COGNITIVE AND PSYCHOSOCIAL OUTCOME FOLLOWING KIDNEY TRANSPLANTATION

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Shannon R. Gelb
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Name: Shannon (Lund) Gelb

Degree: Masters of Arts (Department of Psychology)

Title of Thesis: Cognitive and Psychosocial Outcome Following Kidney Transplantation

Chair: Dr. Thomas Spalek
Assistant Professor, Psychology

Dr. Wendy Thornton
Senior Supervisor
Assistant Professor, Psychology

Dr. Jean Shapiro, M.D
Supervisor
Associate Professor, Dept. of Medicine, UBC

Dr. Rachel Fouladi
Supervisor
Assistant Professor

External Examiner: Dr. Aiko Yamamoto
Psychologist
St. Paul's / Mount St. Joseph Hospitals

Date Approved : July 14, 2006

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Abstract

While compromised cognition has been identified in individuals at various stages of Chronic Kidney Disease (CKD), few studies have examined cognition following successful kidney transplants. Kidney transplantation typically leads to improvement of metabolic factors associated with CKD; however, co-morbid diseases independently linked with cognitive compromise often persist. To clarify the neuropsychological presentation following successful kidney transplantation, we assessed cognition and distress in 43 kidney transplant recipients, 47 outpatients with CKD and 52 healthy controls. Findings indicated that post-transplant and CKD participants demonstrated significantly poorer verbal memory and response inhibition than controls. In addition, CKD participants performed significantly poorer than controls on the set-shifting task. No significant differences were found for attention. Only transplant participants were significantly more distressed than controls. Results suggest that poor memory and executive functioning performance are present in both CKD and transplant participants. Further research is needed to determine the etiology and extent of cognitive compromise.

Keywords: cognitive, neuropsychological, kidney, renal, transplantation, CKD, depression, anxiety

Dedication

To my parents and siblings, for their support and encouragement throughout each step of my education.

And to Sancho, my husband, my best friend.

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INTRODUCTION

Renal disease is becoming an increasingly common chronic illness of middle and older adulthood. As of 2002, the prevalence rate of patients with kidney failure in Canada (i.e., requiring some form of renal replacement therapy) was 158 per million population. This represents a 55% increase from 1993 (CIHI/CORR Report 2002/2003). The fact that renal disease appears to be associated with a high risk for cognitive difficulties further complicates the management of this illness. While compromised cognition has long been reported in persons undergoing dialysis treatment (e.g., Teschan, et al., 1979; Kurella, Chertow, Luan, & Yaffe, 2004), accumulating evidence suggests that individuals may be at increased risk for cognitive difficulties relatively early in the course of the disease, even before renal failure occurs (Thornton, Shapiro, Deria, Gelb, & Hill, under review; Kurella, et al., 2004). In contrast, quite little is known regarding cognitive performance following successful renal transplantation. While it is commonly believed that cognitive abilities will return to pre-morbid levels following successful kidney transplantation (Teschan, et al., 1979; Kramer, et al., 1996; Griva, et al., 2004), to date, there is insufficient evidence either to support or to refute this assertion. The development of a better understanding of cognitive functioning following successful kidney transplantation may lead to more accurate patient expectations, and provide important information for those assisting with the management of this important illness.

Renal Disease

Chronic Kidney Disease (CKD) can be briefly described as a decrease in renal function due to kidney damage (Levey, et al., 2003). Untreated CKD results in the gradual development of uremia, which is thought to be a result of the accumulation of metabolic waste products, some of which are thought to be neurotoxic (Burn & Bates, 1998). Glomerular Filtration Rate (GFR), an estimation of the filtration capacity of the functioning nephrons (i.e., the ability of the kidney to filter substances from the blood), is the best overall indicator of level of kidney function (Levey, et al., 2003). Lower GFR levels indicate either a decrease in the filtration rate of the nephrons or a decline in the number of nephrons in the kidneys (Stevens & Levey, 2005). Kidney failure, also referred to as End Stage Renal Disease (ESRD), occurs when GFR drops below 15mL/min per 1.73 m^2. When a patient enters a state of renal failure, they must begin renal replacement therapy to survive (Levey, et al., 2003).

To date, there are three major forms of kidney replacement therapy: hemodialysis, peritoneal dialysis, and renal transplantation (Pliskin, Kiolbasa, Hart, & Umans, 2001). The first form of dialysis, hemodialysis, involves an exchange of solutions across a semi-permeable membrane which filters metabolic wastes from the blood. Hemodialysis is the most prevalent treatment and involves a clinical visit three times a week for several hours each time (Gonzalez-Perez, Stearns, & Wordsworth, 2005). Even with this treatment, individuals may still experience severe renal insufficiency. The concept of peritoneal dialysis is similar, but it involves the use of the patient's own peritoneal membrane to filter metabolic wastes. This treatment is self-administered, either nightly or four to five times daily. The patient on peritoneal dialysis may also remain in a state of severe renal

insufficiency (Kidney Disease Outcome Quality Initiative (K/DOQI; National Kidney Foundation, 2002).

The last treatment modality is kidney transplantation. When successful, transplantation usually stabilizes renal functioning at 60-70% of normal levels (R. J. Shapiro, personal communication, June 28, 2006). In 2003, 997 adults received kidney transplants in Canada. Of these, 63% were received from deceased donors and the remaining 37% were from living donors (CIHI/CORR Report 2002/2003). From 1997 to 2000, the 1-year patient survival rates were greater than 95% and the 3-year patient survival rates were greater than 90% for adult kidney transplant recipients (CIHI/CORR Report 2002/2003). Relative to dialysis, renal transplantation provides an improvement in long-term survival rates (Polkoff-Rubin & Goes, 2004). Although the recipient must remain on immunosuppressive drugs for life, this is still a highly preferred treatment modality because it usually prevents kidney disease from progressing and stabilizes or improves renal functioning (Pliskin, et al., 2001).

Cognitive Function in Renal Disease

CKD. Pliskin and colleagues note that early studies of cognition in renal disease do not meet current standards regarding quantification of renal function, duration of disease, and uremic control, and thus do not meet current criteria for the classification of early CKD (Pliskin, et al., 2001). However, findings from recent studies suggest that even individuals with mild CKD may be at risk for relatively poor cognitive performance in comparison to healthy individuals. For example, a recent study using a variety of cognitive measures found that individuals with mild-to-moderate CKD (i.e., GFR $\geq$ 25.5mL/min per 1.73 m^2) scored significantly lower on tasks involving memory and

executive functions when compared with published age-matched norms (Kurella, et al., 2004). Specifically, participants with mild-to-moderate CKD were reportedly slower than published norms on a measure of set-shifting (Trailmaking Test B; Reitan & Wolfson, 1985), and recalled less information both during learning trials (i.e., immediate recall) and over time (i.e., delayed recall) on a measure of learning and memory (California Verbal Learning Test – 2nd Edition (CVLT-II); Delis, Kramer, Kaplan, & Ober, 2000). In contrast, individuals with CKD performed within normal limits on a global cognitive screening measure (Modified Mini-Mental State Examination (3MS; Teng & Chui, 1987).

Additionally, research from our lab revealed that individuals with CKD (i.e., GFR < 60 mL/min per 1.73 m^2) scored significantly lower on measures of attention, learning and memory, and executive functioning in comparison to age-matched controls (Thornton, et al., under review). The tests utilized included the CVLT-II, and the Trails Letter-Number Sequencing Task and Color-Word Inhibition Task from the Delis-Kaplan Executive Function System (D-KEFS; Delis, Kaplan, & Kramer, 2001). Cognitive functioning was not found to be associated with measures of illness severity (i.e., hemoglobin levels, estimated GFR, or stage of kidney disease), nor depressive symptomatology. However, older CKD participants generally performed less well than younger CKD participants on measures of attention and executive functioning. In comparison to the controls, the CKD participants had higher rates of co-morbid conditions (e.g., diabetes, hypertension, hypercholesterolemia) that are understood to be independently associated with reduced cognitive capacities (see Schindler, et al., 2005).

Therefore, we suggested that cerebrovascular risk factors likely contributed to the cognitive findings in our study.

ESRD. In contrast to the paucity of studies conducted to date regarding cognition in early CKD, the study of cognition in ESRD, particularly with hemodialysis patients, has received considerably more attention. This could be because the dialysis procedure itself may lead to cognitive compromise in ESRD (i.e., dialysis-associated dementia), a condition first recognized by Alfrey and colleagues in 1972 (Alfrey, Le Gendre, & Kaehny, 1976, cited in Burn & Bates, 1998). However, since 1980, dialysis-associated dementia can be most often avoided by preventing aluminium toxicity via the use of water purification techniques (Burn & Bates, 1998; Rob, Niederstadt, & Reushche, 2001). In addition to the dialysis procedure, anemia, a condition that usually accompanies ESRD (Pereira, Weiner, Scott, & Sarnak, 2005), has also been noted to result in compromised attention, mental processing speed, learning, and memory apart from CKD (see Pliskin, et al., 2001). Prior to the 1990s, effective treatment for anemia did not exist. Currently, recombinant human erythropoietin (rHuEPO) treatment can effectively reverse anemia. Since a substantial portion of the CKD cognitive literature pertains to data collected prior to the development of rHuEPO, it is challenging to summarize cognitive functioning in ESRD. Furthermore, Pliskin and colleagues (2001) point out that many of the early ESRD studies not only failed to control anemia, but also did not quantify dialysis delivery, nor consider the duration of kidney disease, time between testing and dialysis delivery, and demographic factors such as ethnicity and education. For these reasons, we will only consider relatively recent studies in this brief review of cognition in ESRD.

Bremer, Wert, Durica, & Weaver (1997) discovered that despite similar performances on measures of attention (Trails A) and complex concept formation (Computerized Category Test; Defilippis, 1993), dialysis participants did not perform as well as controls on a measure of set shifting (Trails B). In a series of studies, Fazekas and colleagues (1996), using the Mini-Mental Status Exam (MMSE; Folstein, Folstein, & McHugh, 1975) and the Mattis Dementia Rating Scale (DRS; Mattis, 1976) identified significantly worse cognitive performance in dialysis participants in comparison with age- and gender-matched controls (Fazekas, Fazekas, Schmidt, et al., 1996).

Similarly, Fazekas et al. (1995) found that 60% of the dialysis participants in their study showed marked cognitive impairment on dementia screening measures. Applying the criteria for dementia from the Diagnostic and Statistical Manual of Mental Disorders Revised (DSM-III-R), these authors reported a significantly greater prevalence of dementia in ESRD participants than in controls matched on age, gender, and cerebrovascular risk factors. In addition, MRI findings revealed significantly higher volumes of brain atrophy in dialysis participants than matched controls. The authors suggested that known cerebrovascular attacks, longstanding and severe hypertension, metabolic factors (e.g., hyperparathyroidism), and the dialysis procedure might have contributed to the MRI findings. However, the authors found that poor cognitive performance was associated with brain atrophy rather than vascular damage and therefore, favored the role of metabolic factors and dialysis in the etiology of compromised cognition (Fazekas, Fazekas, Schmidt, et al., 1995).

In the aforementioned study by Kurella and colleagues (2004), cognitive performance of pre-dialysis CKD participants was also compared with hemodialysis

participants. Cognitive performance was significantly worse for hemodialysis participants in comparison to pre-dialysis CKD participants. In particular, hemodialysis participants obtained lower scores on immediate and delayed memory (CVLT-II), set shifting (Trails B), and a brief cognitive screening measure (3MS).

Despite recent behavioral and neuroimaging findings that suggest that individuals with ESRD may be at risk for cognitive impairments, other studies have not found cognitive difficulties associated with dialysis. For example, in a study of dialysis participants who were compared to controls with a variety of chronic medical conditions, no clear differences were found on an extensive test battery assessing intelligence, memory, attention, processing speed, language abilities, and complex problem solving (Pliskin, Yurk, Ho, & Umans, 1996). Similarly, Maugeri, et al. (1999), using the MMSE, did not discover any significant differences between dialysis participants and healthy controls, and Umans and Pliskin (1998) did not find differences between well-dialyzed persons with ESRD and controls on measures of attention or executive functioning.

Thus, to date, findings regarding cognitive performance in ESRD are contradictory. Some studies report worse performance in ESRD and others suggest equivalent performance with that of the control participants. These discrepancies may be due partially to differences in composition of the comparison groups. For example, Pliskin and colleagues (1996) included a small sample size (n = 16) of ESRD participants and their control group included a considerable proportion of individuals with hypertension and diabetes, conditions that are independently associated with compromised cognition (e.g., Strachan, Deary, Ewing, & Frier, 1997; Raz, Rodrigue, & Acker, 2003). While Maugeri and colleagues' study (1999) included a larger sample size

(n = 39), their conclusions are restricted by the use of only a cognitive screening measure (i.e., MMSE) with recognized limitations in detecting mild cognitive impairment (see Tombaugh, McDowell, Kristjansson, & Hubley, 1996). Lastly, the Umans and Pliskin study (1998) also had a small sample size (n = 10). It is important to note that studies reporting reduced cognition in persons with ESRD have had considerably larger samples (e.g., Kurella et al., 2004). In fact, effect size calculations between dialysis participants and controls for Umans and Pliskins'(1998) study reveal effect estimates to be small to medium for most measures (e.g., Trails Test, Digit Span, *d*'s range from .02 to .41), medium for the Stroop test ($d = .50$), and medium to large for the Continuous Performance Test ($d = .76$). Given the fact that a sample size of 26 would be required to detect a large between-group effect (Cohen, 1992), it is likely that power limitations have influenced reports of null cognitive findings in ESRD to date.

While the behavioral data suggests that renal disease prior to transplantation may be associated with reduced cognitive performance in both mild and severe forms of the disease, the etiology of these compromised states remains elusive. Three mechanisms have been advanced (Lass, Buscombe, Harber, Davenport, & Wilson, 1999). The first and generally most accepted explanation involves the metabolic derangements associated with renal disease (e.g., Griva, et al., 2004). Untreated renal impairment can result in uremic encephalopathy; however, because present clinical practice standards mean that dialysis is initiated at an earlier stage of the disease, occurrences of this condition are limited (Rob, et al., 2001). Although dialysis may help to avoid uremic encephalopathy, this does not imply that symptoms of uremia entirely disappear. In fact, researchers have

suggested that uremia may affect cognition even in well-dialyzed individuals (e.g., Kramer, et al., 1996).

Secondly, factors associated with the dialysis procedure have been linked to cognitive deficits. While dialysis dementia occurred in 600 per 100 000 dialysis patients in 1976 and 1977 (see Burn & Bates, 1998), the condition can now be avoided (Rob, et al., 2001). Even so, it has been noted that hemodialysis results in decreased cerebral blood flow (i.e., decreased velocity of blood flow to the middle cerebral artery and the basilar artery; Hata, et al., 1994). Although the reason that dialysis decreases blood flow to these regions is unknown, Hata and colleagues observed negative correlations between blood flow and loss of body weight following initiation of hemodialysis, the amount of fluid removed during dialysis, and changes in hematocrit levels. Lass and colleagues (1999) have suggested that the decreases in blood flow to cerebral regions might result in compromised cognition.

Finally, it has recently been argued that co-morbid cerebrovascular disease may underlie at least some of the cognitive difficulties associated with renal disease (e.g., Pereira, et al., 2005). In fact, neuroimaging studies suggest that cerebrovascular disease, a condition that is independently associated with cognitive compromise (see Schindler, 2005), may exist in CKD participants prior to the initiation of dialysis treatment (Fazekas, Fazekas, Schmidt, et al., 1995 & 1996). In Canada, diabetes and renal vascular disease (a condition closely linked to hypertension) have been identified as the leading causes of CKD for over 20 years. Diabetes has accounted for etiology in 32.0% of the cases and renal vascular disease has accounted for 20.8% of the cases (2002/2003 CORR Report, 2003). The importance of the prevalence of diabetes and hypertension is

highlighted by evidence for poor cognitive performance in both conditions apart from CKD (Strachan, et al., 1997; MacKnight, et al., 2002; Raz, et al., 2003; Head, Raz, Gunning-Dixon, Williamson, & Acker, 2002). For example, Raz and colleagues (2003) used magnetic resonance imaging (MRI) and cognitive tests and found that hypertensive individuals often had smaller prefrontal cortical volumes, a greater extent of white matter hyperintensities in the frontal regions, and worse executive functioning when compared to demographically matched controls. Furthermore, in a review of case-controlled studies, type II diabetes has been found to be associated with poor verbal memory (Strachan, et al., 1997). Poor executive functioning and psychomotor abilities have also been associated with type II diabetes, although not as consistently as poor verbal memory performance (Strachan, et al., 1997).

In addition to diabetes and hypertension, there are many other co-morbid conditions (e.g., coronary artery disease and depression) that may contribute to the cognitive difficulties manifested by individuals with CKD even after successful renal transplantation (see Pliskin, Kiolbasa, Hart, & Umans, 2001). Despite restoration of renal functioning after renal transplantation, compromised cognition may not improve to pre-illness baseline because of co-morbid conditions. This brings one to the issue of cognition following renal transplantation, which we will now discuss.

Transplant. In contrast to the substantial literature on cognition in ESRD, the effects of kidney transplantation on cognitive functioning are not as well known. While it is generally believed that cognitive capacities will improve following successful renal transplant (TX), supportive research is lacking. A number of studies have examined cognitive functioning in children with successful kidney TXs (e.g., Brouhard et al., 2000;

Fennell, et al., 1990; Fennell, Fennell, Mings, & Morris, 1986; Fennell, Rasbury, Fennell, & Morris, 1984; Hobbs & Sexson, 1993; Kuyer, Hulstign – Dirkmaat, & van Aken, 1990; Lawry, Brouhard, & Cunningham, 1994; Mendley & Zelko, 1999). Even so, the studies employed a variety of methodologies and no clear findings have emerged. Furthermore, many of these studies focused on intelligence and achievement test performance (e.g., Kuyer, et al., 1990; Brouhard, et al., 2000; Lawry, et al., 1994), in contrast to studies of adults that tend to focus on specific domains of cognition (e.g., memory and attention).

Two primary questions emerge when considering the effects of kidney transplantation on cognition. The first question concerns whether, from a state of renal failure to a state of renal compensation, cognition improves. This is typically assessed by both cross-sectional and longitudinal comparisons of individuals pre- and post-kidney TX. To date, only a few studies have examined cognitive functioning in adults with kidney TXs and compared it to individuals on dialysis (Griva, et al., 2004; Kramer et al., 1996; Takuma, Sanaka, & Sugino, 1987; Teschan et al., 1979), and findings remain equivocal.

For example, in a cross-sectional comparison, Teschan and colleagues (1979) compared cognition in TX recipients (n = 18) and persons on dialysis (n = 77). Significant differences did not emerge between TX and dialysis participants on measures of working memory (i.e., Continuous Memory Test) or on one measure of processing speed and sustained attention (i.e., Choice Reaction Time test; Woodworth, 1940); however, TX participants did perform significantly better than dialysis participants on another measure of processing speed and sustained attention (i.e., Continuous Performance Test; Rosvold, Mirsky, Sarason, Branscome, & Beck, 1956). In sum,

Teschan, et al.'s (1979) study provides some support for improvement in attention processes following kidney TX in comparison to persons on dialysis.

Additionally, a more recent study (Griva, et al., 2004) compared cognitive performance in a large sample of TX (n = 117) and dialysis participants (n = 145), and expanded the cognitive battery to include tests of memory and executive functioning. Griva and colleagues (2004) found further support for improvements in attention for TX participants in comparison to dialysis participants. In addition, they found indications of better memory, but not executive abilities or fine motor coordination in persons with TXs when compared with those on dialysis. Specifically, TX participants scored significantly higher than dialysis participants on all three measures of attention (i.e., Trails A, Symbol Digit Modalities Test (SDMT) – written, and SDMT – oral; Smith, 1973), and on one measure of memory (Rey Auditory Verbal Learning Test (RAVLT) Trials 1-5; Rey, 1964). However, Griva and colleagues did not find the performance of TX participants to be significantly better than that of dialysis participants on a task which required the executive functioning ability of set shifting (Trailmaking Test B) or on fine motor coordination (Grooved Pegboard; Matthews & Klove, 1964).

While cross-sectional comparisons suggest improvements in some abilities (i.e., attention and memory) and not others (i.e., executive functioning) following kidney transplantation, the data from longitudinal studies is somewhat less clear. Two longitudinal studies have been performed and both look at measures of attention (Takuma, et al., 1987; Kramer, et al., 1996). Takuma et al. (1987) considered the performance of TX participants (n = 16) on a measure of attention (i.e., the Uchida-Kraepelin continuous simple addition test; Uchida, 1951) both before and after successful

kidney transplantation (the average amount of time post-transplant was not reported). At the time of second testing, TX participants showed 32% improvement on the simple addition test, although significance tests were not reported.

Kramer and colleagues (1996) also assessed longitudinal changes in patients pre- and post-TX. Fifteen TX participants were tested using an attention task (Trails A) and a cognitive screening measure (MMSE). The TX participants were tested prior to and 9-19 months after receiving a kidney TX. Post-TX performance exceeded that of pre-TX (i.e., while on hemodialysis) performance, but not at a level of significance.

While these findings provide some support that a few domains of cognition (i.e., attention and memory) improve from the state of renal failure (dialysis) to the state of renal compensation (post-TX), the research does not address to what extent reduced cognitive performance that presents in early CKD (i.e., prior to dialysis) may persist following renal transplantation. In previous work (Thornton, et al., under review), we have argued that the pattern and stability of reduced cognitive performance observed in early CKD are most consistent with co-morbid cerebrovascular illness, which is not likely to rescind following transplantation. To date, studies have not compared cognitive performance in early CKD with that of participants post-renal TX. Such a comparison may allow better elucidation of the role of metabolic derangements and other illness-related features.

Another important question concerns whether renal transplantation returns one to a state of pre-morbid or baseline cognitive abilities. To answer this question, one must compare the performance of renal TX recipients to that of healthy controls. To date, studies have examined this question with varying methods and results.

In addition to comparisons with dialysis patients, Teschan et al., 1979, Kramer et al., 1996, and Takuma, et al., 1987 also compared the cognitive performance of TX participants to that of controls. Teschan and colleagues (1979) did not find significant differences between TX participants and controls on measures of processing speed, working memory, and sustained and selective attention (i.e., Continuous Memory Test, Choice Reaction Time Test and Continuous Performance Test). In Kramer and colleagues' (1996) study, post-TX participants did not perform significantly worse than controls on the attention task (i.e., Trails A) or the cognitive screening measure (i.e., MMSE). Lastly, Takuma, et al. (1987) found that while TX participants showed 32% improvement on the second administration of the simple addition test, controls showed 10% improvement. The study did not indicate whether or not the TX participants' performance at second testing was significantly different than that of the controls. To review, studies comparing TX participants and controls are not suggestive of differences between the two groups in terms of attention.

Although they did not make comparisons to within-study controls, Griva, et al. (2004) and Bermond, et al. (2005) did compare TX performance to that of published normative data. In Griva and colleagues' (2004) study, the performance of TX participants was similar to that of published normative data on the measures of fine motor coordination, attention, memory, and executive functioning. However, Bermond, et al. (2005) used the Dutch version of the RAVLT (Saan & Deelman, 1998) to evaluate memory in TX participants in comparison to published normative data, and their research led to different findings. They found that TX participants performed significantly worse on verbal memory tasks in comparison to normative data. In particular, TX participants

performed poorly on both immediate and delayed recall of a concrete word list, and on delayed recall of an abstract word list. The authors found that higher dosages of prednisone (i.e., an immunosuppressant commonly administered to TX recipients) were associated with a number of memory scores (immediate recall, abstract; delayed recall, abstract and concrete). The authors have suggested that long-term administration of prednisone leads to increased occupation of glucocorticoid receptors in the hippocampus and this may lead to poor memory performance.

In summary, comparisons between TX participants and controls suggest no reliable differences in attention and executive functioning post-successful kidney TX. Results regarding memory remain equivocal with Griva, et al.'s study (2004) suggesting superior memory post-TX, and Bermond, et al.'s study (2005) indicating poorer memory post-TX. However, the previously mentioned studies of cognition in renal TX participants are limited by a narrow range of cognitive domains tested (Kramer, et al., 1996; Takuma, et al., 1987; Teschan, et al., 1979; Bermond, et al., 2005), methodological issues such as a lack of in-study control groups (Griva, et al., 2004; Bermond, et al., 2005), failure to account for practice effects (Kramer, et al., 1996; Reeve & Lam, 2005), qualitative reporting of improvement (Takuma, et al., 1987), outdated standards of dialysis delivery and transplantation procedures (Teschan, et al., 1979), and small samples of TX participants. For example, the sample sizes in two studies reporting null differences between controls and persons post-TX ($n = 18$ for Teschan, et al., 1979; and $n = 15$ for Kramer, et al., 1996) do not provide enough power to detect even large effects.

Clearly, additional research is necessary to further delineate the extent and pattern of cognitive compromise in this medical population, especially regarding memory and

executive functions (i.e., only one study assesses executive functioning (Griva, et al., 2004), and two studies address memory functioning (Griva, et al., 2004; Bermond, et al., 2005)). The current study will lead to better understanding of cognition in this population and assist health professionals in addressing the unique challenges which kidney TX recipients face by including multiple measures of cognition and making comparisons of TX participants with pre-dialysis CKD participants and within-study controls. Furthermore, it is anticipated that a two-dimensional model (i.e., considering cognition in light of resolution of metabolic dysregulation and persistence of co-morbid conditions) will be useful for interpreting cognitive findings in TX participants.

Psychosocial Factors in Renal Disease

Currently, psychosocial differences between healthy controls and CKD, ESRD, and TX participants are not well explained. Depression has been identified as the most prevalent psychological problem among ESRD participants (Kimmel, Weihs, & Peterson, 1993); however, while several studies have assessed depressive symptoms in ESRD (see Kimmel, 2002), fewer investigations have considered the role of depression in early CKD (e.g., Shidler, Peterson, & Kimmel, 1998 and Thornton, et al., under review) and following kidney transplantation (e.g., Akman, Özdemir, Sezer, Micozkadioğlue, & Haberal, 2004).

Shidler, et al. (1998) and Thornton, et al. (under review) evaluated self report of depressive symptoms in pre-dialysis CKD patients. Shidler and colleagues (1998) used the Beck Depression Inventory (BDI) and discovered pre-dialysis CKD participants to have similar levels of depressive symptoms in comparison with dialysis participants. In the study from our lab, we used the Center for Epidemiological Studies Depression Scale

questionnaire (CES-D; Radloff, 1977) and found that CKD participants acknowledged significantly more symptoms of depression than the healthy controls (Thornton, et al., under review).

While depressive symptoms appear to be common amongst both CKD and ESRD populations, there is conflicting research regarding depressive symptomatology in TX participants. Ackman and colleagues (2004) compared depressive symptoms (using the BDI) in TX participants to individuals receiving dialysis, and TX participants were found to assert significantly lower levels of depressive symptoms than the dialysis participants. Zimmermann and colleagues also used the BDI to assess depression and found that TX participants asserted significantly less symptoms of depression than dialysis participants (Zimmermann, Poli de Figueiredo, & Fonseca, 2001).

However, two other studies present a conflicting picture. Christensen and colleagues (2000) used the BDI and Yeh and colleagues (2004) used the Chinese version of the Hamilton Depression Rating Scale and each study found no detectable differences in levels of depressive symptomatology between TX recipients and dialysis participants (Christensen, Ehlers, Raichle, Bertolatus, & Lawton, 2000; Yeh et al., 2004).

Even less is known about changes in anxiety across the stages of renal disease. However, based on the significant overlap in the occurrence of anxiety and depression in other clinical and normal populations (see Eysenck, Payne, and Santos, 2006), it seems reasonable to expect similar levels of anxiety symptoms as depressive symptoms in CKD and TX participants. Consistent with this prediction, Qingfeng, Dong and Minhua (2004) found that 44.3% and 56.8% of their sample of peritoneal dialysis participants experienced elevated symptoms of anxiety and depression, respectively. Kimmel and

colleagues (1998) further highlight the importance of assessing anxiety in CKD. They compared the incidence of anxiety and other mental disorders in ESRD to other medical conditions (diabetes, ischemic heart disease, cerebrovascular disease, and peptic ulcer disease), and found significantly higher rates of anxiety in persons with ESRD (Kimmel, Thamer, Richard, & Ray, 1998).

Similar to research regarding depression, little information is available which compares anxiety in kidney TX recipients with that of pre-TX patients. Zimmerman and colleagues, using the State-Trait Anxiety Inventory, discovered that both TX and dialysis patients asserted elevated symptoms of anxiety, but did not detect statistical differences between the two groups (Zimmerman, et al., 2001). In addition, Yeh and colleagues (2004) used the Chinese version of the Hamilton Anxiety Rating Scale and did not find significant differences between TX and ESRD participants.

To summarize, current research suggests that levels of depression and anxiety are similar between CKD and ESRD participants and symptoms of depression and anxiety may be less frequent amongst kidney TX recipients, although the results from studies vary regarding the latter.

The importance of assessing depression and anxiety in renal disease is further highlighted by previous findings that these conditions have been found to effect cognitive performance in other populations (e.g., Brown, Scott, Bench, & Dolan, 1994; Chamelian & Feinstein, 2006). Interestingly, one study has assessed the role of depression (using the Cognitive Depression Index) as a predictor of cognitive performance in a large sample of persons with ESRD (Yount, Jacobs, Bustamante, & Brickman, 1998). No relationship could be identified between depressive symptomatology and the measures of attention

(CPT, Digit Span, and Digit Symbol Coding), executive functioning (Trailmaking Test B, Stroop test; Stroop, 1935), or memory (Enhanced Cued Recall test). While these findings suggest that reduced cognitive performance in persons with ESRD cannot be explained by depressive symptomatology alone, the current study will help to elucidate the role that depression and anxiety play in cognition for individuals with kidney TXs.

HYPOTHESES AND OBJECTIVES

Reduced cognitive capacity can negatively impact one's ability to comply with treatment regimens and ultimately, one's quality of life. Currently, there has been minimal research on this topic within kidney TX populations; therefore, the primary aim of this study was to better describe the cognitive capacities of these individuals. Our second objective was to describe psychosocial functioning (i.e., anxiety and depression) in persons with kidney TXs. Following the second objective, if we found levels of depression and anxiety (i.e., distress) to be elevated and cognitive performance to be poor, we wished to assess whether distress was associated with cognitive performance for persons with kidney TXs. To achieve each of these goals, we compared cognitive functioning and distress in TX participants, individuals in the early stages of CKD (i.e., pre-dialysis CKD participants), and healthy controls. We also assessed associations of depression and anxiety with cognitive performance in the study sample.

Based on a two-dimensional model (i.e., resolution of metabolic dysregulation and persistence of co-morbid conditions) and the existent literature, the following hypotheses were formulated regarding the comparison of cognitive and psychosocial functioning of TX participants to that of CKD participants (i.e., persons with kidney disease who are not receiving renal replacement therapy) and healthy controls. Three primary hypotheses guided our investigation. First, it was predicted that both CKD and TX participants would perform worse than controls on measures of executive functioning. As one of the leading causes of CKD, hypertension was anticipated to be

prevalent in our TX recipient subject pool (Levey, et al., 2003). As previously discussed, hypertension has been associated with increased white-matter hyperintensities and decreased executive functioning capacities (Raz, et al., 2003; Gunning-Dixon & Raz, 2003). As well, since differences in executive functioning have not been detected between TX and dialysis participants (Griva, et al., 2004) and poorer executive functioning has been found amongst CKD participants relative to controls (e.g., Kurella, et al, 2004; Thornton, et al., under review), both CKD and TX participants were anticipated to perform significantly worse on measures of executive function in comparison to controls.

Secondly, both TX participants and controls were predicted to perform significantly better than CKD participants on measures of attention, and learning and memory. Because a two-dimensional model of factors was presumed to underlie cognitive difficulties in renal disease, we predicted that the resolution of metabolic abnormalities would result in improvements in memory and attention performance related to the accumulation of metabolic wastes and toxins characteristic of kidney disease. In addition, results from previous studies suggest that attention and learning and memory capacities of kidney TX participants are similar to controls and are significantly greater than that of dialysis participants (e.g., Kramer, et al., 1996; Griva et al., 2004). Considering previous research findings and the anticipated contribution of common co-morbid conditions, it was predicted that TX participants and controls would perform significantly better than CKD participants on tasks of attention and learning and memory.

The third hypothesis concerned depression and anxiety. Although minimal research has specifically addressed the trajectory of depression and anxiety throughout

the course of renal disease and kidney transplantation, some, but not all, studies suggest that individuals with kidney TXs exhibit fewer symptoms of depression and anxiety than those with ESRD. Thus, it was anticipated that symptoms of depression and anxiety would be highest amongst CKD participants, followed by TX participants, and lastly, healthy controls.

METHODS

Participants

Neuropsychological tests and psychosocial questionnaires were administered to 52 healthy controls, 47 CKD participants, and 43 kidney TX recipients. The current study was, in part, based on data collected for a large ongoing research project designed to examine cognitive and psychosocial functioning in persons with CKD and matched healthy controls (Thornton, et al., under review). For the current study, 47 CKD participants and 52 healthy controls were selected from the existing data set to maximize matching of age for the three groups of interest. Specifically, those younger than age 81 were selected from amongst the CKD and control participants to match the age range of the TX participants in the current study.

Recruitment. To be considered eligible for the current study, all participants met the following criteria: (1) were capable of giving informed consent; (2) were not visually impaired (corrected vision must be at least 20/50) or hearing impaired (or other sensory or motor impairments which might interfere with the testing procedure); (3) were fluent in the English language; (4) had a minimum of grade six education; (5) had an absence of psychosis; (6) had an absence of acute illness (e.g., metastatic cancer), neurological disease, and other major organ failure (e.g., end stage liver disease).

The three groups of participants were selected from separate populations. The CKD group was derived from outpatients seen at the Vancouver General Hospital (VGH)

Renal Clinic. Eligible CKD participants had an estimated GFR less than 60 ml/minute per 1.73 m^2 (i.e., less than half of normal kidney functioning; Levey, et al., 2003) and were not receiving any form of renal replacement therapy. A research coordinator (T. Pentland) invited consecutive patients at the renal clinic to participate during their routine clinic visits, and the recruitment success rate was approximately 70%.

The TX participants in this study consisted of outpatients seen at the VGH Solid Organ Transplant (SOT) Clinic. Eligible TX participants included those who had maintained a successful kidney graft and had stable renal functioning (with their current estimated GFR above 14ml/minute per 1.73 m^2) for at least six months. Appendix A addresses how the stability of renal functioning was evaluated. Recruitment of TX participants occurred via two methods: (1) through in-person invitations from the author (S. Gelb) during their routine clinic visits, and (2) through a research study information letter. Some of the individuals who received the information letter called us back to indicate their willingness to participate. In addition, the author called as many of the other letter recipients as possible and gave these individuals an opportunity to learn more about the study and to indicate if they were willing to participate in the study. The in-person recruitment rate was approximately 33%; however, many of the individuals who declined to participate likely would have not met the eligibility requirements for the study (e.g., it is estimated that at least 30% of individuals declined because they were not fluent in the English language); therefore, it is believed that a 33% recruitment rate is most likely an underestimation of true rates among eligibles. The overall letter recruitment rate was approximately 21%, and 85% of persons contacted by phone agreed to participate in the study. Overall, recruitment rates are similar to that of Bremer and colleagues, who had a

recruitment success rate of approximately 43% with potential dialysis participants via telephone calls (Bremer, et al., 1997). Both TX and CKD participants received $40.00 as reimbursement for their travel and time associated with the cognitive testing.

The third group of participants consisted of healthy controls. These individuals were recruited from the community via advertisements, presentations at community centres, and from Simon Fraser University (i.e., staff members employed at SFU). Controls received $10.00 as reimbursement for their time and travel expenses. All participants signed letters of informed consent and the study protocol was approved by the University of British Columbia and Simon Fraser University research ethics boards. Testing of the participants occurred between March 2003 and May 2006.

Missing Data. Several TX participants (n = 10) were not able to complete the entire testing battery either due to a difficulty distinguishing color stimuli that prohibited completion of the Color-Word Inhibition task (n = 5), an experimenter error (n = 4), or a participant's refusal to complete a given task (n = 1). Each individual who was unable to complete the Color-Word Inhibition task had diabetic retinopathy and this was likely the cause of their inability to distinguish between color stimuli. Experimenter error resulted in missing raw scores for one TX participant's Color-Word Inhibition task, one TX participant's Trails Number-Letter Sequencing task, one TX participant's Long Delay score from the CVLT-II test, and one control's IADL questionnaire. In addition, one TX participant became frustrated with the Trails Number-Letter Sequencing task and refused to finish it. The remaining data from these participants were included in all other analyses.

Measures

According to standardized protocol, trained research assistants and graduate students individually administered and scored the tests. Healthy controls were tested at the Simon Fraser University Human Neuropsychology Laboratory or at community sites (e.g., community centres). TX and CKD participants were tested at the VGH renal or SOT clinic for CKD and TX participants, respectively. In addition, a few CKD and TX participants were tested at the Simon Fraser University Human Neuropsychology Laboratory. All participants completed a 2-hour battery of tests and questionnaires. With these instruments, information was gathered on demographics, health characteristics, psychosocial functioning, and cognition.

Demographics. Demographic information included age, gender, ethnicity, education, marital status, and employment status.

Daily living skills. These were quantified using the Instrumental Activities of Daily Living questionnaire (IADL; Lawton & Brody, 1967). The IADL questionnaire consists of 8 skills that are scored according to a hierarchical Guttman scoring format (i.e., less able versus more able to do a given task) with a dichotomous scale.

Psychosocial Functioning. Psychosocial functioning was evaluated using measures of depression and anxiety. The Center for Epidemiological Studies Depression Scale (CES-D) was administered. This 20-item inventory has been found to have adequate internal consistency reliability (Cronbach's $\alpha = .90$) in medical populations (Verdier-Taillefer, Gourlet, Fuhrer, & Alpérovitch, 2001). In addition, the Multidimensional Anxiety Questionnaire (MAQ; Reynolds, 2003) was given to the participants. This scale consists of 40 items and has adequate test-retest reliability ($r >$

.90). In the current sample, internal consistency reliability was adequate for both the CES-D and MAQ (Cronbach's α's = .84 & .91, respectively).

Medical Measures. The *Health Questionnaire* is a self-report measure that assesses medical history and current health concerns (i.e., cerebrovascular risk factors, medications). This measure, previously used with success in other studies of neuropsychological functioning (e.g., Raz, et al., 1997), was used to identify exclusionary factors (e.g., neurological disease, brain injury, etc.) and to provide a description of the study population. Each participant in the study completed this questionnaire.

For CKD and TX participants, information gathered from laboratory tests included hemoglobin levels (g/L) and estimated GFRs. The Modification of Diet in Renal Disease (MDRD) prediction equation was used to estimate GFR in TX and CKD participants. The MDRD formula takes into account serum creatinine (umol/L), serum urea (mmol/L), and serum albumin (g/L) levels, as well as age, ethnicity, and gender. The MDRD is one of two measures of GFR that the National Kidney Foundation of the United States in the Kidney Disease Outcome Quality Initiative recommends (K/DOQI; National Kidney Foundation, 2002). Cognitive testing occurred within four weeks of the laboratory tests. In addition, current medications and corresponding dosages, CKD diagnosis, and information on co-morbidity was gathered from the patients' medical records.

Cognitive Instruments

1. The *California Verbal Learning Test - Second Edition* (CVLT-II) is a neuropsychological test used to assess verbal memory abilities including free recall and recognition memory. Participants are read a list of words and, immediately following, are

asked to recall as many items as they can and again, after a delay period. The initial learning trial (Trial 1) of the CVLT-II is generally considered to be a measure of auditory attention span and has a test-retest reliability of .57 (Delis, et al., 2000). The learning and memory measures of interest for the present study are the raw scores for Trials 1-5 and Long Delay Free Recall. The sum of correct responses from Trials 1-5 indicates the total number of items an individual is able to recall after hearing the list five times and measures one's ability to learn verbal information (Delis, et al., 2000). Long Delay Free Recall provides an estimate of the amount of verbal information an individual is able to retain after a delay of approximately 20 minutes. Trials 1-5 and Long Delay Free Recall are two of the most stable measures on the CVLT-II (test-retest reliability: r = .82 and .88, respectively). Overall, the CVLT-II has adequate reliability and validity and is well tolerated by individuals with cognitive impairment (Delis, et al., 2000).

3. The *Delis-Kaplan Executive Function System* (D-KEFS; Delis, et al., 2000) provides an assessment of complex tasks that require cognitive flexibility. The subtests that were used from the system were the Trail Making Test and the Color-Word Interference Test, which assess flexibility of thinking and verbal inhibition of a dominant response, respectively (Delis, et al., 2000). Specifically, the raw scores (time to completion in seconds) from the Letter-Number Sequencing Task and Color-Word Inhibition Task served as independent variables. Test-retest reliability of Trails Letter-Number Sequencing is .38 and Color-Word Inhibition is .75. Cognitive complexity of executive functioning tasks appears to make these tests susceptible to greater performance variability, which may impact reliability estimates (Delis, Kramer, Kaplan, & Holdnack, 2004). Although test-retest reliability estimates are moderate, the measures were selected

because of their theoretical utility and known sensitivity to executive function impairment (Delis, et al., 2004).

Data Analysis

Assuming a moderate effect size with alpha set at .05, an *n* of 64 subjects in each group would provide adequate statistical power for the present study (i.e., power = .80; Cohen, 1992). While these group sizes would be ideal, practical limitations, such as participant recruitment, prevented us from collecting information from 64 participants per group. Prior to the initiation of the study, it was felt that an *n* of at least 30 for each group was a reasonable and attainable number of participants for the study. Therefore, the effect size estimates have been calculated for the measures of interest and the impact of power limitations will be discussed.

One-way ANOVA (for continuous data) and χ^2 (for categorical data) were performed to compare groups (TX vs. CKD vs. controls) according to the previously mentioned demographic and psychosocial variables, as well as clinical measures for TX participants (e.g., case mix differences as a result of receiving a kidney from a deceased donor vs. living donor). Because of the recognized potential for age, education, gender, and distress to influence cognitive outcomes (e.g., Brady, Sprio, & Gaziano, 2005; Le Carret, et al., 2003; Brown, et al., 1994; Norman, Evans, Miller & Heaton, 2000), if significant between-group differences for any of the variables met the p-value criterion of $\leq .001$, they were added to the model as either factors or covariates as appropriate.

For the primary analysis, group membership (TX, CKD, and controls) served as the independent variable and four scores (raw scores obtained from CVLT-II Trial 1,

calculated t-scores for CVLT-II Trials 1-5 and Long Delay, and raw scores from D-KEFS Trails Letter-Number Sequencing and Color-Word Inhibition Tasks) served as the dependent variables. Correlational analysis revealed that Trials 1-5 and Long Delay scores from the CVLT-II were highly correlated ($r = .80, p < .001$). Consequently, a composite "learning and memory" score was created by computing and equally weighting t-scores for Trials 1-5 and Long Delay (the mean and standard deviation of the control group was used for the t-score conversion).

Planned comparisons were run using Tukey's honestly significant difference (Tukey's HSD) test, which adjusts significance values for multiple comparisons. When heterogeneity of variances was present for a given variable, the Brown-Forsythe robust test of equality of means was used in place of the standard ANOVA F statistic, and the Games-Howell test was used for planned comparisons. Lastly, estimates of effect sizes (Cohen's d) were calculated with the Effect Size (ES) analysis software version 1.0 using a pooled standard deviation.

For the third objective, to explore group differences in terms of psychosocial factors, one-way ANOVA was used to analyze the data. Since the measures of anxiety (MAQ) and depression (CES-D) were highly correlated ($r = .76, p < .001$), a "distress" measure was created. Individual scores were standardized by converting raw scores to t-scores (the mean and standard deviation of the control group was used for the t-score conversion), and the t-scores from the two measures were averaged to create a single measure of distress.

In addition, Pearson bivariate correlations were carried out in order to study the relationship of psychosocial factors, demographics, and additional clinical factors with

cognitive measures. All analyses were conducted using SPSS 14 software, and all *p*'s reflect two-tailed tests with a p-value less than .05 considered statistically significant.

Assumptions of ANOVA

Prior to proceeding with the primary analyses, data were assessed to evaluate whether the three primary assumptions (i.e., assumption of independence, assumption of normality, and assumption of homogeneity) of ANOVA were met. Based on recruitment and study design characteristics, there was little reason to suspect that the assumption of independence had been violated. Assumptions of normality were assessed by considering values of skewness and kurtosis, and by evaluating Q-Q plots, histograms, and boxplots. All of the variables of interest were approximately normally distributed with the exception of three extreme outliers (i.e., values that are above or below the mean by more than 3 times the interquartile range) on the Color-Word Inhibition measure. Based on the recommendations of Tabachnick and Fidell (2006), raw scores for the three outliers were changed to one unit above the next highest scores.

In addition, homogeneity of variance was assessed using Levene's test of heterogeneity of variances. Heterogeneity of variance was present for the Trails Letter-Number Sequencing measure, therefore the Brown-Forsythe robust test of equality of means was used in place of the standard ANOVA F statistic and the Games-Howell test was used in place of Tukey's HSD for planned comparisons. According to Levene's test, there was homogeneity of variance for the rest of the measures.

In this study, the sample sizes of each group differed from each other (e.g., TX sample size = 43, CKD sample size = 47, and control sample size = 52). Removing participants to equalize group *n*s would result in reduced error degrees of freedom and

decreased power. Myers and Well (2003) state that using ANOVA with unequal *n*s is a straightforward adjustment in a one-factor between-subjects design; therefore no participants were removed from the dataset, and analyses were completed with unequal sample sizes.

RESULTS

Participant Characteristics

Participant characteristics, including demographics, diagnoses, medications, and levels of distress, are presented in Table 1 and Table 2. Table 1 presents means, frequencies, and main effects for the three groups, and Table 2 presents the results from planned comparisons. As can be seen in Table 1, the 43 TX participants, 47 CKD participants, and 52 controls were matched in terms of age, education, and gender. On the IADL, all CKD participants scored either a 7 or 8 with a mean of 7.94 (*S.D.* = .25), all TX participants scored 6, 7, or 8 with a mean of 7.88 (*S.D.* = .45), and all controls received a score of 8 on the IADL. No main effects were found for scores on the IADL ($F(2,138) = 1.96, p = ns$).

Medications. Since anti-depressants, benzodiazepines, and opiates are all central nervous system-active medications (Ensrud, et al., 2003), they could potentially affect cognition. As can be seen in Table 1, main effects were found for the incidence rate of individuals on anti-depressants ($\chi^2 = 8.45$, $df = 2$, $p < .05$) and opiates ($\chi^2 = 6.20$, $df = 2$, $p < .05$). While the CKD group did not differ from controls for usage of anti-depressant medications ($\chi^2 = .04$, $df = 1$, $p = ns$), more TX participants were found to be on anti-depressants than both CKD participants and controls ($\chi^2 = 5.78$, $df = 1$, $p < .05$; $\chi^2 = 5.36$, $df = 1$, $p < .05$, respectively). In contrast, there was a trend for CKD participants to be

taking more opiates than the controls and TX participants ($\chi^2 = 3.42$, $df = 1$, $p = .06$; $\chi^2 = 2.84$, $df = 1$, $p = .09$, respectively).

Co-morbidity. Since diabetes and hypertension commonly occur in individuals with CKD, and, as mentioned earlier, past research has implicated a relationship between these conditions and poor cognitive performance, it is important to assess group differences in the prevalence rates of these conditions. As can be seen in Table 1, main effects were present for both hypertension and diabetes. Pairwise contrasts revealed that both CKD and TX participants, in comparison to controls, had significantly higher rates of hypertension ($\chi^2 = 47.59$, $df = 1$, $p < .001$; $\chi^2 = 25.23$, $df = 1$, $p < .001$, respectively) and diabetes ($\chi^2 = 18.04$, $df = 1$, $p < .001$; $\chi^2 = 16.61$, $df = 1$, $p < .001$, respectively). Also of interest is the significantly higher rate of hypertension for the CKD group in comparison to the TX group (see Table 2).

Past history of diabetes becomes an important variable when taking into account that eight (18.6%) of the TX participants also received a pancreas TX, and, as a result, were no longer considered diabetic. Pancreas TX's effectively reversed type 1 diabetes for these participants, and although they no longer have the condition, the history of diabetes remains an important vascular risk factor for these individuals. For this reason, as can be seen on Table 2, an additional chi-square test was run with the incidence of diabetes for the TX group referring to both those with diabetes at time of testing and those with a history of diabetes.

Table 1. Demographic and Clinical Variables

Participant Characteristics	CKD (n = 47)	Controls (n = 52)	Transplant (n = 43)	p-value
Age (mean ±SD)	60.45 ± 12.21	56.92 ± 13.22	55.63 ± 11.30	*ns*
Female (n; %)	24 (51.1 %)	33 (63.5%)	17 (39.5%)	*ns*
Right Handedness (n; %)	42 (89.4%)	47 (90.4%)	37 (86.0%)	*ns*
Ethnicity				*ns*
Caucasian (n; %)	32 (68.1%)	50 (96.2%)	36(83.7%)	
Asian (n; %)	11 (23.4%)	2 (3.8%)	4 (9.3%)	
Other (n; %)	4 (8.5%)	0 (0.0%)	3 (7.0%)	
Education (mean years ±SD)	13.64 ± 3.05	14.62 ± 2.32	13.72 ± 2.48	*ns*
Distress (mean t-score ±SD)	54.99 ± 10.30	50.00 ± 9.48	56.79 ± 12.34	<.01
Smoke cigarettes (n; %)	6 (12.8%)	4 (7.7%)	1 (2.4%)	*ns*
Hypertension (n; %)	44 (93.6%)	13 (25.0%)	33 (76.7%)	< .001
Diabetes mellitus (n; %)	14 (29.8%)	0 (0%)	12 (27.9%)	< .001
Coronary Artery Disease (n; %)	2 (4.3%)	0 (0%)	9 (20.9%)	< .001
Hypercholesterolemia (n; %)	19 (40.4%)	5 (9.6%)	16 (37.2%)	<.01
Anti-depressants (n; %)	4 (8.5%)	5 (9.6%)	12 (27.9%)	<.05
Benzodiazepines (n; %)	5 (10.6%)	1 (1.9 %)	6 (14.0%)	.09
Opiates (n; %)	3 (6.4 %)	0 (0%)	0 (0%)	< .05
Anti-cholesterol agents (n; %)	21 (44.7%)	4 (7.7%)	19 (44.2%)	< .001
Anti-hypertensives (n; %)	46 (97.9%)	12 (23.1%)	33 (76.7%)	< .001
Anti-diabetic medications (n; %)	13 (27.7%)	0 (0%)	9 (20.9%)	< .001

p-values derived from 1-way ANOVA for continuous data; p-values derived from χ^2 for categorical data.

Table 2. Comparisons of CKD and TX patients only

Participant Characteristics	CKD (n = 47)	Transplant (n = 43)	p-value
Age (mean ±SD)	60.45 ± 12.21	55.63 ± 11.30	*ns*
Female (n; %)	24 (49.0%)	17 (39.5%)	*ns*
Right Handedness (n; %)	44 (89.8%)	37 (86.0%)	*ns*
Ethnicity (n; %)			*ns*
Caucasian	32 (68.1%)	36 (83.7%)	
Asian	11 (23.4%)	4 (9.3%)	
Other	4 (8.5%)	3 (7.0%)	
Education (mean years ±SD)	13.64 ● 3.05	13.72 ± 2.48	*ns*
Distress (mean t-score ±SD)	54.99 ± 10.30	56.79 ± 12.34	*ns*
Smoke cigarettes (n; %)	6 (12.8%)	1 (2.4%)	.07
Hypertension (n; %)	44 (93.6%)	33 (76.7%)	<.05
Diabetes mellitus (DM) (n; %)	14 (29.8%)	12 (27.9%)	*ns*
DM & History of DM (n; %)	14 (29.8%)	20 (46.5%)	*ns*
Coronary Artery Disease (n; %)	2 (4.3%)	9 (20.9%)	<.05
Hypercholesterolemia (n; %)	19 (40.4%)	16 (37.2%)	*ns*
GFR (mean ±SD)	23.67 ± 11.28	58.93± 19.03	< .001
Haemoglobin (g/L) (mean ±SD)	124.00 ± 13.45	134.84 ± 13.81	< .001
EPREX (n; %)	23 (48.9%)	5 (11.6%)	< .001
Anti-depressants (n; %)	4 (8.5%)	12 (27.9%)	<.05
Benzodiazepines (n; %)	5 (10.6%)	6 (14.0%)	*ns*
Opiates (n; %)	3 (6.4 %)	0 (0%)	.09
Anti-cholesterol agents (n; %)	21 (44.7%)	19 (44.2%)	*ns*
Anti-hypertensives (n; %)	46 (97.9%)	33 (76.7%)	< .01
Anti-diabetic medications (n; %)	13 (27.7%)	9 (20.9%)	*ns*
Oral agents	7 (14.3%)	3 (7.0%)	*ns*
Injectable agents	8 (16.3%)	6 (14.0%)	*ns*

p-values derived from 1-way ANOVA for continuous data; p-values derived from χ^2 for categorical data.

Additionally, both coronary artery disease and hypercholesterolemia are co-morbid conditions that may also be associated with compromised cognition (see Pliskin, et al., 2001). As can be seen in Table 1, there are main effects for the rates of coronary artery disease and hypercholesterolemia. Planned comparisons revealed that CKD participants did not differ in rates of coronary artery disease from controls ($\chi^2 = 2.26$, $df = 1$, $p = ns$). However, TX participants had a higher incidence of coronary artery disease than both CKD participants and controls ($\chi^2 = 5.82$, $df = 1$, $p < .05$; $\chi^2 = 12.02$, $df = 1$, $p < .01$, respectively). In addition, both CKD and TX participants had significantly higher rates of hypercholesterolemia than controls ($\chi^2 = 12.76$, $df = 1$, $p < .001$; $\chi^2 = 10.41$, $df = 1$, $p < .01$, respectively).

Clinical characteristics of TX and CKD participants. The causes of kidney disease (i.e., this is typically determined by clinical diagnosis; diagnoses given are most often not biopsy-confirmed) for CKD and TX participants are listed in Table 3, and clinical characteristics specific to TX participants are listed in Table 4. As can be seen in Table 3, hypertension as an etiology of CKD was significantly more common in the CKD group than the TX group. This may reflect a selection bias in the TX population, in that older individuals are less likely to receive a kidney TX and are also more likely to have kidney disease caused by hypertension (Valderrábano, Gómez-Campderá, & Jones, 1998). Nonetheless, Table 2 shows that hypertension was prevalent in both groups irrespective of the CKD diagnosis.

Table 3. CKD Diagnoses

Participant Diagnoses	**CKD (n = 47)**	**Transplant (n = 43)**
Diabetic Nephropathy	12 (25.5%)	13 (30.2%)
Hypertensive Nephrosclerosis/Ischemic Nephropathy	8 (17.0%)	0 (0%)
GN (e.g., IgA, FS, FSGS)	17 (36.2%)	19 (44.1%)
Chronic Glomerulonephritis		7
Focal Glomerulosclerosis	6	4
Focal Segmental Glomerulosclerosis	3	
IgA Nephropathy	4	4
Congenital Glomerulonephritis		1
Poststreptococcal Glomerulonephritis		1
Childhood Glomerulonephritis		1
Chronic Interstitial Nephritis	1	
Reflux Nephropathy	1	1
Hepatitis C MPGN Type I	1	
Post-Infective GN/Acute Tubular Necrosis	1	
Polycystic Kidney Disease	6 (4.3%)	6 (14.0%)
Unknown	2 (4.3%)	2 (4.7%)
Other	2 (4.3%)	3 (7.0%)
Cysteinuria		1
Alport's Syndrome		1
Cholesterol Emboli	1	1
Acute Tubular Necrosis	1	

Table 4. Transplant Participant Characteristics

Participant Characteristics (n =43)		
Time since transplant (years; mean ± SD)	5.11 ± 4.80	
Kidney and Pancreas transplant %	8 (18.6%)	
Dialysis History %	38 (88.3%)	
Hemodialysis		25 (58.1%)
Peritoneal Dialysis		9 (20.9%)
Both Hemodialysis & Peritoneal Dialysis		4 (9.3%)
Time Spent on Dialysis (years; mean ± SD)	2.92 ± 2.42	
Immunosuppressant Type		
Cyclosporine	14 (32.6%)	
Tacrolimus	29 (67.4%)	
Deceased Donor %	27 (62.8%)	
Previously on Dialysis %	26 (96.3%)	
Living Donor %	16 (37.2%)	
Previously on Dialysis %	14 (87.5%)	
Number of Kidney Transplants Received		
1 Transplant %	37 (86.0%)	
2 Transplants %	6 (14.0%)	

Cognitive Performance

Our primary research question was regarding the cognitive performance of TX participants in relation to CKD participants and controls. Results from ANOVA are reported in Table 5, and results from planned comparisons are reported in Table 6. Graphs of the results can be seen in Figures 1-4. ANOVA revealed main effects for all cognitive measures under consideration. As predicted, CKD and TX participants performed more poorly than controls on the executive functioning task of response inhibition (Color-Word Interference; $p < .01$ & $p < .05$, respectively). However, while CKD participants performed significantly more poorly than controls for the executive functioning task of set switching (Trails Letter-Number Sequencing; $p < .01$), TX recipients performed only marginally worse than controls on this task ($p = .09$). In contrast to predictions, planned comparisons revealed significantly poorer performance

for both CKD and TX participants in relation to controls on learning and memory (CVLT Trials 1-5 and Long Delay; both p's $< .001$), and trends for both CKD and TX participants to perform more poorly than controls on the measure of attention (CVLT Trial 1; both p's $= .06$).

Estimates of effect sizes (d) were calculated between the treatment groups and the control group (i.e., CKD versus controls and TX versus controls) for each of the cognitive domains under study. The magnitude of effect sizes was near medium for the measure of attention ($d = -.46$ and $d = -.44$), medium to large for the set-shifting task ($d = -.68$ and $d = -.45$) and the response inhibition task ($d = -.69$ and $d = -.62$), and large for the learning and memory tasks ($d = -1.04$ and $d = -.86$) for CKD and TX participants, respectively.

Figure 1 **Mean Scores on CVLT-II Trial 1**

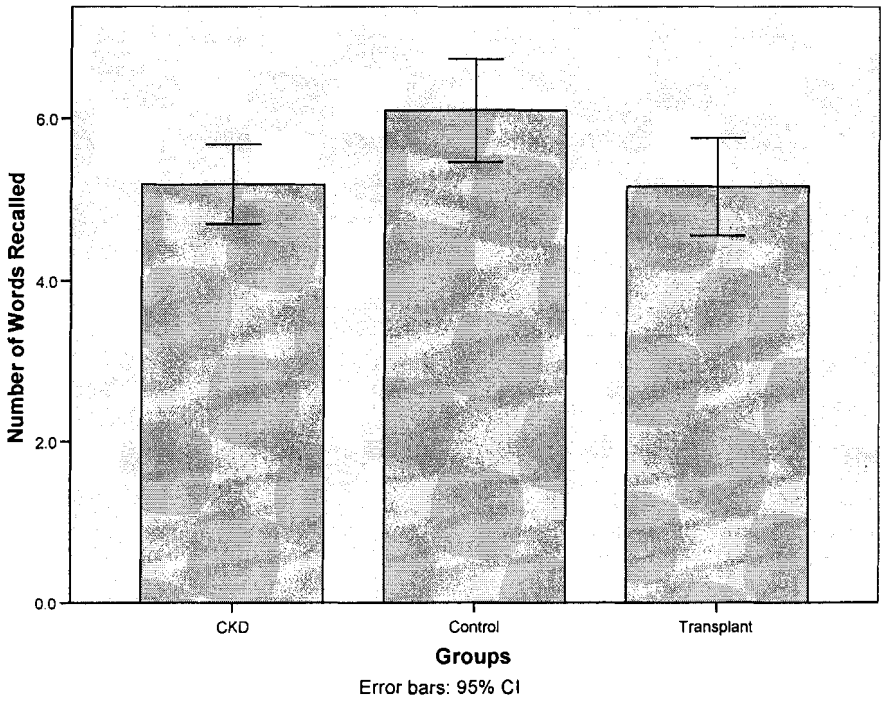

Figure 2. Mean T-Scores on Learning and Memory Composite Measure

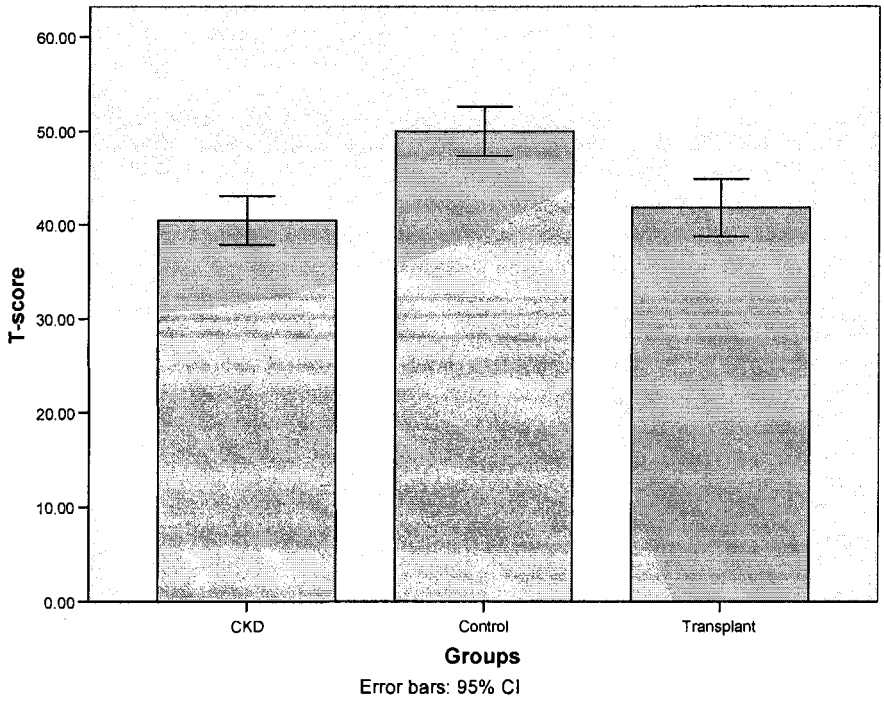

Figure 3. Mean Scores on Trails Letter-Number Sequencing

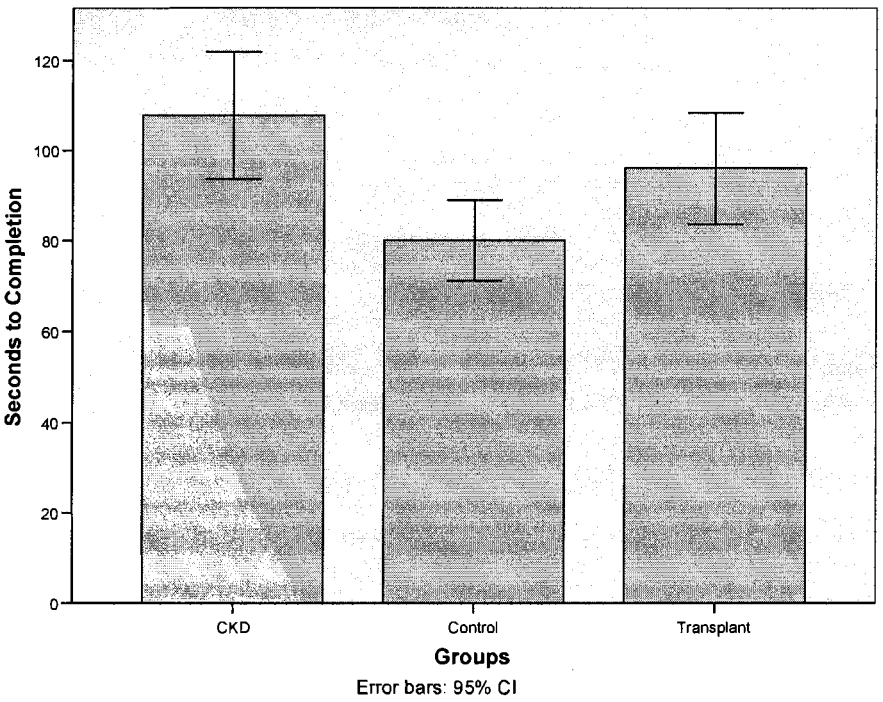

Figure 4. Mean Scores on Color-Word Inhibition

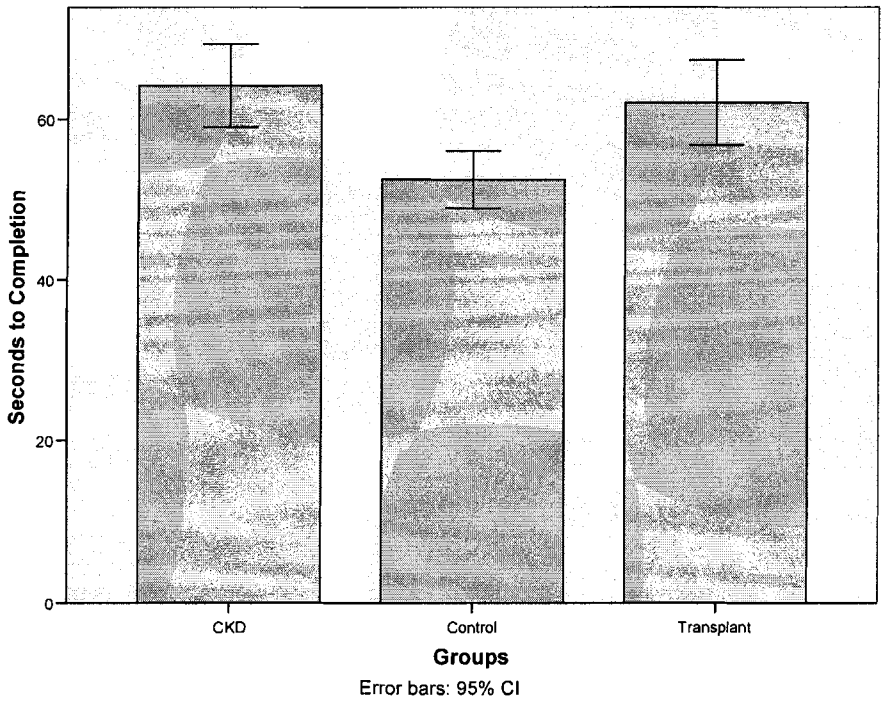

Table 5. ANOVA results for Cognitive Performance

Cognitive Measures	Group	N	M	(SD)	F	df
CVLT -Trial 1	CKD	47	5.19	(1.66)	3.53*	(2, 139)
	TX	43	5.16	(1.95)		
	Control	52	6.10	(2.26)		
Learning & Memory	CKD	47	40.47	(8.88)	15.11**	(2, 138)
	TX	42	41.78	(9.79)		
	Control	52	50.00	(9.40)		
Trails-Letter-Number Sequencing	CKD	47	107.68	(48.22)	5.95**	(2,137)
	TX	41	95.98	(39.21)		
	Control	52	80.06	(31.62)		
Color-Word Inhibition	CKD	47	64.11	(17.23)	7.99**	(2,133)
	TX	37	62.44	(15.43)		
	Control	52	53.76	(12.70)		

*$p < .05$. **$p < .01$.

Table 6. Planned Comparisons for Cognitive Performance

Cognitive Measures	Group	N	M	(SD)	p-value	d
CVLT -Trial 1	CKD	47	5.19	(1.66)	.06	-.46
	Control	52	6.10	(2.26)		
Learning & Memory	CKD	47	40.47	(8.88)	< .001	-1.04
	Control	52	50.00	(9.40)		
Trails-Letter-Number Sequencing	CKD	47	107.68	(48.22)	< .01	-.68
	Control	52	80.06	(31.62)		
Color-Word Inhibition	CKD	47	64.11	(17.23)	< .01	-.69
	Control	52	53.76	(12.70)		

Cognitive Measures	Group	N	M	(SD)	p-value	d
CVLT -Trial 1	TX	43	5.16	(1.95)	.06	-.44
	Control	52	6.10	(2.26)		
Learning & Memory	TX	42	41.78	(9.79)	< .001	-.86
	Control	52	50.00	(9.40)		
Trails-Letter-Number Switching	TX	41	95.98	(39.21)	.09	-.45
	Control	52	80.06	(31.62)		
Color-Word Inhibition	TX	37	62.44	(15.43)	< .05	-.62
	Control	52	53.76	(12.70)		

Cognitive Measures	Group	N	M	(SD)	p-value
CVLT -Trial 1	CKD	47	5.19	(1.66)	*ns*
	TX	41	5.16	(1.95)	
Learning & Memory	CKD	47	40.47	(8.88)	*ns*
	TX	40	41.78	(9.79)	
Trails Letter-Number Sequencing	CKD	47	107.68	(48.22)	*ns*
	TX	39	95.98	(39.21)	
Color-Word Inhibition	CKD	47	64.11	(17.23)	*ns*
	TX	36	62.44	(15.43)	

Severity of cognitive impairment. A cognitive score that is 1.5 *SD*s below the control mean is commonly considered to reflect moderate cognitive impairment (Tuokko, Frerichs, & Kristjansson, 2001). In general, rates of impairment appeared similar between the CKD and TX groups in comparison with the healthy controls. Overall, only one (2.1%) CKD participant and one (2.3%) TX participant were impaired on all four cognitive measures, suggesting that few exhibited what may be considered a broad range of moderate impairments. Considering attention performance, seven (14.9%) CKD participants were impaired on auditory attention (CVLT-II Trial 1) in comparison to nine (20.9%) TX participants. On the learning and memory tasks, thirteen (27.7%) CKD participants and twelve (27.9%) TX participants were impaired. Similarly, on the executive functioning tasks, thirteen (27.7%) CKD participants and seven (16.3%) TX participants were impaired on the set switching task (Trails Letter-Number Sequencing), and ten (21.3%) CKD participants and eight (21.6%) TX participants were impaired on the response inhibition task (Color-Word Inhibition).

Psychosocial Factors

Our second objective was to describe group differences in terms of anxiety and depression. As can be seen on Table 1, there were main effects for the distress measure. In contrast to our predictions, planned comparisons revealed that TX participants asserted significantly more symptoms of distress than controls ($p < .05$), CKD participants asserted marginally more symptoms of distress than controls ($p = .06$), and the two medical groups did not differ from each other ($p = ns$).

Variables Associated with Cognition

One of our main objectives was to assess the relationship between distress and cognition. In addition to distress, Table 7 displays the correlations between cognitive measures and participant characteristics thought to be of potential importance (Table 7 presents the correlations under discussion; the full correlation matrix can be seen in Appendix B). Correlations for age, education, and distress refer to the entire sample. Correlations for GFR, hemoglobin, and duration of CKD refer to CKD and TX participants only. Correlations for time on dialysis and time since TX refer to TX participants only.

As can be seen in Table 7, no significant associations were found between distress and the cognitive measures. However, Table 7 shows that there are significant associations between age and all the measures of cognition, indicating that older individuals tend to perform more poorly on these tasks. Since age was consistently associated with cognition, it was thought that it might mask other variables' associations with cognition, such as that of distress. For this reason, we also examined partial correlations with age as the control variable. Partial correlations were examined independently in the TX and CKD populations (Tables 8 and 9 present the correlations under discussion; full correlation matrices can be seen in Appendix B).

As can be seen in Table 8, no significant associations were found between levels of distress and cognition in CKD participants. Interestingly, however, Table 9 shows that there was a significant association between more distress and poorer performance on the response inhibition task (Color-Word Inhibition) in the TX group. Perhaps this latter finding is related to the other significant associations identified: participants with longer

time since TX tended to perform better on the inhibition task, and also tended to be less distressed. In sum, it appears as though individuals who have had their TX for longer tend to be less distressed, and perhaps as a result, were able to perform better on the inhibition task.

In this study, there are a number of additional factors that could potentially influence cognitive outcome. For example, if the metabolic derangements that accompany CKD were responsible for cognitive impairment, one might expect indicators of renal disease severity and duration of CKD to be associated with cognition. For this reason, bivariate correlations were run for illness severity measures (i.e., GFR and hemoglobin) and duration of CKD for the two medical populations. As can be seen in Table 7, individuals with lower GFR (i.e., indicating poorer renal function) tended to perform more poorly on the set-shifting task, but no other significant associations with illness were discovered. In addition, bivariate correlations of TX participant characteristics revealed that neither duration of dialysis nor time since TX was associated with any of the cognitive measures.

Since it is possible that biomedical and illness measures could behave differently in CKD and TX populations, their associations with cognition were also reconsidered in the analyses of partial correlations in Tables 8 and 9. There were trends for CKD participants with longer duration of renal disease to perform more poorly on the response inhibition task (Color-Word Inhibition), and for TX participants with lower GFR (indicating poorer renal functioning) to perform worse on the set-shifting task (Trails Letter-Number Sequencing).

Table 7. Correlations

		Distress	CVLT - Trial 1	Learning & Memory	Trails Letter-Number Sequencing	Color-Word Inhibition
Age	Pearson Correlation	**-.13**	**-.25****	**-.39****	**.50****	**.55****
Education	Pearson Correlation	.05	.02	**.26****	**-.25****	**-.17***
Distress	Pearson Correlation	1	-.02	-.10	.06	-.01
Glomerular Filtration Rate†	Pearson Correlation	.10	.08	.10	**-.22***	-.10
Hemoglobin†	Pearson Correlation	.01	-.11	-.09	**-.19#**	.04
Duration of CKD (yrs)†	Pearson Correlation	.11	-.07	-.10	-.08	.08
Time on Dialysis (yrs)††	Pearson Correlation	-.05	-.06	.14	-.004	-.15
Time since Transplant (yrs)††	Pearson Correlation	-.35*	-.21	.05	.13	-.19

*p < .05. **p < .01. #p < .10. †Correlations referring to TX and CKD participants only. ††Correlations referring to TX participants only.

Table 8. Partial correlations for CKD participants

Control Variables			Distress	CVLT - Trial 1	Learning & Memory	Trails Letter-Number Sequencing	Color-Word Inhibition
Age	Education	r-value	.19	.01	**.42****	**-.37****	-.06
	distress	r-value	1	.01	.04	-.03	-.23
	GFR	r-value	-.09	.15	.22	-.12	-.07
	Hemoglobin	r-value	-.21	-.20	-.03	-.06	.05
	Duration of CKD (yrs)	r-value	-.02	-.05	-.16	.01	**.29#**

*p < .05. **p < .01. #p < .10.

Table 9. Partial correlations for TX participants

Control Variables			Distress	CVLT - Trial 1	Learning & Memory	Trails Letter-Number Sequencing	Color-Word Inhibition
Age	Education	r-value	.06	-.05	-.05	-.16	-.11
	Distress	r-value	1	.13	-.26	.19	**.39***
	GFR	r-value	.15	.18	.01	**-.29#**	-.11
	Hemoglobin	r-value	.15	-.004	-.26	-.25	.19
	Duration of CKD (yrs)	r-value	.19	-.09	-.13	-.11	.01
	Time on Dialysis (yrs)	r-value	-.02	.01	.22	-.04	-.23
	Time since transplant (yrs)	r-value	**-.31***	-.11	.18	.07	**-.33***

*p < .05. **p < .01. #p < .10.

The potential influence of organ donor type (i.e., deceased donor or living donor) and immunosuppressant type (i.e., cyclosporine or tacrolimus) on cognitive performance has been of interest in the past. Reasons for interest in immunosuppressants are twofold. First, it is theoretically possible that the immunosuppressants have cognitive side effects. Second, case mix differences may result in differing cognitive performance. For example, Griva, et al. (2004) found that participants on tacrolimus were younger and had spent less time on dialysis and with a functioning kidney TX than patients on cyclosporine. These findings are likely related to tacrolimus being a relatively new medication. Furthermore, they found that cyclosporine, but not tacrolimus, was associated with poorer performance on measures of attention and executive functioning. Another factor to consider with TX recipients is that with the type of kidney received (i.e., deceased versus living donor) there are case mix differences that may independently influence cognitive performance. One concern is that since deceased donor recipients often have to wait longer than living donor recipients to receive a TX, they are more likely to have been in a later stage of CKD and on dialysis. If cognitive performance is related to either metabolic derangements or the dialysis procedure, it would stand to reason that deceased donor recipients, assuming that they have experienced more severe kidney disease and more time on dialysis, would present with worse cognitive performance than living donor recipients. As can be seen in Table 5, similar proportions of deceased donor recipients and living donor recipients were on dialysis prior to receiving a TX. However, living donor recipients were on dialysis for significantly less time (mean = 1.73 years; S.D. = 1.50) than deceased donor recipients (mean = 3.62 years; S. D. = 2.59; $F(1, 41) = 7.07$, p

< .01). Since this difference exists, deceased donor and living donor recipients were compared in terms of cognitive performance.

In separate analyses, ANOVA was performed with organ donor type and immunosuppressant type as the between-groups factors. No significant differences in cognition were found for organ donor type (*p*'s = *ns*) or immunosuppressant type (*p*'s = *ns*). For TX donor type comparisons, calculation of estimated effect sizes revealed small effects for attention (d = .18); all other effect sizes were with d < .14. For the immunosuppressant types, there were small effects for the set switching and response inhibition tasks (d = .25; d = .27, respectively); all other effect sizes were with d < .12. Since group sizes were as small as 12 per group, power limitations for these analyses are clear.

DISCUSSION

To our knowledge, this is the first study to compare a pre-dialysis CKD population with a kidney TX population. It is also the first study to utilize multiple measures of executive function and to take into consideration the contribution of co-morbid conditions to compromised cognition in a kidney TX population. Although we did not longitudinally examine cognitive functioning from pre-illness state through early CKD, ESRD and successful kidney TX it was anticipated that we would be able to infer a trajectory of cognitive changes through these stages.

Our first objective was to better describe cognitive performance in TX recipients. This was achieved by comparing the cognitive performance of TX participants to CKD participants and controls. The results indicated that both TX and CKD participants performed significantly poorer than controls on the learning and memory (CVLT-II Trials 1-5 and Long Delay) and response inhibition (Color-Word Inhibition) tasks. In addition, there were trends for TX and CKD participants to perform worse than controls on the attention task (CVLT-II Trial 1). While CKD participants performed significantly poorer than controls on the set shifting task, TX participants performed only marginally worse than controls. CKD and TX participants did not significantly differ from each other on any of the cognitive measures. The estimated effect sizes for these findings (i.e., between medical groups and control participants) ranged from medium to large, with effects approaching a medium size for the measure of attention (CVLT Trial 1), medium to large effects for the set-switching (Trails Letter-Number Sequencing) and response

inhibition (Color-Word Inhibition) tasks, and large effects for the learning and memory measure (composite of CVLT Trials 1-5 and Long Delay).

We hypothesized that both CKD and TX participants would perform significantly worse than controls on the executive measures. This hypothesis was supported for both groups on the response inhibition measure (Color-Word Inhibition), and for only the CKD participants on the set-shifting task (Trails Letter-Number Sequencing), which, notably, is a less reliable measure than the Color-Word task (published test-retest reliabilities are $r = 0.38$ and $r = 0.75$ for set-shifting and response inhibition, respectively).

We also hypothesized that TX participants and controls would perform significantly better than CKD participants on measures of attention and learning and memory; however, evidence did not support these hypotheses. The findings suggest that the commonly held belief that poor cognition resolves following kidney TX does not necessarily hold true for the current sample. In fact, both CKD *and* TX participants performed worse than healthy controls on the measure of learning and memory.

Although attention effects were not present for CKD or TX participants and set-switching effects were not present for TX participants, it is important to note that effect sizes approaching medium were still present between these participants and the controls. According to Cohen's recommendations, at least 64 subjects would be necessary to provide enough power (0.80) to detect effect sizes of this magnitude. As the sample sizes were smaller than this ($n = 42$ & $n = 47$ for TX and CKD, respectively), it appears as though there were power limitations in the current study. These limitations highlight the importance of revisiting the issues in future research with a larger sample size.

Given the fact that both CKD and transplant recipients exhibited worse cognitive performance than controls, the important questions remains what factors may be accounting for these differences, and are the etiologies similar in both illness groups? Our second objective was to describe group differences in levels of distress and to see if distress was associated with cognition. To achieve this goal, we assessed group differences by comparing combined scores from depression and anxiety checklists. Based on the minimal research to date (e.g., Akman, et al., 2004; Yeh, et al., 2004), it was anticipated that the symptoms of depression and anxiety would be most prevalent in early CKD participants, followed by TX participants, and lastly, healthy controls. Surprisingly, our results did not support these predictions. TX participants asserted significantly more symptoms of distress than controls, and CKD participants asserted marginally more symptoms of distress in comparison with controls. Furthermore, significantly more TX participants were taking anti-depressants than either the CKD or control groups. While one may infer that receiving a kidney TX would lead to less psychological distress than having to cope with the stressors accompanying kidney disease, results from our study do not support such suppositions. This may be due to the remaining stresses of living with a medical condition, including the continual requirement for strict adherence to medication regimes and other potential factors, such as compromised cognition or difficulty returning to work. However, it could be that in comparison to when on dialysis, participants may have experienced an alleviation of distress following kidney transplantation.

After identifying this group difference, we evaluated correlations between the distress measure and the cognitive tasks. In the overall sample, associations between distress and cognition were not found. However, when partial correlations were run with

age as the control variable, associations were found between TX participants' performance on the response inhibition task (Color-Word Inhibition) and distress, with the tendency for more distressed individuals to perform more poorly on this measure. Thus, it appears that depression may in fact influence cognitive performance on tasks involving executive functioning.

In addition to distress, we looked at the association of a number of other variables (e.g., education, GFR) but discovered that only a few of these variables were related to cognitive performance. While the executive functioning test of set-shifting (Trails Letter-Number Sequencing) was significantly correlated with GFR in both the CKD and TX groups, hemoglobin was not significantly associated with any of the cognitive measures. Duration of kidney disease was not significantly associated with cognition for either CKD or TX participants, nor was duration of dialysis or time since TX significantly associated with cognitive performance in TX participants. Also, differential cognitive performance was not present when comparing type of organ donor (i.e., deceased or living donor) or type of immunosuppressant (i.e., cyclosporine or tacrolimus).

The results from our study differ from the findings presented in earlier research. While Griva, et al. (2004) found significant differences for verbal memory and attention between TX and dialysis participants, measures of executive functioning were roughly equivalent for the two groups. In contrast, our results did not indicate any differences between TX and pre-dialysis participants. Although these results for attention and learning and memory were not predicted, it is possible that this is a reflection of the clinical group chosen for comparison in the present study (i.e., pre-dialysis CKD participants). Recall that in Kurella, et al.'s (2004) study dialysis participants performed

significantly worse on cognitive measures than pre-dialysis CKD participants. Perhaps if the TX participants from the present sample were compared to dialysis participants, findings similar to those of Griva and colleagues' would have emerged.

It is also possible that the results in the present study differed from Griva and colleagues' (2004) research due to case mix differences (i.e., etiology of CKD and co-morbid conditions). For example, more patients had hypertension identified as the etiological cause of CKD in Griva, et al.'s (2004) study, but our sample had a greater prevalence of the co-morbid condition of diabetes. However, the relative contribution of co-morbid conditions to cognitive performance in CKD and TX participants is speculative at this point, since this has not been directly assessed in any research studies to date.

The findings from our study need to be considered in light of certain limitations. Since we used a between subjects design, case mix differences between the TX and CKD groups may have added additional variability to the present study which would increase the difficulty of distinguishing the relative contributions of various factors to compromised cognition. Only a portion of the individuals in the CKD group will receive a kidney TX or even be accepted onto the kidney TX waitlist for a variety of reasons (e.g., age of CKD onset, co-morbid conditions, lifestyle choices, et cetera), and as a result, a number of group differences other than those addressed in this study may be present. Ideally, participants would be followed longitudinally throughout the course of CKD. While previous studies have used longitudinal designs (e.g., Kramer, et al., 1996) they only administered measures of attention and cognitive screening measures. As well, the exclusionary criteria of the present study limit the generalizability of the results (e.g.,

the results are *not* applicable to participants who have suffered from a major stroke or who have a major mental disorder, since such individuals were not included in the study) to the kidney TX population at large. In fact, it is likely that we would have observed even greater cognitive impairments if such individuals would have been included.

Although we are not able to clearly define the mechanisms of compromised cognition, it is felt that this study has made potential etiologies more apparent. Our analyses suggest that metabolic factors may play a small role in cognition in at least TX participants (e.g., GFR was associated with the set-shifting task in TX participants). In addition, while distress appears to contribute to poor executive functioning performance in TX participants (specifically, response inhibition), no associations were identified between distress and the other measures of cognition. In sum, these two factors appear to account for little cognitive variance in the current sample. Given the prevalence of hypertension and diabetes in this study, it seems likely that these conditions contribute to the levels of cognitive performance seen in CKD and TX participants.

Another possibility worthy of exploration is that some of the mechanisms of poor cognition in the TX and CKD groups may differ. For instance, Bermond, et al.'s study (2005) suggests that poor memory performance in TX participants is associated with the immunosuppressant prednisone. In the future, studies that compile cumulative dosages of prednisone and other central nervous system-active medication, include other medical populations (e.g., diabetic patients without CKD) as comparison groups, and use of longitudinal designs could all aid in further clarification of origins of compromised cognition in CKD and kidney TX populations. The impetus for such research is readily

apparent as the prevalence of CKD, and consequently, the demand for kidney transplantation, continues to grow.

In summary, the current findings suggest that cognitive difficulties are observed after successful kidney transplantation. The results from the present study clearly indicate the need for further research in this field. Given the fact that reduced cognitive performance has been identified in both CKD and kidney TX recipients, it will be paramount to elucidate the functional consequences in terms of medication adherence, ability to return to work, satisfaction with choice to receive a TX, and overall quality of life. Such research could prove invaluable in assessing the relevance of cognitive findings to everyday living, as well as further highlight the potential benefits of formal evaluation of cognition to develop and implement treatment compliance strategies throughout the course of kidney disease.

APPENDIX A

To assess stability of renal functioning in TX participants, the most current GFR (GFR1; the GFR closest to the time of testing), and the two most recent GFRs (GFR2 = 2nd most recent, and GFR3 = 3rd most recent) were collected for TX participants. This data was then analyzed to identify, if any, major concerns regarding kidney stability, including decreases in kidney functioning to the point of ESRD. In the interpretation of this data, it is important to note that kidney functioning in kidney TX recipients is rarely restored to a level of normal kidney function. This may be because TX recipients typically have only one functioning kidney rather than two. Therefore, even if a patient is considered to have a successful kidney TX, GFR levels would represent a degree of renal insufficiency in a majority of the cases.

GFR1-GFR2

The difference scores were calculated between GFR1 and GFR2 (GFR2-GFR1) as well as overall means. Difference scores were approximately normally distributed. The mean difference score was 4.72 (*S.D.* = 3.74). GFR difference scores that were greater than one standard deviation below the mean at the time of testing were identified (i.e., indicating a relative drop in GFR and overall kidney functioning). Two individuals were within this range (T19, T22). Both of these individuals at the time of testing had stage 2 kidney damage (mild damage; GFR between 59 and 90). The same two individuals also met the criterion of 2 standard deviations below the mean.

GFR1-GFR3

We used similar procedures for GFR1 and GFR3 (GFR1-GFR3). Again, difference scores were approximately normally distributed. The mean difference score was 5.79 (*S.D.* = 5.47). Two individuals were identified who were one standard deviation below the mean (T22 & T40). Once again, at the time of testing both individuals were at the level of stage 2 kidney damage (i.e., mild). When the criterion was set at 2 standard deviations below the mean, only one individual was within this range (T22).

Individuals with Stage 4 Kidney Damage

For individuals with stage 4 kidney disease, additional qualifications were applied: (1) Their GFR levels must not have decreased more than 1 SD below the mean; and (2) none of the past three measurements of GFR could be within the range of stage 5 kidney disease (i.e., kidney failure). At time of testing, none of the three individuals with stage 4 kidney damage showed a decrease of kidney functioning of one standard deviation or more below the mean in comparison with the two most recent measures of GFR. However, one of three participant's GFR levels fell in the range of stage 5 kidney disease. This participant was excluded from further analyses, while the other two participants remained in the study.

APPENDIX B

B.1 Correlations for entire sample

		Age	Education	Distress	GFR
Age	Pearson Correlation	1	-.03	-.13	-.14
	N	142	142	142	90
Education	Pearson Correlation	-.03	1	.05	.05
	N	142	142	142	90
Distress	Pearson Correlation	-.13	.05	1	.10
	N	142	142	142	90
Glomerular Filtration Rate	Pearson Correlation	-.14	.05	.10	1
	N	90	90	90	90
Hemoglobin	Pearson Correlation	-.06	.03	.01	**.51****
	N	90	90	90	**90**
Duration of CKD (yrs)	Pearson Correlation	-.03	-.03	.11	.11
	N	89	89	89	89
Time on Dialysis (yrs)	Pearson Correlation	.120	.23	-.05	-.25
	N	43	43	43	43
Time since Transplant (yrs)	Pearson Correlation	.24	.04	**-.35***	.21
	N	43	43	**43**	43
CVLT - Trial 1	Pearson Correlation	**-.25****	.02	-.02	.08
	N	**142**	142	142	90
Learning & Memory	Pearson Correlation	**-.39****	**.26****	-.10	.10
	N	**141**	**141**	141	89
Trails Letter – Number Sequencing	Pearson Correlation	**.50****	**-.25****	.06	**-.22***
	N	**140**	**140**	140	**88**
Color-Word Inhibition	Pearson Correlation	**.55****	**-.17***	-.01	-.10
	N	**136**	**136**	136	84

*$p < .05$. **$p < .01$. $^{\#}p < .10$.

B.1 Correlations for entire sample, continued

		Hemoglobin	Duration of CKD (yrs)	Time on Dialysis (yrs)	Time Since Transplant (yrs)
Age	Pearson Correlation	-.06	-.03	.12	.24
	N	90	89	43	43
Education	Pearson Correlation	.03	-.03	.23	.04
	N	90	89	43	43
Distress	Pearson Correlation	.01	.11	-.05	**-.35***
	N	90	89	43	**43**
Glomerular Filtration Rate	Pearson Correlation	**.51****	.11	-.25	.21
	N	**90**	89	43	43
Hemoglobin	Pearson Correlation	1	.13	-.20	-.02
	N	90	89	43	43
Duration of CKD (yrs)	Pearson Correlation	.13	1	-.07	-.07
	N	89	89	42	42
Time on Dialysis (yrs)	Pearson Correlation	-.20	-.07	1	-.20
	N	43	42	43	43
Time since Transplant (yrs)	Pearson Correlation	-.02	-.07	-.20	1
	N	**43**	42	43	43
CVLT - Trial 1	Pearson Correlation	-.11	-.07	-.06	-.21
	N	90	89	43	43
Learning & Memory	Pearson Correlation	-.09	-.10	.14	.05
	N	89	88	42	42
Trails Letter – Number Sequencing	Pearson Correlation	**-.19#**	-.08	-.004	.13
	N	**88**	87	41	41
Color-Word Inhibition	Pearson Correlation	.04	.08	-.15	-.19
	N	84	83	37	37

*$p < .05$. **$p < .01$. #$p < .10$.

B.1 Correlations for entire sample, continued

		CVLT - Trial 1	Learning & Memory	Trails Letter-Number Sequencing	Color-Word Inhibition
Age	Pearson Correlation	**-.25****	**-.39****	**.50****	**.55****
	N	**142**	**141**	**140**	**136**
Education	Pearson Correlation	.02	**.26****	**-.25****	**-.17***
	N	142	**141**	**140**	**136**
Distress	Pearson Correlation	-.02	-.10	.06	-.01
	N	142	141	140	136
Glomerular Filtration Rate	Pearson Correlation	.08	.10	**-.22***	-.10
	N	90	89	**88**	84
Hemoglobin	Pearson Correlation	-.11	-.09	**-.19#**	.04
	N	90	89	**88**	84
Duration of CKD (yrs)	Pearson Correlation	-.07	-.10	-.08	.08
	N	89	88	87	83
Time on Dialysis (yrs)	Pearson Correlation	-.06	.14	-.004	-.15
	N	43	42	41	37
Time since Transplant (yrs)	Pearson Correlation	-.21	.05	.13	-.19
	N	43	42	41	37
CVLT - Trial 1	Pearson Correlation	1	**.58****	**-.36****	**-.32****
	N	142	**141**	**140**	**136**
Learning & Memory	Pearson Correlation	**.58****	1	**-.52****	**-.54****
	N	**141**	141	**139**	**136**
Trails Letter – Number Sequencing	Pearson Correlation	**-.36****	**-.52****	1	**.65****
	N	**140**	**139**	140	**134**
Color-Word Inhibition	Pearson Correlation	**-.32****	**-.54****	**.65****	1
	N	**136**	**136**	**134**	136

$^{*}p < .05$. $^{**}p < .01$. $^{\#}p < .10$.

B.2 Partial correlations for CKD participants

Control Variables			Education	Distress	GFR
Age	Education	Correlation	1	.19	.05
		df	0	44	44
	Distress	Correlation	.19	1	-.09
		df	44	0	44
	GFR	Correlation	.05	-.09	1
		df	44	44	0
	Hemoglobin	Correlation	.15	-.21	.24
		df	44	44	44
	Duration of CKD (yrs)	Correlation	-.13	-.02	-.16
		df	44	44	44
	CVLT - Trial 1	Correlation	.01	.01	.15
		df	44	44	44
	Learning & Memory	Correlation	**.42****	.04	.22
		df	**44**	44	44
	Trails - Number-Letter Sequencing	Correlation	**-.37***	-.03	-.12
		df	**44**	44	44
	Color-Word Inhibition	Correlation	-.06	-.23	-.07
		df	44	44	44

*$p < .05$. **$p < .01$. $^{\#}p < .10$.

B.2 Partial correlations for CKD participants, continued

Control Variables			Hemoglobin	Duration of CKD (yrs))	CVLT - Trial 1
Age	Education	Correlation	.15	-.13	.01
		df	44	44	44
	Distress	Correlation	-.21	-.02	.01
		df	44	44	44
	GFR	Correlation	.23	-.16	.15
		df	44	44	44
	Hemoglobin	Correlation	1	.14	-.20
		df	0	44	44
	Duration of CKD (yrs)	Correlation	.14	1	-.05
		df	44	0	44
	CVLT - Trial 1	Correlation	-.20	-.05	1
		df	44	44	0
	Learning & Memory	Correlation	-.03	-.16	**.40****
		df	44	44	**44**
	Trails Number-Letter Sequencing	Correlation	-.06	.01	-.08
		df	44	44	44
	Color-Word Inhibition	Correlation	.05	**.29**#	-.18
		df	44	**44**	44

*$p < .05$. **$p < .01$. #$p < .10$.

B.2 Partial correlations for CKD participants, continued

Control Variables			Learning & Memory	Trails Letter-Number Sequencing	Color-Word Inhibition
Age	Education	Correlation	**.42****	**-.37****	-.06
		df	**44**	**44**	44
	Distress	Correlation	.04	-.03	-.23
		df	44	44	44
	GFR	Correlation	.22	-.12	-.07
		df	44	44	44
	Hemoglobin	Correlation	-.03	-.06	.05
		df	44	44	44
	Duration of CKD (yrs)	Correlation	-.16	.01	**.29#**
		df	44	44	**44**
	CVLT - Trial 1	Correlation	**.40****	-.08	-.18
		df	**44**	44	44
	Learning & Memory	Correlation	1	**-.46***	-.15
		df	0	**44**	44
	Trails Number-Letter Sequencing	Correlation	**-.46***	1	**.44****
		df	**44**	0	**44**
	Color-Word Inhibition	Correlation	-.15	**.44****	1
		df	44	**44**	0

$^{*}p < .05$. $^{**}p < .01$. $^{\#}p < .10$.

B.3 Partial correlations for TX participants

Control Variables			Education	Distress	GFR
Age	Education	Correlation	1	.06	.05
		df	0	40	40
	Distress	Correlation	.063	1	.15
		df	40	0	40
	GFR	Correlation	.05	.15	1
		df	40	40	0
	Hemoglobin	Correlation	-.18	.15	**.46****
		df	40	40	**40**
	Duration of CKD (yrs)	Correlation	.04	.19	.04
		df	39	39	39
	Time on Dialysis (yrs)	Correlation	.22	-.02	**-.26#**
		df	40	40	**40**
	Time since transplant (yrs)	Correlation	.01	**-.31***	.19
		df	40	**40**	40
	CVLT - Trial 1	Correlation	-.05	.13	.18
		df	40	40	40
	Learning & Memory	Correlation	-.05	-.26	.01
		df	39	39	39
	Trails Number-Letter Sequencing	Correlation	-.16	.19	**-.29#**
		df	38	38	**38**
	Color-Word Inhibition	Correlation	-.11	**.39***	-.11
		df	34	**34**	34

*$p < .05$. **$p < .01$. #$p < .10$.

B.3 Partial correlations for TX participants, continued

Control Variables			Hemoglobin	Duration of CKD (yrs)	Time on Dialysis (yrs)
Age	Education	Correlation	-.18	.04	.22
		df	40	39	40
	Distress	Correlation	.15	.19	-.02
		df	40	39	40
	GFR	Correlation	**.46****	.04	**-.26#**
		df	**40**	39	**40**
	Hemoglobin	Correlation	1	-.01	-.23
		df	0	39	40
	Duration of CKD (yrs)	Correlation	-.01	1	-.08
		df	39	0	39
	Time on Dialysis (yrs)	Correlation	-.23	-.08	1
		df	40	39	0
	Time since transplant (yrs)	Correlation	-.08	-.10	-.24
		df	40	39	40
	CVLT - Trial 1	Correlation	-.004	-.09	.01
		df	40	39	40
	Learning & Memory	Correlation	-.26	-.13	.22
		df	39	38	39
	Trails Number-Letter Sequencing	Correlation	-.25	-.11	-.04
		df	38	37	38
	Color-Word Inhibition	Correlation	.19	.01	-.23
		df	34	33	34

*$p < .05$. **$p < .01$. #$p < .10$.

B.3 Partial correlations for TX participants, continued

Control Variables			Time since transplant (yrs)	CVLT - Trial 1	Learning & Memory
Age	Education	Correlation	.01	-.05	-.05
		df	40	40	39
	Distress	Correlation	**-.31***	.13	-.26
		df	**40**	40	39
	GFR	Correlation	.19	.18	.01
		df	40	40	39
	Hemoglobin	Correlation	-.07	-.004	-.26
		df	40	40	39
	Duration of CKD (yrs)	Correlation	-.10	-.09	-.13
		df	39	39	38
	Time on Dialysis (yrs)	Correlation	-.24	.01	.22
		df	40	40	39
	Time since transplant (yrs)	Correlation	1	-.11	.18
		df	0	40	39
	CVLT - Trial 1	Correlation	-.10	1	**.43****
		df	40	0	**39**
	Learning & Memory	Correlation	.18	**.43****	1
		df	39	**39**	0
	Trails Number-Letter Sequencing	Correlation	.07	**-.27#**	-.18
		df	38	**38**	37
	Color-Word Inhibition	Correlation	**-.33***	-.10	**-.44****
		df	**34**	34	**34**

*$p < .05$. **$p < .01$. #$p < .10$.

B.3 Partial correlations for TX participants, continued

Control Variables			Trails Letter-Number Sequencing	Color-Word Inhibition
Age	Education	Correlation	-.16	-.11
		df	38	34
	Distress	Correlation	.19	**.39***
		df	38	**34**
	GFR	Correlation	**-.29#**	-.11
		df	**38**	34
	Hemoglobin	Correlation	-.25	.19
		df	38	34
	Duration of CKD (yrs)	Correlation	-.11	.01
		df	37	33
	Time on Dialysis (yrs)	Correlation	-.04	-.23
		Df	38	34
	Time since transplant (yrs)	Correlation	.07	**-.33***
		df	38	**34**
	CVLT - Trial 1	Correlation	**-.27#**	-.10
		df	**38**	34
	Learning & Memory	Correlation	-.18	**-.44****
		df	37	**34**
	Trails Letter-Number Sequencing	Correlation	1	**.52****
		df	0	**32**
	Color-Word Inhibition	Correlation	**.52****	1
		df	**32**	0

$^{*}p < .05.$ $^{**}p < .01.$ $^{\#}p < .10.$

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