medication appear to have comparable effects on patients’ NP performance.

Univariate associations are reported in Table 3. Correlation analysis showed that increasing serum/plasma levels of cyclosporin correlated significantly with poorer NP performance in GP-D (rₛ = 0.27, P = 0.035), GP-ND (rₛ = 0.36, P = 0.006), SDMT-O (rₛ = −0.29, P = 0.024), TMT-A (rₛ = 0.47, P < 0.000) and TMT-B (rₛ = 0.33, P = 0.011). In contrast, tacrolimus serum levels were unrelated to NP scores.

Variables associated with NP scores in TX patients

Univariate associations are reported in Table 3. Correlational analysis indicated that higher educational level and younger age were significantly associated with better NP functioning. The observed correlation coefficients ranged from r = 0.35 to r = 0.56 for age and from r = 0.37 to r = 0.58 for educational level, indicating moderate sized correlations.

Significant correlations were also noted between certain medical variables and NP scores. ESRD severity was significantly associated with more compromised cognitive functioning in all NP tests, with the observed correlation coefficients ranging from rₛ = 0.25 to rₛ = 0.39. GFR was associated with more efficient performance in SDMT-W (r = 0.26, P = 0.007), SDMT-O (r = 0.23, P = 0.022) and GP-ND (rₛ = −0.28, P = 0.005).

Blood pressure correlated with NP scores but not consistently across all measures. Correlation coefficients varied between DBP and SBP and between measurements taken in standing or lying positions. Concurrent levels of SBP (lying) correlated significantly with measures of psychomotor speed (i.e. GP) and attention (SDMT-W, SDMT-O, TMT-A and TMT-B), with correlation coefficients ranging from 0.20 to 0.28. The direction of observed correlations indicated that higher levels of SBP were associated with less efficient cognitive functioning.

Pulse pressure ratings were also significantly associated with all NP scores. For example, higher standing pulse pressure ratings correlated significantly with RAVLT-T (r = −0.20, P = 0.045), SDMT-O (r = −0.26, P = 0.009), SDMT-W (r = −0.26, P = 0.008), GP-D (r = 0.20, P = 0.045), GP-ND (rₛ = 0.21, P = 0.036), TMT-A (r = 0.28, P = 0.004) and TMT-B (r = 0.29, P = 0.005). Similar sized correlations were found between lying pulse pressure ratings and NP scores. Interestingly, neither DBP measurement nor the presence of hypertension was associated with cognitive functioning (i.e. ANOVA comparisons showed no significant NP differences between patients with hypertension vs those not diagnosed with hypertension).

Only a few significant, albeit weak, correlations, in the expected direction, were found between NP scores and biochemical measures. These, however, were not consistently replicated across all NP scores and therefore the findings should be treated with caution. Increasing urea levels correlated with poorer performance in SDMT-W (rₛ = −0.211, P = 0.029), SDMT-O (rₛ = −0.19, P = 0.05) and TMT-A (rₛ = 0.205, P = 0.033). The correlation between urea and GP-ND scores approached but did not reach significance (rₛ = 0.193, P = 0.054). Higher albumin levels correlated with SDMT-W (rₛ = 0.295, P = 0.036), SDMT-O (rₛ = 0.21, P = 0.036) and TMT-A (rₛ = −0.218, P = 0.024). Creatinine correlated significantly with GP-ND scores (rₛ = 0.197, P = 0.049).

A series of hierarchical multiple regressions was performed to examine predictors of NP performance in TX from a combination of socio-demographic and biochemical measures. These, however, were not consistently replicated across all NP scores and therefore the findings should be treated with caution.

Table 3. Correlations between socio-demographic and medical variables and NP scores

<table>
<thead>
<tr>
<th></th>
<th>TMT-A</th>
<th>TMT-B</th>
<th>SDMT-W</th>
<th>SDMT-O</th>
<th>RAVLT-T</th>
<th>GP-D</th>
<th>GP-NDa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.461+</td>
<td>0.408+</td>
<td>−0.564+</td>
<td>−0.507+</td>
<td>−0.451+</td>
<td>0.391+</td>
<td>0.346+</td>
</tr>
<tr>
<td>Education</td>
<td>−0.443+</td>
<td>−0.582+</td>
<td>0.49+</td>
<td>0.464+</td>
<td>0.496+</td>
<td>−0.368+</td>
<td>−0.378+</td>
</tr>
<tr>
<td>ESRD-SI</td>
<td>0.380+</td>
<td>0.248+</td>
<td>−0.434+</td>
<td>−0.387+</td>
<td>−0.303**</td>
<td>0.312***</td>
<td>0.327***</td>
</tr>
<tr>
<td>GFR</td>
<td>−0.169</td>
<td>−0.009</td>
<td>0.261**</td>
<td>0.225*</td>
<td>0.131</td>
<td>−0.157</td>
<td>−0.281**</td>
</tr>
<tr>
<td>DBP-ly</td>
<td>0.018</td>
<td>−0.042</td>
<td>−0.048</td>
<td>0.024</td>
<td>0.045</td>
<td>0.055</td>
<td>0.042</td>
</tr>
<tr>
<td>DBP-st</td>
<td>−0.003</td>
<td>0.021</td>
<td>0.026</td>
<td>0.086</td>
<td>−0.018</td>
<td>0.179</td>
<td>−0.018</td>
</tr>
<tr>
<td>SBP-ly</td>
<td>0.275**</td>
<td>0.218*</td>
<td>−0.254**</td>
<td>−0.22*</td>
<td>−0.204*</td>
<td>0.221*</td>
<td>0.226*</td>
</tr>
<tr>
<td>SBP-st</td>
<td>0.247*</td>
<td>0.247*</td>
<td>−0.218*</td>
<td>−0.188</td>
<td>−0.196*</td>
<td>0.123</td>
<td>0.198</td>
</tr>
<tr>
<td>PPR-ly</td>
<td>0.263**</td>
<td>0.221**</td>
<td>−0.273**</td>
<td>−0.303**</td>
<td>−0.144</td>
<td>0.240*</td>
<td>0.212*</td>
</tr>
<tr>
<td>PPR-st</td>
<td>0.278**</td>
<td>0.287**</td>
<td>−0.261**</td>
<td>−0.262**</td>
<td>−0.204*</td>
<td>0.20*</td>
<td>0.214*</td>
</tr>
<tr>
<td>BUN*</td>
<td>0.205*</td>
<td>0.088</td>
<td>−0.211*</td>
<td>−0.193*</td>
<td>−0.122</td>
<td>0.094</td>
<td>0.193</td>
</tr>
<tr>
<td>Cr*</td>
<td>0.129</td>
<td>0.075</td>
<td>−0.155</td>
<td>−0.107</td>
<td>0.157</td>
<td>0.078</td>
<td>0.197*</td>
</tr>
<tr>
<td>Alb*</td>
<td>−0.218*</td>
<td>−0.110</td>
<td>0.295**</td>
<td>0.207*</td>
<td>0.035</td>
<td>−0.143</td>
<td>−0.178</td>
</tr>
</tbody>
</table>

TMT-A = Trail Making Test part A; TMT-B = Trail Making Test part B; SDMT-W = Symbol Digit Modality Test written administration; SDMT-O = Symbol Digit Modality Test oral administration; RAVLT-T = Rey Auditory Verbal Learning Test total word; GP-D = Grooved Pegboard dominant hand; GP-ND = Grooved Pegboard non-dominant hand; ESRD-SI = end-stage renal disease severity index; GFR = glomerular filtration rate; DBP-ly = diastolic blood pressure (ly); DBP-st = diastolic blood pressure (standing); SBP-ly = systolic blood pressure (ly); SBP-st = systolic blood pressure (standing); PPR-ly = pulse pressure rating (ly); PPR = pulse pressure rating (standing); BUN = blood urea nitrogen; Cr = creatinine; Alb = albumin.

ªSpearman’s correlation coefficient.

*P < 0.05; **P < 0.01; ***P < 0.001; + P < 0.000.
education and ESRD severity, emerged as significant NP scores and that only three variables, i.e. age, education and ESRD severity, emerged as significant predictors of NP scores. These three variables in conjunction explained 33.2% (adjusted $R^2 = 30.8$) in the variance of SDMT-O; age and ESRD severity accounted for 36% (adjusted $R^2 = 34.5$%) in SDMT-W, $R^2 = 21\%$ (adjusted $R^2 = 19.2\%$) in GP-ND and $R^2 = 18.6\%$ (adjusted $R^2 = 16.8\%$) in GP-D. Finally, age and education were significant predictors of TMT-A ($R^2 = 27.6\%$; adjusted $R^2 = 26.1\%$), TMT-B ($R^2 = 26.7\%$; adjusted $R^2 = 25\%$) and RAVLT-T ($R^2 = 27\%$; adjusted $R^2 = 25.4\%$).

Discussion

On all main measures of cognitive function, the mean performance of TX recipients was no worse than that of respective age reference populations. Although slightly more TX age reference patients scored 1 SD below their age-referenced norms than anticipated in a normal distribution, caution must be exercised in assigning clinical significance to these findings. Besides the near or above normal z-score group means, there are also inherent limitations in using any normative database for comparison purposes [23]. No normative study ordinarily allows a perfect fit to the population under study, and the limitations of any data set used for inferential purposes should be kept in mind when interpreting comparative findings. Although existing normative databases were scrutinized to identify the one that most closely matched the characteristics of the sample in this study with comparable test administration and scoring procedures, the resulting choices were not optimal. The concurrent assessment of a large group of closely matched healthy volunteers would have overcome some of these issues and hence is warranted in future research.

These formal observations of normal NP functioning post-TX are nevertheless in accord with previous data from earlier small studies [8,9]. It is possible that other tests might have detected deficits not appreciated in our study, but the NP tests performed are widely used, well standardized and covered a range of cognitive areas [15]. That normal or near normal NP functioning can be expected following TX will be reassuring to patients.

Methodological factors might account for the inconsistent findings. Significance levels were not adjusted for multiple comparisons. Other investigators have also used uncorrected $P$-values [24] to ensure that no potential findings would be overlooked. In this study, adjusting for multiple comparisons would have negated the significance of SDMT-O and TMT-A differences (as $P$ would have been dropped to 0.0071). It is important that the memory differences would still be significant after adjustment for multiple comparisons. The effect on memory may therefore reflect true differences between dialysis and TX patients, suggesting that this is an area of functioning particularly sensitive or vulnerable to the effects of dialysis. Alternatively, it may relate to differences in the baseline, sensitivity of NP tests of attention and memory.

It is also possible that other aspects of the TX groups' performance may have reduced the likelihood of finding NP differences in comparison with the dialysis group. Most of the NP tests with the exception of the memory task are timed and involve motor activity. Slowness in execution might be related to other factors such as tremor, common in some TX patients. This is unlikely, however, as none of the TX recipients presented with visible evidence of tremor and no differences were found in the SDMT-O in which no manual activity is involved. In addition, when comparisons (ANCOVAs not reported) were repeated controlling for concurrently reported symptoms, no differences between dialysis and TX patients in other tests involving motor ability (GP-D, GP-ND, TMT-B and SDMT-W) were found.

The timing of NP assessments may have created unfavourable comparisons for HD patients in the dialysis group as these were taken immediately before dialysis, when they are at their worst. Significant acute NP improvements in cognitive abilities have been found in HD patients from pre- to 24 h post-dialysis [5]. Although post-dialysis scores were collected, they were not used in comparative analysis with TX patients as these would reflect both learning effects and improved physiological state for HD patients.

This study has shown that when case mix differences are controlled for, dialysis and TX patients have
roughly equivalent cognitive performance on tests of attention and psychomotor abilities. The one area where clear evidence of differences was found was in verbal memory. This contrasts with commonly held views that TX, by improving the organ system functioning and restoring kidney function, should result in amelioration of NP functioning. These findings might be related to technological improvements of dialysis over recent years, with resulting improved renal clearance. It may also relate to the characteristics of the dialysis samples, which consisted of clinically stable and adequately dialysed patients. It is possible that more marked NP differences between TX and dialysis groups would have emerged had the inclusion criteria for this study been less strict. A prospective design assessing NP function before and after TX would overcome limitations related to sample selectivity and would provide a stronger test of the NP changes brought about by TX.

The links between biochemical markers of renal function and NP performance in TX patients were weak and inconsistent and were not replicated in the multiple regressions performed. The findings of the univariate analysis did suggest that immunosuppressive medication may adversely impact upon NP outcomes within the TX group [3]. Correlational analysis indicated that plasma levels of cyclosporin were inversely associated with NP scores although NP performance was equivalent between patients treated with cyclosporin and those on tacrolimus. One may speculate that the vasoconstriction properties of cyclosporin and the possibility of it inducing confusion may be related to this finding, but further research is needed to examine the NP effects of these and the newer immunosuppressive agents such as sirolimus. In addition, SBP correlated significantly with measures of psychomotor speed and attention in the univariate analysis but not in the multivariate analysis. Research on the relationship of blood pressure and cognitive functioning has not presented a clear picture, with some studies finding a relationship and others not [25]. The direction of the correlations in this study indicated that higher levels of SBP were associated with less efficient cognitive functioning. Only age, education and renal co-morbidity predicted cognitive function post-TX in the multiple regression analysis, and these variables have commonly been found to be associated with NP performance in non-patient samples [13,20]. The total variance in NP performance explained was, however, small to moderate, suggesting that there are probably factors other than those assessed in this study which might be more important determinants of NP performance in TX patients.

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Conflict of interest statement. None declared.

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